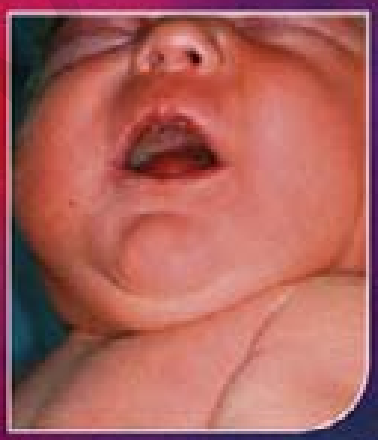
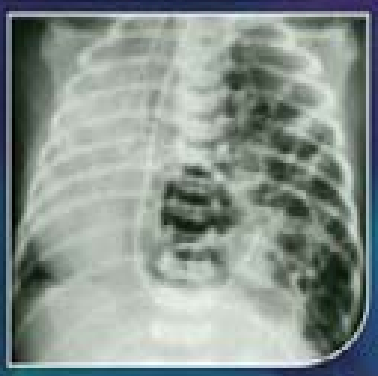
Newborn Surgery

Third edition





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Newborn Surgery

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Third edition

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To Veena, Abir, Anita and Niki for their love and patience

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Preface to the third edition

It has been eight years since the second edition of the book was published in 2003. Over the last decade, major advances have occurred in the understanding and treatment of neonatal surgical conditions. Advances in prenatal diagnosis, imaging, intensive care, and minimally invasive surgery have transformed the practice of surgery in the newborn. The third edition of Newborn Surgery has been extensively revised and contains 105 chapters by 160 contributors from all five continents of the world. This edition contains many new chapters taking account of the recent advances in neonatal surgery. The new chapters include: Perinatal physiology; Clinical anatomy of the newborn; Epidemiology of birth defects; Fetal counselling for surgical malformations; Neonatal sepsis; Liver transplantation; Congenital pouch colon; Megacystis microcolon intestinal hypoperistalsis syndrome; and Urinary tract infections. Each chapter has been written by world class experts in their respective fields, along with their co-authors.

This textbook provides an authoritative, comprehensive and complete account of the pathophysiology and treatment of various surgical conditions in the newborn. This book should be of interest to all those who have a clinical responsibility for newborn babies. It is particularly intended for trainees in pediatric surgery, established pediatric surgeons, general surgeons with an interest in pediatric surgery as well as neonatologists and pediatricians seeking more detailed information on newborn surgical conditions.

I wish to thank most sincerely all the contributors for their outstanding work in producing this innovative text-book. I also wish to express my gratitude to Ms Vanessa Woods and Ms Lisa Kelly for their skilful secretarial help. I am grateful to Dr G.P. Seth for reading each and every word of the galley proofs of the entire book. I wish to thank the editorial staff of Hodder Arnold, particularly Mr Stephen Clausard, for their help during preparation and publication of this book. I am thankful to the Children's Medical & Research Foundation, Our Lady's Children's Hospital, Dublin for their support.

Prem Puri
2011

Preface to the second edition

The 2nd edition of *Newborn Surgery* has been extensively revised. Many new chapters have been added to take account of the recent developments in the care of the newborn with congenital malformations. This edition, which comprises 97 chapters by 121 contributors from all five continents of the world, provides an authoritative, comprehensive, and complete account of the various surgical conditions in the newborn. Each chapter is written by the current leading expert(s) in their respective fields.

Newborn surgery in the twenty-first century demands of its practitioners detailed knowledge and understanding of the complexities of congenital anomalies, as well as the highest standards of operative techniques. In this textbook, great emphasis continues to be placed on providing a comprehensive description of operative techniques of each individual congenital condition in the newborn. The book is intended for trainees in pediatric surgery, established pediatric surgeons, general surgeons with an interest in pediatric surgery, as well as neonatologists and pediatricians seeking more detailed information on newborn surgical conditions.

I wish to thank most sincerely all the contributors for the outstanding work they have done for the production of this innovative textbook. I also wish to express my gratitude to Mrs Karen Alfred and Ms Ann Brennan for their secretarial help and to the staff of Hodder Arnold for their help during the preparation and publication of this book. I am grateful to the Children's Medical & Research Foundation, Our Lady's Hospital for Sick Children, Dublin for their support.

Prem Puri
2003

Preface to the first edition

During the last three decades, newborn surgery has developed from an obscure subspecialty to an essential component of every major academic pediatric surgical department throughout both the developed and the developing world. Major advances in perinatal diagnosis, imaging, neonatal resuscitation, intensive care, and operative techniques have radically altered the management of newborns with congenital malformations. Embryological studies have provided new valuable insights into the development of malformations, while improvements in prenatal diagnosis are having a significant impact on approaches to management. Monitoring techniques for the sick neonate pre- and postoperatively have become more sophisticated and there is now greater emphasis on physiological aspects of the surgical newborn, as well as their nutritional and immune status. This book provides a comprehensive compendium of all these aspects as a prelude to an extensive description of surgical conditions in the newborn. Modern-day newborn surgery demands detailed knowledge of the complexities of newborn problems. Research developments, laboratory diagnosis, imaging, and innovative surgical techniques are all part of the challenge facing surgeons dealing with congenital conditions in the newborn. In this book, a comprehensive description of operative techniques of each individual condition is presented. Each contributor was selected to provide an authoritative, comprehensive, and complete account of their respective topics. The book, comprising 90 chapters, is intended primarily for trainees in pediatric surgery, established pediatric surgeons, general surgeons with an interest in pediatric surgery, and neonatologists.

I am most grateful to all contributors for their willingness to contribute chapters at considerable cost of time and effort. I am indebted to Mr Maurice De Cogan for artwork, Mr Dave Cullen for photography, and Ms Ann Brennan and Ms Deirdre O'Driscoll for skilful secretarial help. I am grateful to the Children's Research Centre, Our Lady's Hospital for Sick Children, for their support. Finally, I wish to thank the editorial staff, particularly Ms Susan Devlin, of Butterworth-Heinemann for their help during the preparation and publication of this book.

Prem Puri
1996

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PART I

GENERAL

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Embryology of malformations

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INTRODUCTION

Approximately 3% of human newborns present with congenital malformations.[1] Without surgical intervention, one-third of these infants would die since their malformations are not compatible with sustained life outside the uterus.[1,2] In figures, this means that in a country such as Germany, nearly 6000 children are born every year with a life-threatening malformation.

Due to the development of prenatal diagnostic procedures, advanced surgical techniques, and intensive post-operative care, most infants with otherwise fatal malformations can be rescued by an operation in the neonatal period. However, morbidity remains high in some of these children[2] with the necessity of repeated operations and hospitalizations despite a successful primary operation. This may also be the fate of many children with non-life-threatening malformations such as hypospadias or cleft palate.

Mortality is still high in newborns with certain malformations such as congenital diaphragmatic hernias or severe combined defects. As a consequence, congenital malformations today are the main cause of death in the neonatal period. In the United States, 21% of neonatal mortality can be related to congenital malformations.[3]

These figures probably do not reflect a real increase of the actual incidence of congenital malformation. The observed mortality shift might rather be due to improved intensive care medicine in today's Western world countries where neonates (even those with birth defects) have a better chance of survival. On the other hand, this statistical shift indicates that knowledge about congenital malformations lags behind the progress clinical research has made in the surrounding fields. Efforts are needed to close the gap and learn more about baby killer No. 1. Identification of teratogens will help to reduce the incidence of malformations when exposure can be avoided, and pathogenetic studies might aid in designing therapeutic measures. Both treatment and prevention critically depend on basic embryological research.

GENERAL REMARKS ON EMBRYOLOGY AND THE EMBRYOLOGY OF MALFORMATIONS

Despite many efforts, the embryology of numerous congenital anomalies in humans is still a matter of speculation. This is due to the following reasons:

- a shortage of study material (both normal and abnormal embryos);
- various technical problems (difficulties in the interpretation of serial sections, shortage of explanatory three-dimensional reconstructions);
- misconceptions and/or outdated theories concerning normal and abnormal embryology.

Fortunately, a number of animal models are known today which allow advanced embryological studies in various embryological fields. Especially for the studies of anorectal malformations, a number of animal models is at hand. In addition, a Scanning Electron-Microscopic Atlas of human embryos has been published recently which provides detailed insights into normal human embryology.[4]

Appropriate and illustrative findings in various fields of embryology are still lacking. This explains why today many typical malformations are still not explained satisfactorily. Pediatric surgeons are still confused when they are confronted with the embryological background of normal and abnormal development.

For the described misconceptions and/or outdated theories, Haeckel's 'biogenetic law'[5] is one example. According to this theory, a human embryo recapitulates in its individual development (ontogeny) the morphology observed in all life-forms (phylogeny). This means that during its development an advanced species is seen to pass through stages represented by adult organisms of more primitive species. This theory still has an impact on the nomenclature of embryonic organs and explains why human embryos have 'cloacas' like adult birds and 'branchial' clefts like adult fish.

Another very popular misconception is the theory that malformations actually represent 'frozen' stages of normal

embryology ('Hemmungsmißbildung').[6] As a result, our understanding of normal embryology stems more from pathological-anatomic interpretations of observed malformations than from proper embryological studies. The theory of the 'rotation of the gut' as a step in normal development is a perfect example of this misconception.

DEFINITION OF THE TERM 'MALFORMATION'

After birth, neonates can present with a broad spectrum of deviations from normal morphology. This extends from minor variations of normal morphology without any clinical significance to maximal organ defects with extreme functional deficits of the malformed organs or of the whole organism.

The degree of functional disorder is decisive when dealing with the question of whether a variation of normal morphology has to be viewed as a dangerous malformation requiring surgical correction. This means that functional disturbance is essential when using the term 'malformation'. Inborn deviations can be detrimental, neutral, or even beneficial, otherwise evolutionary progress could not take place. An example of a beneficial deviation is the longevity syndrome of people with abnormally low serum cholesterol levels. Abnormalities with little or no functional disturbance might still require surgical correction when patients are in danger of social stigmatization. Coronal or glandular hypospadias might serve as an example for this condition.

ETIOLOGY OF CONGENITAL MALFORMATIONS

In most cases, the etiology of congenital malformations remains unclear. Possible etiological factors are listed in Table 1.1.

In about 20% of cases genetic factors (gene mutation and chromosomal disorders) can be identified.[1,2,7] In 10% an environmental origin can be demonstrated.[1,2] In 70% the factors responsible remain obscure.

Table 1.1 Etiology of congenital malformations.

Etiology	%
Genetic disorders	20
Environmental factors	10
Unknown etiology	70

Environmental factors

A large number of agents are known which might interfere with the normal development of organ systems during embryogenesis.[1,7] The underlying mechanisms of this interference is poorly understood in most cases. Characteristically, during organogenesis, different organs of the embryo show distinct periods of greatest sensitivity to the action of the teratogen. These phases of greatest sensitivity are called the 'teratogenetic period of determination'.[8] The typical patterns of some syndromes can be explained by an overlap of these phases during embryological development.

In 1983, Shepard[2] published a catalog of suspected teratogenic agents. Over 900 agents are known to produce congenital anomalies in experimental animals. In 30, evidence for teratogenic action in humans could be demonstrated. Teratogenic agents can be divided into four groups (Table 1.2).

The teratogenic potential of virus infections,[1] especially rubella and herpes, and that of radiation[1] has been clearly established. Maternal metabolic defects and lack of essential nutritives can be teratogenic. After a vitamin A-free diet[9] and riboflavin-free diet[10] various congenital malformations were observed in rats and mice. Among these were diaphragmatic hernias, isolated esophageal atresias, and isolated tracheoesophageal fistulas. Similarly, inappropriate administration of hormones can be associated with intrauterine dysplasias.[11]

Industrial and pharmaceutical chemicals such as tetrachlor-diphenyl-dioxin (TCDD) or thalidomide have inflicted tragedies by their teratogenic action. When thalidomide was prescribed to women in the early 1960s as a 'safe' sleeping medication, numerous children were born with dysmelic deformities.[7,12,13] In addition, atresias of the esophagus, the duodenum, and the anus were observed in some children.[12] The data collected suggest that teratogenic agents do not cause new patterns of malformations but rather mimic sporadic birth defects. This had posed problems in identifying thalidomide as the responsible agent. It appears likely that among those 70% congenital malformations with unclear etiology a considerable percentage might be precipitated by as yet unidentified environmental factors. In a rat model, the herbicide nitrofen (2.4-dichloro-phenyl-p-nitrophenyl ether) has been shown to induce congenital diaphragmatic hernias, cardiac abnormalities and hydronephrosis.[14–18] In 1978, Thompson *et al.*[19] described the teratogenicity of the anticancer drug adriamycin in rats and rabbits. More recently, Diez-Pardo *et al.*[20] re-described this model with emphasis to its potentials as a model for foregut anomalies. Today, the adriamycin model is generally described as a model for the VACTERL-association (V = vertebral, A = anorectal, C = cardiac, T = tracheal, E = esophageal, R = renal, L = limb).[21,22] Thus, classic malformations such as atresias of the esophagus and the intestinal tract, intestinal duplications and others can be mimicked by teratogens in animal models.

Table 1.2 Teratogenic agents in congenital malformations.

Teratogenic agents	
Physical agents	Radiation, heat, mechanical factors
Infectious agents	Viruses, treponemes, parasites
Chemical, drug, environmental agents	Thalidomide, nitrofen, hormones, vitamin deficiencies
Maternal, genetic factors	Chromosomal disorders, multifactorial inheritance

After Nadler.[1]

Genetic factors

Approximately 20% of congenital malformations are of genetic origin. Most surgically correctable malformations are associated with chromosomal disorders, e.g. trisomy 21, 13, or 18, or are of multifactorial inheritance[23] with a small risk of recurrence. The assumption of multifactorial inheritance results from the fact that with nearly all major anomalies familiar occurrences had been observed.[1] In animals, inheritance has also been found for some malformations.[24–27]

EMBRYOLOGY AND ANIMAL MODELS

Over the last two decades a number of animal models were developed with the potential to gain a better understanding of the morphology of not only malformed but also of normal embryos. These animal models can be divided into four subgroups.

Surgical models

In the past, the chicken was an important surgical model to study embryological processes. Due to the easy access to the embryo, its broad availability and its cheapness, the chicken is an ideal model for experimental studies. It has been widely used by embryologists, especially in the field of epithelial/mesenchymal interactions.[28–30] Pediatric surgeons used this model to study morphological processes involved in intestinal atresia formation,[31,32] gastroschisis,[33] and Hirschsprung's disease.[34]

The Czech embrologist Lemez[35] used chicken embryos in order to induce tracheal agenesis with tracheo-esophageal fistula.

Apart from these purely embryonic models, a large number of fetal models exist. However, these models were mainly used in order to demonstrate the feasibility of fetal interventions.[36]

Chemical models

A large number of chemicals can have an impact on the normal development of humans and animals alike. Most important today are: (1) the adriamycin model,[19,20] (2) etretinate,[37,38] (3) all-trans retinoic acid (ATRA),[39–41] (4) ethylenethiourea,[42–44] and (5) nitrofen.[15,16,18]

While models (1)–(4) are used to study the embryology of atresias of the esophagus, the gut, and the anorectum, model (5) was developed to study the malformations of the diaphragm, the lungs, and the heart and kidneys (hydronephrosis).

Genetic models

A number of genetic models had been developed which were used for embryological studies in the past:

- models of spontaneous origin: the SD-mouse model;[25,27]
- inheritance models: the pig model of anal atresia;[24,26]
- 'knock-out' models.[45–47]

These animals can be the product of spontaneous mutations or are the result of genetic manipulations mainly in mice (transgenic mice).

The number of transgenic animal models is growing fast. For pediatric surgeons those models which result in abnormalities of the fore- and hindgut are of major importance. Here, interference with the sonic hedgehog (Shh) pathway has proven to be very effective.[45–47] There are two ways to interfere with that pathway: (1) targeted deletion of Shh;[45,46] and (2) deletion of one of the three transcription factors, Gli1, Gli2, and Gli3.[46,47]

In the foregut, targeted deletion of Shh in homozygous Shh-null mutant mice causes esophageal atresia/stenosis, tracheo-esophageal fistulas, and tracheal/lung anomalies.[45] In the hindgut, the deletion of Shh caused the formation of 'cloacas'[46] while Gli2 mutant mice demonstrated the 'classic' form of anorectal malformations and Gli3 mutants showed minor forms such as anal stenosis.[46,47] Interestingly, the morphology of Gli2 mutant mice embryos resembles that of heterozygous SD-mice embryos while Shh-null mutant mice embryos had morphological similarities with homozygous SD-mice embryos. Interestingly, after administration of adriamycin, changes in the normal pattern of Shh distribution in the developing foregut were demonstrated.[48]

Viral models

Animal models that use virus infections to produce malformations important for pediatric surgeons are very rare. One exception is the murine model of extrahepatic biliary atresia (EHBA). In this model, newborn Balb/c mice are infected with rhesus rotavirus group A.[49] As a result the full spectrum of EHBA develops, as is seen in newborns with this disease. However, this model is not a model to mimic failed embryology, but it highlights the possibility that malformations are not caused by embryonic disorders but are caused by fetal or even postnatal catastrophes.

This part on embryology and animal models further highlights the importance of the study of normal animal embryos. Today, much information in current textbooks on human embryology stems from studies carried out in animals of varies species. Many of these are outdated. However, the wide use of transgenic mice in order to mimic congenital malformations makes morphological studies of the various organ systems in normal mice mandatory, otherwise the interpretation of the effects of the deletion of genetic information can be very difficult.[50]

EMBRYOLOGY OF MALFORMATIONS

Disturbances of normal embryological processes will result in malformations of organs. This was first shown by Spemann[51] in 1901 by experimentally producing supernumary organs in

the triton embryo after establishing close contact between excised parts of triton eggs and other parts of the same egg. Spemann and Mangold[5] coined the term 'induction' to describe this observation. They found that certain parts of the embryo obviously were able to control embryonic development of other parts. These controlling parts were called 'organizers'.[5] The process of influence itself was called 'induction'.

It was believed by many scientists in the field that 'induction' could serve as the overall principle of hierarchical control of embryonic development. Ensuing investigations, however, made modifications necessary, which finally resulted in a very complex model of organizers and inductors. The nature of inductive substances remained obscure and attempts to isolate inductive substances, meanwhile called 'morphogenes', were unsuccessful.[52] Interestingly, not only live cells could induce development in certain experiments, but also dead and denaturated material.[5]

A process essential for the formation of early embryonic organs is the invagination of epithelial sheets. This invagination is preceded by a thickening of the epithelial sheet,[53] a process known as placode formation. The thickening itself is caused by elongation of individual cells of the placode. This process can be studied in detail in epithelial morphogenesis.[54] The same sequence of developmental events has been observed in the formation of the neural plate, in the formation of the otic and lens placode and in the development of most epitheliomesenchymal organs including lung, thyroid gland, and pancreas. From these observations it can be concluded that most epithelial cells behave uniformly in the early phase of embryonic development.

Today, it is generally accepted that early embryonic organs are especially sensitive for alterations. Therefore researchers are more and more interested to understand the formation of early embryonic organs.

In 1985, Ettersohn[55] stated that most invaginations are the result of mechanical forces that are local in origin. He focused on three possible mechanisms which might lead to placode formation and subsequent invagination:

1. change of cell shape by cell adhesion;
2. microfilament-mediated change of cell shape;
3. cell growth and division.

In the following text, we will discuss some aspects of these mechanisms.

A teratological method used to determine the function of cell adhesion molecules *in vivo* during embryogenesis has been reported recently.[56] Mouse hybridoma cells producing monoclonal antibodies against the avian integrin complex were grafted into 2- or 3-day-old chick embryos. Depending on the site of engraftment, local muscle agenesis was observed. This is an example that the immunologic immaturity of the embryo can be exploited to study the contribution of cell attachment molecules to organ development in a functional fashion. A number of monoclonal antibodies directed against cell attachment molecules of various species have become available over the last years, and the structure of the binding molecules has been elucidated biochemically and by cDNA cloning. Functionally, adhesion molecules may be grouped into three families: cell adhesion molecules (CAMs), which mediate specific and mostly transient cell recognition of other cells; substrate adhesion molecules (SAMs), necessary for attachment to extracellular matrix proteins; and cell-junctional molecules (CJMs), found in tight and gap junctions. Whereas CJMs apparently play an important role for metabolic signaling within established tissues, CAMs and SAMs are necessary for the formation of histologically distinct structures and directed migration of single cells. Among CAMs and SAMs, at least three families have been identified biochemically: integrins,[57] members of the immunoglobulin superfamiliy, and LEC-CAMs.[58] Integrins are heterodimeric molecules consisting of a larger α chain, which is associated with a smaller β chain in a calcium-dependent way. Usually, one given α chain might be found in association with various chains but promiscuity of β chains has been described recently. Functionally, members of the integrin family present as SAMs (adhesion to vitronectin, collagen, fibronectin, complement components, or other intercellular matrix proteins) or CAMs (direct adhesion to other cells via corresponding cell surface target molecules). For example, cells bearing the integrin LFA-1 on their cell surface bind to cells expressing ICAM-1 or ICAM-2, both of which are members of the immunoglobulin superfamily.[59,60] Other members of the immunoglobulin superfamily which are known to be important during morphogenesis include L-CAM[61] (liver cell adhesion molecule) and N-CAM[62,63] (neural cell adhesion molecule). Both show homophilic aggregation, that is, N-CAM serves as a target structure for N-CAM, and L-CAM serves as a target structure for L-CAM, but there is no crossreactivity. In developing feather placodes in avian embryos, L-CAM and N-CAM are mutually exclusive expressed on epidermal or mesodermal cells, respectively. When the placodes are incubated with antibodies to L-CAM, primarily only epidermal cell-to-cell contact is disturbed.[64] However, the structure of the surrounding mesoderm is altered subsequently, suggesting an inductive signal loop between epidermal and mesodermal cells. A third group of adhesion molecules has been termed LEC-CAMs to indicate that their extracellular part consists of a lectin domain, an epidermal growth factor-like domain, and a complement regulatory protein repeat domain. The lectin domain is presumed to contain the active center; binding mediated by the murine homolog to the leukocyte adhesion molecule 1 (LAM-1)[65] can be blocked by mannose-6-phosphate or its polymers.[66] Lectin-dependent organ formation should be accessible experimentally by administration of the respective carbohydrates, but few if any data have been reported so far.

Cell shape is mainly maintained by microtubules forming the cellular cytoskeleton. In addition, contractile elements exist such as actin, which are essential for cell movement, the so-called microfilaments. These structures are thought to be essential for the process of placode formation and invagination.[67] Microfilament-mediated change of cell shape is based on the idea that actin filaments could alter the shape of cells by contraction. Most of these filaments are found at the apex

of epithelial cells. Contraction of these filaments in each individual cell of a cell layer would result in an increasing infolding of the whole cell layer,[67,68] finally resulting in invagination. It is a disadvantage of this model, however, that there is no apparent reason why apical constriction should be preceded by cell elongation.[55]

Cell proliferation is probably an essential factor in the morphogenesis of epithelio-mesenchymal organs. During morphogenesis of these organs repeated invagination can be observed, which might be dependent upon cell proliferation.[69] The way in which epithelial cell growth and proliferation is controlled in the embryo is not clear. However, it is believed that the surrounding mesenchyme might regulate the timing and location of invagination of the epithelial layer. Goldin and Opperman[28] proposed that epidermal growth factor (EGF) might be excreted by mesenchymal cells, which would stimulate epithelial cell proliferation and repeated invagination. When agarose pellets impregnated with EGF were cultured alongside 5-day embryonic chick tracheal epithelium, supernumerary buds were induced to form at those sites. EGF and the related peptide transforming growth factor-β (TGFβ) have been shown to lead to precocious eyelid opening when injected into newborn mice.[70] Thus, complex changes of late-stage organ development can be induced by physiological stimuli in the laboratory. Interestingly, EGF is a mitogen for many epithelial cells *in vitro* without affecting most mesenchymal cells. A large variety of cells have been demonstrated to display the receptor for EGF/TGFβ on their cell surface, which is encoded by the cellular proto-oncogene c-erbB. Structural alterations of this receptor are known to result in uncontrolled proliferation and ultimately malignant transformation. When secreted locally, EGF might provide physically associated cells with appropriate on- and off-signals required for the formation of complex organs. Other polypeptides, such as platelet-derived growth factor (PDGF) or transforming growth factor-α (TGFα) appear to function in an antagonistic way in that they stimulate rather the proliferation of mesenchymal cells.[71,72] In defined experimental situations, TGFα has been shown to be a mitogen for osteoblasts while being a potent inhibitor of the proliferation of epithelial and endothelial cells at the same time. Embryonic fibroblasts, however, are also inhibited by TGFα.[73] TGFα is a powerful chemotactic agent for fibroblasts and enhances the production of both collagen and fibronectin by these cells. There is, however, little data available concerning the involvement of these factors during normal and pathologic development of the embryo. Future investigations using such powerful approaches as *in situ* hybridization with cloned genes, preparation of transgenic animals, and direct administration of the recombinant proteins to various parts of the embryo might shed some light on signaling pathways mediated by soluble cytokines.

The surrounding mesenchyme might limit the epithelial bud to expand,[74] forcing the epithelial sheet to fold in characteristic patterns. If a growing cell layer is restricted from lateral expansion, 'mitotic pressure' by dividing cells will result in elongation of cells and then invagination of the 'crowded' cell sheet. This does not necessarily imply that cells divide more rapidly in the region of invagination than in the surrounding areas. The main effect is caused by restriction of lateral expansion.[29,30] In the early anlage of the thymus, cell proliferation counts are actually lower in the thymus anlage than in the surrounding epithelium.[75] Steding[29] and Jacob[30] have shown experimentally that restriction of lateral expansion might be responsible for thickening and subsequent invagination of epithelial sheets. In their experiments, restriction of lateral expansion was caused by a tiny silver ring placed on the epithelium of chick embryos.

EXAMPLES OF PATHOLOGICAL EMBRYOLOGY

The focus of our research has been the embryology of foregut, anorectal, and diaphragmatic malformations. We studied the normal development of all embryonic organs involved by scanning electron microscopy (SEM).[76–82] In addition, we employed two rodent animal models to study malformations of the anorectum and the diaphragm. Pathogenetic concepts concerning these malformations were controversial in the past due to lack of detailed data.

EMBRYOLOGY OF FOREGUT MALFORMATIONS

The differentiation of the primitive foregut into the ventral trachea and dorsal esophagus is thought to be the result of a process of septation.[83] It is guessed that lateral ridges appear in the lateral walls of the foregut, which fuse in midline in a caudo-cranial direction thus forming the tracheo-esophageal septum. This theory of septation has been described in detail by Rosenthal and Smith.[84,85] However, others[86,87] were not able to verify the importance of the tracheo-esophageal septum for the differentiation of the foregut. They instead proposed individually that the respiratory tract develops simply by further growth of the lung bud in a caudal direction.

Using SEM, we studied the development of the foregut in chick embryos.[76,77] In this study, we were unable to demonstrate the formation of a tracheo-esophageal septum (Fig. 1.1). A sequence of SEM photographs of staged chick embryos suggests that differentiation of the primitive foregut is best explained by a process of 'reduction of size' of a foregut region called 'tracheo-esophageal space' (Fig. 1.2). This reduction is caused by a system of folds that develops in the primitive foregut. They approach each other but do not fuse (Fig. 1.2).

Based on these observations, the development of the malformation can be explained by disorders either of the formation of the folds or of their developmental movements:

- Atresia of the esophagus with fistula (Fig. 1.3a):
  - The dorsal fold of the foregut bends too far ventrally. As a result the descent of the larynx is blocked. Therefore the tracheo-esophageal space remains partly undivided and lies in a ventral position. Due to this ventral position it differentiates into trachea.

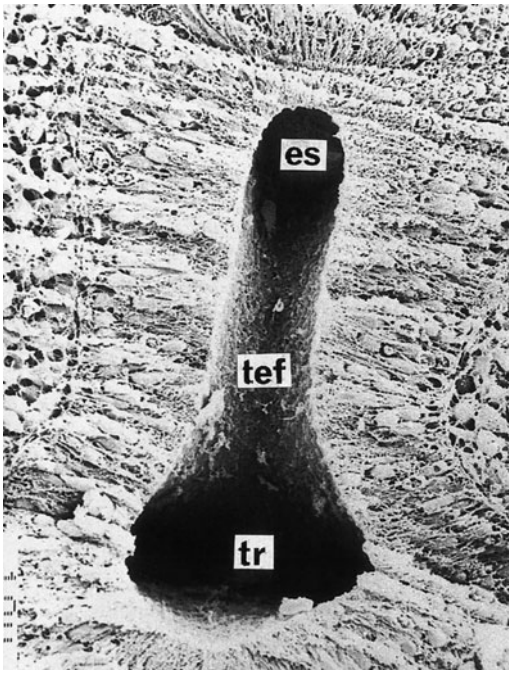

Figure 1.1 SEM photograph of the inner layer of foregut epithelium in a chick embryo (approximately 3.5 days old). View from cranial. Between trachea (tr) on bottom and esophagus (es) on top, the tip of the tracheo-esophageal fold (tef) is recognizable. Lateral ridges or signs of fusion are not found.

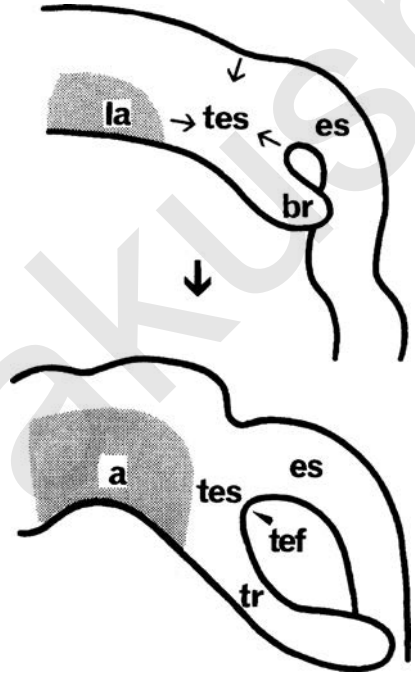

Figure 1.2 Summarizing sketch of foregut development. The tracheo-esophageal space (tes) is reduced in size by developmental movements of folds (indicated by arrows) (es, esophagus; la, anlage of larynx; br, bronchus; tr, trachea). Short arrow marks tip of tracheo-esophageal fold (tef) (compare Fig. 1.1).

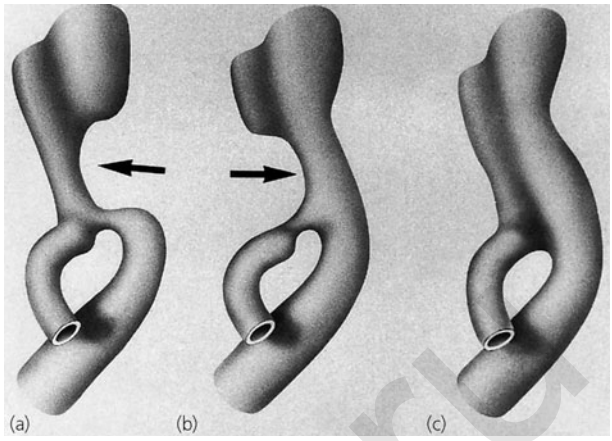

Figure 1.3 Sketch of formal pathogenesis of typical foregut malformations (see text for details): (a) atresia of esophagus with fistula; (b) atresia of trachea with fistula; (c) laryngotracheo-esophageal cleft. Arrows indicate sites of possible deformation of the developing foregut.

- Atresia of the trachea with fistula (Fig. 1.3b):
  - The foregut is deformed on its ventral side. The developmental movements of the folds are disturbed and the tracheo-esophageal space is dislocated in a dorsal direction. Therefore it differentiates into esophagus.
- Laryngotracheo-esophageal clefts (Fig. 1.3c):
  - Faulty growth of the folds results in the persistence of the primitive tracheo-esophageal space.

Recently it has been shown that esophageal atresias and tracheo-esophageal fistulas can be induced by maternal application of adriamycin into the peritoneal cavity of pregnant rats.[19,20] The dosage may vary between 1.5 and 2.0 mg/kg depending on the number of days it will be given. In most reports the most promising dosage is 1.75 mg/kg given on days 6–9 of pregnancy. The adriamycin model has been intensively studied over the last couple of years, resulting in more than 70 reports between 1997 and 2010.[88] It could be demonstrated that in this model not only foregut malformations but also atypical patterns of malformation can be observed which are usually summarized under the term 'VATER' or 'VACTERL' association.[21,22] Therefore, this model is not only promising for the studies of foregut anomalies but also for anomalies of the hind- and midgut.

DEVELOPMENT OF THE DIAPHRAGM

In the past, several theories were proposed to explain the appearance of posterolateral diaphragmatic defects:

- defects caused by improper development of the pleuro-peritoneal membrane;[89,90]
- failure of muscularization of the lumbocostal trigone and pleuro-peritoneal canal, resulting in a 'weak' part of the diaphragm;[89,91]
- pushing of intestine through posterolateral part (foramen of Bochdalek) of the diaphragm;[92]

- premature return of the intestines into the abdominal cavity with the canal still open;[89,91]
- abnormal persistence of lung in the pleuro-peritoneal canal, preventing proper closure of the canal;[93]
- abnormal development of the early lung and posthepatic mesenchyme, causing non-closure of pleuro-peritoneal canals.[18]

Of these theories, failure of the pleuro-peritoneal membrane to meet the transverse septum is the most popular hypothesis to explain diaphragmatic herniation. However, using SEM techniques,[78] we could not demonstrate the importance of the pleuro-peritoneal membrane for the closure of the so-called pleuro-peritoneal canals (Fig. 1.4).

As stated earlier, most authors assume that delayed or inhibited closure of the diaphragm will result in a diaphragmatic defect that is wide enough to allow herniation of the gut into the fetal thoracic cavity. However, this assumption is not the result of appropriate embryological observations but rather the result of interpretations of anatomical/pathological findings. In a series of normal staged embryos we measured the width of the pleuro-peritoneal openings and the transverse diameter of gut loops.[82] On the basis of these measurements we estimated that a single embryonic gut loop requires at least an opening of 450 μ size to herniate into the fetal pleural cavity. However, in none of our embryos were the observed pleuro-peritoneal openings of appropriate dimensions. This means that delayed or inhibited closure of the pleuro-peritoneal canal cannot result in a diaphragmatic defect of sufficient size. Herniation of gut through these openings is therefore impossible. Thus the proposed theory about the pathogenetic mechanisms of congenital diaphragmatic hernia (CDH) development lacks any embryological evidence. Furthermore, the proposed timing of this process is highly questionable.[79,80]

Recently, an animal model for diaphragmatic hernia has been developed[14–18] using nitrofen as noxious substance. In these experiments CDHs were produced in a reasonably high percentage of newborns.[15,16] Most diaphragmatic hernias were associated with lung hypoplasias. Using electron microscopy, our group[79–82] used this model to give a detailed description of the development of the diaphragmatic defect. Our results are discussed in the following.

Timing of diaphragmatic defect appearance

Iritani[1] was the first to notice that nitrofen-induced diaphragmatic hernias in mice are not caused by an improper closure of the pleuro-peritoneal openings but rather the result of a defective development of the so-called post-hepatic mesenchymal plate (PHMP). In our study in rats, clear evidence of disturbed development of the diaphragmatic anlage was seen on day 13 (left side) and day 14 (right side, Fig. 1.5).[79,82] In all embryos affected, the PHMP was too short. This age group is equivalent to 4–5-week-old human embryos.[79]

Location of diaphragmatic defect

In our SEM study, the observed defects were localized in the PHMP (Fig. 1.5). We identified two distinct types of defects: (1) large 'dorsal' defects and (2) small 'central' defects.[79] Large defects extended into the region of the pleuro-peritoneal openings. In these cases, the closure of the pleuro-peritoneal openings was usually impaired by the massive in-growth of liver (Figs. 1.6 and 1.7). If the defects were small, they were consistently isolated from the pleuro-peritoneal openings closing normally at the 16th or 17th day

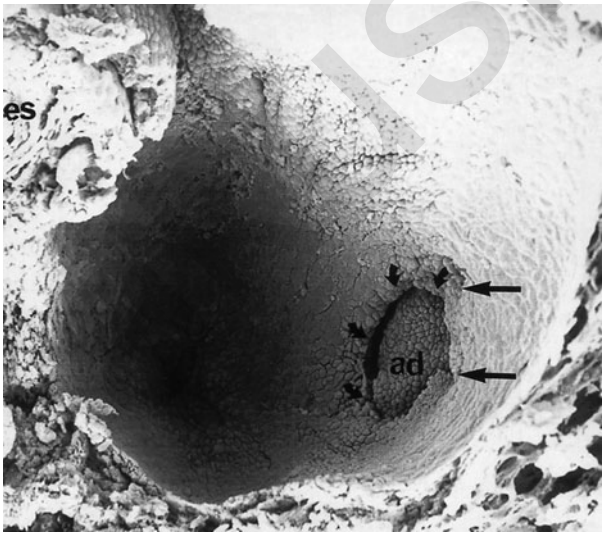

Figure 1.4 SEM photograph of right pleural sac in a rat embryo (approximately 16.5 days old). View from cranial. The so-called pleuro-peritoneal canal (PPC) is nearly closed. Small arrows point at the margin of PPC. In the depth of the abdomen the right adrenals (ad) are seen. Large arrows point at margins of the so-called pleuro-peritoneal membrane. Its contribution to the closure of the canal is minimal (es, esophagus).

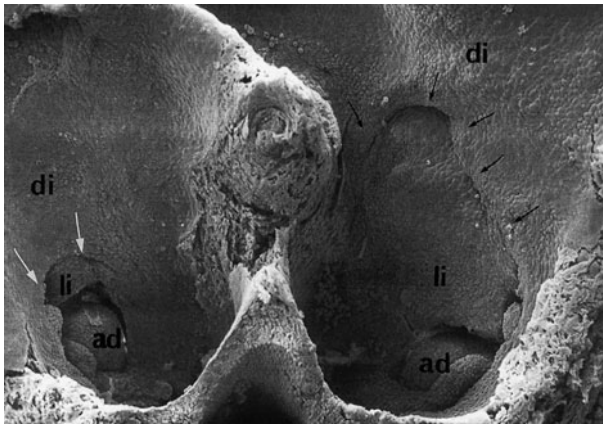

Figure 1.5 Cranial view of the pleural sacs in a rat embryo after exposition to nitrofen on day 11 of pregnancy. The embryo is approximately 15 days old. Note the big defect of the right diaphragmatic primordium. Small black arrows point at margins of the defect, which leaves parts of the liver (li) uncoated. On the left, the diaphragmatic anlage is normal. Note the low position of the cranial border of the pleuro-peritoneal opening on this side (white arrows). (ad, adrenals; di, anlage of diaphragm.)

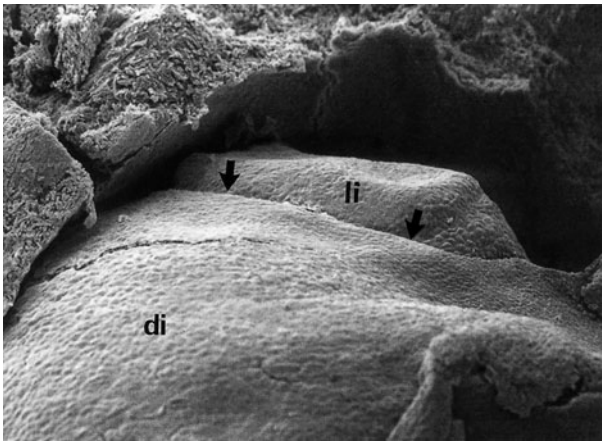

Figure 1.6 Liver (li) protrudes through diaphragmatic defect. Arrows point to the margin of the defect (di, diaphragmatic anlage). Rat embryo (approximately 16 days old), nitrofen exposition on day 11 of pregnancy.

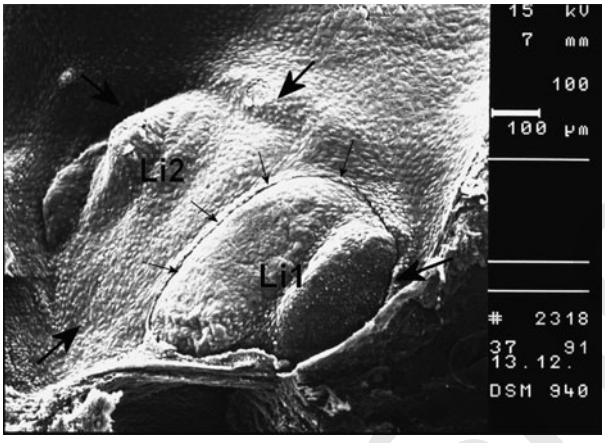

Figure 1.7 SEM photograph of a right pleural sac in a rat embryo after nitrofen exposure on day 11 of pregnancy. The embryo is approximately 15.5 days old. Note the big defect of the right dorsal diaphragm (large arrows). The closure of the pleuro-peritoneal canal (PPC) is impaired by the in-growths of liver (small arrows). Li1 = liver growing through PPC. Li1 + Li2 = liver growing through the defect of the diaphragm.

of gestation. Thus, in our embryos with CDH, the region of the diaphragmatic defect was a distinct entity and was separated from that part of the diaphragm where the pleuro-peritoneal 'canals' are localized. We conclude therefore that the pleuro-peritoneal openings are not the precursors of the diaphragmatic defect.

Why lungs are hypoplastic

Soon after the onset of the defect in the 14-day-old embryo, liver grows through the diaphragmatic defect into the thoracic cavity (Fig. 1.6). This indicates that from this time on the available thoracic space is reduced for the lung and further lung growth hampered. In the following stages, up to two-thirds of the thoracic cavity can be occupied by liver (Fig. 1.7). Herniated gut was found in our embryos and fetuses only in late stages of development (21 days and newborns). In all of these the lungs were already hypoplastic when the bowel entered the thoracic cavity.[79]

Based on these observations, we conclude that the early in-growth of the liver through the diaphragmatic defect is the crucial step in the pathogenesis of lung hypoplasia in CDH. This indicates that growth impairment is not the result of lung compression in the fetus but rather the result of growth competition in the embryo: the liver that grows faster than the lung reduces the available thoracic space. If the remaining space is too small, pulmonary hypoplasia will result.

DEVELOPMENT OF THE CLOACA

In the literature, several theories have been put forward to explain the differentiation of the cloaca into the dorsal anorectum and the ventral sinus urogenitalis. To many authors this differentiation is caused by a septum which develops cranially to caudally and thus divides the cloaca in a frontal plane. Disorders in this process of differentiation are thought to be the cause of cloacal anomalies such as persistent cloaca and anorectal malformations.

However, there is no agreement on the mechanisms of the septational process. While some authors[94,95] believe that the descent of a single fold separates the urogenital part from the rectal part by in-growth of mesenchyme from cranial, others[96] think that lateral ridges appear in the lumen of the cloaca, which progressively fuse along the midline and thus form the septum. In a recent paper[97] the process of septation had been questioned altogether.

Using SEM techniques, our group studied cloacal development in rat and SD-mice embryos. The SD-mouse is a spontaneous mutation of the house mouse characterized by having a short tail (Fig. 1.8). Homozygous or heterozygous offspring of these mice show skeletal, urogenital, and anorectal

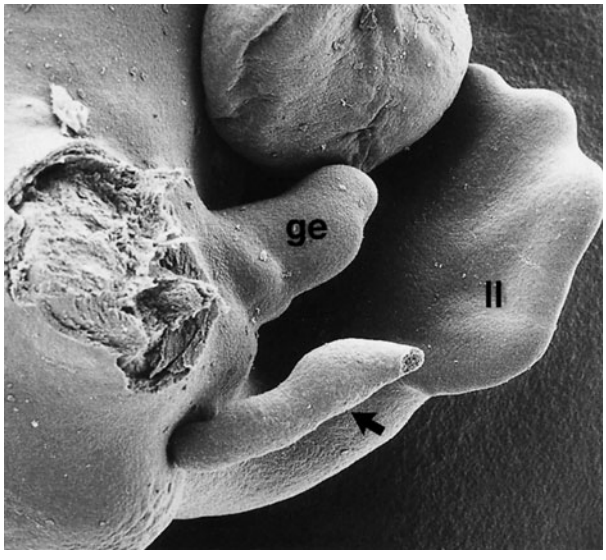

Figure 1.8 Characteristic short tail (arrow) of SD-mouse embryo (approximately 13 days old) (ll, left lower limb; ge, genital tuberculum, abnormal).

malformations.[25,28] Therefore these animals are ideal for the study of the development of anorectal malformations.

Normal cloacal embryology (rat)

As in the foregut of chick embryos, signs of median fusion of lateral cloacal parts could not be demonstrated during normal cloacal development in the rat. However, in contradiction to vdPUTTE,[97] we think that down-growth of the urorectal fold takes place, although it is probably not responsible for the formation of cloacal malformations.

Abnormal cloacal embryology (SD-mouse)

Cloacal malformations are caused by improper development of the early anlage of the cloacal membrane as demonstrated in SD-mice embryos.[98,99]

Our studies of abnormal cloacal development in SD-mice had the following results:

- the basis of the pathogenesis of anorectal malformations is too short a cloacal membrane;
- the anlage of the cloacal membrane is too short and results in a maldeveloped anlage of the cloaca, which is undeveloped in its dorsal part (Fig. 1.9);
- the caudal movement of the urorectal fold is impaired by the malformed cloaca. Thus the hindgut remains in abnormal contact with the cloaca. This opening is true ectopic and will develop into the recto-urogenital fistula (Fig. 1.10).

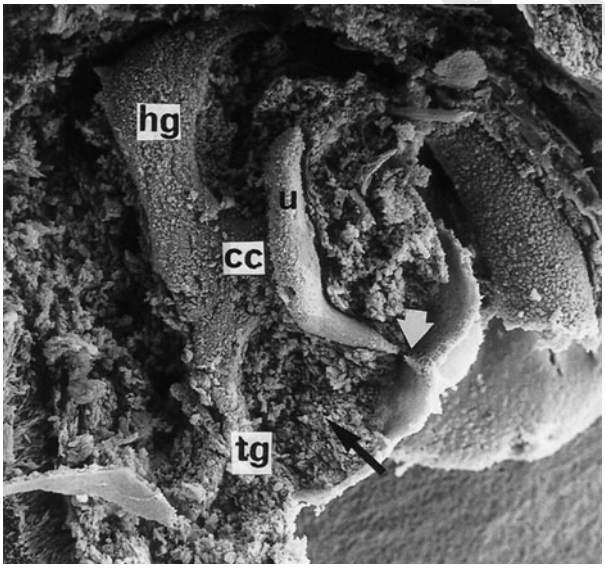

Figure 1.9 Malformed cloaca of SD-mouse embryo (approximately 11 days old). The surrounding mesenchyme is removed by microdissection. View on the basal layer of the cloacal entoderm. The cloaca has lost its contact to the ectoderm of the genitals (white arrow). The dorsal part of the cloaca is missing (black arrow). Tailgut (tg) and hindgut (hg) are hypoplastic. This malformed cloaca developed because the anlage of the cloacal membrane was too short in early embryogenesis (see text for details) (cc, rest of cloaca; u, urachus, rudimentary).

Figure 1.10 Malformed cloaca of SD-mouse, embryo (approximately 13 days old). Urachus (u) and rectum (re) nearly normal (cl, ventral part of cloaca with short cloacal membrane). The dorsal part of the cloaca is missing (long white arrows). Short white arrow points to the region of the future fistula.

It is interesting to note that the morphology of the anorectal malformations observed is very similar in all animal models used irrespective of the source of the malformed embryo (spontaneous mutation versus chemically induced versus transgenic models).

HYPOSPADIAS

Many investigators[100–103] believe that the urethra develops by fusion of the paired urethral folds following the disintegration of the urogenital membrane. Impairment of this process is thought to result in the different forms of hypospadia.[103] However, in our study of normal cloacal development,[104] we were puzzled by the fact that disintegration of the urogenital part of the cloacal membrane could not be observed in rat embryos (Fig. 1.11). This finding caused us to call into question the generally assumed concepts of hypospadia formation. Instead we found that:

- the urethra is always present as a hollow organ during embryogenesis of rats and that it is always in contact with the tip of the genitals, and that;
- an initially double urethral anlage exists. The differentiation in female and male urethra starts in rats of 18.5 days old. On the other hand, we found no evidence for:
  - the disintegration of the urogenital cloacal membrane, and;
  - a fusion of lateral portions within the perineum.

In our opinion, more than one embryological mechanism is at play in the formation of the hypospadias complex. The moderate degrees, such as the penile and glandular forms, represent a developmental arrest of the genitalia (Fig. 1.12). They take their origin from a situation comparable to the 20-day-old embryo. Consequently the penis, not the urethra, is the primary organ of the malformation.

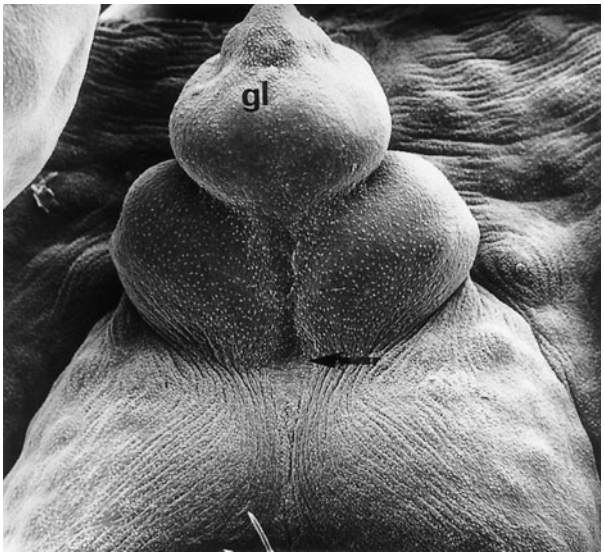

Figure 1.11 Genitals of a normal female rat embryo (approximately 18.5 days old) (gl, glans). Arrow points to future opening of the female urethra. No signs of disintegration of the cloacal membrane.

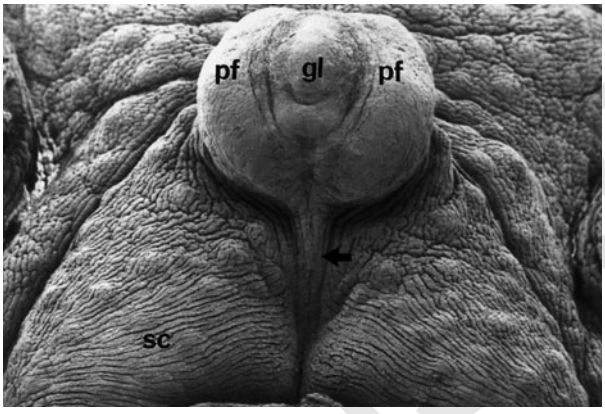

Figure 1.12 Genitals of a normal male rat embryo (approximately 20 days old) (gl, glans; pf, preputial fold; sc, scrotum). Arrow points to the raphe up to this stage; disintegration of the urogenital part of the cloacal membrane was not seen. Note similarity with clinical picture of hypospadia!

Perineal and scrotal hypospadias are different from the type discussed previously. Pronounced signs of feminization in these forms suggest that we are dealing with a female-type urethra. Origin of this malformation complex is an undifferentiated stage as may be seen in the 18.5-day-old rat embryo.[104]

CONCLUSION

Despite the long history of experimental embryology, we know very little about etiology and pathogenesis of congenital malformations. For decades, hypotheses were abundant while few data existed to support them. The tremendous progress of neighboring biological sciences is now providing powerful tools for researchers in the field, such as recombinant DNA and hybridoma technology. Future investigations will monitor closely how genes are switched on and off during embryogenesis and determine the relation of spatial and temporal disturbances to ensuing malformations. Target structures of chemical or viral teratogens within the embryonic cells await identification. Finally, improved understanding of growth coordination *in utero* will extend to related areas such as wound healing and proliferation of cancer cells.

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Perinatal physiology

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INTRODUCTION

Perinatal physiology is a field of medicine which studies the life of an individual, human, or animal during gestation and its preparations to adapt to a new world. This world will demand from the individual to breathe air and obtain its food from the environment instead of depending on the circulatory system to perfuse an area where metabolic waste will be disposed of and nutrients and oxygen will be acquired. Successful transition at birth is dependent on establishment of the lungs as the organ of gas exchange.

The transition is very fast and it demands and depends on capable organs and systems in order to make a soft landing and provide survival and good quality of life. In order to succeed the respiratory system must be developed enough to assure a sufficient alveolar exchange area, it must have a drive to offer a continuous breathing activity and the circulatory system should start perfusing the lungs instead of the placenta.

The objective of this chapter is to provide a general overview of the mechanisms preparing the fetus to be born, the transition at birth, and the successful adaptation to the air-breathing world. We will consider two main systems: the respiratory system including lung development, maturation, and role of surfactant system, lung fluid dynamics, lung expansion at birth and its maintenance, respiratory drive and chemoreceptor role; the circulatory system including fetal circulation and its changes at birth, fetal circulatory adaptations to oxygenation challenges, role of the ductus arteriosus in the fetal circulation and mechanisms for its closure, or failure to close, after birth.

FETAL BREATHING MOVEMENTS

Periodic non-air intrauterine breathing patterns must change at birth to a continuous air-breathing pattern. This change happens after clamping the umbilical cord, full perfusion of the lungs, changes in temperature, changes in behavioral state, increase in metabolism, increase in afferent input to the central nervous system, and many other changes associated with the moment of birth.

Breathing-like activity *in utero* is present from very early in gestation and is the consequence of rhythmic activation of respiratory neurons in the brainstem,[1,2] however these breathing movements play no part in fetal gas exchange. The efferent activity of these respiratory neurons activates the respiratory motoneurons and hence the muscles, mainly the diaphragm, which generate a negative intrathoracic pressure. In fetal lambs, spasm of the diaphragm at the 38th day of gestation (term 147 days) and rhythmic movements of the diaphragm at the 40th day of gestation have been described.[3] Chronic recordings from fetal lambs *in utero* performed at approximately 50 days of gestation showed two types of diaphragmatic activity: (1) unpatterned discharge, (2) patterned, bursting discharge.[4] In the human fetus thoracic movements were observed from the 10th to the 12th week of gestation.[5] At this time in gestation there is still not a clear pattern and fetal breathing movements (FBM) appear to be more 'free-wheeling'.

Later in gestation in the fetal lamb (75–110 days), movements of the diaphragm start to become periodic. At this age they are often associated with nuchal muscle activity and rapid eye movements.[6,7] A more definitive pattern starts to appear at 108–120 days of gestation when breathing movements become organized into a more complex state, now associated with the presence of rapid eye movements and nuchal muscle activity.[6–9] At this time in gestation the electroencephalographic (ECoG) activity, commonly known as electrocortical activity, still does not show any signs of differentiation. However, by 120–125 days of gestation the ECoG shows a clear differentiation into low voltage electroencephalographic (LVECog), high frequency activity (range 13–30 Hz; LVECoG) and high voltage electroencephalographic (HVECog), low frequency activity (3–9 Hz; HVECoG).[6,10–12] At this gestational age breathing movements are rapid and irregular, with a frequency of 0.1–4 Hz and an amplitude of 3–5 mmHg and they produce small movements of tracheal fluid (<1 mL).[13] There are now two

clearly defined fetal behavioral states in the fetal lamb: there is no nuchal muscle activity during LVECoG but rapid eye movements and FBM are present. Polysynaptic spinal reflexes are also relatively inhibited during the LVECoG state.[14] During HVECoG, there are no eye movements or FBM, but nuchal muscle activity is present and polysynaptic reflexes are stronger. The link between ECoG state and FBM implies either that breathing activity is facilitated (or even stimulated) during LVECoG and/or that it is inhibited during HVECoG. During LVECoG there is more neural activity in cortical and subcortical structures, including the brainstem reticular formation. This facilitatory state could increase the sensitivity for tonic stimuli, such as the level of arterial CO_2, and generate respiratory output. This hypothesis is supported by the observation that there are no breathing movements during fetal hypocapnia even during the LVECoG state.[15] Extending this idea, the absence of FBM during HVECoG could be due to a disfacilitation, as reported during quiet sleep in the adult when slow waves appear on the EEG.[16,17] Other evidence also leads us to believe that during HVECoG there is an active inhibition of breathing activity, because in fetal sheep FBM and ECoG were dissociated after the brainstem was transected at the level of the colliculi.[18] Furthermore, FBM response to hypercapnia is limited to LVECoG activity in the intact fetus but hypercapnia can produce continuous breathing in both LV and HVECoG after small bilateral lesions are made in the lateral pons.[19] The mechanisms, origin, and location for this inhibition are not clear, but it is known that it is of central origin, and that it can be overridden *in utero* and at the time of birth when breathing becomes continuous.

Control of fetal breathing movements

The work of Barcroft[20] gave rise to the concept that inhibitory mechanisms, which descend from higher centers, are involved in producing apnoeic periods in the fetus. This inhibitory control develops during the second half of gestation. This work also showed that the inhibition of FBM by hypoxemia is not seen early in gestation, and the descending inhibitory processes develop later. While the inhibition of FBM in HVECoG and in hypoxia involves descending inhibitory processes, they do not necessarily utilize the same neural mechanisms. Barcroft employed similar brainstem transection techniques to those of Lumsden[21] to show that neural structures above the level of the pons do not exert significant control over FBM. These studies were extended by Dawes and co-workers[22] who employed the technique of transection in the chronically instrumented late gestation fetal sheep. They showed that transection at the level of upper midbrain/caudal hypothalamus resulted in FBM which were episodic but not related to the ECoG. These FBM were still inhibited by hypoxia. This makes it clear that the processes that mediate the inhibition of FBM in HVECoG are different from those that produce the inhibition in hypoxia. Transection through the rostral pons/caudal midbrain produced FBM that occurred almost continuously and were not inhibited by hypoxia. This focused attention on the upper pons in the inhibition of fetal breathing movements in hypoxia. Gluckman and Johnston[23] pursued this by making lesions in the rostrallateral pons, and compiled a diagram showing areas not needed for the inhibition to be manifest, and the location of an area in the lateral pons which, if lesioned bilaterally, prevented the inhibition.

One of the key questions which emerged from these brainstem studies was whether the descending inhibitory mechanism is capable of inhibiting the input from peripheral chemoreceptors. Once it had been established that the peripheral chemoreceptors are active *in utero* and respond to natural stimuli such as hypoxia or hypercapnia (see below), it was no longer necessary to view the effect of modest hypoxia in inhibiting FBM as a direct depression of the medulla. The results of transection and lesion studies suggested that stimulation of FBM occurred during hypoxia after the damage to the brainstem, as if a stimulatory effect of the peripheral chemoreceptors had been unmasked. Direct confirmation of this idea came from the study of Johnston and Gluckman,[24] who conducted a two-stage procedure: first, lesions were placed as before in the brainstem to prevent the inhibition of FBM in hypoxia or to give an overt stimulation; this was then prevented by chemodenervation at a second operation.

The nature (and indeed the location) of the inhibitory processes is not known. Because the inhibition occurs even in chemodenervated fetuses[25] it is clear that the neurons involved do not receive an excitatory input from the chemoreceptors. They may therefore be chemoreceptors themselves or receive input from other cells thought to be sensitive to hypoxia, e.g. in the rostral ventro-lateral medulla (RVLM).[26] The neural activity as a whole behaves as a chemoreceptor because the chemoreceptor stimulant drug almitrine mimics the effects of hypoxia in inhibiting FBM, irrespective of the integrity of the peripheral chemoreceptors.[27] As expected from the discussion above, the stimulatory effect of the drug on the peripheral chemoreceptors only becomes manifest when lesions were placed in the lateral pons,[28] unmasking its peripheral actions.

PERIPHERAL CHEMORECEPTOR FUNCTION *IN UTERO*

The concept that peripheral chemoreceptors could produce effects on breathing can be traced to experiments conducted over 50 years ago[20] in which breathing was shown to be stimulated in exteriorized mid-gestation animal fetuses by hypoxia or cyanide.[29] In late gestation the descending inhibitory effects on breathing arising from the fetal brainstem in hypoxia and HVECoG dominate. It was perhaps the increasing interest in these processes that caused the scientific community to lose sight of the implications of the earlier observations. The idea became prevalent that the carotid chemoreceptors were quiescent *in utero* and were activated at birth, perhaps by the increase in sympathetic nervous activity. In addition, when it became clear that normal fetal arterial PO_2 in late gestation, both in the sheep and the human fetus, was ca. 3 Kpa (25 mmHg), it was thought that if the chemoreceptors were functional they would be so

intensely stimulated that powerful reflex effects would be induced continuously. This was clearly not the case, although it had been shown that brainstem transection removed inhibitory effects on breathing[20,22] and permitted stimulation of breathing activity during hypoxia. It was therefore essential to readdress the question of arterial chemoreceptor function *in utero*. It was found that both carotid[30] and aortic[31] chemoreceptors were spontaneously active at the normal arterial PO_2 in fetal sheep and that they responded with an increase in discharge if PO_2 fell or PCO_2 rose. There were several very important implications of these findings. First, it was clear that the peripheral chemoreceptors would be able to stimulate fetal breathing under some circumstances but that it was the balance between this stimulatory input and the normally dominant, inhibitory input from higher centers which determined the characteristics of fetal breathing. Second, it redirected attention to the role the carotid chemoreceptors play in initiating cardiovascular reflex responses to hypoxia.[32,33] Lastly, the observation that the fetal peripheral chemoreceptors discharge spontaneously (at ca. 5 Hz) at the normal fetal arterial PO_2 made it clear that the rise in PO_2 at birth would silence them. Their sensitivity to PO_2 would then have to reset to the adult range postnatally, and this has generated research into the mechanisms of this resetting.[34,35]

PHARMACOLOGICAL CONTROL

A range of agents that mimic hypoxia, by lowering tissue PO_2 in the central nervous system, inhibit fetal breathing movements, e.g. CO poisoning,[36] oligomycin B,[37] and anemia.[38] Adenosine is also released in neural tissue during hypoxia and exerts a range of actions: it stimulates the peripheral chemoreceptors, but reduces respiratory output in the fetus and neonate. The stimulation of FBM by adenosine after caudal brainstem transection[39] is explicable in terms of the removal of descending inhibitory processes discussed earlier in this chapter. In addition, the role of glutamate as an excitatory amino acid in the fetus and the neonate has recently been addressed.[40,41]

Adrenergic agonists and antagonists have also been used to investigate catecholamines in the control of FBM. Murata *et al.*[42] showed that noradrenaline inhibits FBM in the rhesus monkey while isopreterenol, a β-adrenergic agonist, stimulates FBM. However, Bamford *et al.*[43] showed that the α_2-agonist clonidine increases and the α_2-antagonist idazoxan inhibits FBM fetal sheep. α_2-Adrenoreceptors exert a presynaptic inhibition on noradrenaline release suggesting that noradrenaline stimulates, rather than inhibits, FBM as indicated by Murata *et al.*[42] In a subsequent study, Bamford and Hawkins[44] showed that the α_2-adrenergic antagonist MSDL 657743 also stimulated FBM in normoxia and also maintained FBM during hypoxia in the fetal sheep. Giussani *et al.*[45] have reported a similar effect after treatment with phentolamine, an α_1- and α_2-antagonist. Furthermore, Joseph and Walker[46] blocked the re-uptake of noradrenaline from the synaptic cleft in fetal sheep and showed that FBM were initially increased and then decreased, presumably owing to a depletion of presynaptic stores of noradrenaline. The conclusion is that noradrenaline stimulates FBM, but that the predominant action of these drugs is on the presynaptic α_2-adrenergic receptor, which when stimulated inhibits endogenous release of noradrenaline.

Prostaglandins exert a powerful influence on FBM and postnatal breathing. Prostaglandin E_2 (PGE_2) decreases the incidence of FBM[47] whereas meclofenamate and indomethacin, inhibitors of prostaglandin synthesis, increase FBM.[48–50] The effect of prostaglandins appears to be central, as it is independent of the peripheral chemoreceptors[51] and because central administration of meclofenamate stimulates FBM.[52,53] The same effects can be produced postnatally, with PGE_2 decreasing, and meclofenamate and indomethacin increasing, ventilation in lambs.[54,55] However, the change in the concentration of PGE_2 that occurs around birth cannot be solely responsible for either the decrease in FBM seen immediately before birth,[56,57] or the onset of continuous breathing postnatally.[58] The well-established effects of ethyl alcohol to reduce the incidence of FBM[59] are not mediated by prostaglandin[60] but by adenosine.[61]

Bennet *et al.*[62] showed that large doses of thyroid releasing hormone (TRH) can induce stimulation of FBM. This effect may be at the level of the respiratory neurons where TRH can be localized, but its physiological significance is not known. This may also be true of the effects of the cholinergic agonist, pilocarpine, and serotonin (5-HT) precursor L-5-hydroxytryptophan (L-5-HTP)[63,64] Both of these agents stimulate FBM, but pilocarpine induces LVECoG and L-5-HTP induces HVECoG. This stresses again the coincidental rather than causal relationship between FBM and LVECoG. 5-HTP has been implicated in neural mechanisms controlling adult sheep, but the site of action in the fetus is not known. A range of opiates has effects on FBM[65] but the physiological localization of their effects has not been established.

The high rate of progesterone synthesis by the placenta in late gestation exposes the fetus to high concentrations of progesterone and its metabolites. Progesterone can influence fetal behavior, and normal progesterone production tonically suppresses arousal or wakefulness in the fetus.[66,67]

Lastly, one of the striking aspects of FBM is that they cease 24–48 hours before parturition. The mechanism involved is not known. Kitterman *et al.*[48] excluded a rise in plasma PGE_2 and Parkes *et al.*[68] showed that it did not occur if the fall in plasma progesterone was prevented.

LUNG GROWTH ASSOCIATED WITH FETAL BREATHING MOVEMENTS

Fetal breathing movements are necessary for fetal lung growth and maturation. By opposing lung recoil, FBM help to maintain the lung expansion that is now known to be essential for normal growth and structural maturation of the fetal lungs. FBM induce complex and variable changes in thoracic dimensions; these induce small alterations in the shape of the lungs that may act as a stimulus to lung growth. The prolonged absence or impairment of FBM is likely to result in a reduced mean level of lung expansion, which can

lead to hypoplasia of the lungs.[69] Moreover, static distension decreases steady-state SP-A and SP-B mRNA levels in whole lung whereas cyclic stretching increases SP-B and SP-A expression two- to four-fold and enhances 3H-choline incorporation into saturated phosphatidylcholine.[70]

CHANGES AT BIRTH

At birth, breathing activity must become continuous in order to fulfill its gas exchange function. After occlusion of the umbilical cord the neonatal ECoG still cycles between low and high voltage states, which seem to have identical spectral characteristics to the fetal states. LVECoG activity is associated with the absence of nuchal muscle activity, rapid eye movements, and inhibition of polysynaptic reflexes, and HVECoG is associated with the presence of nuchal muscle activity, lack of rapid eye movements, and enhanced polysynaptic reflexes.[71] However, despite the fact that after birth the HVECoG state seems to be similar to the equivalent fetal state, breathing activity is present. The reason for this is not known. It may be that answering this question will require detailed spectral analysis of the ECoG from different areas of the brain before birth and during the first hours of postnatal life. It is worth noting that some mammals, such as the rat, cat, and rabbit, develop organized behavioral states 2–3 weeks after birth; however they do not breathe continuously *in utero* and these species demonstrate the same transition to continuous breathing after birth as do more precocial species.

Studies of the mechanisms involved in the establishment of continuous breathing at birth have followed two lines: (1) attempts to induce continuous breathing *in utero*, or (2) observation of establishment of continuous breathing during situations aimed at mimicking birth.

It is well established that the inhibition of FBM during HVECoG can be overridden, as demonstrated by the presence of continuous breathing during metabolic acidosis,[72,73] administration of prostaglandin synthetase inhibitors,[48,49,53] 5-hydroxytryptophan,[64,74] catecholamines,[75] pilocarpine,[63] thyrotrophin releasing hormone,[76] corticotrophin releasing factor,[61] central or peripheral fetal cooling,[77,78] and by lesions within the central nervous system (CNS). These experiments show that FBM can become continuous through the operation of various mechanisms including disinhibition during HVECoG, changes in the balance between stimulatory and inhibitory neuromodulators, increased arousability, and changes in chemoreceptor sensitivity.[79] Some, but not all, of these mechanisms are likely to play an important role at birth.

Experiments designed to observe changes in breathing activity after cord occlusion have led to two main hypotheses: (1) the exclusion of fetal-placental circulation leads to the disappearance of hormones or neuromodulators which exert continuous tonic inhibition (through the CNS) during fetal life, and that this allows continuous breathing postnatally.[80–83] There are reports indicating that prostaglandins originating from placental tissue can inhibit fetal breathing activity.[84] Although this is a possible explanation, it is not yet demonstrated that such a substance is responsible for the modulation by ECoG of FBM. It was shown that breathing movements of goat fetuses maintained in an extrauterine incubation system for more than 24 hours were episodic, suggesting that intermittent breathing movements are intrinsic to the fetus, independent of placenta-derived factors;[85] (2) breathing activity is dependent on the level of $PaCO_2$ *in utero* and at birth.[15] It is known that during hypocapnia, fetal and neonatal breathing is reduced.[15,78,80] Hypercapnia stimulates breathing activity but *in utero* this is inhibited during quiet sleep.[81] However, this inhibition can be overridden after lesions in the lateral pons[19] or when hypercapnia is combined with cooling.[78] This might be explained by changes in the CO_2 sensitivity of central and/or peripheral chemoreceptors or due to changes in the balance between central inhibitory and excitatory mechanisms caused by an increase in afferent input at birth. In this hypothesis, both changes in afferent input from chemo- and thermoreceptors to the CNS, and/or changes in CNS sensitivity to these inputs, are important in the transition from fetal to neonatal breathing. Changes in the plasma level of a placental neuromodulator at birth may then serve to maintain postnatal breathing after its initiation. More insight into these mechanisms may offer an explanation for the occurrence of apnoeic periods after birth.

POSTNATAL BREATHING

Studies to identify brainstem mechanisms that regulate breathing have been conducted in the neonate, in which hypoxia also inhibits breathing but after a transient chemoreceptor-mediated stimulation. Therefore, the reasoning is that similar inhibitory processes to those that operate in the fetus produce the postnatal inhibition of ventilation by hypoxia. Transection of the brainstem through the rostral pons does indeed remove the secondary fall in ventilation,[86] as does placement of lesions in the lateral pons.[87] However, these studies did not identify any clear group of neurons involved in mediating the effect. Investigators focused their attention on the red nucleus, located above the pons in the mesencephalon. The transection studies implicate structures in either the rostral pons or caudal mesencephalon, so it is likely that the red nucleus would have been affected. In neonatal rabbits, electrical stimulation of the red nucleus produces a profound inhibition of respiratory output, and bilateral lesions in the red nucleus prevent the inhibition of respiratory output in hypoxia while not affecting the cardiovascular responses. Evidence that neurons in the red nucleus are involved in this effect comes from the observation that chemical stimulation with glutamate also produces an inhibition of respiratory output.[88] Interestingly, the efferent pathway for these cells, rubrospinal tract, runs in precisely the ventrolateral region of the pons lesioned by Gluckman and Johnston in their fetal studies.[23]

The observations on the red nucleus are interesting because in postnatal life it has been implicated in producing the hypotonia of postural muscles, which occurs in rapid eye movement (REM) sleep. Such hypotonia also occurs in the fetus[30] but at that time it is associated with presence, and not absence, of FBM. Once again, behaviorally related and

hypoxia-induced inhibition of FBM appears to be distinct. In addition, the brainstem reticular formation and related nuclei associated with sleep and arousal have not been greatly studied in the postnatal period. In one study, Moore *et al.*[89] reported that cooling the locus coeruleus by a few degrees, sufficient to reduce neuronal activity but not conducted action potentials, prevented the secondary fall in ventilation in hypoxia in neonatal lambs. The locus coeruleus has been implicated in producing arousal at birth.[90] There are also reports that structures as high in the brain as the thalamus are implicated in the descending inhibition of breathing during hypoxia.[91]

While the effects of acute hypoxia on FBM have been widely studied, the effects of prolonged hypoxemia are quite different. Over a period of 6–12 hours, FBM return to their control incidence as does cycling of the ECoG.[92] Studies reveal that the peripheral chemoreceptors are necessary for the return of FBM during sustained hypoxia produced by reduced uterine blood flow, but the mechanisms involved are not known.[93]

In summary, spontaneous breathing movements are present during fetal life and they are important for normal development of the fetal lungs. Early in gestation they seem to represent free-running activity of the respiratory centers, not controlled by peripheral mechanisms but probably dependent on a tonic CO_2 drive. Maturation of sleep states brings into play powerful brainstem inhibitory mechanisms that control this activity.

Fetal breathing activity is present during physiological and normal fetal conditions and it can be monitored noninvasively by ultrasound, therefore its monitoring could be used to interrogate fetal well-being. A recent Cochrane systematic review did not support its usefulness when included in a biophysical profile to detect high-risk fetuses.[94] However, the monitoring of fetal breathing activity could be used to predict premature labor.[95]

Birth clearly involves some irreversible processes, the transition to continuous breathing being one. However, breathing remains linked to behavioral and sleep states in the neonate as in the fetus and clearly there is continuity of some control processes from late gestation to early postnatal life. Some of these processes mature relatively slowly after birth, such as resetting of chemoreceptor hypoxia sensitivity and the diminishing influence of descending inhibitory effects on breathing in hypoxia. Understanding these effects will be of vital importance to prevention of sudden infant death syndrome (SIDS) and the care of newborn, especially preterm babies.

THE FETAL CIRCULATION AND ITS TRANSITION AT BIRTH

The fetal circulation is characterized by high pulmonary vascular resistance (PVR), low systemic vascular resistance (SVR), presence of an additional low resistance vascular bed (i.e. the placental bed), and right-to-left shunting via the foramen ovale and ductus arteriosus (DA). Local vascular resistance determines distribution of blood flow to the lungs, systemic organs, and placenta. The placental vascular bed receives about 40–50% of the combined ventricular output whereas the lungs receive less than 10%. In response to fetal hypoxemia, distribution of cardiac output and venous return is altered in an effort to maintain perfusion and O_2 delivery to the vital organs such as the heart, brain, and adrenal glands.[96,97] Thus, during maternofetal hypoxia, the percentage of systemic venous blood not sent to the placenta for oxygenation is decreased, whereas the proportion of umbilical venous blood contributing to fetal cardiac output is increased.[96,97]

The human placenta was widely thought of as a passive organ in which blood flow depends only on the pressure difference between the umbilical arteries and veins connecting it to the fetus.[98,99] However, more recent evidences indicate that the regulation of vasomotor tone in the vessels of the fetoplacental circulation is important to maintain an adequate blood supply that makes possible maternofetal gas and solute exchange.[98–100] As fetoplacental blood vessels lack autonomic innervation, control of vascular tone is mainly influenced by circulating and/or locally released vasoactive agents as well as by physical factors, such as flow or oxygen tension.[101] Accordingly, constriction and relaxation of fetoplacental arteries and veins have been demonstrated in response to a number of agonists and physical stimuli. Moreover, various authors have suggested that the fetoplacental vasculature shows some form of flow matching similar to hypoxic pulmonary vasoconstriction. This mechanism, termed hypoxic fetoplacental vasoconstriction,[100,102,103] would divert blood flow to the placental areas with better maternal perfusion as hypoxic pulmonary vasoconstriction diverts pulmonary blood flow to the better ventilated areas of the lung.[103–105]

Clamping of the umbilical cord at birth eliminates the placental circulation producing a conspicuous increase in SVR. Parallel, as the lung assumes the respiratory function, the pulmonary circulation undergoes a striking transition characterized by an immediate eight- to ten-fold rise in pulmonary blood flow and a sustained decrease in PVR.[106–109] The postnatal fall in PVR and rise in SVR results in a reversal of the relationships present in the fetus. Increasing blood return to the heart via the pulmonary veins raises the pressure of the left atrium above that of the right, causing a functional closure of the foramen ovale. While the DA is still patent, the flow of blood through it will change to a left-to-right shunt but the DA normally achieves functional closure within 48 hours after birth. Because the foramen ovale and ductus arteriosus are only functionally closed and the pulmonary circulation is very sensitive to vasoconstrictive stimuli, the neonatal circulatory pattern can readily revert to the fetal pattern. In the following paragraphs the different circulatory events that take place during the transition between fetal and postnatal life will be analyzed in more detail.

CLOSURE OF THE DUCTUS VENOSUS

The ductus venosus is a shunt between the umbilical vein and the inferior vena cava which allows highly oxygenated and

nutrient-rich umbilical venous blood to bypass the liver and reach the central circulation rapidly. A large proportion of inferior vena cava return crosses the foramen ovale into the left atrium to the left ventricle, and is thus distributed to the coronary and cerebral circulations. The PO_2 of blood supplying the heart, brain, head, and neck is higher by 4–5 mmHg than that of blood in the descending aorta. Although the ductus venosus has received less attention than the DA, it is now well accepted that it plays a major role in the regulation of fetal circulation. Inlet of the vessel is under active control and a compensatory mechanism, supported by transient dilatation, is supposed to increase oxygenated blood flow through the ductus venosus during hypoxia or reduced umbilical flow.[110] Absence of the ductus venosus is associated with a high incidence of fetal anomalies and adverse outcomes, including associated malformations, chromosomal aberrations, *in utero* heart failure and absence of the portal vein.[111] Functional closure of the ductus venosus, which is followed by anatomic closure, is virtually complete within a few weeks of birth. However, the ductus venosus of almost all neonates remains open for a certain period after birth with important variations in the volume of blood flow.[112] Closure of the ductus venosus is more delayed in preterm neonates and patent ductus venosus appears to be related to alterations in ammonia detoxification, blood coagulation, and regulation of serum total bile acid concentration.[112]

CLOSURE OF THE FORAMEN OVALE

Anatomically, the foramen ovale comprises overlapping portions of septum primum and septum secundum, acting as a one-way flap valve allowing continuous right-to-left flow during fetal life.[113] Immediately after birth, with the acute increase in pulmonary blood flow, left atrium pressure rises to exceed right atrium pressure, pushing septum primum rightward, against septum secundum, shutting the flap of the foramen ovale. Afterwards, septum primum fuses to septum secundum, completing septation of the atria. However, in 20–25%, incomplete fusion leads to the persistence of the flap valve, leaving a patent foramen ovale.[113] In general, individuals with patent foramen ovale are never identified because they have no symptoms. However, there is increasing interest in the evaluation and treatment of patent foramen ovale, which has been associated with various pathologic conditions, such as cryptogenic stroke, decompression sickness, platypnea-orthodeoxia syndrome and migraine.[114]

FALL IN PULMONARY VASCULAR RESISTANCE

The ability to adapt to changes in the availability of O_2 underpins vital changes to the circulation during the transition from fetal to independent, air-breathing life.[115] The fetal lung is continuously exposed to a low O_2 tension which induces a vigorous hypoxic pulmonary vasoconstriction.[107,116,117] The fetal pulmonary circulation can sense small changes in Po_2, which is at least partly responsible for maintaining high PVR *in utero*.[107,116,117] The acute response to hypoxia in the fetal lamb is characterized by increased pulmonary and systemic arterial pressures and a fall in pulmonary blood flow.[118] This response is mediated by carotid chemoreceptors,[119] is already present before 0.7 term, and increases with gestational age.[120] However, acute elevation of fetal PVR is likely to be due to direct effects of lowered PO_2 on smooth muscle and modulated by various neural and humoral mediators.[107,121]

Besides the increase in oxygen tension, several other mechanisms contribute to the normal fall in PVR at birth, including the establishment of a gas–liquid interface in the lung, rhythmic distension of the lung, and shear stress.[106,107,122] These physical stimuli act, at least partially, through the production of vasoactive products, especially the release of potent vasodilator substances, such as nitric oxide (NO) and prostaglandin I_2.[106,109,123] Normally, pulmonary arterial pressure falls to the half of the systemic pressure by 24 h and then progressively decreases to adult levels within 2–6 weeks.[124] Therefore, the process of pulmonary circulatory transition is not limited to the first moments of extrauterine life, but it extends during the following weeks.[124]

Failure of the pulmonary circulation to undergo a normal transition results in persistent pulmonary hypertension of the newborn (PPHN), a clinical syndrome of various neonatal cardiopulmonary disorders, which are characterized by sustained elevation of PVR after birth, leading to right-to-left shunting of blood across the ductus arteriosus or foramen ovale and severe hypoxemia.[107,109] PPHN is a pathophysiological phenomenon occurring in a heterogeneous group of diseases with a wide diversity of etiologies. These range from transient reversible pulmonary hypertension attributable to perinatal insults to irreversible fixed structural malformations of the lung. Diseases associated with the syndrome of PPHN can be classified in three categories:[106,108]

1. maladaptation, in which vessels are presumably of normal structure but have abnormal vasoreactivity;
2. excessive muscularization, in which smooth muscle cell thickness is increased and muscle extends distally to vessels that usually are not muscular;
3. underdevelopment, in which lung hypoplasia is associated with decreased number of pulmonary arteries.

Either as a primary condition or secondary to other pulmonary or extrapulmonary diseases, PPHN is an important cause of cardiorespiratory failure and is responsible for a relevant percentage of morbidity in the neonatal intensive care units.[106,108]

CLOSURE OF THE DUCTUS ARTERIOSUS

Low oxygen tension, high levels of circulating PGE_2, and locally produced PGE_2 and PGI_2 are the main factors maintaining patency of the DA *in utero*.[125–127] During fetal life, the DA normally has an intrinsic tone due to components that are both dependent on and independent of extracellular

calcium.[125] Endothelin-1 also appears to play a role in the intrinsic tone of the ductus.[127–129]

Several events promote the constriction of the DA in the full term newborn: (1) the increase in arterial PO_2, (2) the decrease in blood pressure within the ductus lumen (due to the postnatal decrease in PVR), (3) the decrease in circulating PGE_2 (due to the loss of placental prostaglandin production and the increase in prostaglandins removal by the lung), as well as the decrease in the number of PGE_2 receptors in the ductus wall.[125,126,129] The timing of closure of the DA after birth varies between species, but in humans it is usually completed within 48 hours.[129] In the full term infant, closure of the DA at birth occurs in two phases. The first phase, the 'functional' closure of the lumen, occurs within the first hours after birth by smooth muscle constriction. Constriction produces ischemic hypoxia of the vessel wall, and this hypoxia inhibits local production of PGE_2 and NO and induces production of growth factors. This leads to the second phase that involves 'anatomic' occlusion of the lumen over the next several days due to extensive neointimal thickening and loss of smooth muscle cells (SMC) from the inner muscle media.[125,127–129]

Failure of DA closure after birth is a common complication of premature delivery that is still presenting challenges in terms of diagnosis, assessment, and treatment options.[127] Even when it does constrict, the premature ductus frequently fails to develop profound hypoxia and anatomic remodeling and is, therefore, susceptible to reopening.[129] Failure of DA closure in very preterm infants is associated with several comorbidities, such as necrotizing enterocolitis, intracranial hemorrhage, pulmonary edema/hemorrhage, bronchopulmonary dysplasia, and retinopathy of prematurity.[125–127]

LUNG DEVELOPMENT: STRUCTURAL DEVELOPMENT, SURFACTANT, AND LUNG FLUID

Lung development

The primary goal of lung development is to create a large gas exchange surface area, a thin air–blood barrier, a mature surfactant system, a conductive airway tree, and a set of vascular tubes to supply the organism with sufficient oxygen and to remove excess CO_2. Lung development comprises six different stages.[130]

During the embryonic stage (3–7 weeks post-conception) the lung primordium appears as a ventral diverticulum of the foregut and elongates caudally. The resulting bud branches for the first time and gives rise to the main bronchi of the two lungs. These bronchi divide dichotomously and form the future bronchi.

During the pseudoglandular stage (5–17 weeks in the human) the whole bronchial tree is formed by dichotomous branching. Also, differentiation of epithelial cells starts with the appearance of ciliated cells, goblet and basal cells, and production of cartilage.

During the canalicular stage (16–26 weeks in human) the air–blood interface is formed by the appearance of vascular canals or capillaries that multiply in the interstitial compartment. In addition, differentiation of pulmonary epithelial cells into type II cells, the producers of surfactant, is seen as well as a subsequent development of type I cells, which contribute to the formation of the thinned prospective air–blood barrier.

Entering the saccular stage (24–38 weeks in human) is crucial for extrauterine survival. On the one hand there is dilation and expansion of the acinar tubules and buds into thin, smooth walled, transitory alveolar sacules and ducts. On the other hand there is reduction of the surrounding mesenchymal tissue which allows for sufficient gas exchange. Further branching of the alveolar ducts occurs and the peripheral regions of the lung increase in size. Preparation for real alveolarization begins with the development of intersaccular and interductal septa. Maturation of type II epithelial cells continues and surfactant production starts. Further differentiation of other alveolar and bronchial cells occurs.

The alveolar stage (36 weeks of gestation to two years postnatal age) starts before birth but lasts well into the postnatal period. The hallmark of this stage is secondary septation, namely the formation of new interalveolar walls. They originate from low ridges projecting into the airspaces. Typically, elastic fibers are located at the tip of the crests where the secondary septa originate.[131] Originally the septa still consist of a doubled capillary layer separated by a sheet of connective tissue.

During the last stage of lung development, the stage of microvascular maturation (the first 2–3 years after birth) the septa are restructured into a mature interalveolar wall, consisting of minimal interstitial tissue and a capillary monolayer.[130,132] At the end of this stage most of the alveolar capillary endothelium and flattened type I epithelium are in direct contact supporting optimal gas exchange.

At birth the lung contains up to 50 million alveoli and most of the remaining alveoli are formed by so-called 'bulk alveolarization' during the alveolar stage, mainly postnatally. However, it is very well possible that a stage of late alveolarization exists, as described by Burri,[132] where about 50% of the adult 300 million alveoli are formed. Especially in the subpleural areas in the periphery of the lung, new alveolar septa can be newly formed at a slower pace, but later than the bulk alveolarization phase.

In most cases it is easy to link lung abnormalities or syndromes to the stage of lung development.[133] For example, treacheo-esophagal fistulae, pulmonary agenesis or aplasia, and extralobar pulmonary sequestration originate during the embryonic stage of lung development. Pulmonary cysts, renal pulmonary hypoplasia, and lung hypoplasia due to congenital diaphragmatic hernia originate during the pseudoglandular and canalicular stage. Alveolar capillary dysplasia originates during the canalicular and saccular stage. Pulmonary hypoplasia due to oligohydramnion also originates during the canalicular and saccular stage. In general, branching will be permanently impaired by insults prior to 16 weeks of gestation while the number of alveoli will be reduced by a

later insult. From the stages of lung development it is also easy to understand the border of survival in extreme prematurity. Although there is some overlap between the stages, in general the saccular stage starts at 24 weeks, not surprisingly the gestational age where significant survival starts. Still, at this stage of lung development surface area for gas exchange is small, epithelia are not sufficiently flattened and interstitium is still present between the epithelial layer and the endothelial layer. As the alveolarization phase has not taken place yet, many insults can disturb this process leading to fewer and larger alveoli, typical of the so-called 'new bronchopulmonary dysplasia'.[134] Many prenatal and postnatal factors can influence this process such as chorioamnionitis, interauterine growth retardation, oxygen toxicity, positive pressure ventilation, infections, a patent ductus arteriosis, and some therapeutical interventions such as the use of postnatal corticosteroids.[134]

Surfactant

In 1959, Avery and Mead[135] showed that pulmonary surfactant deficiency is a major factor in the pathophysiology of respiratory distress syndrome (RDS). Since then the physiology and metabolism of surfactant has been extensively studied. In 1980 Fujiwara[136] administered exogenous surfactant successfully to preterm infants with RDS for the first time followed by numerous clinical trials in the 1990s.[137] In addition, a disturbed surfactant metabolism plays a role in many neonatal lung diseases such as meconium aspiration syndrome and congenital diaphragmatic hernia.[138]

The primary function of surfactant is to decrease the surface tension at the air–liquid interface in the alveoli and distal bronchioli, to promote lung expansion during inspiration, and to prevent alveolar collapse at expiration. A secondary role of surfactant is innate host defence.[139] Surfactant is produced by alveolar type II cells, which are situated at the corners of the alveolar spaces. It is a complex mixture of about 90% lipids and 10% proteins.[140] Of the surfactant lipids, 80–90% are phospholipids, of which phosphatidylcholine (PC) is quantitatively the most important, accounting for 70–80% of the total. The four surfactant proteins are simply named surfactant protein (SP) A, B, C, and D.[141] SP-A enhances uptake of surfactant by the type II cells and together with SP-D plays a role in innate immune defense: it binds pathogens and influences the activity of immune cells such as macrophages.[142] Both proteins are large glycoproteins. In contrast, SP-B and SP-C are small, very hydrophobic proteins and are essential for the spreading of surfactant phospholipids at the air–liquid interface of the alveoli. The role of SP-B is so essential that a congenital deficiency is lethal due to severe respiratory insufficiency.[143] Surfactant is synthesized by type II alveolar cells from precursors such as fatty acids, choline, glucose, and amino acids in the endoplasmatic reticulum and via the Golgi apparatus is then stored in lamellar bodies.[144] These lamellar bodies serve as the intracellular storage form of surfactant and are secreted into the alveolar space. After secretion they unravel to form lattice-like structures, named tubular myelin. From this structure the monolayer of surfactant at the air–liquid interface is generated. This monolayer is the essential surface-tension-lowering component. Alveolar surfactant can be cleared by different pathways.[145] Surfactant can be removed from the lung by macrophages or via the upper airways or can be recycled by uptake by the type II cell and reinsertion in the lamellar bodies, which are ready for resecretion. In the neonate more than 90% of surfactant is recycled in this way, in contrast to the adult where recycling is about 50%.[146,147]

Surfactant kinetics have been studied in animals with the use of radioactively labeled substrates.[148] In recent years stable isotope techniques were used to study surfactant metabolism in human infants. Labeled precursors, such as [U-^{13}C]glucose, [1-^{13}C]acetate, or [U-^{13}C]palmitic acid were infused intravenously and incorporation of label was measured by mass spectrometry in surfactant PC isolated from tracheal aspirates.[138] In term ventilated neonates without lung disease the first appearance of label in surfactant was found after about 9 hours with a maximal enrichment at about 44 hours.[149–151] In comparison, preterm infants with RDS showed a much slower surfactant synthesis and metabolism with a first enrichment after about 17 hours and maximal enrichment at about 75 hours.[149,152–154] When the fractional synthesis rate of surfactant was calculated, preterm infants with RDS only had a value of 4%/day compared to 15%/day or more in term infants.[149–154] Catabolism and pool sizes of surfactant were studied by giving a bolus of labeled surfactant PC endotracheally. Half-life was calculated by the disappearance of the label from tracheal aspirates and pool size from the dilution of the label. Preterm infants only had less than 10 mg/kg of surfactant, which is consistent with animal models of RDS.[155] No feedback inhibition was found of surfactant therapy on endogenous surfactant synthesis.[156] It was also proven in human infants that prenatal corticosteroids stimulate surfactant synthesis, as was extensively known from *in vitro* studies and animal experiments.[157,158] Controversy has long existed about a possible surfactant deficiency in neonates with congenital diaphragmatic hernia (CDH). In several animal models of CDH a decrease in surfactant was found.[159–161] In humans, surfactant was measured from tracheal aspirates or bronchoalveolar lavages with contradictory results.[162–165] Studies with stable isotopes did not completely clarify the issue. Cogo *et al.*[166] found a decrease in pool size in infants with CDH but Janssen *et al.*[167] found no decrease in pool size (about 73 mg/kg) in infants on extracorporeal membrane oxygenation (ECMO). However, surfactant synthesis was decreased in the patients in this study comparable with the synthesis of preterm infants with RDS (fractional synthesis 2.4%/day versus 8%/day in control infants).[168] In patients with less severe CDH, Cogo found no decreased synthesis rate of surfactant.[150,169] Similar studies were performed in neonates with meconium aspiration syndrome (MAS). Some infants with MAS have severe respiratory insufficiency. From animal studies it is well known that meconium inhibits surfactant function. With stable isotope techniques it was shown that the sickest infants on ECMO have a decreased surfactant synthesis.[151,170]

From a clinical perspective the incidence of RDS is inversely related to gestational age. This reflects the low amount of surfactant leading to RDS in infants with a low gestational age. Although surfactant production starts at the beginning of the saccular stage (at around 24 weeks) it remains low until 32–34 weeks of gestation and then rapidly increases towards term. As mentioned before, preterm infants with RDS are treated with surfactant nowadays, which has been shown to decrease mortality and air leaks.[137] Also, in infants with severe MAS, surfactant therapy was shown to be beneficial in that it decreases the need for ECMO. In infants with CDH, the use of surfactant therapy is still controversial which is consistent with the studies on surfactant metabolism mentioned above. Standard use of surfactant in CDH is not currently recommended.[137]

Lung liquid secretion and absorption

From early in gestation, fluid is present in the embryonic lung.[171] This fluid is secreted by the developing lung epithelia and is very important for normal lung development and growth.[172] At birth, transition to air breathing requires removal of the lung liquid for gas exchange.

Strong evidence for active secretion of lung liquid was found by the observation that the Cl^- concentration of fetal lung liquid was higher than that of plasma.[173] Indeed, later it was shown that Cl^- secretion is the driving force for the secretion of lung liquid.[174] In fetal sheep the rate of liquid secretion increases from about 1.5 mL/kg per hour at mid-gestation to about 5 mL/kg per hour in late gestation.[175] The pressure in the lung is approximately 2 mmHg higher than the pressure in the amniotic fluid, caused by a restriction to the outflow of fluid by the vocal cords and the larynx and nasopharynx.[175–177] The essential role of this lung liquid for lung development[178] was shown by experimental continuous drainage of lung liquid from fetal sheep lungs which resulted in lung hypoplasia.[179] The opposite was found after tracheal ligation with overdistention of the fetal lung resulting in lung hyperplasia.[180,181] Also, in humans, early and severe oligohydramnion leads to lung hypoplasia because of continuous drainage of lung fluid from the lungs. Plugging of the fetal trachea is an experimental therapy to overcome lung hypoplasia in CDH.[182]

At birth, rapid removal of the fetal lung liquid is essential for air breathing. Liquid clearance starts before birth during the process of labor. The basic mechanism is a switch from Cl^- secretion to Na^+ absorption. This switch is triggered by a surge in fetal catecholamine secretion during labor. Activation of the β-adrenoreceptor recruits and stimulates Na^+, K^+-adenosine triphosphatase (ATPase) at the basoateral membrane and Na^+ channels of the luminal membrane.[172,183] The main Na^+ channel is the epithelial Na^+ channel, or ENaC, which has been cloned.[183] Of course part of the fluid is squeezed out during the birth process. Active liquid absorption is continuous after birth and most of the liquid is cleared from the full-term newborn lung within 2 hours after birth. Infants born by Cesarean section without labor have a slowed lung liquid clearance and sometimes show signs of respiratory distress called transient tachypnea of the newborn (TTN).[184–187] The switch from liquid secretion to liquid absorption is disturbed in preterm infants because of immaturity of the absorption processes described above. This adds to the respiratory problems of preterm infants with RDS. Prenatal corticosteroids have been shown to improve liquid absorption,[183,188–190] besides the well-known positive effect on surfactant synthesis.

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3

Clinical anatomy of the newborn

MARK D STRINGER

INTRODUCTION

A newborn infant more than triples in height and increases in weight some 20-fold before reaching maturity. During the process, structures change in size and position. Some, which are critically important during fetal development, disappear. Most persist but grow at different rates and at different ages. It is therefore not surprising that newborn anatomy differs from adults; some of these differences are particularly important for the pediatric surgeon (Table 3.1 and Fig. 3.1). This chapter summarizes the applied anatomy of the newborn, emphasizing aspects that are clinically relevant and different to adults.

GROWTH AND PROPORTIONS

Growth can be defined as 'the progressive development of a living being or any of its parts from its earliest stage to maturity, including the attendant increase in size'.[1] It involves changes in size and mass, and includes processes such as cell division, specialization, and apoptosis. Growth can be proportional but is often differential. For example, the head of a full-term newborn infant accounts for about 25% of its body length and 20% of its body surface area. In adults, these figures are about 13 and 9%, respectively (Fig. 3.2). Similarly, the pelvis and lower limbs are proportionately small in the neonate.[2] Body surface area to weight ratio decreases with age: the absolute surface area of a neonate is about 0.25 m^2 compared to 1.73 m^2 in an adult. Neonates are consequently more vulnerable to heat loss.

The mean length of the full-term newborn measured from crown to heel is around 48–50 cm and weight 2.7–3.8 kg. About 75–80% of this weight is water and 15–28% is fat.[3] By one year of age, total body water has decreased to adult values of around 60% of body weight.

CARDIOVASCULAR SYSTEM

Circulatory changes after birth

In the fetus, oxygen rich blood is transported from the placenta via the umbilical vein to the left branch of the portal vein lying within the umbilical recess of the liver (Fig. 3.3). The ductus venosus arises from the posterior aspect of the left branch of the portal vein directly opposite the opening of the umbilical vein and passes superiorly and laterally between the left lobe and caudate lobe of the liver to terminate in the left hepatic vein near its entry into the inferior vena cava (IVC). A valve along the anterior margin of the opening of the IVC into the right atrium directs the oxygenated blood through the foramen ovale to the left atrium. Deoxygenated systemic blood returning from the fetal superior vena cava and coronary sinus is directed preferentially to the right ventricle. However, not more than 20% of the fetal cardiac output reaches the lungs[4] because the ductus arteriosus shunts blood from the pulmonary trunk to the aortic arch, just distal to the origin of the left subclavian artery. At term, the ductus arteriosus is about 8–12 mm long and 4–5 mm wide at its origin from the beginning of the left pulmonary artery; the thoracic aorta by comparison measures about 5–6 mm in diameter.[3] The walls of the ductus arteriosus are rich in smooth muscle fibers. In the fetus, ductal patency is maintained by locally produced prostaglandins, which inhibit muscle contraction in response to oxygen.

At birth, the lungs inflate and, as a result of mechanical effects and oxygen-induced pulmonary vasodilatation, pulmonary vascular resistance falls. The ductus arteriosus starts to close. Blood is diverted from the pulmonary trunk into the pulmonary circulation. Increased venous return to the left atrium causes a rise in left atrial pressure. Right atrial pressure falls as a result of reduced venous return secondary to occlusion of the umbilical vein. These changes in atrial pressure force the thin primary atrial septum against the free lower margin of the secondary atrial septum (which lies to the

Table 3.1 Key anatomical differences between neonates and adults.

Cardiovascular system	Recent transition from fetal circulation
	Relatively large heart
	Potential for congenital heart defects
	Prominent thymic shadow on chest x-ray
Respiratory system	Obligate nose breathing
	Short neck with high larynx
	Ability to breathe while suckling
	Subglottis is narrowest part of the airway
	Highly compliant chest wall
	Greater reliance on diaphragm for breathing
Abdomen	Relatively wide abdomen
	Short inguinal canal
	Propensity to inguinal hernias and undescended testes
	Small amount of intra-abdominal fat
	Proportionately large liver
	Poor radiological distinction between small and large bowel
	Small pelvic cavity
	Intra-abdominal bladder and body of uterus
	Proportionately large suprarenal glands
Musculoskeletal system	Proportionately large head, small pelvis, and lower limbs
	Open fontanelles
	Relatively underdeveloped face and mandible
	Horizontal auditory tube
	No spinal curvatures (other than shallow sacral curve)
	Absence of most secondary ossification centers
	Shallow acetabulum
	Relatively small gluteal muscles
Nervous system	Relatively large brain with full complement of neurones but incomplete myelination of axons
	Proportionately large cerebral ventricles
	Spinal cord terminates at lower level
Skin	Variable subcutaneous fat (some brown fat)
	Thin skin, immature sweating
	Greater body surface area to weight ratio
	Head accounts for 20% of body surface area

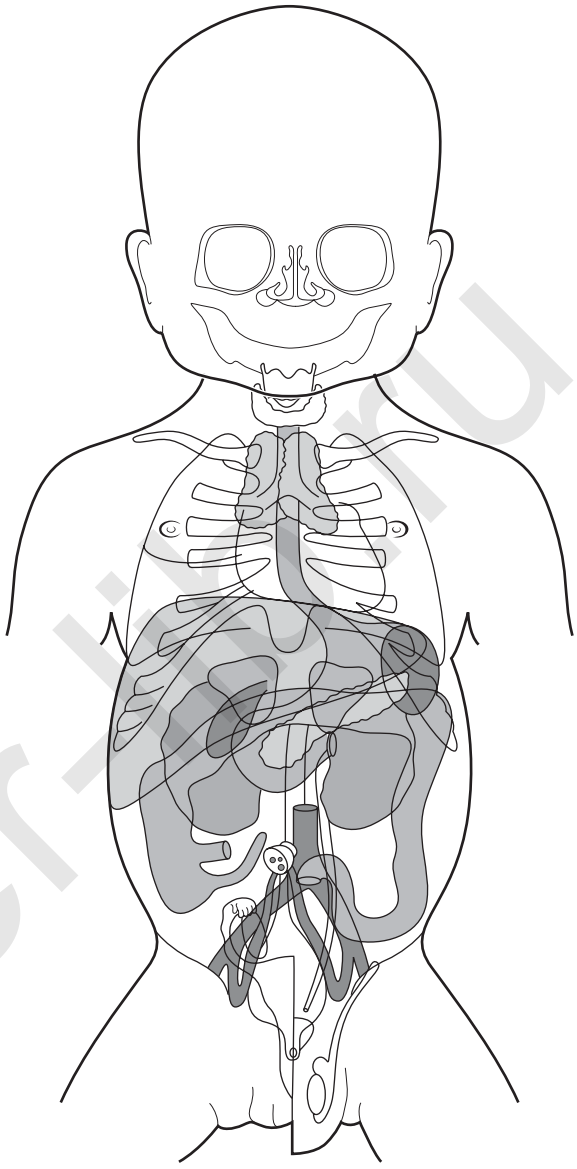


Figure 3.1 Diagram illustrating the relative proportions of viscera in the newborn (based on information from Ref. 19).

right) resulting in functional closure of the foramen ovale. A permanent seal usually develops during the first year of life.

Cardiovascular adaptation to neonatal life therefore requires the functional closure of three fetal conduits:

1. Foramen ovale. Incomplete fusion of the primary atrial septum with the free lower margin of the secondary atrial septum occurs in up to 25% of individuals,[5] resulting in a small potential atrial communication, a patent foramen ovale (PFO). Typically, this has no consequences because of the flap-like arrangement of the opening and differential atrial pressures. However, a PFO may rarely be associated with paradoxical embolism (passage of an embolus from the venous system through an abnormal communication between the chambers of the heart causing a systemic arterial embolus, e.g. an embolic stroke) and an increased risk of decompression sickness in divers.[6] After closure of the foramen ovale, the valve of the IVC that was prominent in the fetus becomes flimsy or disappears.
2. Ductus arteriosus. In full-term neonates with no congenital heart disease, the ductus arteriosus starts to close immediately after birth. Smooth muscle contraction within the ductus is probably mediated by several mechanisms: an increased arterial oxygen concentration, suppression of endogenous prostaglandin I_2 synthesis, plasma catecholamines, and neural signaling. In addition, ductal blood flow is reversed as a result of increased systemic vascular resistance (due to absence of the placental circulation), and decreased pulmonary vascular resistance. Functional closure is complete within 3 days in more than 90% of

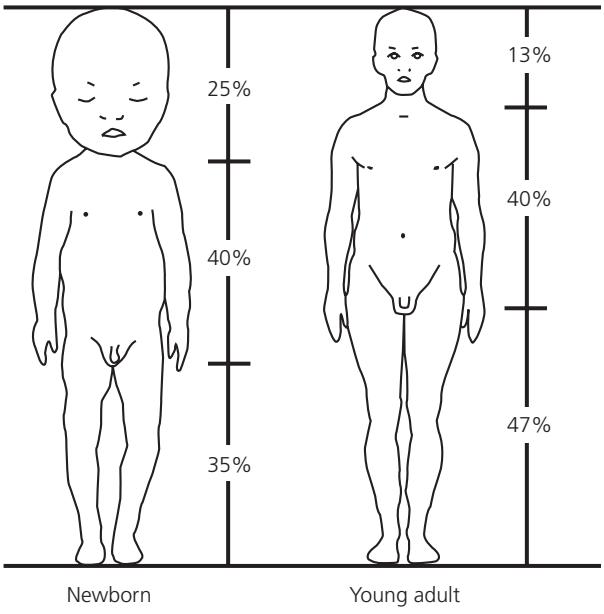


Figure 3.2 The relative proportions of the head, trunk, and lower limbs in a neonate and adult (adapted from Ref. 2).

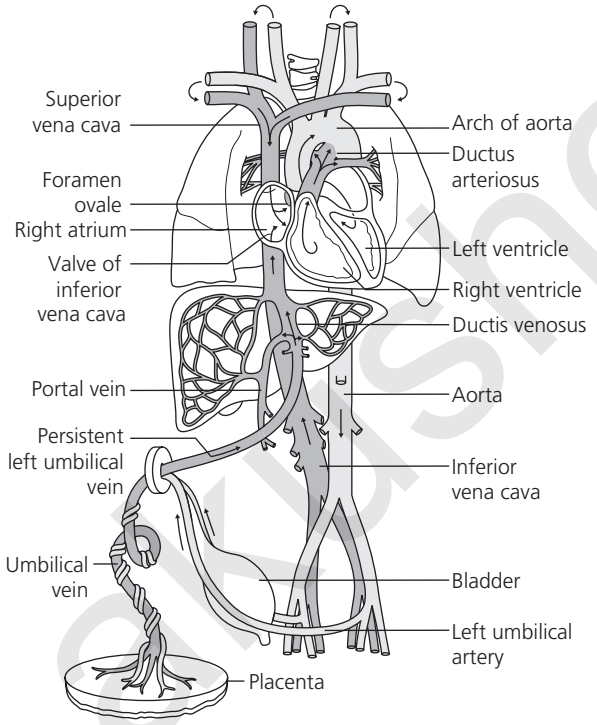


Figure 3.3 The fetal circulation.

term infants.[7] Structural closure occurs more gradually, leaving the fibrous ligamentum arteriosum connecting the origin of the left pulmonary artery to the underside of the aortic arch. Persistent ductal shunting can occur in preterm infants with respiratory distress.[7]

3. Ductus venosus. Spontaneous closure of the ductus venosus begins immediately after birth[8] and is usually complete by about 17 days of age.[9,10] Closure may be temporarily delayed in the presence of congenital heart disease, presumably as a result of elevated venous pressure. In the adult, the remnant ligamentum venosum runs within the fissure separating the anatomic left lobe of the liver and the caudate lobe. Persistent patency of the ductus venosus is rare, more common in boys, and may cause long-term problems such as hepatic encephalopathy.[11]

The heart

In the full-term neonate, cardiac output measured by Doppler studies is about 250 mL/kg per min, mean systolic blood pressure in the first week is 70–80 mmHg (lower in preterm infants), and heart rate settles within hours of delivery to 120–140 beats/min. As the pulmonary circulation is established, the work of the right side of the heart decreases and the left increases, reflected by changes in ventricular muscle thickness; at birth, the mean wall thickness of both ventricles is about 5 mm whereas in adults the left ventricle is about three times as thick as the right.[3] The neonatal heart is relatively large in relation to the thorax and lungs and consequently it occupies a larger proportion of the lung fields on a chest radiograph compared to an adult (Fig. 3.4).

Congenital cardiac malformations account for up to a quarter of all developmental anomalies (eight per 1000 live births[4]) and include dextrocardia (isolated or part of situs inversus), isomerism, and structural defects (septal defects, abnormal atrioventricular or ventriculoarterial connections, and valvular anomalies). Ventriculoseptal defects are the most frequent, more often affecting the membranous than the muscular part of the interventricular septum. A true atrial septal defect occurs when there is a failure of normal development of the septum primum and/or atrioventricular endocardial cushions. Coarctation of the aorta is often

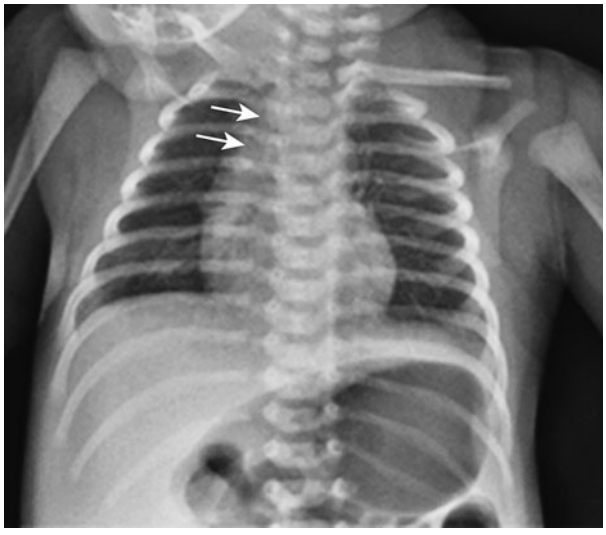


Figure 3.4 Supine anteroposterior neonatal chest x-ray. Note the prominent superior mediastinal thymic shadow which is asymmetric on this rotated film (white arrows). Compared to an adult, the hemidiaphragms are relatively flat, the ribs are more horizontal, and the heart size is relatively large (although the transverse cardiothoracic ratio should still be less than 60%[12]).

included within the spectrum of congenital heart disease. Typically, there is narrowing or occlusion of the juxta-ductal segment of aorta just distal to the origin of the left subclavian artery, although preductal (involving the aortic arch and its branches) and even postductal coarctation can occur.

Neonatal central venous catheters are generally positioned such that the catheter tip lies outside the cardiac outline on a chest radiograph in order to reduce the small but serious risk of atrial perforation and cardiac tamponade.

Umbilical vessels

The normal umbilical cord contains two thick-walled umbilical arteries and, near the 12 o'clock position, one larger but thin-walled umbilical vein. The presence of a single umbilical artery may be associated with other congenital anomalies, particularly renal, vertebral, and anorectal malformations,[13] and an increased risk of perinatal mortality.[14] However, routine karyotyping and renal sonography in an infant with an isolated single umbilical artery is not indicated.[14,15]

At birth, the umbilical vessels constrict rapidly in response to a fall in umbilical cord temperature and hemodynamic changes. Occlusion of the umbilical artery is facilitated by the 'folds of Hoboken', constriction rings along the length of the umbilical artery produced by oblique or transverse bundles of myofibroblasts.[16] Numerous mediators of umbilical vessel vasoconstriction have been proposed, including bradykinin and endothelin-1, some of which are produced locally within the umbilical cord. After birth, the obliterated umbilical arteries become the paired medial umbilical ligaments, usually visible under the peritoneum of the anterior abdominal wall below the umbilicus; the proximal parts of each umbilical artery remain patent as the superior vesical artery. The intra-abdominal segment of the umbilical vein becomes the ligamentum teres. The urachus has normally involuted before birth, leaving the fibrous median umbilical ligament.

The umbilical artery and vein can be catheterized within 24–48 hours of birth to provide vascular access for resuscitation, intravascular monitoring, fluid administration, blood transfusion, and parenteral nutrition.[17] The tip of an umbilical artery catheter is usually positioned above the diaphragm but below the ductus arteriosus ('high' position equivalent to T6–9 vertebral level). Sometimes, the catheter tip is sited below the origin of the renal and inferior mesenteric arteries but above the aortic bifurcation ('low' position at L3–4 vertebral level).

Arteries

The femoral artery is palpable midway between the anterior superior iliac spine and pubic tubercle in the neonate;[18] it is therefore more lateral than in an adult where the surface marking is midway between the anterior superior iliac spine and symphysis pubis.[3] The renal arteries are at a higher vertebral level in the neonate (T12–L1) compared to the adult (upper border of L2)[3] and the aortic bifurcation is at the upper rather than the lower border of L4.

RESPIRATORY SYSTEM

Upper airway

Relative to an adult, the newborn infant has a large head, short neck, small face and mandible, and large tongue.[19] The entire surface of the tongue is within the oral cavity, unlike the adult where its posterior third is in the oropharynx. Neonates are obligate nose breathers and do not begin to breathe orally until about four months of age. All these features predispose to airway obstruction.

The neonatal nasopharynx curves smoothly backwards and downwards to join the oropharynx, rather than almost at a right angle as in adults (Fig. 3.5). The hyoid bone and larynx are high in the neck. Consequently, the upper margin of the neonate's epiglottis extends to the level of the soft palate and the posterior nares are in direct continuity with the larynx. This allows the infant to breathe while suckling. Ingested liquids pass lateral to the epiglottis via the piriform fossae. Despite immature coordination of swallowing and breathing, the risk of aspiration is reduced by the high position of the larynx. The higher, more anterior position of the larynx also means that it is easier to intubate the trachea with a straight-bladed laryngoscope. As the infant grows, the larynx descends and the epiglottis loses contact with the soft palate. Gender differences in laryngeal shape and size only begin to appear at about three years of age.[19] The narrowest part of the infant's upper airway (about 3.5 mm in a term neonate) is the subglottis at the level of the cricoid cartilage, rather than the vocal cords as in adults.

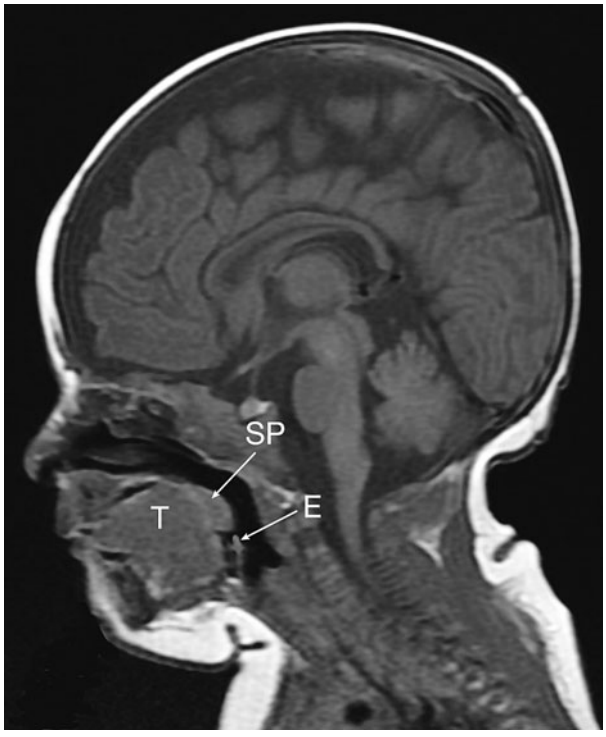


Figure 3.5 Sagittal magnetic resonance image of the upper airway in a newborn. T = tongue, SP = soft palate, E = epiglottis. Courtesy of Professor Terry Doyle.

Trachea and bronchial tree

The trachea is short, measuring as little as 3 cm in premature neonates, making positioning of an endotracheal tube critical. The tip of the tube is usually sited between the clavicles, 1–2 cm above the carina, which corresponds to the vertebral body of T1. As in adults, the trachea starts at the level of the sixth cervical vertebra but bifurcates relatively higher at T3/4 (rather than T4/5 in adults). The trachea is rich in elastic tissue[20] and readily deformable. The right main bronchus is wider and steeper than the left and the carina is more likely to lie to the left of the midline. Contrary to some reports, an aspirated foreign body is therefore more likely to enter the right lung.[21] The left brachiocephalic vein lies at a relatively higher level and is at greater risk of injury during tracheostomy.

The bronchial tree is developed by the 16th week of intrauterine life; thereafter, conducting airways increase in size but not number.[22] Postnatal lung growth is dominantly by alveolar development. Lung volume increases rapidly during infancy. Most alveoli have been formed by two years of age and only increase in size thereafter.[23,24] Before the infant takes its first breath, the terminal bronchioles and alveoli are filled with fluid, mostly produced in the lung. There is more fluid in the lungs of a newborn infant delivered by Cesarean section than after vaginal delivery. For the alveoli to expand adequately surface tension must be reduced; this is achieved by the release of surfactant from type II pneumocytes lining the alveoli. Surfactant also prevents alveolar collapse on expiration, which explains why very premature infants with inadequate surfactant production develop respiratory distress. Remodeling of the pulmonary vessels begins immediately after birth to reduce pulmonary vascular resistance.

Thorax and mechanics of breathing

The neonatal thorax has the shape of a truncated cone and is more rounded in circumference. Unlike the adult in whom the compliance of the chest wall and lung are similar, the neonate's chest wall is up to five times more compliant than its lungs.[3] Consequently, it is easily deformable, a fact that is readily apparent in the presence of respiratory distress.

The respiratory rate of a newborn at term is about 40–44 breaths/min. The ribs are more horizontal and contribute less to chest expansion. Infants rely mainly on diaphragmatic breathing. The diaphragm is relatively flat at birth (Fig. 3.4) and becomes more dome-shaped with growth. Diaphragmatic contraction tends to pull the ribs inwards; concomitant outward movement of the abdomen (thoracoabdominal paradox) is a normal finding in newborns. The work of breathing is greater in a neonate than an adult and still greater in a preterm infant.

The neonatal thymus is large (up to 5 cm wide and 1 cm thick) but variable in size at birth. It is a prominent feature on a chest x-ray (Fig. 3.4). The gland overlies the trachea, great vessels (especially the left brachiocephalic vein), and the upper anterior surface of the heart. After the first year of life it becomes progressively less vascular, and the lymphoid tissue is increasingly replaced by fat.

ABDOMINAL WALL AND GASTROINTESTINAL TRACT

Abdominal and pelvic cavities

The neonatal abdomen is relatively wide and protruberant because the diaphragm is flatter and the pelvic cavity smaller. The distance between the costal margin and iliac crest is proportionately greater in the neonate. For these reasons, transverse supraumbilical incisions provide good surgical access. The inguinal canal in the newborn is short and relatively vertical since the superficial inguinal ring almost overlies the deep ring. The canal lengthens with growth. The rectus abdominis muscles may be relatively wide apart creating devarication, which improves with growth.

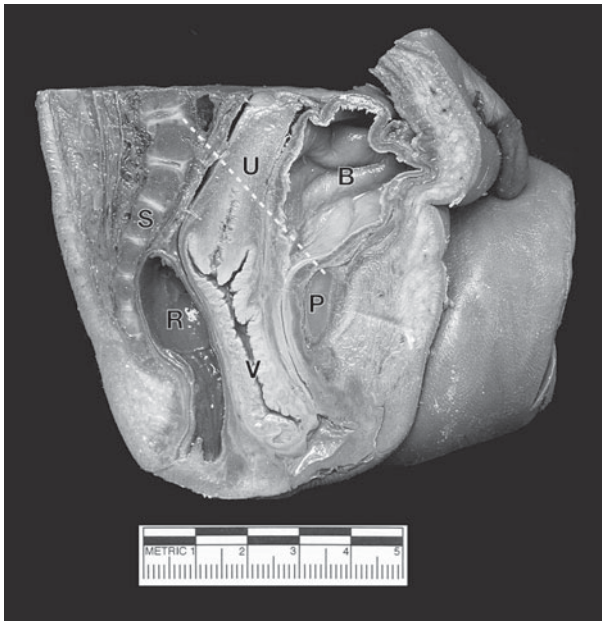
Compared to an adult the true pelvis in the neonate is small, both relatively and absolutely, more circular in cross section, orientated more vertically, and has a less pronounced sacral curve. The peritoneal cavity is shallow anteroposteriorly because there is no lumbar lordosis and the paravertebral gutters are poorly developed. The urinary bladder, ovaries, and uterus are all partly intra-abdominal and the rectum occupies most of the true pelvis (Fig. 3.6). The greater omentum is delicate and membranous, rarely extending much below the level of the umbilicus. Indeed, the neonate has altogether less fat in the mesenteries and around the viscera.

Gastrointestinal tract

At term, the newborn esophagus measures about 8–10 cm in length from cricoid to diaphragm;[19] the upper and lower oesophageal sphincters each extend over about 1 cm.[25] Lower esophageal sphincter pressure is particularly low during the first month or two of life. The narrowest part of the upper digestive tract is where the cricopharyngeus muscle blends with the upper esophagus, a potential site of esophageal perforation during the passage of a nasogastric tube.[26]

The anterior surface of the stomach is overlapped by the left lobe of the liver, which extends almost to the spleen. The capacity of the neonatal stomach is 30–35 mL at term but reaches 100 mL by the fourth week. Gastric emptying is relatively slow and poorly coordinated in the first few weeks. The small bowel of the newborn is distributed more horizontally because of the shape of the abdominal cavity. The mean length of the small intestine from the duodenojejunal flexure to the ileocecal junction is around 160 cm when measured at term along its antimesenteric border *in vivo*[27], but considerably longer when measured at autopsy.[28]

The mean *in vivo* length of the colon from the ileocecal junction to the upper rectum is 33 cm at term.[27] The cecum, ascending and descending colon are relatively short compared to the adult and the transverse colon, sigmoid colon, and rectum relatively long. The cecum tapers to a proportionately large appendix with a relatively wide orifice. The anal canal has well-defined anal columns and prominent anal sinuses;[29] stasis within these sinuses may be a cause of perianal sepsis, particularly in male infants.[30]



(a)

(b)

Figure 3.6 Midline sagittal section of a plastinated neonatal (a) and adult (b) female pelvis. Note the relative positions of the bladder (B) and uterus (U), the curvature of the sacrum (S), and the angle of the pelvis (dotted line between sacral promontory and pubic bone (P)). V = vagina, R = rectum. Courtesy of the WD Trotter Anatomy Museum, University of Otago.

The neonatal small bowel has few circular folds (valvulae conniventes) and the neonatal colon has no haustra. This makes it difficult to distinguish the small and large bowel on plain abdominal radiographs. Their relative position (central versus peripheral) and caliber are a guide but a contrast study may be required to accurately differentiate small from large bowel.

Liver and spleen

The neonatal liver weighs about 120 g at term and comprises about 4% of body weight (compared to 2% in the adult); it more than doubles in weight during the first year. The relatively large liver fills much of the upper abdomen. Its inferior border extends 1–2 cm below the costal margin. The premature baby's liver is particularly fragile and vulnerable to injury (e.g. from an abdominal retractor). The neonatal gallbladder is more intrahepatic and its fundus may not extend below the liver margin.

The tip of the newborn's spleen is often palpable just below the left costal margin. The pancreatic tail is in contact with the spleen, usually at its hilum, in more than 90% of cases, a much greater proportion than in adults.[31] Accessory spleens are found at autopsy in about 14% of fetuses and neonates as compared to 10% of adults[32] but it is uncertain whether this is a true increased prevalence.

GENITOURINARY SYSTEM

Genitourinary anomalies are among the most common congenital malformations and so it is especially important to understand normal anatomy in the newborn.

Kidneys and suprarenal glands

At birth the kidneys are about 4–5 cm in length compared to a mean length of 11 cm in adults. Fetal lobulation of the kidneys is still present at birth. Individual nephrons consist of a renal corpuscle with (1) a central glomerulus concerned with plasma filtration and (2) a renal tubule that produces urine by selective reabsorption of the filtrate. At birth there are about one million renal corpuscles in the cortex of each kidney. Postnatally, cortical nephron mass increases but no new nephrons are made. The glomerular filtration rate (GFR) is low in newborns, particularly in the premature, but in the term infant the GFR doubles by 2 weeks of age and reaches adult values (120 mL/min per 1.73 m^2) by 1–2 years.[33]

The suprarenal glands are relatively large at birth with a proportionately thick cortex. Their average combined weight is 9 g compared with 7–12 g in an adult. Both glands shrink in the neonatal period.

Bladder and ureter

The bladder is largely intra-abdominal at birth (Fig. 3.6) with its apex midway between the pubis and the umbilicus in the unfilled state. Suprapubic aspiration and manual expression of urine are therefore relatively easy. The bladder does not achieve its adult pelvic position until about the sixth year.[3] The intravesical segment of the ureter (intramural and submucosal portions) lengthens from about 0.5 cm in neonates to 1.3 cm (the adult value) by 10–12 years of age. An abnormally short submucosal tunnel is one of the causes of vesicoureteric reflux (VUR) in preschool children; this type of VUR tends to resolve spontaneously with growth.[34]

Genitalia and reproductive tract

By about the sixth month *in utero*, the testis lies adjacent to the deep inguinal ring connected to the developing scrotum by the gubernaculum. About one month later, the testis begins its inguinoscrotal descent surrounded by the elongating processus vaginalis. At term, about 4% of boys have an undescended testis(es); the figure is higher in premature infants. By three months of age, the prevalence of cryptorchidism has fallen to 1.5%. The timing and process of closure of the processus vaginalis are both uncertain.[35] Surgical studies have shown that a patent processus vaginalis is present in around 60% of contralateral groin explorations in infants with a unilateral inguinal hernia in the first two months, falling to around 40% after two years of age. Autopsy studies have indicated that the processus is patent in about 80% of newborns, decreasing to about 15–30% in adults. Boys with cryptorchidism have higher patency rates.

The prostate and seminal vesicles are well developed at birth. The penis and scrotum are relatively large and the scrotum has a broad base and relatively thick walls. The prepuce begins to separate from the glans *in utero* but is usually only partially retractile at birth.

In baby girls, the ovary lies in the lower part of the iliac fossa and only descends into the ovarian fossa within the true pelvis during early childhood as the pelvis deepens. At birth the ovaries are relatively large and contain the full complement of primary oocytes, each surrounded by a single layer of follicular cells forming primordial follicles. Of the seven million oocytes estimated to be present in the female fetus, only one million remain at birth and this number decreases further to approximately 40 000 by puberty.

In the term infant, the uterus is about 3–5 cm long and the cervix forms two-thirds or more of its length (Fig. 3.6). Female newborns have a relatively prominent clitoris and labia and the vagina, which is about 3 cm in length, is relatively thick-walled with a fleshy hymen. After withdrawal of maternal hormones, the uterus and vagina shrink in size.

MUSCULOSKELETAL SYSTEM

Skull and face

The skull vault is formed by intramembranous ossification, the facial skeleton is derived from neural crest membrane bones, and the skull base and some bony pharyngeal arch derivatives (e.g. hyoid bone and ossicles) by endochondral ossification.[3] During birth, the margins of the frontal and parietal bones are able to slide over each other. In the first 2 days of life, palpable over-riding of the bones of the vault is common. Persistent ridging of suture lines may indicate craniosynostosis. Growth at the coronal suture is mostly responsible for fronto-occipital expansion of the skull; premature fusion causes brachycephaly if bilateral and plagiocephaly if unilateral. Growth at the metopic and sagittal sutures increases skull breadth, the metopic suture fusing at around 18 months of age and the sagittal at puberty. Premature fusion produces the elongated skull of sagittal craniosynostosis, the most common form of craniosynostosis. Premature babies have a tendency to develop a long thin head (dolichocephaly) secondary to postnatal gravitational molding but this is not caused by premature sutural fusion.

Fontanelles are formed where several skull vault bones meet. The two most prominent are the anterior fontanelle overlying the superior sagittal venous sinus at the junction of the metopic and sagittal sutures (bregma), and the posterior fontanelle at the junction of the sagittal and lambdoid sutures (lambda).[36] The size of the anterior fontanelle at birth is very variable; if unduly large, it may be an indication of congenital hypothyroidism or a skeletal disorder.[37] The timing of closure is also variable but the anterior fontanelle is obliterated by two years of age in 95% of children[38] and the posterior by two months of age.[39]

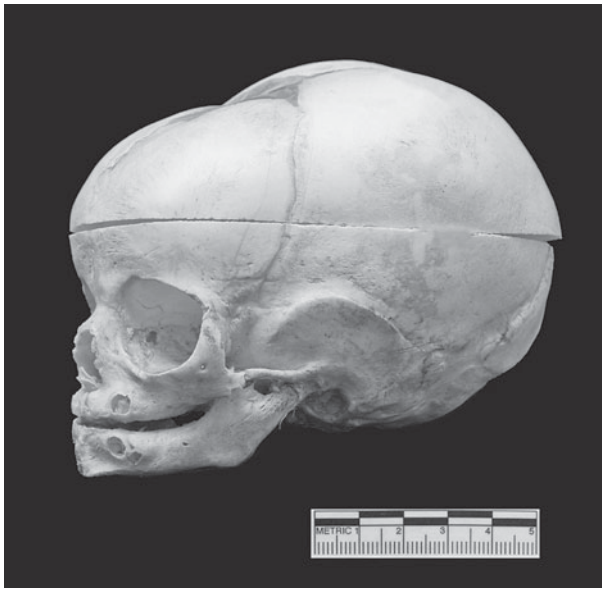
Postnatal growth of the skull vault is accompanied by disproportionate growth of the facial skeleton and mandible (Fig. 3.7). At birth, the bony external ear canal is poorly developed and the mastoid process is absent. The facial nerve is therefore more at risk of injury where it emerges from the stylomastoid foramen (e.g. from obstetric forceps). At birth, the two halves of the mandible are united by a symphysis that fuses in early childhood. The rami are at a more obtuse angle to the body of the mandible. The mandible subsequently changes shape as the teeth erupt and the muscles of mastication and chin develop.

The maxillary and ethmoid sinuses are present at birth but the sphenoid sinus is poorly developed and the frontal sinuses are absent.[19] The auditory tube is almost horizontal, increasing the risk of middle ear disease; it becomes more vertical during childhood. The hard palate is short, only slightly arched, and ridged by transverse folds which assist with suckling. The nasolacrimal duct which drains tear secretions from the conjunctival sac to the inferior meatus of the nasal cavity is relatively short and wide at birth but may be obstructed due to incomplete canalization. This can cause excessive tearing, discharge, and infection.

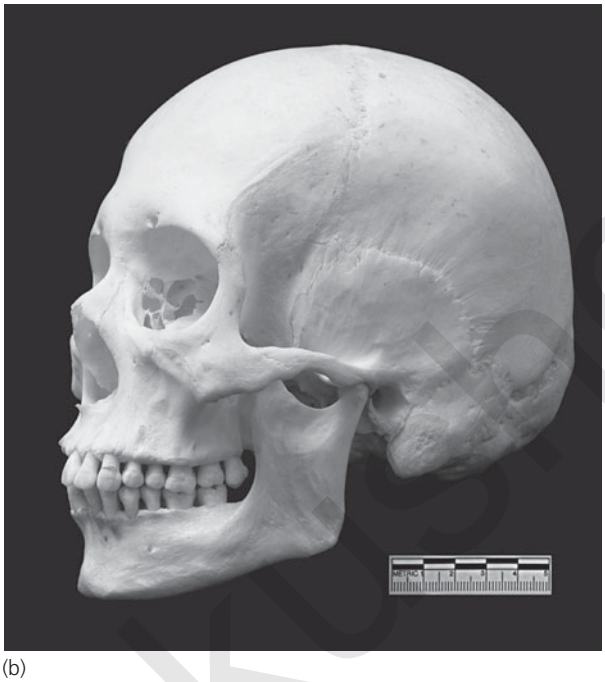
Vertebral column, pelvis, and limbs

The vertebral column in the neonate has no fixed curvatures other than a mild sacral curve. After birth, the thoracic curvature develops first and then, as the infant learns to control its head, sit, stand and walk, curvatures in the lumbar and cervical spine develop which help to maintain the centre of gravity of the trunk when walking. The sacral promontory 'descends' and becomes more prominent. Hemopoiesis occurs in the liver, spleen, and bone marrow in the fetus, but is largely restricted to the bone marrow of the vertebrae, ribs, sternum, proximal long bones, and diploe of the skull after birth.

Of the 800 or so ossification centers in the human skeleton, just over half appear after birth; these include most secondary ossification centers (Fig. 3.8). Cartilage is abundant at birth. None of the carpal bones have ossification centers. The only secondary centers of ossification in the long bones at birth are in the femoral and tibial condyles and humeral head.[19] The iliac crest, acetabular floor, and ischial tuberosity are all cartilaginous.



(a)



(b)

Figure 3.7 Comparison of a neonatal (a) and adult male (b) skull. Note the relatively small size of the face and mandible in the neonate, the cranial vault sutures and the anterior fontanelle. The mastoid process has not developed at birth. Courtesy of the WD Trotter Anatomy Museum, University of Otago.

The acetabulum is relatively large and shallow at birth and has a characteristic Y-shaped triradiate cartilaginous epiphyseal plate between the ilium, ischium, and pubis. Nearly one-third of the neonatal femoral head lies outside the acetabulum, making the hip joint easier to dislocate. Developmental dysplasia of the hip affects about one in 100 live births and is more common in girls. The neonatal femoral neck is short and the femoral shaft is straight. The proximal femoral growth plate in early infancy is intra-articular so that

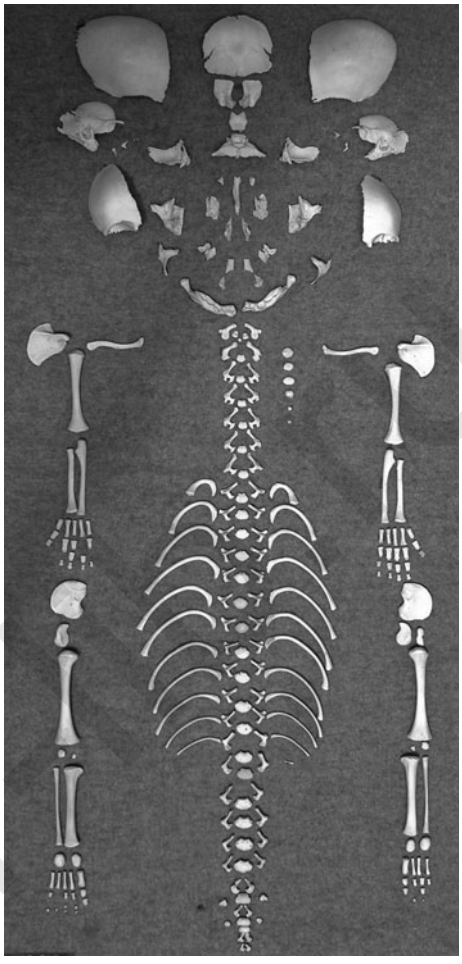


Figure 3.8 The bony skeleton of a newborn baby. There are no carpal bones at birth, there are separate ossification centers for the hip, and secondary centers of ossification in the long bones are absent except for the lower end of the femur and upper end of tibia. Specimen prepared by Professor JH Scott in 1895. Courtesy of the WD Trotter Anatomy Museum, University of Otago.

infection in the proximal femoral metaphysis may cause a septic arthritis. The lower limb muscles in the newborn are relatively underdeveloped and the gluteal muscle mass is small. The thighs tend to be abducted and flexed, the knees flexed, and the foot dorsiflexed and inverted. In congenital talipes equinovarus (club foot), there is impaired development of the talus causing inversion and supination of the foot and adduction of the forefoot.

NERVOUS SYSTEM

At term, the neonatal brain weighs between 300 and 400 g, accounting for about 10% of body weight (compared to 2% in the adult).[19] Brain growth is especially rapid during the first year, when it reaches 75% of its adult volume. The number of neurones is already established at birth and brain growth is due to an increase in size of nerve cell bodies, further development of neuronal connections, proliferation of neuroglia and blood vessels, and myelination of axons.

Myelination is at its peak in the first six months of life but continues until maturity.[3] The arrangement of sulci and gyri at birth is similar to the adult, although the central sulcus is slightly further forward and the ventricles are proportionately larger. Mean head circumference at term is 34 cm.

The termination of the spinal cord in the neonate may reach as low as L3 whereas it is usually around the lower border of L1 in the adult. The supracristal plane between the tops of the iliac crests is slightly higher (L3/4 rather than L4); a lumbar puncture in the newborn should not be performed above this level.

SKIN AND SUBCUTANEOUS TISSUE

Body fat is laid down in the fetus from about 34 weeks' gestation and, with appropriate intrauterine nutrition, increases until term. Plantar fat pads give the neonate a flat-footed appearance. Brown fat is a modified form of adipose tissue concentrated at the back of the neck, in the interscapular region, and in pararenal areas. It is composed of adipocytes with mitochondria that have large and numerous cristae adapted for heat production. However, the neonate's ability to regulate temperature is poorly developed.

At birth, breast tissue is similarly developed in girls and boys. It may appear prominent due to the influence of maternal hormones, even leading to the secretion of a small amount of fluid (witch's milk). Supernumerary nipple(s) may be found along the mammary ridges (milk lines) which extend from the axilla to the groin.

Neonatal skin is relatively thin but the ability to see peripheral veins is very dependent on the thickness of the subcutaneous tissues. Common sites for peripheral venous cannulation (and long line access) include: the dorsal arch veins of the hands and feet; the cephalic vein at the wrist; the volar aspect of the wrist (where the veins are small and fragile); the cubital fossa; the saphenous vein immediately anterior to the medial malleolus or behind the medial aspect of the knee; and the superficial temporal vein anterior to the ear.

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4

The epidemiology of birth defects

EDWIN C JESUDASON

INTRODUCTION

Globally, birth defects are emerging as a leading cause of infant death. During the last century, surgical correction of such defects helped define the new specialty of pediatric surgery. In the same era, congenital rubella syndrome and the thalidomide disaster promoted the epidemiological investigation of birth defects and established the field of teratology. In the twenty-first century, improved birth defects surveillance can help delineate the causes of unsolved anomalies, improve fetal counseling (and therapy), identify anomaly associations (that illuminate both management and underlying developmental biology) and facilitate outcomes comparison by appropriate classification of surgical caseload.

BIRTH DEFECTS HELPED DEFINE PEDIATRIC SURGERY

The surgical correction of birth defects helped create the specialty of pediatric surgery during the middle of the last century. Around this time, pioneering neonatal operations were successfully performed to allow survival of babies with, for example, esophageal atresia or congenital diaphragmatic hernia (CDH). Indeed, along with innovations such as parenteral nutrition, the concentration of surgical, anesthetic, nursing, and critical care expertise now allows high survival to be achieved for many previously fatal anomalies. Moreover, for certain conditions that retain high mortality and/or morbidity, fetal surgery represents a promising experimental procedure to further reduce the harm of birth defects. Given these successes it would be tempting to assume that the problem of birth defects was largely solved.

BIRTH DEFECTS ARE LEADING CAUSES OF GLOBAL INFANT MORTALITY

However, given the huge progress made against infectious disease in particular, birth defects are now emerging as a leading cause of infant mortality. Moreover, this state of affairs pertains not only to places with expensive healthcare systems but in fact anywhere that infant mortality rates have fallen below about 50 per thousand births.[1] Hence, as progress against other infant killers continues, it is likely that birth defects will gradually become one of the most significant global causes of infant mortality. In addition, birth defects are a leading contributor to both premature birth (itself a major cause of infant mortality) and chronic disability (with its substantial personal and societal costs). Tragically, many such problems are already preventable: for example, the birth defects associated with congenital rubella syndrome might be virtually eradicated by an effective program of maternal immunization.[2] Moreover, a subset of neural tube defects continue to occur due to inadequate implementation of preconceptual folate prophylaxis.[3,4] However, the epidemiological challenges for clinicians extend beyond the known, preventable defects to unsolved conditions and their changing circumstances (e.g. increased gastroschisis prevalence, Fig. 4.1).[5,6]

BIRTH DEFECTS EPIDEMIOLOGY AND TERATOLOGY EMERGED FROM OUTBREAK INVESTIGATION

With birth defects emerging as leading infant killers, the need for epidemiological investigation of birth defects is increasing. Although birth defects have been described with horror and fascination since antiquity, teratology and scientific birth defects epidemiology date, like pediatric surgery, from the mid-twentieth century. Key historical developments include the recognition of congenital rubella syndrome (noted by clinical ophthalmological examination) and the thalidomide disaster (phocomelia and other defects associated with maternal thalidomide administration for morning sickness).[7,8] These episodes vividly illustrated the devastating consequences of prenatal infection and drug exposure, respectively. Moreover, these chastening experiences highlighted the urgent need to formalize birth defects

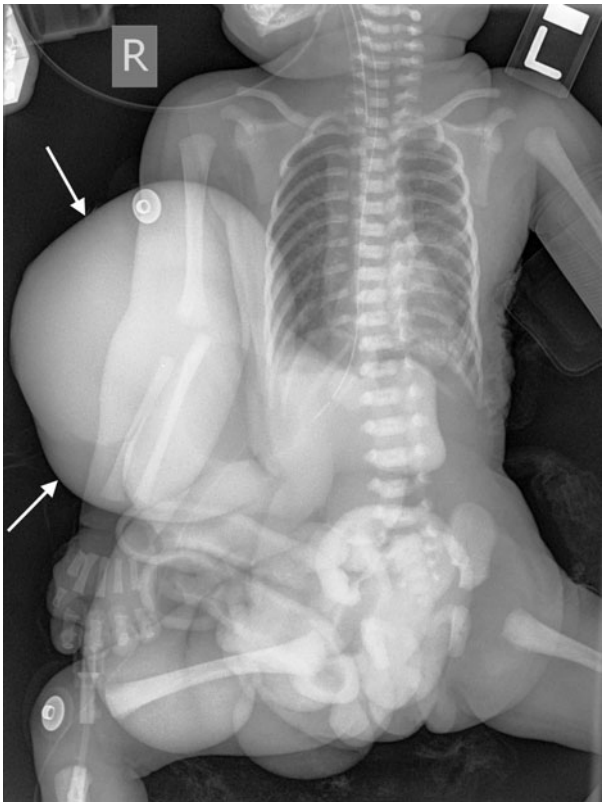

Figure 4.1 Gastroschisis – a birth defect on the move? Data from birth defect registries indicate an unexplained increase in gastroschisis prevalence. It remains to be seen if the severity of gastroschisis is also increasing: in this severe and unusual example, in addition to the gut, the liver (arrowed) lies outside the neonatal abdomen. Furthermore, the thorax is narrowed; this child needed ventilation immediately from birth (image used courtesy of the author).

surveillance. Such birth defects monitoring can now be said to serve a range of important purposes including outbreak early-warning, identification of possible environmental or genetic causes, rational planning for neonatal surgical provision, facilitation of prenatal counseling based on accurate data, establishment of associations between birth defects (that guide management and yield clues as to underlying developmental biology) and comparison of outcomes (that thereby guide us toward best practice).[9]

CAUSATION OF BIRTH DEFECTS REMAINS OFTEN COMPLEX AND UNCERTAIN

Before considering the methods of birth defects surveillance, it is worth sketching the developmental biology that underpins birth defects from a surgeon's perspective.[10] Causes of birth defects can be classified as parental, fetal, and environmental. An example of the former includes the impact of maternal age on Down syndrome prevalence.[11] Alternatively, maternal diseases such as diabetes are well-described risk factors for birth defect formation.[12] The role of paternal age and/or exposures remain more difficult to clarify.[13] Fetal causes might include genetically determined inborn errors of metabolism such as those causing intersex anomalies in congenital adrenal hyperplasia, chromosomal lesions such as Edwards etc., and twinning (with its increased risk of birth anomalies). Environmental causes include those related to prenatal drug exposure (alcohol, smoking, illicit drugs, thalidomide, valproate, phenytoin, warfarin, etc.) as well as the impact of intrauterine infections (e.g. toxoplasmosis, rubella, cytomegalovirus).[14–16] The impact of assisted reproductive technologies such as *in vitro* fertilization and intracytoplasmic sperm injection on birth defects prevalence are actually quite difficult to assess.[17] Suggestions that anomaly rates are higher in such assisted pregnancies need to contend with the confounding increased rates of multiple pregnancy. Also, given the parents need to use assisted reproductive technology, it may be that they are importantly different to parents conceiving naturally: increased anomaly risk could therefore be due to parental abnormality/predisposition rather than a result of the techniques themselves. More controversially still, other environmental contributors to birth defects may include 'endocrine disrupters': these estrogenic compounds are conjectured to contribute to anomalies of sexual development in fetal males (e.g. hypospadias) as well as putative impairment of adult male sperm quality.[16] In light of such difficulties in attributing cause, it is beneficial to recognize that only the minority of birth defects are known to arise from a simple genetic or environmental cause. At present, the remainder appear to have multifactorial origins: in such circumstances it is helpful to consider birth defect causation as the result of complex interactions between genes and environment. Hence many cases of spina bifida may result from micronutrient deficiency in the context of predisposing enzyme polymorphisms.[18] Similarly, teratogenic drugs may interact with pharmacogenomic predispositions to help explain why certain pregnancies are affected.[19] Beyond considerations of even complex causation, it remains likely that simple chance has a major role to play (similar to stochastic effects seen in radiation biology).[20]

BIRTH DEFECTS APPEAR TO ARISE TYPICALLY (BUT NOT EXCLUSIVELY) IN THE FIRST TRIMESTER

Developmental biologists refer to 'competence windows' to describe periods in development when particular cells and tissues are capable of responding appropriately to certain growth and transcription factors.[21] In a similar manner, developing organs are contended to have particular temporal windows when an otherwise nonspecific teratogenic stimulus will impact disproportionately on formation of that organ system. During the first trimester, organ morphogenesis predominates while later trimesters are devoted to organ growth and maturation. Unsurprisingly, therefore, sensitivity to teratogens is held to peak during the first trimester. Hence pregnant women are advised to avoid medications during this part of gestation in particular. Teleologically, 'morning sickness' that peaks during the first trimester is postulated to help reduce ingestion of potential teratogens during this period of maximum vulnerability. While the model of first

trimester teratogenesis appears appropriate for many birth defects, it is now clear that certain anomalies may arise during later development as a result of fetal events, for example amniotic band formation, intussusceptions, or vascular accident. Gastroschisis and intestinal atresiae may be considered in this latter category.[22–24] Indeed the contrast between exomphalos and gastroschisis in terms of associated anomalies (and hence prognosis) can be considered due to the different times they are usually held to originate in development. Exomphalos is considered an embryonic lesion that is accompanied by contemporaneous lesions of organogenesis in other systems such as the heart. In contrast, like associated intestinal atresiae, gastroschisis is thought to result from a discrete fetal vascular accident and hence lack extraintestinal manifestations. An alternative view, however, is that intestinal atresiae result only rarely from fetal accidents such as intussusception and are in fact better understood as failures of mesenteric vascular development.[25] A similar contrast between duodenal atresia and small bowel atresia may be likewise understood as the result of their differing onsets and etiologies. Duodenal atresia was historically explained as an embryonic failure of luminal recanalization; although this 'solid core' theory has been contradicted by more recent animal studies, the association between duodenal atresia and other defects (e.g. cardiac lesions, oesophageal atresia, and Down syndrome) supports an embryonic origin of this malformation.[26,27] In contrast, small bowel atresiae are claimed to follow mesenteric vascular occlusion usually in fetal life.[28] Hence, aside from gastroschisis, associated structural lesions are unlikely. Between these two 'extremes' are birth defects where an embryonic lesion has deleterious 'knock-on' effects later in fetal development: based on experimental models, the neurological sequelae of spina bifida are postulated to result from not only the primary failure of neural tube closure but also from consequent exposure of the neural placode to amniotic fluid.[29] Similarly, lung hypoplasia in CDH may emerge as an embryonic lesion prior to CDH only for compression by the visceral hernia to exacerbate the pulmonary lesion.[30] In circumstances such as these, where the pathology is thought to progress during fetal life, prenatal surgical correction has been a logical proposal to meet the challenge of refractory mortality and morbidity.[31] Results of ongoing clinical trials in these areas are awaited.

CLASSIFICATION OF BIRTH DEFECTS FOR EPIDEMIOLOGICAL PURPOSES

Birth defect epidemiology involves the registration of anomalies by type. At present, birth defects registries such as the European Surveillance of Congenital Anomalies (EUROCAT), use a classification scheme based around organ systems (see Table 4.1), specific diagnoses, and International Classification of Diseases (ICD) codes (see Table 4.2: both tables are derived from data published by EUROCAT – www.eurocat.ulster.ac.uk/pubdata/tables.html). Cooperation between registries helps by pooling data and also by building consensus on, for example, exclusion of minor anomalies without major and/or long-term sequelae (e.g. cryptorchidism or congenital hydrocele) or how abnormalities of gut fixation in CDH might be recorded. Although anomalies are currently classified by structural anomaly (e.g. CDH, esophageal atresia) or defined diagnosis (e.g. Down syndrome), it is likely that in the future, anomalies may be classified or at least subgrouped by genotypic differences rather than anatomic details alone. Such distinctions may be prognostically and therapeutically important: for example, in contrast to isolated omphaloceles, exomphalos in Beckwith–Wiedemann syndrome is associated with hypoglycemia, macrosomia, and increased tumor risk due to disordered gene imprinting.[32] Hence the anatomic defect (exomphalos) becomes less important than the genetics and its multisystem sequelae. Similarly, it is postulated that subgroups of spina bifida may be folate resistant due to underlying genetic/enzymatic variation.[18,33] Designing preconceptual prophylaxis for birth defects may need to acknowledge pharmacogenomically distinct subgroups to avoid benefits within one subgroup being overlooked due to a larger surrounding non-responder cohort.

Table 4.1 Birth prevalence of malformations 1980–2007 grouped by EUROCAT category. Note rates for each category are inclusive of cases with chromosomal lesions and derived from registries with full EUROCAT membership.

Organ system	Live birth + fetal death + termination/10 000 births (to 2 s.f.)
All	220
Congenital heart disease	67
Limb	42
Chromosomal	31
Urinary	28
Nervous system	23
Digestive system	19
Genital	16
Oro-facial clefts	15
Musculo-skeletal	11
Other malformations	10
Respiratory	5.7
Abdominal wall defects	4.9
Genetic syndromes + microdeletions	4.8
Eye	4.6
Ear, face, neck	4.1
Teratogenic syndromes with malformations	1.1

Having a system of classification is, however, only part of the task. Notification and classification in practice are subject to local variations. When resources exist for expert-mediated classification of birth defect by diagnosis, this approach to birth defects epidemiology appears the best currently available.[34] However, even some North American registries lack clinician input in the classification/assignment of observed birth defects. The consequence(s) of this omission for data quality remain to be determined. In the contrasting circumstances of rural China, expert-led assignment of cases has been substituted by simple photographic recording of

Table 4.2 Birth prevalence of malformations of relevance to pediatric surgery (1980–2007) grouped by diagnosis from registries with full EUROCAT membership. Note rates for each category are inclusive of cases with chromosomal lesions; (b) these are birth prevalences (including fetal death/terminations) and not necessarily the prevalences at pediatric surgical units.

Anomaly	Live birth + fetal death + termination/10 000 births
Down	18
Hypospadias	13
Congenital hydronephrosis	8.9
Spina bifida	5.3
Edward's	3.8
Anorectal malformations	3.0
Diaphragmatic hernia	2.8
Exomphalos	2.7
OA/TOF	2.3
Gastroschisis	1.9
Bilateral renal agenesis	1.6
Duodenal atresia/stenosis	1.2
Hirschsprung's disease	0.94
Posterior urethral valves/ prune belly	0.87
Indeterminate sex	0.76
Intestinal atresia/stenosis	0.75
Bladder extrophy/ epispadias	0.58
CCAM	0.56
Situs inversus	0.56
Amniotic band	0.46
Biliary atresia	0.28
Conjoined twins	0.18

malformations: this system allows the registry to function but also allows difficult cases to be assigned later after remote assessment of images by experts.[35] In addition, the photographs potentially allow the classifiers to calibrate their judgments against those from other registries.

COUNTING OF BIRTH DEFECTS IS AFFECTED BY THE DEFINITION OF STILLBIRTH

Birth defects epidemiology becomes difficult whenever the classification of defects is not uniform or straightforward. However, an equal challenge remains the counting of birth defects. This task is complicated by practical barriers to case ascertainment (e.g. inadequate resources), the definition of stillbirth and the effects of prenatal diagnosis and terminations.

Recording of anomaly prevalence lies at the core of birth defects epidemiology. To account for the unknowable incidence of a defect among vast numbers of naturally miscarried pregnancies, epidemiologists measure the prevalences of defects within a defined birth cohort; i.e. the number of live and stillborn cases of the defect, as a proportion of all births (live and stillborn). This definition depends on the artificial distinction between miscarriage and stillbirth: EUROCAT's recommendation is that spontaneous pregnancy losses prior to 20 weeks' gestation are counted as miscarriages (and do not contribute to anomaly prevalence) while similar losses at 20 weeks of gestation and beyond are counted as stillbirths (and included in prevalence statistics). Despite these guidelines, several countries have established different demarcations (e.g. 24 or 28 weeks or even 500 g weight). Clearly some estimate of prenatal birth defects is required to avoid seriously underestimating overall prevalences.[36] However, the demarcation of stillbirths begins to complicate matters. Countries where later gestational cut-off points are used may underestimate birth defect prevalence compared to registries where 20 weeks is used. Hence minor changes in convention can lead to large but artificial differences in anomaly prevalence.

While a definition of stillbirths is needed for data collection, the sharp demarcation (whether 20 weeks or later) also appears arbitrary from a biological perspective. Consider a hypothetical prenatal medical therapy that reduces the prevalence of a specific birth defect. When the anomaly is rare (as most are), it may be difficult to determine whether an observed reduction in prevalence is truly due to fewer malformations or is instead due to the promotion of earlier loss of affected pregnancies (i.e. prior to the 20 week or other agreed margin). This latter phenomenon, termed 'terathanasia', has even been invoked to explain how folate supplementation reduces neural tube defect prevalence.[37]

Prenatal diagnosis: the greatest challenge to birth defect epidemiology?

While classification of birth defects and definition of stillbirth make anomaly surveillance complex, the impact of prenatal diagnosis is arguably still more important. Prenatal diagnosis (in particular nonspecific ultrasound screening) confounds birth defects surveillance in a number of ways: (1) it increases identification of birth defects within the cohort of assessment (still and liveborn) by diagnosing those who may otherwise have perished prenatally (and uncounted), or those who may have presented beyond the neonatal period (if at all). Consider prenatal identification of cystic lung lesions: some would never have been diagnosed (either regressing spontaneously or persisting asymptomatically) while even symptomatic lesions would often have presented later (beyond the scope of the birth defects registry); (2) prenatal diagnosis alters antenatal management and results in terminations (or fetal intervention) that affect the numbers of birth defects being counted; most registries therefore attempt to keep separate data on terminations for birth defects. However, where prohibitions on termination exist, such data becomes still harder to find; (3) prenatal diagnosis may be inaccurate but unchecked: pathological verification after termination may be incomplete or absent yet the diagnosis is included in the birth defect tally; (4) resources and expertise to perform prenatal sonography vary with location (thereby hampering national and international comparison of birth defects prevalences). In summary, therefore, the apparently simple task of counting live and stillborn cases for

birth defects surveillance is fraught with difficulty once (a) the arbitrary definition of stillbirth is imposed and (b) ubiquitous prenatal imaging prompts both terminations and identification of previously occult 'cases'.

Given these challenges in data collection, epidemiologists are aided by being able to compare a variety of surveillance databases. Many European registries are incorporated into the EUROCAT initiative. Similarly several other registries feed into birth defects surveillance data furnished by the World Health Organization (WHO). Their Birth Defects Atlas is an interesting publication available in the public domain (www.who.int/genomics/publications/en/). Most importantly, it is instructive to read and consider the caveats that EUROCAT and WHO place upon their data. The interpretational issues raised highlight not only the problems discussed in the previous sections but also allude to the ongoing challenge of inadequate resources and expertise for birth defects reporting. This in turn impairs the data accuracy and may help explain insufficient action upon findings. Recent papers in the *British Medical Journal* reinforce the logistical shortcomings of birth defects reporting in the UK.[38]

PEDIATRIC SURGEONS OFTEN REPORT INSTITUTIONAL SERIES OF BIRTH DEFECTS

Given the difficulties in collecting and interpreting data from population-based registries, it should come as no surprise that similar issues afflict institutional series that are the staple of pediatric surgeons' reporting. Again, ascertainment is the most significant problem: prenatal diagnosis, terminations, or deaths prior to transfer of high-risk cases can give the misleading impression that changed institutional practice is impacting on outcome (when in fact it is pre-institutional interventions that are changing the results). Moreover, pediatric surgeons like to estimate disease severity in their cohort to show that their (good) results are not simply the product of low-risk caseload (Fig. 4.2). However, in such circumstances it can be highly misleading to use the frequency of interventions (e.g. decision to patch and/or use extracorporeal membrane oxygenation (ECMO) or nitric oxide in CDH) to estimate severity in a birth defect cohort: use of these techniques may in fact owe more to institutional protocols rather than any pathophysiological differences between cases. A number of studies have highlighted that institutional series remain subject to biases and confounding.[39–41]

THE CHALLENGE FOR MODERN PEDIATRIC SURGERY

Despite its confounding influence on modern birth defects surveillance, the impact of prenatal diagnosis will not disappear. On the contrary, advances in prenatal imaging may only serve to identify more 'defects' of unknown significance. Moreover, functional fetal imaging and genotyping may evolve to allow better prenatal prognostication and hence case selection for future fetal therapies.[42] In the midst of all these potentially exciting developments, pediatric surgeons retain a key role: using the best available birth defects epidemiology, we may gradually learn which defects need what intervention and when. To achieve this, pediatric surgeons need to keep abreast of birth defects epidemiology and work collaboratively with other surgeons, perinatologists, obstetricians and public health physicians. As a model for such cooperative endeavors, the Children's Cancer Leukemia Group (CCLG) is led by collaborating pediatric oncologists and surgeons: they achieve remarkably high recruitment rates of pediatric cancer cases into multicenter trials that are helping transform clinical management. A similar consortium approach to birth defects and their surgical correction may allow pediatric surgeons to retain a central role in this evolving field. As a beginning, the British Association of Paediatric Surgeons Congenital Anomalies Surveillance System (BAPS-CASS) and the National Perinatal Epidemiology Unit are undertaking an annual UK census of a selected birth defect for each year. Hence, as birth defects emerge as the leading cause of infant mortality, such projects will establish how pediatric surgeons can work together to understand these human healthcare problems.

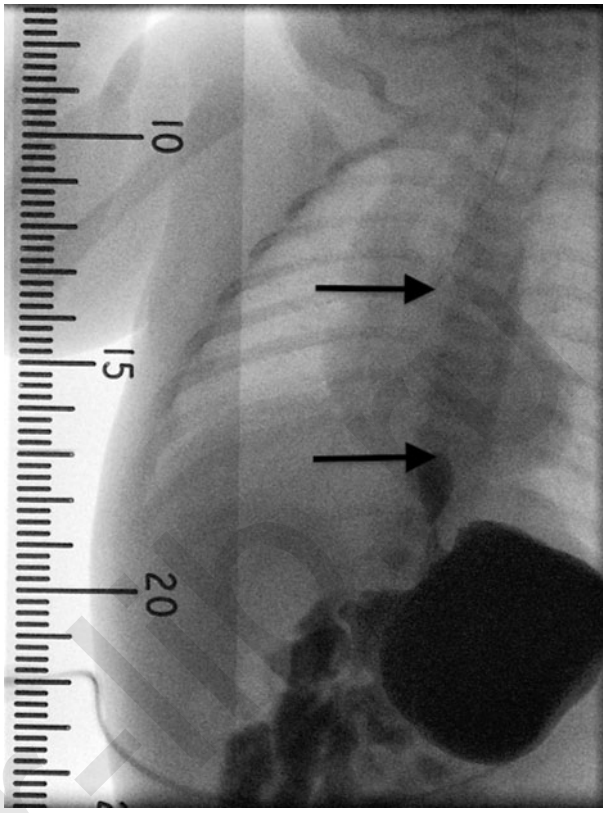

Figure 4.2 Birth defect registries and disease severity. Birth defect registries generally do not distinguish anomaly severity (despite implications for service provision and outcome measures). This gap assessment x-ray for pure esophageal atresia (EA) shows the tip of the oral tube pressed down (upper arrow) and refluxed contrast in the distal pouch (lower arrow). Treated by the author with a single-stage 'Bax' jejunal interposition at 7 weeks of age, this anomaly is registered just like the more common EA with distal fistula, despite the very different management and resources required.

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5

Perinatal diagnosis of surgical disease

TIPPI C MACKENZIE AND N SCOTT ADZICK

INTRODUCTION

Prenatal diagnosis has undergone an explosion of growth in the past decade. The primary impetus for this rapid expansion has come from the widespread use of prenatal ultrasonography. Most correctable malformations that can be diagnosed *in utero* are best managed by appropriate medical and surgical therapy after maternal transport and planned delivery at term. Prenatal diagnosis may influence the timing (Box 5.1) or the mode (Box 5.2) of delivery, and in some cases, may lead to elective termination of the pregnancy. In rare cases, various forms of *in utero* therapy may be possible (Table 5.1).

Prenatal diagnosis has defined a 'hidden mortality' for some lesions such as congenital diaphragmatic hernia, bilateral hydronephrosis, sacrococcygeal teratoma, and cystic hygroma. These lesions, when first evaluated and treated postnatally, demonstrate a favorable selection bias. The most severely affected fetuses often die *in utero* or immediately after birth, before an accurate diagnosis has been made. Consequently, such a condition detected prenatally may have a worse prognosis than the same condition diagnosed after delivery.[1] The perinatal management of the patients involves many different medical disciplines, including obstetricians, sonographers, neonatologists, geneticists, pediatric surgeons, and pediatricians. It is essential that the affected family be managed using a team approach, and that information and experience be exchanged freely.

In this chapter we discuss the prenatal diagnosis of neonatal surgical lesions. First, a brief summary of the diagnostic methods currently available is given, then a review of prenatal diagnosis by organ system is presented.

Box 5.1 Defects that may lead to induced preterm delivery

- Obstructive hydronephrosis
- Gastroschisis or ruptured omphalocele
- Intestinal ischemia and necrosis secondary to volvulus, meconium ileus, etc.
- Sacrococcygeal teratoma with hydrops

Box 5.2 Defects which may require cesarian delivery

- Myelomeningocele
- Giant omphalocele
- Large sacrococcygeal teratoma
- Giant neck masses or lung lesions (EXIT procedure)

Table 5.1 Diseases amenable to fetal surgical intervention in selected cases.

Malformation	Effect on development	*In utero* treatment
Congenital diaphragmatic hernia	Pulmonary hypoplasia, respiratory failure	Tracheal occlusion and release
CCAM or BPS	Pulmonary hypoplasia, hydrops	Thoracoamniotic shunting, lobectomy, steroids
Sacrococcygeal teratoma	Massive arteriovenous shunting, placentomegaly, hydrops	Excision
Urethral obstruction	Hydronephrosis, lung hypoplasia	Vesicoamniotic shunting, laser ablation of PUV
Myelomeningocele	Damage to spinal cord, paralysis	Closure of defect

ULTRASOUND

Ultrasound testing has become a routine part of the prenatal evaluation of almost all pregnancies. It is especially important to perform ultrasound for pregnancies with maternal risk factors (e.g. age over 35 years, diabetes, previous child with anatomic or chromosomal abnormality) and if there is an elevation in maternal serum alphafetoprotein (MSAFP). Most defects can be reliably diagnosed in the late first or early second trimester by a skilled sonographer. Nuchal translucency measurements are an independent marker of chromosomal abnormalities, with a sensitivity of about 60%.[2] This abnormality may be detected on transvaginal ultrasound at 10–15 weeks' gestation, thus providing an early test for high-risk pregnancies. Nuchal cord thickening may also be a marker for congenital heart disease[3] and may be a valuable initial screen to detect high-risk fetuses for referral for fetal echocardiography. It is important to remember that sonography is operator-dependent; the scope and reliability of the information obtained is directly proportional to the skill and experience of the sonographer.

MAGNETIC RESONANCE IMAGING

Until recently, the long acquisition times required for magnetic resonance imaging (MRI) were not conducive to fetal imaging because fetal movements resulted in poor quality images. Obtaining adequate images with the traditional spin-echo techniques required fetal sedation or paralysis.[4] With the development of ultrafast scanning techniques, the artifacts caused by fetal motion have almost been eliminated.[5] This technique is now an important part of prenatal evaluation of fetuses referred to our institution and has greatly enhanced our ability to diagnose and treat fetal malformations.

AMNIOCENTESIS

The first report of the culture and karyotyping of fetal cells from amniocentesis was by Steele and Breg in 1966.[6] Since then, it has become the gold standard for detecting fetal chromosomal abnormalities by karyotyping. It is usually performed at 15–16 weeks' gestation and involves a very low risk of fetal injury or loss. Attempts at early amniocentesis (11–12 weeks' gestation) have been complicated by a higher pregnancy loss, increased risk of iatrogenic fetal deformities, and increased postamniocentesis leakage rate.[7] For this reason, the most reliable method for first trimester diagnosis remains chorionic villus sampling. Our ability to detect particular mutations associated with single gene disorders as well as syndromes such as 22q deletion continues to improve.

CHORIONIC VILLUS SAMPLING

Chorionic villus sampling (CVS) may be performed at 10–14 weeks' gestation and involves the biopsy of the chorion frondosum, the precursor for the placenta. Either a transcervical or transabdominal approach may be used, both under ultrasound guidance. The cells obtained may be subjected to a variety of tests including karyotype, genetic probes, or enzyme analysis. Due to the high mitotic rate of the chorionic villus cells, results for karyotyping may be obtained in less than 24 hours. Disadvantages include diagnostic errors due to maternal decidual contamination or genetic mosaicism of the trophoblastic layer of the placenta. When preformed by experienced operators, the pregnancy loss rate is equivalent to second trimester amniocentesis.[8]

BIOCHEMICAL MARKERS

Maternal blood and amniotic fluid can be screened for the presence of various biochemical markers that indicate fetal disease. About two-thirds of women in the United States currently undergo screening for Down syndrome and other chromosomal abnormalities with the 'triple test,' which includes measuring serum alpha-fetoprotein with human chorionic gonadotropin and unconjugated estriol.[9] This screening is performed in the early second trimester, and the detection rate for Down syndrome is 69%, with a 5% false positive test.[10] A positive result on the serum screening test indicates a need for chromosome analysis by amniocentesis.

PERCUTANEOUS UMBILICAL BLOOD SAMPLING

Obtaining umbilical venous blood can also be used to determine the karyotype and diagnose various metabolic and hematological disorders. The procedure is performed at around 18 weeks' gestation under ultrasound guidance. Karyotype results may be obtained within 24–48 hours. In various large series, the mortality from the procedure has been reported to be 1–2%, with increasing mortality with long procedure times and multiple punctures.[11–13]

FETAL CELLS IN THE MATERNAL CIRCULATION

Since the advent of fluorescence-activated cell sorting (FACS), there has been growing interest and progress in detecting circulating fetal cells or cell-free nucleic acids in maternal blood for diagnostic purposes.[14] While the number of intact cells in the circulation is limited, amplification of fetal cell-free nucleic acids using real-time polymerase chain reaction (PCR) has growing utility in early prenatal diagnosis.[15] Fetal DNA can be detected reliably by 9 weeks and increases with gestational age.[16] This method can be used for gender determination in the first trimester (if Y chromosome sequences are found the fetus is male and if not, is assumed to be female) and can thus be helpful in counseling for X-linked disorders. Rhesus factor determinations are also accurate and can avoid unnecessary treatment of Rh-negative mother if the fetus is also negative. In the future, it may be expanded to detecting paternally inherited single gene

mutations. Although this is an extremely promising area of investigation, there are currently significant limitations in distinguishing fetal from maternal DNA. Therefore, invasive testing remains the standard of care for prenatal diagnosis of aneuploidies and other genetic abnormalities.

PRENATAL DIAGNOSIS OF SPECIFIC SURGICAL LESIONS

Neck masses

Fetal airway obstruction could be a result of extrinsic compression of the airway by lesions such as cervical teratoma or cystic hygroma, or intrinsic defects in the airway such as congenital high airway obstruction syndrome (CHAOS). Although large congenital neck masses causing airway obstruction previously carried an enormous perinatal mortality,[17] the advent of the *ex utero* intrapartum treatment (EXIT) procedure[18,19] has improved their outcome by providing a means of controlling the airway during delivery and converting an airway emergency into an elective procedure (Fig. 5.1).

Cystic hygroma diagnosed *in utero* is a severe diffuse lymphatic abnormality which is frequently associated with hydrops, polyhydramnios, and other abnormalities.[20] Chromosomal abnormalities are very common (62% overall) with the most common being Turner's sydrome.[21] There are two groups of prenatally diagnosed cervical lymphangiomas: those diagnosed in the second trimester are usually in the posterior triangle of the neck, have a high incidence of associated abnormalities, and carry a very poor prognosis.[22] Those diagnosed later in gestation are most often isolated lesions and generally do not lead to hydrops. Hydrops is an ominous finding in fetuses with cystic hygroma,[17] as is the presence of aneuploidy and septations in the mass.[23] However, fetuses with normal karyotype, non-septated masses, and no evidence of hydrops may have a good prognosis.[24] Therefore, it is important to monitor the fetus for development of hydrops by serial evaluations. Some fetuses with neck masses also have severe pulmonary hypoplasia with its attendant morbidities and this possibility should be addressed during prenatal counseling.[25]

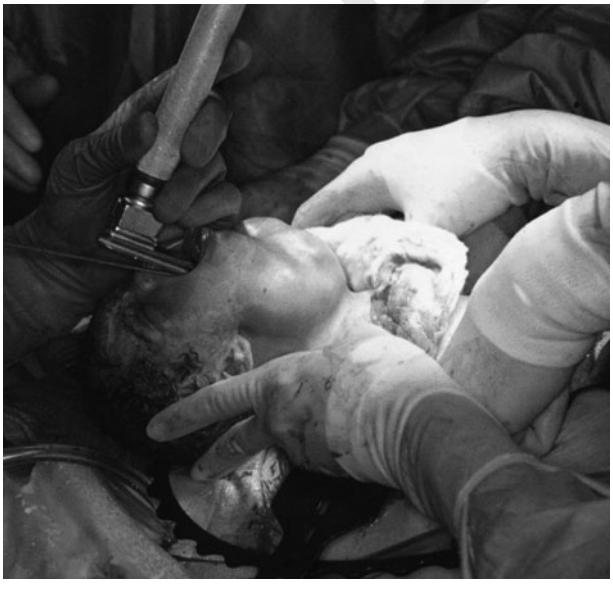

Figure 5.1 *Ex utero* intrapartum treatment (EXIT) procedure for giant neck mass.

Teratomas are asymmetrical lesions which are frequently unilateral, with well-defined margins. They may also be multiloculated, irregular masses with solid and cystic components. Most teratomas contain calcifications. MRI is a very useful adjunct to ultrasound in evaluating giant neck masses. We have used it successfully for showing the relationship of the mass to the airway in preparation for EXIT procedure.[26] T1-weighted images may help differentiate teratomas from lymphangiomas.[27]

The EXIT procedure, originally designed for removal of tracheal clips,[18] has proven life-saving for many fetuses with giant neck masses.[19,28,29] This procedure involves performing a maternal hysterotomy and obtaining control of the fetal airway while the fetus remains on placental support. In order to prevent uterine contractions during the procedure, the mother is given inhalational anesthetic and tocolytics, warm saline is infused through a level I device, and only the head and shoulders of the fetus are delivered. After attaching a pulse oximeter to the fetal hand to monitor heart rate and oxygen saturation, direct laryngoscopy and, if possible, endotracheal intubation is performed. If the airway cannot be secured in this way, a rigid bronchoscope is inserted to determine the anatomy. If secure airway establishment is still unsuccessful, a tracheostomy can be performed. After securing the airway, surfactant is administered for premature fetuses, the cord is clamped, and the infant is taken to an adjacent operating room for resuscitation and possible immediate resection of the mass. In our review of the EXIT procedure,[28] 31 fetuses underwent the procedure with 30 survivors. In 25 patients, endotracheal intubation was accomplished, five patients needed a tracheostomy, and one patient expired due to parental refusal for a tracheostomy.

The EXIT procedure has also been useful in the perinatal resuscitation of fetuses with a range of anomalies expected to cause hemodynamic compromise at birth, such as giant lung masses (EXIT to congenital cystic adenomatoid malformation (CCAM) resection),[30] CHAOS,[31] severe congenital heart disease with congenital diaphragmatic hernia (CDH) (EXIT to extracorporeal membrane oxygenation (ECMO)),[32] and even thoracopagus conjoined twins with a single functioning heart.[33] One important caveat in its use is communication between the surgery and anesthesia teams: deep inhalational anesthesia (necessary to maximize uteroplacental blood flow) can predispose to extensive maternal bleeding, as was recently reported.[34]

Sacrococcygeal teratoma

Sacrococcygeal teratoma (SCT) is the most common newborn tumor, occurring in 1/35 000–40 000 births.[35] The American Academy of Pediatrics Surgical Section (AAPSS) classification[36] defines four types with differing prognoses: type 1 tumors are external, with at most a small presacral

component and carry the best prognosis; type 2 tumors are predominantly external with a large intrapelvic portion; type 3 lesions are predominantly intrapelvic with abdominal extension with only a minor external component; and type 4 lesions are entirely intrapelvic and abdominal. The latter have the worst prognosis since they are difficult to diagnose, sometimes less amenable to surgical resection, and are frequently malignant at the time of diagnosis because of the delay in diagnosis. Overall, prenatally diagnosed SCT has a worse prognosis than those diagnosed at time of birth.

On prenatal ultrasound, SCT appears as a mixed solid and cystic lesion arising from the sacral lesion. The tumor frequently contains calcifications. Since there is acoustic shadowing by the fetal pelvic bones, it is not always possible to determine the most cephalad portion of the tumor by ultrasound. Ultrafast fetal MRI is superior,[37,38] since it can determine the intrapelvic dimensions of the tumor as well as the presence of hemorrhage (Fig. 5.2). Those fetuses with mainly solid and highly vascular SCT have a higher risk of developing hydrops.[39,40] High output cardiac failure may occur as a result of the hemodynamic effects of the large blood flow to the tumor[41,42] and anemia from hemorrhage into the tumor may compound this problem. In severe cases, the mother with placentomegaly develops 'mirror syndrome,' a severe pre-eclamptic state with vomiting, hypertension, proteinuria, and edema. This phenomenon may be mediated by the release of vasoactive compounds from the edematous placenta**.** As with other fetal masses, the development of hydrops is a grave sign, with almost 100% mortality without fetal intervention.[43,44]

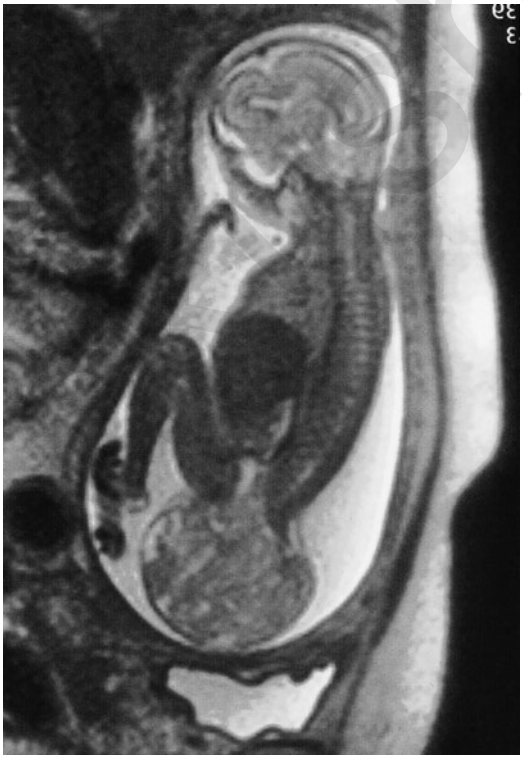

Figure 5.2 Magnetic resonance imaging of large sacrococcygeal teratoma.

The prediction of which fetuses with SCT are at highest risk for developing hydrops is therefore the crucial issue in prenatal management. A thorough prenatal evaluation with ultrasound (US), MRI, and fetal echocardiography is important in defining such a group. In a series of 23 cases seen at the Children's Hospital of Philadelphia (CHOP) between 2003 and 2006,[45] we observed that rapid tumor growth ($>150\,cm^3$/week) identifies a group of fetuses with a higher risk of prenatal mortality. The combined cardiac output (CCO) correlates with tumor growth, with those fetuses >600 mL/kg per min portending a higher risk of complications. The solid component of the mass is an important prognostic indicator: a recent report showed that when the solid tumor volume is normalized to the head volume, fetuses with a ratio <1 all survive whereas those with a volume >1 have 61% mortality.[46] A similar classification scheme based on size, growth, and vascularity has also been reported.[47]

Prenatal interventions for SCT include cyst aspiration (for those with a dominant cystic component), amnioreduction (for those with severe, symptomatic polyhydramnios with an amniotic fluid index (AFI) >35), amnioinfusion (for those with bladder outlet obstruction, to facilitate placement of a vesioamniotic shunt), or open fetal surgery for resection of the mass. In our current management algorithm, the latter option should only be considered for fetuses with impending high output failure, rapid growth, type I lesion amenable to resection, and gestational age between 20 and 30 weeks. Since our initial report of the first successful case of fetal SCT resection,[48] we have reported four additional cases, with three survivors.[49] One patient died postoperatively due to cardiac failure from indomethacin-mediated closure of the ductus arteriosus. Other complications included an embolic event leading to renal agenesis and jejunal atresia (one), chronic lung disease (one), and tumor recurrence (one). Minimally invasive prenatal interventions such as laser vessel ablation and alcohol sclerosis have been reported for the management of hydropic fetuses, albeit with limited success (6/7 *in utero* or neonatal deaths).[50] For fetuses older than 30 weeks and impending hydrops, emergent delivery with postnatal resection should be considered. The combined perinatal mortality from both of our recent series is 43% (19/44) excluding terminations,[45] illustrating the severity of this disease.

CONGENITAL CHEST LESIONS

CCAM and bronchopulmonary sequestration

CCAM represents a spectrum of disease characterized by cystic lesions of the lung.[51] Macrocystic lesions are larger than 5 mm in diameter and may be solitary cysts that grow to several centimeters (Fig. 5.3). Microcystic disease has multiple cystic lesions less than 5 mm in diameter. Prenatal US can generally distinguish individual cysts in macrocystic disease while microcystic lesions usually have the appearance of an echogenic, solid lung mass.[52] Bronchopulmonary sequestration (BPS) is an aberrant lung mass which is

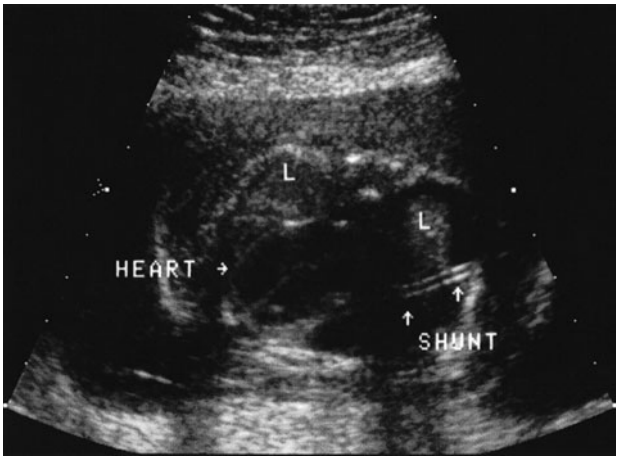

Figure 5.3 Ultrasound image of large congenital cystic adenomatoid malformation following the placement of a thoracoamniotic shunt. L, lung.

non-functional and usually has a systemic blood supply. It may be difficult to distinguish microcystic CCAM from BPS on US. Indeed, there is growing evidence that the two lesions may be related embryologically, with several reported cases of hybrid lesions which have CCAM-like architecture and a systemic blood supply.[53,54] Some of these lesions may decrease in size or 'disappear' altogether during fetal life[55] but postnatal evaluation is still warranted to detect residual disease for resection[56] because of the risk of pulmonary infections and the development of tumors such as pleuropulmonary blastoma.

MRI is useful in delineating normal lung from abnormal.[57] In CCAM, the number and size of cysts contribute to the signal intensity on T2-weighted images.[5] MRI can also define BPS from surrounding lung due to its high signal intensity and homogeneous appearance.[57] To date, ultrasound has been more accurate in demonstrating systemic feeding vessels. MRI may also be helpful in making the correct diagnosis in cases where US is ambiguous. In a series of 18 lung lesions which were viewed with both US and MRI, multiple chest abnormalities were misdiagnosed as CCAM on the US, including CDH, tracheal atresia, pulmonary agenesis, neurenteric cyst, bronchial stenosis, and BPS.[57] MRI helped form the correct diagnosis in these cases and was thus crucial for perinatal management.

Polyhydramnios is a frequent accompanying finding in fetuses with large chest masses. This is likely due to esophageal compression caused by the large thoracic mass, decreasing the fetal ability to swallow amniotic fluid.[58] The most important prognostic indicator in fetuses with CCAM is the development of hydrops. Hydrops is secondary to obstruction of the vena cava or cardiac compression from extreme mediastinal shift.[59] Historically, the development of hydrops has indicated a grave prognosis with 100% mortality[58] and it is important to predict which fetuses are at high risk for this complication. The volume of the CCAM compared to the head circumference (CCAM volume ratio, CVR) is an important prognostic indicator: fetuses with a CVR greater than1.6 are more likely to develop hydrops.[60]

For fetuses with large macrocystic CCAMs with a dominant cyst, or large pleural effusion causing pulmonary hypoplasia, thoracoamniotic shunting may be life-saving: in our series of 19 high-risk fetuses who underwent prenatal shunt placement,[61] survival was 67% (6/9) in the pleural effusion group and 70% (7/10) for the CCAM group, with an average age of delivery at 33+ weeks. However, we have reported an increased risk of chest wall anomalies if shunts are placed prior to 20 weeks' gestation.[62]

Fetuses with large microcystic CCAMs (thus not amenable for shunting) and signs of hydrops are more problematic. After 32 weeks' gestation, delivery with immediate resection is the optimum management. In fact, given the high risk of perinatal circulatory collapse secondary to mediastinal shift and inability to ventilate, we currently perform an EXIT procedure with resection of the mass on placental support.[30] EXIT to ECMO strategy for severe masses has also been described.[63] For those fetuses <32 weeks with hydrops, open fetal surgery with thoracotomy and resection of the mass may be offered at select centers. At CHOP, we have performed 24 cases of *in utero* resection of fetal lung lesions for hydrops between 21 and 31 weeks' gestation.[52] There were 13 healthy survivors, all of whom had resolution of hydrops at 1–2 weeks after the operation. Eleven fetuses had *in utero* demise, with six intraoperative deaths. Intraoperative hemodynamic compromise secondary to acute changes in cardiac output upon delivery of the mass has led us to adopt a method of continuous intraoperative cardiac monitoring, with volume resuscitation of the fetus and administration of atropine prior to thoracotomy.[64] Grethel and colleagues have reported a similar experience at the University of California, San Francisco (UCSF), in which open resection of the mass in fetuses with hydrops led to the survival of 15 of 30 fetuses.[65] While minimally invasive methods such as intrathoracic YAG laser therapy have been described,[66] technical limitations leading to damage to adjacent normal lung and ribs should prohibit offering such treatments until proven in animal models.

The recognition that maternal administration of steroids can reverse hydrops has been an exciting new development in the antenatal management of CCAM, with survival of all three hydropic fetuses in the initial report.[67] The experience at CHOP has also been favorable:[68] eleven fetuses (ten microcystic, one macrocystic) were given maternal betamethasone, with survival of all five hydropic fetuses and all seven fetuses with CVR >1.6 (compared to a mortality of 100 and 56%, respectively, in historical controls). Only one patient still needed fetal intervention while one needed resection on EXIT due to large size of the mass; the remaining nine fetuses underwent vaginal delivery with postnatal resection without complication. The salutary effects of steroids cannot simply be ascribed to reductions in the size or rate of growth of the CCAM as there was variable growth in these patients and a natural growth plateau is well-described.[56,69,70] Further studies into the basic biology of CCAM to understand how steroids may influence alveolar maturation or hydrops are areas of active research interests in many laboratories. However, a recent report on the experience with 15 fetuses

with large CCAM who received steroids[71] did not show a beneficial effect in 6/13 hydropic fetuses, while three additional fetuses in the group of initial responders still needed fetal intervention (two thoracoamniotic shunts, one open fetal surgery). Our current algorithm for the management of hydropic fetuses with CCAM prior to 32 weeks is to administer steroids with close observation and open lobectomy if hydrops fails to resolve.

Congenital diaphragmatic hernia

Herniation of abdominal viscera into the chest *in utero* occurs most commonly due to failure of the pleuroperitoneal folds to fuse normally. The left side is affected five times more commonly than the right. The ultrasonographic diagnostic criteria include herniated abdominal viscera, abnormal upper abdominal anatomy, mediastinal shift away from the side of herniation, and, in severe cases, polyhydramnios. The extent of pulmonary hypoplasia is proportional to the timing of herniation, the size of the diaphragmatic defect, and the amount of viscera herniated. Despite earlier impressions that CDH was infrequently associated with other serious congenital lung lesions, recent reports state that other major anomalies occur in 10–50% of cases, including a high proportion of chromosomal abnormalities and cardiac anomalies.

Distinguishing CDH from other congenital chest conditions and gastrointestinal lesions can be difficult. The presence of abdominal contents intrathoracically on a transverse sonographic scan at the level of a four-chamber view of the heart is required for diagnosis. In the case of a right-sided defect, the presence of liver, and especially gallbladder, in the chest makes the diagnosis more clear cut. MRI is superior in defining the position of the liver in CDH (above or below the diaphragm), which carries important prognostic significance (Fig. 5.4).[72,73] MRI is also better at determining the exact diagnosis, when ultrasound may mistake CDH for congenital lung masses. Since the extent of pulmonary hypoplasia is an important prognostic indicator, MRI has the potential to become a very useful tool for more accurate measurement of hypoplastic and contralateral lung volumes as well as the extent of liver herniation.[74–76]

The best predictor of outcome in CDH has been the right lung to head circumference ratio (LHR), defined as right lung area (measured at the level of the transverse four-chamber cardiac view) divided by head circumference (Fig. 5.5).[77] The utility of LHR in predicting survival has been validated prospectively[78] and in a recent multicenter trial,[79] with LHR <1 portending a very poor prognosis. The position of the liver is an independent prognostic indicator. For example, in our experience, fetuses who have an intrathoracic liver ('liver up') need ECMO more frequently than those with the liver down (80 versus 25%) and have a higher mortality (45 versus 93%).[80] Given the age-related changes in normal lung area compared to head circumference through gestation, another commonly used approach is to normalize the LHR to the expected mean LHR for that gestational age, thus obtaining an 'observed to expected' ratio.[81] Furthermore, the timing of these measurements is important and the 'prognostic LHR' should be measured between 24 and 28 weeks' gestation. Right-sided CDH is less common than on the left, but is a more severe disease with a particularly high rate of prenatal complications such as polyhydramnios, premature rupture of membranes, and preterm labor.[82]

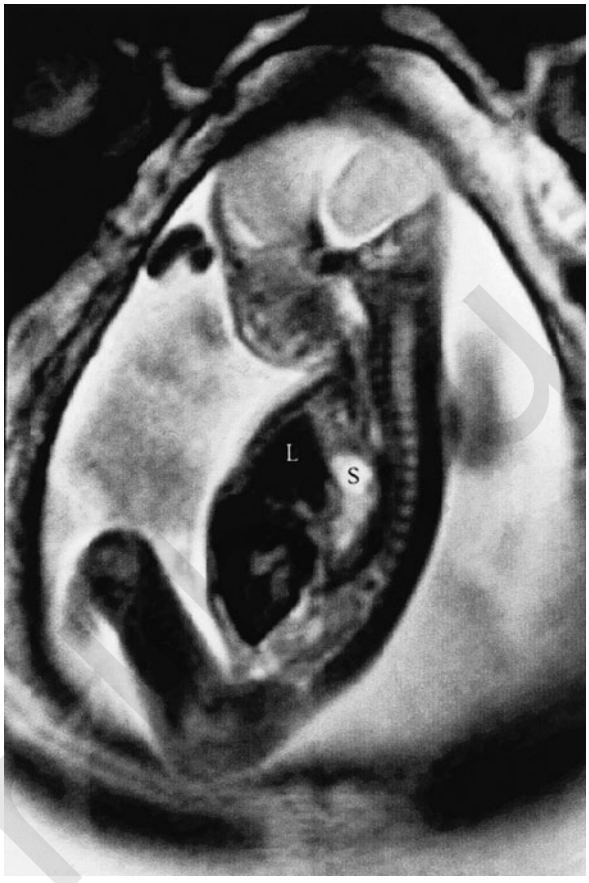

Figure 5.4 Magnetic resonance imaging of a congenital diaphragmatic hernia showing liver (L) and stomach (S) in the chest.

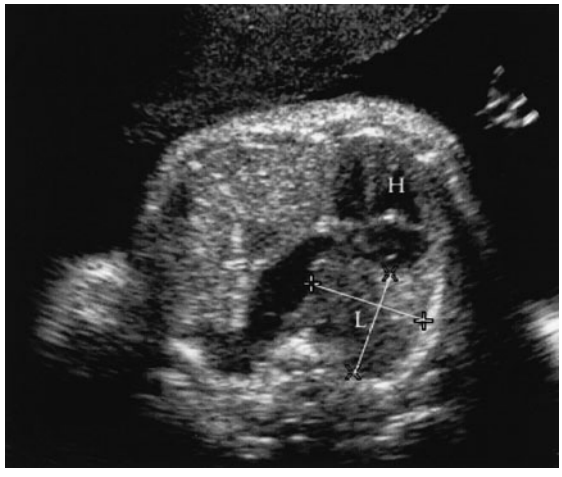

Figure 5.5 Ultrasound of congenital diaphragmatic hernia at the level of the transverse four-chamber view of the heart (H) showing measurements used for LHR calculation on the right lung (L).

The realization that infants with severe CDH succumb to pulmonary hypertension (more so than pulmonary hypoplasia) has fueled interest in measuring prenatal surrogates of this parameter to guide counseling and management. Fetal echocardiography may be used to measure pulmonary artery diameter,[83,84] peak early diastolic reversed flow velocity,[85] as well as pulmonary artery reactivity to maternal hyperoxygenation.[86]

The strategy for *in utero* treatment of CDH has undergone many permutations in the last two decades, with the current approach involving tracheal occlusion using a percutaneous, fetoscopically placed balloon (FETO) and subsequent reversal of occlusion prior to delivery (reviewed in Refs 87 and 88). The basis for this approach is the recognition that fetal tracheal occlusion leads to compensatory lung growth due to decrease in lung liquid egress, as confirmed in lamb models of CDH.[89] Given the embryology of lung growth, occlusion earlier in gestation, prior to the pseudoglandular stage of lung development, may lead to more reliable lung growth. The outcome in fetuses after tracheal occlusion has been favorable in both the lamb model[90] and in initial clinical reports.[91,92] Although a subsequent randomized clinical trial comparing prenatal tracheal occlusion (using a clip or balloon, but without reversal) did not show a treatment benefit,[93] this may have been secondary to a generous inclusion criteria (LHR <1.4) as well as preterm labor, still the Achilles heel of fetal surgery. Furthermore, reversal of occlusion may confer more benefit. The European experience with fetal occlusion and reversal has been quite favorable. Deprest and colleagues reported on 24 fetuses (LHR <1, liver up) that underwent FETO between 26 and 28 weeks, with 12 undergoing reversal at 34 weeks and 12 undergoing delivery via EXIT.[94] Survival to discharge was 50% overall (83% in the *in utero* reversal group; 33% in the EXIT group) compared to 9% in historical controls with the same disease severity. The mean gestational age at delivery was 33.5 weeks although preterm premature rupture of membranes (PPROM) was still seen in 17% of patients at 28 weeks and 33% at 32 weeks. A similar approach is also currently offered at UCSF for fetuses with LHR $=1.0$ with liver up.

GASTROINTESTINAL LESIONS

Esophageal and bowel atresias

Esophageal atresia is typically diagnosed on prenatal ultrasound by the presence of a small or absent stomach bubble and polyhydramnios, but no ultrasound finding is sensitive or specific for esophageal atresia.[95] Esophageal atresia is associated with anatomic and chromosomal abnormalities in 63% of cases,[96] most notably trisomy 18 and VACTERL (vertebral anomalies, anal atresia, cardiac anomalies, tracheoesophageal fistula, renal agenesis, and limb defects).

Duodenal atresia has a characteristic 'double bubble' appearance on prenatal ultrasound, resulting from dilatation of the stomach and proximal duodenum. The incidence of associated malformations is high (57% in one recent series[97](classically with Down syndrome and endocardial cushion defects) and those who are prenatally diagnosed are more likely to have associated anomalies.[97] In a recent review of all small intestinal atresias, Hemming *et al.*[98] reported that 25% have chromosomal anomalies and 25% have other structural anomalies.

There are many bowel abnormalities which may be noted on prenatal ultrasound (dilated bowel, ascites, cystic masses, hyperperistalsis, polyhydramnios); however, none is absolutely predictive of postnatal outcome. Patients with obstruction frequently have findings of increased bowel diameter (especially in the third trimester), hyperperistalsis, or polyhydramnios, but ultrasound is much less sensitive in diagnosing large bowel anomalies than those in the small bowel.[99] Since the large bowel is mostly a reservoir, with no physiologic function *in utero*, defects in this region, such as anal atresia or Hirschsprung's disease, are very difficult to detect, although low MSAFP may be a marker for anal atresia.[100] Bowel dilatations may be associated with cystic fibrosis; therefore, all such fetuses should undergo postnatal evaluation for this disease.[99]

ABDOMINAL WALL DEFECTS

Omphalocele is thought to be secondary to failure of the abdominal viscera to return to the abdomen in the 10th week of gestation.[101] It characteristically has a viable sac composed of amnion and peritoneum containing herniated abdominal contents. The defect is in the midline, usually near the insertion point of the umbilical cord. Ultrasound may demonstrate the internal viscera and sometimes the liver within the sac. Ascites may also be present. Since chromosomal and structural abnormalities are very common in omphalocele (cardiac and renal anomalies, chromosomal anomalies including Beckwith–Wiedemann syndromes and Pentalogy of Cantrell), fetuses with this defect should be screened by karyotype in addition to a detailed sonographic review and echocardiogram.[102] Omphalocele is rarely seen as part of the omphalocele, extrophy of the bladder, imperforate anus, and spinal anomalies (OEIS) sequence,[103] requiring multiple operations with considerable morbidity Patients with giant omphaloceles (containing predominantly liver, with a defect >5 cm) can have a prolonged course with high long-term morbidity, especially with respiratory and feeding difficulties.[104]

Gastroschisis is more often an isolated lesion with a right para-umbilical defect.[102] There is no membrane covering the exposed bowel. On ultrasound, the bowel appears free-floating and the loops may appear thickened due to peel formation from exposure to amniotic fluid (Fig. 5.6). Dilated loops of bowel may be seen from obstruction secondary to protrusion from a small defect or from the presence of an atresia, seen in 8–10% in most series. The pathophysiology of bowel damage is likely due to amniotic fluid exposure and bowel constriction, the latter leading to ischemia and venous obstruction.[105,106] There is a high rate of *in utero* fetal demise,[107] highlighting the need for careful serial monitoring once the diagnosis is made. Many infants have intrauterine growth retardation: 70% are below the

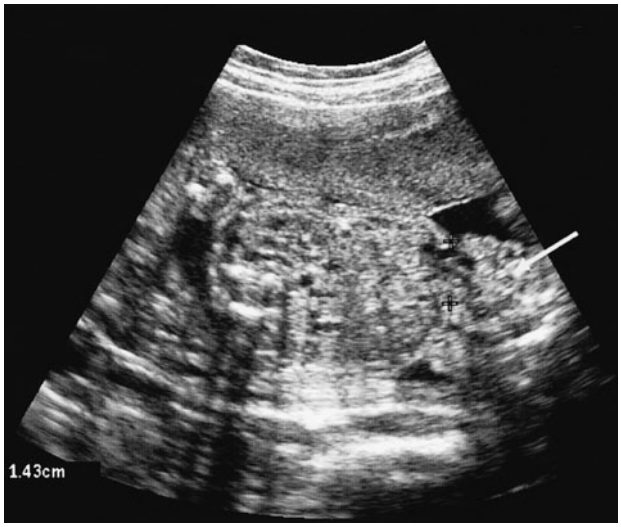

Figure 5.6 Ultrasound of fetus with gastroschisis with cross-marks showing the abdominal wall defect and arrow indicating extra-abdominal bowel.

50th percentile at birth (this number is overestimated on prenatal measurements, since the abdominal cavity is small because of the defect).[102]

Predicting outcome in fetuses with gastroschisis based on prenatal ultrasound findings remains a challenge. Analysis of infants with gastroschisis has led to the definition of two groups of patients: simple (isolated gastroschisis, very low mortality) versus complex (those who also have bowel atresias, perforation, volvulus, or bowel necrosis and a higher mortality (28% in Ref. 108; 8.7% in Ref. 109)). It is therefore crucial to develop prenatal diagnostic criteria for prediction of postnatal outcome. In addition, the timing of delivery has been an unanswered question: the urgency to prevent *in utero* bowel damage must be tempered with the risks of prematurity in these infants, many of whom are small for gestational age. Both ultrasound and biochemical characteristics have been examined to address this issue. Examination of amniotic fluid for markers of fetal distress such as meconium[110] and β-endorphin[111] may carry prognostic significance but is not currently used in clinical practice. Ultrasound characteristics such as bowel dilatation, bowel wall thickening, and mesenteric flow have been studied by many groups as possible prognostic indicators. We recently reviewed our experience with 64 cases of gastroschisis seen at CHOP between 2000 and 2007.[112] Fifty-three were simple and 11 were complex (17%). There were three *in utero* mortalities (two fetal demises and one termination) with an overall postnatal mortality of 9%. Interestingly, prenatal ultrasound findings were not predictive of the postnatal course for any of the parameters examined (simple versus complex, primary versus silo, hospital length, time to enteral feedings, etc).

The question of whether Cesarian section delivery would protect the exposed bowel from further damage during delivery has been considered but does not appear to confer any outcome benefit.[113,114] Thus, the mode of delivery for abdominal wall defects can be vaginal except in cases of giant omphalocele, in whom the risk of liver rupture and dystocia mandate a Cesarian section. The issue of whether transport prior to delivery impacts outcome (secondary to ongoing ischemia and damage to the exposed intestines during transport) has also been studied and, interestingly, does not appear to make a difference in one series.[115] Our current strategy for management is serial ultrasounds to monitor for signs of fetal distress, with planned delivery at term and either primary or silo closure.

PRENATAL DIAGNOSIS OF RENAL ANOMALIES

Prenatally diagnosed hydronephrosis (HN) represents a broad spectrum of diseases with widely disparate prognoses (reviewed in Ref. 116). The ultrasound findings of HN include dilated renal pelvis and calyces, with or without dilatation of the bladder and ureter, depending on the cause of HN (Fig. 5.7). The Society for Fetal Urology defines four grades with increasing severity, with grade 1 being split pelvis only, and grade 4 being dilated pelvis with distended calyces and thinned parenchyma.[117] In addition, an anterior-posterior diameter >10 mm has been suggested as being predictive of fetuses who will need some postnatal intervention.[118] The differential diagnosis of prenatal hydronephrosis includes ureteropelvic junction (UPJ) obstruction, multicystic kidney, primary obstructive megaureter, ureterocele, ectopic ureter, and posterior urethral valves.[119] Severe, bilateral hydronephrosis leads to oligohydramnios with a fetus small for gestational age. Because of the lack of amniotic fluid, ultrasound diagnosis may be difficult and MRI may help define the cause of hydronephrosis.[5]

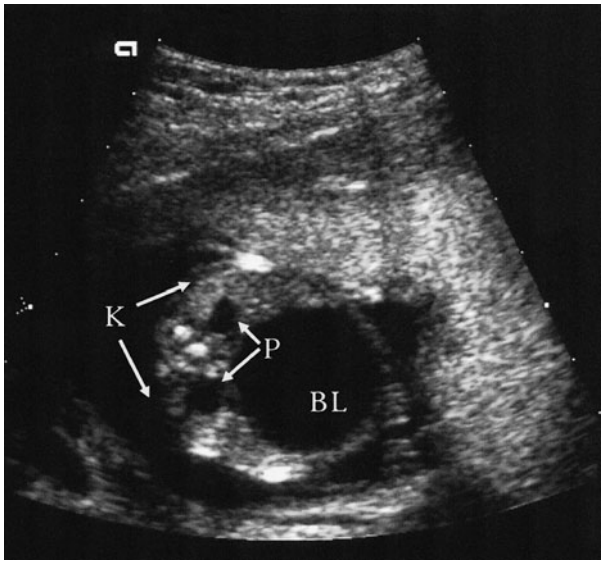

Figure 5.7 Ultrasound of hydronephrosis showing enlarged bladder (BL), compressed renal parenchyma (K), and dilated renal pelvises (P).

UPPER URINARY TRACT OBSTRUCTION

The most common cause of prenatal HN is UPJ obstruction. The prognosis of prenatally diagnosed HN is excellent, if there is unilateral disease[120] and if the renal pelvic diameter is less than 10 mm.[121] In one large series, 80% were normal at three years and 17% were normal at birth, suggesting spontaneous resolution of the problem.[122] Only 17% needed surgical intervention. Prenatally diagnosed HN requires follow-up with ultrasound at birth and at one month. If there is any evidence of abnormality, a voiding cystourethrogram, and diuretic renal scintigram should be performed.[123]

LOWER URINARY TRACT OBSTRUCTION

The most common cause of lower urinary tract obstruction is posterior urethral valves (PUV); it is also seen in prune belly syndrome and urethral atresia.[124] The most important factor in the morbidity and mortality from fetal urethral obstruction is pulmonary hypoplasia secondary to oligohydramnios.[125] For patients with posterior urethral valves, prenatal diagnosis defines a subgroup of patients with very poor prognosis, with 64% incidence of renal failure and transient pulmonary failure, compared to 33% in the postnatally diagnosed group.[126] Serial fetal urine analysis may provide prognostic information in this group of fetuses. Drainage of the bladder three times at 48–72 hour intervals with measurement of sodium, chloride, osmolality, calcium, α-2 microglobulin, and total protein should be performed to determine renal function. In this strategy, the later taps indicate the characteristics of recently produced urine and a decrease in the electrolytes, proteins, and tonicity correlate with a favorable outcome.[124]

The rationale for prenatal intervention originates from sheep models of the disease, in which bladder outlet obstruction in fetal lambs reproduced the pulmonary hypoplasia and renal dysplasia seen in patients with bilateral obstructive uropathy.[127] Correction of the obstruction led to normal lung growth.[128] Fetal intervention in prenatal obstructive uropathy is only warranted in male fetuses with oligohydramnios, bladder distention, and bilateral hydronephrosis (with no other abnormalities), who have improving urine profiles with serial bladder drainage.[129] In female fetuses, lower urinary tract obstruction (LUTO) is generally part of a complex cloacal anomaly and fetal intervention has not been beneficial. Male fetuses may be considered for vesico-amniotic shunting or fetal cystoscopy with cystoscopic ablation of posterior urethral valves.[130] More recently, fetal microcystoscopy and mechanical disruption has been reported.[131] This method is promising in that it provides a more physiologic method for bladder drainage.

Although vesico-amniotic shunting in a fetus with oligohydramnios can be technically challenging, the survival benefit of prenatal shunting in carefully selected populations of fetuses has been reported, with 43% of patients having normal renal function two years after birth.[132] We recently reported our series of 18 patients who had vesico-amniotic shunts for PUV (seven), prune belly syndrome (seven) and urethral atresia (four).[133] Eight patients have good renal function, four have mild renal insufficiency, and six required hemodialysis with subsequent transplantation. Respiratory problems and frequent urinary tract infections were seen in eight and nine patients, respectively. While short-term outcomes are variable in different reports,[120] a recent meta-analysis[134] determined that *in utero* drainage improved survival compared to postnatal management alone in the group of fetuses with poor prognosis. Patients who have been shunted can still die from pulmonary hypoplasia as well as renal failure. Given the need to select only those fetuses that would benefit from fetal intervention, a randomized controlled trial for prenatal management of LUTO (PLUTO) is currently under way in Europe.[135]

MYELOMENINGOCELE

Myelomeningocele (MMC) is a neural tube defect characterized by the protrusion of the spinal cord and meninges through open vertebral arches. It is the most common form of spina bifida, which affects one in 2000 births per year. Maternal serum testing identifies 75–80% of pregnancies with MMC by 16 weeks of age.[136] If an increase in serum alphaprotein (AFP) is noted, amniocentesis is performed to assess amniotic fluid AFP and acetycholinesterase to confirm the diagnosis.[137] The ultrasound characteristics include the 'lemon' and 'banana' signs which are scalloping of the frontal bone and abnormal anterior curvature of the cerebellar hemispheres, respectively.[138] Most fetuses have an associated Arnold–Chiari malformation, characterized by the caudal displacement of the vermis and cerebellum with midbrain herniation through the foramen magnum. Ultrasound confirmation can be made as early as 18 weeks, which allows localization of the defect as well as assessment of limb function, the presence of clubbing or of the Arnold–Chiari malformation (Fig. 5.8).

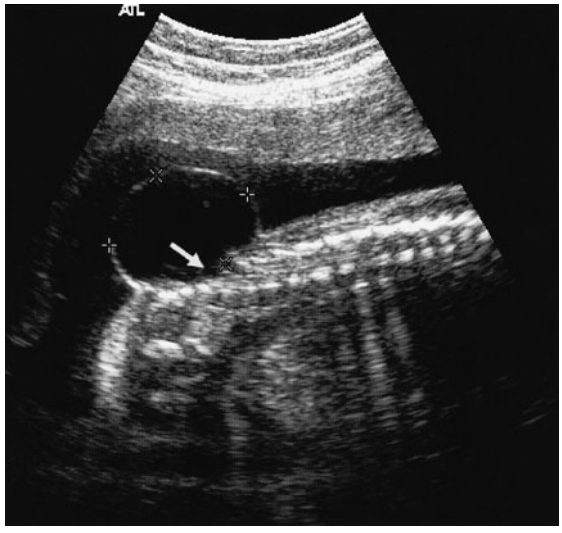

Figure 5.8 Ultrasound of fetus with myelomeningocele showing the sac (crossmarks) over the spinal defect (arrow).

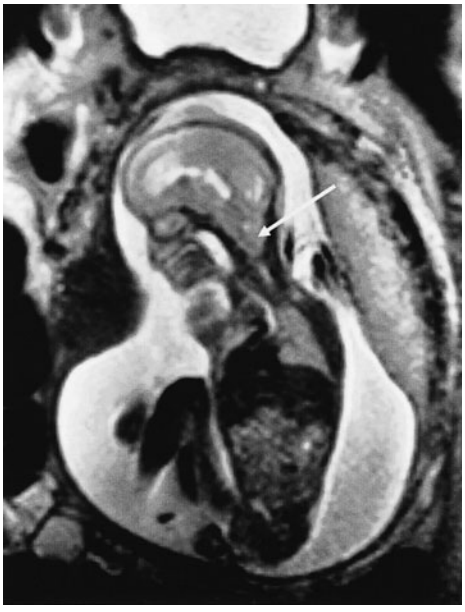

Figure 5.9 Magnetic resonance imaging of fetus with myelomeningocele showing hindbrain herniation (arrow).

Analysis of the potential benefits of fetal repair of MMC has been accomplished in sheep models of the defect,[139–141] thus providing a compelling reason for *in utero* repair, the first non-lethal disease to be considered for this treatment. The goals of fetal repair are to prevent the chemical and mechanical trauma to the exposed spinal cord, to resolve the hindbrain herniation frequently seen with this defect, to decrease the need for postnatal ventriculoperitoneal shunt, and to allow time for possible neural regeneration after repair. We reported the first open repair of fetal MMC which led to improved neurological outcome[142] and resolution of the Arnold–Chiari malformation (Fig. 5.9). Long-term analysis of patients who underwent *in utero* repair has indicated that this may lead to a decreased need for ventriculoperitoneal shunting[143,144] as well as improved brainstem function[145] and neurodevelopmental outcomes.[146] The initial promising observations have led to the institution of a randomized clinical trial comparing prenatal repair to postnatal treatment alone. This trial is partly funded by the National Institutes of Health in the United States and is called the Management of Myelomeningocele Study (MOMS). It is currently underway at CHOP and UCSF. If fetal repair is not performed, fetuses with MMC should be delivered by planned Cesarian section to avoid trauma to the cord during the birth process.[147,148]

CONCLUSIONS

Prenatal ultrasound has led to a rapid increase in the number of pediatric surgical conditions diagnosed *in utero*. Prenatal detection and serial sonographic study of fetuses with anatomic lesions now make it possible to define the natural history of these abnormalities, determine the pathophysiologic causes that affect outcome, and formulate management based on prognosis. Since many congenital anomalies are associated with others, it is important to perform a careful ultrasound evaluation and karyotype analysis when one abnormality is discovered.

Careful evaluation of patients followed pre- and postnatally, as well as studies of congenital defects in animal models, has defined select populations of fetuses who may benefit from prenatal intervention. In most cases, these are fetuses that would not be expected to survive the prenatal period given the natural history of their disease. Further progress in prenatal diagnosis and monitoring as well as continued re-evaluation of outcomes will doubtless tune our current algorithms regarding the management of these congenital anomalies. Pediatric surgeons have a unique opportunity to continue to shape this exciting field in the new millennium.

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6

Fetal counseling for surgical malformations

KOKILA LAKHOO

INTRODUCTION

Pediatric surgeons are often called to counsel parents once a surgical abnormality is diagnosed on a prenatal scan. The referral base for a pediatric surgeon now includes the perinatal period. Expertise in surgical correction of congenital malformations may favorably influence the perinatal management of prenatally diagnosed anomalies by changing the site of delivery for immediate postnatal treatment, altering the mode of delivery to prevent obstructed labor or hemorrhage, early delivery to prevent ongoing fetal organ damage, or treatment *in utero* to prevent, minimize or reverse fetal organ injury as a result of a structural defect.[1,2] Crombleholme *et al.*[3] have confirmed the favorable impact of prenatal surgical consultation in influencing the site of delivery in 37% of cases, changing the mode of delivery by 6.8%, reversing the decision to terminate a pregnancy by 3.6%, and influencing the early delivery of babies by 4.5%.

The pediatric surgeon performing prenatal consultations must be aware of differences between the prenatal and postnatal natural history of the anomaly. There is often a lack of understanding of the natural history and prognosis of a condition presenting in the newborn and the same condition diagnosed prenatally.[4,5]

The diagnosis and management of complex fetal anomalies require a multidisciplinary team encompassing obstetricians, neonatologists, geneticists, pediatricians, pediatric surgeons, and occasional other specialists with expertise to deal with all the maternal and fetal complexities of a diagnosis of a structural defect.[6] This team should be able to provide information to prospective parents on fetal outcomes, possible interventions, appropriate setting, time and route of delivery, and expected postnatal outcomes. The role of the surgical consultant in this team is to present information regarding the prenatal and postnatal natural history of an anomaly, its surgical management, and the long-term outcome.[2,6,7]

CONGENITAL MALFORMATION

Congenital malformations account for one of the major causes of perinatal mortality and morbidity. Single major birth defects affect 3% of newborns and 0.7% of babies have multiple defects. The prenatal hidden mortality is higher since the majority abort spontaneously. Despite improvements in perinatal care, serious birth defects still account for 20% of all deaths in the newborn period and an even greater percentage of serious morbidity later in infancy and childhood.[8] The major causes of congenital malformation are chromosomal abnormalities, mutant genes, multifactorial disorders, and teratogenic agents.

PRENATAL DIAGNOSIS

Prenatal diagnosis has remarkably improved our understanding of surgically correctable congenital malformations. It has allowed us to influence the delivery of the baby, offer prenatal surgical management, and discuss the options of termination of pregnancy for seriously handicapping or lethal conditions. Antenatal diagnosis has also defined an *in utero* mortality for some lesions such as diaphragmatic hernia and sacrococcygeal teratoma so that true outcomes can be measured. Prenatal ultrasound scanning has improved since its first use 30 years ago, thus providing better screening programs and more accurate assessment of fetal anomaly. Screening for Down syndrome may now be offered in the first trimester (e.g. nuchal scan combined test) (Fig. 6.1), or second trimester (e.g. quadruple blood test). Better resolution and increased experience with ultrasound scans has led to the recognition of ultrasound soft markers which have increased the detection rate of fetal anomalies but at the expense of higher false-positive rates.[9]

Routine ultrasound screening identifies anomalies and places these pregnancies in the high risk categories with

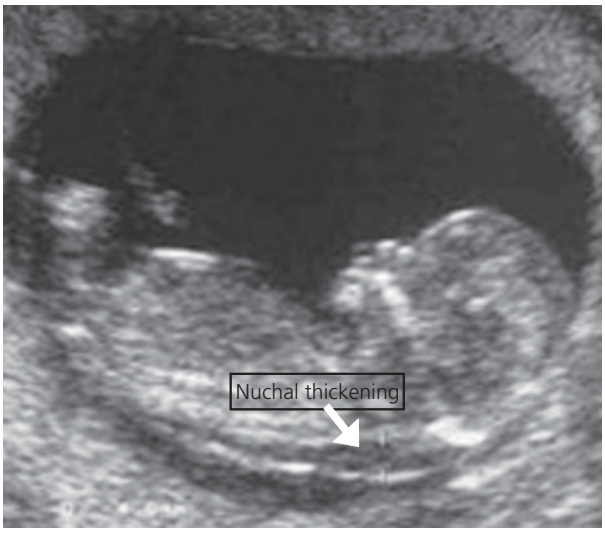


Figure 6.1 Nuchal thickening.

maternal diabetes, hypertension, genetic disorders, raised alphafeto protein (AFP), etc. High risk pregnancies may be offered further invasive diagnostic investigations such as amniocentesis or chorionic villous sampling (CVS). Structural abnormalities difficult to define on ultrasound, such as hindbrain lesions, or in the presence of oligohydramnios are better imaged on ultrafast magnetic resonance imaging. With the increasing range of options and sophistication of diagnostic methods, parents today are faced with more information, choice, and decisions than ever before, which can create as well as help to solve dilemmas. The different tests and screening procedures commonly in use are outlined below.

Ultrasound examination

Ultrasound scan is routinely performed at 18–20 weeks' gestation as part of the prenatal screening for all pregnancies in England and Wales. Older mothers are routinely screened but in addition are offered invasive testing. Pregnancies with maternal risk factors such as raised AFP levels, genetic disorders, family history of chromosomal abnormalities, or monochorionic twins that carry a high risk for chromosomal anomalies are offered earlier scans in the first trimester. Abnormalities such as diaphragmatic hernia may be detected as early as 11 weeks' gestation. First trimester scans are also useful for accurately dating pregnancies and defining chorionicity in multiple pregnancies.

Recently, nuchal translucency (NT) measurements have emerged as an independent marker of chromosomal abnormalities with a sensitivity of 60%,[10] structural anomalies (particularly cardiac defects),[11] and for some rare genetic syndromes.[12] It involves measuring the area at the back of the fetal neck at 11–14 weeks' gestation (Fig. 6.1). The mechanisms by which some abnormalities give rise to this transient anatomical change of nuchal translucency are poorly understood.[13] Although some abnormalities can be seen at the time of the nuchal scan (11–14 weeks), most are detected at the 18–20 week anomaly scan. Some abnormalities such as gastroschisis have a higher detection rate on a scan than others, e.g. cardiac abnormalities.

If the NT measurement is increased and the karyotype is normal there is a higher risk for a cardiac anomaly and these high-risk fetuses may be referred for fetal echocardiography, which provides better prenatal cardiac assessment than the routine screening scan.[14] Ultrasound surveillance is essential during the performance of invasive techniques such as amniocentesis, CVS, and shunting procedures. It is also useful for assessing fetal viability before and after such procedures. Some abnormalities, such as tracheo-oesophageal fistula, bowel atresia, diaphragmatic hernia and hydrocephaly, may present later in pregnancy and thereby are not detected on the routine 18 week scan.

Overall, around 60% of structural birth defects are detected prenatally[10] but the detection rate varies from 0% (isolated cleft palate) to close to 100% (gastroschisis) depending on the defect. True wrong diagnoses are rare but false-positive diagnoses do occur; some are due to natural prenatal regression, but most are due to ultrasound 'soft markers'.

Ultrasound 'soft markers' are changes noted on prenatal scan that are difficult to define. Examples are echogenic bowel,[15] hydronephrosis, and nuchal thickening. Their presence creates anxiety among sonographers since the finding may be transient with no pathological relevance or may be an indicator of significant anomalies such as chromosomal abnormalities, cystic fibrosis (echogenic bowel), Down syndrome (nuchal thickening), or renal abnormalities (hydronephrosis). Once soft markers are detected, whether should they be reported or further invasive tests offered is a dilemma faced by obstetricians. Reporting these markers has increased detection rates at the expense of high false-positive rates.

Ultrasound is routinely performed as a prenatal screening test. The reliability of the information obtained is dependent on the expertise and experience of the person performing the scan. In a recent study, congenital anomalies noted at birth were diagnosed on prenatal scan in 64% of cases with 0.5% opting for termination.[16]

Invasive diagnostic tests

Amniocentesis[17] and CVS[18] are the two most commonly performed invasive diagnostic tests.

AMNIOCENTESIS

Amniocentesis is commonly used for detecting chromosomal abnormalities and less often for molecular studies, metabolic studies, and fetal infection. It is performed after 15 weeks' gestation and carries a low risk of fetal injury or loss (0.5–1%). Full karyotype analysis takes approximately 2 weeks but newer rapid techniques using fluorescent *in situ* hybridization (FISH) or polymerase chain reaction (PCR) can give limited (usually for trisomies 21, 18, 13) results within 2–3 days.

CHORIONIC VILLOUS SAMPLING

CVS is the most reliable method for first trimester diagnosis and may be performed at 10–14 weeks' gestation. The test involves ultrasound-guided biopsy of the chorionic villi. The added risk for fetal loss is approximately 1–2%. The samples obtained may be subjected to a variety of tests including full karyotype, rapid karyotyping (FISH–PCR), enzyme analysis, or molecular studies. Approximate timing of chromosomal results is 1–2 weeks for karyotyping and 2–3 days for FISH and PCR.

PRENATAL MATERNAL SERUM SCREENING

Interest in detecting circulating fetal cells in maternal blood for diagnostic purposes has grown since the advent of fluorescence-activated cell sorting (FACS).[19] The observation by Brock and Sutcliffe[20] of high levels of AFP in amniotic fluid of pregnancies complicated by open neural tube defects (NTDs) popularized this test. However, with increasing accuracy of ultrasound diagnosis, maternal serum screening of AFP solely for identification of NTDs cannot be justified. The more popular maternal serum screening test is the triple test (hCG, AFP, estrogen) used in combination with the nuchal scan.

FETAL BLOOD SAMPLING

Rapid karyotyping of CVS and amniotic fluid samples FISH and PCR has replaced fetal blood sampling for many conditions. However, fetal blood sampling (FBS) is still required for the diagnosis and treatment of hematological conditions and some viral infections. When required, it is best performed by ultrasound-guided needle sampling after 18 weeks' gestation rather than the more invasive fetoscopic technique. Mortality from this procedure is reported to be 1–2%.[21]

FETAL SURGERY

There is a spectrum of interventions ranging from simple aspiration of cysts to open fetal surgery. Minimally invasive techniques such as ablation of vessels in sacrococcygeal teratoma, fetoscopic ablation of posterior urethal valves, tracheal occlusion for congenital diaphragmatic hernia, etc. are currently under trial. However, laser ablation in twin-to-twin transfusion is now well established.

Genetic diagnoses

Antenatal detection of genetic abnormalities is increasing, especially in high-risk pregnancies. Previously undiagnosed conditions such as cystic fibrosis, Beckwith–Wiedemann syndrome, Hirschsprung's disease, sickle cell disease, etc. may be detected prenatally following invasive testing and genetic counseling and assessment offered early in pregnancy.

Future developments

The aim of prenatal diagnosis and testing is to have 100% accuracy without fetal loss or injury and no maternal risk. National plans to improve Down syndrome screening using ultrasound and biochemical combination tests are now in place in the UK. Research into new markers for chromosomal abnormalities is ongoing. The fetal nasal bone is one such example, which may assist in detecting babies with chromosomal abnormalities.[22]

Management of Rhesus disease is showing promise whereby fetal blood groups may be determined from maternal blood samples through detection of free fetal DNA.[23] The search for fetal components in maternal blood is an exciting and expanding field of research since past and present efforts to isolate and use them for diagnosis have met with little success.[24] Rapid detection techniques versus traditional cultures for karyotyping are currently under debate at present.[25]

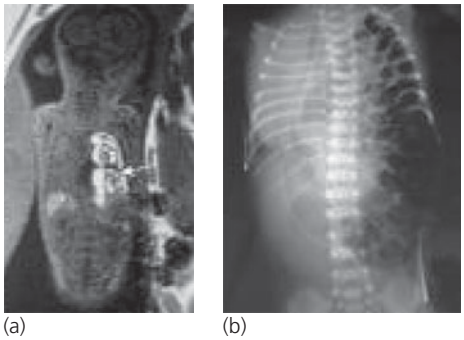
Three-dimensional images from new ultrasound machines may have a useful role in diagnosis and assessment of facial deformities such as cleft lip and palate. Magnetic resonance imaging (MRI) may assist in better defining some lesions difficult to view on conventional prenatal scanning such as the presacral teratoma, posterior urethral valves in the presence of oligohydramnios and hindbrain lesions.

SPECIFIC SURGICAL CONDITIONS

Congenital diaphragmatic hernia

Congenital diaphragmatic hernia (CDH) accounts for one in 3000 live births and challenges the neonatologist and pediatric surgeons in the management of this high-risk condition (Fig. 6.2). Mortality remains high (more than 60%) when the 'hidden' mortality of *in utero* death and termination of pregnancy are taken into account.[26] Lung hypoplasia and pulmonary hypertension account for most deaths in isolated CDH newborns. Associated anomalies (30–40%) signify a grave prognosis with a survival rate of less than 10%.[27]

In the UK, most CDH are diagnosed at the 20 week anomaly scan with a detection rate approaching 60%, although as early as 11 weeks' gestation has been reported.[28]



(a) (b)

Figure 6.2 Congenital left diaphragmatic hernia shown on prenatal magnetic resonance imaging on the left and postnatal radiograph on the right.

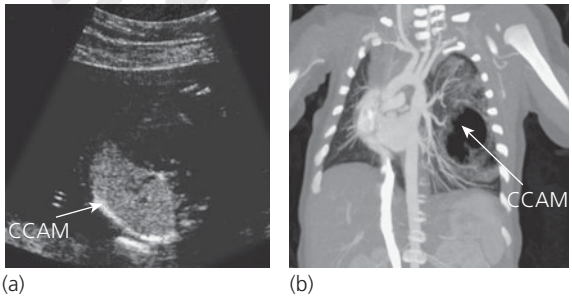
MRI has a useful role in accurately differentiating CDH from cystic lung lesions[29] and may be useful in measuring fetal lung volumes as a predictor of outcome.[30] Cardiac anomalies (20%),[31] chromosomal anomalies of trisomy 13 and 18 (20%),[32] and urinary, gastrointestinal, and neurological (33%)[33] can coexist with CDH and should be ruled out by offering the patient fetal echocardiogram, amniocentesis, and detailed anomaly scan. These associated anomalies and, in isolated lesions, early detection, liver in the chest, polyhydramnios, and fetal lung head ratio (LHR) of less than one are implicated as poor predictors of outcome.[34] In these patients with poor prognostic signs, fetal surgery for CDH over the last two decades has been disappointing, however benefit from fetal intervention with tracheal occlusion (FETO) awaits randomized studies.[35,36] Favorable outcomes in CDH with the use of antenatal steroids have not been resolved in the clinical setting.[37] Elective delivery at a specialized center is recommended with no benefit from Cesarean section.[38,39]

Postnatal management is aimed at reducing barotrauma to the hypoplastic lung by introducing high frequency oscillatory ventilation (HFOV) or permissive hypercapnea,[39] and treating the severe pulmonary hypertension with nitric oxide. No clear benefits for CDH with extracorporeal membrane oxygenation (ECMO) have been concluded in a 2002 Cochrane ECMO study.[40]

Surgery for CDH is no longer an emergency procedure. Delayed repair following stabilization is employed in most pediatric surgical centers.[41] Primary repair using the transabdominal route is achieved in 60–70% of patients with the rest requiring a prosthetic patch. Complications of sepsis or reherniation with prosthetic patch requiring revision is recorded in 50% of survivors.[42]

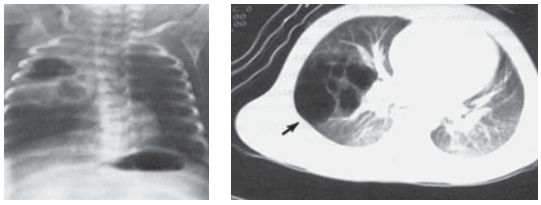
Cystic lung lesions

Congenital cystic adenomatoid malformations (CCAM), bronchopulmonary sequestrations (BPS) or 'hybrid' lesions containing features of both are common cystic lung lesions noted on prenatal scan. Less common lung anomalies include bronchogenic cysts, congenital lobar emphysema and bronchial atresia. Congenital cystic lung lesions are rare anomalies with an incidence of one in 10 000 to one in 35 000 (Figs 6.3 and 6.4).[43,44]



(a) (b)

Figure 6.3 Prenatal diagnosis of congenital cystic adenomatoid malformation (CCAM) and reconstruction computed tomography scan of a large CCAM of the left upper lobe.



(a) (b)

Figure 6.4 Chest radiograph and congenital cystic adenomatoid malformation of right upper lobe.

Prenatal detection rate of lung cysts at the routine 18–20 week scan is almost 100% and may be the most common mode of actual presentation. Most of these lesions are easily distinguished from congenital diaphragmatic hernia, however sonographic features of CCAM or BPS are not sufficiently accurate and correlate poorly with histology.[45] MRI, though not routinely used, may provide better definition for this condition, however inaccuracies were reported in 11% of cases.[46]

Bilateral disease and hydrops fetalis are indicators of poor outcome, whereas mediastinal shift, polyhydramnios, and early detection are not poor prognostic signs.[47–49] In the absence of termination the natural fetal demise of antenatally diagnosed cystic lung disease is 28%. Spontaneous involution of cystic lung lesions can occur[50] but complete postnatal resolution is rare,[45] and apparent spontaneous 'disappearance' of antenatally diagnosed lesions should be interpreted with care, as nearly half of these cases subsequently require surgery.[45,49]

In only 10% of cases does the need for fetal intervention arise. The spectrum of intervention includes simple centesis of amniotic fluid, thoracoamniotic shunt placement, percutaneous laser ablation, and open fetal surgical resection.[51,52] Maternal steroid administration has also been reported to have a beneficial effect on some CCAMs although the mechanism is unclear.[53] A large cystic mass and hydrops in isolated cystic lung lesions are the only real indication for fetal intervention.[47,49]

Normal vaginal delivery is recommended unless maternal condition indicates otherwise. Large lesions are predicted to become symptomatic shortly after birth (as high as 45% in some series), thus delivery at a specialized center would be appropriate, however smaller lesions are less likely to be symptomatic at birth and could be delivered at the referring institution with follow up in a pediatric surgery clinic.[54]

Postnatal management is dictated by clinical status at birth. Symptomatic lesions require urgent radiological evaluation with chest radiograph and ideally computed tomography (CT) scan (Fig. 6.2) followed by surgical excision. In asymptomatic cases postnatal investigation consists of chest CT scan within one month of birth, even if regression or resolution is noted on prenatal scanning.[45,49,54] Plain radiography should not be relied upon since it will miss and underestimate many lesions.[54]

Surgical excision of postnatal asymptomatic lesions remains controversial, with some centers opting for conservative management.[55,56] The approach to treating this asymptomatic group has evolved in some centers, whereby a

CT scan is performed within one month post-birth, followed by surgery before six months of age due to the inherent risk of infection and malignant transformation.[54] Small lesions less than 1 cm may be managed expectantly, bearing in mind that the true resolution of these lesions is exceptional.[45,54] Successful outcomes of greater than 95% have been reported for these surgically managed asymptomatic lung lesions.[45,49,54]

Abdominal wall defects

Exomphalos and gastroschisis are both common but distinct abdominal wall defects with an unclear etiology and a controversial prognosis. Attention may be drawn to their presence during the second trimester because of raised maternal serum AFP level, or abnormal ultrasound scan.

EXOMPHALOS

Exomphalos is characteristically a midline defect, at the insertion point of the umbilical cord, with a viable sac composed of amnion and peritoneum containing herniated abdominal contents (Fig. 6.5). Incidence is known to be one in 4000 live births. Associated major abnormalities which include trisomy 13, 18, and 21, Beckwith–Wiedemann syndrome (macroglossia, gigantism, exomphalos), Pentology of Cantrell (sternal, pericardial, cardiac, abdominal wall, and diaphragmatic defect), cardiac, gastrointestinal, and renal abnormalities are noted in 60–70% of cases,[57] thus karyotyping, in addition to detailed sonographic review and fetal echocardiogram, is essential for complete prenatal screening. Fetal intervention is unlikely in this condition. If termination is not considered, normal vaginal delivery at a center with neonatal surgical expertise is recommended and delivery by Cesarean section only reserved for large exomphalos with exteriorized liver to prevent damage.[57]

Surgical repair includes primary closure or a staged repair with a silo for giant defects. Occasionally, in vulnerable infants with severe pulmonary hypoplasia or complex cardiac abnormalities, the exomphalos may be left intact and allowed to slowly granulate and epithelialize by application of antiseptic solution.[58] Postnatal morbidity occurs in 5–10% of cases.[59] Malrotation and adhesive bowel obstruction does contribute to mortality in isolated exomphalos, however the majority of these children survive to live normal lives.[60]

GASTROSCHISIS

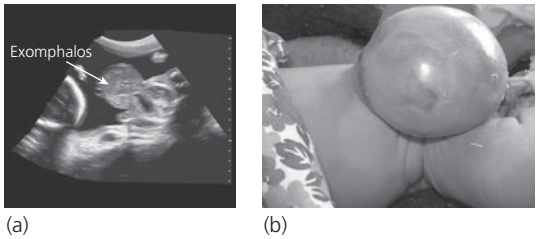
Gastroschisis is an isolated lesion that usually occurs on the right side of the umbilical defect with evisceration of the abdominal contents directly into the amniotic cavity (Fig. 6.6). The incidence is increasing from 1.66 per 10000 births to 4.6 per 10000 births affecting mainly young mothers, typically less than 20 years old. Associated anomalies are noted in only 5–24% of cases, with bowel atresia the most common coexisting abnormality.[61,62] On prenatal scan with a detection rate of 100%, the bowel appears to be free floating, and the loops may appear to be thickened due to damage by amniotic fluid exposure causing a 'peel' formation. Dilated loops of bowel (Fig. 6.3) may be seen from obstruction secondary to protrusion from a defect or atresia due to intestinal ischemia.[63,64]

Predicting outcome in fetuses with gastroschisis based on prenatal ultrasound finding remains a challenge. There is some evidence that maximum small bowel diameter may be predictive,[65] however thickened matted bowel[66] and Doppler measurements of the superior mesenteric artery are not accurate predictors of outcome.[67] To reduce the rate of third trimester fetal loss, serial ultrasounds are performed to monitor the development of bowel obstruction and delivery around 37 weeks is recommended at a center with neonatal surgical expertise.[68]

A recent study by Logghe *et al.*[68] has challenged elective preterm delivery with a randomized control trial. Delivery by Cesarean section has no advantage to the normal vaginal route. Despite efforts to plan elective delivery, 50% of cases will require emergency Cesarean section due to the development of fetal distress.[69]

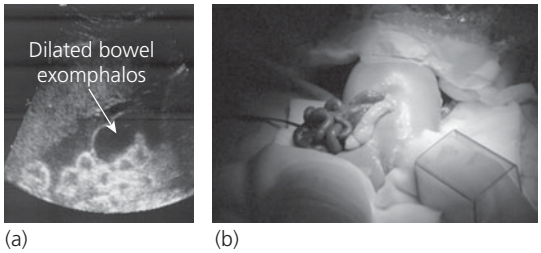
Various methods of postnatal surgical repair include the traditional primary closure, reduction of bowel without anesthesia,[70] reduction by preformed silo,[71] or by means of a traditional silo. Coexisting intestinal atresia could be repaired by primary anastamosis or staged with stoma formation. Variation in achieving full enteral feeding due to prolonged gut dysmotility is expected in all cases.

The long-term outcome in gastroschisis is dependent on the condition of the bowel. In uncomplicated cases the outcome is excellent in more than 90% of cases.[72] The mortality of live born infants is 5% with a further 5% suffering short bowel syndrome and 10% requiring surgery for adhesive bowel obstruction.[72] Late third trimester fetal loss should always be mentioned during fetal counseling.



(a) (b)

Figure 6.5 Prenatal and postnatal images of exomphalos.



(a) (b)

Figure 6.6 Prenatal and postnatal images of gastroschisis.

Tracheo-esophageal fistula and esophageal atresia

Repair of trachea-esophageal fistula (TOF)/esophageal atresia (EA) is a condition which measures the skill of pediatric surgeons from trainee to independent surgeon (Fig. 6.7). The incidence is estimated at one in 3000 births. Prenatally, the condition may be suspected from maternal polyhydramnios and the absence of a fetal stomach bubble at the 20-week anomaly scan. Prenatal scan diagnosis of TOF/EA is estimated to be less than 42% sensitive with a positive predicted value of 56%.[15,73,74] Additional diagnostic clues are provided by associated anomalies such as trisomy (13, 18, 21), vertebral, anorectal, cardiac, tracheo-esophageal, renal, limbs (VACTERAL) sequence and coloboma, heart defects, atresia choanae, retarded development, genital hypoplasia, ear abnormality (CHARGE) association. These associated anomalies are present in more than 50% of cases and worsen the prognosis, thus prenatal karyotyping is essential.[75] Duodenal atresia may coexist with TOF/EA. The risk of recurrence in subsequent pregnancies for isolated TOF/EA is less than 1%.[76] Delivery is advised to be at a specialized center with neonatal surgical input.

Postnatal surgical management is dependent on the size and condition of the baby, length of esophageal gap, and associated anomalies. Primary repair of the esophagus is the treatment of choice however, if not achieved, staged repair with upper esophageal pouch care and gastrostomy or organ replacement with stomach or large bowel are other options. Associated anomalies require evaluation and treatment.

Long-term outcomes are indicated by improved perinatal management and inherent structural and functional defects in the trachea and esophagus.[77] In early life, growth of the child is reported to be below the 25th centile in 50% of cases, respiratory symptoms in two-thirds of TOF/EA, and gastro-esophageal reflux recorded in 50% of patients.[78–80] Quality of life is better in the isolated group with successful primary repair as compared to those with associated anomalies and delayed repair.[81]

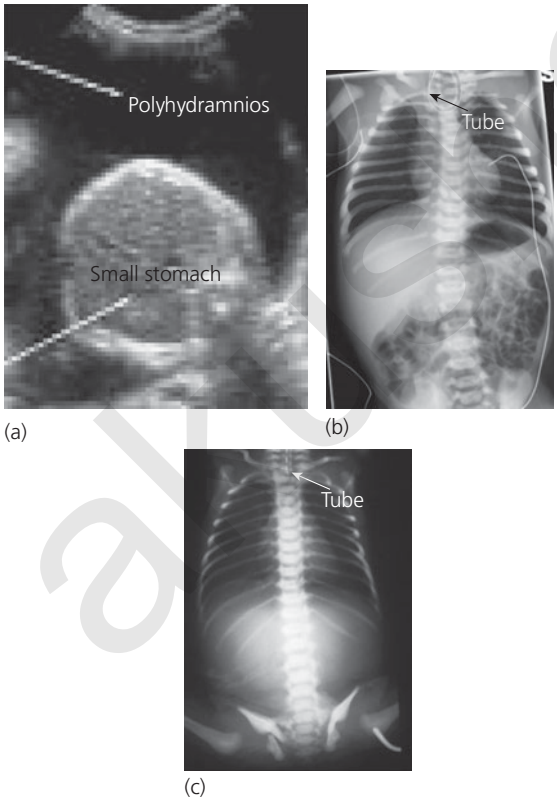


Figure 6.7 (a) Prenatal imaging of suspected tracheo-esophageal (TOF) with polyhydramnios and small stomach. (b) Plain radiograph showing esophageal pouch tube and distal gas confirming TOF with esophageal atresia. (c) Plain radiograph showing esophageal pouch tube and no abdominal gas confirming isolated esophageal atresia.

Gastrointestinal lesions

The presence of dilated loops of bowel (>15 mm in length and 7 mm in diameter) on prenatal ultrasound scan is indicative of bowel obstruction.

Duodenal atresia has a characteristic 'double bubble' appearance on prenatal scan, resulting from the simultaneous dilatation of the stomach and proximal duodenum.[82] Detection rate in the second trimester anomaly scan is almost 100% in the presence of polyhydramnios and the 'double bubble' sign. Associated anomalies are present in approximately 50% of cases with most notably trisomy 21 in 30% of cases, cardiac anomalies in 20%, and the presence of the VACTERL.[82]

The incidence of duodenal atresia is one in 5000 live births. The postnatal survival rate is >95%[15] with associated anomalies, low birth weight, and prematurity contributing to the <5% mortality. Temporary delay in enteral feeding occurs due to the dysmotility in the dilated stomach and duodenum.

There are many bowel abnormalities which may be noted on prenatal scanning (dilated bowel, ascites, cystic masses, hyperparistalsis, polyhydramnios, and echogenic bowel,[83] however none is absolutely predictive of postnatal outcome. Patients with obstruction frequently have findings (especially in the third trimester) of bowel dilatation (Fig. 6.8), polyhydramnios, and hyperparistalsis, but ultrasound is much less sensitive in diagnosing large bowel anomalies than those in the small bowel.[15] Since the large bowel is mostly a reservoir, with no physiologic function *in utero*,

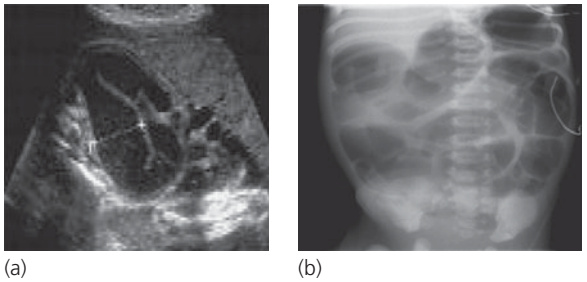


Figure 6.8 Prenatal and postnatal imaging of intestinal atresia.

defects in this region such as anorectal malformations or Hirschsprung's disease are very difficult to detect. Bowel dilatation and echogenic bowel may be associated with cystic fibrosis, therefore all such fetuses should undergo postnatal evaluation for this disease.[6] Prenatally diagnosed small bowel atresia does not select for a group with a worse prognosis and survival rates are 95–100%.

Abdominal cysts

Abdominal cystic lesions are not uncommonly diagnosed at antenatal ultrasound examination. A cystic mass identified in this way may represent a normal structural variant or a pathological entity requiring surgical intervention postnatally. Despite increasingly sophisticated equipment some congenital anomalies have significant false-positive rates on ultrasound and fetal cystic abdominal masses in particular can be difficult to diagnose accurately.[83] Excluding cysts of renal origin, the differential diagnosis includes ovarian cysts, enteric duplication cysts, meconium pseudocyst, mesenteric cysts, and choledochal cysts. Less common diagnoses include extralobar pulmonary sequestration and pancreatic, splenic, urachal, and adrenal cysts. Almost all cysts are benign and many are self-limiting, however these cysts create a high level of anxiety for the prospective parents, especially suspected adrenal cysts. Regular antenatal consultation and fetal counseling by the appropriate team may reduce parental anxiety levels. There is a very small role for fetal intervention. Resolution of these cysts were reported in 25% of cases and 30% came to surgical intervention.[83] Postnatal imaging is essential (Fig. 6.9).

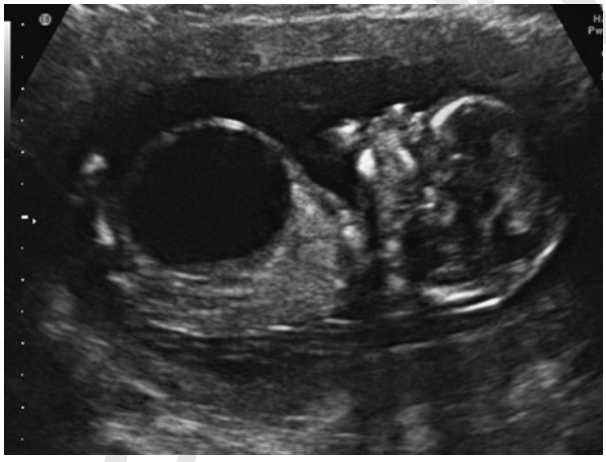
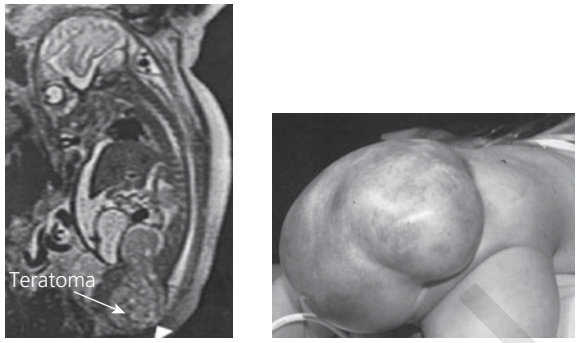


Figure 6.9 Nonspecific prenatal cyst showed complete resolution on postnatal imaging.

Sacrococcygeal teratoma

Sacrococcygeal teratoma (SCT) is the most common neonatal tumor, accounting for one in 35000–40000 births (Fig. 6.10). Four types have been defined:[84]

1. type 1 external tumor with a small presacral component;
2. type 2 external tumors with a large presacral component;



(a) (b)

Figure 6.10 Prenatal MRI and postnatal image of sacrococcygeal teratoma.

3. type 3 predominantly presacral with a small external component;
4. type 4 entirely presacral.

The latter carry the worst prognosis due to delay in diagnosis and malignant presentation. Doppler ultrasound is the diagnostic tool, however fetal MRI provides better definition of the intrapelvic component.[85] SCT is a highly vascular tumor and the fetus may develop high cardiac output failure, anemia, and ultimately hydrops with a mortality of almost 100%.[86,87] Fetal treatment of tumor resection or ablation of feeding vessel has been attempted in hydropic patients.[88] Cesarean section may be offered to patients with large tumors to avoid the risk of bleeding during delivery. Postnatal outcomes following surgery in type 1 and 2 lesions are favorable, however type 3 and 4 tumors may present with urological problems and less favorable outcomes. Long-term follow up with AFP protein and serial pelvic ultrasounds is mandatory to exclude recurrence of the disease.

Renal anomalies

Urogenital abnormalities are among the most common disorders seen in the perinatal period and account for almost 20% of all prenatally diagnosed anomalies.[89] The routine use of antenatal ultrasound scans has resulted in the early detection of these conditions and in selected cases has led to the development of management strategies including fetal intervention aimed at preservation of renal function. Two major issues are the indications for intervention in bladder outlet obstruction and early pyeloplasty in infancy in cases with hydronephrosis.[90]

Prenatal evaluation of a dilated urinary tract is based on serial ultrasound scans as well as measurement of urinary electrolytes. Ultrasonography provides measurements of the renal pelvis, assessment of the renal parenchyma, as well as the detection of cysts in the cortex. In severe disease, lack of amniotic fluid may make ultrasound assessment of the renal tract difficult and MRI may be helpful.[91] Oligohydramnios is indicative of poor renal function and poor prognosis owing to the associated pulmonary hypoplasia. Urogenital anomalies coexist with many other congenital abnormalities and

amniocentesis should be offered in appropriate cases. It is estimated that 3% of infants will have an abnormality of the urogenital system and half of these will require some form of surgical intervention.[92]

Upper urinary tract obstruction

Antenatal hydronephrosis accounts for 0.6–0.65% of pregnancies.[93] The most common cause of prenatal hydronephrosis is pelviureteric junction obstruction (PUJ), others being transient hydronephrosis, physiological hydronephrosis, multicystic kidney, posterior urethral valves, ureterocele, ectopic ureter, etc. The prognosis of antenatally diagnosed hydronephrosis in unilateral disease and in renal pelvic diameter of <10 mm is excellent. Spontaneous resolution is noted in 20% of patients at birth and 80% at three years of age.[94] Only 17% of prenatally diagnosed hydronephrosis needs surgical intervention. Postnatal management of hydronephrosis requires ultrasound at birth and at one month of age, and further evaluation with radiology and scintigraphy if an abnormality is suspected.[95]

Lower urinary tract obstruction

Posterior urethral valves (PUV) are the most common cause for lower urinary tract obstruction in boys with an incidence of one in 2000–4000 live male births (Fig. 6.11). The diagnosis of PUV is suspected on the prenatal ultrasound finding of bilateral hydronephrosis, associated with a thickened bladder and decreased amniotic fluid volume. Serial fetal urine analysis may provide prognostic information on renal function.[96] Prenatal diagnosis for patients with PUV is a poor prognostic sign with 64% incidence of renal failure and transient pulmonary failure, compared to 33% in the postnatally diagnosed patients.[97] Pulmonary hypoplasia secondary to oligohydramnios largely contributes to the morbidity and mortality from fetal urethral obstruction. Outcomes of fetal intervention with vescicoamniotic shunting[98,99] or fetal cystoscopic ablation of urethal valve[100] is still under review and awaits a multicenter trial.

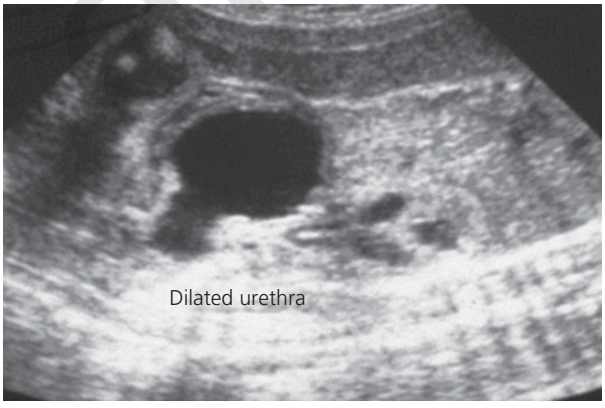


Figure 6.11 Keyhole sign of posterior urethal valves.

Postnatal management includes ultrasound confirmation of the diagnosis, bladder drainage via a suprapubic or urethral route, and contrast imaging of the urethra. Primary PUV ablation, vescicostomy, or ureterostomy are postnatal surgical options. The overall outcome from this disease is unfavorable.

CONCLUSION

The boundaries of pediatric surgical practice have been extended by prenatal diagnosis. The care of patients with surgically correctable defects can now be planned prenatally with the collaborative effort of obstetricians, geneticists, neonatologists, and pediatric surgeons. Essential to prenatal counseling is the understanding of the specific surgical condition's prenatal natural history, the limitations of prenatal diagnosis, the detection of associated anomalies, the risks and indications of fetal intervention programs, and postnatal outcomes. Prenatal counseling is an essential component of pediatric surgical practice and should be ensured in the training program for future pediatric surgeons.

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7

Fetal and birth trauma

PREM PURI AND PIOTR HAJDUK

FETAL TRAUMA

Traumatic injuries in pregnancy are a major cause of nonobstetrics maternal and neonatal morbidity and mortality.[1–7] About 40 years ago,[5,8] it was estimated that 6–8% of pregnant women were affected by accidental injury. This number is likely to be greater now because more active lifestyles led by pregnant women in today's society may put them at increased risk of injury.[3] When a pregnant woman presents with a major trauma, two lives are at risk. The survival of the fetus depends primarily on maternal survival[9] but occasionally the extent of maternal injury does not correlate with the degree of fetal injury.[1,10,11]

Treatment priorities for traumatic pregnant women remain the same as in patients who are not pregnant, although resuscitation and stabilization should be modified to account for the anatomical and physiological changes of the pregnancy.[12,13] The first consideration in the management of maternal trauma in an accident is to ensure the survival of the mother, as is recommended by the Advanced Trauma Life Support Program.[12]

Assessment of the fetus forms part of the secondary survey of the mother, and should be performed in conjunction with an obstetrician as beyond 24–28 weeks' gestational age the fetus is potentially viable if urgent delivery is required.[12]

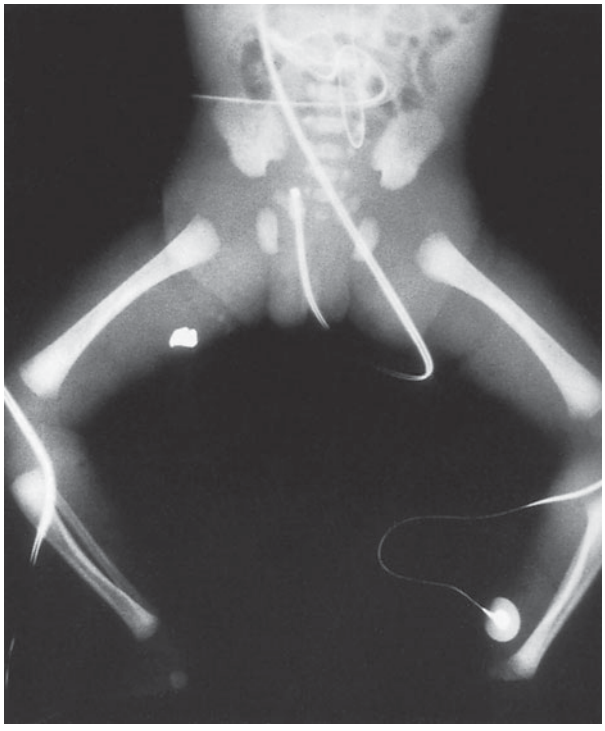
Assessment of the fetus includes: the date of the last menstrual period, measuring the fundal height, examination for uterine contractions and tenderness, fetal movements, and fetal heart rate. An important part is the vaginal examination for amniotic fluid or blood.

Fetal distress can occur at any time and without warning. The fetus should be continually monitored to ensure early recognition of fetal distress by using the ultrasonic Doppler cardioscope. Signs of fetal distress include: bradycardia (<110 bpm), inadequate accelerations in fetal heart rate in response to uterine contraction, and late decelerations in fetal heart rate in response to uterine relaxation.

In blunt maternal–fetal trauma, placental abruption is the leading cause of death with maternal survival.[14,15] Occasionally, minor maternal trauma may disrupt the placenta 'lifeline' by shearing the relatively rigid placenta from the more elastic uterine wall, thereby leading to fetal distress and subsequent fetal death.[10] The clinical signs of placental abruption include vaginal bleeding, uterine irritability, abdominal tenderness, increasing fundal height, maternal hypovolemic shock, and fetal distress. Although the common classical presentation of placental abruption involves vaginal bleeding and abdominal pain, some cases of traumatic abruption occur without these symptoms and fetal distress may not develop for several hours.

The fetus should be considered salvageable in the face of severe or even mortal maternal injury, and more than 150 cases of successful post-mortem Cesarean section delivery and numerous deliveries of normal neonates just before maternal death have been described.[16,17] Fetal injuries after trauma may be treatable, but only if they are recognized. Penetrating trauma by gunshot or stab wounds, although rare,[10] are usually obvious, and thus appropriate surgical intervention has to be undertaken (Fig. 7.1a,b). Although most cases of penetrating fetal trauma are fatal to the fetus, some cases of fetal salvage have been reported.[18,19] In contrast, surgically treatable fetal injury may go unrecognized after blunt maternal trauma, while these injuries are much more frequent. Thus, one can recognize that after 28 weeks' gestation, Cesarean section for fetal salvage is indicated in the presence of placental abruption with fetal distress, treatable life-threatening fetal injury, or if there is obvious impending or recent maternal death.

A pediatric surgeon should participate in the evaluation and management of both the pregnant patient and the neonate delivered after maternal trauma, together with the obstetrician and neonatologist. Pregnant women should be hospitalized after trauma for appropriate evaluation and fetal monitoring, in the hope of decreasing trauma-related fetal deaths. In recent years, it is expected that every pediatric surgeon would be familiar with the treatment of pediatric trauma. The treatment of the traumatic pregnant woman and the fetus must be part of this skill, especially if the fetus is to be considered a patient.



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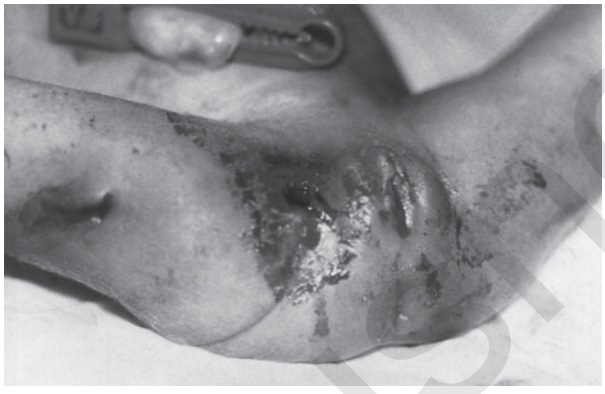


(b)

Figure 7.1 (a) X-ray of a neonate born to a mother who sustained accidental gunshot wounds to her abdomen. Note metallic pellet in the right thigh. (b) Clinical photograph of the same infant showing entry wound in the right thigh.

BIRTH TRAUMA

Birth injuries are defined as injuries associated with mechanical forces producing hemorrhage, edema, tissue disruption, or alteration of organ function occurring during the intrapartum period.[20] With the improvement in obstetric techniques, increased frequency of Cesarean section in potentially difficult deliveries, decreased use of difficult forceps and utilization of fetal heart rate, and determination of acid–base status to monitor the fetus during labor, the incidence of birth injuries has decreased in recent years.[21] Furthermore, use of prenatal ultrasonography has allowed early identification of the risk factors for possible birth trauma, including fetal size and position and enlarged fetal organs or masses. Nevertheless, birth injuries still occur and represent an important problem for the clinician; the incidence of birth trauma is reported to be two to eight per 1000 live births.[22,23]

Birth injury is usually associated with unusual compressive or traction forces in association with abnormal presentation of the fetus. Factors that predispose birth injury include primiparity, cephalopelvic disproportion, dystocia, prematurity, prolonged labor, macrosomia, abnormal presentation, forceps application, version, and extraction.[20,22,23] The newborn at greatest risk for birth injury is the one in breech presentation.

Types of birth trauma

HEAD INJURIES

Caput succedaneum

Caput succedaneum is a diffuse edematous, occasionally hemorrhagic swelling of the scalp, superficial to the periosteum, occurring secondary to compression of the presenting part during prolonged labor. Usually, caput succedaneum requires no treatment and the swelling disappears spontaneously in a week or so. Rarely, hemorrhage into soft tissue may cause anemia that requires blood transfusion or may lead to hyperbilirubinemia or both.[24]

Cephalhematoma

Cephalhematoma is a subperiosteal collection of blood most often found in the parietal region and sharply delineated by the surrounding suture lines (Fig. 7.2). In 10–25% of cephalhematomas there is an underlying skull fracture which is usually of linear type and clinically unimportant.[25] The precise mechanism of production of cephalhematoma is not well established. Repeated buffeting of the fetal skull against the maternal pelvis during a prolonged labor and mechanical trauma caused by the use of forceps and vacuum extractor in delivery have been implicated as important factors. Cephalhematomas have been reported to originate *in utero*, antepartum.

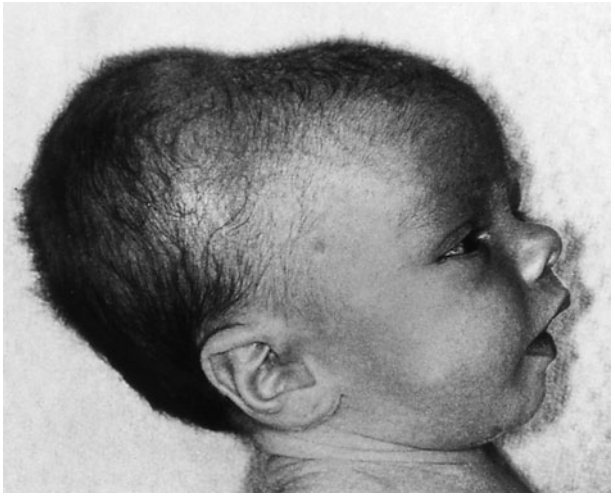


Figure 7.2 Large cephalhematoma.

Petrikovsky *et al.*[26] found seven cases of cephalhematomas identified prenatally on 16292 fetuses during comprehensive ultrasound examinations. Premature rupture of the membranes was seen and was suggested as an associated factor.

Most cephalhematomas resolve spontaneously within a few weeks. Aspiration of the hematoma is contraindicated because of the risk of introducing infection. Drainage and antibiotic therapy are only indicated in the rare case of superinfection of the cephalhematoma.[23] Occasionally, serious complications such as anemia, jaundice, abscess, septicemia, meningitis, osteomyelitis, disseminated intravascular coagulation, shock with acute hemorrhage, and depressed skull fractures have been reported in association with cephalhematomas.[20,27–29] Management involves careful observation for these complications.

Skull fractures

Most of the skull fractures are linear, occurring in association with cephalhematomas and usually involving the parietal bones (Fig. 7.3a). No specific treatment is required for linear fractures, but skull x-rays should be repeated when the infant reaches 2–4 months of age to rule out 'growing fracture of the skull' associated with a leptomeningeal cyst (Fig. 7.3b). A leptomeningeal cyst can occur rarely if the trauma causing the linear fracture tears the underlying dura, thereby permitting herniation of the meninges and brain. This requires surgical intervention to avoid progressive brain damage.[28,30]

Depressed skull fractures are most often caused by pressure of the fetal head against the maternal pelvis or in association with forceps delivery (Fig. 7.4). Several nonsurgical techniques for elevation of depressed skull fracture in the newborn have been described, including suction with a breast pump or vacuum extractor,[31–33] and by digital manipulation. Indications for surgical elevation of depressed skull fracture include:[34]

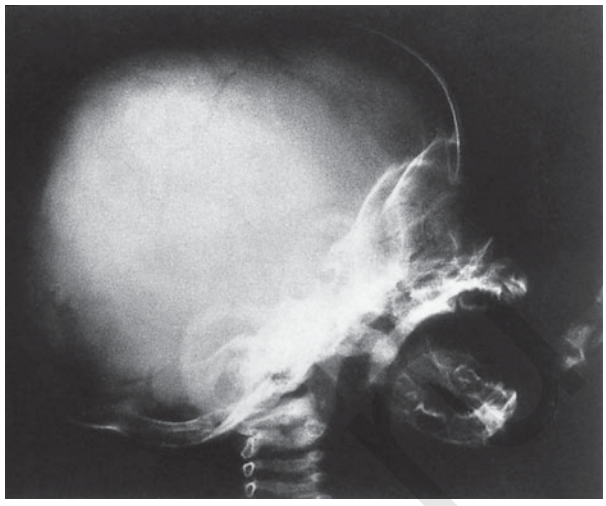
- radiographic evidence of bone fragments within the brain;
- neurological deficit;
- signs of increased intracranial pressure;
- failure to elevate the fracture by closed manipulation.

Intracranial hemorrhage

Intracranial hemorrhage following birth trauma may occur in the subarachnoid space, the subdural space, or within the brain.

Subarachnoid hemorrhage is the most common form of birth-related traumatic intracranial hemorrhage in the newborn.[25] Blood in the subarachnoid space can be documented by lumbar puncture and the diagnosis confirmed by computed tomography (CT) scan.[35] In the vast majority of cases, traumatic subarachnoid hemorrhage is benign and does not require any treatment. Occasionally it may result in a communicating hydrocephalus.

Subdural hemorrhage is caused by rupture of the cerebral veins bridging the subdural space, occurring as a result of excessive molding of the baby's head during labor or delivery. Most subdural hematomas are infratentorial and bilateral,



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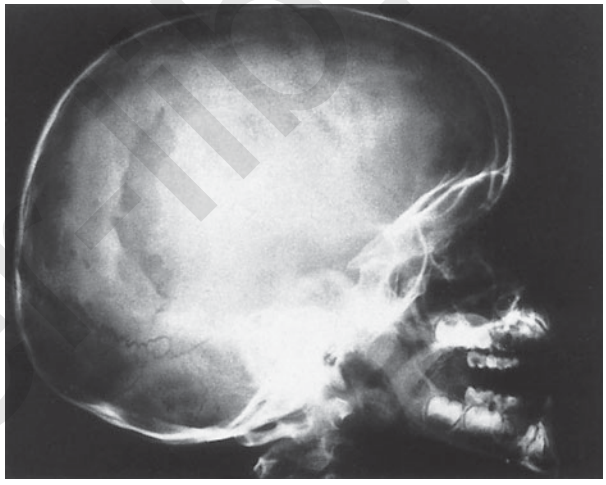


(b)

Figure 7.3 (a) Linear fracture of left parietal bone at birth. (b) Three years later the patient presented with a pulsatile swelling in the left parietal region. X-ray shows an extensive bone defect due to leptomeningeal cyst.

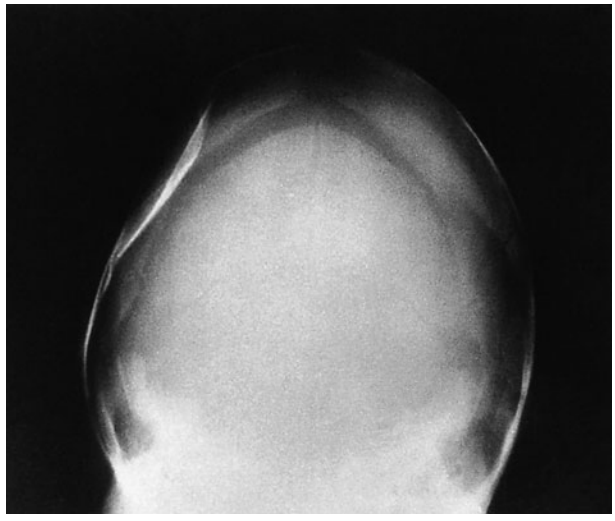


Figure 7.4 Depressed fracture or right parietal bone following forceps delivery.

but occasionally they have been described in the posterior fossa. Principal factors that predispose to the occurrence of subdural hematoma include large-size infants,[25] breech delivery,[36] and forceps extraction in primiparous women.[37] Clinical features of neonatal subdural hemorrhage may include pallor, vomiting, irritability, seizures, unequal pupils, drowsiness, hypotonia, high-pitched cry, tense fontanelle, and retinal hemorrhages. The diagnosis is confirmed by a subdural tap, CT scan (Fig. 7.5), or magnetic resonance imaging (MRI).[38] Although ultrasound (US) is a standard practice for detecting germinal matrix hemorrhage in the preterm neonate,[39] it is unlikely to be as accurate as a CT scan in diagnosing peripheral lesions in subarachnoid or subdural space.[40] MRI imaging, in general, has high sensitivity for intracranial hemorrhage, and, with its lack of ionizing radiation, is the favorable technique for the further evaluation of birth trauma over CT, especially for a neonate.[41,42] The treatment consists of repeated tapping of the subdural space using a 20-gauge needle at the lateral margin of the anterior fontanelle. In most cases, subdural collections can be treated successfully with repeated taps. Rarely, membrane stripping or subdural space shunting may be required to deal with persistent subdural collections.

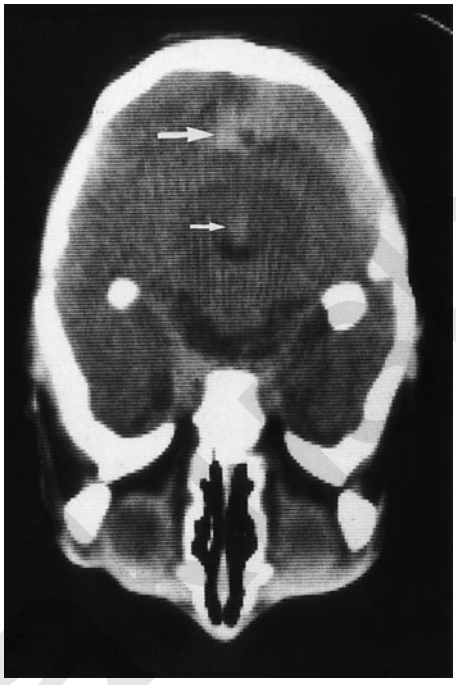


Figure 7.5 Computed tomography brain scan without i.v. contrast medium in a newborn, showing blood in the subarachnoid space (large white arrow) and blood in the floor of fourth ventricle (small white arrow).

Intracerebral hemorrhage

Traumatic intracerebral hemorrhage is the least common of intracranial hemorrhage in the newborn.[25] The clinical features are those of increased intracranial pressure. The diagnosis can be made with cerebral ultrasonography, CT scan or MRI, and regression or complications can be monitored with serial studies.[38]

SPINAL CORD INJURIES

The incidence of birth injury to the spinal cord is difficult to determine because most neonatal post-mortem examinations do not include complete examination of the spinal cord.[43] The leading cause of neonatal spinal cord injury is delivery of the fetus with marked hyperextension of the neck in a breech presentation. Approximately 75% of reported spinal cord injuries occurred in infants delivered vaginally in the breech presentation.[44] Other predisposing factors are prematurity, shoulder dystocia, intrauterine hypoxia, and precipitous delivery.[45] The application of compressive forceps to the fetal spine during fundal pressure to relieve shoulder dystocia has been reported to result in lower thoracic spinal cord injury in the newborn.[46] The site of spinal cord injury following breech delivery is usually in the lower cervical and upper thoracic region, while injury following vertex presentation is usually located in the upper or midcervical level.[25] The injury is usually caused by stretching of the cord and not by compression. The most common mechanism responsible for spinal cord injury is the use of excessive longitudinal traction on the trunk while the head is still engaged in the pelvis.[33] The spinal cord is relatively inelastic compared with the vertebral fracture or dislocation, or both, and cord transection.

The clinical manifestations of spinal cord injury may fit into one of the following four recognized groups, depending on the severity of the damage incurred:[27,47]

1. babies who are stillborn or die immediately after birth due to a high cervical or brainstem lesion;
2. neonates who die shortly after birth due to respiratory depression and complications and who generally have upper and midcervical lesions;
3. long-term survivors who have flaccid paralysis in the neonatal period and proceed to develop spasticity and hyper-reflexia in the ensuing months;
4. those with minimal neurological signs or spasticity who are often classified as having cerebral palsy.[48]

The symptoms in these patients result from partial spinal cord injury or cerebral hypoxia. When spinal cord injury is suspected, definition of the underlying pathology can be difficult using standard diagnostic procedures, including plain x-ray and CT, with or without myelography. MRI, with its excellent definition and low risk of complication, is the best diagnostic tool available to evaluate clinically suspected spinal cord pathology.[49,50] Spinal ultrasound is a good imaging method for guiding diagnosis of traumatic spinal cord lesions.[51]

Treatment of spinal cord injuries is supportive and includes physiotherapy, braces, and urological, orthopedic, and psychological care. Surgery has little to offer to patients with these types of injuries. Great emphasis should be placed on prevention of spinal cord injury in the newborn.

PERIPHERAL NERVE INJURIES

Injury to the peripheral nerves in the newborn is usually caused by excessive traction or direct compression of nerves

during delivery. The nerves most commonly involved are the brachial plexus, facial nerve, and phrenic nerve.

Brachial plexus injury

With the improvement in obstetric techniques, the incidence of birth-related brachial plexus injuries has decreased considerably in recent years. The incidence of brachial plexus birth palsy is estimated to be between 0.4 and four per 1000 live births.[52–54] The injury is usually caused by traction and stretching of the plexus. All lesions occur in the plexus above the level of the clavicle and range from simple neuropraxia, classified by Sunderland[55] as grade I, to full neurotemesis when associated with root avulsion, classified as grade V. Perinatal risk factors include large-for-gestational age infants (macrosomia), multiparous pregnancies, previous deliveries resulting in brachial plexus birth palsy, prolonged labor, breech delivery, and assisted (vacuum or forceps) difficult deliveries, shoulder dystocia, and/or asphyxiated infant.[52,56,57] Whereas a mechanical basis for brachial plexus injury is well accepted, delivery by Cesarean does not exclude the possibility of birth palsy.[53]

Brachial plexus injury has been divided into three main types depending on the site of the injury:

1. Erb's palsy, which results from injury of the fifth and sixth cervical nerve roots, is by far the most common type of injury. The affected arm hangs limply adducted and internally rotated at the shoulder, and extended and pronated at the elbow with flexed wrist in the typical 'waiter's tip' posture (Fig. 7.6). The Moro, biceps, and redial reflexes are absent on the affected side. The grasp reflex is intact. These clinical findings are the result of paralysis of the deltoid, supraspinatus, infraspinatus, brachioradialis, and supinator brevis muscles.
2. Klumpke's paralysis results from injury of the eighth cervical and first thoracic nerve roots and is extremely rare as an isolated entity. The intrinsic muscles of the hand and flexors of the wrist and fingers are affected. The grasp reflex is absent. Injury involving the cervical sympathetic fibers of the first thoracic root may result in ipsilateral Horner syndrome.
3. Injury to the entire brachial plexus results in a flaccid arm with absence of sweating, sensation, and deep tendon reflexes. The differential diagnosis includes fracture of the clavicle or humerus, traumatic epiphysiolysis of the proximal epiphysis of the humerus, and shoulder dislocation.[58] These injuries can of course occur in addition to the plexus paralysis.[59] Another associated injury is a phrenic nerve palsy.[60] A radiograph of the shoulder, upper arm, and clavicle should be taken. A chest x-ray should be obtained because of the possibility of an associated phrenic nerve palsy. Electromyography, although of limited value, may be useful in determining the extent and site of injury and evaluating the prognosis.[58,61]

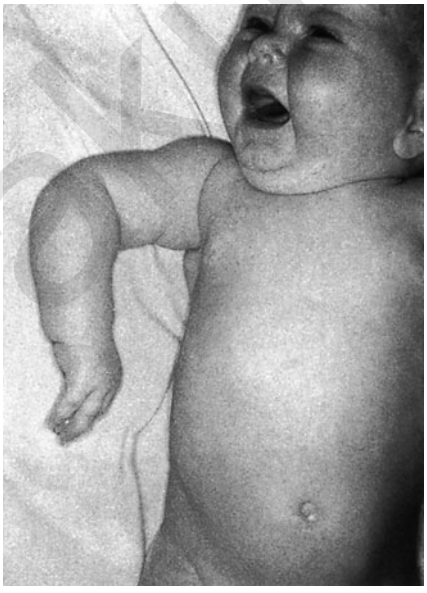


Figure 7.6 Erb's palsy. Characteristic deformity of right arm.

Serial physical examination of children with brachial plexus injury is recommended, because it is essential to predict recovery and determine the need for additional therapeutic or surgical intervention. Passive range of motion and active muscle strength should be assessed. Assessing infants often requires approximation of function by observing spontaneous activity and assessing reflexes (Moro reflex, asymmetric tonic neck, and symmetric tonic neck).[54] Most neonates with brachial plexus injury make a complete or partial recovery on conservative treatment.[25,54,60] The main principle of management is to maintain the range of 'motion' in the affected joints. Treatment should be delayed for a period of 3–4 weeks after the trauma, in which immobilization of the hand and stretched nerve fibers will allow a spontaneous cure. During the first 4 weeks, the arm has to be adducted to the thorax. Abduction and external rotation position of the shoulder must be prevented due to considerable tension on the brachial plexus in that position. In the other joints, careful passive physiotherapy should be carried out. Thereafter, a gentle range of motion exercises to shoulder, elbow, wrist, and small joints of the hand may have to be started.

The prognosis of brachial plexus paralysis is better in the Erb's patient than in the patient with the Klumpke variety and in both of these groups is better than in total paralysis. In the majority of Erb's palsy cases, a partial or complete recovery can be achieved.[62] Surgical exploration and repair of brachial plexus birth injuries are recommended only when there is no recovery of the biceps by three months of age. An electromyography and myelogram with CT scanning are performed preoperatively.[58] Advances in microsurgical techniques and reconstruction of the injured plexus by grafting from the sural nerve can significantly improve the functional result.[58,63,64] Recent use of synthetic collagen nerve conduits has shown very good results in select short-segment brachial plexus repairs.[65] The advantages of synthetic grafts over conventional autologous grafts include eliminating donor site morbidity, increasing the amount of graft material available, and providing direct conduits for neural growth factors produced by the proximal segment to reach the distal segment.

Facial nerve injury

Facial palsy secondary to birth trauma is usually unilateral and most commonly follows compression of the peripheral portion of the nerve, either near its emergence from the stylomastoid foramen or where the nerve transverses the ramus of the mandible. The mechanism of injury is usually either direct trauma from forceps or compression of the side of the face and nerve against the sacral promontory. The affected infant has absent or decreased forehead wrinkling, a persistently open eye, a decreased nasolabial fold, and flattening of the corner of the mouth on the affected side (Fig. 7.7). Treatment is conservative, since spontaneous recovery occurs within one month in most cases of birth-related facial palsy.[23,57] Initial treatment should be directed at protecting the corneal epithelium from drying with the use of methylcellulose drops instilled every 4 hours. Rarely, there is need for surgical intervention and neurolysis or a nerve cable transplant for the injured or degenerative facial nerve, after confirming the diagnosis by electromyographic and electroneurographic tests.[66]

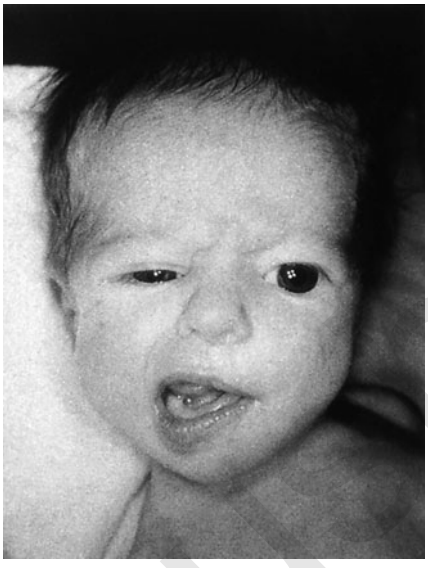


Figure 7.7 Left facial nerve palsy following difficult forceps. Note obliteration of left nasolabial fold with typical deformity of mouth and wide-open left eye.

Phrenic nerve injury

Diaphragmatic paralysis in the neonate results from stretching or avulsion of the fourth and fifth cervical roots, which form the phrenic nerve. The most common cause of phrenic nerve injury is a difficult breech delivery. The majority of injuries are unilateral. Bilateral diaphragmatic paralysis is rare.[67] Approximately 75% of cases of birth-related phrenic nerve injury have an associated brachial plexus injury.[68,69]

The clinical features of diaphragmatic paralysis are nonspecific and include respiratory distress with tachypnea, cyanosis, and recurrent atelectasis or pneumonia. Chest x-ray demonstrates an elevated hemi diaphragm about two intercostal spaces higher than the adjacent diaphragm (Fig. 7.8a). Diagnosis is confirmed on fluoroscopy, which shows an immobile diaphragm or an abnormal elevation of the diaphragm during inspiration constituting paradoxical movement.[70] Real-time ultrasonography can also be employed to diagnose phrenic nerve paralysis and can be performed in the intensive care unit in very young babies (Fig. 7.8b).

Initial supportive management usually includes mechanical ventilation, oxygen, chest physiotherapy, antibiotics, and nasogastric tube feedings to avoid failure to thrive and to ensure weight gain. Some patients who have severe or increasing respiratory distress may be managed by continuous positive airway pressure (CPAP).[71,72]

Most infants with diaphragmatic paralysis make a complete recovery after conservative treatment (Fig. 7.8c). Surgery may be required if there is persistent paralysis after 2 weeks of mechanical ventilation or three months of medical treatment. The procedures employed include plication of the diaphragm via thoracoscopy or thoracostomy[25,72] or incision and replacement of the diaphragm.[73]

INTRA-ABDOMINAL INJURIES

Birth trauma involving intra-abdominal organs is relatively uncommon. The organs most commonly involved are the liver, spleen, adrenal, and kidney.

Liver

The liver is the most commonly injured abdominal organ during the birth process. Factors that predispose to liver trauma include breech presentation, infants with hepatomegaly, large infants, prematurity, and coagulation disorders.[23] The mechanism of birth-related liver injury is thought to be either: (1) thoracic compression and pulling of the hepatic ligaments with consequent tearing of the liver parenchyma; or (2) direct pressure on the liver leading to subcapsular hemorrhage or rupture.[23]

Hepatic trauma more commonly results in subcapsular hemorrhage than actual rupture of the liver. The infant with subcapsular hemorrhage usually appears to be normal for the first 3 days of life, when the capsule ruptures and there is extravasation of blood into the peritoneal cavity. This is followed by sudden circulatory collapse, abdominal distension, and a rapid drop in the hematocrit value. If the processus vaginalis is patent, blood may be seen in the scrotum, suggesting hemoperitoneum. In patients with primary rupture of the liver, major intraperitoneal bleeding occurs immediately, resulting in severe shock and abdominal distension. Abdominal x-rays are not usually very helpful, but may show uniform opacity of the abdomen, indicating free intraperitoneal fluid. Abdominal ultrasonography may confirm the diagnosis and is also useful in differentiating a solid liver tumor from an unruptured subcapsular hemorrhage. A CT scan is recommended, but only if the patient is hemodynamically stable (Fig. 7.9a–d). Abdominal paracentesis is the procedure of choice for rapid diagnosis of hemoperitoneum. Immediate management consists of blood transfusion to restore the blood volume and recognition and correction of any coagulation disorder. This is followed by an immediate laparotomy, with evacuation of the hematoma and repair of any laceration by sutures or by fibrin glue.[74]

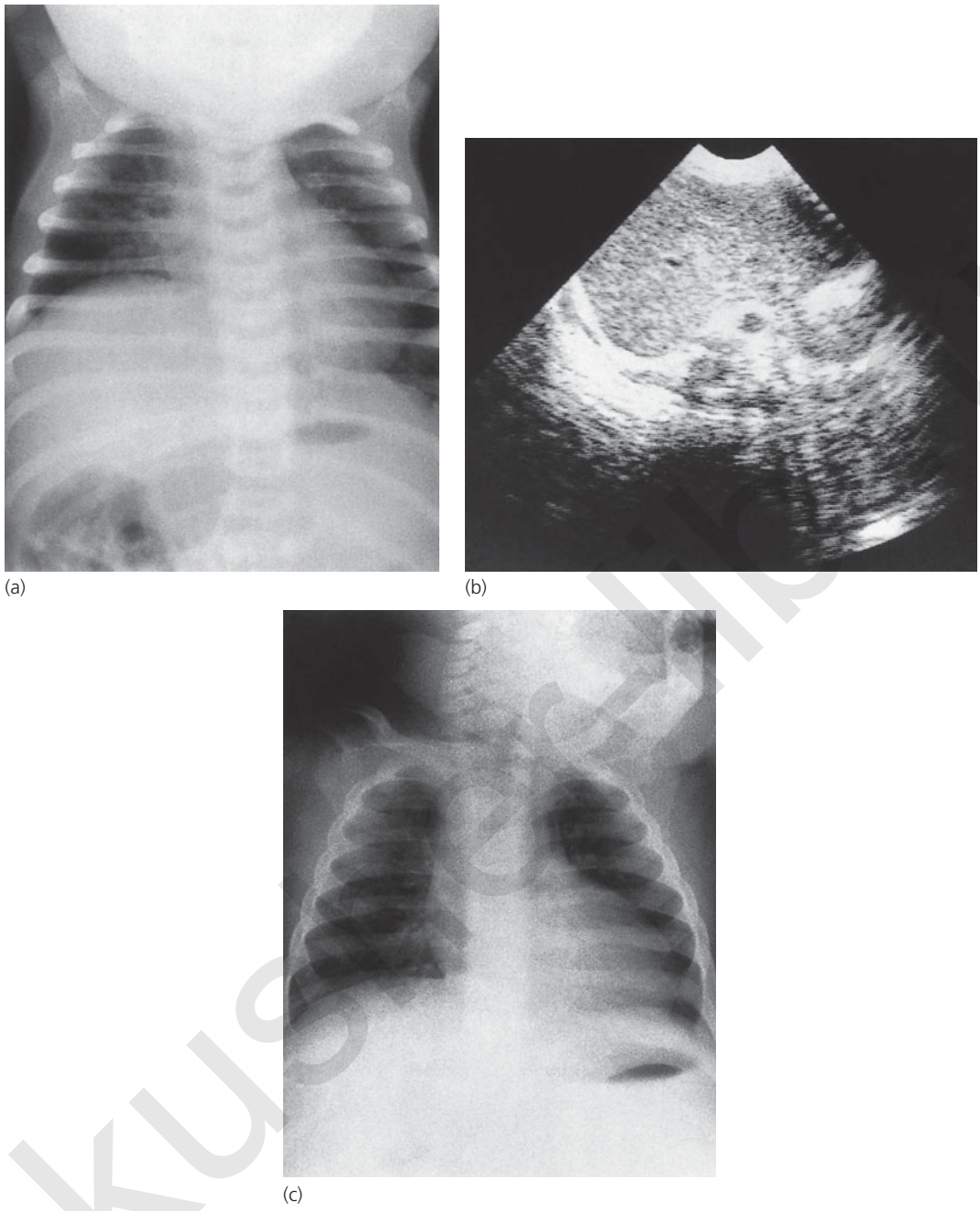


Figure 7.8 Phrenic nerve paralysis. (a) Chest x-ray shows elevated right diaphragm. (b) Transverse real-time sonogram showing blurring in the region of left diaphragm due to respiratory movement. Right diaphragm did not move and is sharply outlined along the liver. (c) Chest x-ray three months later shows normal right diaphragm after conservative treatment.

Spleen

Rupture of the spleen in the newborn occurs much less often than does rupture of the liver. The predisposing factors and mechanism of injury are quite similar to those of rupture of the liver. Although splenomegaly increases the risk, the vast majority of splenic injuries occur in spleens of normal size.[28] The presenting features are cardiovascular collapse and abdominal distension. Abdominal x-ray may indicate free fluid in the peritoneal cavity. Ultrasound scan, abdominal, and pelvic CT are recommended to confirm diagnosis.

Nonoperative management of pediatric splenic injuries is now recognized as the treatment of choice in most of cases.[75] This typically involves following vital signs, serial hematocrits, and physical examination. Blood transfusions are administered as required. Hemodynamically unstable newborns, usually with immediate massive hemorrhage, may require exploratory laparotomy.[75] In recent years, repair of the spleen has been advocated because of the risk of subsequent serious infections following splenectomy.[76] Since there is a critical mass of spleen which prevents overwhelming post-splenectomy infection (OPSI),[77,78] every surgeon should do the utmost to preserve

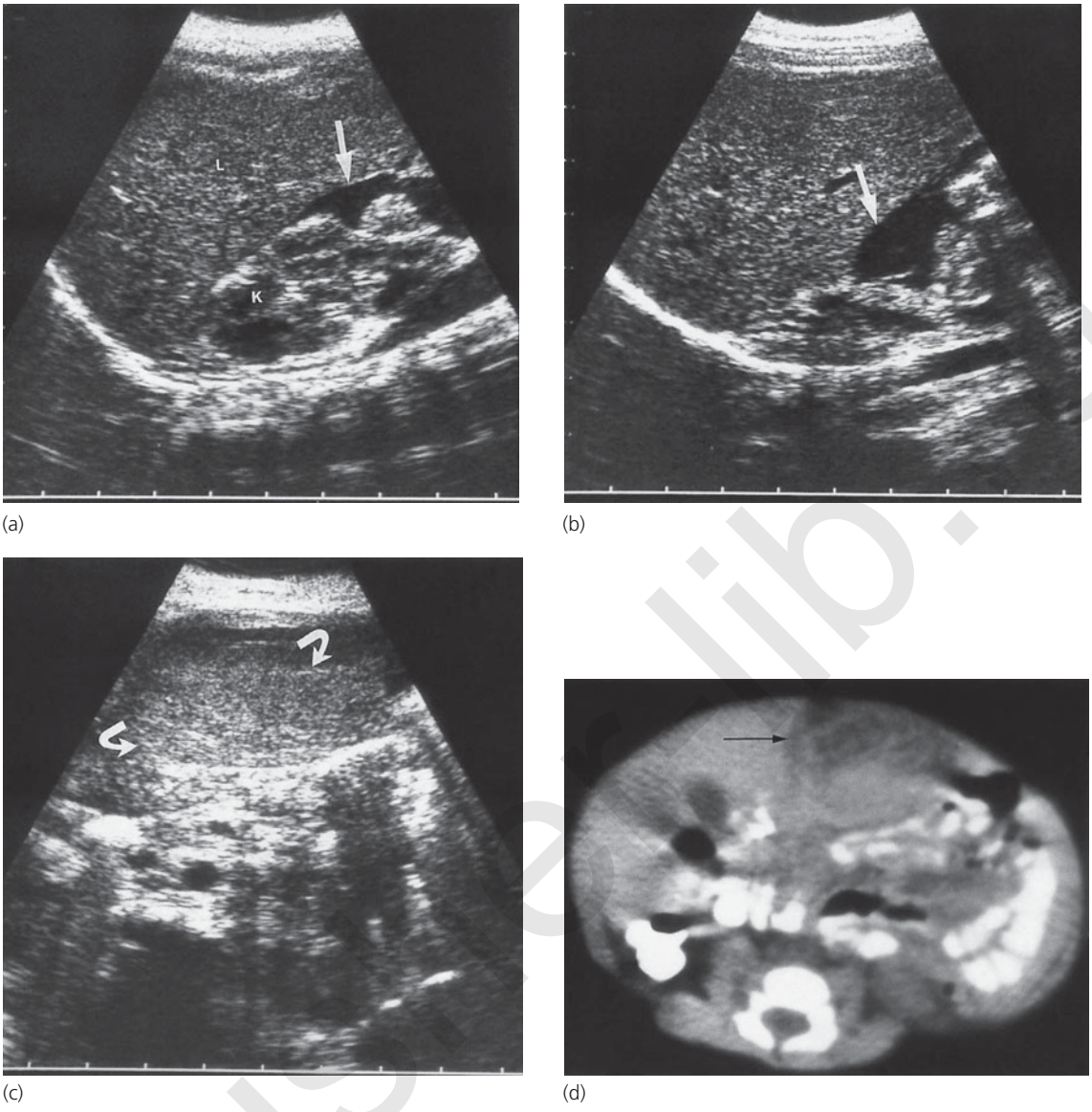
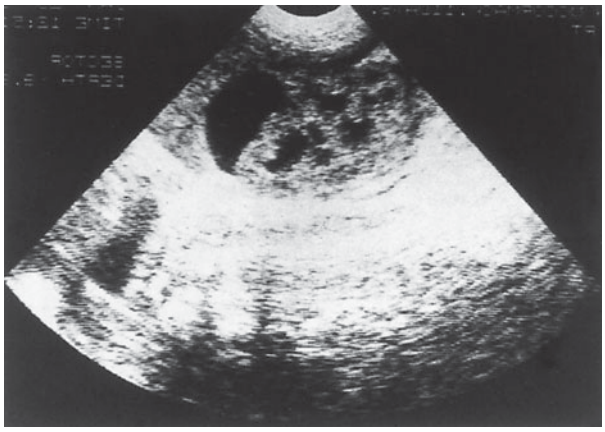


Figure 7.9 Newborn who developed a distended abdomen post-delivery. (a,b) Sonographic scan at 36 hours shows echo-poor material due to fresh hemorrhage (white arrow) between the anterior aspect of the right kidney (K) and the inferior aspect of the right lobe of liver (L). (c) Scan through left lobe of liver demonstrating an area of increased echogenicity in keeping with hemorrhage at site of laceration (curved arrows). (d) Laceration in left lobe confirmed on computed tomography scan (black arrow).

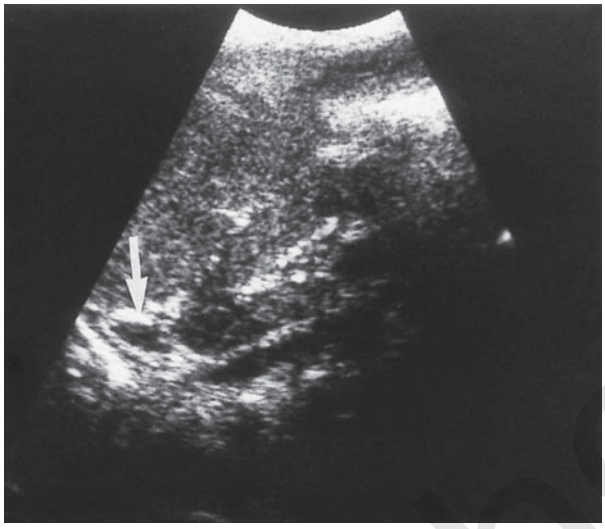
as much of the injured spleen as possible. Fibrin glue, splenorrhaphy, or partial splenectomy are the preferred surgical procedures.[23,79–81] This conservative surgical approach is advocated not only because of the OPSI, but also because of the absence of regeneration of the injured spleen after partial splenectomy, which has been proven in animals.[82]

Adrenal

Neonatal adrenal hemorrhage occurs most commonly following a prolonged and difficult labor, culminating in a traumatic delivery. Other contributing factors include asphyxia, prematurity, placental hemorrhage, hemorrhagic disease of the newborn, septicemia, renal vein thrombosis, increased vascularity, and congenital syphilis.[83–88] The right adrenal is involved in over 70% of cases, with bilateral involvement in 5–10%.[89,90] The presenting features vary with the degree of bleeding. The classical adrenal hemorrhage usually presents between birth and the fourth day of life as an abdominal mass with fever and jaundice or anemia.[88] The differential diagnosis may include adrenal cyst, neuroblastoma, and Wilms' tumour. Diagnosis of neonatal adrenal hemorrhage may be confirmed with a combination of ultrasound and i.v. pyelogram. Sonography would reveal a suprarenal mass that initially is echogenic, and subsequent changes to a cyst-like structure probably indicating fragmentation of the clot (Fig. 7.10a,b). An i.v. pyelogram should demonstrate downward displacement of the kidney on the affected side. An early total body opacification film may show a lucent region above the kidney. A 'rim' suprarenal calcification may be seen on abdominal radiographs 2–4 weeks after hemorrhage.[83,91]



(a)



(b)

Figure 7.10 (a) Right suprarenal echo-poor mass representing a right adrenal hemorrhage (between cursors) in an infant who suffered birth asphyxia. (b) Scan performed one month later, showing that hemorrhage has almost cleared. Small residual echo-poor area persists (white arrow).

In patients with retroperitoneal hemorrhage, treatment consists of blood transfusion, close observation, and follow-up ultrasound studies. In infants with massive intraperitoneal hemorrhage, surgical intervention consists of abdominal paracentesis, laparotomy, evacuation of hematoma, ligation of bleeders, or adrenalectomy if indicated. It must be remembered that the underlying pathology may be a neuroblastoma[92,93] and a biopsy should always be taken. Infrequently, a suspicion of an adrenal abscess ensues. In such a situation, a drainage procedure must be performed either percutaneously with ultrasound guidance or by operative exploration.

KIDNEY

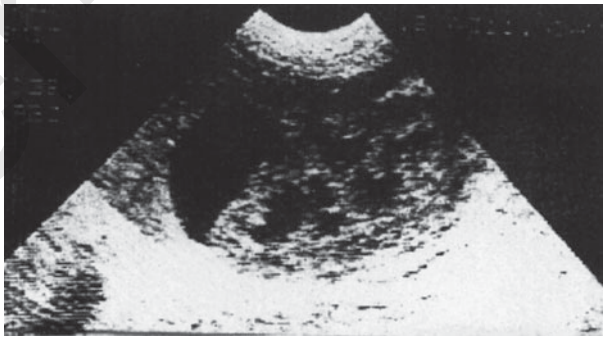
Birth-related trauma is rare. Rupture of the kidney in the newborn is usually associated with an underlying congenital anomaly.[94] The presenting signs are hematuria and renal mass. An i.v. pyelogram may show absence of excretion or leakage of contrast through the renal parenchyma into the perirenal space. Renal ultrasonography may demonstrate renal rupture (Fig. 7.11) or ascites. Treatment consists of conservative management if possible. Only in cases of severe bleeding or a total rupture of parenchyma or pelvis is a laparotomy indicated, with the correction of underlying congenital anomaly whenever it is necessary.

BONY INJURIES

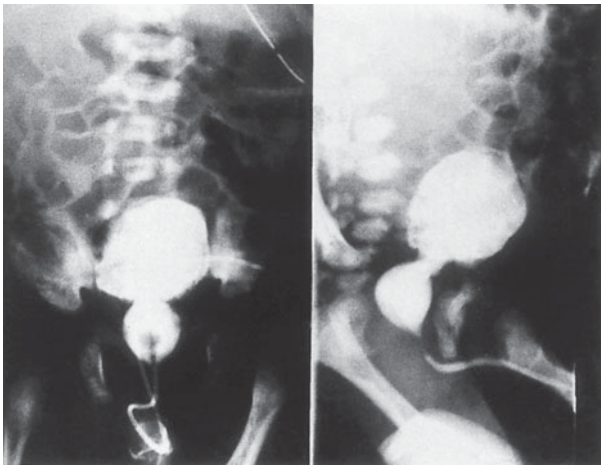
Fractures due to birth trauma almost always involve the clavicle, humerus, or femur. Epiphyseal separations usually involve upper and lower humeral and upper femoral epiphyses. Dislocations caused by birth trauma are rare.

Fracture of the clavicle

Fracture of the clavicle is the most common fracture in the newborn, usually occurring during a difficult delivery associated with large infants, breech presentation, and shoulder dystocia.[95] Most fractures are of the greenstick type, occurring in the middle third of the clavicle, but occasionally the fracture is complete (Fig. 7.12). Undisplaced fractures require no treatment. Fractures with marked displacement should be immobilized with a figure-of-eight bandage. Recovery is usually excellent.



(a)



(b)

Figure 7.11 (a) Longitudinal sonogram showing an echolucent area in upper pole of right kidney consistent with an intracapsular rupture. Both ureters were hydronephrotic with dilated bladder on sonography. (b) Voiding cystogram in the same patient confirmed posterior urethral valves.

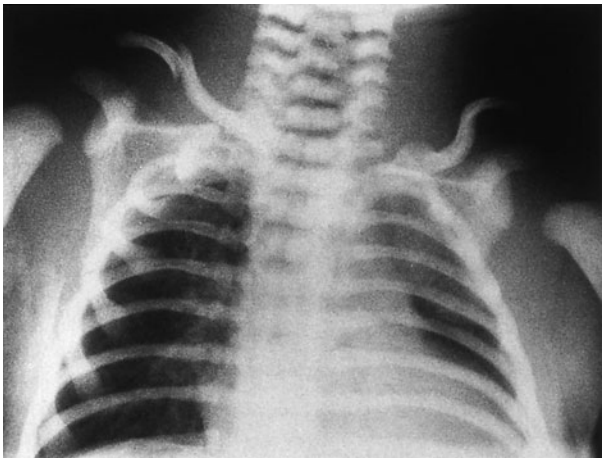


Figure 7.12 Fracture of right clavicle. Typical fracture of middle third of clavicle following forceps delivery.

Fracture of the humerus

Fractures of the humerus usually occur in the middle third of the shaft and are either transverse or spiral. They are usually greenstick fractures, but occasionally complete fracture with overriding of fragments may occur. The most common mechanisms responsible for fracture are believed to be traction on the extended arm in the breech presentations and axillary traction to disengage an impacted shoulder in vertex presentations. Treatment consists of strapping the arm to the chest. Complete healing of the fracture fragments usually occurs by 3 weeks.

Fracture of the femur

Femoral shaft fractures usually occur in the middle third and are transverse. The injury usually follows a breech delivery. X-ray invariably shows overriding of the fracture fragments. Treatment consists of Bryant's traction for 3–4 weeks. The prognosis in femoral fractures is usually excellent.

Epiphyseal separations

The epiphyseal separation or fracture occurs through the hypertrophied layer of cartilage cells in the epiphysis. The most common cause is a difficult breech delivery.[96] A fracture through the proximal epiphyseal plate of the humerus is the most common epiphyseal cartilage injury. Fractures entirely confined to the epiphyseal cartilage cannot be demonstrated radiologically. However, in many cases the fracture extends through a part of the metaphysis, separating a tiny bony fragment. This fragment is attached to the epiphysis and if no displacement of the epiphysis has occurred, the fragment may be the only radiographic evidence of fracture. An increased distance of the metaphysis from the joint compared with the opposite side can also indicate fracture through the epiphyseal plate. After 1–2 weeks, callus becomes visible, confirming the nature of the injury. Diagnosis at the initial stage has to be made primarily on clinical findings of pain on passive motion, swelling, and impaired movement around the joint. Recent reports suggest that epiphyseal separation can be studied by sonography and without the common use of arthrography.[96,97] Treatment of a fracture of the proximal epiphysis of the humerus consists of immobilization of the arm by the side with a sling in 90° flexion.

Epiphysiolysis of the proximal femur is sometimes confused with congenital dislocation of the hip and septic arthritis, and can occur not only after normal delivery but also after delivery by Cesarean section.[98] Treatment for a fracture of the proximal epiphysis of the femur is by traction and spica cast for two months.

TRAUMA TO THE GENITALIA

The breech delivery is the common cause of tissue injuries involving the external genitalia. Edema, ecchymoses, and hematomas of the scrotum or the labia majora can occur. No treatment is needed. Spontaneous resolution of edema occurs within 24–48 hours and of discoloration within 4–5 days.

If the tunica vaginalis is injured and blood fills its cavity, a hematocele is formed. The differential diagnosis should include neonatal torsion and patent processus vaginalis.[99,100] An iatrogenic injury to the scrotum with resultant castration during breech extraction has been reported.[101]

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8

Transport of the surgical neonate

PREM PURI AND RESHMA DOODNATH

INTRODUCTION

The successful outcome of an operation performed on a newborn with congenital anomalies depends not only on the skill of the pediatric surgeon, but also on that of a large team consisting of a pediatrician, anesthetist, radiologist, pathologist, biochemist, nurses, and others necessary for dealing satisfactorily with the newborn subjected to surgery. The pediatric transport team is a natural physical extension of the pediatric intensive care unit and should be able to provide advanced critical care management for children at remote sites and during transport to a tertiary center.[1] Advances in neonatal intensive care (NIC) dictate that effective and efficient treatment of the sickest neonates can only be available by concentrating resources such as equipment and skilled staff in a few specialist pediatric centers which have responsibilities to a particular region.[2,3] There has been a marked change over the past 20 years with regards to the knowledge, capabilities, and delivery of neonatal transport.[4] Neonates with congenital malformations will therefore have to be transported safely to these centers, sometimes over considerable distances.

PRENATAL TRANSFER

It has been stated before that prenatal transport of term fetuses with antenatally diagnosed surgical abnormalities does not improve the outcome if the quality of care before and during transport is good.[5] The distance involved does not influence the outcome. However, several other studies support the *in utero* transportation of the high risk fetus, particularly the very low birth weight (VLBW) babies and those with life-threatening neonatal surgical problems.[6–9] Hypothermia remains a main problem in these babies and it adversely affects neonatal outcome.[10] Poor post-transfer temperature seems to be an independent predictor of death.[10,11] Therefore, whenever possible, antenatal *in utero* transfer remains the method of choice for threatened delivery of an extremely preterm delivery before 28 weeks' gestation.[10,12]

PRE-TRANSFER MANAGEMENT

Transferring a newborn without proper stabilization is associated with increased morbidity and mortality. The golden rule still is that no neonate should be transported unless his or her condition has been sufficiently stabilized to survive the expected duration of the journey.[9] The transport environment is usually noisy and access to the patient is restricted, and so, careful attention to pre-transfer management will provide a higher margin of safety during the journey, when it may be difficult to provide adequate treatment should problems arise.[5] All babies must be properly resuscitated before the journey is undertaken.[9] All drugs, fluids, and equipment that is necessary for transfer should be carried by the transport team (Box 8.1).[13]

Box 8.1 Items necessary for transfer of surgical neonate

- Monitors – ECG, BP, pulse oximeter, temperature
- Infusion pumps
- Resuscitation drugs and equipment
- Portable oxygen supply
- Ventilator
- Document folder with all relevant information of patient and parents
- Maps – if ambulance crew are driving in unfamiliar area
- Portable telephone

Airway management

It should be ensured that the airway is clear and that the baby is well oxygenated, and that ventilation can be maintained

during transport. If any risk for deterioration of spontaneous breathing is present, the child should be intubated before departure[5] as emergency intubation while travelling is often difficult or hazardous. Except in patients with a fractured base of skull, nasal obstruction, or significant coagulopathy, every child should be intubated nasotracheally.[13] All intubated patients need to be suctioned regularly/hourly.

Temperature regulation

Thermoregulation requires critical attention. Hypothermia causes an increase in the neonate's metabolic rate with a subsequent increase in glucose and oxygen use ensuing acidosis and, if not reversed, persistent pulmonary hypertension of the neonate develops.[8] A core body temperature below 36.4°C (97.5°F) in neonates has been correlated with poor brain and somatic growth and increased mortality.[14] This can all be avoided by warming the baby to a core temperature of at least 35°C and using a pre-warmed transport incubator in a pre-warmed ambulance, with the thermal environment adjusted so as to maintain correct rectal temperature.[15] Hyperthermia above 37°C (98.6°F) should be avoided.[16]

Circulation

Two reliable and secure routes of venous access should be in place. Many surgical newborns have abnormal losses of water, electrolytes, and proteins, which must be replaced to prevent hypovolemia and shock. Intravenous fluids must be initiated immediately and sometimes initiation of inotropic vasopressors such as dopamine or dobutamine may be warranted.[5,6,8] A urinary catheter should be inserted to closely monitor urinary output in any patient in whom there will be excessive fluid losses.

Every neonate requiring transport must have an adequately sized functioning nasogastric tube to prevent vomiting and aspiration. It should be taped securely in position and kept on open drainage or attached to a low-pressure suction pump which should be aspirated every 10–20 minutes to prevent occlusion.[5] Glucose homeostasis must also be maintained and close monitoring of glucose blood levels should be performed regularly and corrected if necessary.[8]

Documentation

Furthermore, a number of essential data should be transferred with the infant. A copy of the infant's chart with completed medical notes, all x-rays/ultrasound scans, and nursing documentation (urine output, passage of stools, eye prophylaxis, hepatitis vaccine, other medication administration) should accompany the patient. All laboratory reports should be included, and the time noted when tests were carried out. It should be clearly documented whether vitamin K was given. Prophylactic broad-spectrum antibiotics should be started if there is a risk of infection. A sample of maternal blood (5–7 mL clotted) should be sent to facilitate cross-matching. A parental consent for operation, signed by the mother if the parents are not married, should be sent together with a contactable phone number to be able to explain to the parents the surgical condition of their child and the operative procedure. Where possible, a cord blood specimen should be sent, along with a copy of maternal records including complete maternal history, labor, and delivery records.

TRANSPORT TEAM

It is now widely accepted that specific transport training is required by staff who will be called upon to transfer neonatal patients.[17] Local and individual circumstances will determine whether the referring or specialist center will send a transport team. The composition of the team may also vary from institution to institution. The team should ideally consist of a transport physician/pediatrician and a trained neonatal nurse familiar with and able to anticipate potential problems associated with specific lesions.[8,10] They should be familiar with all equipment and its function and should be experienced in stabilizing an infant in suboptimal conditions. A more recent option is the use of Advanced Neonatal Nurse Practitioners (ANNPs), who have been shown to provide comparable care to trainee pediatricians.[17] Careful delineation of responsibility is important. Some institutions have formed a nursing transport team trained and experienced in the transfer of sick neonates. They guide the doctors and operate the equipment.[11]

TRANSPORT VEHICLES

Selection of a transport vehicle is dependent on the distance traveled, geography, weather conditions, the nature of the infant's problem, and the need for speed.[2] A variety of conveyances are in popular use, including ground ambulances, helicopters, and fixed-wing aircraft. Ambulance transport is generally preferable to that by helicopter, but it is rather slow.

Air transport has several disadvantages. A major disadvantage is that separate ground transport must be arranged at both ends to move the baby between the airport and the hospital. The exception arises in those circumstances in which helicopter landing sites are available at both receiving and referring institutions. Vibration is not usually detrimental to the infant, but can dislodge lines and tubes and adversely affect monitoring equipment.[18] Excessive noise may give rise to communication issues and it is important to ensure that staff headsets are equipped with the correct impedance microphone for that particular aircraft.[18] Noise, vibration, and poor lighting make in-flight monitoring of the infant difficult in a rotary-wing aircraft (helicopter).[8,9,19] This problem is not experienced to such a significant degree in a fixed-wing aircraft. Overall, the noise and vibrations may cause distress and discomfort to the infant, leading to a

deteriorating clinical condition and thus it is logical to minimize these as much as possible.[18]

The transport incubator should be securely strapped in case of turbulence of the plane. The infant in the incubator should be well fixed with a lockable piece of cloth. Moreover, the space in a plane is limited and can cause difficulties in manipulating the airway.[8,9]

The negative effects of altitude on the neonate's body can be detrimental.[19] With increasing altitude, the partial pressure of oxygen decreases, therefore diffusion of oxygen across the alveolar membranes becomes more difficult, arising in decreasing oxygen saturation in the infant. To maintain the same level of oxygenation, a higher percentage of oxygen may be required. Moreover, the barometric pressure will also decrease with increasing altitude, the volume of gas will increase and any air trapped in a body cavity will expand. This could have a dramatic effect on pulmonary function[8] and small insignificant air leaks can become dangerous. This is particularly important in the setting of pneumothoraces, pneumoperitoneum, or intramural gas.[18] It is therefore important to ensure that all air leaks are drained if possible. It is also very important to have well-functioning medical and nursing equipment in the event that this emergency arises.[10]

Monitoring is essential during transfer because clinical assessment can be limited due to suboptimal lighting, noise, vibration, and lack of space. Invasive and noninvasive measures of arterial pressure, pulse oximetry, electrocardiograph (ECG), core temperature measurement, and pressure transducers for central venous and intracranial pressure readouts must be present. All monitors and syringe pumps should be battery operated.[6] A range of airway and ventilatory equipment, including self-inflating resuscitation bags, masks, airways, laryngoscope handles and blades, uncuffed neonatal endotracheal tubes of various size, humidifiers, portable suction apparatus, and oxygen supplies, must be available in case airway problems should occur. There must be a source of suction for clearing blocked endotracheal tubes. Intravenous infusion pumps, along with an appropriately stocked box including i.v. supplies, intraosseous needles, chest tubes, and umbilical catheter kits with sterile equipment and emergency drugs should be present.[8] After each transport, a record which documents equipment that is used should be filled in and the equipment unit checked and restocked. The equipment kit should be controlled weekly by the neonatal transport nurse on duty and servicing of the transport incubator and the monitoring equipment should be carried out.[10]

Because of the very different nature of air travel compared to ground travel, it is imperative that staff receive training specifically directed at both the environment and specific problems that they may encounter in each situation. These include logistics (landing sites), airborne environment, and safety issues specific to each situation.[17]

TRANSPORT INCUBATORS

Standard requirements for transport incubators are established in an International Standard.[20,21] The currently available portable incubator (Fig. 8.1) is designed and equipped for transporting sick newborns.[22] It is a central piece of equipment that has to provide warmth, visibility, and access. The incubator should be able to maintain a specific temperature under a variety of different ambient conditions (e.g. −15°C/5°F to 28°C/82°F).[20] The patient compartment of the transport incubator must be equipped with a front flap for loading and so that there is good access to the neonate in the event of an emergency.[20] It should also be able to run on batteries, and must be equipped with its recharger. Guidelines state that the energy of the battery should be sufficient for a minimum of 90 minutes in an ambient temperature of 15°C/59°F.[21] It should be equipped with a cardiorespiratory monitor, pulse oximeter, infusion pump, oxygen analyzer, oxygen and air cylinders, double Plexiglas walls, and shock-absorbing wheels.[8] In the case of transporting very sick neonates and preterm babies, ventilation may be required. In these cases, the incubator should be equipped with a mechanical ventilator which is time-cycled, pressure-limited, and capable of delivering conventional ventilations and constant positive airway pressure (CPAP).[20] When securing the neonate in the incubator, one must bear in mind the size of the infant, extreme sensitivity of preterm skin, reduced muscle tone, low body profile, and body weight distribution.[23]

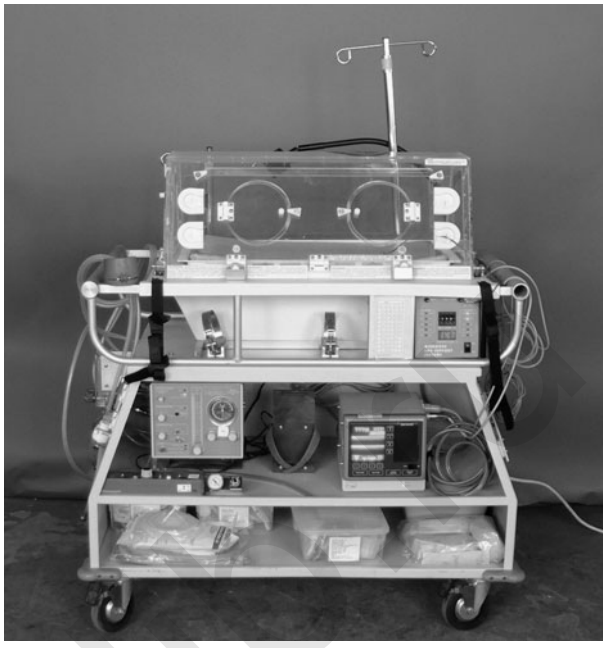

Figure 8.1 A portable incubator.

TRANSPORT PROCEDURE

The perfect transfer does not exist yet. It involves early and effective communication between the referring and specialist center, stabilization of the baby pre-transfer, and provision of special needs and care during transport.[5] All too often, transport is hastily arranged and conducted in a vacuum of communication, resulting in preventable catastrophes such as vomiting and aspiration, hypothermia, hypovolemia, and airway obstruction,[7] and in the majority of cases, most

adverse events arise from poor planning and preparation. Ideally, transfer is arranged at as senior a level as possible, i.e. a telephone conversation between a specialist pediatric registrar or consultant pediatrician in the referring center and specialist surgical registrar or consultant pediatric surgeon in the receiving center.[24] A standardized transfer-form booklet was introduced by the current authors in their institution. A form is filled in during the initial conversation with the referring center. It contains all the necessary medical and practical details regarding actual transfer and specific management of the surgical problem of the newborn. By increasing awareness of potential problems, referring hospitals will be less inclined to neglect precise instructions concerning specific surgical conditions.

RECEIVING CENTER

Continuation of care is essential to improving neonatal outcome. On arrival at the tertiary center, a brief report of prenatal, labor, and delivery history should be given by the transport nurse to the newborn intensive care nurse, together with details of the newborn's resuscitation and any problems experienced during transfer.[8] The accompanying pediatrician should review the baby and all documents together with the accepting surgeon and anesthetist, if necessary. The parents should be introduced to all staff who will be involved in the care of their baby. Every procedure should be explained in a clear and comprehensive language to avoid confusion and parental fear. The consent form should be updated if necessary. Blood tests and radiological examinations can be ordered subsequently.

SPECIAL CONSIDERATIONS

Gastroschisis

The baby with gastroschisis is at a higher risk for hypothermia, excessive fluid loss, shock, and infection due to lack of a covering peritoneal/amniotic membrane which gives rise to exposed viscera and peritoneal surfaces. Therefore, radiant heating should be available in the room and the baby should be kept in a warmed incubator with the incubator's temperature monitored frequently. Intestinal strangulation, necrosis, and obstruction may also occur due to the small size of the paraumbilical defect. Treatment starts immediately after delivery in order to prevent fluid loss and hypothermia (Box 8.2). Intubation and ventilation is carried out if required, and immediate resuscitation with adequate i.v. fluids (120 mL/kg/24hours) to overcome substantial water, electrolyte, and protein loss is started. Because the fluid losses are primarily of serum and interstitial fluids, these neonates require isotonic fluids resuscitation, which consists of colloids, saline, or lactate Ringer's solution.[25,26] Pulse rate and mean arterial pressure are observed and blood is taken and glucose level measured. At the same time, vitamin K is given and broad-spectrum antibiotics (ampicillin, gentamicin, and metronidazole) are commenced to reduce contamination of the exposed intestinal loops. A nasogastric tube is passed for intestinal decompression and prevention of pulmonary aspiration. A urinary catheter is passed to decompress the bladder and to monitor urinary output. In many instances, the viscera are wrapped in sterile gauze that has been soaked in warm sterile saline and then the abdomen, along with the covered defect, are wrapped in dry sterile gauze. This may, however, induce hypothermia as the gauze cools. If the gauze is allowed to dry, this may stick to the intestinal surface and cause serosal injury when trying to be removed.[27] Ideally, the bowel should be placed in a sterile clear plastic bag or silo (Fig. 8.2). If this is not available, the bowel is localized in the center of the abdomen and cling film is used to encircle the exposed intestine and is wrapped around the infant. These measures minimize heat loss and trauma to the exposed viscera.[28] The positioning of the infant is very important for preventing bowel ischemia. If the infant is supine and the

Box 8.2 Stabilization of a newborn with anterior abdominal wall defect prior to transfer to a referral center

Warm environment
Evaluate respiratory status
Nasogastric tube
Gastroschisis: wrap cling film around defect
Omphalocele: wrap dry gauze around sac
Intravenous fluids, correct deficits
Antibiotics
Vitamin K

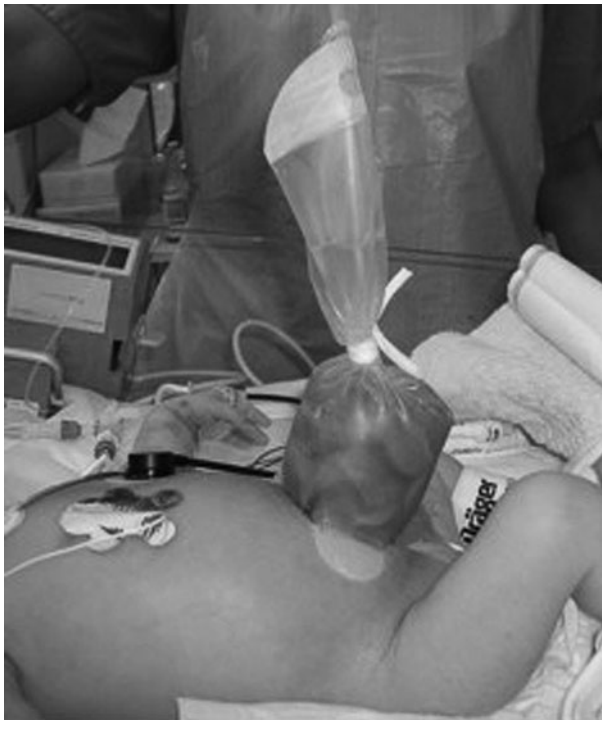

Figure 8.2 Gastroschisis with silo placement.

bowel lies on one side, there is a risk of ischemia to the bowel if the superior mesenteric artery becomes kinked. Hence, the best position is to keep the intestines directly above the abdominal wall defect so that the superior mesenteric artery exits straight from the defect.[27]

Omphalocele

As with any abdominal wall defect, the care of the neonate begins with resuscitation. The initial objectives for the neonatologist are to assess and treat respiratory distress, to protect the sac from rupture and infection, and to minimize heat loss.[29,30] A nasogastric tube is passed immediately to decompress the stomach and bowel. Intravenous fluids, broad-spectrum antibiotics, and vitamin K should be started. The defect must be inspected to ensure that the sac is intact.[31] The sac should be stabilized in the middle of the abdomen to prevent kinking of the vessels and covered with a sterile, dry, non-adherent dressing to prevent trauma and heat loss. If the sac is ruptured, then the exposed bowel is treated as it is for gastroschisis.[31]

Pierre Robin syndrome

Babies with Pierre Robin syndrome carry a high risk of tongue swallowing and asphyxiation. The baby should be nursed prone to prevent the tongue from falling back into the airway, and an oropharyngeal airway inserted.[7]

Choanal atresia

Neonates with choanal atresia suffer from intermittent hypoxia. The baby should be nursed with an appropriately sized oral airway with the end or teeth cut off to keep the mouth open.[5] One must ensure the airway does not go too far into the pharynx as it may enter the esophagus and occlude the airway. This must be secured in place to prevent dislodging.

Myelomeningocele

The infant with myelomeningocele should be nursed prone in order to prevent trauma and pressure on the spinal area. A warm, sterile, saline-soaked dressing is placed over the lesion and cling film wrapped around the baby to prevent drying and dehiscence. If the sac is ruptured and cerebrospinal fluid (CSF) is leaking, or if the myelomeningocele is open, it should be covered with Betadine-soaked gauze and i.v. broad-spectrum antibiotics started. Care must be taken to prevent fecal contamination in sacral lesions.[8] Careful observation and documentation of neurological function is essential before, during, and after transportation, including evaluation of the sensorimotor level and assessment of the degree of hydrocephalus.[8,29]

Bladder extrophy

At birth, the umbilical cord should be ligated close to the abdominal wall and the umbilical clamp removed to prevent mechanical damage to the bladder mucosa and excoriation of the bladder surface.[6,32,33] Trauma and damage to the exposed bladder mucosa and plate should be avoided by covering the defect with cling film wrapped around the baby to prevent the mucosa from sticking to clothing or diapers. This will allow urine to escape while establishing a barrier between the environment and the fragile bladder mucosa. Old urine, mucus, and any detritus should be washed from the surface of the bladder with sterile saline warmed to body temperature at each diaper change and a clean layer of cling film applied, also during transfer.[32,33] Prophylactic antibiotics should be started immediately.

Cloacal extrophy

The same measurements to protect the omphalocele sac as discussed under omphalocele are applicable.

Esophageal atresia with tracheo-esophageal fistula

Most babies with esophageal atresia become symptomatic soon after birth. Symptoms include excessive drooling, coughing, or choking with the first feed. Once the diagnosis of esophageal atresia is suspected, the baby should be transferred to a tertiary referral center for further investigation and surgery. Some babies will require endotracheal intubation and ventilation. These infants are particularly at risk because mechanical ventilation is relatively ineffective due to the presence of a fistula. Therefore, the tip of the endotracheal tube should be placed proximal to the carina but distal to the fistula. Urgent transfer and ligation of the fistula are essential. Generally, the infant should be handled with care and crying avoided to reduce the risk of aspiration and abdominal distension and thereby, respiratory distress.[6] Moreover, the baby should be well oxygenated at all times and kept in a warm environment. Regurgitation of gastric contents through the fistula during transport can be prevented by keeping the head of the baby in a slightly elevated position or nursing the baby prone or in a right lateral position and thereby decreasing the work of breathing and improving oxygenation.[6,34] The blind upper esophageal pouch should be kept empty. A Replogle sump catheter should be placed in the pouch and connected to low-intermittent or low-continuous suction in order to prevent accumulation of saliva. The perforations along the side of the catheter are located only near the tip and therefore minimize the possibility of suctioning oxygenated air away from the larynx.[35] However, these double lumen esophageal tubes have a tendency to become blocked with mucus and therefore should be irrigated at frequent intervals during transport. Intravenous fluids should be started to provide maintenance and supplemental fluids and electrolytes to compensate esophageal secretion losses. Infection should be prevented and any

existing pneumonitis treated by broad-spectrum antibiotics. Vitamin K should be administered prior to transfer.

Congenital diaphragmatic hernia

The initial objective for the neonatologist and anesthetist is to stabilize the critically ill neonate before transport to the referral center (Box 8.3). A nasogastric tube should be passed immediately on diagnosis to decompress the gastrointestinal tract and to prevent further compression of the lung. Endotracheal intubation should be performed promptly in a baby with respiratory difficulty or poor gas exchange. Full sedation and paralysis and gentle ventilation will reduce the risk of barotraumas in the setting of hypoplastic, delicate lungs. Mask ventilation should be avoided because it will distend the stomach and further compromise the respiratory status. Hyperventilation, using low pressures and high oxygen content, correction of acidosis and prevention of thermal and metabolic stress are recommended to prevent pulmonary hypertension.[8] Some infants need high frequency oscillatory ventilation (HFOV) when conventional ventilation proves ineffective. The rational is that small tidal volumes and gas transport by augmented diffusion result in a lower shear stress and less barotraumas.[36] These patients may, however, pose a problem, as there is no oscillatory ventilation option commonly available on transport ventilators.[37] Clinical teams will usually have to convert oscillation to standard ventilation for the duration of transfer.[37] Careful attention to fluid balance with i.v. fluids, fresh-frozen plasma (FFP) and dopamine, if necessary, should be started to maintain adequate peripheral perfusion without causing pulmonary overload.[36] Prophylactic antibiotics should be started and vitamin K administered. Venous access through the umbilicus is useful for obtaining mixed venous blood gas specimens and monitoring central venous pressures if passed across the liver into the right atrium. Arterial access with an umbilical artery catheter will allow monitoring of systemic blood pressure and blood gas measurements at the postductal level. The baby will also need a right radial arterial line to measure preductal blood gases, and a preductal pH $\geq$7.2 and arterial oxygen pressure of $\geq$6.5 kPa with an oxygen saturation of 85–90% is acceptable.[36] This can be inserted on arrival at the referral center. Acute deterioration of the infant's condition can occur during transfer due to a pneumothorax. Equipment for intercostal drainage must be available since it can be a life-saving maneuver.[8,34]

Box 8.3 Stabilization of a neonate with congenital diaphragmatic hernia prior to transport

Maintain warm environment
Nasogastric tube
Intubation and ventilation
Intravenous fluids
Arterial blood gases
Antibiotics
Vitamin K

There has been tremendous growth in the use of extracorporeal life support for neonatal cardiopulmonary failure in the last decade. Extracorporeal membrane oxygenation (ECMO) has been used as a salvage procedure with an 80% survival rate in high-risk neonates with congenital diaphragmatic hernia who fail to respond to mechanical ventilation and meet entry criteria. ECMO is able to partly take over oxygenation and carbon dioxide removal, and thereby may allow respiratory settings to be adjusted to the mechanical and gas exchange properties of the diseased lung. In this way the goals of lung and protective mechanical ventilation can be reached.[38] The number of centers providing ECMO is still limited, so special services are needed to transport critically ill neonates to these centers. These special transport teams should be familiar with the pathophysiology of cardiac and respiratory failure and be equipped to continue the monitoring and treatment started at the referral center. They must also be able to maintain that level of care during transport, and to treat complications of the disease or therapy itself.[39,40] Now, transportable ECMO systems exist that can effectively stabilize and transport high-risk neonates to an ECMO-competent center.[41] The use of inhaled nitric oxide (NO) leads to a reduction in endogenous production of NO and its value in patients with congenital diaphragmatic hernia (CDH) is unclear.[36] Recent studies have shown that there is an immediate short-term improvement in oxygenation seen in some treated infants and this may be of benefit in stabilizing infants for transport and initiation of ECMO. However, for term and near-term infants with CDH and hypoxic respiratory failure unresponsive to conventional therapy, inhaled NO did not reduce the need for ECMO.[42]

Intestinal obstruction

Intestinal obstruction can occur as a result of a number of conditions, e.g. malrotation, duplication of the alimentary tract, intestinal atresias, necrotizing enterocolitis, Hirschsprung's disease, meconium ileus, and anorectal anomalies. The principles of care are the same irrespective of the level or cause of the obstruction.[6] The main objectives are to decompress the bowel and prevent aspiration, accurately estimate and correct fluid losses and minimize heat loss. A nasogastric tube should be passed to minimize distension and suction carried out every 15–30 minutes and left on free drainage between aspirations prior to and during transport. Serum electrolytes and proteins sequester in the intestinal wall and lumen, and isotonic i.v. fluids and colloids should be started to correct acid–base and volume deficits.[27] These must be reviewed and adjusted on a 6–8-hourly basis according to the needs of the infant.[5] Broad-spectrum antibiotics should be started prophylactically.

Necrotizing enterocolitis

Neonates with necrotizing enterocolitis (NEC) are usually transferred only if surgery is required in case of perforation

of gangrenous bowel resulting in pneumoperitoneum or progressive clinical deterioration with evidence of peritonitis.[5] Usually they are critically ill with sepsis and shock. The transfer is done preferably while the infant's condition is as stable as possible. Prompt resuscitation with crystalloids, colloids, or blood to correct acidosis is started prior to departure. Ventilation with intermittent positive pressure and inotropic support is often required.[6] Blood pressure and blood glucose must be closely monitored in these patients. A sump nasogastric tube on continuous suction is passed and suctioned regularly prior to and during transport. Broad-spectrum antibiotics to cover for Gram-positive, Gram-negative and anaerobic coverage are started.[27]

CONCLUSION

The approach to the care of the high-risk newborn has changed dramatically in the past 20 years. The newborn with a serious congenital malformation requires assessment and stabilization by experienced staff prior to and during transport to the regional center. Several studies have demonstrated that stabilization of the high-risk newborn before transport is associated with a reduction in perinatal morbidity and mortality. The pediatric transport team plays a vital role in the transport of these patients to tertiary pediatric facilities. The overall aim of transport of the surgical neonate should be to bring the services of the Pediatric Intensive Care Unit to the patient's bedside during transport to a specialist centre.

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9

Preoperative assessment

PREM PURI AND JOHN GILLICK

INTRODUCTION

Many congenital defects that are of interest to the pediatric surgeon can now be detected before birth, thus the preoperative assessment of the newborn with a possible congenital anomaly starts *in utero*. When serious malformations incompatible with postnatal life are diagnosed early enough, the family may have the option of terminating the pregnancy in some countries. It is extremely beneficial for parents if the pediatric surgeon who is likely to manage the infant postnatally is available antenatally to provide information, be involved in management decisions, and counsel the family before birth.[1] The main goal of prenatal diagnosis is to improve the prenatal care by maternal transport to an appropriate center and delivering the baby in the timing and mode that are appropriate for the specific fetal malformation. Multidisciplinary meetings in which obstetric, neonatal, and pediatric surgical expertise is present are commonplace in most large pediatric institutions. They undoubtedly improve postnatal outcome, but as always effective communication between all disciplines is vital. Prenatal intervention for certain congenital anomalies has been reported extensively in recent years. The success of fetal surgery has varied from condition to condition; for instance antenatal closure of myelomeningocoele is associated with a lesser requirement for subsequent ventricular shunting but no significant improvement in neurologic deficit.[2] Likewise vesico-amniotic shunting for posterior urethral valves has not proved to be the 'cure-all' it was once hoped to be,[3] but it seems clear that fetal surgical intervention is here to stay and is likely to continue to expand its repertoire.[4,5] At present, however, almost all congenital malformations can be successfully managed after birth.

During the past two decades there have been significant advances in modes and techniques for prenatal diagnosis. These modes include: amniocentesis, amniography, fetoscopy, fetal sampling, and ultrasonography. The latter, enabling direct imaging of fetal anatomy, is a noninvasive technique, safe for both the fetus and the mother.[6] With further advances in screening techniques, and combining various antenatal screening modalities, such as the Serum, Urine and Ultrasound Screening Study (SURUSS) for Down syndrome,[7] the efficacy and safety of antenatal screening has improved. However, it is important to remember that sonography is operator dependent and the reliability of the information obtained is directly proportional to the skill and experience of the sonographer. For example, it is important to distinguish duodenal from jejunal obstruction in a fetus with polyhydramnios, because duodenal obstruction is associated with Down syndrome and requires further genetic evaluation while jejunal obstruction does not.

The real-time sonography may yield important information on fetal malformation, fetal movement, and fetal vital functions such as breathing movements and heart rate variability. Again, this information may guide postnatal intervention.[8,9] Serial sonographic evaluations are particularly useful in following the progression or regression of any fetal disease. All this important information is an integral part of the preoperative assessment of a newborn with any kind of congenital malformation (Figs 9.1 and 9.2).

Neonates born with congenital malformations are usually in urgent need of surgery and, in addition to their surgical problem, may suffer from a multitude of medical problems. Furthermore, they are at a period when significant physiological and maturational changes involving transition from fetal to extrauterine life are occurring. The surgical and anesthetic intervention at this time may affect this transition by interfering with normal homeostatic controls of circulation, ventilation, temperature, fluid, and metabolic balance. To facilitate a smooth preoperative course, close cooperation among the neonatologist, pediatric surgeon, and pediatric anesthesiologist is necessary.

All neonates undergoing surgery must be carefully assessed preoperatively, giving particular attention to the following:

- history and physical examination;
- maintenance of body temperature;
- respiratory function;
- cardiovascular status;

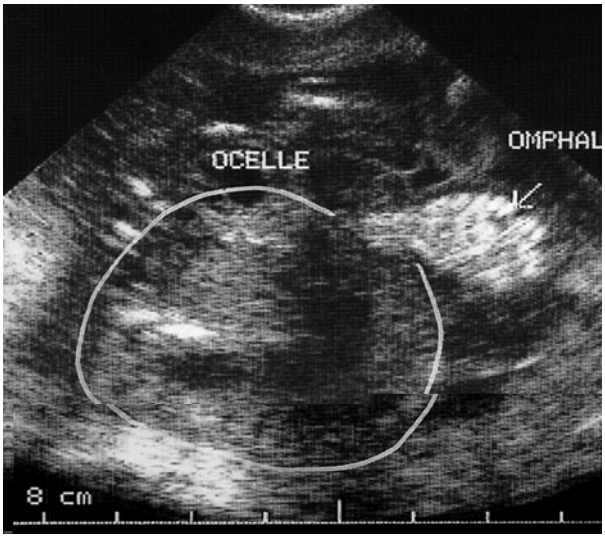

Figure 9.1 Transvaginal ultrasonogram showing a 15-week-old fetus with omphalocele (arrow). Bowel loops protrude through the abdominal wall defect.

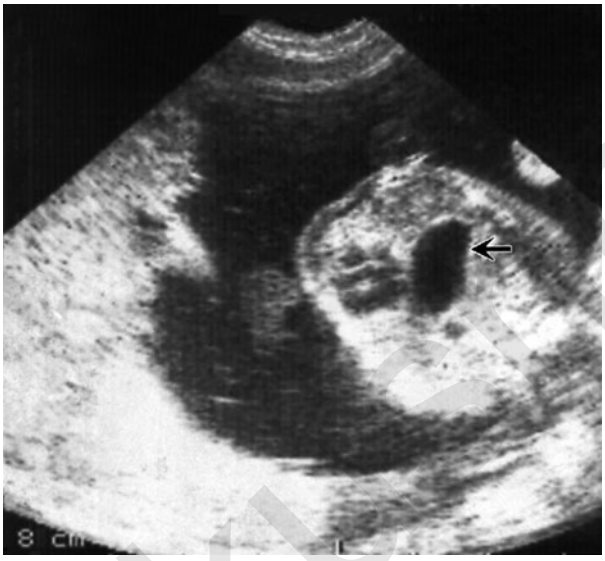

Figure 9.2 Transvaginal ultrasonogram showing a 16-week-old fetus with diaphragmatic hernia. The dilated stomach (arrow) appears in the left hemithorax adjacent to the heart.

- metabolic status;
- coagulation abnormalities;
- laboratory investigations;
- vascular access;
- fluid and electrolytes, and metabolic responses.

HISTORY AND PHYSICAL EXAMINATION

The history of a newborn starts months before delivery, as many of the congenital malformations (e.g. Bochdalek hernia, omphalocele, gastroschisis, sacrococcygeal teratoma, and others) nowadays are known to the pediatric surgeon prenatally. The increasing importance of antenatal pediatric surgical input in counseling parents has been recently reported.[10,11] Not only are the anatomical and structural anomalies important, but even more so are metabolic abnormalities or chromosomal aberrations, which must be diagnosed prenatally or immediately after birth.

Anticipation of a problem in the delivery room is often based on prenatal diagnosis. For example, identification of a trisomy 21 in the fetus will increase the neonatologist's awareness in evaluating the infant for those abnormalities closely associated with this chromosomal defect, e.g. evaluation for duodenal atresia and congenital heart disease. Conversely, prenatal identification of specific fetal anomalies should signal the pediatrician to evaluate the infant for a chromosomal abnormality.[12]

The most important recent advance in prenatal detection of anatomical problems has been the development of fetal ultrasonography, and in experienced hands this mode of imaging can be used to detect a wide range of fetal problems and guide postnatal prognosis,[13] ranging from relatively minor abnormalities to major structural defects. However, this anatomical prenatal diagnosis is only one of the tools that aid in planning care management. An accurate and well-documented family history may increase the suspicion that an infant is at risk for an anatomical defect linked to an inherited disorder. In other cases, only the evidence of polyhydramnios should significantly increase suspicion of congenital anomalies.

Most problems are best managed expectantly by natural labor and vaginal delivery. Opinion remains divided on the benefits of elective Cesarean section for abdominal wall defects, with some authorities finding only limited usefulness,[14] and others suggesting that elective preterm delivery for gastroschisis results in an improved surgical outcome.[15] Certain malformations, however, such as conjoined twins, giant omphalocele, sacrococcygeal teratoma, or large cystic hygroma, often require Cesarean section for delivery.[16]

After birth, the assessment of the degree of prematurity, which is an integral part of the physical examination, and the specific type of congenital anomaly must be identified and recorded because of the profound anesthetic and post-operative implications that are involved. The normal full-term infant has a gestational age of 37 weeks or more, and a body weight greater than 2500 g. Infants born with a birth weight of less than 2500 g are defined as being of low birth weight (LBW). Babies may be of LBW because they have been born too early (preterm – earlier than 37 weeks' gestational age), or because of intrauterine abnormalities affecting growth (growth retardation). Small-for-gestational-age (SGA) infants are those whose birth weight is less than the 10th percentile for their age. Infants may, of course, be both growth retarded and born preterm.

The principle features of prematurity are:

- a head circumference below the 50th percentile;
- a thin, semi-transparent skin;
- soft, malleable ears;
- absence of breast tissue;

- absence of plantar creases;
- undescended testicles with flat scrotum and, in females, relatively enlarged labia minora.

The physiological and clinical characteristics of these babies are:

- apneic spells;
- bradycardia;
- hypothermia;
- sepsis;
- hyaline membrane disease;
- blindness and lung injury due to use of high levels of oxygen;
- patent ductus arteriosus.

In the SGA infant, although the body weight is low, the body length and head circumference approach that of an infant of normal weight for age. These babies are older and more mature. Their clinical and physiological characteristics are:

- higher metabolic rate;
- hypoglycemia;
- thermal instability;
- polycythemia;
- increased risk of meconium aspiration syndrome.

In relation to these differences, three important observations have been reported:

1. LBW infants have a mortality ten times that of full-sized infants.
2. More than 75% of overall perinatal mortality is related to clinical problems of LBW infants.
3. The rate of anatomical malformation in LBW infants is higher than for infants at term.[17]

MAINTENANCE OF BODY TEMPERATURE

The mean and range of temperature for newborns are lower than previously described and most temperatures $\leq 36.3^{\circ}C$ are, in fact, within the normal range.[18] Newborn infants, particularly premature infants, have a poor thermal stability because of a higher surface area/weight ratio, a thin layer of insulating subcutaneous fat, and a high thermoneutral temperature zone. The newborn readily loses heat by conduction, convection, radiation, and evaporation, with the major mechanism being radiation. Shivering thermogenesis is absent in the neonate, and the heat-producing mechanism is limited to non-shivering thermogenesis through the metabolism of brown fat.[19] Cold stress in these neonates leads to an increase in metabolic rate and oxygen consumption, and calories are consumed to maintain body temperature. If prolonged, this leads to depletion of the limited energy reserve and predisposes to hypothermia and increased mortality. Hypothermia can also suggest infection and should trigger diagnostic evaluation and antibiotic treatment if required.[18]

Illness in the newborn, particularly when associated with prematurity, further compounds the problems in the maintenance of body temperature. The classic example for such an illness is the newborn with omphalocele or gastroschisis. In their group of 23 neonates with gastroschisis, Muraji *et al.*[20] found that hypothermia (31–35.4°C), which was found in seven patients upon arrival at the hospital, was the most serious preoperative problem. To minimize heat losses, it is desirable that most sick neonates be nursed in incubators within a controlled temperature. These incubators are efficient for maintaining the baby's temperature, but do not allow adequate access to the sick baby for active resuscitation and observation. Overhead radiant heaters, servo-controlled by a temperature probe on the baby's skin, are preferred and effective in maintaining the baby's temperature; they also provide visual and electronic monitoring and access for nursing and medical procedures. Hyperthermia should be avoided, because it is associated with perinatal respiratory depression and detrimental outcomes in the short-term period post-delivery.[21]

The environmental temperature must be maintained near the appropriate thermoneutral zone for each individual patient because the increase in oxygen consumption is proportional to the gradient between the skin and the environmental temperature.[22] This is 34–35°C for LBW infants up to 12 days of age and 31–32°C at 6 weeks of age. Infants weighing 2000–3000 g have a thermoneutral zone of 31–34°C at birth and 29–31°C at 12 days. In an incubator, either the ambient temperature of the incubator can be monitored and maintained at thermoneutrality, or a servo system can be used. The latter regulates the incubator temperature according to the patient's skin temperature, which is monitored by means of a skin probe on the infant. The normal skin temperature for a full-term infant is 36.2°C, but because of many benign factors such as excessive bundling, ambient temperature may affect body temperature. Diurnal and seasonal variations in body temperature have also been described.[18] Thus, the control of the thermal environment of the newborn and especially the ill baby with congenital malformations is of the utmost importance to the outcome.

RESPIRATORY FUNCTION

Assessment of respiratory function is essential in all neonates undergoing surgery. The main clinical features of respiratory distress are restlessness, tachypnea, grunting, nasal flaring, sternal recession, retractions, and cyanosis. These symptoms are occasionally present in the delivery room due to anatomical abnormalities involving the airway and lungs and require the most urgent therapy.[23] Table 9.1 lists some common conditions that may be present with respiratory distress at birth. These conditions include: diaphragmatic hernia (Bochdalek), lobar emphysema, pneumothorax, esophageal atresia with or without tracheoesophageal fistula, congenital airway obstruction, congenital cystic adenomatoid malformation of the lung, meconium

Table 9.1 Approach to respiratory distress post-delivery.

Condition	Prenatal and perinatal associations	Clinical features	Chest radiographic findings[a]	Initial therapy
Respiratory distress syndrome (RDS)	Prematurity, lung immaturity, asphyxia, maternal diabetes, male sex	Increasing respiratory distress after birth, tachypnea, grunting, rib retractions or nasal flaring	Diffuse reticulogranular pattern, air bronchograms	Oxygen, assisted ventilation
Air leak syndromes				
Pneumothorax	RDS, meconium aspiration, endotracheal resuscitation, diaphragmatic hernia, assisted ventilation	Acute onset of sternal recession, tachypnea, cyanosis, shift in apex beat position	Intrapleural air, mediastinal shift; varying degrees of lung collapse which is always symmetrical toward the hilum	Oxygen, needle aspiration, chest drain; additional tubes may be needed when large leaks from the lung tissue are present
Diaphragmatic hernia (Bochdalek)	Polyhydramnios	Sudden respiratory distress usually soon after birth, dyspnea, cyanosis, scaphoid abdomen, shift in heart sounds, decreased breaths sounds in one hemithorax (usually left)	Bowel pattern in one hemithorax, mediastinal shift with compression of the contralateral lung. Abdominal bowel gas is sparse or absent	Nasograstic decompression; intubation and ventilation
Lung abnormalities				
Lobar emphysema	Occasionally associated with congenital malformations of the heart and great vessels	Rapidly progressive respiratory distress with dyspnea and cyanosis. Absent or diminished breath sounds over the affected side and displacement of the mediastinum	Hyperinflation of the affected side – usually left upper (increased translucency). Mediastinum may be shifted	Thoracotomy and lobectomy required. During induction of anesthesia, the ventilator pressures must be kept as low as possible until the chest is open
Congenital cystic adenomatoid malformation (CCAM)	Fetal hydrops, polyhydramnios, pulmonary hypoplasia, mediastinal shift, type II – associated anomalies including prune belly syndrome and pectus excavatum. 25% of infants are stillborn	Severe respiratory distress as above, often within hours of birth	Homogeneous mass or multicystic lesion on chest x-ray, mediastinal shift. The normal location of the stomach is of help in differentiating CCAM and diaphragmatic hernia	Thoracotomy and lobectomy
Esophageal atresia with tracheo-esophageal fistula	Polyhydramnios, associated malformations (VACTERL), excessive nasopharyngeal saliva	Mild respiratory distress. Early chest auscultation is normal. The abdomen may show progressive distension. (In the common case of atresia and fistula)	Wide, air-filled pouch in the neck or upper mediastinum. Aspiration may be noted, usually in the right upper lobe. Radio-opaque nasogastric tube will be seen to stop and coiled in the blind pouch. The abdomen frequently shows hyperaeration of the intestines	Position of the infant with head elevated 45° or prone position. Place Replogle tube in the blind proximal pouch and connect it to continuous suction. Antibiotics. Evaluate associated congenital malformations
Airway abnormalities				
Choanal atresia and supralaryngeal lesions	None	Cyanosis at rest, pink when crying; inability to pass catheter through nares; noisy upper airway	None	Placement or oral airway

[a]Combined chest and abdominal film is recommended in every newborn baby presenting with respiratory distress. An opaque nasogastric tube in the stomach has an important role both in diagnosis and treatment.

aspiration syndrome, and aspiration pneumonia. It is important to recognize that more than one condition may be present in the same patient.

If there is any clinical suspicion or sign of respiratory insufficiency, a chest x-ray should be obtained immediately after the resuscitation to determine the cause of respiratory distress. All babies with respiratory distress should have a radio-opaque nasogastric tube passed and an x-ray taken that includes the chest and abdomen in order to localize the esophagus, stomach, and bowel gas, and to avoid misdiagnosis, for example, a diaphragmatic hernia which can be mistaken for a cystic adenomatoid malformation of the lung.[24] Blood gas studies are essential in the diagnosis and management of respiratory distress. Arterial PO_2 and PCO_2 indicate the state of oxygenation and ventilation, respectively. In the newborn,[25] repeated arterial blood samples may be obtained either by catheterization of an umbilical artery or by cannulation of radial, brachial, or posterior tibial arteries. An important alternative is noninvasive monitoring techniques with transcutaneous PO_2 monitors or pulse oximeters.[26] Monitoring of arterial pH is also essential in patients with respiratory distress. Acidosis in the neonate produces pulmonary arterial vasoconstriction and myocardial depression. Respiratory alkalosis causes decreased cardiac output, decreased cerebral blood flow, diminished oxyhemoglobin dissociation, and increased airway resistance with diminished pulmonary compliance.[27]

Respiratory failure is the leading cause of death in the neonate. High-frequency ventilation, use of surfactant, use of inhaled nitric oxide (iNO) and extracorporeal membrane oxygenation (ECMO) have been shown to improve survival dramatically in selected neonates.[28–31] ECMO provides long-term cardiopulmonary support for patients with reversible pulmonary and/or cardiac insufficiency. It is well accepted as a standard of treatment for neonatal respiratory failure refractory to conventional techniques of pulmonary support.[29] Typically, patients considered for ECMO are 34 gestational weeks or older or weigh more than 2000 g, have no major cardiac lesions, intracranial hemorrhages less than grade 2, no significant coagulopathies, and have had mechanical ventilation for fewer than 10–14 days. Our knowledge of the benefits and associated risks of neonatal ECMO continue to evolve.[32]

Congenital diaphragmatic hernia (CDH) represents one of the most common surgical conditions requiring the intervention of ECMO. Recently, the discovery of significant adverse outcomes following ECMO's application in CDH neonates has begun to temper its usage.[32] More recently, a respiratory strategy based on permissive hypercapnea has proven to be successful. This strategy focuses on avoiding volutrauma/barotraumas/oxygen toxicity while using preductal oximetry to guide therapeutic interventions. Oxygen is administered to maintain the preductal SaO_2 >90% (PO_2 >60 mmHg), with a corresponding PCO_2 of less than 60 mmHg and pH of more than 7.2 An important feature of this strategy is the minimal use of a muscle relaxant. Muscle paralysis not only eliminates the infant's inherent respiratory effort but also predisposes the infant to develop tissue edema, while also accelerating lung injury.[33,34]

Surfactant replacement is commonly used in the clinical management of neonates with respiratory distress syndrome (RDS). It may also be effective in other forms of lung disease, such as meconium aspiration syndrome (MAS), neonatal pneumonia, the 'adult' form of acute respiratory distress syndrome (ARDS), and CDH. It ensues that alveolar stability is promoted, atelectasis is reduced, edema formation is decreased, and the overall work of respiration is minimized.[30]

Nitric oxide (NO) is available for treatment of persistent pulmonary hypertension of the neonate (PPHN). It decreases pulmonary vascular resistance leading to diminished extrapulmonary shunt and has a microselective effect which improves ventilation/perfusion matching. Unfortunately the beneficial effects of NO in premature infants are less clear cut, with a risk of intracranial hemorrhage being observed in some studies.[31,35] In newborns with severe lung disease, high frequency oscillatory ventilation (HFOV) is frequently used to optimize lung inflation and minimize lung injury. Further studies are needed in order to elucidate the benefits of HFOV compared to conventional ventilation in term or near-term infants with pulmonary dysfunction.[36]

In summary, the type of respiratory care in particular neonates will always depend upon clinical and radiological findings supported by blood gas estimations.

CARDIOVASCULAR STATUS

At birth, the circulation undergoes a rapid transition from fetal to neonatal pattern. The ductus arteriosus normally closes functionally within a few hours after birth, while anatomical closure occurs 2–3 weeks later.[37] Prior to birth the pulmonary arterioles are relatively muscular and constricted. With the first breath, total pulmonary resistance falls rapidly because of the unkinking of the vessels with expansion of the lungs and also because of the vasodilatory effect of inspired oxygen. However, during the first few weeks of life, the muscular pulmonary arterioles retain a significant capacity for constriction, and any constricting influences such as hypoxia may result in rapid return of pulmonary hypertension.[23]

The management of neonates with congenital malformation is frequently complicated by the presence of congenital heart disease. At this time of life, recognition of heart disease is particularly difficult. There may be no murmur audible on first examination, but a loud murmur can be audible a few hours, days or a week later.[38] A newborn undergoing surgery should have a full cardiovascular examination and a chest x-ray. The presence of cyanosis, respiratory distress, cardiac murmurs, abnormal peripheral pulses, or congestive heart failure should be recorded. If there is suspicion of a cardiac anomaly, the baby should be examined by a pediatric cardiologist. In recent years the use of the noninvasive technique of echocardiography allows accurate anatomical diagnosis of cardiac anomalies, in many cases prenatally.[8]

METABOLIC STATUS

Acid–base balance

The buffer system, renal function, and respiratory function are the three major mechanisms responsible for the maintenance of normal acid–base balance in body fluids. Most newborn infants can adapt competently to the physiological stresses of extrauterine life and have a normal acid–base balance. However, clinical conditions such as RDS, sepsis, congenital renal disorders, and gastrointestinal disorders may result in gross acid–base disturbances in the newborn. Four basic disturbances of acid–base physiology are metabolic acidosis, metabolic alkalosis, respiratory acidosis, and respiratory alkalosis. In a newborn undergoing surgery, identification of the type of disorder, whether metabolic or respiratory, simple or mixed, is of great practical importance to permit the most suitable choice of therapy, and for it to be initiated in a timely fashion.[39] The acid–base state should be determined by arterial blood gases and pH estimation, and must be corrected by appropriate metabolic or respiratory measures prior to operation.

Hypoglycemia

The mechanisms of glucose homeostasis are not well developed in the early postnatal period; this predisposes the neonate, especially the premature neonate, to the risk of both hypoglycemia and hyperglycemia. Prenatally, the glucose requirements of the fetus are obtained almost entirely from the mother, with very little derived from fetal gluconeogenesis. Following delivery, the limited liver glycogen stores are rapidly depleted and the blood glucose level then depends on the infant's capacity for gluconeogenesis, the adequacy of substitute stores and energy requirements. From a glucose metabolism point of view, the neonate is considered to be in transition between the complete dependence of the fetus and the complete independence of the adult.[40] Box 9.1 identifies infants who are at risk for developing hypoglycemia according to three mechanisms: (1) those with limited glycogen stores, (2) hyperinsulinism, and (3) diminished glucose production. Premature and LBW infants (especially SGA infants) are at increased risk of hypoglycemia due to immature postnatal metabolic and hormonal adaptation.[41] Surgical stress and concomitant feeding practices may further exacerbate matters. Interestingly, operative stress in neonates causes significantly less energy expenditure than comparable procedures in adult practice.[42]

Box 9.1 Categories of hypoglycemia

Limited glycogen stores
- Prematurity
- Prenatal stress
- Glycogen storage disease

Hyperinsulinism
- IDM (infant of diabetic mother)
- Nesidioblastosis/pancreatic islet adenoma
- Beckwith–Wiedemann syndrome
- Erythroblastosis fetalis/exchange transfusion
- Maternal drugs

Diminished glucose production
- SGA
- Rare inborn errors

From Ogata[38] with permission.

Hypoglycemia is usually defined as a serum glucose level <1.6 mmol/L in the full-term neonate and <1.1 mmol/L in the LBW infant during the first 3 days of life. After 72 hours, serum glucose concentration should always be above 2.2 mmol/L.

Hypoglycemia may be asymptomatic or associated with a number of nonspecific signs such as apathy, apnea, a weak or high-pitched cry, cyanosis, hypotonia, hypothermia, tremors, and convulsions. The differential diagnosis includes other metabolic disturbances or sepsis. The possibility of hypoglycemia must be anticipated to prevent avoidable brain damage.

All neonates undergoing surgery should have an infusion of 10% glucose at a rate of 75–100 mg/kg body weight per 24 hours and blood glucose levels should be monitored every 4–6 hours by Dextrostix estimation and/or by blood sugar determinations. Blood glucose level should be maintained above 2.5 mmol/L at all times. The symptomatic infant should be treated urgently with 50% dextrose, 1–2 mL/kg intravenously, and maintenance i.v. dextrose 10–15% at 80–100 mL/kg per 24 hours.

Hypocalcemia

Hypocalcemia is usually defined as a serum calcium value <1.8 mmol/L. However, occasionally the ionized fraction of the serum calcium may be low, but without a great reduction of the total serum calcium level concomitantly and with the end result of clinical hypocalcemia. This may occur in newborns undergoing exchange transfusion, or in any surgical baby receiving bicarbonate.

Hypocalcemia occurs usually during the first few days of life, with the lowest levels of serum calcium seen during the first 48 hours. The most common causes of neonatal hypocalcemia include decreased calcium stores and decreased renal phosphate excretion. The LBW infants are at greater risk, particularly if they are premature, or associated with a complicated pregnancy or delivery. Hypocalcemia may be asymptomatic or associated with nonspecific signs such as jitteriness, muscle twitching, vomiting, cyanosis, and convulsions. Asymptomatic hypocalcemia can be effectively treated by a continuous infusion of 10% calcium gluconate 75 mg/kg per day and can be prevented by adding calcium gluconate to daily maintenance therapy. The symptomatic patients should be treated by slow i.v. administration of 10% calcium gluconate, 6 mL in a LBW infant and 10 mL in a full-term infant, with monitoring of heart rate to prevent too rapid an injection. Serum calcium levels should be maintained within the 2.0–2.63 mmol/L (8–10.5 mg%) range.

Hypomagnesemia

Hypomagnesemia may occur in association with hypocalcemia in SGA infants and neonates with increased intestinal losses. If there is no response to correction of calcium deficiency, a serum magnesium level should be obtained. The treatment of hypomagnesemia is by i.v. infusion of 50% magnesium sulphate 0.2 mL/kg every 4 hours until the serum magnesium level is normal (0.7–1.0 mmol/L).

Hyperbilirubinemia

Jaundice in the newborn is a common physiological problem seen in 25–50% of all normal newborn infants and in a considerably higher percentage of premature and SGA infants.[43] It is the result of a combination of shortened red cell survival, with a consequent increase in bilirubin load, and an immature glucuronyl transferase enzyme system with a limited capacity for conjugating bilirubin. This results in transient physiological jaundice which reaches a maximum at the age of 3–4 days, but returns to normal levels at the end of the first week and the bilirubin level does not exceed 170 mmol/L.

Hyperbilirubinemia in the newborn may have a pathological basis such as severe sepsis, Rh and ABO incompatibilities, and congenital hemolytic anemias. Neonatal hemolytic jaundice usually appears during the first 24 hours of life, whereas physiological jaundice, as mentioned before, reaches a peak between 2 and 5 days of life. Other causes for prolonged hyperbilirubinemia, including those often associated with surgical conditions are: biliary obstruction, hepatocellular dysfunction, and upper intestinal tract obstruction. The diagnosis of extrahepatic biliary obstruction should be done as early as possible, because early operations for biliary atresia are essential to obtain good short-term as well as long-term results.[44] The major concern in neonatal hyperbilirubinemia (high levels of unconjugated bilirubin) is the risk of kernicterus (bilirubin deposition in the brain) that can result in brain damage.

Predisposing factors for jaundice include: hypoalbuminemia (circulating bilirubin is bound to albumin), hypothermia, acidosis, hypoglycemia, hypoxia, caloric deprivation, and the use of drugs (e.g. gentamicin, digoxin, furosemide). When the serum bilirubin concentration approaches a level at which kernicterus is likely to occur, hyperbilirubinemia must be treated. The infant's gestational age must be taken into account, as kernicterus can occur in the absence of profound hyperbilirubinaemia in premature infants. In most patients, other than those with severe hemolysis, phototherapy is a safe and effective method of treating hyperbilirubinemia. When the serum indirect bilirubin level rises early and rapidly and exceeds 340 mmol/L, hemolysis is usually the reason, and exchange transfusion is indicated.

COAGULATION ABNORMALITIES

Coagulation abnormalities in the neonate should be sought preoperatively and treated. The newborn is deficient in vitamin K and this should be given as 1 mg prior to surgery in order to prevent hypoprothrombinemia and hemorrhagic disease of the newborn. Thus, 1 mg vitamin K should be administered by i.m. or i.v. injection to every newborn undergoing surgery. Neonates with severe sepsis, such as those with necrotizing enterocolitis, may develop disseminated intravascular coagulopathy with a secondary platelet deficiency. Such patients should be given fresh-frozen plasma, fresh blood, or platelet concentrate preoperatively.

Bleeding has been one of the major risks associated with neonatal ECMO.[45] However, recently the addition of the fibrinolysis inhibitor, aminocaproic acid, along with strict control of coagulation while on ECMO has been reported to decrease bleeding while undergoing CDH repair on ECMO,[46] Lately, there is an interest in developing heparin-bonded circuits, which would allow ECMO without systemic heparinization.[47]

The potential of an increased rate of intraventricular hemorrhage (IVH) has also been reported in preterm neonates following NO therapy. NO leads to a prolonged bleeding time and an inhibition of platelet aggregation.[35]

LABORATORY INVESTIGATIONS

A newborn undergoing surgery should have blood drawn on admission for the various investigations, including full blood count, serum sodium, potassium and chloride, urea, calcium, magnesium, glucose, bilirubin, and group and cross-match. Blood gases and pH estimation should also be obtained to assess acid–base state and the status of gas exchange. The availability of micromethods in the laboratory has minimized the amount of blood required to do the above blood tests. The coagulation status of infants who have been asphyxiated may be abnormal and should be evaluated.[48] Neonatal sepsis can result in disseminated intravascular clotting and severe thrombocytopenia. A platelet count $<50\,000/mm^3$ in the neonate is an indication of preoperative platelet transfusion. Blood cultures should be obtained wherever there is any suspicion of sepsis.

VASCULAR ACCESS

Most newborns with surgical conditions cannot be fed in the operative and early postoperative period. It is essential, therefore, to administer fluids in these patients by the i.v. route. With the availability of 22–24 gauge plastic cannulas, percutaneous cannulation of veins has become possible even in small premature infants. Scalp veins and veins of the dorsum of the hand and palmar surface of the wrist are the most common sites used for starting i.v. infusion. With the improvements of techniques and equipment, it is now rarely necessary to perform a 'cut-down' in order to administer i.v. fluids.

Longer-term venous access can be obtained with fine percutaneous intravascular central catheters inserted at bedside without general anesthesia; so-called PICC lines (percutaneously inserted central venous catheters). These catheters

can be successfully inserted by dedicated nursing personnel[49] and provide long-term venous access with a reduced incidence of thromboembolic complications. To minimize thrombotic complications, it is important to ensure that the catheter tip resides in a central vein.[50]

Adequacy of the intravascular volume and the function of the heart can be assessed by a central venous catheter (CVC), which can be inserted through the umbilical vein, internal jugular vein, subclavian and femoral vein. Usually catheters are placed using the Seldinger technique. This central line is often mandatory and a basic monitoring device for the anesthetist at the time of operation, and sometimes can be performed at the theatre immediately before starting the operation. It is a useful instrument for fluid resuscitation, administration of medication, and central venous pressure monitoring. The next step in the venous access hierarchy is the tunneled central line (commonly Hickman or Broviac). These are commonly placed in either a neck or groin vein in neonates. Catheters inserted in a groin site in Neonatal Intensive Care Unit (NICU) babies seem to have a lower incidence of complications.[51] PICC and tunneled central lines are relatively comparable in terms of efficacy and complications, however if access is required for longer than 15 days a tunneled central line is more suitable.[52] However, CVC lines are not free from risks. Incidence of sepsis in neonates with central lines has been reported at 24%, and in these patients the presence of a stoma is strongly linked with sepsis.[53] Most catheter-related bloodstream infections respond to appropriate antibiotic treatment and/or catheter removal.[54]

Critically ill neonates will require an arterial line especially at the time of operation, either because of the surgery, when it is expected to result in significant fluid shift and hemodynamic instability, or because of a significant underlying cardiopulmonary disease of the newborn. This arterial line is for monitoring the hemodynamic and biochemical status, especially throughout the operative procedure. Right radial artery percutaneous catheterization is preferred because it allows sampling of preductal blood for measurement of oxygen tension. If the neonate has already had an umbilical artery catheter, it is safer to use it strictly for the purpose of blood pressure monitoring and blood sampling and not for the administration of drugs.

A good fixation of all these venous and arterial lines is essential as these newborns have to be transported frequently, and reinsertion of these vascular lines can be very difficult.

In an emergency, temporary vascular access can also be obtained by the intraosseous route.[54]

FLUID AND ELECTROLYTES, AND METABOLIC RESPONSES

Estimation of the parental fluid and electrolyte requirements is an essential part of management of newborn infants with surgical conditions. Inaccurate assessment of fluid requirements, especially in premature babies and LBW infants, may result in a number of serious complications.[55] Inadequate fluid intake may lead to dehydration, hypotension, poor perfusion with acidosis, hypernatremia, and cardiovascular collapse. Administration of excessive fluid may result in pulmonary edema, congestive heart failure, opening of ductal shunts, bronchopulmonary dysplasia, and cerebral intraventricular hemorrhage.

In order to plan accurate fluid and electrolyte therapy for the newborn, it is essential to understand the normal body 'water' consumption and the routes through which water and solute are lost from the baby. In fetal life around 16 weeks' gestation, total body water (TBW) represents approximately 90% of total body weight, and the proportions of extracellular and intracellular water components are 65 and 25%, respectively.[56] At term, these two compartments constitute about 45 and 30%, respectively, of total body weight, indicating that: (1) a shift from extracellular water to intracellular water occurs during development from fetal to neonatal life, and (2) relative TBW and extracellular fluid volume both decrease with increasing gestational age.[56] Small for gestational age infants have greater total body water than corresponding appropriate for gestational age infants.[57]

In very small premature infants water constitutes as much as 85% of total body weight and in the term infant it represents 75% of body weight. The total body water decreases progressively during the first few months of life, falling to 65% of body weight at the age of 12 months, after which it remains fairly constant.[58] The extracellular and intracellular fluid volumes also change with growth. These changes are shown in Table 9.2.

The objectives of parenteral fluid therapy are to provide:

- maintenance fluid requirements needed by the body to maintain vital functions;
- replacement of pre-existing deficits and abnormal losses;
- basic maintenance requirement of water for growth.

Maintenance fluid requirement consists of water and electrolytes that are normally lost through insensible loss, sweat, urine, and stools. The amount lost through various sources must be calculated to determine the volume of fluid to be administered. Insensible loss is the loss of water from the pulmonary system and evaporative loss from the skin. Approximately 30% of the insensible water loss occurs through the pulmonary system as moisture in the expired gas; the remainder (about 70%) is lost through the skin.[58]

Table 9.2 Changes in total body water (TBW) and body compartments during development.

Age	TBW (% body weight)	Extracellular fluid (% body weight)	Intracellular fluid (% body weight)
Premature	75–80	–	?–
Newborn	70–75	45	35
3 months	70	35	35
1 year	60	27	40–45
Adolescence			
Male	60	20	40–45
Female	55	18	40

Numerous factors are known to influence the magnitude of insensible water loss. These include the infant's environment (ambient humidity and ambient temperature[22]), metabolic rate,[59] respiratory rate, gestational maturity, body size, surface area, fever, and the use of radiant warmers and phototherapy.[60] In babies weighing less than 1500 g at birth, insensible loss may be up to three times greater than that estimated for term infants.[61] Fanaroff and colleagues found insensible water loss in infants weighing less than 1250 g to be 60–120 mL/kg per day.[62] Chief among the factors that affect insensible water loss are the gestational age of the infant and the relative humidity of the environment.[63] Recently it has been reported that the application of a semipermeable polyurethane membrane ('Tegaderm') to skin of extremely LBW infants shortly after birth decreased postnatal fluid and electrolyte disturbances and significantly improved their outcome by reducing severity of lung disease and decreasing mortality.[64]

Respiratory water loss is approximately 5 mL/kg per 24 hours and is negligible when infants are intubated and on a ventilator. Water loss through sweat is generally negligible in the newborn except in patients with cystic fibrosis, severe congestive heart failure, or high environmental temperature. Fecal water losses are 5–20 mL/kg per day.

RENAL FUNCTION, URINE VOLUME AND CONCENTRATION IN THE NEWBORN

The kidneys are the final pathway regulating fluid and electrolyte balance of the body. The urine volume is dependent on water intake, the quantity of solute for excretion and the maximal concentrating and diluting abilities of the kidney. Renal function in the newborn infant varies with gestational age and should be evaluated in this context. Very preterm infants younger than 34 weeks' gestational age have a reduced glomerular filtration rate (GFR) and tubular immaturity in the handling of the filtered solutes when compared to term infants. Premature infants between 34 and 37 weeks gestational age undergo rapid maturation of renal function similar to term infants with rapid establishment of glomerulotubular balance early in the postnatal period.[65] Extremely premature infants followed to school-age, however, demonstrate a reduced GFR compared to term infants, presumably due to impaired postnatal nephrogenesis.[66]

The full-term newborn infant can dilute urine to osmolarities of 30–50 mmol/L and can concentrate it to 550 mmol/L by approximately one month of age. The solute for urinary excretion in infants varies from 10–20 mmol per 100 cal metabolized, which is derived from endogenous tissue catabolism and exogenous protein and electrolyte intake. In this range of renal solute load, a urine volume of 50–80 mL/100 cal would provide a urine concentration of between 125 and 400 mmol/L. If the volume of fluid administered is inadequate, urine volume falls and concentration increases. With excess fluid administration, the opposite occurs. We aim to achieve a urine output of 2 mL/kg per hour, which will maintain a urine osmolarity of 250–290 mmol/kg (specific gravity 1009–1012) in newborn infants. For older infants and children, hydration is adequate if the urine output is 1–2 mL/kg per hour, with an osmolarity between 280 and 300 mmol/kg.

Accurate measurements of urine flow and concentration are fundamental to the management of critically ill infants and children, especially those with surgical conditions, and extensive tissue destruction or with infusion of high osmolar solutions. In these situations, it is recommended that urine volume be collected and measured accurately.

SERUM ELECTROLYTES AND METABOLIC RESPONSES IN NEONATAL SURGICAL PATIENTS

Electrolyte and metabolic responses to surgical trauma in neonates must be assessed against the background of the normal metabolic responses of an infant to extrauterine life. Table 9.3 represents a reasonable composite of some of the changes occurring in the metabolism of electrolytes, nitrogen, water, and calories in healthy newborn infants.[67] After birth, the neonate must make a transition from the assured continuous transplacental supply of glucose to a variable fat-based fuel economy. The normal infant born at term accomplishes this transition through a series of well-coordinated metabolic and hormonal adaptive changes. In premature and growth-retarded infants there is impaired ketogenesis, in addition to imprecise neonatal insulin secretion in response

Table 9.3 Metabolic and electrolyte changes of the healthy newborn.[a]

Variable	Phase I	Phase II	Phase III
Age	1–3 days	3–6 days	6–7 days
Intake	Low consumption of breast milk	Intake of breast milk rose progressively	Intake of breast milk stable
Body weight	Decrease	Begin to rise	Increase
K^+ metabolism	Negative balance	Positive balance[b]	Positive balance
Na^+ metabolism	Negative balance	Positive balance	Positive balance
Cl^- metabolism	Negative balance	Positive balance	Positive balance
H_2O metabolism	Negative balance	Negative balance	$\pm$ Balance[c]
Urine volume	Small output	Increased	Stable
N metabolism	Negative balance	Positive balance	Positive balance
Caloric metabolism	Negative balance	Positive[d]	Positive balance

From Wilkinson *et al.*,[48] with permission.

[a]This group of ten male newborn babies include five who were healthy and five who suffered degrees of fetal distress.

[b]Potassium probably gives the most sensitive indication of metabolic changes at this time of life. The day on which potassium balance first became positive varied a good deal.

[c]Balance may be slightly positive or slightly negative.

[d]Transition to positive balance. In preterm infants all three phases can last longer and have more profound changes.

to blood glucose.[41] In response to sepsis or surgical trauma it seems that neonates divert the products of protein synthesis/breakdown from growth to tissue repair. Following surgical stress, oxygen consumption and energy expenditure in neonates return to baseline figures after 12–24 hours.[42] This is greatly different to the situation in adult surgical practice.

Table 9.4 shows fluid and electrolyte disturbances, their mechanisms, and treatment of common neonatal surgical conditions.

PREOPERATIVE MANAGEMENT OF VARIOUS SURGICAL NEONATAL CONDITIONS

Preoperative management is critical to the success of surgical intervention and the postoperative restoration of normal function. It has been observed that patients who have operations conserve sodium postoperatively.[68] In fact, this sodium concentration is usually caused by hypovolemia, which has its genesis in preoperative dehydration, because of various surgical conditions. The remedy is to provide parenteral maintenance fluid preoperatively when oral restriction of fluid is required. Some patients may need fluid resuscitation preoperatively, and their extracellular fluid volume must be restored. Assessment of adequacy of the intravascular space can be done by measurement of pulse, blood pressure, capillary filling in the skin, core temperature, temperature of the skin, urine output, specific gravity, and urinary sodium level. In addition to vital signs, an accurate weight, and especially changes in weight, electrolyte levels and calcium and blood gas analyses should be obtained. Attempts should be made to correct any abnormalities encountered during this assessment.

Newborn surgical patients shift large amounts of protein and water into tissues or into potential spaces such as the peritoneal or pleural cavity. These so-called third-space losses

Table 9.4 Fluid and electrolyte disturbances in common neonatal surgical conditions.

Neonatal condition	Fluid and electrolyte disturbances	Mechanism	Treatment
Tracheo-esophageal fistula	Mild dehydration Hyponatremia	External loss of salivary secretions, lack of intake	Volume replacement with dextrose–saline
Pyloric stenosis Pyloric atresia Peritonitis	Dehydration, hypokalemia, hypochloremia, metabolic alkalosis	Loss of gastric secretions, hydrogen ions, potassium and chloride	Volume replacement with dextrose–saline and potassium chloride
Necrotizing enterocolitis	Severe dehydration	Shift of fluids into third space, loss of sodium in stool or emesis. Low blood pressure with poor peripheral perfusion	Fast volume replacement
Perforated viscous	Hyponatremia Metabolic acidosis, hyperkalemia, high levels of BUN		Blood or blood products Dextrose–saline
Upper intestinal obstruction Duodenal atresia Malrotation (Ladd's bands) Midgut volvulus Low intestinal obstruction	Mild to severe dehydration Hypothermia, *hypochloremia, hypocalcemia*	Loss of gastric and duodenal fluids: hydrogen ions, chloride, and bicarbonate	Volume replacement with dextrose–saline and potassium chloride
Ileal atresia Hirschsprung's disease Imperforate anus Abdominal wall defects	Dehydration, hyponatremia, metabolic acidosis, hypokalemia	Loss of fluids into the intestine. Enterocolitis	Fluid replacement by dextrose–saline, plasma, and blood as needed
Omphalocele Gastroschisis	Severe dehydration, metabolic acidosis, hyponatremia	Loss of serum from the intestinal wall in gastroschisis. Aspiration of large volume of bile by nasogastric catheter. Low perfusion	Urgent fluid replacement by plasma, albumin, Ringer's lactate

are hard to quantify. Inadequate replacement of these losses can cause hypovolemia and shock. This is commonly seen in peritonitis (e.g. necrotizing enterocolitis, perforated viscus) and other congenital abnormalities such as gastroschisis and omphalocele. Infusion of colloid in the form of fresh-frozen plasma, 5% albumin, packed red cells, whole blood, or plasma-like product is required to maintain intravascular integrity in the face of protein and fluid losses. Enterocolitis complicating Hirschsprung's disease or other intestinal obstructive lesions can cause massive losses of fluid and electrolytes and result in hypovolemia, hyponatremia, metabolic acidosis, and hypokalemia. In the presence of severe enterocolitis secondary to obstruction, with accompanying large fluid losses into the intestine, adequate preoperative fluid replacement is mandatory to ensure a reasonable outcome. Intraoperative homeostasis should be maintained through administration of appropriate volumes of isotonic crystalloid and colloid.[69] The benefits of colloid over crystalloid solutions in pediatric practice are as yet unproven and are based on results extrapolated from adult practice.

Vomiting of gastric contents as a result of gastric outlet obstruction caused by a duodenal obstruction, pyloric stenosis, intestinal bands, or malrotation results in a chronic loss of gastric contents and primary hydrogen and chloride ions, in turn resulting in hypochloremic alkalosis. Chronic hypochloremic alkalosis results in hypokalemia. In renal compensation, hydrogen ions are conserved at the expense of potassium loss. Preoperative management of patients with gastric outlet obstruction includes fluid replacement and at least potential correction of the hypochloremic alkalosis by infusion of chloride and potassium chloride (Table 9.4). This preoperative metabolic correction greatly enhances surgical outcome. Table 9.5 represents the electrolyte content of bodily fluids, which are lost by various routes, and must be corrected with the appropriate balance to be replaced accurately.

Bilateral obstruction uropathy exhibits a number of important and sometimes complex abnormalities of electrolyte metabolism and acid–base regulation. Depending on the severity of a lesion, patients can have dehydration, fluid overload, hypernatremia, hyponatremia, hyperkalemia, renal tubular acidosis, and azotemia with variable degrees of renal failure. Patients with water and salt-losing nephropathy need additional salt and water supplements. Patients with defective dilutional capacity and renal failure require fluid restriction. Patients with renal tubular acidosis require bicarbonate supplementation with or without potassium exchange resins.

FLUID MANAGEMENT PROGRAM

Based on a consideration of the sources of water loss, an average parenteral fluid design for an infant receiving no oral feeding should provide about 40 mL of water per 100 cal metabolized for insensible loss and 50–80 mL/100 cal for urine, with about 5 mL/100 cal for stool water, resulting in a total volume of 100–125 mL/100 cal for the maintenance fluid losses under baseline conditions per 24 hours. LBW infants will require considerably more fluid because of an increasing insensible loss. Neonates weighing less than 1000 g may need 160 mL/kg per 24 hours and those over 1000 g may require 110–130 mL/kg per 24 hours. With premature infants, a fluid intake >170 mL/kg per 24 hours is associated with an increased risk of congestive cardiac failure, patent ductus arteriosus, and necrotizing enterocolitis.

Serial measurements of body weight are a useful guide to total body water in infants. Fluctuations over a 24-hour period are primarily related to loss or gain of fluid, 1 g body weight being approximately equal to 1 mL water. Errors will occur if changes in clothing, dressings, and tubes are not accounted for and if scales are not regularly calibrated.

The assessment of hydration status in every newborn surgical patient is essential for the infant's outcome. This can best be obtained by changes in body weight, measurement of urine flow rate, concentration of urine, hematocrit, and total serum protein. Estimation of serum electrolytes, urea, sugar, and serum osmolarity gives a good indication of the hydration status.

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10

Anesthesia

DECLAN WARDE AND NICHOLAS EUSTACE

INTRODUCTION

Over the past 70 years or so, provision of anesthesia for the neonate requiring surgery has developed from being a relatively haphazard affair to achieving the status of a recognized subspecialty. The improved survival rates seen following surgery, where even the smallest and sickest infants are concerned, have been due in no small part to advances in anesthetic management. Equally important has been an increased appreciation of the need for an efficient smooth-working team. The success of neonatal surgery depends on maximum cooperation between surgeon, anesthetist, neonatologist, and nursing and paramedical personnel. It is appropriate therefore that everyone involved in the care of neonates, whether working inside or outside the operating theater, should be familiar with the basic techniques used in maintaining a favorable physiologic milieu in the face of surgical intrusion, while at the same time ensuring adequate anesthesia. This chapter will consider the preoperative evaluation and preparation of the surgical neonate, anesthetic equipment, choice of anesthetic agent and technique (with reference to the pharmacology of the newborn), induction of anesthesia and endotracheal intubation, maintenance and reversal of anesthesia, perioperative monitoring and fluid therapy, the anesthetic implications of congenital anomalies and, finally, specific considerations for the premature infant undergoing surgery.

PREOPERATIVE PREPARATION AND EVALUATION

Much neonatal surgery is performed on an emergency basis. However, operation is rarely so urgent as not to allow for adequate evaluation and stabilization beforehand. The cornerstone of preoperative anesthetic management is a detailed knowledge of the infant's history combined with a thorough physical examination. Consideration must also be given to the specific surgical procedure to be undertaken and its implications in terms of potential blood loss, monitoring requirements, and postoperative care.

History

Although many neonates requiring surgery are aged only a few hours, considerable information that is useful as regards anesthetic management will have been accumulated by the time of the anesthetist's visit. This information should be obtained from the parent(s) (if available) and medical and nursing colleagues. Of profound importance is an accurate estimation of gestational age, as prematurity has profound implications for the anesthetist (see later). Trends in blood pressure and heart rate, body weight, fluid intake and output, laboratory measurements, x-ray appearances, and the extent of any respiratory support required will normally be readily available and are very helpful both in planning anesthetic technique and in anticipating problems. A knowledge of recent or current drug therapy is also important.

Physical examination

The anesthetist should make a brief appraisal of the infant's overall condition and follow this with a careful assessment of individual body systems. Overhydration or hypovolemia can be detected by assessment of skin turgor, the anterior fontanelle, and liver size. Peripheral vasoconstriction may indicate either hypovolemia or acidosis. Jaundice will normally be self-evident, but anemia and cyanosis can be difficult to detect in the neonate. Pulmonary function is also less easily evaluated than in older children and adults, but any of the following may indicate impending respiratory failure: nasal flaring, tachypnea, chest wall recession, grunting respiration, or apneic spells. Airway anatomy should be carefully assessed in order that potential difficulties with endotracheal intubation can be anticipated. One should look for *other* associated congenital anomalies in the surgical neonate. This is particularly so when examining the cardiovascular system

(e.g. one-third of infants with esophageal atresia also have some form of congenital heart disease). Accurate preoperative neurological assessment is mandatory in infants presenting for anesthesia for neurosurgery.

Laboratory investigations

Minimum laboratory data required include full blood count, blood urea and serum electrolytes, blood glucose and calcium, coagulation profile, and urine specific gravity. Arterial blood gas analysis for pH, oxygen and carbon dioxide partial pressure (PO_2 and PCO_2), and bicarbonate levels is also frequently indicated. The preoperative hemoglobin level should be at least 12 g/dL – if lower, consideration should be given to transfusion with packed red blood cells prior to anesthesia and surgery. Any dehydration, hypovolemia, hypoglycemia, hypocalcemia, or hypo- or hyperkalemia should be corrected. pH, PO_2, PCO_2, and body temperature should be normalized.

Premedication

Sedative premedication is not used in neonates. However, many pediatric anesthetists consider it advisable to administer an anticholinergic drug in order to reduce secretions and to protect against bradycardia. Atropine is the most widely used drug, usually in a dose of 0.02 mg/kg by intravenous (i.v.) injection immediately prior to induction of anesthesia.

Prior to transfer to the operating theater, the anesthetist should confirm that:

- the infant has been fasting for at least 3 hours (but not for much longer unless an i.v. fluid infusion is in progress);
- blood has been crossmatched (if indicated);
- vitamin K, 0.5–1 mg i.m., has been administered (to allow for possible deficiency in vitamin K-dependent clotting factors);
- the stomach has been decompressed (especially in cases of intestinal obstruction).

Estimated blood volume, allowable blood loss, and maintenance fluid requirements should be calculated. Where it is anticipated that multiple vascular access routes will be required (e.g. for central venous pressure or direct arterial pressure monitoring), it may be advisable to establish these in the intensive care unit (ICU) before transfer to the operating theater, as it is usually easier to maintain an infant's body temperature in the ICU environment. Overall fitness must be assessed in the light of the urgency of surgery. This may require consultation between anesthetist, surgeon, and other interested personnel. If transfer to the operating theater is considered to be unacceptably hazardous, for example in the case of some extremely ill and low birth weight infants, it may be advantageous to undertake surgery in the ICU itself.[1,2]

TRANSFER TO THE OPERATING THEATER

The time during which the neonate is transferred to the operating theater is one which is not without hazard. Risks are minimized if he or she is accompanied by experienced medical and nursing personnel and if the theater is close at hand. Transfer should be in either an incubator or an isolette with overhead heater to reduce heat loss. Any treatment in progress (e.g. i.v. fluid or drug infusion, respiratory support) should be continued by the use of battery-operated infusion pumps and portable respiratory equipment. Monitoring should not be interrupted during this critical phase.

OPERATING THEATER AND ANESTHETIC EQUIPMENT

The prime objectives of neonatal anesthesia are the provision of sleep, analgesia, life support, intensive surveillance, and appropriate operating conditions for the infant requiring surgery. In order for these to be achieved it is imperative that both operating theater environmental conditions and anesthetic equipment be appropriate. It has been shown that maximum heat loss occurs between the time of arrival of the neonate in theater and the skin incision. Measures should be taken to minimize the risk and extent of this occurrence. Before the infant arrives, the theater, which should be draught free, should be warmed to a temperature of 24 or 25°C. Once the baby is removed from the incubator or isolette, he or she should be placed on a water or air mattress which has been heated to 40°C and kept covered as much as possible – plastic drapes and blankets are particularly useful in this regard. The warming mattress used must be electrically safe and accurately monitored, have an easily adjustable thermostat and a fail-safe cut-out device in the event of thermostat failure. If an overhead radiant heater is available, it should be set to maintain skin temperature at 36°C. Other measures which assist in maintaining body temperature during this critical period include warming and humidifying inspired anesthetic gases and warming i.v. and skin preparation fluids.

Breathing systems

An appropriate anesthetic circuit for use in infants needs to be light, have minimal resistance and dead space, allow for warming and humidifying of inspired gases and be adaptable to spontaneous, assisted, or controlled ventilation. While the T-piece system originally designed by Philip Ayre[3] and later modified by Rees[4] is still used by some, circle systems are currently more popular. Connectors and tubes should also offer minimal flow resistance and dead space.

Most endotracheal tubes used during neonatal anesthesia are manufactured of polyvinyl chloride. A knowledge of the probable diameter and length of tube appropriate for any given infant is essential, but must always be confirmed clinically. The optimal diameter is the largest which will pass easily through the glottis and subglottic region and will produce a slight leak when positive pressure is applied. A convenient guideline for length of orotracheal tube from gum to mid-trachea is 7 cm for an infant weighing 1 kg, with an

additional centimeter for each kilogram increase in weight.[5] Use of an endotracheal tube of too large a diameter may result in tracheal wall damage, while excess length leads to endobronchial intubation. The presence of a cuff limits the diameter of tube which can be used, with consequent increased resistance to airflow. For this reason, uncuffed tubes are invariably used in neonates. Once satisfactory positioning has been confirmed visually and by auscultation of both lungs, the tube should be taped securely to prevent accidental extubation. Consideration should be given to secondary fixation to the forehead to prevent rotational movement. Face masks are generally used for only brief periods in neonates, but should provide a good fit and have a low dead space. Oral airways are not generally necessary except in cases of choanal atresia, but have the advantage of splinting the endotracheal tube and preventing lateral movement.

The incidence of airway complications associated with the laryngeal mask airway (LMA) in infants is high.[6] However, the device can occasionally prove useful, especially when endotracheal intubation is difficult.[7–9]

Laryngoscopes

Because of the anatomical peculiarities of the infant's airway, most anesthetists prefer to use a laryngoscope with a straight blade, lifting the epiglottis forwards from behind to facilitate intubation. The Miller number 0 and 1 blades are suitable in most cases.

Ventilators

Most infants and children can be ventilated using standard adult ventilators provided the ventilator is of low internal compliance and equipped with pediatric breathing tubes. The ventilator should be capable of delivering small tidal volumes and rapid respiratory rates, and have an adjustable inspiratory flow rate and inspiratory:expiratory ratio so that peak airway pressure is kept as low as possible.[10] Pressure-controlled ventilation is widely used in order to minimize the risk of pulmonary barotrauma. A suitable temperature-controlled humidifier should be incorporated in the inspiratory side of the ventilator circuit. The ability to deliver air/oxygen mixtures through the ventilator or anesthetic circuit should be available.

Monitoring equipment

A complete range of monitoring equipment suitable for infant use is required.

CHOICE OF ANESTHETIC AGENT AND TECHNIQUE

Neonates perceive pain, while even babies born at 28 weeks' gestation mount a substantial and potentially harmful response to surgically induced stress.[11,12] Thus, few would argue with the contention that adequate anesthesia must be provided for all infants undergoing surgery. The anesthetic agents employed are similar to those used for older children and adults. However, the responses of the neonate to these potent drugs differ in a number of respects from those seen in older patients. An understanding of these differences is essential for the safe conduct of neonatal anesthesia and also influences choice of anesthetic agent and technique. The issue of possible neurotoxic effects of general anesthetics on the developing brain has received considerable attention in recent years and there seems little doubt that until there is more clarity as regards the actual degree of risk, any surgery which is truly elective should be deferred until the infant attains an as yet undefined older age.[13,14]

Inhalation agents

Inhalation induction of anesthesia with either air or nitrous oxide, oxygen and a volatile agent remains popular. Provided that respiration is not depressed, both induction of and emergence from anesthesia are rapid in infants. The reasons for this are multiple, but include the relatively higher cardiac output, greater alveolar ventilation, smaller functional residual capacity, and larger proportion of vessel-rich tissues relative to body mass seen in the newborn infant.[15–17] All potent inhalation agents lead to a dose-related depression of spontaneous respiration.[18] This is particularly important in the neonate, in whom the ventilatory response to hypoxia is one of hypoventilation. An additional consideration is that the minimal alveolar concentration (MAC) of inhaled agents required to prevent reflex responses to surgical stimulation varies with age.

HALOTHANE

Halothane was for many years the most widely used volatile anesthetic for inhalation induction in infants and young children. This is largely because it is usually associated with a smooth induction without irritant effects on the airway. It has been superseded in patients of all ages by agents which offer greater hemodynamic stability to the extent that it is currently unavailable in many parts of the world.

ISOFLURANE

Despite its lower blood gas solubility coefficient, inhalation induction with isoflurane is generally not as rapid or as smooth as with halothane. Indeed this agent has been shown to be associated with a significant incidence of hypoxic episodes during inhalation induction of anesthesia in older children.[19] Sedative premedication[20] and use of a high inspired isoflurane concentration from the outset[21] both reduce the incidence of these adverse occurrences, but are relatively contraindicated in the surgical neonate. Isoflurane has been shown to maintain systolic arterial pressure in the normal range even in preterm neonates and, unlike

halothane, does not sensitize the myocardium to the effects of circulating catecholamines. It has considerable potentiating effects on non-depolarizing muscle relaxants, so that lower doses of the latter can be used. Metabolic degradation of the agent is minimal and recovery rapid. In summary, isoflurane is an excellent agent for maintenance of anesthesia, perhaps the agent of choice in the neonate.

ENFLURANE

This agent is rarely used in neonatal and pediatric anesthesia because its irritant effects render it relatively unsatisfactory for inhalation induction.

DESFLURANE

Airway irritant effects also render desflurane unsuitable for inhalation induction in pediatric practice. However, recovery times in infants are shorter than those following other volatile anesthetics. The agent has been recommended for maintenance of anesthesia in the ex-premature infant prone to apnea and ventilatory depression.[22]

SEVOFLURANE

Sevoflurane has replaced halothane for the induction of anesthesia in neonates and children. It lacks the airway irritation associated with other newer inhalation agents and provides cardiovascular stability. Induction time with sevoflurane is shorter than with halothane in older children.[23] However, this does not appear to be the case where infants are concerned.[24] Infants undergoing inguinal herniotomy with sevoflurane anesthesia have a slower recovery than those in whom desflurane has been used with no difference in the incidence of postoperative respiratory events.[25] Higher concentrations of sevoflurane, commonly used for induction of anesthesia, can be associated with epileptiform EEG changes.[26] In older children the agent is associated with emergence delirium.[27]

NITROUS OXIDE

This gas does not provide adequate anesthesia when used alone with oxygen.[12] It is most often employed as a carrier which supplements potent volatile anesthetics, thereby reducing the concentration required and minimizing cardiovascular depressant effects. Animal work indicated that it might induce pulmonary vasoconstriction, with resultant increased right-to-left shunting in the newborn,[28] but this does not appear to be so.[29] It does cause moderate respiratory and cardiovascular depression. One limitation to the use of nitrous oxide in neonatal anesthesia is the fact that it is many times more soluble in blood than is nitrogen. As a result, the inhalation and subsequent diffusion of the gas causes an increase in the volume of compliant spaces. It follows that the agent should not be used in infants with congenital diaphragmatic hernia, lobar emphysema, or bowel obstruction.

Intravenous agents

THIOPENTONE

Despite the fact that it was introduced to anesthetic practice over 70 years ago and that many supposedly superior agents have since been developed, some still consider this drug to be the preferred agent for i.v. induction in infants. The induction dose (ED_{50} 3.4 mg/kg) is lower in neonates less than 14 days of age than in older infants.

PROPOFOL

Propofol is a highly lipophilic short-acting anesthetic agent. It has a rapid onset and short duration of action. It is currently unlicensed for use in neonates in many countries. Despite this, it is increasingly used for the induction of anesthesia in the newborn. The clearance of propofol in neonates is slower than in older pediatric patients to the extent that they are at risk of longer recovery.[30] A randomized study in infants found it to be more effective at facilitating intubation than a morphine, atropine, and succinylcholine combination.[31] It has been been used successfully in the management of pyloric stenosis.[32]

KETAMINE

This agent is associated with greater cardiovascular stability than many other anesthetic drugs.[33] However, its metabolism is considerably delayed in infants below one year of age. It has the advantages of having a profound analgesic effect and of being capable of being given by intramuscular injection.

Neuromuscular blocking agents

SUCCINYLCHOLINE

Succinylcholine has the advantage of having both a rapid onset (30 seconds) and short duration of action. Relatively higher doses (2 mg/kg) of this drug are required to produce full relaxation in infants than in adults (1 mg/kg). This is because of the neonate's larger extracellular fluid space, throughout which the drug is distributed. Succinylcholine is metabolized by plasma pseudocholinesterase. Although plasma levels of this enzyme are low in the first six months of life, activity is adequate to metabolize the drug, and recovery occurs after a similar time to that seen in adults (approximately 4 minutes).

Because of the number of side effects, including bradycardia, hyperkalemia, and triggering of malignant hyperpyrexia reactions associated with this agent,[34] it has been suggested that its use in young infants should be re-evaluated. However it remains widely used in neonates.[35]

Non-depolarizing muscle relaxants

For many years it was generally agreed that newborn infants exhibited an increased sensitivity to these agents, but recent

studies have demonstrated that full relaxation demands doses similar to those used in adults. A lower plasma concentration is required (presumably because of immaturity of the neuromuscular junction), but this is produced in any event by distribution of injected drug throughout the relatively larger extracellular fluid compartment. Alterations in plasma protein binding may also play a role in determining dose requirements which are much more variable than in adults.[36] It follows that careful titration of dose against response is advisable and that these drugs should be administered slowly to neonates. Use of a peripheral nerve stimulator as a guide to degree of relaxation is strongly recommended.[37]

ATRACURIUM AND VECURONIUM

These two agents were introduced because their duration of action was intermediate between that of succinylcholine and older non-depolarizing muscle relaxants such as pancuronium and because they offered increased cardiovascular stability. In addition, atracurium is attractive in that its metabolism is independent of hepatic and renal function, although it is dependent on pH and temperature. Recommended initial doses are 0.3–0.5 mg/kg for atracurium and 0.05–0.1 mg/kg for vecuronium. Because of their pharmacokinetic profiles, both drugs are suitable for use by continuous i.v. infusion, although atracurium infusion requirements show marked individual variation.[38]

Nightingale found the duration of effect of atracurium to be longer in infants less than 3 days of age.[39] Other studies have shown the dose-response curves of this agent to be parallel in infants, older children, and adults and in fact demonstrate recovery times to be shorter in infants.[40,41] Histamine release, an occasional problem with the drug in adults, has not caused problems in the pediatric population.[39]

Vecuronium, on the other hand, has been found to have a longer recovery time in infants compared to older children and adults and should be regarded as a long-acting muscle relaxant in this age group.[42]

MIVACURIUM

Mivacurium is a short acting non-depolarizing neuromuscular agent which is rapidly hydrolyzed by plasma pseudocholinesterase. The time course of block produced by the drug is more rapid in younger pediatric patients.[43] Satisfactory intubating conditions are not achieved as quickly as with succinylcholine but serious side effects occur less frequently.

ROCURONIUM AND SUGAMMAADEX

Rocuronium is a member of the aminosteroid family of neuromuscular blocking drugs similar to vecuronium. It has the advantage of providing a rapid onset of action similar to that of suxamethonium without the side effects associated with it. Its duration of action is similar to vecuronium. The recommended doses to provide optimal intubation conditions are 0.3–1 mg/kg.[44] It is felt that the duration of action of rocuronium in neonates is longer than in older children.[45]

Sugammadex is a selective muscle relaxant binding agent which was designed to specifically reverse the effects of aminosteroid muscle relaxants. It encapsulates rocuronium forming a tightly bound complex that prevents the muscle relaxant from acting at the receptors. Doses prescribed in adults are greater than 2 mg/kg when reversing profound muscle relaxation.[46] Data for neonates are currently unavailable.

D-TUBOCURARINE AND PANCURONIUM

These drugs were widely used in neonatal anesthetic practice in the past but have been replaced by alternatives with a shorter duration of action.

ANALGESIA

There is no doubt whatsoever that neonates perceive and respond to pain and that the intraoperative administration of potent analgesics to infants undergoing major surgery can be beneficial.[12] The neonate exhibits an exaggerated response to narcotic administration when compared with the older child.[47] The reasons for this include immaturity of hepatic enzyme systems leading to impaired conjugation and glucuronide excretion[48] and the greater permeability of the infant blood–brain barrier to these drugs.[49] Morphine elimination half-life is prolonged in babies less than 4 days old, while morphine clearance in the newborn in less than one-half that of older infants.[50] Despite concerns about adverse effects, such as respiratory depression, this drug continues to be the standard analgesic after major surgical procedures in young infants.[51,52]

It follows that where narcotic analgesics are administered to neonates, dosage regimens should be modified so that patient safety is not compromised. Morphine (0.05–0.1 mg/kg) and fentanyl (0.005–0.02 mg/kg) given intravenously are the two most widely used drugs, with the latter being particularly well tolerated haemodynamically.[33,53] Intraoperative infusions of ultra-short acting opioids such as remifentanil have been used successfully although recovery times were prolonged in some infants aged less than 7 days.[54,55]

Continuous infusions of i.v. morphine are popular for provision of postoperative analgesia in ventilated infants and those nursed in high-dependency areas. Infusion rates above 0.01 mg/kg per hour are rarely necessary. Respiratory monitoring should be continued for 24 hours after discontinuation of the infusion. The situation with regard to other infants is more difficult. It should be recognized that while failure to treat discomfort or pain effectively may have significant long-term effects, overaggressive treatment has its own morbidity.

Combined analgesic regimens, leading to adequate analgesia with lower doses of opioids and reduced side effects, have been proposed.[56,57] One study assessed the potential morphine sparing effect of acetaminophen in infants (0–2 months) after major thoracic or abdominal surgery. There was no significant benefit from acetaminophen over placebo as an adjuvant to i.v. morphine as assessed by additional

morphine boluses, incidence of increase in continuous morphine infusion, or incidence of continuous morphine infusion decrease in the second 24 hours after operation. There was no significant difference in total morphine consumption between acetaminophen and placebo groups.[58]

Codeine has been used for many years in the treatment of mild to moderate pain. However, protocols for its use in infants and children are not well-documented in the literature.[59] Non-steroidal anti-inflammatory drugs are not widely used for analgesia in infants.[60]

Regional anesthesia

It should not be forgotten that local or regional anesthetic techniques (e.g. thoracic, lumbar, or caudal epidural block, intrathecal block, intercostal block, wound infiltration, etc.) can often be used as an alternative method of providing analgesia for infants during and after surgery. They may be particularly valuable in the high-risk infant.[61–65] The recently described transverses abdominis plane (TAP) block has been used to provide analgesia following pyloromyotomy surgery.[66]

Induction of anesthesia and endotracheal intubation

Most pediatric anesthetists advocate that infants should have anesthesia induced and a muscle relaxant administered prior to attempts at endotracheal intubation. Induction technique depends on: (1) the age, size, and physical status of the infant, (2) the relative hazard of regurgitation, and (3) the personal preference of the anesthetist. In most instances, i.v. induction followed by administration of a short-acting muscle relaxant is satisfactory. Inhalation induction is an acceptable alternative. In either case, i.v. access should be established beforehand and the induction itself should be preceded by a short period of preoxygenation.

Intubation is best accomplished with the infant's head extended at the atlanto-occipital joint. This position allows the straightest and shortest distance between the lips and larynx.[67] The laryngoscope blade is inserted into the right side of the mouth, displacing the tongue to the left. As the blade is advanced the epiglottis comes into view. In the neonate this structure is long and floppy and it should be displaced anteriorly from behind to aid visualization of the larynx. If difficulty is encountered, the little finger of the left hand can be used to press gently on the larynx to improve visualization. The use of an atraumatic but rigid bougie can also be extremely valuable in these cases. Once intubation has been achieved, one should carefully auscultate both lungs to check for equal air entry, and the endotracheal tube should be securely fixed.

If it is considered at the time of induction of anesthesia that postoperative mechanical ventilation will be required, the tube should be inserted by the nasal rather than the oral route. It is difficult to manipulate a Magill's forceps in the mouth of a small infant, but flexing the neck usually facilitates passage of nasotracheal tubes.

MAINTENANCE OF ANESTHESIA

Because of the vulnerability of the infant's respiratory system, spontaneous respiration is not used for long periods in the anesthetized neonate. Mechanical ventilation helps ensure adequate gas exchange and also leaves the hands of the anesthetist free to perform other tasks. Suitable ventilators have already been discussed and, depending on the particular machine available, may be set in either pressure or volume cycled modes. With the former, suitable settings would include a fresh gas flow of 2–3 L/min, peak airway pressure of approximately 20 cmH_2O of water, a ventilatory rate of 30–40 per minute with an inspiratory time of approximately 0.6 seconds. With the latter, a delivered tidal volume of approximately 8–10 mL/kg at a rate of 30–40 breaths per minute is appropriate. Inspired gases should be warmed and humidified to prevent damage to the mucosal lining of the respiratory tract and to minimize heat loss. Manual ventilation allows rapid detection of airway obstruction or disconnection, and is particularly useful during thoracic surgery.

The most widely used agents for maintenance of anesthesia in the neonatal population are isoflurane and sevoflurane, usually combined with 50% oxygen in nitrous oxide or air, along with a small dose of relaxant.

Consideration should be given to the use of air/oxygen mixtures in preterm neonates.

REVERSAL AND EXTUBATION

If a volatile agent has been used for maintenance of anesthesia it should be discontinued shortly prior to the end of surgery. Once surgery has been completed, residual muscle relaxation is reversed by either neostigmine (0.06 mg/kg) or edrophonium (1 mg/kg) combined with either atropine (0.02–0.03 mg/kg) or glycopyrrolate (0.01 mg/kg). Sugammadex may also be used if rocuronium was the muscle relaxant used during surgery. Controlled ventilation is continued with 100% oxygen or with oxygen in air until spontaneous respiration has returned. Suctioning through the endotracheal tube is carried out if secretions are obviously present. The nostrils should be gently suctioned as a routine. The infant should not be extubated until fully awake and breathing adequately. In most cases, reversal of neuromuscular blockade and resumption of spontaneous respiration occur rapidly.[68] If difficulty is encountered this may be due to hypothermia, acidosis or hypoglycemia, or the fact that an incremental dose of relaxant has been given too close to the end of surgery.

MONITORING

The clinical condition of the anesthetized neonate can deteriorate more rapidly and with less warning than that of patients in any other age group. It follows that careful and continuous monitoring is essential. While no piece of machinery will adequately replace the careful anesthetist, there are a number of devices available which provide helpful

information that cannot be gleaned by clinical means alone. The monitoring employed in any particular case depends upon the physical status of the infant and the surgical procedure to be undertaken.

The following should be positioned prior to induction (and, indeed, regarded as the minimum equipment required for monitoring anesthetized neonates):

- ECG leads and electrodes;
- blood pressure cuff;
- core temperature probe;
- pulse oximeter probe;
- end-tidal carbon dioxide monitor;

Most neonates undergoing anesthesia and surgery require additional monitoring. The various options available will be discussed in relation to the particular body system being monitored.

Respiration

Chest wall movement should be observed continuously if at all possible. When mechanical ventilation is employed, airway pressure and minute volume alarms are mandatory. It should not be forgotten that alarms can fail. Oxygenation and adequacy of gas exchange are monitored continuously by pulse oximetry and breath by breath end-tidal anesthetic agent and carbon dioxide measurement. Serial arterial blood gas analysis is mandatory in critically ill infants undergoing major surgery.

Cardiovascular function

Observation of peripheral perfusion and palpation of a peripheral pulse are both useful but may be difficult to achieve because of problems of access. Blood pressure monitoring is essential because of the reduced cardiovascular reserve of the neonate and the risk of hypotension if high concentrations of inhaled anesthetics are used. Automated oscillotonometry is employed in most instances but concern has been expressed about the accuracy of the devices used when blood pressure is low. The cuff should be of appropriate width (approximately 4 cm).

If either the infant's physical status or the type of surgery to be performed necessitates continuous monitoring of blood pressure, a suitable vessel (usually the right radial artery) should be cannulated, the cannula being connected to a pressure transducer by narrow-bore tubing.

Central venous pressure monitoring is useful in infants with congenital heart disease, and also if significant blood loss (and replacement) is anticipated. The right internal jugular vein is usually the simplest to cannulate. Ultrasound is increasingly used to guide placement of central lines in neonates. Monitoring of left atrial pressure and/or pulmonary capillary wedge pressure is rarely indicated in the newborn.

Fluid balance

The goal of intraoperative fluid management is to sustain homeostasis by providing the appropriate amount of parenteral fluid to maintain adequate intravascular volume, cardiac output, and, ultimately, oxygen delivery to tissues at a time when normal physiological functions are altered by surgical stress and anesthetic agents.[69] Maintenance fluid requirements vary considerably within the neonatal period itself, but may be taken as being approximately 4 mL/kg per hour for infants older than 5 days of age. Assuming there is no preoperative fluid deficit, an i.v. infusion set at the usual maintenance rate should be commenced prior to induction of anesthesia. In practice, this will usually have been done in the ward. The composition of the administered fluid will vary according to the maturity of the baby and preoperative electrolyte and glucose levels. Because of the problems associated with hyperglycemic states in infancy and hyponatremia, care should be taken with the use of 10% dextrose infusions.[70,71] It is important to take into account the volume of drug diluents administered during anesthesia and surgery when calculating fluid balance.

Blood and fluid loss can be extensive and very difficult to measure during neonatal surgery. The former is best estimated by the use of small volume suction traps, by weighing small numbers of surgical swabs before they dry out, and by serial hematocrit measurements. During lengthy surgery, serum electrolytes and blood glucose should be measured at regular intervals. Urine output may be monitored by the use of adhesive collecting bags or bladder catheterization. Estimated third space loss may be replaced by continuous administration of lactated Ringer's solution at 3–5 mL/kg per hour.

While volume replacement should be undertaken when blood loss is expected to exceed 5–10% of circulating blood volume, concern has been expressed regarding the cost-benefit ratio of colloidal solutions such as albumen.[72] Because of the high hematocrit at birth, red cell replacement is seldom required during most routine neonatal surgical procedures. When required, the blood used should be as fresh as possible. The most convenient and accurate method of administration is by syringe, through a three-way tap in the i.v. line. Adequacy of volume replacement can be assessed by monitoring of blood pressure, heart rate, central venous pressure, acidosis on arterial blood samples, and urine output.

ANESTHESIA FOR SPECIFIC SURGICAL CONDITIONS

Esophageal atresia

Once a diagnosis of esophageal atresia (with or without fistula) has been made, the blind upper pouch should be continuously aspirated using a Replogle or similar tube. In general, operation may be safely delayed pending improvement of any aspiration pneumonia which has developed.[73]

Because of the high incidence of associated congenital heart disease, preoperative cardiology assessment, including echocardiography, is essential. Pre-thoracotomy bronchoscopy is practiced in some centers and may influence subsequent management.[74] Anesthesia is similar to that for other neonatal procedures, but special care must be taken with positioning of the endotracheal tube, the tip of which should be located above the carina but below any fistula present. Surgical retraction during the operation may compromise either respiratory or cardiac function, so that close monitoring is essential. If serious contamination has not occurred, or the anastamosis is not too tight, extubation may occasionally be possible at the end of the procedure.

Congenital diaphragmatic hernia

This condition was formerly regarded as one of the great emergencies of pediatric surgical practice, but it is now agreed that operation should be postponed until adequate gas exchange has been obtained and the infant is hemodynamically stable.[75,76]

Positive pressure ventilation using bag and mask should be avoided prior to endotracheal intubation, as expansion of the viscera contained within the hernia will cause further lung compression. Nitrous oxide should be avoided for the same reason. A reasonable anesthetic technique includes controlled ventilation with fentanyl 0.01–0.02 mg/kg, intermediate-acting muscle relaxant and 100% oxygen or oxygen in air as required. Great caution should be exercised in the use of volatile anesthetic agents. Airway pressures should be kept as low as possible. Should advanced ventilatory techniques such as high frequency oscillation or nitric oxide be required in order to achieve preoperative stabilization, these may be safely continued during surgery.[77,78] Most infants will require mechanical ventilation, sedation, and muscle relaxation in the postoperative period.

Intestinal obstruction

The various forms of neonatal intestinal obstruction account for approximately 35% of all surgical procedures in the newborn. The major anesthetic problems are those of fluid and electrolyte imbalance (which must be corrected preoperatively), abdominal distension (causing respiratory embarrassment), and the risk of regurgitation and aspiration of gastric contents into the lungs. Following decompression of the stomach, a rapid-sequence induction incorporating preoxygenation, thiopentone, or propofol and succinylcholine with gentle cricoid pressure is advised. Anesthesia is then continued in the usual way.

Exomphalos and gastroschisis

Exomphalos is associated with other midline defects, especially cardiac anomalies, so that preoperative echocardiography is required. This is not true of neonates with gastroschisis. Anesthetic concerns include heat and fluid loss from the exposed bowel and the fact that closure of the abdominal wall defect may push the diaphragm cephalad, thus compromising respiratory function. Special care must be taken to keep heat loss to a minimum. Fluid requirements are much greater than in normal neonates. To maintain plasma oncotic pressure, at least 25% of fluid intake should be given as colloid. Often gastroschisis is closed following staged procedures using a silastic silo. The extent of respiratory compromise can assist the anesthetist in advising the surgeon whether or not primary closure is feasible. A proportion of infants, especially after repair of gastroschisis, require postoperative mechanical ventilation. Increasingly, neonates born with a large exomphalos have the defect closed in stages over a prolonged period requiring a tracheostomy and long-term ventilation.

Congenital lobar emphysema

This condition may cause severe respiratory distress in the neonatal period. Induction of anesthesia for lobectomy should be as smooth as possible – struggling may trap large amounts of air in the affected lobe during violent inspiratory efforts.[79] Nitrous oxide can also increase the volume of trapped air considerably[80] and is contraindicated. Great care should be taken with controlled ventilation because of the risk of pneumothorax.

Myelomeningocele

If the defect is large, heat and fluid loss during surgery can pose problems and should be monitored as closely as possible. Surgery is carried out with the infant in the prone position and the chest and pelvis should be supported with pads so that the abdomen remains free from external pressure. Precautions should be taken to limit the patient's exposure to latex in theater.

SPECIAL CONSIDERATIONS FOR THE PREMATURE INFANT

Congenital defects occur more commonly in preterm infants, so that surgery is frequently required. Organs and enzyme systems are very immature and meticulous attention to detail during anesthetic and surgical management is imperative if survival rates are to be high. The large body surface area and lack of subcutaneous fat make maintenance of body temperature even more difficult than in term infants, so that a high neutral thermal environment is essential. Respiratory fatigue occurs very easily and may be exacerbated by residual lung damage following mechanical ventilation, persistent fetal circulation and oxygen dependency. The response to exogenous vitamin K is less satisfactory than in term infants and there is an increased risk of bleeding. In addition, anemia is common because of reduced erythropoiesis, a short

erythrocyte lifespan, and iatrogenic causes such as frequent blood sampling. Fluid and electrolyte management can be difficult – insensitive losses are high and hypoglycemia and hypocalcemia occur easily, while renal function and the ability of the cardiovascular system to tolerate fluid loads are reduced.

Premature infants with a history of idopathic apneic episodes preoperatively are more prone than other infants to develop life-threatening apnea during recovery from anesthesia.[81] It is recommended that infants born prematurely who undergo anesthesia and surgery while less than 60 post-conceptual weeks of age should have respiratory monitoring for at least 12 hours postoperatively in order to prevent apnea-related complications.[82] Intravenous caffeine 5 mg/kg given intravenously at induction appears to reduce the risk of apneic episodes, but respiratory monitoring is still required.[83]

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11

Postoperative management

DESMOND BOHN

INTRODUCTION

The past 40 years have seen major advances in the management of critically ill surgical newborns. Advances in surgical and anesthetic management have led to corrective surgery being performed on complex lesions both prenatally and in low birth weight infants, placing a demand for higher levels of care in the postoperative period. While the surgery itself may be only of a relatively short duration, success or failure will inevitably depend on the level and skill of the postoperative care. During this period we have seen the introduction of innovative treatments for critically ill newborns, particularly in the management of acute hypoxemic respiratory failure including surfactant replacement therapy, extracorporeal membrane oxygenation (ECMO), and alternate ventilation which have resulted in improved survival of both term and preterm infants.

There are some distinct differences in the physiology of the newborn infant compared to the older child which may impact on postoperative management. Pulmonary vascular resistance is elevated in the first week of life, which increases the potential right to left shunting at ductal level. There are distinct differences in the coagulation system as plasma levels and activities are low at the time of birth and then increase in the first few months of life. Total body water is higher in the newborn, especially the preterm and glomerular filtration rate (GFR) is low in the first few days of life. Thermoregulation mechanisms are also poorly developed. The newborn increases cardiac output by increasing heart rate because stroke volume is relatively fixed. Finally, there are important hormonal-metabolic responses to surgery which have major implications for analgesia and sedation during and after surgery. While a comprehensive review of these topics is beyond the scope of this chapter, the significance of these physiological changes to the postoperative care of the newborn will be discussed.

RESPIRATORY MANAGEMENT

The respiratory system is probably the most vulnerable area in the maintenance of a normal physiological milieu. Abnormalities in the cardiovascular, renal, and central nervous systems are rapidly reflected in changes in function of the respiratory apparatus, which the newborn infant is ill equipped to deal with. The chest wall itself is highly compliant and increasing respiratory efforts, due to a fall in lung compliance, can result in increasing chest wall distortion and eventual apnea from respiratory muscle fatigue. Major abdominal or thoracic surgical procedures in the newborn renders the infant particularly vulnerable to develop respiratory failure, as surgery frequently has an adverse effect on the mechanics of the respiratory system. Repair of congenital abnormalities such as gastroschisis or congenital diaphragmatic hernia (CDH) frequently result in rises in intra-abdominal pressure, upward displacement of the diaphragms and a fall in total thoracic compliance.[1] Normal tidal respiration in the infant occurs around the closing capacity and therefore any loss of lung volume will result in further atelectasis and hypoxemia. Similarly, the use of inhalational anesthetic agents, narcotics, and muscle relaxants will adversely affect diaphragmatic function not only during surgery, but have an effect which extends well into the postoperative period. In order to prevent respiratory compromise in the immediate postoperative period, infants undergoing major abdominal or thoracic surgery will benefit from a period of ventilatory support, the duration of which will depend on the maturity of the infant, the underlying surgical problem, and the presence or absence of disease or abnormalities within the lung itself. Prolonged surgical procedures with large amounts of blood loss may also result in pulmonary edema secondary to large volume transfusion of blood products and electrolyte solutions.

POSITIVE PRESSURE VENTILATION

Mechanical ventilation in newborn infants came into widespread use in the early 1970s when it was appreciated that long-term intubation was both safe and feasible in small infants and that positive pressure ventilation was not necessarily damaging to the newborn lung. Very few of the

initial ventilators were specifically designed for use in children and the initial approach was to adapt adult ventilators to the child. Ventilator technology has improved significantly in the past 20 years and the currently available machines are adaptable enough to ventilate both adults and children, including infants. The most commonly used newer generation machines have a pneumatic system where oxygen and air are mixed at 50 psi. A microprocessor controls an inspiratory valve which when opened delivers heated humidified gas to the patient. The microprocessor also controls an expiratory valve which opens during expiration and filtered gas is vented to the atmosphere. The expiratory valve also controls the amount of positive end-expiratory pressure (PEEP) applied at end-expiration. The basic concept is to use positive pressure to generate a gas flow into the lung, sufficient to expand alveoli by overcoming the opposing forces generated by the elastic properties of the lung (compliance) as well as the resistance of endotracheal tube and airways. In the small child the endotracheal (ET) tube is the site of greatest resistance in the circuit. An outline description of the various types of ventilators is provided in Table 11.1.

PRESSURE PRESET VENTILATION

Time-cycled pressure limited ventilation is the most commonly used mode in neonates. A preselected pressure is set, defined as the peak inspiratory pressure (PIP), and is chosen depending on that required to deliver an adequate tidal volume, taking into account the compliance of the lung and the airway resistance. In uncomplicated postoperative ventilation adequate tidal volume can be delivered at a PIP of 15–20 cmH_2O. This may increase significantly when resistance in the lung or airway distal to the ET tube rises or when pulmonary or thoracic (lung plus chest wall) compliance falls. The airway pressure at end expiration (normally zero during spontaneous breathing) can be increased to 5–10 cmH_2O, depending on whether PEEP is required to prevent lung collapse at end expiration. Inflations are generally delivered at 30–120 bpm. When rates above 60 bpm are used this is termed high-frequency positive pressure ventilation (HFPPV). Inspiratory times vary between 0.3 and 0.5 seconds. In severe hypoxic lung disease the inspiratory time may be prolonged to increase the mean airway pressure (reverse I:E ratio ventilation). It is important to note that the tidal volume delivered by a ventilator in the pressure preset mode will change significantly according to conditions within the thorax. A fall in compliance or a rise in airway resistance results in the ventilator rapidly reaching its preselected inspiratory pressure. A reduction in delivered alveolar ventilation will inevitably follow, which can only be overcome by increasing the preset pressure. A large leak around the ET tube may prevent the ventilator reaching its cycling pressure. With pressure preset ventilation, PIP is constant but tidal volume may vary. Historically, mechanical ventilation in newborns has used the pressure control mode but with advances in ventilator technology volume ventilation has become an option.

Table 11.1 Commonly used forms of positive pressure ventilation and terminology.

Terminology	Descriptor	Comments
Volume ventilation or volume control ventilation	Preset TV. Patient cannot trigger the ventilator. Tidal volume is constant while peak inspiratory pressure (PIP) may vary	Most commonly used mode in adults and older children. Also effective in smaller children with minimal endotracheal tube leaks
Pressure ventilation or pressure control ventilation	Preset pressure. Patient cannot trigger the ventilator. PIP is constant but tidal volume may vary	Commonly used in neonates. Increasing use in adults to prevent ventilator-induced lung injury in patients with acute respiratory distress syndrome
Continuous positive airway pressure (CPAP)	Spontaneous breathing mode with no mechanically delivered breaths and positive end expiratory pressure. High gas flow delivered by a demand valve	First introduced to treat preterm infants with lung disease of prematurity. Now commonly used as a pre-extubation mode of respiratory support.
Assist control ventilation	Minimum rate and TV (or pressure) set. Patient may trigger inspiration at a more rapid rate	Common form of weaning from mechanical ventilation
Assisted ventilation	All breaths are patient triggered at the ventilator's set volume or pressure	Most commonly used as pressure support ventilation
Mandatory ventilation, intermittent mandatory ventilation (IMV) or synchronized intermittent mandatory ventilation (SIMV)	Machine-generated breath that is triggered, limited and cycled by the ventilator	Not commonly used
High frequency positive pressure ventilation (HFPPV)	Positive pressure delivered at rates >60/min by a conventional ventilator	Commonly used in neonates with severe hypoxic respiratory failure
Noninvasive ventilation (NIV), commonly known as bilevel positive airway pressure (BiPAP)	Positive pressure delivered by either nasal or face mask. Commonly used as a bilevel device with preselected inspiratory airway pressure (IPAP) and expiratory airway pressure (EPAP)	Increasingly used in patients with less severe lung disease and in premature infants. Avoids the need for intubation and risk of ventilator associated pneumonia (VAP)

VOLUME PRESET VENTILATION

The alternative ventilation system is a time-cycled, volume preset mode which will deliver a set tidal volume at a preselected rate determined by the operator. A tidal volume is chosen based on body weight and is usually in the range of 6–8 mL/kg, depending on the patient's resistance and compliance. In certain machines, the operator chooses the minute volume and ventilatory rate and the tidal volume can be calculated from these two settings. Alternatively, in other types of respirators the tidal volume and rate are selected and the minute volume calculated. The more modern machines have the ability to measure and display both the inspired and expired tidal volume at the peak of the airway, although in the event of a leak around the tube these numbers will not be accurate. As with the pressure type respirator, the duration of the inspiratory and expiratory time can be adjusted according to conditions within the thorax. With a minimal tube leak a fall in compliance or rise in airway resistance will not result in a small fall in alveolar ventilation as the machine will merely increase the pressure in order to overcome these changes. However, the PIP will rise. The respirator, however, will not compensate for leaks around the ET tube and a significant proportion of the preset volume will be vented around the tube when there is a large leak. In volume ventilation, tidal volume is constant while PIP may vary. These ventilators are most commonly used for ventilating older children where cuffed ET tubes can be used or tubes with small leaks are not a concern. They can also be used effectively in infants as long as the leak is not large. Also, with improved ET tube design, the option of using cuffed tubes in newborns can be exercised.

PATIENT–TRIGGERED VENTILATION AND SYNCHRONIZED VENTILATION

One of the major problems in the ventilation of neonates is dealing with patient/machine asynchrony. This type of asynchrony may result in suboptimal gas exchange, increased risk of barotraumas, and an increased incidence of intraventricular hemorrhage. One method of overcoming this is to use sedatives or neuromuscular blocking drugs, both of which carry with them an alternative set of problems. Neuromuscular blockade is associated with loss of vasomotor tone and circulatory insufficiency while the immature drug metabolism of the newborn may result in a prolonged effect of sedation. A more ideal solution to this problem is to use a form of synchronized patient-triggered ventilation that does not compete with the patient's own breathing pattern. The term 'triggering' in mechanical ventilation refers to the process that results in the opening of the inspiratory valve and the initiation of an inspiratory effort. This can be triggered in either the pressure or volume control modes as a patient-initiated assist/control (A/C), pressure support ventilation (PSV), synchronous intermittent mandatory ventilation (SIMV), or completely independent of the machine in the continuous positive airway pressure (CPAP) mode. The sensitivity of the inspiratory valve can be set by the operator. Patient-generated triggering is also favored because it facilitates weaning and allows the patient to use his or her respiratory muscles. Most experience in neonatal intensive care has been with the SIMV mode where the ventilator senses either airway flow or pressure and the set rate or mandatory breaths from the ventilator are triggered so they do not interfere with the expiratory phase of respiration. The potential drawback to this system was that it was frequently not sensitive enough to pick up the small negative inspiratory efforts frequently seen in the tachypneic newborn infant.

There have been a large number of randomized trials comparing different modes of ventilation in neonates with acute respiratory failure, most commonly in those with lung disease of prematurity. End points have included the incidence of bronchopulmonary dysplasia (BPD), air leak, duration of ventilation, and the incidence of intraventricular hemorrhage. Comparisons have been made between synchronized HFPPV, or triggered ventilation as A/C, SIMV, and SIMV plus pressure support with conventional mechanical ventilation. A recent meta-analysis of these trials concluded that both HFPPV and triggered ventilation were associated with reduction in air leak and shorter duration of ventilation.[2]

WEANING FROM VENTILATION

Weaning from mechanical ventilation has been considerably simplified by the widespread use of intermittent mandatory ventilation and other forms of ventilatory patient-initiated assist modes (pressure support). With these systems the infant may take spontaneous breaths from a gas flow provided either through a demand valve or from a separate spontaneous breathing circuit. In this manner the mandatory breaths are gradually reduced as spontaneous respiratory effort improves, until the child is breathing entirely spontaneously through a CPAP system. The pace of weaning depends on the type of surgery and any additional pathology within the lung and is set by observing the spontaneous respiratory rate and the measured blood gas response to changes in ventilation settings. In order to tolerate the transition from CPAP to extubation, the patient should be on FiO_2 0.4, PEEP 5 cmH_2O, with normal blood gases and a leak around the ET tube. A more recent innovation has been the introduction of pressure support ventilation where each spontaneously initiated breath generates a positive pressure from the machine to a preset inspiratory level. This helps to overcome the fixed resistance of small endotracheal tubes.

CONTINUOUS POSITIVE AIRWAY PRESSURE AND NONINVASIVE VENTILATION

An important advance in the management of respiratory failure in both newborns and older children has been the increasingly widespread use of noninvasive ventilation either in the form of a face mask or nasal cannulae. The high gas flow used in this system means that airway pressure remains positive throughout both the inspiratory and expiratory cycle. Functional residual capacity (FRC) is maintained, decreasing the work of breathing and preventing lung

collapse. There is an additional potential advantage in that avoiding invasion of the airway reduces the risk of nosocomial lung infections. The system has proved effective in the treatment of lung disease of prematurity as a primary mode of therapy. It has also been used to avoid reintubation in patients who remain tachypneic with increased work of breathing following extubation. The widespread use of CPAP in lung disease of prematurity is in fact the rediscovery of an old technique first described for the treatment of this condition by Gregory in 1971.[3] In its more modern iteration it is frequently referred to as 'bubble CPAP.' The system has proved effective in the treatment of lung disease of prematurity both as a primary mode of therapy and as a method of preventing extubation failure in premature infants.[4–10]

Noninvasive positive pressure ventilation commonly in the form of bi-level positive airway pressure (BiPAP) is defined as phasic increases in airway pressure delivered by face mask on a background of CPAP. These can be either synchronized or nonsynchronized. These systems have been used in neonates' additional support because of respiratory muscle fatigue and CO_2 retention. Although feeding intolerance, gastric distention, and/or perforation are concerns with this form of therapy, the incidence is no higher than in other forms of CPAP.[11,12]

ALTERNATIVE (NONCONVENTIONAL) MODES OF VENTILATION

High frequency ventilation

One of the major innovations in mechanical ventilation in children has been the use of high frequency ventilation (HFV) which allows patients to be ventilated at tidal volumes well below anatomical dead space and very low airway pressures (Table 11.2). HFV exists in two forms, either high frequency oscillatory ventilation (HFOV) or high frequency jet ventilation (HFJV). The former generates a high frequency sine wave which accelerates diffusion and elimination of CO_2 from the lung with very little in the way of bulk gas flow. Oxygenation is achieved by a high fresh gas flow into the circuit and, by adjusting this, the device is capable of generating mean airway pressures in excess of 30 cmH_2O. HFJV was first developed in clinical anesthesia to provide small tidal volume ventilation for procedures involving the larynx and tracheobronchial tree where the ability to achieve a normal CO_2 with low airway pressures provided ideal operating conditions. In HFJV the lung is ventilated by the rapid injection of gas into the airway at rates of 100–600 per minute with a supplemental air/oxygen gas flow entrained. Gas exchange occurs by a combination of very small amounts of bulk flow and enhanced diffusion.

High frequency oscillatory ventilation

One of the principal strategies for the prevention of ventilator-associated lung injury is the use of HFOV. This has been tested in a large number of randomized clinical trials in preterm infants. Although the original multicenter trial in 1989[13] suggested that there was an increased incidence of intraventricular hemorrhage associated with its use, subsequent trials have led to a general acceptance that it is a safe and effective form of ventilation without there being any clear demonstrable benefit in terms of increased survival or decreased incidence of chronic lung disease.[14–18] This may be because the lung recruitment strategies (the open lung approach) in the initial studies were not aggressive enough or introduced early enough. Most of the protocols in neonatal trials have used levels of mean airway pressure (MAP) of 1–2 cmH_2O above that on conventional mechanical ventilation (CMV) increased in small increments. The PROVO trial in 1996,[19] which was an early intervention study and used a clearly defined lung recruitment protocol with all patients receiving surfactant, was the first to show a reduction in chronic lung disease with HFOV (24 versus 44%), less surfactant usage and decreased hospital stay. Clearly, if one is to use HFOV, early intervention before the lung sustains significant damage is key and has been demonstrated by the excellent results published by Rimensberger[20] where premature infants at risk from infant respiratory distress syndrome (IRDS) were placed on HFOV in the delivery suite. The incidence of chronic lung disease, as defined as oxygen dependency at 36 weeks' postgestation age, was zero compared to 34% in historical controls. The optimal recruitment strategy also needs to be determined. Copying the recruitment maneuvers (30 cm H_2O for 15 seconds) used in the original experimental lung lavage model is frequently insufficient to achieve this in premature infants. Thome[21] has shown that lung volume recruitment on HFOV is both time and pressure dependent in these patients. He was able to show that stabilization of mean lung volume after modification of mean airway pressure took 2–25 minutes (median, 9 minutes) in premature infants. HFOV has also proved effective in the management of term and near term infants with persistent pulmonary hypertension of the newborn (PPHN), meconium aspiration, and in the preoperative stabilization of infants with CDH.[22–24]

Table 11.2 Characteristics of high frequency ventilators.

	HFOV	HFJV
Rate	180–900 per min	100–600 per min
TV	At high rates (>10 Hz) minimal TV. TV increases as rates decreases	TV 2–5 mL/kg
Expiration	Active	Passive
Gas movement	Diffusion	Diffusion plus bulk flow
Indications	Used in lung disease associate with low lung compliance (MAS, IRDS) as part of an open lung strategy. Also has been extensively used in CDH	IRDS, MAS, and bronchopleural fistula

Hz, cycles per second; IRDS, infant respiratory distress syndrome; MAS, meconium aspiration syndrome; TV, tidal volume.

High frequency jet ventilation

High frequency jet ventilation was first developed in clinical anesthesia to provide small tidal volume ventilation for procedures involving the larynx and tracheobronchial tree where the ability to achieve a normal CO_2 with low airway pressures provided ideal operating conditions. Although HFJV and HFOV operate on the same physiological principles of very small tidal volumes delivered at high rates, they should not be considered as merely two variations on the same theme. HFJV uses a high pressure gas source to deliver small tidal volumes at frequencies of 1–5 Hz. Apart from the slower rates used in HFJV, the other major difference is that expiration is passive in the former while it is active in HFOV. The published experience with jet ventilation in neonatal respiratory failure is considerably less than oscillation and until recently only documented its use as a rescue therapy in patients with either hypoxemia despite high PEEP or established air leak. The rationale for the switch is usually the avoidance of further barotrauma by the use of smaller tidal volumes while maintaining a high mean airway pressure, but with lower peak airway pressures. Improvements in oxygenation can be obtained by driving up the MAP but this usually involves some compromise to cardiovascular function because of the transmitted pressure. A randomized controlled clinical trial of HFJV in neonates with pulmonary interstitial emphysema (PIE) has shown an improvement in PIE and lower mortality rate in infants treated with HFJV compared to conventional ventilation.[25]

Several prospective randomized trials have compared HFJV in both premature and term infants with acute hypoxemic respiratory failure (AHRF).[25–27] The two studies on the premature infants showed conflicting results. Keszler[25] found better pulmonary outcomes in patients randomized to HFJV without a difference in survival while Wiswell[27] found no difference in pulmonary outcomes but increased risk of death and intraventricular hemorrhage associated with the use of HFJV. Engle,[26] in a randomized trial in term and near term infants, found improved oxygenation without any difference in survival.

There are some technical safety concerns about the adequacy of humidification both in this system as well as HFOV. In addition there are reported cases of tracheal damage (necrotizing tracheobronchitis) in severely ill newborn infants. The airway pressures measured in HFJV from the catheter within the trachea probably represent a significant underestimate of true MAP because of the Bernoulli effect and consequently there is likely to be a significant amount of auto-PEEP present.

Although HFJV and HFOV operate on the same physiological principles of very small tidal volumes delivered at high rates, they should not be considered as merely two variations on the same theme. Apart from the slower rates used in HFJV, the other major difference is that expiration is passive in the former while it is active in HFOV. Both techniques have the potential advantage of reducing the incidence of ventilator-induced lung injury and have been extensively used in newborn infants with lung disease of prematurity and meconium aspiration syndrome.

There is now 20 years of accumulated clinical experience with the use of HFV in neonatal lung disease, either as a primary or rescue therapy in lung disease of prematurity. The impact on the reduction in mortality associated with the widespread use of surfactant replacement therapy in this disease over the same era has meant that clinical trials of HFV compared with CMV were unable to demonstrate any survival benefit. The same can be said of clinical trials that use the incidence of chronic lung disease as their end point.[28,29] On the other hand, case series have suggested improved outcomes when used in the rescue mode in term and near term infants with CDH, meconium aspiration, and bronchopleural fistula.

RESPIRATORY GAS EXCHANGE

Carbon dioxide elimination

Adequate CO_2 elimination depends on the ratio between CO_2 production (metabolic rate) and alveolar ventilation (tidal volume − dead space). In the normal spontaneous respiration, the two sides of the equation balance and normal CO_2 homeostasis is preserved. An increase in CO_2 production, as seen during a rise in body temperature or sepsis, can normally be met by increased alveolar ventilation and the child achieves this by increasing its respiratory rate. Similarly, abnormalities within the thorax will result primarily in an increase in respiratory rate rather than volume in order to achieve the same alveolar ventilation. In mechanical ventilation, the $PaCO_2$ level can be controlled by adjusting both ventilator rate and the volume delivered by each respiratory cycle (alveolar ventilation = tidal volume − dead space × frequency). With a pressure preset ventilator, minute ventilation is increased by increasing the PIP and rate, while in the volume respirator $PaCO_2$ is controlled by adjusting rate and delivered volume.

Oxygen uptake

The diffusion gradient for oxygen within the lung is high as the PO_2 in the pulmonary artery is 40 mmHg (5.3 kPa) compared with alveolar PO_2 (PAO_2) of 105 mmHg (14 kPa) while breathing air. Despite this favorable gradient for oxygen diffusion, the alveoli must remain open for gas exchange to occur. In the normal lung, due to the hysteresis, the alveoli open during inspiration and remain open during most of expiration and only cease gas exchanging at end expiration. In the diffusely atelectatic lung, of which lung disease of prematurity is a prime example, the alveoli become unstable and tend to collapse at low lung volumes because of surfactant deficiency. The degree of alveolar expansion depends to a large part on mean airway pressure (Paw), which is a measure of the average pressure that the alveoli are exposed to during the respiratory cycle. This in turn is determined by a combination of the PIP, PEEP, and the duration of the inspiratory phase of the respiratory cycle. Attempts to improve oxygenation are based on the manipulation of one or more of these variables in order to increase Paw. The simplest and most time-honored of these measures

is to increase the amount of PEEP, which was first introduced to improve oxygenation in lung disease of prematurity. Abnormalities within the lung that cause a large difference between PAO_2 and PaO_2 (A-a DO_2) may also be compensated for by increasing the FiO_2.

Setting ventilator parameters

Choosing the options in ventilatory management of the newborn are in a large part determined by conditions within the patient. The objective is to maintain gases within a physiological range (PaO_2 8–12 kPa, $PaCO_2$ 5–6.5 kPa) using the lowest FiO_2 and airway pressure compatible with that aim. This may be relatively simple where the lungs are normal, but may require a completely different strategy in the presence of abnormalities within the abdomen or thorax. Therefore, one must take these considerations into account when selecting ventilator settings for the newborn infant. Generally speaking, the term infant with normal respiratory system compliance and airways resistance on a pressure preset ventilator would require a PIP of 10–20 cmH_2O, a rate of 30–40/minute, an FiO_2 0.25–0.35 and an inspiratory to expiratory ratio (I:E ratio) of 1:2 or 1:2.5 and a minimum of 3–5 cmH_2O PEEP as a routine. Using a volume respirator, a tidal volume of 6–8 mL/kg would be adequate in a newborn with normal lungs. Having selected these settings, the adequacy of gas exchange must be verified by an arterial blood gas sample to ensure that hyperventilation is avoided.

HYPERVENTILATION AND VENTILATOR-ASSOCIATED LUNG INJURY

Since the first introduction of intubation and ventilation for the treatment of neonates with acute respiratory failure, the objective has been to adopt a pattern of ventilation designed to produce blood gases within normal physiological parameters. Since the original description of the induction of a respiratory alkalosis to reverse ductal shunting in PPHN,[30] hyperventilation became one of the mainstays of treatment in neonatal respiratory failure. Although there may be a short-term benefit from this approach, there have been no prospective trials that have shown improved outcome with the use of hyperventilation. In addition, there is now increasing concern that this may result in serious adverse consequences. The high inflation pressures required to reduce the CO_2 can frequently result in a ventilator-induced injury to the lung, thereby compounding a pulmonary vascular problem with a pulmonary parenchymal problem. There are numerous animal models of ventilator-induced lung injury where pulmonary edema, hyaline membrane formation, and pulmonary epithelial cell injury can be produced in normal lungs with peak inflation pressures as low as 30 cmH_2O. As few as six manual inflations using high pressure at the time of birth have been shown to induce lung injury in an animal model.[31] In 1985, Wung was the first to suggest that PPHN could be treated effectively without the use of hyperventilation and showed excellent outcomes with pressure limited ventilation and hypercarbia.[32] This is true not only in the premature lung but also in the dysplastic lung of infants with CDH which are equally vulnerable to injury.[33] There are several series reporting improved survival using a pressure limited strategy which does not use hyperventilation to treat ductal shunting.[34–36] There is also increasing evidence that low $PaCO_2$s may adversely affect cerebral blood flow and injure the developing brain[37] and may partly account for the alarmingly high incidence of neurosensory deafness seen in these infants.[38–43] Conversely, hypercarbia increases cerebral protection in experimental models of neonatal brain injury.[37,44] The first human randomized trial that has addressed the issue of hypercarbia in neonates showed a decrease in ventilator days and no adverse events when permissive hypercapnia was compared with the conventional approach in 1999.[45] While the case for 'permissive hypercapnia' in improving the outcomes in the treatment of newborns with acute respiratory failure remains to be proven there is increasing recognition that hyperventilation may have adverse consequences for long-term brain function.[46] In terms of avoidance of ventilator-associated lung injury, the use of nasal CPAP together with early intervention with surfactant has been shown to improve the outcome in premature infants with moderately severe forms of IRDS.[8,9,47]

RESPIRATORY MONITORING

Blood gas measurement

Monitoring of respiratory function in the postoperative period requires measurement of gas exchange. The most reliable and accurate method is to measure PaO_2, $PaCO_2$, and pH from an arterial sample. The common sites for invasive arterial monitoring are umbilical artery (newborns) and radial or dorsalis pedis arteries in older children. In the newborn, a blood gas drawn from the right radial will measure pre-ductal PaO_2 values whereas the other sites will be post-ductal. On some occasions the left subclavian artery is juxta-ductal and will therefore measure similar values to the right. With the newer generation of automated blood gas machines, samples as small as 0.1 mL are sufficient for a full blood gas and pH profile. This is particularly important in premature infants in whom frequent sampling may necessitate 'top up' transfusions. An alternative method of measuring $PaCO_2$, PaO_2, and pH is to use 'arterialized' capillary blood taken from an area of skin that has been vasodilated by warming, usually the heel. This technique is generally reliable for $PaCO_2$ and pH. With arterial PaO_2 levels above 60–70 mmHg, accuracy drops off considerably.

Noninvasive oxygenation and CO_2 monitoring

The development of pulse oximetry has made it possible to measure arterial saturation and heart rate on a beat-to-beat basis and has proved to be a reliable and effective method of monitoring and trending oxygenation. The absolute values do not correlate well when measured at blood saturations of

less than 70% and in low cardiac output states where there is inadequate perfusion for a pulse to be recorded by the probe. Careful sensor placement is important to prevent distorting by light and the probes are sensitive to light artifact. It is a useful monitor to record the rapid response of PO_2 to interventions such as suctioning and changes in ventilation. Due to the shape of the oxygen hemoglobin dissociation curve, high PaO_2 levels (>95 mmHg, 12.6 kPa) will not be accurately reflected by saturation measurements. In the premature neonate (<1000 g), where high PaO_2 levels may predispose to the development of retinopathy of prematurity (ROP), the transcutaneous PO_2 ($TcPO_2$) probe is the preferred method of monitoring oxygenation as it indirectly measures the actual PaO_2.

The $TcPO_2$ technique uses a modified Clark electrode with a heating element that raises skin temperature to between 41 and 44°C in order to augment cutaneous blood flow. These devices correlate well with arterial oxygen in small infants who have little subcutaneous tissue, and are reliable where cardiac output and peripheral perfusion are adequate. However, quality declines in the older child and in low cardiac output states. Transcutaneous CO_2 monitoring uses the modified Severinghaus probe with a heating element, which heats the skin to 41–44°C. These have proved to be reliable in small infants. While transcutaneous PO_2 and PCO_2 monitoring are useful trending devices, absolute values should be occasionally checked against an arterial sample. Greater accuracy is obtained by careful maintenance of the probes and care in calibration and application to the skin. The risk of skin damage from the heating element requires that the measuring site be changed every 4–6 hours.

End-tidal CO_2 monitoring

Capnography is the measurement and display of CO_2 concentration in the airway using an infrared technique and has recently become a standard fixture on most mechanical ventilators. In the normal capnogram CO_2 is zero during inspiration and at the beginning of expiration as anatomical dead space gas is washed out. The concentration then rises as alveolar gas mixes with anatomical dead space gas and reaches a plateau with an upward slope when pure alveolar gas reaches the sensor. The end expiratory point of the plateau before the inspiratory cycle starts is the end-tidal pressure ($PetCO_2$) and approximates alveolar PCO_2 ($PACO_2$). This is usually approximately 5 mmHg less than the $PaCO_2$. The $PetCO_2$ provides useful information of the adequacy of alveolar ventilation in patients with normal lungs but in the presence of lung disease $PaCO_2$–$PetCO_2$ gradient widens.

MANAGEMENT OF THE INTUBATED PATIENT

Tube size and position

Newborns are commonly managed with nasotracheal tubes rather than oral tubes unless there is some congenital abnormality of or injury to the nasal area that precludes their use. They provide for greater patient comfort and acceptability and the tube may be more securely fastened to the face and upper lip. In older children oral tubes are satisfactory for brief periods of ventilation but nasal are frequently preferred. In terms of length, the tip of the tube should reach to the level of the clavicles on the chest film. Tubes that extend lower may enter a main bronchus, especially during flexion or extension movements of the head. A routine chest film should be obtained immediately after intubation or change of tube position to ascertain correct placement. The proximal end of the tube should protrude sufficiently far from the nose so that the tube connector does not impinge upon the external nares. Severe excoriation of nares and erosion of cartilage can occur with long-term intubation. In selecting a tube of correct diameter, the size should be sufficient to provide a small leak under positive pressure, but not large enough to provide an airtight seal. Tight fitting tubes left *in situ* for prolonged periods will lead to tracheal stenosis and vocal cord granuloma formation, requiring tracheostomy and extended postoperative care. At the same time, too large a leak will make positive pressure ventilation extremely difficult. In the term newborn 3, 3.5 or 4 mm tubes may be used depending on the size of the infant; 2.5 or 2 mm may be used in premature infants, but these are prone to block with secretions (Table 11.3). Cuffed tubes in pediatric sizes are now available with low pressure inflatable cuffs that have been used successfully in small children and newborns.

Endotracheal tube suctioning

Routine suctioning to maintain the patency of the endotracheal tube and prevent atelectasis is of prime importance, especially in newborns. However, even skillful suctioning can lead to a profound fall in PaO_2 and bradycardia, especially in patients who are already hypoxemic. Consequently, prior to suctioning, all patients should have their lungs inflated with 100% oxygen by manual hyperventilation. A catheter of a size that does not occlude the lumen of the endotracheal tube should be chosen so that the suctioning does not generate large enough negative pressures to cause atelectasis. End-hole catheters should be used rather that the side-hole type, which can trap and injure the respiratory tract mucosa. Suction should only be applied while the catheter is being withdrawn and for not longer than a few seconds. Between each suctioning, the patient should be ventilated with 100% oxygen. The onset of bradycardia during suctioning is an

Table 11.3 Endotracheal tube size selection.

Age	Endotracheal tube diameter (mm)
Preterm	2.0–2.5
Term newborn	3.0–3.5
1 month	3.5
1–6 months	3.5 or 4.0
1 year	4.5

immediate indication to stop and ventilate with oxygen, as it is almost always indicative of hypoxemia.

Endotracheal suctioning should always be performed as a sterile procedure using surgical gloves and a sterile catheter. The objective should be to pass the catheter down as far as it will go to beyond the carina and down either one or the other main bronchus, at the same time stimulating the patient to cough. The catheter tip may be encouraged to pass down either one or the other side by rotating the head to the opposite side. The presence of unduly thick secretions in the respiratory tract should alert one to the possibility of inadequate humidification. Intrapulmonary hemorrhage increases the chances of endotracheal tube blockage substantially and indicates the need for more frequent suctioning.

Humidification

Humidification is one of the least emphasized but most important aspects of respiratory care. The small diameter endotracheal tube in the newborn patient is notoriously prone to blockage from secretions, especially where they become inspissated due to inadequate humidification. Too much humidification leads to 'rainout', as the inspired gas cools during its passage between the humidifier and the infant's airway and can lead to the absorption of considerable amounts of water.

The goal of optimal humidity is to deliver fully saturated gases (44 mg/L H_2O) at a temperature of 37°C to the peak of the airway. This can only be achieved with the heated water bath type humidifier as opposed to the nebulizer type. The temperature of the water bath must be raised above body temperature, to about 40°C in order to deliver gases at 35–37°C at the ET tube. Between the humidifier and the ET tube, considerable condensation of water vapor may occur as the gases cool, which may impede gas flow. This problem has been overcome to some extent with the newer humidifiers which have a heated electric coil inside the inspiratory line. This maintains a consistent temperature throughout the inspiratory line by means of a dual servo mechanism with temperature sensors in both the water bath and at the patient's airway. There is therefore less cooling of gases in the respirator tubing and inspired gas is delivered to the ET tube fully saturated and at 37°C.

The condenser humidifier or 'Swedish nose' is also capable of supplying moisture and preventing heat loss from the respiratory tract. While obviously not as efficient as the water bath type, it is particularly useful for patient transport or for providing humidity to children who have been intubated for upper airway problems. As the condenser humidifier becomes increasingly saturated, the airway resistance tends to rise and they must be changed every 24 hours.

ACUTE HYPOXIC RESPIRATORY FAILURE IN THE NEWBORN: NONVENTILATOR THERAPIES

A number of innovative techniques have recently been introduced into the management of acute respiratory failure which include high frequency ventilation, inhaled nitric oxide, and, if all else fails, ECMO. It is very likely that a significant number of these therapies are being resorted to as rescue therapy from ventilator-induced injury. This speculation is supported by the figures from the Extracorporeal Life Support Organization (ELSO) Registry which show the annual number of cases is actually falling for the first time since neonatal ECMO was first introduced in the late 1970s. It is likely that we will recognize that the single most important advance in ventilator management will be the recognition that the solution is part of the problem and that we need to adapt our ventilator to the underlying pathophysiology of the lung rather than outmoded physiological imperatives.

Inhaled nitric oxide

As well as having a key role in the modulation of vascular tone, exogenously administered nitric oxide (NO) has been shown to be a highly selective pulmonary vasodilator. When administered by inhalation NO diffuses rapidly from the alveolus into the endothelial cell and the vascular smooth muscle where it stimulates guanylate cyclase to produce cGMP. The systemic nitrodilators currently in clinical use work by a similar mechanism but their pulmonary vasodilator effects cannot be separated from the systemic. In the case of inhaled nitric oxide (iNO), the vasodilator properties are confined to the pulmonary circulation because the marked affinity of NO for the hememoiety of hemoglobin results in its rapid binding and inactivation as soon as it crosses the alveolar capillary membrane which explains its highly selective effect on the pulmonary vascular bed.

A series of randomized control trials (RCTs) have shown that iNO improves oxygenation[7,48–51] and decreases the need for ECMO[52–54] in term and near term infants with PPHN. Although the response in terms of oxygenation may be dramatic, by no means do all infants respond. Those infants with pure right to left ductal shunting and little parenchymal lung disease would be expected to respond best while the infant with extensive pulmonary parenchymal disease as a cause of their hypoxemia (eg. meconium aspiration) may have little response. The combination of HFOV and iNO together has proved particularly effective in one RCT.[55]

An interesting alternative approach to iNO is to enhance the effect of endogenous production of NO in the vascular endothelium by blocking the inactivation of cGMP by phosphodiesterase inhibition. Two phosphodiesterase inhibitors, dipyridamole and sildenafil, have been successfully used to treat the rebound pulmonary hypertension associated with withdrawl of iNO.[56–58] Sildenafil by i.v. infusion has also been shown to be effective in infants with PPHN who have not been responsive to iNO.[59]

SURFACTANT REPLACEMENT THERAPY

Probably the most important advance in neonatal medicine in the past 30 years has been the introduction of surfactant

replacement therapy for the treatment of lung disease of prematurity. Surfactant, either used prophylactically in patients at risk for or with established lung disease of prematurity, has resulted in a reduction in mortality and in the incidence of air leak but has not made a major impact on the incidence of chronic lung disease.[60] This may be because it has not been used with an optimal ventilation strategy that minimizes ongoing lung injury. Also, there are important differences between synthetic and natural surfactants, the latter containing surfactant proteins which may have important anti-inflammatory properties.[61,62] In term and near-term infants with meconium aspiration the situation is less clear cut. These infants are not surfactant deficient but it may be inactivated by lung injury. Human studies have shown that the use of surfactant replacement therapy in this patient population is associated with decreased need for ECMO.[63,64]

VENTILATOR MANAGEMENT OF CONGENITAL DIAPHRAGMATIC HERNIA

The pre- and postoperative ventilator management of infants with CDH is one of the key factors in the improvement in survival seen over the past few years.[34–36,65] Newborn infants presenting with this anomaly have a mixture of pulmonary hypolasia, i.e. reduced alveolar number, as well as pulmonary vascular disease consisting of a reduced pulmonary vascular bed as well as a reactive and potentially reversible component due to the increased smooth muscle in the small pulmonary arterioles. The dysplastic lungs of these infants are highly susceptible to pulmonary barotrauma caused by high peak inflation pressures. The end result is hyaline membrane formation and pulmonary alveolar hemorrhage.[33] Improved survival has been noted in several centers where the focus has been on the use of low peak airway pressures with less emphasis paid to treatment of right to left shunting through the ductus arteriosus and patent foramen ovale (PFO).[34,66] Attempts to reverse this by inducing alkalosis with hyperventilation will only cause pulmonary barotrauma. Therefore the focus should be on maintaining a pre-ductal SaO_2 greater than 85% and not treating right and left shunting at the ductal level with hyperventilation. The objective for mechanical ventilation should be to maintain the PIP at $<25\,cmH_2O$ without necessarily striving to achieve a normal $PaCO_2$. It is our practice to switch to HFOV if the PIP is above $25\,cmH_2O$ on conventional ventilation as this is a less injurious mode of ventilation. The strategy with HFOV in CDH is very different to that used in other forms of neonatal lung disease. In this instance the lung is hypoplastic and not recruitable and therefore we use a mean airway pressure of no more than $14–16\,cmH_2O$. With this approach we find that HFOV is a very efficient way of maintaining normal $PaCO_2$ levels without inflicting further injury on the lung. Survival rates of >80% and decreased ECMO use have been reported by centers using this approach.[24,67] It is also our practice to obtain a cardiac echo on all CDH infants to rule out structural heart disease and to assess the degree of right to left shunting. In most infants the right ventricular pressure is elevated with either bi-directional shunting, indicating that right ventricular pressure is systemic, or pure right and left shunting in which case it is supra-systemic. iNO has been used extensively in CDH although it does not seem to be as effective as in other forms of PPHN.[52] In the event that pulmonary artery (PA) pressure is suprasystemic, prostaglandin can be infused to maintain ductal dependency and prevent right heart failure.[68–70]

POSTOPERATIVE SEDATION AND ANALGESIA

One of the most important advances in postoperative care in the past decade has been a far greater understanding of the need for analgesia and sedation in newborn infants who have had major surgery. There is now strong evidence that neonates exposed to multiple painful procedures, either during intrauterine or early in extrauterine life, exhibit acute physiological responses which are detrimental.[71–73] This has been associated with an increased physiological stress response resulting in hypertension and an increased incidence of intraventricular hemorrhage in preterm newborns. The increased hormonal and metabolic responses to major operations and to painful stimuli associated with procedures in the ICU also have the potential to increase the incidence of morbidity and mortality.[74–76] Given the limited endogenous reserves of carbohydrates, proteins, and fats in the newborn it is perhaps not surprising that in the stressed state these reserves are rapidly exhausted. There is also evidence that failure to blunt painful stimuli in the developing nervous system results in changes within the spinal cord with altered long-term sensitivity to pain.[77] There are now a number of studies which show that the use of narcotics and anesthetic drugs can blunt these responses and bring about a decrease in morbidity associated with both surgical procedures and painful interventions in the ICU.[78,79] These include reductions in catecholamine levels, lower airway pressures during mechanical ventilation, and less acute rises in blood pressure and pulmonary artery pressure.[80–83] The most commonly used narcotic agents in neonatal practice are i.v. morphine or fentanyl infusions. These are commonly combined with i.v. benzodiazepines usually in the form of midazalam or lorezepam (Table 11.4).[84] The combination of narcotics and benzodiazepams may cause hypotension when given together. Oral sucrose is effective in newborns for analgesia during minor procedures. Long-acting local anesthetic (bupivacaine), when injected into surgical wounds at the time of closure, can provide extended periods of pain relief, particularly after thoracotomies.

HEMODYNAMIC SUPPORT IN THE NEWBORN

Cardiac output is a product of heart rate × stroke volume with increases in output dependent on the ability to increase heart rate or vary stroke volume. Stroke volume in turn is influenced by three interrelated factors: (1) preload or venous return that determines end diastolic volume; (2) afterload or the impedance to left or right ventricular output;

Table 11.4 Commonly used agents for anesthesia and analgesia in newborns.

Drug	Classification	Comments	Commonly used dosages
Morphine	Narcotic	Good analgesic effect with sedation. Cumulative effect in newborns. Withdrawal effects with sustained usage	20–30 μg/kg per hour in ventilated patients
Fentanyl	Short-acting narcotic	Potent, short-acting narcotic. Commonly used for procedural sedation in ventilated patients	1–2 μg/kg per hour as a stat dose. 0.5–2 μg/kg per hour as an infusion
Midazolam	Short-acting benzodiazepine	Used as sedation either as a stat dose or by continuous infusion	1–4 μg/kg per min by continuous i.v. infusion. Stat dose 0.1–0.2 mg/kg
Lorazepam	Benzodiazepine	More prolonged effect than midazolam. Potent anticonvulsant	For seizures 0.05 mg/kg i.v.
Ketamine	Dissociative anesthetic agent. Can be given by i.m. or i.v. injection	Good analgesic properties. Used for procedural sedation/anesthesia. Sympathomimetic effect increases blood pressure	Stat dose for induction of anesthesia 1–2 mg/kg i.v.
Acetaminophen	COX inhibitor. Available as oral or rectal preparation	Useful for mild procedural pain and as an anti-pyuretic	10–15 mg/kg per dose
Sucrose	Stimulates endogenous opiods	Useful for procedural analgesia	2 mL p.o. for term infants

(3) contractility or the contractile state of the myocardial muscle, which in turn depends on its end diastolic fiber length and the speed of shortening for a given load.

In the newborn, where the myocardium is relatively immature, there is little capacity to increase stroke volume. Therefore, cardiac output is to a large part rate dependent and the neonate will primarily compensate for a fall in output by increasing its heart rate. Blood pressure reflects cardiac output poorly in this age group as this is maintained at the expense of increasing heart and vasoconstriction, until a sudden decompensation and hypotension occurs. The combination of heart rate, blood pressure, urine output, and peripheral perfusion provide a reasonably accurate estimation of cardiac output. This can be combined with serum lactate and mixed venous oxygen saturation (SvO_2) drawn from a central venous line in more critically ill newborns. In these patients measurement of central venous pressure (CVP) is particularly useful in optimizing cardiac output by the adjustment of right atrial filling pressures. Central venous access may be established through the internal jugular, subclavian, or femoral veins in the neonate, the complication rate associated with the different approaches being related to the experience and skill of the operator rather than the approach chosen.[85,86] The cannulation of the radial, posterior tibial, dorsalis pedis, or femoral arteries with a 22 or 24 GA cannula will provide reliable direct arterial pressure measurement together with access to sampling for blood gas, electrolyte, and acid–base measurement. Umbilical arterial lines are satisfactory for short-term use only due to the potential to cause renal or gut ischemia if not positioned correctly.

The initial approach to the infant with shock or low CO, indicated by tachycardia, vasoconstriction, oliguria, and hypotension, is to increase preload by volume expansion with 10–20 mL/kg of fluid either in the form of saline or colloid and then reassess the effect on the measured parameters.[87] Further boluses of fluid may be necessary. The CVP measurement may prove very useful in this context, as a guide to repeated volume increments which may have to be increased to as high as 12–14 mmHg in severe refractory shock. Failure to raise output by increasing preload is an indication to attempt to decrease afterload or increase contractility by the use of vasoactive drugs, a condition referred to as fluid refractory shock.[87]

The use of vasoactive drug therapy

In order that the correct therapeutic option is chosen when dealing with a low cardiac output state in the newborn, it is important to know what effects vasodilators and inotropes have on the circulation in this situation. Since the objective is improved tissue oxygen delivery, changes in heart rate, filling pressures and afterload, which in turn profoundly affect myocardial work and therefore oxygen consumption, should always be considered when electing to use a particular drug. While one could use a vasoconstricting agent to maintain blood pressure in an infant in low cardiac output, this would be unsuccessful in most circumstances because this could only be achieved at the expense of a greatly increased afterload, decreased tissue perfusion and oxygen delivery. The aim must be to move the depressed myocardial function curve upwards and to the left as depicted in the Starling curve (Fig. 11.1), either by increasing contractility or by reducing preload or afterload. In the case of contractility, this can be achieved by using an inotrope which may cause significant increases in heart rate, which the neonate, with its relative freedom from ischemia, is able to tolerate reasonably well. The ideal vasoactive drug would be that which increased contractility and decreased afterload with no change in heart rate, while at the same time maintaining renal and splanchnic perfusion.[88] There are a limited

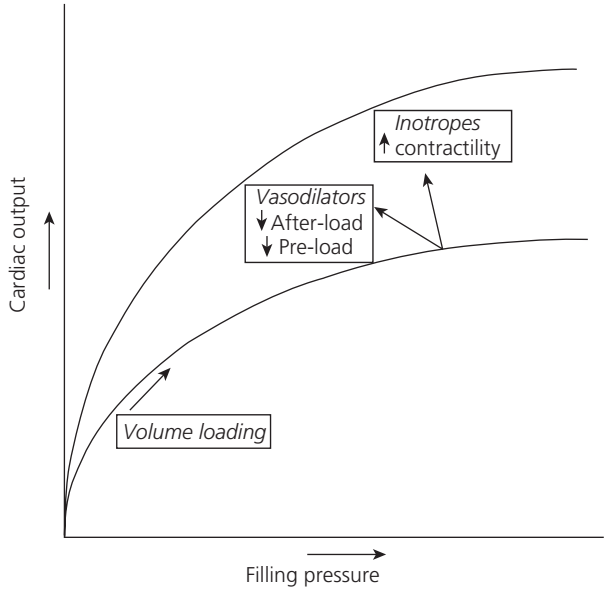

Figure 11.1 Effect of increasing right atrial filling pressures, vasodilator drugs and inotropes on cardiac output (Frank–Starling curve).

number of studies of the effect of vasoactive agents in the newborn and many of these are in premature infants or term infants after open heart surgery.

INOTROPES

Dopamine

Dopamine is an endogenous precursor of norepinephrine with sympathomimetic properties. It has been shown to be useful in the management of shock associated with cardiovascular surgery, sepsis, and severe asphyxia with demonstrable inotropic, vasoconstricting, and renal vasodilating effects. It has a well-documented range of activity with selective vasodilatory effects on cerebral, mesenteric, coronary, and renal vascular beds through stimulation of dopaminergic receptors in a dose range of 0.5–3.0 μg/kg per minute. As the dose increases from 3 to 10 μg/kg per minute it directly stimulates β_1 receptors of the myocardium causing a rise in blood pressure, CO, and heart rate, in addition to indirect stimulation through the release of norepinephrine. As the dose increases from 10 to 20 μg/kg per min, progressive α adrenergic stimulation negates the effect of β stimulation causing a rise in systemic vascular resistance (SVR) and renal vasoconstriction.

Dopamine has been shown to be an effective inotrope following cardiopulmonary bypass in children.[89,90] Studies on the effective dose in neonates have generally been anecdotal and sometimes contradictory.[91–95] Evidence has been presented for the need for high dose dopamine to achieve measurable clinical effect, yet others have shown demonstrable effects at low doses. On balance it would seem demonstrable clinical benefit can be achieved with dopamine using modest doses (<8 μg/kg per minute), with a titratible dose-response increase in effect and little likelihood of side effects. Dopamine can be expected to increase mean arterial pressure, improve echocardiographically determined indices of ventricular function, and improve urine output with a low incidence of side effects at doses <10 μg/kg per minute. Its effect on ventricular filling pressures remains uncertain. Dopamine's effect on systemic vascular resistance appears secondary to the effect on CO at doses <10 μg/kg per minute, where there will be a drop in SVR. At higher doses there will be an increase in SVR as the α effects of dopamine become predominant (Table 11.5). Limitations on the effectiveness of dopamine in this patient population were demonstrated in a study in newborn infants after the Norwood procedure where it increased heart rate and oxygen consumption without increasing oxygen delivery.[96] Different effects on renal and pulmonary blood flow have been seen in premature infants.[95,97,98]

Dobutamine

Dobutamine is a synthetic analog of dopamine with predominately β_1 effect and relatively weak β_2 and α receptor stimulating activity. In addition, it does not seem to lead to indirect stimulation through release of norepinephrine. In

Table 11.5 Vasoactive drugs used for hemodynamic support.

Drug	Site of action	Dose
Dopamine	β1 effects on myocardium peripheral α effects at high doses indirect release of noradrenaline renal vasodilation through dopamergic receptors in kidney	1–10 μ/kg per min β effects 10–20 μg/kg per min α and β effects >20 μg/kg per min α effects
Dobutamine	β1 effects on myocardium weak α and β2 effects at periphery	5–15 μg/kg per min
Epinephrine	β1 effects on myocardium β2 effects at periphery peripheral α effects	0.01–0.1 μg/kg per min
Norepinephrine	Predominantly α effects. Potent vasoconstrictor. Pressor only with minimal intropic properties	0.01–0.1 μg/kg per min
Milrinone	Phosphodiesterase inhibitor. Acts by increasing cGMP. Vasodilator and inotropic effects	0.33–1 μg/kg/min
Vasopressin	Acts on V1 receptors in the vascular bed via cAMP. No effect on heart rate	0.002–0.0004 μg/kg per min

adults at doses of 5–15 μg/kg per minute it has been shown to increase contractility, CO, MAP, improve tissue perfusion and, unlike dopamine, results in a decrease in cardiac filling pressures. Pulmonic and systemic vascular resistances uniformly fall. It therefore can be described as having afterload reducing properties in addition to its inotropic effect.

Experience of its use in children generally parallels that of the adult literature with an increase in cardiac index and MAP in a dose-dependent fashion with doses from 2 to 7.5 μg/kg per minute.[99–101] Neonatal experience has usually been in the treatment of PPHN, frequently in combination with dopamine. In a study of critically ill neonates, dobutamine up to a dose of 7.5 μg/kg per minute increased cardiac output without changing blood pressure or heart rate.[102] Comparative studies of dobutamine and dopamine in preterm infants would suggest that dopamine is more effective in raising blood pressure while dobutamine has more effect on cardiac output and blood flow.[103–107]

Epinephrine

Epinephrine is the final product of catecholamine synthesis and has been used in emergency resuscitation for a number of years. It stimulates both α and β receptors in a dose-dependent fashion; in low doses (0.05–0.1 μg/kg per minute) it affects predominately β receptors resulting in inotropic and chronotropic effects. In higher doses (0.2–1.0 μg/kg per minute) it is a potent vasoconstrictor, the α stimulation increasing MAP and diastolic pressure. This latter effect is the key to its effectiveness in resuscitation, where it can be given as a bolus i.v., endotracheally or rarely, intracardiac injection can be used.

Epinephrine is a potent inotropic agent for the newborn myocardium, its major disadvantages being tachycardia and increased SVR. Renal vasoconstriction can impair renal function and mesenteric vasoconstriction may cause bowel ischemia. Although epinephrine is not commonly used as a first choice inotropic agent, there are instances where it can be very useful when the more commonly used inotropes fail to produce an effect. In such instances we would commence an adrenaline infusion at 0.05 μg/kg per minute, increasing to 0.1 μg/kg per minute according to response, sometimes combined with vasodilator therapy. Comparative studies of epinephrine and dopamine in the treatment of hypotensive preterm infants have not demonstrated that one is superior to the other.[108–110]

VASOCONSTRICTORS

Norepinephrine and vasopressin

Norepinephrine is a potent vasoconstrictor with predominant α agonist effects. As such it is effective in raising blood pressure at the expense of raising afterload on the heart and decreasing peripheral perfusion. It therefore has no place in the routine treatment of low cardiac output. However, in vasodilated septic shock, as seen in Gram-negative sepsis, it can be effective in restoring perfusion to vital organs, the unwanted effects such as decreased splanchnic and renal perfusion notwithstanding. Its potent vasoconstrictor properties require it to be infused via a central vein to prevent skin ischemia and necrosis. The usual dose range is 0.01–0.1 μg/kg per minute. There has been an increasing interest in the vasoconstrictor effects of vasopressin in vasodilated shock in children. This acts through a catecholamine independent mechanism on the V1 receptors in the peripheral circulation. Although clinical experience in neonates is so far limited, published studies show that it increases blood pressure and urine output.[111–115] In the only randomized trial published in children with vasodilated shock, the use of arginine vasopressin (AVP) did not improve survival.[116]

Hydrocortisone in catecholamine-resistant hypotension

The use of i.v. inotropes for an extended period can result in downregulation of end organ receptors manifested by a decreasing response to escalating doses. Stress doses of steroid therapy can be effective in resensitizing β receptors and restoring the inotropic and pressor response. There are a number of published studies in term and preterm newborns demonstrating that doses of hydrocortisone of 1–2 mg/kg can be effective in treating hypotension and allows the doses of β agonist therapy to be reduced without any significant adverse effects.[117–124]

VASODILATORS

Vasodilators are thought to be of benefit in low cardiac output states through a number of mechanisms: (1) by decreasing impedance to ventricular emptying resulting in increased stroke volume and decreased end-systolic volume, (2) increasing venous capacitance which decreases venous return and therefore end-diastolic pressure; appropriate use of vasodilators will shift the heart to a more favorable Starling curve, so that there is an improved SV for a given filling pressure (Fig. 11.1), (3) a drop in filling pressure with preservation of MAP will improve coronary perfusion and thereby improved load tolerance, (4) decreased end-diastolic volume may favorably alter the compliance characteristics of the heart with less pronounced limitation to filling exerted by either ventricle on the other and on both ventricles by the pericardium.

With the newborn infant functioning at a high level of performance and limited reserve capacities as described above, acute preload or afterload increase, in addition to that imposed by postnatal adaptation, may be particularly harmful. Volume loading of the right ventricle from left to right shunts, excessive volume administration, or vasoconstriction from pharmacologic therapy may all lead to profound cardiovascular decompensation. A number of investigators have documented success with afterload reduction in conditions where inotropes have failed or have described additional benefit in function with the addition of vasodilators to inotropic therapy.[125–127]

Sodium nitroprusside

Sodium nitroprusside (SNP) is a direct acting arteriolar dilator that reduces SVR by predominately affecting resistance vessels and in addition reduces filling pressures by increasing venous capacitance. It is given by continuous i.v. infusion due to its short half-life of 1–2 minutes and is light sensitive. Its effect reverses within minutes of discontinuation. It is metabolized to thiocyanate which is excreted by the kidneys. Cyanide toxicity can potentially occur if conversion to thiocyanate is impaired with formation of cyanmethemoglobin and reduced red cell oxygen carrying capacity. Since its predominant effect is on arteriolar resistance vessels and LV afterload, there may be a reduction in MAP. Doses range from 0.5 to 5 μg/kg per minute. SNP is frequently combined with inotropic drugs, especially where high dose dopamine or adrenaline infusions are being used, in order to counteract the unwanted vasoconstrictor effects.

Phosphodiesterase inhibitors

A more recent innovation in pharmacotherapy for the management of low cardiac output has been the introduction of the phosphodiesterase inhibitors which act by blocking the breakdown of cGMP. This represents an alternative pathway for increasing myocardial performance rather than the traditional route via catecholamines, which can lose their effectiveness due to downregulation of β receptor activity. They also have important vasodilator properties. There are several studies of the effective use of phosphodiesterase inhibitors in the treatment of low cardiac output following open heart surgery in infants.[128–134] The most commonly used drug in this class is milrinone in a dose of 0.25–1 μg/kg per minute. The drug has a long half-life and its metabolism is prolonged in hepatic or renal failure.[135,136] A recent study of milrinone in preterm infants showed no difference in superior vena cava (SVC) flow at a dose of 0.2 μg/kg per minute compared with placebo.[137]

FLUID MANAGEMENT AND RENAL FUNCTION

Preserving normal fluid and electrolyte homeostasis is a more significant problem in the neonate compared with the older child, as the renal system is somewhat immature in the newborn. Glomerular filtration rate (GFR) is lower in the preterm compared with the term infant. However, the term newborn is capable of producing a dilute urine (30–50 mOsm/L) and will maintain a positive sodium balance with normal levels of sodium intake.[138] The kidney in the preterm infant, however, is inefficient at conserving sodium. On the other hand, there is also resistance to the effects of antidiuretic hormone (ADH) and the infant can only concentrate urine to 400–600 mOsm/L. The preterm neonate also has an increase in extracellular fluid volume (ECFV) compared to the term infant and this tends to rapidly expand immediately after birth.[139] Fluid balance in the neonate depends on the balance between fluid loss (evaporative, renal, and gastrointestinal tract (GIT)) and the intake required for maintaining normal homeostasis organ function and growth. When calculating normal fluid requirements in the newborn, all these factors need to be taken into consideration. Full maintenance fluid requirements for the non-ventilated term newborn start at 60 mL/kg per 24 hours in the first day of life and increase to 100–150 mL/kg per 24 hours by 5–7 days of life in the form of a dextrose–saline solution. Losses from the GIT due to nasogastric suction should be replaced with normal saline.

The stimulus of surgery, the use of anesthetic agents and narcotic drugs, positive pressure ventilation, and CPAP will all result in inhibition of ADH secretion and the failure to excrete a dilute urine. The frequent use of hypotonic i.v. solutions results in the accumulation of electrolyte free water and hyponatremia. In addition, intermittent positive pressure ventilation (IPPV) with humidification of the respiratory tract eliminates not only evaporative losses from the respiratory tract but will frequently result in a net fluid gain. For this reason it is common practice to calculate the maintenance requirements for fluid for an infant on a respirator as being 70% of normal requirements in order to prevent fluid retention. The use of hypotonic saline solutions for maintenance therapy in older children after elective surgery has been associated with cerebral edema and death from acute hyponatraemia.[140–145] Although this complication is rarely reported in newborns, frequent electrolyte measurements should be carried out and the i.v. fluid prescription adjusted accordingly.

A urine output of >1 mL/kg per hour is generally regarded as a manifestation of adequate renal function following surgical procedures in the newborn. However, a period of oliguria in the presence of normal renal function is not uncommon in the immediate postoperative period, especially where PPV is being used. Persistent oliguria or anuria, on the other hand, may be associated with renal failure due to either pre-renal, post-renal, or intrinsic renal damage.

Pre-renal failure is most frequently due to decreased renal plasma flow associated with blood or fluid loss or inadequate fluid resuscitation preoperatively. A fluid challenge of 20 mL/kg of isotonic fluid or 5% albumin will frequently result in restoration of urine output. Although critically ill newborns are frequently hypoalbuminemic and the maintenance of colloid osmotic pressure would seem to be an important factor in decreasing tissue edema, there is no evidence as to the efficacy of albumin compared with crystalloid solutions.[146–149] A further fluid bolus/boluses with or without a diuretic may be tried, depending on CVP measurement, if there is no initial response.

Intrinsic renal failure is a more serious complication and more difficult to manage. Causes include congenitally abnormal kidneys (cystic or dysplastic), prolonged intraoperative renal ischemia or vascular abnormalities of the kidney, arterial thrombosis associated with umbilical artery catheters, renal venous thrombosis secondary to dehydration, and prolonged hypotension due to sepsis.[150] Drugs such as indomethicin and aminoglycoside antibiotics can also cause intrinsic renal damage. This form of renal failure can be differentiated from pre-renal by the finding of red

cells, protein, and casts in the urine in association with high urinary sodium losses. Management of acute renal failure consists of eliminating the underlying cause if possible, restricting fluids to urine output plus insensible losses and treating hyperkalemia with dextrose infusions and potassium exchange resins. This is only likely to be a short-term solution as the fluid restriction will also entail restricted calorie intake and a cycle of catabolism with protein breakdown and weight loss.

TEMPERATURE REGULATION AND METABOLISM IN THE NEONATE

Temperature

To maintain a normal body temperature, the neonate has to balance heat loss with heat production. With a large body surface area to body weight ratio, the neonate tends to lose heat rapidly by: (1) conduction due to direct contact with cold surfaces; (2) convection by the cooling effects of air currents on exposed skin; (3) radiation to nearby objects such as an incubator wall; (4) evaporation of fluid from skin and respiratory tract. Failure to eliminate areas of heat loss result in the infant attempting to raise its heat production by metabolism of brown fat stores and glucose. The preterm infant is poikulothermic and will not defend its body temperature and is therefore particularly vulnerable to the effects of cold injury. These include acidosis, hypoglycemia, increased O_2 consumption, and weight loss.

It is therefore of great importance that the critically ill neonate be protected from the effects of cold stress following surgery. Nursing the infant in an incubator with an internal temperature of 32–36°C will eliminate conductive and convective heat losses. Radiation can be reduced by using double glazed incubators and evaporative heat losses reduced by humidification. Incubators do, however, limit access to the critically ill infant whereas the radiant warmer bed, while less efficient in conserving heat losses, does provide excellent access. Evaporative and convective heat loss may be reduced with this system by covering the infant with plastic cling film stretched between the side walls of the warmer bed.[151]

METABOLISM IN THE NEWBORN

Glucose and calcium

Glucose metabolism is not well developed in the newborn period and the critically ill neonate is liable to develop hypoglycemia at times of acute stress, particularly the preterm infant. This may be as a result of: (1) diminished glycogen stores (inadequate stores in the premature or depletion from catecholamine stimulated glycogen breakdown release in perinatal stress); (2) hyperinsulinemia in infants of diabetic mothers; (3) inadequate glucose production in small for gestational age infants. Failure to recognize and correct neonatal hypoglycemia will result in seizures and brain damage. In order to prevent this it is recommended that a minimum of 10% dextrose with saline be used in all maintenance fluid infusions in the newborn after surgery. In addition the blood sugar should be regularly measured to prevent hypoglycemia ($<$1.1 mmol/L in the preterm and $<$1.7 mmol in the term infant). Persistent hypoglycemia may require further boluses and increasing the infusion to 15% dextrose. Where the hypoglycemia is due to delay in glucose release from glycogen stores in the liver, the administration of glucagon 300 μg/kg or steroid may result in a rise in blood sugar.[152] Infants receiving high concentration dextrose infusions have increased blood insulin levels. Abrupt discontinuation of the infusion will result in rebound hypoglycemia and therefore these should be weaned gradually.

Hypocalcemia is common in the newborn period, but measurements of the total serum calcium do not accurately reflect the level of ionized calcium (Ca^{++}) in the blood. Levels of total serum Ca above 1.75 mmol/L rarely cause problems but levels below 1.5 mmol/L may result in seizures, apnea, and low cardiac output. Critically ill infants in the first 24–48 hours of life, infants of diabetic mothers, and newborns who have undergone large volume blood transfusions are all at risk for developing hypocalcemia. Calcium infusions should be given preferentially through central venous lines because of the tendency to cause intense venous irritation and damage to skin.

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12

Fluid and electrolyte balance in the newborn

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INTRODUCTION

Infants are born into a low humidity, gaseous environment from the liquid intrauterine world. Term and preterm neonates have different fluid requirements and electrolyte changes to older children and adults, especially at this time of rapid postnatal transition.

WATER DISTRIBUTION IN THE FETUS AND THE NEWBORN INFANT

Fetal body composition alters progressively throughout pregnancy. Throughout pregnancy the amount of protein and fat in the fetus increases. Preterm neonates have more water and they may lose 10–15% of their weight in the first week of life. At 1 kg birth weight (approximately 28 weeks' gestation) the fetus comprises about 80% of its weight as water, by full term water content is 75% and by three months of age (~5 kg) 60%.[1–3] Small for gestational age (SGA) preterm infants may have a higher proportional body water content: 90% for SGA infants versus 84% for appropriate for gestational age (AGA) infants at 25–30 weeks' gestation.[4] At 23 weeks' gestation infants are composed of 90% water comprising 60% extracellular fluid (ECF) and 30% intracellular fluid (ICF) (Fig. 12.1).

The total intracellular water content of the fetus and the newborn infant's body increases directly in proportion to cell mass. Twenty-five percent of the weight of the very immature fetus early in pregnancy is intracellular water and this increases to 35% at birth and 40% by three months of age. Body fat content increases from about 1% in the very early fetus to 15% at birth and 30% at three months of age.[1] Fat has a low water content.[1] The SGA infant with a low body fat content has a greater proportion of body weight as water than the AGA infant.

FUNCTIONAL ADJUSTMENTS TO POSTNATAL LIFE

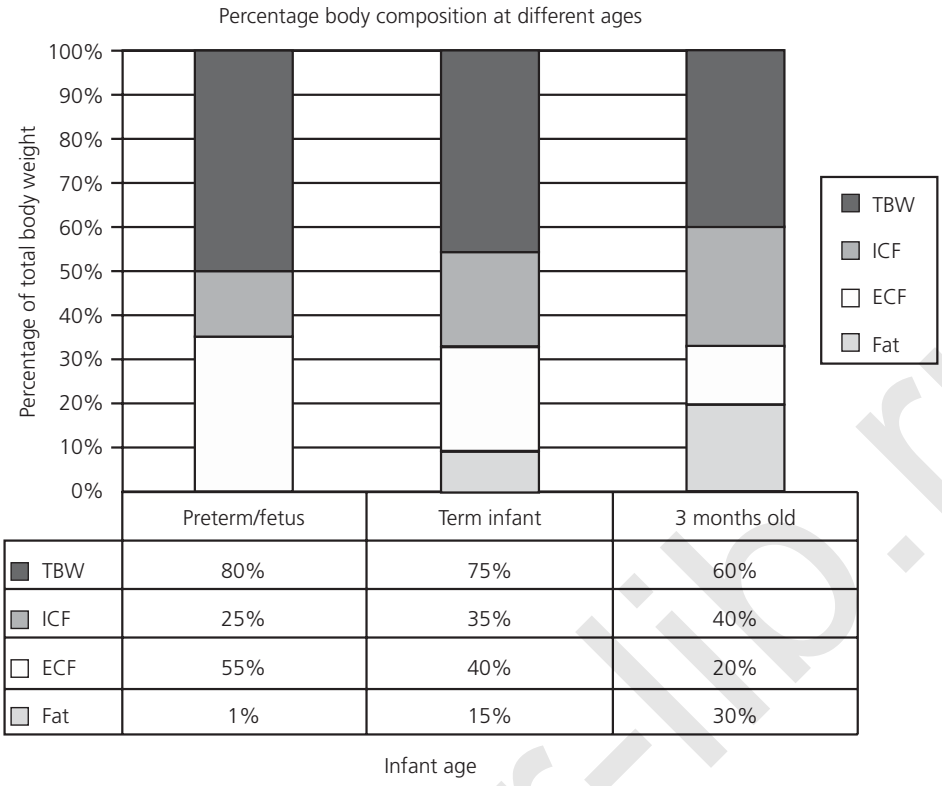
Renal blood flow

Functional nephrons are first present in the fetus at approximately 8 weeks' gestation. Nephrons develop in a centrifugal pattern with juxtamedullary nephrons developing first. The full complement of glomeruli is present by 34 weeks' gestation. Renal blood supply arises from the aorta between T12 and L2, a relationship that remains constant between 24 and 44 weeks' gestation. As the renal arteries divide into segmental end arteries, the renal tissue in their area of distribution is very vulnerable to ischemia, thus follows the recommendation that umbilical artery catheters should not be positioned between T12 and L3.[5,6]

Renal blood flow and glomerular filtration rate (GFR) *in utero* increase gradually with gestational age. Growth of nephrons accounts for the increases in GFR in the fetus. Vascular resistance is high in the fetal kidney and restricts renal blood flow and glomerular filtration *in utero*. The proportion of cardiac output that is distributed to the kidneys during fetal life is about 2–3%.[5–7] It increases to about 6% during the first week of life and approximates 15–18% during the first month of life. In adults, the kidneys receive 20–25% of the cardiac output. The low renal blood flow during fetal life results from a high renal vascular resistance. Factors that may contribute to renal dysfunction in neonates include prematurity, medication (gentamicin, cephalosporin, non-steroidal anti-inflammatory drugs (NSAIDs), frusemide), hypoxia and excessive fluid loss.

Glomerular filtration rate

Glomerular filtration begins between 9 and 12 weeks' gestation in the human fetus and contributes to amniotic



	Preterm/fetus	Term infant	3 months old
TBW	80%	75%	60%
ICF	25%	35%	40%
ECF	55%	40%	20%
Fat	1%	15%	30%

Figure 12.1 Body fluid/fat composition at different ages: TBW, total body water; ICF, intracellular fluid; ECF, extracellular fluid.

fluid. In fetal sheep, glomerular filtration rate increases by 2.5 times during the last trimester and parallels the rise in fetal body weight and kidney weight.[8–10] At delivery there is a positive correlation between GFR and gestational age in newborn infants delivered between 27 and 43 weeks' gestation.[11]

In the first 24 hours after delivery, there is a three-fold increase in GFR in the term but not preterm infant, although there is no increase in total renal blood flow or increase in systemic blood pressure. Changes in GFR at birth may be influenced by plasma adrenaline and noradrenaline,[12,13] renin-angiotensin, prostaglandin, arginine vasopressin,[14–16] and plasma cortisol.[17] Indomethacin use in the preterm neonate has been shown to increase the resistance of the renal vascular bed, thereby decreasing renal perfusion.[18] Each of these, or a combination of these, hormones may influence glomerular filtration by decreasing glomerular vascular resistance and recruiting superficial cortical nephrons.

Water homeostasis

The diluting segment of the distal tubule and ascending limb of the loop of Henle develop relatively early in nephrogenesis. When challenged with a water load both the term and the preterm infant can dilute their urine to osmolalities to 50 and 70 mOsm/kg water. Glomerular filtration, however, is low and this limits the quantity of urine that can be excreted, even in the presence of a potent dilutional capacity. The newborn kidney of both the term and preterm infant has relatively low osmolality in the renal medulla and this limits the effectiveness of the countercurrent concentrating mechanism in the loop of Henle.[19,20] In the term infant, urine can be concentrated to a maximum of 600–700 mOsm/L, considerably less than that of 1200 mOsm/L in the older child or adult. Thus both the preterm and full-term neonate are unable to handle either fluid deprivation or overload, thus underlining the need for accurate assessment of fluid requirements.[21]

Immediately after birth a physiological acute isotonic volume contraction occurs, predominantly in the extra cellular water with the corresponding postnatal weight loss. Weight loss is greater and lasts longer in infants with less advanced gestational age.

Insensible water loss

Insensible water loss is the continuous invisible loss of water by evaporation that occurs from the skin and lung surface. Insensible water loss needs inclusion in the estimation of total fluid requirements.[22] Transepidermal water loss accounts for about two-thirds of insensible water loss while respiratory water loss accounts for one-third. Insensible water loss is greater in less mature infants.[23]

SWEATING

Sweating occurs to only a very limited extent in response to a thermal stimulus in the term infant, despite the fact that the

full complement of sweat glands is present at birth. Although even the most immature infant soon develops the ability to sweat in response to heat stress, the efficiency of sweating as a thermoregulatory process is poor.[24]

TRANSEPIDERMAL WATER LOSS

Evaporation of water from the skin surface occurs continuously by diffusion.[25,26] The quantity of water lost is determined by the relative humidity of the infant's surrounding atmosphere, particularly in the preterm infant with immature skin keratinization.

Transepidermal water loss (TEWL) is closely related to thermal balance – there is heat loss whenever water evaporates from a surface (1 g water = 0.58 kcal of heat loss). In a term baby under stable environmental conditions TEWL can be elevated, accounting for as much as 70 cal/kg per day heat loss (more than half of the caloric intake of the preterm infant). Preterm infant TEWL is greatly increased as gestational age decreases due to the large ratio of surface area to weight and the immature epidermal barrier to water. TEWL is exaggerated by postnatal trauma to the skin, for example from adhesive tape applied to the skin for attachment of monitors.

However, placing impermeable plastic sheets over and under the baby or the use of plastic bags can significantly reduce TEWL of the infant surgical patient.[27]

After birth, regardless of gestation, the skin matures and skin permeability to water falls. However, in the extremely preterm infant this maturation may be extremely slow and extracellular water loss has been shown to be higher than normal at 28 days postnatal age.[28,29] Transepidermal water loss gradually decreases over the first 7 days of life and is significantly lower in infants whose mothers had received prenatal steroids. However, Jain *et al.* failed to demonstrate any maturational effect of antenatal steroids on transepidermal loss in preterm infants.[30–32] Maximizing incubator humidity can reduce TEWL.[33] Insensible water loss in infants weighing <1 kg is reduced to <40 mL/kg per day if ambient humidity is above 90%.[34]

Respiratory water loss

Respiratory loss represents 39% of insensible water loss in term infants. Inspired air becomes fully saturated with water in the upper respiratory tract and some water is lost as this air is expired. Similarly, tachypnea increases water loss. The relative humidity of the air before inspiration also has an influence; the higher the humidity, the less water needs to be added and the less lost. Ventilated infants inspire humidified air delivered, reducing respiratory water loss by a third.[35]

FLUID AND ELECTROLYTE MANAGEMENT

Infants admitted to a neonatal intensive care unit who are unable to exclusively feed orally require careful management of fluid and electrolyte balance. Additional difficulties may occur if the infant is preterm and if, as frequently happens in babies requiring surgery, there are additional losses from the intestine or the kidneys as a result of a complex surgical problem. When planning maintenance fluid therapy for an infant, all the variables that have already been discussed that may influence fluid requirements must be taken into account. Any guidelines for fluid and electrolyte therapy must be modified to suit an individual infant's requirements. Tables 12.1 and 12.2 give some guidelines that may be used and modified appropriately.[36]

Preterm infants <1.5 kg should be commenced on total parenteral nutrition in the first few hours of life to optimize their nutrition. Further discussion of neonatal enteral and parenteral nutrition is beyond the scope of this chapter.

Table 12.1 Fluid requirement in the newborn.

	Fluid volume (mL/kg)	Fluid type
Baby nursed in incubator		
Day 1	60	10% dextrose/TPN
Day 2	80	Electrolyte solution/10% dextrose/TPN
Day 3	100	Electrolyte solution/10% dextrose/TPN
Day 4	120	Electrolyte solution/10% dextrose/TPN
Day 5	150	Electrolyte solution/10% dextrose/TPN
Baby nursed under radiant warmer		
Day 1 (5% dextrose if bwt <1500 g)	80	10% dextrose/TPN
Day 2	100	Electrolyte solution/10% dextrose/TPN
Day 3	120	Electrolyte solution/10% dextrose/TPN
Day 4	140	Electrolyte solution/10% dextrose/TPN
Day 5	150	Electrolyte solution/10% dextrose/TPN

Restricted fluids – two-thirds of normal maintenance fluids.
Very low birth weight infants frequently require even higher initial rates of fluid administration and frequent reassessment of serum electrolytes, urine output, and body weight.

Table 12.2 Maintenance electrolyte therapy.

	Per kg/day
Sodium	2–4 mmol
Potassium	1–3 mmol
Calcium	5–10 mL of 10% calcium gluconate (1.125–2.25 mmol calcium)

Increased fluid requirements may occur in the following circumstances:

- Low birth weight infants <1.5 kg. The very low birth weight infant has a very high insensible loss of fluid and thus increased requirements for free water.
- Phototherapy. Phototherapy increases insensible water loss by evaporation, thus fluid intake should be increased by 10 mL/kg per day per number of phototherapy unit light used in the infant >1.5 kg and 20 mL/kg per day per number of lights used with birth weights <1.5 kg.[37,38]
- Radiant warmer. Nursing in a radiant warmer increases insensible fluid loss by a mean of 0.94 mL/kg per hour[39] when compared with incubators. This increased water loss is not prevented by using a heat shield but may be prevented by using a plastic blanket.[39–41] Use of a humidified incubator is preferable, especially in preterm babies.
- Polyuric renal failure (especially in infants <26 weeks' gestation). Maintenance fluids will require very frequent readjustment, guided by regular monitoring of the weight and the serum electrolytes.

Maintenance fluid therapy may need to be decreased in the following circumstances:

- inappropriate ADH secretion;
- congestive heart failure;
- oliguric renal failure;
- patent ductus arteriosus.

Conservative patent ductus arteriosus (PDA) management involves fluid restriction to a total fluid intake of 120 mL/kg per day.[42] A high PDA closure rate (up to 100%) in preterm infants with PDA managed conservatively with fluid restriction (130 mL/kg per day), and adjustment of ventilation (reducing inspiration time and increasing the peak end expiratory pressure) may be achieved.[43]

In assessing the infant's water requirements, one needs to evaluate weight change, urine output, specific gravity and osmolality, serum sodium and creatinine, and blood urea and osmolality. Normal urine output is 2–4 mL/kg per hour. In the first 24 hours of life, urinary output may be very low or even absent. During recovery from a severe illness associated with fluid retention or edema, polyuria may occur. A physiological diuresis (water loss) of up to 10% of body weight occurs over the first 4–5 days of life. This diuresis has the effect of decreasing total body water content by contracting the ECF volume. It is greater in the preterm infant whose total body water content is higher than that of the term infant. This water loss occurs despite usual fluid intakes and is typically accompanied by a negative sodium balance even when sodium is provided.

High fluid intake (>170 mL/kg per day) increases the likelihood of symptomatic PDA.[44] High fluid intake and/or high sodium intake may also increase the likelihood of respiratory complications both in the short term and in the longer term by increasing the frequency of chronic lung disease.[45,46]

Sodium regulation

Maintenance of normal serum sodium (135–140 mmol/L) is principally controlled by the kidneys. The amount of sodium that can be excreted is limited by the GFR and the ability of the kidney to excrete a sodium load is diminished as compared with adults and falls progressively with decreasing gestational age.[47–49]

Preterm infants have a higher fractional sodium excretion than full-term infants.[47] Extrauterine existence accelerates tubular sodium reabsorption but not GFR, whose maturation is related to post-conceptual age. Al-Danhan *et al.* demonstrated that preterm infants <30 weeks' gestation require a minimum of 5 mmol/kg per day of sodium and those of 30–35 weeks' gestation require 4 mmol/kg per day to achieve a positive sodium balance and maintain normal serum sodium.[47,50]

Intestinal absorption of sodium in the very preterm infant is low and improves progressively with increasing gestational age.[48] Neonates undergoing intensive care may gain significant amounts of fluid and sodium from drugs, bronchial lavage, and flushing of catheters, sources that are often overlooked. Hypernatremia may occur, especially in the very low birth weight infant, and may have adverse effects.[51]

Prenatal steroids induce maturation of renal tubular function. Infants who have been exposed to prenatal steroids have an earlier diuresis and natriuresis.[30] Randomized controlled trials have shown that early sodium administration increases the risks of hypernatremia, particularly if TEWL is high and water intake is limited, and increases the risks of respiratory morbidity by impeding the normal, physiological loss of extracellular fluid. Subsequently, once nutritional intake is sufficient to support growth, the extremely preterm infant is at risk of chronic sodium depletion. At this stage, an intake of at least 4 mmol/kg per day is required, or more particularly in the absence of antenatal steroid exposure.[52–56]

Renal response to antidiuretic hormone

The human fetal pituitary secretes antidiuretic hormone (ADH) from 12 weeks' gestation onwards. Labor and delivery are associated with a surge in ADH secretion in cord blood. Both term and preterm infants are capable of an appropriate ADH response to stimuli. Although ADH levels in newborn infants are similar to adults, the antidiuretic response to ADH is blunted because a lower concentration gradient in the renal medulla lessens its effectiveness and low numbers of ADH receptors. Excess ADH can cause a drop in urine output and hyponatremia.[57,58]

Factors that result in excess or inappropriate secretion of antidiuretic hormone (SIADH) in the newborn include birth asphyxia, surgery, hypoxia, severe lung disease, positive pressure ventilation, intracranial hemorrhage, and pneumothorax. SIADH results in weight gain, hyponatremia, and oliguria. SIADH is diagnosed by documenting hyponatremia in association with low serum osmolality and high or normal urine osmolality and high urinary sodium due to continued excretion of sodium in urine despite low serum

sodium. There is usually no evidence of fluid depletion. It is also important to note that the renal, adrenal, and thyroid functions are usually normal in SIADH. Management is by fluid restriction in addition to alleviating the primary cause.[59]

Sodium balance

Sodium is not required during the first 24 hours of life, during which time urine and sodium output are low. Sodium supplementation of 2–4 mmol/kg per day should be given when weight loss of approximately 5–10% of birth weight has occurred and postnatal diuresis has occurred.

Hyponatremia, defined as $Na^+ < 130$ mmol/L, may occur in the following circumstances:

- laboratory error;
- excess antidiuretic hormone secretion, where low urinary loss of water results in dilutional hyponatremia;
- large renal tubular losses of sodium as occurs in extreme prematurity or polyuric renal failure;
- congestive heart failure with dilutional hyponatremia;
- diuretic therapy with loss of sodium via the renal tubules;
- hypoadrenalism: congenital Addison's disease, septic shock with adrenal failure, salt-wasting adrenogenital syndrome;
- maternal hyponatremia;[60]
- factitious hyponatremia as a result of hyperglycemia or hyperlipidemia;
- inadequate sodium intake in preterm infants with excessive renal sodium loses;
- excessive large intakes of free water or electrolyte-free solutions like dextrose water.

Hypernatremia, serum sodium > 145 mmol/L, may occur in the following circumstances:

- laboratory error;
- high insensible water loss which is incompletely replaced;
- high urinary water losses which are not replaced;
- maternal hypernatremia;
- deficiency of antidiuretic hormone;
- rarely, excessive administration of Na^+ in i.v. fluid flushes;
- excessive sodium bicarbonate administration in infants with metabolic acidosis.

Potassium balance

Potassium is predominantly an intracellular ion. No potassium is required on the first day of life. After this, intakes of 1–3 mmol/kg per day should replace losses and maintain a normal serum potassium of 3.5–5.8 mmol/L (Table 12.2). Potassium should be cautiously administered in infants with renal dysfunction and the very low birth weight infant whose ability to excrete potassium may be limited. Early non-oliguric hyperkalemia may occur in 30–50% of infants with birth weight < 1 kg as a result of a potassium shift from intracellular to extracellular space. Hyperkalemia will be exaggerated by hypoxia, metabolic acidosis, catabolic stress, and oliguria. The hyperkalemia may be severe enough to cause life-threatening arrhythmias.[8,61–64]

Hyperkalemia, serum $K^+ > 6$ mmol/L in a sample that is not hemolyzed, becomes concerning when > 6.5 mmol/L or if ECG changes occur. ECG changes in hyperkalemia vary from peaked T waves, as the earliest sign, to a widened QRS complex, bradycardia, tachycardia, supraventricular tachycardia (SVT), ventricular tachycardia, and ventricular fibrillation.

Hyperkalemia may occur in the following circumstances:

- laboratory error or hemolysis of blood sample;
- severe metabolic acidosis: with each 0.1 pH drop serum potassium increases by 0.6 mmol/L;
- tissue cell death with release of intracellular potassium, e.g. release of K^+ from neuronal cells and red blood cells (RBCs) post-intraventricular hemorrhage, trauma, or surgery;
- acute renal failure;
- very low birth weight in the absence of renal failure;
- very low birth weight in the absence of antenatal steroids;
- adrenal insufficiency secondary to acute adrenal failure as in sepsis/shock or congenital adrenal hyperplasia;
- severe hemolytic anemia.

MANAGEMENT OF HYPERKALEMIA

- Avoid potassium in all infusions in the first day of life.
- Infants born < 28 weeks' gestation should have serum potassium levels recorded from 12 to 48 hours of age. Blood gas analysis will identify the neonate with rising potassium levels. Laboratory measurement of serum potassium should be performed 12-hourly for the first 48–72 hours of life.
- Only blood from umbilical arterial line, peripheral arterial line, arterial stab, or free flowing venous sample should be used.
- Treatment of hyperkalemia should be commenced if serum $K^+ \geq 7$ mmol/L confirmed on a non-hemolyzed arterial/venous sample and/or ECG changes are present and serum $K^+ \leq 7$ mmol/L.
- ECG changes include tall peaked T waves, prolonged PR interval, small/absent P waves, widening of the QRS complex, asystole.

Treatments used in premature infants with non-oliguric hyperkalemia aim to decrease the arrhythmogenicity of hyperkalemia, redistribute potassium into the intracellular space, or remove potassium from the body[65] (Fig. 12.2). Sodium bicarbonate is not recommended. If acidosis is present, the underlying cause should be treated. Ion exchange resins are also not recommended. They have been shown to cause intestinal obstruction and perforation. Also, gastric masses found at autopsy were devoid of potassium, indicating that no exchange had occurred.

CAUSES OF HYPOKALEMIA

Hypokalemia, serum potassium < 3.5 mmol/L, may occur in the following circumstances:

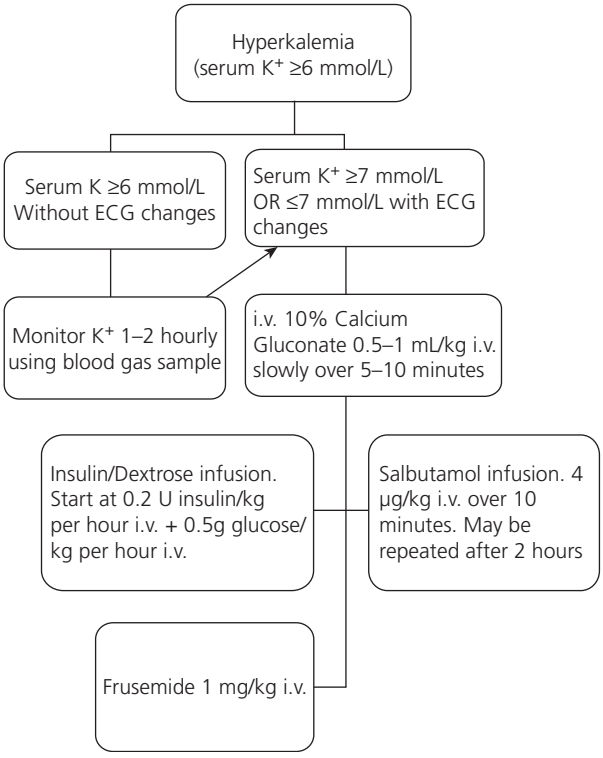


Figure 12.2 Management of hyperkalemia.

- laboratory error;
- alkalosis lowers serum potassium by shifting the potassium load intracellularly, but does not lower total body potassium;
- polyuric renal failure;
- gastrointestinal losses through vomiting or diarrhea or pooling of fluid in a 'third space', such as dilated loops with intestinal obstruction;
- diuretic therapy;
- inadequate intake;
- NG aspirate losses not replaced with appropriate fluids.

Hypokalemia predisposes to cardiac arrhythmias, paralytic ileus, urinary retention, and respiratory muscle paralysis. Thus potassium balance must be carefully monitored, taking into account the influence that pH may have on the serum potassium, in that alkalosis shifts potassium which is predominantly an intracellular ion into the cells and acidosis has the reverse effect and that both hyper- and hypokalemia will have adverse effects.

Acid–base balance

Normal values for pH are similar to those in the adult; however PCO_2 and serum bicarbonate are both slightly lower in the newborn infant than in the adult. [59,60] The lungs and the kidney both have important roles in the maintenance of acid–base balance. The lung excretes volatile acid formed during metabolism as CO_2. Respiratory failure will cause accumulation of CO_2 and respiratory acidosis.

METABOLIC ACIDOSIS

The normal kidney has a vital role in regulation of serum bicarbonate. In mature subjects serum bicarbonate is maintained at approximately 25 mmol/L, but preterm infants have a lower threshold.[66] The kidney also has an important role in the excretion of non-volatile acid (mainly sulfur containing amino acids) produced by metabolism.

Causes of metabolic acidosis

- Perinatal asphyxia.
- Severe hypotension with impaired tissue perfusion.
- Acute renal failure.
- Acute diarrhea and dehydration.
- Excess ileal loss.
- Excess protein administration, e.g. excess amino acid in parenteral nutrition.
- Inborn errors of metabolism (e.g. organic acidemia).
- Sepsis.

Acute metabolic acidosis is common in the critically ill newborn. Treatment requires management of the underlying cause. Sodium bicarbonate may be used for severe acidosis by giving a dose of 1–2 mmol/kg of 4.2% sodium bicarbonate diluted in equal volume of water. There is currently no evidence from randomized control trials to support its routine use in neonatal resuscitation. Its effect on morbidity and mortality has not been well demonstrated. There is controversy about the value of i.v. sodium bicarbonate for correction of metabolic acidosis. It is no longer recommended for resuscitation in newborn infants and although it may correct acidosis in hypotensive shocked infants, this has not been shown to result in improvement in blood pressure or perfusion.[67] Sodium bicarbonate infusion has potential side effects. Myocardial function may be depressed from the osmolar load with severe acidosis. Paradoxical intracellular acidosis may occur as well as a reduction in cerebral blood flow and increased risk of intraventricular hemorrhage. Use of sodium bicarbonate is therefore discouraged unless the infant has prolonged acidosis not responsive to other therapies including adequate ventilation.

Causes of metabolic alkalosis

Persistent vomiting causes hypochloremic alkalosis and body potassium depletion. This may occur with untreated pyloric stenosis or upper intestinal obstruction. Correction is by replacement of fluid, sodium chloride, and potassium. Rehydration and correction of depleted electrolytes will be followed by correction of the metabolic alkalosis. Chronic respiratory acidosis, as in chronic lung disease (CLD), may cause renal re-regulation of sodium bicarbonate level at a higher threshold until pH is normal. Infants with chronic hypercapnia regularly have a serum bicarbonate of greater than 30 mmol/L. Permissive hypercapnia or controlled ventilation is a strategy adopted to limit the damage done by excessive mechanical ventilation pressures or volumes to the lungs in order to decrease the incidence of CLD.[68]

Glucose homeostasis

Glucose is the most important substrate for brain metabolism and whereas ketones, glycerol, and lactate can be used, a continuous supply of glucose is essential for normal neurological function.[69,70] Fetal blood glucose is identical to that of maternal blood glucose since passive transfer of glucose occurs across the placenta.

HYPOGLYCEMIA

Immediately after delivery, blood glucose falls to ~2.5 mmol/L (45 mg/dL) in the term infant. Following delivery a combination of hormonal responses (glucagon, growth hormone, thyroxine) and oral feeds, or in their absence i.v. fluids, serve to maintain blood glucose within a normal range. There is no consensus regarding the definition of hypoglycemia in the neonate.[69,70] Blood glucose levels between 2.5 mmol/L (45 mg/dL) and 7.2 mmol/L (130 mg/dL) are accepted as being safe. Symptomatic hypoglycemia results in cyanosis, apnea, lethargy, seizures, or coma. Blood sugar values represent a continuum and there is no specific value at which brain damaging hypoglycemia will always occur.[69,71] However,' brain MRI after symptomatic neonatal hypoglycemia (median glucose level 1 mmol/L) without evidence of hypoxic-ischemic encephalopathy reveals white matter injury in 94% and neurodevelopmental impairment in 64% at 18 months.[72]

In the newborn infant requiring surgery, hypoglycemia is most commonly caused by vomiting or inadequate intake of fluids. Other contributing factors may include prematurity, septicemia, hypothermia, or hyperinsulinism as may occur in an infant of a diabetic mother. Infants with Beckwith–Wiedemann syndrome who frequently may have omphalocele, commonly have elevated blood insulin levels and severe hypoglycemia.

Blood sugar in the infant at risk should be monitored at the bedside using a bedside screening glucose analyzer. Blood sugars below 2–2.5 mmol/L should be acted upon by giving a feed or giving a bolus of i.v. 10% dextrose as appropriate for the individual infant. Significant hypoglycemia should be confirmed by laboratory blood sugar before definitive action, such as i.v. glucose being given. This is because all screening methods are not completely accurate at low blood sugar levels.

HYPERGLYCEMIA

A blood glucose > 14 mmol/L (250 mg/dL) may cause a hyperosmolar state with glucosuria, osmotic dieresis, and dehydration. This elevated plasma osmolality increases the risk of intracranial hemorrhage, at least in the infant of less than 32 weeks' gestation. Hyperglycemia most commonly occurs in the very low birth weight infant who is receiving large amounts of fluids to counteract insensible loss and whose ability to metabolize dextrose or glucose is limited. Hyperglycemia may also be due to defective islet cell processing of proinsulin, insulin resistance, and non-suppression of endogenous glucose production during continuous exogenous glucose infusion.[73,74] Infusion of small doses of insulin may be required to counteract intractable hyperglycemia.[73] Extreme low birth weight babies require a higher total dose of insulin for longer periods than low birth weight preterms. Exogenous insulin infusion partially reduces endogenous glucose production in preterm newborn infants. This treatment is efficient and safe when used with caution.[73] The use of insulin in preterm infants and prevention of hyperglycemia could also affect immune function, lipid metabolism, growth, and IGF-I generation leading to improved short-term clinical outcomes such as retinopathy of prematurity. It may also have longer-term health effects, however the outcomes of clinical trials are currently awaited.[74]

Calcium homeostasis

Calcium has a key role in many physiological processes, including activation and inhibition of enzymes, intracellular regulation of metabolic sequences, secretion and action of hormones, blood coagulation, muscle contraction, and nerve transmission. Ninety-nine percent of total body calcium is in bone, to which it gives structural support, with only about 1% in the ECF and soft tissues.[75]

Calcium is present in the extracellular fluid in three fractions: 30–50% is bound to protein, principally albumin; 5–15% is complexed with citrate, lactate, bicarbonate, and inorganic ions; and 5–15% is ionized – this is the metabolically active fraction of calcium. Calcium concentration reported as mg/dL can be converted to molar units by dividing by four (e.g. 10 mg/dL converts to 2.5 mmol/L).[36,76–78] If serum albumin is low, total serum calcium falls, but the serum level of ionized calcium is unchanged. Serum calcium could be corrected for the level of serum albumin using the formula:

$$\text{Corrected calcium} = (0.8 \times [\text{normal albumin} - \text{neonatal albumin}]) + \text{serum Ca}$$

Hydrogen ions compete with calcium for albumin binding sites. Thus acidosis increases serum ionized calcium levels without influencing total serum calcium levels. Prenatally, calcium is actively transported across the placenta from mother to fetus against a concentration gradient, which results in fetal hypercalcemia at the end of the last trimester and immediately after birth. Cord serum calcium in the full-term infant is approximately 2.75 mmol/L.[77] In healthy full term infants calcium concentrations decrease for the first 24–48 hours and reach a nadir of 1.8–2.1 mmol/L. Thereafter, calcium concentrations progressively rise to the mean values observed in older children. This transient drop in serum calcium is exaggerated in the preterm infant. Metabolic bone disease is a common feature, especially in extreme preterm infants less than 28 weeks' gestation, and results from inadequate supply of nutrients (vitamin D, calcium, and phosphate), prolonged period of total parenteral nutrition, and prolonged period of immobilization. The main features which manifest between the 10th and 16th week of life include decreased

bone mineral density and osteopenia with or without other features of rickets.

HYPOCALCEMIA

This is defined as a total serum calcium concentration <2.0 mmol/L in the term infant and <1.7 mmol/L in the preterm infant.[76] Normal serum ionized calcium in the newborn infant is 1–1.5 mmol/L.[77,78]

Causes of hypocalcemia

1. Infants of diabetic mothers
2. Asphyxia
3. Sepsis
4. DiGeorge syndrome/velocardiofacial syndrome
5. Diuretics, especially frusemide
6. Hypomagnesemia
7. Maternal hyperparathyroidism
8. Prematurity
9. Vitamin D deficiency.

Clinical manifestations

The majority of hypocalcemia is asymptomatic. The symptoms when they occur include jitteriness and seizures. An electrocardiographic Q–T_c interval longer than 0.4 seconds may occur.

Management

Early asymptomatic mild neonatal hypocalcemia does not require treatment. Infants receiving i.v. fluids should be provided with maintenance calcium gluconate. Brown and colleagues have shown that aggressive attempts at normalizing serum calcium in sick preterm infants may be ineffective and even hazardous, thus at the least in the first week of life, maintenance of serum calcium at a level of 2.0 mmol/L is adequate.[79]

Symptomatic hypocalcemia should be treated with a slow infusion of i.v. calcium gluconate [5 mL 10% calcium gluconate = 1.1 mmol = 45 mg elemental calcium]. Extreme care should always be taken when infusing calcium as extravasation can cause severe burns to the surrounding skin and subcutaneous tissue. Emergency treatment of hypocalcemia is only required if the infant is symptomatic. Symptoms include jitteriness, seizures, lethargy, poor feeding, and vomiting [bolus 1–2 mL 10% calcium gluconate i.v. (0.45 mmol = 18 mg elemental calcium) i.v. slowly]. Symptoms are uncommon at serum calcium above 1.8 mmol/L and become common at serum calcium <1.5 mmol/L. Oral calcium supplements in the form of Calcium Sandoz provides 2.7 mmol (110 mg) elemental calcium 2.5 mL (50 mg) per kg per day may be given with feeds if the infant on feeds has asymptomatic hypocalcemia, requiring treatment. Symptomatic hypocalcemia unresponsive to calcium therapy may be due to hypomagnesemia. This can be treated with 50% magnesium sulfate either intravenously or intramuscularly.[80]

PERIOPERATIVE MANAGEMENT

Preoperative fluid and electrolyte problems in the neonate

Heird and Winters have summarized the metabolic responses of the normal neonate in the first weeks of life.[82] Preoperatively, infants with abnormalities requiring surgery, especially those of the gastrointestinal tract, may have a variety of electrolyte abnormalities.[81–83] If there has been a delay in recognition of gastrointestinal obstruction and the infant has been vomiting for a period of time, he or she will be dehydrated (Table 12.3).

Upper intestinal obstruction, for example pyloric stenosis, results in loss of hydrochloric acid from the stomach, and small amounts of sodium and potassium. The kidney then conserves hydrogen ions at the expense of potassium and sodium. Bicarbonate is excreted by the kidney along with sodium and potassium and the urine pH is alkaline.

Potassium and sodium depletion occur. As loss of potassium and sodium progress, and the body stores are diminished, the kidney ceases to excrete these ions with bicarbonate. Sodium and potassium are now conserved by the kidney and hydrogen ion is lost instead causing a severe hypochloremic metabolic alkalosis. Correction must be with adequate fluid-containing sodium chloride and potassium chloride, as body stores of all these ions are depleted. Infants with lower intestinal obstruction, such as Hirschsprung's disease or other intestinal obstructive lesions, may pool large amounts of fluid and electrolytes in dilated intestinal loops; this may result in intravascular dehydration with hyponatremia, hypokalemia, and metabolic acidosis.

Neonates with necrotizing enterocolitis, peritonitis, or septic shock may have 'third space' loss of fluid into the peritoneum, pleural fluid, or interstitial tissues with resultant hypoproteinemia and marked interstitial edema. Additionally, many of these infants are ventilated, sedated, and paralyzed. Immobility resulting from paralysis will accentuate peripheral pooling of interstitial fluid. Intravascular dehydration and hypoproteinemia and hyponatremia will result.

Preoperatively, the infant's hydration should be assessed on the basis of weight, pulse, blood pressure, capillary filling time, blood urea and electrolytes and urine output, specific gravity and electrolyte content.

Table 12.3 Electrolyte composition of body fluids.

	Electrolytes (mEq/L)				
Body fluid	Na^+	K^+	Cl^-	HCO_3	pH
Gastric	70	5–15	120	0	1
Pancreas	140	5	50–100	100	9
Bile	130	5	100	40	8
Ileostomy	130	15–20	120	25–30	8
Diarrhea	50	35	40	50	>7

Adapted from Refs 77 and 78.

Intraoperative management

Careful attention to fluid and electrolyte balance intraoperatively is essential, including blood pressure, pulse, and temperature. During major procedures, intravascular lines allow blood pressure and central venous pressure monitoring. Urine output should also be measured and oxygenation and ventilation with blood gases and pulse oximetry.

Loss of fluid and heat from exposed peritoneal surfaces should be taken into account and minimized by keeping the operating room sufficiently warm. Acute blood loss should be replaced.[82]

Postoperative management

Patients who have been adequately managed pre- and intraoperatively may be well hydrated, immediately, postoperatively. If the infant had hypotension, transient renal failure with oliguria may occur and may be managed with fluid restriction and correction of electrolyte abnormalities. Inappropriate secretion of antidiuretic hormone is common and results from pain and/or ventilation, resulting in fluid retention and hyponatremia; thus care must be taken to avoid overhydration which will encourage both of these. Respiratory acidosis should be corrected by appropriate ventilation. Metabolic acidosis may occur postoperatively in the infant who is persistently hypotensive or hypoxic or who has ongoing tissue necrosis (i.e. severe necrotizing entercolitis). This must be addressed by correcting the underlying cause of acidosis and by giving sodium bicarbonate. Fluids lost through nasogastric suctioning or drainage must be replaced at regular intervals by normal saline with maintenance potassium added; if losses are from the small intestine it has been recommended that a small amount of bicarbonate is also added. Where large fluid losses occur from aspiration, calculation of the electrolyte content of these fluids may help plan replacement[80,81] (Table 12.3).

Nitrogen excretion occurs in neonates postoperatively. Thus early attention must be given to beginning parenteral nutrition in infants in whom early feeding is not foreseen. The term infant who will be fed enterally within 3 days need not be fed parenterally; however, the very low birth weight infant (<1.5 kg) who has very inadequate stores of nutrients must begin parenteral nutrition immediately.

FLUID AND ELECTROLYTE BALANCE IN SEPTIC SHOCK

Many surgical conditions predispose to sepsis and shock, including necrotizing enterocolitis, Hirschsprung's disease with enterocolitis, and volvulus. The risk of septicemia with hypotension is even higher if the infant is also preterm. Shock is a stage of acute cardiovascular dysfunction in which the delivery of oxygen and nutrients is insufficient to meet metabolic demands of the tissues. Endotoxin appears to be the common etiological factor in septic shock.[84,85]

Metabolic substrates, i.e. oxygen, glucose, and fatty acid, are available, but their utilization is impaired causing multiple organ failure. Capillary permeability increases and fluid and protein leaks into the interstitial fluid resulting in tissue edema, hypoproteinemia and a fall in intravascular fluid volume. Pulmonary hypertension, followed by marked pulmonary edema, occurs with severe respiratory distress. Myocardial depression results in decreased cardiac output.

Clinical manifestations

Neonatal bacterial septicemia may be fulminant and fatal. A high index of suspicion by the nursing and medical staff is essential. Presenting features are subtle and may be recognized only by an experienced nurse or doctor. The infant may merely appear 'off color'. Early signs of sepsis include lethargy, irritability, apnea and temperature instability, elevated C-reactive protein, and immature to total neutrophil ratio.

Management

Shock must be reversed with rapid infusion of fluid and colloid to replete the intravascular space. Normal saline at a volume of 10–20 mL/kg can be infused over 20–60 minutes.[81] Inotropic agents may be needed to increase cardiac output – dopamine improves cardiac contractility (5–20 μg/kg per minute) and in a low dose (<5 μg/kg per minute) also increases blood flow to the kidneys and the intestine; high doses have the opposite effect. Alternative drugs are dobutamine, milrinone, or isoproterenol. Patients with profound hypotension and myocardial depression may respond only to infusion of epinephrine or norepinephrine. Hydrocortisone at stress doses could be used to treat recalcitrant hypotension not responsive to full doses of inotropes and intravascular volume repletion. Administration of corticosteroids leads to rapid resolution of the hypotension without increasing the risk of spontaneous intestinal perforation, grade III–IV intraventricular hemorrhage (IVH), periventricular leukomalacia, and sepsis (bacterial or fungal).

Hyperkalemia results from oliguria and tissue catabolism; hyponatremia results from increased total body water and inappropriate ADH secretion.

ACUTE RENAL FAILURE

Acute renal failure is common in the seriously ill neonate requiring surgery. It may be prerenal as a result of severe dehydration, hypotension, abdominal distension, or sepsis. It may result from congenital severe intrinsic renal disease. It may be obstructive and result from severe obstruction in the urinary collecting system, e.g. urethral valves.[85,86]

Prerenal failure is the most common form of acute renal failure in the surgical neonate and results from a severe decrease in renal perfusion, usually as a result of profound hypotension from blood loss, sepsis, severe necrotizing

enterocolitis. or intestinal obstruction with loss of fluid into dilated intestinal loops.

Primary fascial closure of omphalocele or gastroschisis carries the risk of placing the abdominal contents under pressure which may cause a reduction in cardiac output, hypotension, bowel ischemia, venostasis, and postoperative renal failure. Limited data suggest that an intragastric pressure >20 mmHg or an increase in central venous pressure of 4 mmHg or more indicate the need of a staged repair using a pouch.[87] Additionally, newborn infants with abdominal wall defects have significantly increased fluid requirements preoperatively as major insensible water losses occur when eviscerated bowel is exposed to air and a perioperative third space is frequently associated. These conditions also favor hypovolemia, hypoperfusion of the kidney, and postoperative renal failure.

Renal vein or renal artery thrombosis, if bilateral, may be associated with acute renal failure. Treatment is by early aggressive fluid replacement until blood pressure normalizes and then by meticulous adjustment of fluid and electrolyte balance, until recovery of renal function occurs. Peritoneal dialysis may be required until renal function recovers. Recovery is associated with a polyuric phase which also requires ongoing care with replacement of large amounts of water, potassium, and sodium via the kidneys.

Renal failure due to obstruction and due to congenital malformations is often associated with severe irreversible renal diseases not compatible with normal extrauterine life. The focus of care must initially be to decide on the appropriateness of active management. Further discussion of renal failure management is outside the scope of this chapter.

CONCLUSION

Major changes in body composition and in fluid and electrolyte balance occur during the transition to extrauterine life. These changes are even more marked in the preterm infant. The newborn infant who has a disorder requiring surgery has additional possible disorders of fluid and electrolyte balance. Future research and audit of fluid management strategies are vital to prevent hypernatremia, hyperglycemia and hyponatremia, and adverse neurodevelopmental sequelae.

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13

Nutrition

AGOSTINO PIERRO AND SIMON EATON

INTRODUCTION

The newborn infant requires nutrition not only for tissue maintenance and normal metabolism, but also for growth – a term newborn grows at a rate of 25–30 g per day over the first six months of life, so that weight has doubled by the age of five months. The newborn infant is in a 'critical epoch' of development not only for the organism as a whole, but also for the individual organs and most significantly for the brain, so a significant period of inadequate nutrition may not only affect short-term outcomes, but may also be a risk factor for the long-term menace of stunted mental and physical development. As well as providing the components necessary for increase in tissue mass, adequate provision of the nutrients required to mount an appropriate immune response is extremely important, as infection and sepsis may impair growth and neurodevelopmental outcome.[1] Hence, where indicated, early intervention with appropriate artificial nutritional support is of paramount importance.

HISTORICAL BACKGROUND

Parenteral nutrition (PN) stepped forward from numerous historical anecdotes in the 1930s with the first successful infusion of protein hydrolysates in humans,[2] followed by the first report of successful total parenteral nutrition in an infant in 1944,[3] and given a huge boost by the first placement of a catheter in the superior vena cava to deliver nutrients for prolonged periods.[4] Using this system, Dudrick and Wilmore showed that adequate growth and development could be achieved in beagle puppies and in a surgical infant.[4] Following these initial reports, Filler and co-authors reported the first series of surgical neonates with gastrointestinal abnormalities treated with long-term total parenteral nutrition.[5] During the 1970s and 1980s, significant improvements were made in the technique itself and in reduction of complications, and the last 30 years have seen considerable changes in the nutritional management of surgical neonates. Various investigators have highlighted the importance of introducing enteral nutrition (EN) as soon as possible in surgical neonates. The beneficial effects of minimal enteral feeding on the immune system, infection rate, and liver function have been elucidated.

BODY COMPOSITION

Newborn infants grow very rapidly, have higher energy expenditure, and lower caloric reserves than adults and therefore do not tolerate prolonged periods of starvation. The body composition of newborn infants is markedly different from that of adults: total body water varies from 87% of body weight at 24–25 weeks' gestation to 71% at term and 50% in adulthood (Fig. 13.1).[6] This decline in body water also reflects an increase in energy content of the body. The ratio between resting energy expenditure (in kcal/kg per day) to non-protein energy reserve (in kcal/kg) gives an

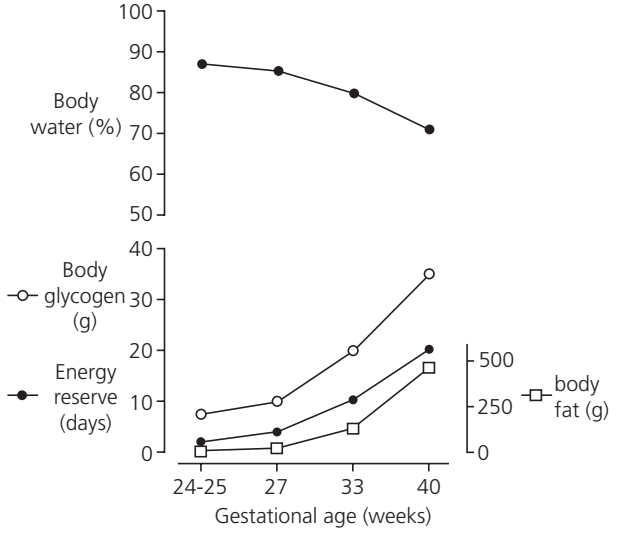

Figure 13.1 Body water and energy stores according to gestational age.

approximate estimate of the energy reserve of the infants. This is only ~2 days at 24–25 weeks' gestation, increases to ~20 days at term as glycogen and fat stores increase (Fig. 13.1)[6] and is in excess of 50 days in the adult, hence the urgent need for adequate caloric intake in very low birth weight (VLBW) and/or extremely low birth weight (ELBW) infants after birth. Early PN in VLBW infants has been shown to be beneficial,[7] although there is controversy on how 'aggressive' nutritional intervention should be in preterm infants. Full-term neonates have higher content of endogenous fat (approximately 600 g) and therefore can tolerate a few days of undernutrition.

ENERGY REQUIREMENTS OF THE NEONATE

Newborn infants have a significantly higher metabolic rate and energy requirement per unit body weight than children and adults: the total energy requirement for an extremely low birth weight (i.e. <1000 g) preterm infant fed enterally is 130–150 kcal/kg per day,[8] and that of a term infant is 100–120 kcal/kg per day, compared to 60–80 kcal/kg per day for a 10-year-old and 30–40 kcal/kg per day for a 20-year-old individual.[9–11] Of the 100–120 kcal/kg per day required by the term infant, approximately 40–70 kcal/kg per day is needed for maintenance metabolism, 50–70 kcal/kg per day for growth (tissue synthesis and energy stored), and up to 20 kcal/kg per day to cover energy losses in excreta.[12–14] Newborn infants receiving total parenteral nutrition (TPN) require fewer calories (110–120 kcal/kg per day for a preterm infant and 90–100 kcal/kg per day for a term infant[15]), due to the absence of energy losses in excreta and to the fact that energy is not required for thermoregulation when the infant is in an incubator. These data are shown diagrammatically in Fig. 13.2, but it should be stressed that energy requirements vary greatly. Several equations have been used to estimate the resting energy expenditure, and therefore the energy requirements, of infants and children. The most frequently used are those of the World Health Organization (WHO),[10] Schofield,[16] and Harris and Benedict.[17] These are based on weight, height, and/or age and are based on measurements of orally fed, healthy individuals, and thus take no account of the abnormal physiology and/or pathology of infants requiring artificial nutritional support. An equation has been developed to predict resting energy expenditure (REE) in stable surgical infants, to which the major contributing predictors are body weight, heart rate (providing an indirect measure of hemodynamic and metabolic status), and postnatal age.[18] Although adults show large increases in REE following trauma, surgery, burns, or during severe infection, this does not appear to be true for infants, although there are few studies in this area. Critically ill, post-surgical ventilated premature neonates,[19] neonates with necrotizing enterocolitis (NEC),[20] and surgical infants (with or without extracorporeal membrane oxygenation (ECMO))[21] were shown to have similar REE values to healthy neonates, whereas others have suggested that REE is increased during neonatal sepsis[22] and that REE correlates with severity of illness during sepsis in neonates.[23] Another study, examining the immediate postoperative response to neonatal surgery, found that there is a peak in REE 4 hours after surgery, which was short-lived, returning to baseline within 12–24 hours after surgery.[24] Thus, there is no clear indication that increased energy should be provided to septic or surgical neonates.[15]

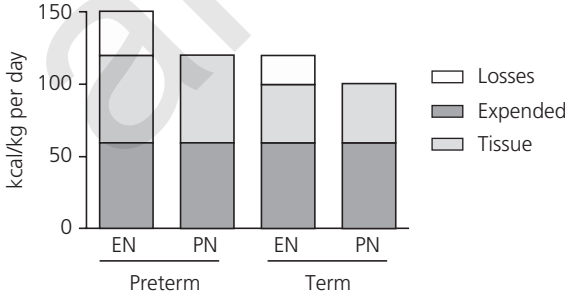

Figure 13.2 Partition of energy metabolism in preterm and term infants receiving nutrition enterally (EN) or parenterally (PN). 'Expended' includes basal metabolic rate, activity, the energy expended in laying down new tissue, and thermoregulation; 'tissue' is the amount of energy actually stored in new tissue; 'losses' include losses in stool etc. Data from: Refs 8, 9, 12, 14, 15.

Effects of operative trauma on energy metabolism

In contrast with adults, the energy requirement of infants and children undergoing major operations seems to be modified minimally by the operative trauma per se. In adults, trauma or surgery causes a brief 'ebb' period of a depressed metabolic rate followed by a 'flow phase' characterized by an increase in oxygen consumption to support the massive exchanges of substrate between organs.[25] In newborn infants major abdominal surgery causes a moderate (15%) and immediate (peak at 4 hours) elevation of oxygen consumption and resting energy expenditure and a rapid return to baseline 12–24 hours postoperatively.[24] There is no further increase in energy expenditure in the first 5–7 days following an operation.[24,26] The timing of these changes corresponds with the postoperative changes in catecholamine levels and other biochemical and endocrine parameters.[27] It has been demonstrated that the postoperative increase in energy expenditure can, at least partially, result from severe underlying acute illness, which frequently necessitates surgery (i.e. sepsis or intense inflammation, see below).[28] Interestingly, infants having a major operation after the second day of life have a significantly greater increase in resting energy expenditure than infants undergoing surgery within the first 48 hours of life. A possible explanation for this may be greater secretion of endogenous opioids in the perinatal period blunting the endocrine and metabolic responses.[27,29,30]

Resting energy expenditure is directly proportional to growth rate in healthy infants, and growth is retarded during acute metabolic stress. Studies in adult surgical patients have shown that operative stress causes marked changes in protein metabolism characterized by a postoperative increase in protein degradation, negative nitrogen balance,[31,32] and a

decrease in muscle protein synthesis.[33] However, changes in whole body protein flux, protein synthesis, amino acid oxidation, or protein degradation do not seem to occur in infants and young children undergoing major operations,[34] which led us to speculate that infants and children divert protein and energy from growth to tissue repair, thereby avoiding the overall increase in energy expenditure and catabolism seen in the adult.[20,34,35]

Effects of critical illness and sepsis on energy metabolism

Nutritional problems in infants and children requiring surgery are not unusual. The real nutritional challenge is not represented by the operation per se but by the clinical condition of the patient. Examples include intrauterine growth retardation in small for gestational age preterm infants, infants who have suffered massive intestinal resection for NEC, and infants with motility disorders of the intestine following surgery for atresia, malrotation and midgut volvulus, meconium ileus, or gastroschisis.

Nutritional integrity, particularly in the neonatal period, should be maintained regardless of the severity of the illness or organ failure due to the limited energy and protein stores in neonates. Infants and children require nutrition for maintenance of protein status as well as for growth and wound healing. One considerable challenge in pediatrics is represented by nutrition support during critical illness and sepsis. Keshen *et al.*[36] have shown that parenterally fed neonates on extracorporeal life support are in hypermetabolic and protein catabolic states. These authors recommend the provision of additional protein and non-protein calories to attenuate the net protein losses.

Sepsis is an intriguing pathological condition associated with many complex metabolic and physiological alterations.[37] Studies in adults have shown that the metabolic response to sepsis is characterized by hypermetabolism,[38] increased tissue catabolism,[38] gluconeogenesis, and hepatic release of glucose.[39] Energy is largely derived from fat, and increased protein catabolism provides precursors for enhanced hepatic gluconeogenesis.[39] However, fat mobilization is far greater than fat oxidation, implying considerable cycling[40] and, in later stages of sepsis, oxidative metabolism[41] and fat utilization may become impaired,[42] although we have shown that septic infants and children are able to oxidize considerable amounts of exogenous lipid.[43]

The existing knowledge on the metabolic response to sepsis in infants is limited. There are conflicting reports on whether critically ill infants are hypermetabolic.[21,44–49] However, most studies suggest that infants with sepsis do not become hypermetabolic[50,51](Fig. 13.3) and that septic neonates with NEC do not show any increase in whole body protein turnover, synthesis, and catabolism.[20] However, the conflicting data may reflect measurements taken at different times in infants with differing degrees of sepsis.[52]

From these studies, it is clear that the metabolic rate and hormonal response to surgery, stress, and sepsis in infants may well be different from that of adults and therefore it is not possible to adapt nutritional recommendations made for adults to the neonatal population. It is possible that neonates divert the products of protein synthesis and breakdown from growth into tissue repair. This may explain the lack of growth commonly observed in infants with critical illness or sepsis. Further studies are needed in this field to delineate the metabolic response of neonates and children to trauma and sepsis, explore the relationship between nutrition and immunity, and to design the most appropriate diet.

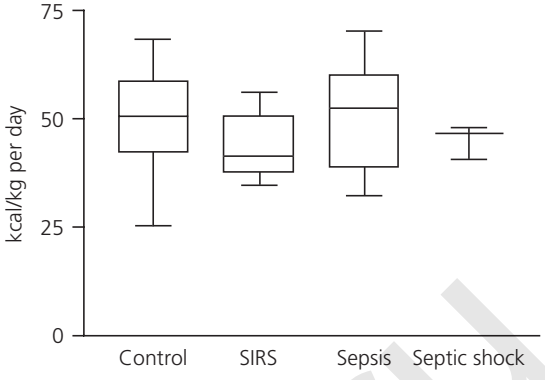

Figure 13.3 Resting energy expenditure in critically ill infants and controls. Indirect calorimetry was performed on infants and children with systemic inflammatory response syndrome (SIRS), sepsis, septic shock, and controls. Results are expressed as median, range, and interquartile range. There were no significant differences between the groups. See Ref. 50.

PARENTERAL NUTRITION

Indications

Parenteral nutrition should be utilized when enteral feeding is impossible, inadequate, or hazardous for more than 4–5 days. The most frequent indications in neonatal surgery are the intestinal obstruction due to congenital anomalies. Frequently after an operation on the gastrointestinal tract, adequate enteral feeding cannot be achieved for more than 1 week and parenteral nutrition becomes necessary. This modality of therapy has significantly improved the survival rate of newborns with gastroschisis, a condition which requires i.v. administration of nutrients for 2–3 weeks. Parenteral nutrition is also used in cases of NEC, shortbowel syndrome, gastroenterological indications, and respiratory distress.

Route of administration

As phlebitis may develop with the use of peripheral veins with solutions exceeding 600 mOsm, it is not possible to administer adequate calories peripherally for the growth of extremely low birth weight infants, and peripheral veins are only used for short-term, partial, nutritional supplementation. In neonates, the umbilical vessels can be used for provision of PN centrally, although the risk of complications increases if umbilical catheters are used for more than 5 days (arterial), or 14 days (venous).[53] Central venous catheters can

either be placed percutaneously directly in a deep vein, with subcutaneous tunneling of the extravascular part of the line, or can be a peripherally inserted central catheter (PICC). Although there has been a systematic review comparing outcomes in neonates administered PN through percutaneous central venous catheters versus peripheral cannulae, the authors concluded that there was insufficient evidence to make form recommendations.[54] For consideration of technical aspects of placement and management, the reader is directed to the ESPGHAN/ESPEN guidelines.[53]

Components of parenteral nutrition

The parenteral nutrition formulation includes carbohydrate, fat, protein, electrolytes, vitamins, trace elements, and water. The caloric needs for total parenteral nutrition are provided by carbohydrate and lipid. Protein is not used as a source of calories, since the catabolism of protein to produce energy is an uneconomic metabolic process compared to the oxidation of carbohydrate and fat which produces more energy at a lower metabolic cost. The ideal total parenteral nutrition regimen therefore should provide enough amino acids for protein turnover and tissue growth, and sufficient calories to minimize protein oxidation for energy.

FLUID REQUIREMENTS

As noted above, the proportion of body weight as water decreases with postnatal age (Fig. 13.1). In addition, the proportion of total body water which is extracellular also decreases, from 65% at 26 weeks' gestation to 40% at term, and 20% in childhood.[55] This contributes to an expected weight loss in the first days of life. Any newborn infant deprived of oral fluids will lose body fluids and electrolytes in urine, stools, sweat, and evaporative losses from the lungs and the skin. The insensible water losses from the skin are particularly high (up to 80–100 mL/kg per day) in VLBW or extremely premature infants.[55,56] This is due to the very large surface area relative to body weight, to the very thin and permeable epidermis, to reduced subcutaneous fat, and to the large proportion of total body water and extracellular water.[55] The preterm infant requires larger amounts of fluid to replace the high obligatory renal water excretion due to the limited ability to concentrate urine. In surgical newborns it is not unusual to have significant water losses from gastric drainage and gastrointestinal stoma. Phototherapy may also increase losses. In order to reduce the water losses it is important to use double walled incubators, to place the infant in relatively high humidity, to use warm humidified air via the endotracheal tube, and in premature babies to cover the body surface with an impermeable sheet. However, overhydration is potentially a problem, leading to complications such as pulmonary edema, and fluid restriction may be necessary for treatment of patent ductus arteriosus, renal insufficiency, and chronic lung disease. A meta-analysis showed that although a liberal fluid regime decreased weight loss in premature infants in the first days of life, it significantly increased the risk of mortality, and the incidence of patent ductus arteriosus and NEC.[57] Thus the recommended fluid intakes of neonates fall between 60 and 80 mL/kg per day (for premature infants on the first day of life) and 140–170 mL/kg per day (for neonates during the stable growth phase).[58] Hence, a 'one-size fits all' prescription is inappropriate, and frequent monitoring of weight, urine output, and urea and electrolytes, with reassessment of fluid prescription, should be mandatory in the first weeks of life.

ENERGY SOURCES

Carbohydrates and fat provide the main energy sources in the diet, and this is reflected by their importance as a source of calories in parenteral nutrition. Glucose is a main energy source for body cells and should be the primary energy substrate in parenteral nutrition, covering 60–70% of non-protein calories.[59] The amount of glucose that can be infused safely depends on the clinical condition and maturity of the infant, as the ability of neonates to metabolize glucose may be impaired by prematurity and low birth weight. Since (1) pancreatic islet cell function is relatively unresponsive for the first 2 weeks of neonatal life; (2) glycogen stores are limited (Fig. 13.1); (3) gluconeogenesis may be impaired; and (4) liver and peripheral tissues are relatively insensitive to insulin, premature neonates are at risk from both hypoglycemia and hyperglycemia.[60] Glucose infusion should be at least at a rate capable of maintaining blood glucose above 2.6 mmol/L, the current consensus definition of neonatal hypoglycemia.[61] As the rate of endogenous glucose metabolism in neonates is of the order of 5 mg/kg per minute, this should be considered the lowest infusion rate likely to avoid hypoglycemia.[59] As glucose tolerance increases, the rate of glucose infusion can be increased. However, carbohydrate conversion to fat (lipogenesis) occurs when glucose intake exceeds metabolic needs. The potential risks associated with this process are two-fold: accumulation of the newly synthesized fat in the liver, and aggravation of respiratory acidosis resulting from increased CO_2 production, although whether these are clinically relevant in PN-fed infants is uncertain. In addition, hyperglycemia in ELBW infants is a risk factor for late onset sepsis, mortality and the risk of developing advanced NEC.[62] A rapid increase in plasma glucose concentration precedes development of NEC,[63] and infants with established NEC have both a high prevalence of hyperglycemia and a worse outcome if hyperglycemic.[64]

Lipids provide an energy-dense (9 kcal/g of fat), isotonic alternative to glucose as an energy source for PN, which also prevents essential fatty acid deficiency and facilitates provision of fat soluble vitamins. Combined infusion of glucose and lipids confers metabolic advantages over glucose, because it lowers the metabolic rate and increases the efficiency of energy utilization.[65,66] There is a close interdependence of carbohydrate and lipid infusion rates on the one hand, and net fat deposition or oxidation on the other (Fig. 13.4). When the intake of glucose calories exceeds 18 g/kg per day (i.e. resting energy expenditure), net fat oxidation is minimal regardless of fat intake, and net fat synthesis takes place.[67] At a carbohydrate intake of 15 g/kg per day, the proportion of energy metabolism derived from fat oxidation does not

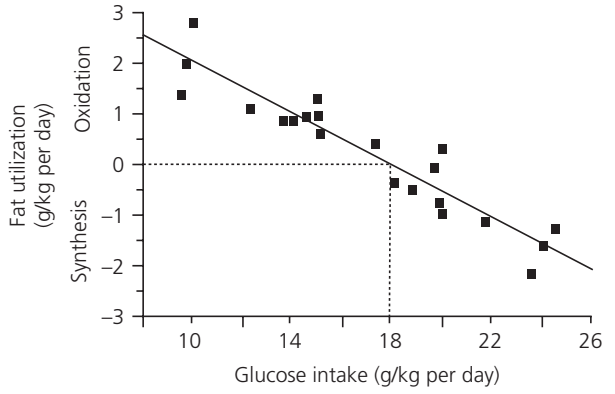

Figure 13.4 Linear relationship between glucose intake and fat utilization ($r = -0.9$; $p < 0.0001$). Lipogenesis is significant when glucose intake exceeds 18 g/kg per day. From Pierro *et al. Proc Nutr Soc* 1993; **52**: 237A with permission from the publisher, Cambridge University Press.[67]

exceed 20%, even with a fat intake as high as 6 g/kg per day. At a carbohydrate intake of 10 g/kg per day this proportion can be as high as 50%.[67] However, lipid utilization is often low and unpredictable in neonates and, consequently, lipids are usually introduced slowly, especially in premature neonates.[68]

The most commonly used fat emulsions for PN in pediatrics are based on soybean oil, in which the lipid is present as long-chain triglycerides (LCT). LCT require carnitine for their oxidation, and as decreased carnitine levels have been found in parenterally fed neonates,[69,70] supplementation has been recommended by some groups. However, carnitine levels have to fall extremely low before fat oxidation is impaired,[71] and a systematic review found no evidence to support the routine supplementation of parenterally fed neonates with carnitine[72] and although one subsequent trial found a beneficial effect of carnitine on catch-up growth,[73] others have found no significant benefits.[74,75] Medium-chain triglycerides (MCT), which do not require carnitine for their oxidation, can increase net fat oxidation without increasing metabolic rate when used to partially replace LCT.[76] Although there have been recent suggestions that MCT/LCT mixtures may improve essential fatty acid status (by protecting essential fatty acids from oxidation),[77] no randomized controlled trials (RCTs) comparing clinical outcomes between LCT and MCT/LCT in neonates are available. Although there is also interest in alternative lipid emulsions containing structured triglycerides (in which medium-chain and long-chain fatty acids are on the same triglyceride molecule), olive oil-based[78] and fish oil-based emulsions, no outcome-based RCTs in neonates on PN have been published.

AMINO ACIDS

In contrast to healthy adults who exist in a state of neutral nitrogen balance, infants need to be in positive nitrogen balance in order to achieve satisfactory growth and development. Preterm infants who are receiving glucose alone lose protein quickly (at the rate of 1–2% body protein per day), so should start to receive at least 1–1.5 g/kg per day amino acids parenterally if not receiving EN.[80] Infants are efficient at retaining nitrogen, and can retain up to 80% of the metabolizable protein intake on both oral and i.v. diets.[81] Protein metabolism, and deposition of body protein for growth, is dependent upon both protein and energy intake, so that above an energy intake of 70 kcal/kg per day, the major determinant of nitrogen retention in preterm infants is the amino acid intake.[81] The PN amino acid requirement of term newborn infants is between 2.5 and 3.0 g/kg per day, which allows for accretion of body protein.[82] Complications like azotemia, hyperammonemia, and metabolic acidosis have been described in patients receiving high levels of i.v. amino acids[83] but are rarely seen with amino acid intake of 2–3 g/kg per day.[84] In patients with severe malnutrition or with additional losses (i.e. jejunostomy, ileostomy), protein requirements are higher.[85] The nitrogen source of TPN is provided as a mixture of amino acids, and mixtures specifically formulated for neonates are available. However, the ideal amino acid composition for term and preterm infants is uncertain. As well as the amino acids usually considered essential for adult humans, histidine is considered essential for infants, and the following amino acids have all been considered 'conditionally essential' for neonates: arginine, cysteine, glutamine, taurine, and tyrosine.[86]

Cysteine is unstable in amino acid mixtures, but is central to sulfur amino acid economy and for glutathione synthesis. It is not certain whether newborn infants, especially those born prematurely, are capable of adequate rates of cysteine synthesis.[86] A meta-analysis of available trials in PN-fed neonates suggested that although cysteine supplementation may improve nitrogen balance, there were insufficient data to evaluate the risks of cysteine addition, such as metabolic acidosis.[87]

Like cysteine, glutamine is excluded from PN amino acid mixtures because of poor stability, although it can now be added as a dipeptide. Glutamine is important for the immune system and the intestine, as well as being essential as a nitrogen-carrier between organs. It has been hypothesized that glutamine supplementation to parenterally fed neonates would decrease the incidence of infection and decrease to time to full enteral feeding. Two small studies examined the effects of PN glutamine supplementation in premature infants and found decreased duration of ventilation and decreased incidence of sepsis.[88,89] However, a larger study in premature infants[90] found no benefit of glutamine supplementation. One RCT[91] in surgical infants found that parenteral glutamine supplementation had no significant effect on intestinal permeability or nitrogen balance, although this study was not powered to detect differences in clinical end points such as incidence of sepsis or duration of PN.

Arginine has also been considered conditionally essential to the neonate[86] and studies have shown low plasma arginine in infants with NEC.[92–94] Supplementation of PN, followed by EN, with arginine decreased the incidence of NEC in an RCT,[95] and recently it has been suggested that infants who have genetic polymorphisms that cause lower arginine levels have an increased susceptibility to NEC.[96]

Tyrosine synthesis from phenylalanine may be impaired in neonates,[82,86] and the measured tyrosine requirement for

neonates is much greater than is available in current neonatal amino acid mixtures, due to poor solubility.[97]

Taurine is a non-protein forming amino acid that has roles in the immune system, as an osmolyte, and in retinal and neurological function, and for bile acid conjugation.[98,99] Neonates on PN may have poor taurine status due to poor renal reabsorption, impaired activity of synthetic enzymes, and low levels of cysteine, the immediate precursor for taurine.[99] Plasma taurine status of preterm infants has now also been suggested to affect neurodevelopmental outcome.[100] Despite the lack of strong evidence from RCTs, most PN amino acid mixtures for neonates now contain taurine. This has been suggested to decrease the incidence of cholestasis in infants on PN.[101]

MINERALS, VITAMINS, AND TRACE ELEMENTS

Minerals, vitamins, and trace elements are important structurally, as cofactors, or as components of enzymes, and provision of adequate supplies is important for the growing neonate. Fe, Ca, P, and Mg should all be provided in adequate amounts for growth and development, but conversely, can cause problems if provided in excess of needs or if their metabolism is impaired. In addition, administration of adequate amounts can be problematic, because of lack of stability in solution or lack of compatibility with other components. Consequently, iron is often only supplemented in longer-term PN[102] whereas calcium and phosphate supply depends on solubility in PN mixtures.[102] Vitamins and trace elements are particularly important in maintenance of the body's antioxidant defences: vitamins C and E, selenium (for glutathione peroxidase), copper, zinc, and manganese (all for superoxide dismutases), chromium, iodine, and molybdenum can all be added to PN. However, for many of these, the precise requirements are not known. Although there is evidence that selenium supplementation may be beneficial, selenium status varies widely geographically, so global recommendations are difficult.[103] It is suggested that if the duration of PN is less than 4 weeks, of the trace elements, only zinc needs to be added.[102,104] There is little specific evidence for individual vitamin requirements, and the current recommendations are to continue with the available vitamin mixtures, which do not appear to cause toxicity or deficiency in the majority of neonates.[104,105] Free radical production and lipid peroxidation will be considered in more detail below.

Complications of parenteral nutrition

INFECTIOUS COMPLICATIONS

In spite of significant improvement in the management of PN, including the introduction of nutrition support teams, infection is still a major problem. In a recent prospective study, we found that around 50% of surgical neonates on PN have at least one suspected episode of sepsis, with around 25% of surgical neonates having at least one positive blood culture.[106] This may lead to impaired liver function,[107,108] critical illness, and removal of central venous catheters. Although catheter-borne infections, which can be reduced by rigorous precautions, are important,[109] microbial translocation from the intestine is also a significant source of infection in surgical infants of PN.[107,108] In a study on surgical neonates on PN[107] all but one episode of microbial translocation occurred in patients with elevated serum bilirubin (cholestasis). Pierro *et al.* have reported that almost half the surgical infants on PN develop abnormal flora and that all cases of septicemia were preceded by gut colonization with abnormal flora.[108] PN itself also impairs neonatal host defences[110] but minimal enteral feeding may help to prevent this.[111] Important factors in reducing the incidence of septic complications are placing i.v. catheters under strict aseptic conditions, preparing the parenteral nutrition solutions in pharmacy in aseptic conditions, and using meticulous care when the catheters are used. Sepsis should be suspected when infants on PN present clinical features of generalized inflammation including one or more of the following features: temperature instability, poor perfusion, hypotension, lethargy, tachycardia, respiratory distress, and fever. In these neonates, blood culture should be performed from the central venous line and/or from a peripheral vein.

METABOLIC COMPLICATIONS

The metabolic complications most frequently observed in newborn infants receiving PN are listed in (Box 13.1). These complications are related to inappropriate administration

Box 13.1 Metabolic complications of parenteral nutrition

Carbohydrate administration
- Hyperglycemia
- Hypoglycemia
- Fatty infiltration of the liver
- Hyperosmolarity and osmotic diuresis
- Increased CO_2 production

Protein administration
- Hyperammonemia, azotemia
- Abnormal plasma amino acid profiles
- Hepatic dysfunction
- Cholestatic jaundice

Fat administration
- Hyperlipidemia
- Fat overload syndrome
- Displacement of albumin-bound bilirubin by free fatty acids
- Peroxidation and generation of free radicals

Fluid administration
- Patent ductus arteriosus
- Pulmonary edema

Electrolyte imbalance
- Sodium, potassium, chlorine, calcium, phosphate

Trace element and vitamin deficiency

of nutrients, fluid, electrolytes, and trace elements or to the inability of the individual patient to metabolize the i.v. diet.

Hyperglycemia occurs frequently during the course of PN, particularly while the glucose concentration of the infusate is being increased, but most patients will produce adequate endogenous insulin to metabolize the carbohydrate load within hours. Hyperglycemia can also be a sign of impending infection, and has also been associated with development of NEC. The treatment of symptomatic hyperglycemia is usually reduction of the infusion rate, but exogenous insulin is sometimes given to ELBW infants with glucose intolerance.[112] Hypoglycemia usually results from sudden interruption of an infusion containing a high glucose concentration.

High doses of fat or an accidental rapid infusion of fat may lead to fat overload syndrome, characterized by an acute febrile illness with jaundice and abnormal coagulation and respiratory problems[68,113] and so lipids are usually advanced slowly, with close monitoring of triglyceride levels, especially in neonates with respiratory insufficiency or suspected infections.[68] Peroxidation in stored fat emulsions and the generation of free radicals during i.v. infusion of fat in premature infants have been reported.[114] However, the degree of free radical production is linked to the rate of lipid oxidation, as we have shown that a reduction in the carbohydrate to fat ratio in PN diet will result in increased oxidation of administered fat and a decrease in free radical-mediated lipid peroxide formation (Fig. 13.5).[115] It is interesting to note that the decrease in malondialdehyde (an index of lipid peroxidation) accompanying increased fat utilization was of a similar magnitude to that observed when the fat infusion was discontinued. Therefore, it is not necessary to discontinue the infusion of fat to reduce the production of oxygen-derived free radicals. Manipulation of the carbohydrate to fat ratio therefore may be a powerful tool in changing the metabolism of fat infusions to mitigate their toxic effects while allowing continued administration.

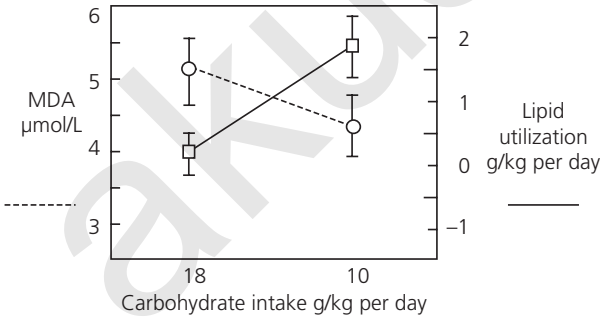

Figure 13.5 Free radical production (assessed as plasma malondialdehyde, MDA, concentration) in response to different carbohydrate contents of PN. Data redrawn from Ref. 115.

Mechanical complications

Mechanical complications related to the i.v. infusion of nutrients are not uncommon. Box 13.2 lists the mechanical complications reported in the literature. Extravasation of PN solution is a common complication of peripheral PN. Unfortunately, even a low osmolarity solution is detrimental for peripheral veins leading to inflammation and extravasation of the solution, which can cause tissue necrosis and infection. Extravasation injury is treated with occlusive dressings or hyaluronidase irrigation, but there is little evidence base for the best treatment in neonates.[116] Intravenous lines may become clogged from thrombus formation, calcium precipitates, or lipid deposition. There is disagreement on the ideal position of central venous lines (CVL) for PN in infants. Some authors advocate the atrium as the ideal position because this would give less chance of catheter dysfunction, whereas others believe that placement in the superior vena cava would reduce the risk of perforation. The current ESPGHAN/ESPEN recommendations are that the catheter tip should lie outside the atrium,[53] but because complications of either approach are very rare (albeit potentially life-threatening), there is a paucity of evidence from RCTs.

Box 13.2 Mechanical complications of parenteral nutrition

Extravasation of parenteral nutrition solution
Blockage of the central venous line
Migration of the central venous line
Breakage of the infusion line
Right atrium thrombosis
Cardiac tamponade (perforation of right atrium or vena cava)

Hepatic complications

The hepatobiliary complications related to PN remain serious and often life-threatening. The most common hepatobiliary complication of PN in neonates is cholestasis. The incidence of parenteral nutrition-associated cholestasis (PNAC) depends on the length of time on PN, so that PNAC occurs in up to 50% of infants receiving PN for at least two months.[117] Although the frequency of this complication seems to be diminishing,[118] this is probably related to the early initiation of oral feeding rather than to an improvement in the i.v. diet. The etiology of cholestatic jaundice in infants requiring PN is still unclear. However, infants requiring long-term PN still develop progressive jaundice, commonly preceded by elevation of biochemical nonspecific tests of hepatic damage, function, and excretion.

Various clinical factors are thought to contribute to the development of PNAC. These include prematurity, low birth weight, duration of PN, immature enterohepatic circulation, intestinal microflora, septicemia, failure to implement enteral nutrition, short bowel syndrome due to resection, and number of laparotomies (reviewed[119]). In addition to the effects of extremely low birth weight, and length of time on PN, infants receiving PN for either gastroschisis or jejunal

atresia seem to be at particular risk.[120] PNAC has a higher incidence in premature infants than in children and adults. This may be due to the immaturity of the biliary secretory system since bile salt pool size, synthesis, and intestinal concentration are low in premature infants in comparison with full term infants.[121] PNAC is a diagnosis of exclusion without any specific marker yet available. Therefore, infants with cholestasis (conjugated bilirubin >2.0 mg/dL) who are receiving or have received PN must have an appropriate diagnostic evaluation to exclude other causes of cholestasis, such as bacterial and viral infections, metabolic diseases (e.g. alpha-1-antitrypsin deficiency, tyrosinemia), and congenital anomalies (e.g. Alagille syndrome, biliary atresia, choledocal cyst).[122] The cholestasis is progressive unless PN is ceased and enteral feeding introduced. Hepatosplenomegaly and severe jaundice are characteristic features of the advanced disease, and portal hypertension may develop. Although PNAC resolves with time after discontinuation of PN, this is not possible in many patients with short bowel, and in these patients, cholestasis is the strongest predictor of mortality.[123]

The etiology of PNAC remains unclear. Possible causes include the toxicity of components of PN, lack of enteral feeding, continuous non-pulsatile delivery of nutrients and host factors, infection, and sepsis.[119] Risk factors are listed in Box 13.3. Most of the components of PN have been implicated in the pathogenesis of cholestasis. Hepatic damage from the components of i.v. diet may result from excessive trace element administration (e.g. aluminum and manganese), deficient amino acid administration (e.g. lack of taurine for bile acid conjugation[101]), or may be related to impurities present in PN lipid.[124,125]

The clinical care of infants and children who require PN and develop progressive jaundice represents a real challenge, compounded by this lack of knowledge. Prevention of PNAC is based on the early usage of enteral feeding and on the administration of i.v. feeding only when appropriate and necessary. In most patients the cholestasis resolves gradually as enteral feedings are initiated and PN is discontinued. It has been shown that minimal bolus enteral feeding (1 mL/kg) during PN in premature infants induces significant gallbladder contraction and after 3 days of starting minimal enteral feeds, the gallbladder volume returns to normal.[126] Unfortunately, as a consequence of gut dysfunction, enteral feeding is often not feasible. Maini *et al.*[127] suggested that cycling the PN may diminish cholestatic hepatic changes in adults. This may explain the less frequent liver disease in children receiving their PN cyclically at home. Experience with this technique in premature infants is extremely limited but encouraging.[128,129] Rebound hypoglycemia is a common complication of this approach. Modification of the PN constituents has been proposed but no prospective trial has demonstrated any benefit in reducing or changing the intake of nutrients.

Box 13.3 Patient risk factors for the development of parenteral nutrition–associated cholestasis

Age
Prematurity
Immaturity of biliary secretory system
Absence of oral/enteral intake
Septicemia
Bacterial overgrowth in the small bowel
Short bowel length
Necrotizing enterocolitis
Hypoxia
Major abdominal operations
General anesthesia

Several reports have described the attempts to use drug therapy to treat or prevent PNAC. Cholecystokinin has been administered to diminish gallbladder stasis and promote bile flow, and has been shown to be effective in preventing stasis and sludge in the gallbladder in a randomized, double-blind controlled trial in adults receiving PN.[130] However, despite promising pilot studies in neonates,[131,132] cholecystokinin was shown not to be effective in preventing PNAC in a randomized, double-blind, controlled trial in 243 neonates receiving PN.[133] Ursodeoxycholic acid can be used in infants and children on PN to correct the decreased secretion of endogenous bile acids. Ursodeoxycholic acid is non-toxic and acts as a natural bile acid after conjugation. Although ursodeoxycholic acid has shown beneficial effects in treatment of children with established PNAC, there have only been limited trials of ursodeoxycholic acid,[134] or the related compound tauroursodeoxycholic acid, in the prevention of PNAC in neonates, neither of which showed a benefit. In a multivariate analysis of the same patients enrolled in the neonatal cholecystokinin trial described above, it was suggested that the presence of taurine in the PN amino acid solution protects against the development of cholestasis.[101] However, most pediatric-specific amino acid solutions now contain taurine, and it is unknown whether supplementation with additional taurine would have any benefit. Recently, much interest has been shown in the use of fish oil-based (omega-3 containing) lipid emulsions in the prevention of PNAC. Two patients who appeared to have a reversal of cholestasis after switching from a soy-based lipid emulsion to a fish oil-based emulsion have been reported,[79] and there have been other anecdotal reports, but until an RCT is performed, the efficacy of fish oil-based emulsions is uncertain.

Cholecystectomy is the treatment of choice for patients with acute and symptomatic cholelithiasis and cholecystitis. Rintala[135] proposed laparotomy and operative cholangiography followed by biliary tract irrigation in patients with progressive cholestatic jaundice not responding to medical treatment. In some patients the hepatic disease may progress to cirrhosis, portal hypertension, and hepatic failure. Bowel lengthening procedures may help transition to EN,[136,137] whereas in those with advanced liver disease and no prospect of enteral autonomy, transplantation may be considered. Isolated liver transplantation, isolated intestinal transplantation, and liver plus intestinal transplant are all feasible in children, and although results are improving, overall outcomes are still poor and organ availability is, of course, a problem.[138]

Enteral nutrition

The energy requirement of an infant fed enterally is greater than the i.v. requirement because of the energetic cost of absorption from the gastrointestinal tract and energy lost in the stools (Fig. 13.2).

FEEDING ROUTES

Alternative feeding routes where neonates are unable to feed orally include naso-gastric or oro-gastric tubes, naso-jejunal tubes, gastrostomy tubes, or jejunostomy tubes. Gastric feeding is generally preferable to intestinal feeding because it allows for a more natural digestive process, i.e. allows action of salivary and gastric enzymes and the antibacterial action of stomach acid. In addition, gastric feeding is associated with a larger osmotic and volume tolerance and a lower frequency of diarrhea and dumping syndrome. Thus, transpyloric feeds are usually restricted to infants: (1) unable to tolerate naso- or oro-gastric feeds; (2) at increased risk of aspiration; (3) with anatomical contraindications to gastric feeds, such as microgastria. Neonates are obligatory nose breathers and therefore oro-gastric feeding may be preferable over naso-gastric feeding in preterm infants to avoid upper airway obstruction. However, naso-gastric tubes are easier to secure and may involve a lower risk of displacement. In infants requiring gastric tube feeding for extended periods (e.g. more than 6–8 weeks) it is advisable to insert a gastrostomy to decrease the negative oral stimulation of repeated insertion of nasal or oral tubes. The tube can be inserted using an open, endoscopic, or laparoscopic approach. In infants with significant gastro-esophageal reflux, fundoplication with gastrostomy tube or enterostomy tube placement is indicated.[139] In preterm infants with gastro-esophageal reflux, enteral feeding can be established via a naso-jejunal tube inserted under fluoroscopy. Naso-jejunal feeding usually minimizes the episodes of gastro-esophageal reflux and their consequences. However, it is common for these tubes to dislocate back in the stomach. Regular analysis of the pH in the aspirate is essential to monitor the correct position of the tube. Feeding jejunostomy tubes can be inserted through existing gastrostomy or directly into the jejunum via laparotomy or laparoscopy.

SELECTION OF ENTERAL FEEDS

Breast milk is the ideal feed for infants because it has specific anti-infectious activities, aids gastrointestinal maturation and neurological development. When breast milk is not available, chemically defined formulae can be used, which are designed either for term infants or specifically for preterm infants. If malabsorption is present and persists, an appropriate specific formula should be introduced. A soy-based disaccharide-free feed is used when there is disaccharide intolerance resulting in loose stools containing disaccharides. For fat malabsorption, a formula containing MCTs should be used. An elemental (free amino acids) or semi-elemental (protein hydrolysate containing di- and tri-peptides) formula may be indicated when there is severe malabsorption due to short bowel syndrome or severe mucosal damage as in NEC. Semi-elemental preparations have the advantage of a lower osmolality, are well absorbed, and have a more palatable taste. Infants recovering from NEC pose a particular problem, as malabsorption may be severe and prolonged. These infants may have had the small bowel resected, in addition to which the remaining bowel may not have healed completely by the time feeds are begun. Feeding may provoke a relapse of the necrotizing enterocolitis and feeding should therefore be introduced cautiously. For persistent severe malabsorption, a modular diet may be necessary. Glucose, amino acid, and MCT preparations are provided separately, beginning with the amino acid solution and adding the glucose and then the fats as tolerated. Minerals, trace elements, and vitamins are also added. These solutions have a high osmolality and if given too quickly may precipitate dumping syndrome, with diarrhea, abdominal cramps, and hypoglycemia. It is important therefore to start with a dilute solution and slowly increase the concentration and volume of each component. This may take several weeks and infants will need PN support during this period.

ADMINISTRATION OF ENTERAL FEEDS

Enteral feeds can be administered as boluses, continuous feeds, or a combination of the two. Bolus feeds are more physiological and are known to stimulate intestinal motility, enterohepatic circulation of bile acids, and gallbladder contraction;[140] continuous enteral feeding leads to an enlarged, non-contractile gallbladder in infants.[141] Contraction is observed immediately after resuming bolus enteral feeds and gallbladder volume returns to baseline after 5 days. Therefore, the mode of feeding has important bearings on the motility of the extrahepatic biliary tree. Bolus feeds mimic or supplement meals and are easier to administer than continuous feeds since a feeding pump is not required. Bolus feeds are usually given over 15–20 minutes and usually every 3 hours; term infants can tolerate a period of 4 hours without feeds before hypoglycemia occurs. In preterm neonates or in neonates soon after surgery, 2-hourly feeds are occasionally given. Where bolus feeds are not tolerated, for example in the presence of gastro-esophageal reflux, continuous feeds should be administered via an infusion pump over 24 hours. This modality of feeding is used in infants with gastro-esophageal reflux, delayed gastric emptying, or intestinal malabsorption. Infants with jejunal tubes should receive continuous feeds and not bolus feeds as the stomach is no longer providing a reservoir.

COMPLICATIONS OF ENTERAL TUBE FEEDING

Enteral tube feeding is associated with fewer complications than parenteral feeding. The complications can be mechanical including tube blockage, tube displacement or migration, and intestinal perforation. Although infection is less of a risk than with PN, the risk of infected enteral feeds should not be ignored.[142] Other complications involve the gastrointestinal tract. These include: gastro-esophageal reflux with aspiration pneumonia, dumping syndrome, and diarrhea. Jejunostomy

tubes inserted at laparotomy can be also associated with intestinal obstruction. The use of hyperosmolar feeds has been associated with development of NEC, dehydration and rarely, intestinal obstruction due to milk curds.[143]

In surgical infants, enteral feeding often results in vomiting, interruption of feeding, inadequate calorie intake, and rarely in NEC. In infants with congenital gastrointestinal anomalies, exclusive enteral feeding is commonly precluded for some time after surgery due to large gastric aspirate and intestinal dysmotility. Therefore, appropriate calorie intake is established initially by total PN. Supplementary enteral feeding is introduced when intestinal motility and absorption improves. The percentage of calories given enterally is gradually increased at the expense of i.v. calorie intake. This transition time from total PN to total enteral feeding could be quite long. The presence of significant gastric aspirate often induces clinicians and surgeons not to use the gut for nutrition. However, minimal enteral feeding can be implemented early in these patients even if its nutritional value is questionable. Minimal enteral feeding may be all that is required to enhance some immunological function. This is supported by studies in animals[144] and infants.[111] Shou *et al.*[144] reported that supplementation of PN with just 10% enteral calories as chew diet improved rat macrophage and splenocyte function. Okada *et al.*[111] have shown that the introduction of small volumes of enteral feed improved the impaired host bactericidal activity against coagulase-negative staphylococci and the abnormal cytokine response observed during total PN. The increase in bactericidal activity against coagulase negative staphylococci after the addition of small enteral feeds in patients on PN was significantly correlated with the duration of enteral feeding. This implies that stimulation of the gastrointestinal tract may modulate immune function in neonates and prevent bacterial infection.

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14

Vascular access in the newborn

SEAN J BARNETT AND FREDERICK C RYCKMAN

INTRODUCTION

Although only a small fraction of all neonates require extensive resuscitation, the large number of births throughout the world ensures that adequate neonatal intensive care facilities remain on the cutting edge of technology. Advancements in monitoring, ventilatory support, vascular access, and maintenance of core body temperature have been paramount in the vast increase in the survival rates of newborns.[1] New innovations in size and materials coupled with new routes of vascular access have been paramount for neonatologists in regards to invasive monitoring, ionotropic support, and total parental nutrition. Invasive monitoring includes both continuous blood pressure measurements and also the ability to obtain arterial blood for up to the minute blood gas measurements for ventilatory support. Smaller catheter size and peripheral central routes have enabled the neonatologist to maximize the use of blood products, electrolytes, drug delivery, and nutrition, especially in those neonates that are unable to tolerate enteral nutrition for long periods of time. These new catheters now allow for smaller and sicker neonates to gain the same advantage that was once only available to larger infants within the intensive care unit.

ARTERIAL CANNULATION

Invasive access to the arterial system has been a mainstay in the monitoring of the critically ill patient for decades. Short-term arterial access has circumvented the need for numerous heel sticks or difficult arterial punctures for blood gas analysis utilized for ventilatory changes. Continuous blood pressure monitoring allows for up to the minute decision-making when using supportive vasoactive medications and can also be used to draw needed blood studies, obviating frequent venopunctures. The majority of these cannulae can be placed by percutaneous insertion techniques at the bedside.

Maintenance

Catheters within the arterial system are particularly prone to thrombosis, which guides their general care. Continuous infusion of a balanced saline solution with heparin (1 unit/mL) at a minimum of 0.5 mL/hour for all arterial lines helps to ensure patency. The type of fluid can be altered, dictated by the clinical situation. Arterial catheters are flushed with 0.5 mL of normal saline over 5 seconds after each blood draw to clear the system.

Blood pressure monitoring devices are connected by three-way stop cocks for ease of blood draws and to ensure sterility. Transducers are leveled to the phlebostatic axis (located at the fourth intercostal space and half the anterior-posterior (AP) diameter of the chest). The system is zeroed with the transducer in this position at the initial set-up, each shift change, and with position change of the transducer. The waveform can become dampened due to microthrombi, positioning, or from mechanical disturbances within the system. Once a waveform appears dampened, all connections are checked and secured, the tubing is evaluated for air within the system (this tends to blunt the actual pressure reading), and the catheter is then irrigated. The infant or catheter can be re-positioned and the limb immobilized if necessary.

Most arterial catheters in infants in our institution are sutured into place to provide stability and promote safety. Transparent dressings (Tegaderm, Opsite) are utilized facilitating inspection of the insertion site while maintaining sterility. The connections, catheter, stitches, and tubing are examined and their status documented every shift to ensure that they are intact. Intravenous fluids are changed every 24 hours and the tubing is changed every 72 hours, utilizing sterile technique. Transducers are changed every 72 hours as well. Nursing assessment of color, pulses, capillary refill, and temperature is documented every 2 hours and the position of deeper indwelling catheters (i.e. umbilical arterial catheters) is documented with x-rays following placement and as indicated.

Complications

Most complications with peripherally inserted arterial catheters arise due to thromboembolic events or vasospasm.[2,3] Treatment is prompt removal at the first sign of blanching of the distal extremities. Further treatment includes the use of heparin or tissue plasminogen activator (TPA) and in rare circumstances surgical removal of clot if extremity tissue viability is compromised. Infectious complications are rare with arterial catheters as long as appropriate measures as described above are followed.

Umbilical artery catheters have a higher risk of thromboembolism, especially when they are placed in the low lying position (L3–L5).[4] The infectious rates are similar to central venous catheter rates.[3] We tend to remove these catheters within 5 days of being placed to help prevent these issues. Studies have also shown that there is no evidence that prophylactic antibiotics are useful with these catheters.[5]

UMBILICAL ARTERY CATHETERIZATION

Cincinnati Children's Hospital Medical Center serves as the regional referral center for neonatal care for southern Ohio, Northern Kentucky, and West Virginia, and for southeast Indiana. As a referral neonatal intensive care unit with no inborn population, the majority of neonates in need of umbilical artery monitoring have had their catheters placed by a referring neonatologist in the initial nursery. There are certain situations which require this invasive type of monitoring, i.e. EXIT procedures and congenital diaphragmatic hernia patients who are either born at our facility or immediately transferred at birth. Whereas this is not a common procedure performed by most pediatric surgeons, the ability to place these catheters is a valuable tool in the invasive monitoring of the critically ill neonate.

One or both umbilical arteries may be cannulated for continuous blood pressure monitoring or for frequent arterial blood gas measurements for complex ventilator management. Resuscitation fluids and medications can be delivered via these cannulae in urgent situations but are best infused using venous access sites discussed later in this chapter.

Access technique

Catheter length should be established prior to initiating the procedure using standardized graphs, which utilize the shoulder to umbilical cord length in centimeters to estimate the position of the catheter.[6] Calculations can also be performed using birth weight (BW) to estimate the desired position of the catheter (high T6–T9, low L3–L5), such as those described by Shukla and Ferrara:[7]

$$\text{Low catheter position UA length (cm)} = \text{birth weight (kg)} + 7$$

$$\text{High catheter position UA length (cm)} = (3 \times \text{BW (kg)}) + 9$$

Since this may not be accurate in very low birth rate infants, Wright *et al.*[8] suggest using the formula UA length (cm) = (4 × BW (kg)) + 7 for those infants less than 1500 g for a high lying position. We generally attempt to place umbilical artery catheters (UACs) in the high lying position to theoretically decrease the rates of thrombosis and intestinal ischemia given previous studies.[4] In all cases, an abdominal x-ray is used to check the catheter position prior to the completion of the procedure (Fig. 14.1).

Standard umbilical catheters measure 3.5 Fr (premature) to 5 Fr (full-term) and can be purchased from various manufacturers. The infant is generally placed under a radiant warmer with the surgeon donning standard sterile equipment. The umbilical stump and surrounding abdominal skin is prepped with a surgical prep solution and the field draped. A minor instrument set including forceps, hemostats, and needle drivers is all that is needed for catheter placement. Appropriate fluids should be available to infuse into the catheter upon gaining access. We prefer to use one-quarter normal saline with heparin (1 unit/mL) to keep the line patent. The catheter should be flushed with sterile saline prior to insertion. The umbilical stump is grasped and umbilical tape is used to encircle the stump below the skin level to prevent bleeding. The stump is cut with care to leave adequate length for ease of manipulation during placement. One umbilical artery is identified, the vein is normally larger and thin walled and the arteries are small, thick walled and

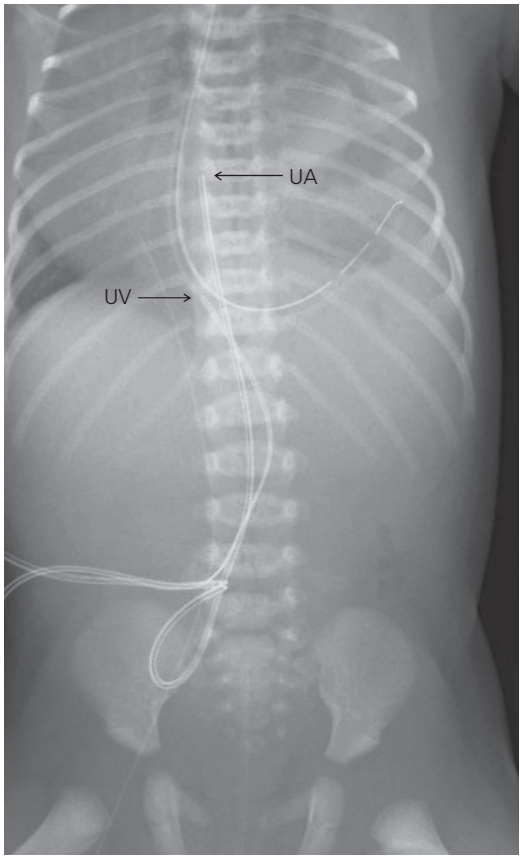


Figure 14.1 X-ray of high lying umbilical artery catheter (UA) and umbilical vein catheter (UV) in desired position.

normally are two in number, and gently dilated with either a hemostat or forceps. Either a 3.5 Fr (infants less than 2 kg) or 5 Fr (those greater than 2 kg) previously flushed catheter is then passed into the lumen with gentle traction applied to the umbilical stump. Blood return is usually encountered when the catheter enters the iliac artery. The catheter is then advanced to the desired position and secured with suture through the substance of the cord. X-rays can be used to confirm position prior to breaking sterile conditions to allow for manipulation. The desired fluids and measurement devices are then secured to the catheter by way of a three-way stopcock mechanism or manifold.

ALTERNATIVE METHOD FOR CANNULATION

At times the umbilical cord is too short or dry to allow for easy cannulation. Access to both umbilical arteries can be achieved through an infraumbilical incision and blunt dissection through the subcutaneous tissues. Once the umbilical arteries are encountered, proximal and distal control can be gained by silk or vicryl sutures. The artery can be accessed by making a transverse arteriotomy through the anterior half of the artery allowing direct catheter passage. The distal control suture is tied to secure the artery and catheter. The incision can be closed with interrupted suture and a sterile dressing applied.

RADIAL ARTERY CANNULATION

The most common site for arterial access is the radial artery. It provides a site that is ideal to access due to its consistent anatomical relationships, collateral blood flow, and this location can be easily maintained by the nursing staff. Most radial arterial lines can be placed percutaneously, which helps to maintain sterility and allows for potential re-cannualization in the future. In rare instances, a cut-down technique is required for direct access to the artery.

Access technique

Collateral circulation of the hand should always be assessed (Allen test) and documented prior to radial or ulnar artery access attempts. Blanching or cyanosis of the fingers or hand should preclude placement. The radial artery can be palpated medial to the styloid process of the radius along the proximal wrist crease. The infant's forearm is placed on an arm board with the wrist dorsiflexed approximately 30–45° (Fig. 14.2). The wrist is then prepped (betadine solution) and draped in a sterile fashion. Local anesthetic can be used but will sometimes obscure the radial pulse and is generally avoided. A 22 or 24 Fr needle catheter is inserted at approximately a 20° angle until blood can be seen within its hub. The catheter tip is then gently advanced into the vessel while removing the needle. If resistance is met, a small guidewire (Cook 0.15″ fixed core guidewire) can be passed into the catheter to aid in manipulation and to allow easier advancement. A T-piece connector and stopcock are then attached to the catheter and it is flushed to ensure patency. The arterial line is then stitched into place and dressed with a transparent dressing (Tegaderm, Opsite).

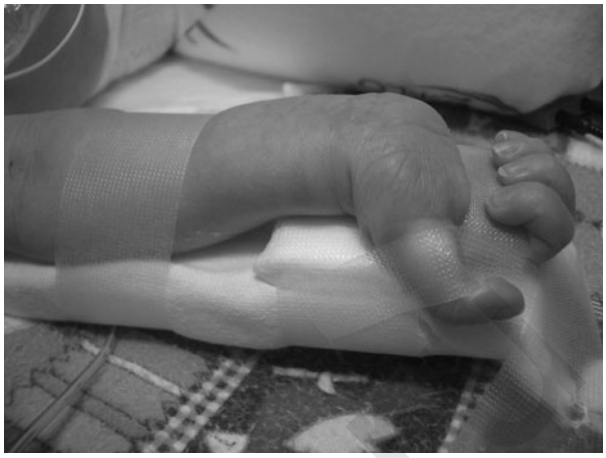


Figure 14.2 Positioning for radial arterial catheter.

If a cut-down approach is necessary, a small transverse incision can be made proximal to the joint over the point of maximal impulse. Blunt dissection is usually all that is necessary parallel to the vessel course for adequate exposure. Once exposure is obtained, proximal and distal control is secured with silk or vicyl suture ties. Once again a 22 or 24 Fr catheter is used to gain percutaneous access with gentle traction on the distal control suture. A guidewire (Cook 0.15″ fixed core guidewire) can also be useful in this setting to guide the catheter into place once blood is obtained within the hub. Backflow of arterial blood ensures successful placement. Distal vascular occlusion to prevent back bleeding is generally not necessary and the control sutures can be removed following the procedure. The skin site is then closed with interrupted sutures and the catheter is sutured into place at the skin level. The catheter is then dressed and accessed in a similar manner as earlier described.

PEDAL ARTERIAL CANNULATION

The next most commonly used sites for arterial cannulation are the posterior tibial and dorsalis pedis arteries. Once again, these sites allow for collateral blood flow and easy maintenance. Access can be obtained percutaneously or by cut-down. The anatomical relationship of the posterior tibial artery posterior to the medial mallelous provides an easy site for surgical access. Insertion techniques are similar to those described for the radial artery. The line is then immobilized in a similar manner.

AXILLARY AND FEMORAL ARTERIAL CANNULATION

These sites are generally reserved for emergent situations where peripheral arterial pulses are weak and access is unobtainable. The high risk of vasospasm and embolization

to the extremities and minimal collateral blood flow preclude their everyday use. In an urgent situation that these lines are required, they should be removed as soon as clinically possible.

Percutaneous access can be obtained via the axillary artery with the arm extended beyond the horizontal and midway through its course. A guidewire is generally not needed for this catheter placement. Access to the femoral artery can be gained below the inguinal ligament, also by percutaneous methods. Guide wires are generally used to ensure correct position within the iliac artery. They are secured in a similar manner to the peripherally placed lines.

VENOUS CANNULATION

The ability to gain venous access in newborns has been available for decades and allows neonatologists and surgeons the ability to provide consistent vascular access to deliver critical care. New catheter materials including plastic and silicone allow for small bore devices and the cannulation of the smallest of veins. Temporary peripheral access can be easily obtained in the newborn at the bedside with 24 Fr angio catheters or by umbilical vein catheterization. This access, however, is temporary and often central i.v. access is needed for long-term parental nutrition or vasoactive medication drips.

New access methods including peripheral intervenous central catheters (PICC) are now the mainstay for central venous access in the neonatal intensive care setting. The ability to insert these catheters at the bedside, coupled with decreased expense and rapid insertion times, have significantly decreased the need for both cut-down and umbilical catheter access in these babies. Opportunities still arise when a PICC line is unable to be placed, is of insufficient size to accommodate all of the needs of the patient, or emergency resuscitation dictates the need for expedited central venous access. It is imperative for the pediatric surgeon to be skilled in all these access modalities.

Maintenance

Many hospitals have established designated central line teams to manage the everyday care of central venous catheters. The neonatal intensive care unit at Cincinnati Children's Hospital Medical Center is no exception and utilizes care teams as well as the bedside nurse to provide consistent daily cares for central venous catheters.

Umbilical vein catheters are cared for in a similar manner as described earlier for umbilical artery catheters. Fluids are maintained at a minimum of 1.0 mL/h to ensure line patency. Lines are flushed in a similar manner and the length and position of the catheter is documented with x-rays after the initial placement (ideal placement is at the junction of the inferior vena cava (IVC) and the right atrium) and their length checked every shift by the bedside nurse. Connections are checked hourly and padded hemostats are available at the bedside for accidental disconnections. All fluids and tubing are changed in similar manner to UACs. Discontinuation of either the UAC or umbilical venous catheters (UVCs) is performed by the physician, nurse practitioner, or qualified bedside nurses. Only 3–5 minutes of firm pressure is needed to maintain hemostasis.

Percutaneous and tunneled catheters are maintained in a similar manner. Access to the central venous catheter (CVC) via the hub, cap, or manifold is preceded by a 30 second scrub and 30 second air dry time with 2% chlorhexidine gluconate with isopropyl alcohol (ChloraPrep). Heparin volumes for unused ports vary depending on the size of the line. We utilize the Biopatch protective disk (Ethicon) to cover and surround all insertion sites for CVCs. This disk and dressing is changed at a minimum of every 7 days or if the site appears erythematous, or the dressing is compromised. The site is cleansed with a 30 second ChloraPrep or 60 second Providone scrub. A new Biopatch and transparent dressing (Tegaderm or Opsite) is then applied after the site has completely dried. All CVCs are checked hourly and documented by the bedside nurse. Each shift the nurse documents the position of any sutures, skin integrity, redness or induration, the position of the cuff in tunneled lines, occlusiveness of the dressing, changes in the extremity, and any site pain or discomfort. Cut-down sites are maintained in a similar manner. Although uncommon, interosseous (IO) needle sets can be placed in an emergency situation but are removed within 24 hours of placement. Providone soaked gauze is placed around the insertion site and is changed every 2–3 hours or when the gauze is dry. Particular attention is paid to the hemodynamic status of the limb for any signs of compartment syndrome.

Complications

Complications associated with central lines are numerous but most can be avoided with careful placement techniques and nursing care. Pneuomothorax, chylothorax, lung injury, malposition of the line, and perforation of the vessel are but a few of the many issues that can arise during the initial placement.[9] Cardiac arrhythmias can occur due to stimulation of the endocardium in those patients whose line is placed deeper than the superior vena cava/right atrial junction. This can be avoided in most cases by using fluoroscopy when placing subclavian or jugular venous access lines. Tunneled line expulsion is very uncommon when using Dacon cuffed tunneled lines.

Neonates in particular are susceptible to thrombosis near the catheter tip of CVCs given their small vessel. Even with continuous heparin infusion, up to 30% of neonates with CVCs have some form of thrombosis detected.[10,11] Most episodes of thrombosis are asymptomatic and generally present as inability to flush or withdraw blood from the CVC. Tissue plasminogen activator (TPA) can be utilized to remove clot build-up on the catheter tip. This is usually successful and can be repeated for stable clots. Continued build-up of clot demonstrated by ultrasonography may necessitate removal of the line. One should be wary of removing lines in neonates unless the child is symptomatic due to the relative difficulty in placing and maintaining these

lines. Rarely do neonates require heparin therapy following removal.[12]

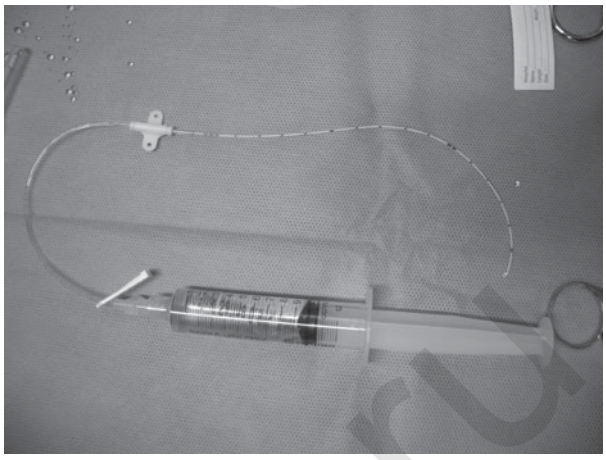
The most common complication of any central catheter is infection. Documented rates as high as 29% are seen in neonates, with smaller infants at greatest risk.[11,13] Differences in infection rates can be attributed to differences in patient populations and practice guidelines.[11] Coagulase-negative staphylococci continue to be the most common cause of central line infection and bacteremia. Numerous other bacteria, including Gram-negatives, anaerobes, and *Candida* species, can cause line infection, especially in the post-surgical neonate. Although many authors advocate treatment with antibiotics for the clearance of central line infection, removal of the foreign body (CVC) associated with the infection may be needed in refractory cases. PICC lines can be inserted as a bridge to replacement of more permanent access during antibiotic treatment of the bacteremia. Insertion site infections can generally be treated with antibiotics alone and do not require removal of the catheter unless bacteremia is documented. With careful guidelines for the placement and maintenance of these catheters, very low infection rates can be achieved.

PERIPHERALLY INSERTED CENTRAL CATHETER

The majority of centrally placed lines in our neonatal unit are PICC lines. These are quickly placed by specially trained nursing personnel, radiologists, or pediatric surgeons at the bedside with little to no sedation. The catheters are made of silicone or polyurethane and come in sizes as small as 2 Fr (Vygon Corp, Ecouen, France) (Fig. 14.3). In contrast, the smallest surgically placed lines are usually 3 Fr catheters. This small size allows for placement in neonates as small as 500 g. Although the initial experience with PICC line placement used fluoroscopy for all cases,[14] this is now generally reserved for those infants who have failed multiple attempts at bedside placement.

Access technique

Sterile technique is maintained throughout the procedure. After the appropriate site is chosen (antecubital, saphenous, or scalp veins) the catheter is flushed with heparinized saline, 2 unit/mL. The proposed length of the catheter is then measured. The site is cleansed with a surgical prep, draped sterially, and a tourniquet is applied. The introducer needle set is then inserted into the vein with return of blood flow confirming position. The catheter is then advanced through the peel-away introducer in 1 cm increments to the premeasured length (Fig. 14.3). The catheter can be flushed with normal saline to facilitate insertion. Once the desired length is reached, blood is aspirated and the line is flushed with heparinized saline. The breakaway needle is released and a securement device is placed. Steri-strips are applied and a Biopatch placed over the insertion site with a transparent dressing as a covering. A chest x-ray confirms the position of the catheter tip.



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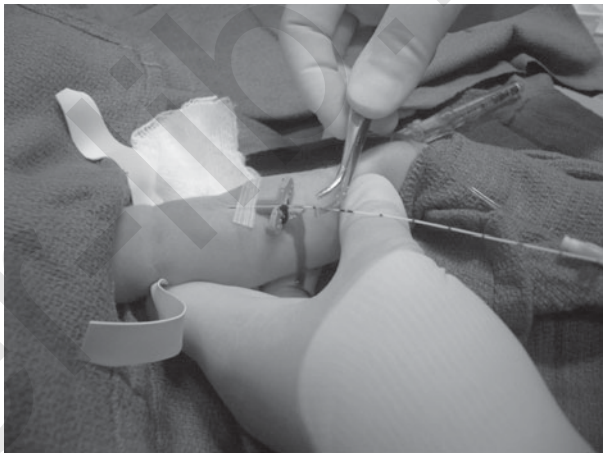


(b)

Figure 14.3 (a) 2 Fr, single lumen, PICC line (Vygon Corp). (b) Advancement of PICC line into sheath.

UMBILICAL VEIN CATHETER

The majority of UVCs are placed by neonatologists at outside facilities prior to transfer. These lines can be used for emergency medications, fluids during resuscitation, transfusions, and longer-term central access for i.v. fluids. The complications are similar to other central venous catheters but do have an increased risk of infectious complications of the liver and heart.[3] The generally accepted optimal position for UVC placement is the tip at the level of the IVC right atrial junction. Cardiac arrhythmia can occur with placement of the UVC within the heart itself and is the most common complication during insertion. Cardiac perforation with pericardial tamponade and subsequent demise has been reported with deep insertion.[15] Hepatic necrosis and portal hypertension can occur with placement into the portal system.

Access technique

The placement of the UVC catheter is similar to the previously described placement of the umbilical artery

catheter. A 3.5 or 5 Fr catheter is used to gain access to the single umbilical vein. Catheters are advanced gently usually only 1–2 cm beyond the point of blood return (generally only about 5 cm in a term infant). X-rays confirm the position of the catheter, preferably at the level of the diaphragm (Fig. 14.1). The catheter is maintained similar to the umbilical artery catheter.

Access can also be gained in emergency situations in the operating theater in the newborn by a supraumbilical incision with gentle dissection and cannulation of the ductus venosus. This site is usually only viable for a few days prior to closure.

PERCUTANOUS CANNULATION

Multiple sites can be utilized for the percutaneous introduction of central venous catheters, including the internal jugular veins, subclavian veins, and femoral veins. Although these can be placed at the bedside in extreme conditions, they are more safely placed in the operating room under general anesthesia with ultrasound or fluoroscopic guidance. The technique of ultrasound-guided placement of central venous lines is particularly effective for the internal jugular vein[16] and is a helpful technique at any age. The improved safety with this placement technique is quickly establishing this as best standard practice. We utilize fluoroscopy liberally while placing any centrally dwelling catheter in the operating room. This not only helps to confirm placement but also allows direct vision while dilating vessels and advancing catheters into the correct position with the Seldinger technique.

Access technique

Percutaneous access for central line placement is accomplished by the use of the guidewire (Seldinger) technique. The patient is placed supine on the operating table and a small towel roll or bump is placed under the infant's shoulders to extend the neck with the head midline. Both sides of the neck and chest are prepped and draped in the standard fashion. The patient is then placed in the Trendelenburg position. The two standard infant-sized Broviac catheters in our facility are the 2.7 and 4.2 Fr single lumen catheters (Bard, Salt Lake City, UT, USA). Temporary 4 Fr double lumen catheters are also available (Cook, Arrow). We prefer for the child to be at least 10 lbs before placing a double lumen catheter, given its size. Standard introducer sets contain introducer needles, guidewires, and introducer sheaths with dilators. In the central approach for internal jugular venous access, the vein lies at the apex of the sternal and clavicular heads of the sternocleidomastoid muscle. Ultrasound guidance is particularly useful in identifying the vein. Once the vein has been accessed and the guidewire placed, fluoroscopy is utilized to confirm position. A site on the chest is chosen and the catheter is tunneled from this site to the insertion site. We prefer to use live fluoroscopy to pass the dilator sheath complex over the guidewire and to measure the appropriate length of the catheter. The dilator and guidewire are then removed and the catheter is placed via the peel-away sheath and into position. The final position of the line is confirmed with fluoroscopy. Incisions are closed and a Biopatch and transparent dressing are applied. This same technique can be used for percutaneous femoral vein catheterization. Subclavian vein access can be facilitated by ultrasound guidance, but the technical considerations are more difficult given the location of the clavicle. Generally, the landmarks of the mid angle of the clavicle and the sternal notch are used for subclavian venopuncture with fluoroscopy used in a similar manner as described.

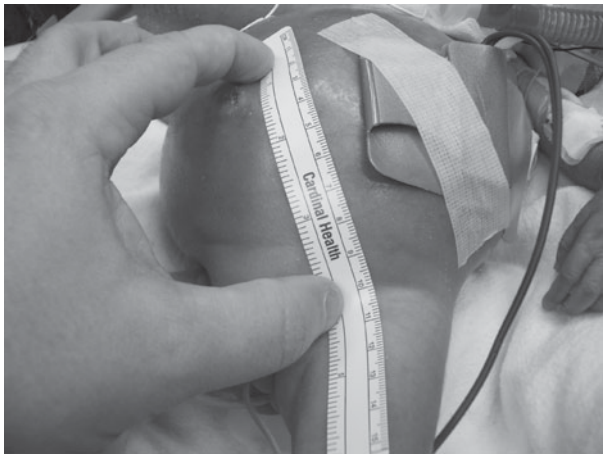
The femoral vein can also be accessed at the bedside by first using a 24 Fr angiocatheter to gain access. A small guidewire (Cook 0.15″ fixed core guidewire) passes easily through this sheath. A larger angiocath can then be placed over the wire to facilitate the larger guidewire in the temporary central line set. Abdominal x-rays can then confirm position.

PERIPHERAL VEIN CUT-DOWN

With the significant increase in PICC lines placed at our institution, we have seen a dramatic decrease in the number of peripheral vein cut-downs performed. These now seem to be reserved for those small infants where percutaneous methods are impossible. The common facial vein, external jugular vein, internal jugular vein, and saphenous vein are the most commonly used sites in our practice. With excellent nursing care and sterile technique, the infection rates are comparable to the percutaneous route of cannulation.

Access technique

The saphenous vein can be accessed at numerous points along its course. The most distal site is just superior to the medial malleolus. This site is not useful for long-term access and is not central in its location. The saphenous vein drains into the femoral vein at the level of the femoral triangle and is an easy access point for central cannulation. The infant is placed in a supine position and a rolled towel is placed under the pelvis to allow easier access. The groin is prepped and draped in the standard fashion. The length of the catheter can be measured by the length from the proposed incision to just superior to the umbilicus (iliac vein/IVC junction) (Fig. 14.4). A transverse incision is made inferior to the groin crease inferior to the inguinal ligament. Gentle dissection is carried out parallel to the expected path of the vessel with a hemostat until the saphenous vein is found. The vein is then elevated and proximal and distal control is gained with 5-0 silk ties. At least 1 cm of the vein should be exposed to allow for easy cannulation. The distal control ligature is then elevated to put tension on the vessel. A 24 Fr angiocath is then used to gain access to the vessel and is advanced as the needle is removed (Fig. 14.4). Care must be undertaken to avoid going through the back wall of the vein. A small guidewire (Cook 0.15″ fixed core guidewire) can then be advanced into the angiocath allowing a 22 Fr angiocatheter to



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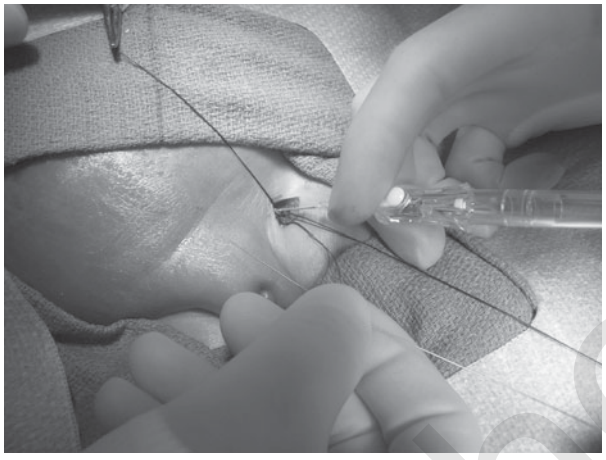

(b)

Figure 14.4 (a) Measurement for length of saphenous vein cut down central line. (b) Access of the saphenous vein with 24 Fr angiocath.

be placed which is large enough to accommodate the guidewire found in most 3 or 4 Fr central line kits. The catheter is then advanced and the proximal suture is tied down to secure the line and the vessel. The distal ligature can be removed or tied down if there is significant back bleeding. The incision is then closed in the usual fashion and the line site is dressed as previously described.

Similar techniques can be used for the facial vein, external jugular, and internal jugular venous cut-downs. There are numerous other devices, such as a vein pick, which can be useful if a venotomy is preferred over a percutaneous technique. Lines can also be easily tunneled with this technique if needed.

INTRAOSSEOUS DEVICES

During trauma or emergency resuscitation, the venous system may be collapsed due to hypovolemia and shock. Gaining intervenous access in these cases can be quite challenging and time consuming. A quick and easy alternative is the placement of an intraosseous device. These devices come in a multitude of sizes with the smallest available in our facility being 1.8 mm × 15 mm in length. Contraindications to their placement include fracture, absence of landmarks, infection at the proposed insertion site, and previous instrumentation of the extremity. These devices have gone through many evolutions and have a very low (<1%) complication rate.[1] The EZ-IO system (Vidacare, San Antonio, TX, USA) allows for quick and stable access even in the newborn.

Access technique

For infants between 3 and 39 kg, the small, 15 g needle system (PD) can be effectively used (Fig. 14.5). The two most common insertion sites are the proximal tibia just below the tibial tuberosity and, less commonly in infants, the humerus at the level of the humeral head. Local anesthesia can be injected at the proposed insertion site once it is prepped and draped. The needle is inserted into the driver system and the needle cap is removed. The needle and driver should be positioned at a 90° angle to the bone. The needle is then pressed into the skin until the tip touches the bone (ensure that at least 5 mm of the catheter is still visible at this point). The bone cortex is penetrated by squeezing the driver's trigger and applying gentle, steady downward pressure. Once a sudden give or pop is encountered the medullary space has been entered. The driver and stylet are removed and the catheter is flushed with at least 5 mL of normal saline. If the catheter flushes well, fluids and medications can be administered.[17] A dressing is placed around the device and changed on a PRN basis. IO devices should be removed within 24 hours to avoid complications such as osteomyelitis and compartment syndrome.

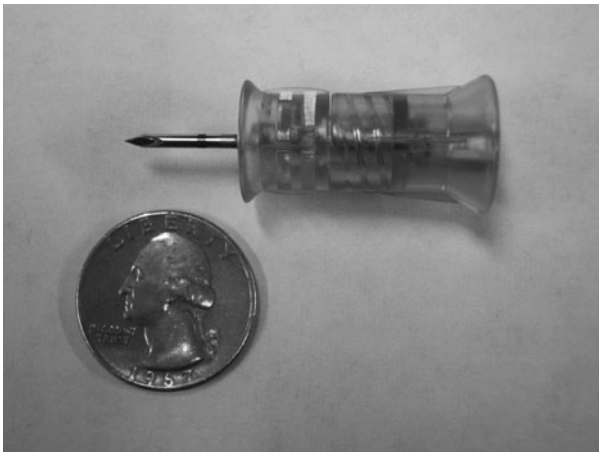

Figure 14.5 15 G intraosseous needle (Vidacare).

CONCLUSION

With smaller, critically ill neonates being managed in our intensive care units, reliable vascular access is a necessity. Improvements in techniques, miniaturization of catheters,

and development of new materials allows for stable access and improved care in premature and newborn infants. As these catheters continue to evolve, newer and safer techniques will soon follow.

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15

Radiology in the newborn

J KELLEHER AND IAN HW ROBINSON

INTRODUCTION

During the past decade, significant developments in surgical techniques, anesthesia, and intensive care have advanced and improved the care of the sick newborn baby. All imaging modalities have reached a new higher level of sophistication and the range of invasive and interventional radiology procedures has also greatly increased. These advances have placed greater demands on pediatric radiology departments which must be well staffed, funded, and equipped to keep pace with these developments. Because of this plethora of available tests, it is essential that both conventional radiographic and high-technology imaging facilities be used efficiently and rationally. A logical sequence of investigations should be applied commencing with the simplest and least invasive, and, where possible, minimizing exposure to ionizing radiation. At all times the As Low As Reasonably Achievable (ALARA) principle should be foremost in our mind. This approach may provide the diagnosis and obviate the need for more complex, invasive, and expensive studies, even if these additional modalities are readily available. Duplication of information, obtained from these various imaging modalities, which does not improve or influence management of the patient, should be avoided.

CONVENTIONAL RADIOGRAPHY

Plain radiography is often the first and most useful study in the evaluation of the surgical neonate. Radiographic examinations should be directed to achieving the required information with the minimum of handling or disturbance while maintaining the infant's body temperature and employing measures to limit radiation exposure. Only relevant projections should be obtained in relation to the clinical problem and condition of the baby (Fig. 15.1). There is no longer a place for routine lateral chest views.

Rooms for examinations in newborns should be kept warm – around 80°F (27°C) – and the baby should be removed from the warm protective environment of the incubator for the

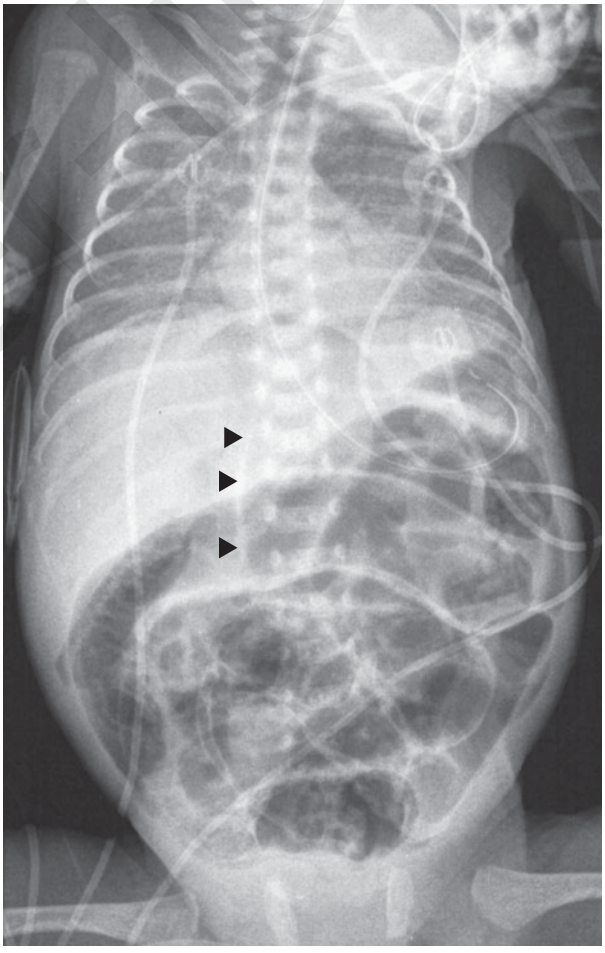


Figure 15.1 Supine chest and abdomen. Supine x-ray of the chest and abdomen in a premature neonate demonstrates abnormal increased lucency over the liver, with free intraperitoneal gas clearly outlining the falciform ligament (arrowheads). A decubitus x-ray is not required in this situation as the diagnosis of perforation is already made. Also evident is intramural gas in keeping with necrotizing enterocolitis and diffuse granular pulmonary parenchymal opacity with central air bronchograms, typical of surfactant deficiency syndrome.

shortest possible time. The use of the newer generation of 'giraffe' type incubators has greatly reduced this problem.

Measures to reduce radiation include the use of rare earth intensifying screens in the cassettes and carbon fiber table tops to give lower exposures and shorter times. High frequency generators, added beam filtration, and digital image receptors all contribute significantly to reducing the radiation burden to the infant.[1] The beam should be collimated to cover only the relevant area and gonad protection with lead shields should be used. Where repeated examination of the chest and mediastinum is anticipated, the use of thyroid shielding should be considered. Good radiographic technique is essential to produce radiographs of high quality, thus avoiding the unnecessary extra irradiation and disturbance of babies resulting from repeat exposure.[2] A sufficient number of well-trained and experienced radiographic technicians should be available to ensure that these high standards are maintained.

MOBILE EXAMINATIONS

In recent years a great increase in demand for portable radiographic examinations has occurred. The position of vascular access catheters and endotracheal tubes may need to be repeatedly checked and frequent examinations may be required in infants with severe respiratory problems on ventilation.[3] Mobile x-ray machines have become smaller, more maneuverable, and give shorter exposure times. Incubators chosen for special or intensive care baby units should be user-friendly for radiography.

Lateral decubitus views of the chest or abdomen are readily performed with a horizontal beam, leaving babies in their incubators. They can be very useful in demonstrating pneumoperitoneum and in evaluating fluid levels in bowel (Fig. 15.2). A dorsal decubitus view of the abdomen is perfectly adequate to either confirm or exclude pneumoperitoneum and is obtained without any re-positioning of the infant in the incubator (Fig. 15.3a–c). Erect views should no longer be requested or performed.

Protocols should be in place to maximize the information obtained while minimizing the disturbance and distress to

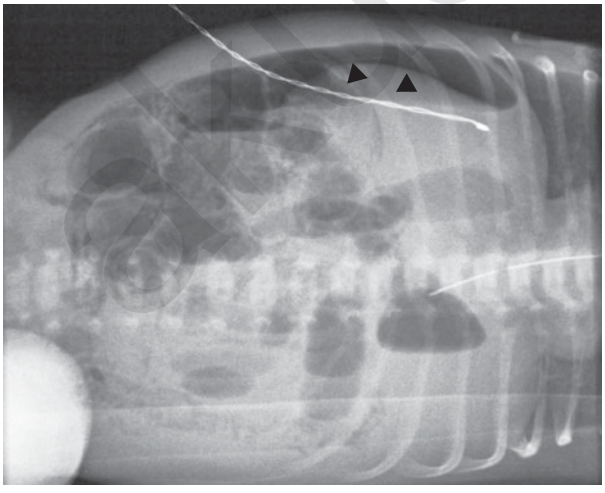
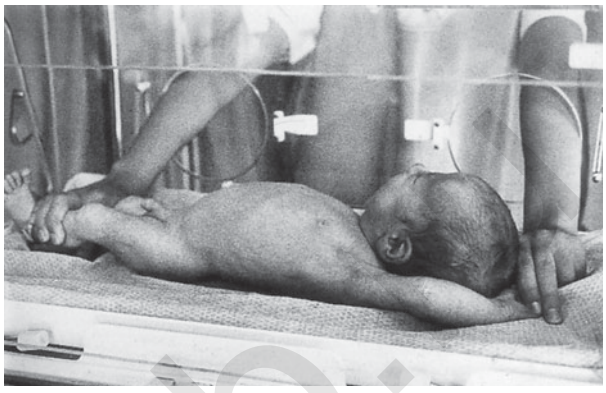


Figure 15.2 Left lateral decubitus. Decubitus x-ray in a neonate with perforated necrotizing enterocolitis. The free intraperitoneal gas rises, outlining the liver (arrowheads). Intramural gas in keeping with NEC is also demonstrated. The decubitus x-ray is also useful in the detection of air fluid levels.



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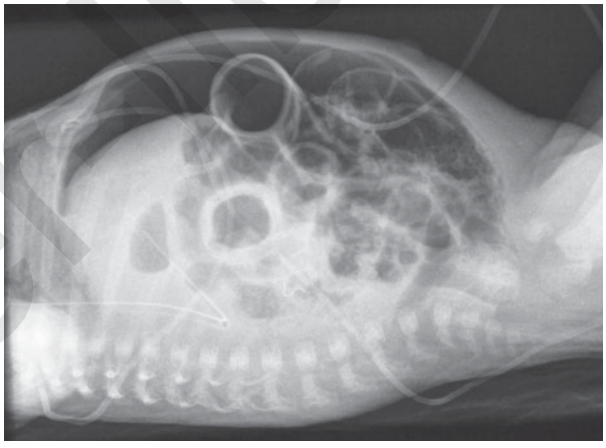

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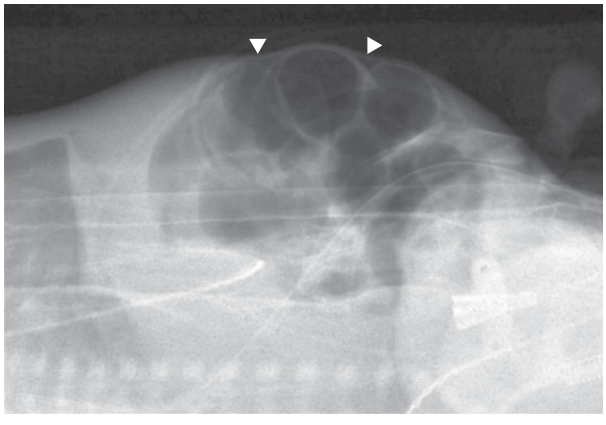
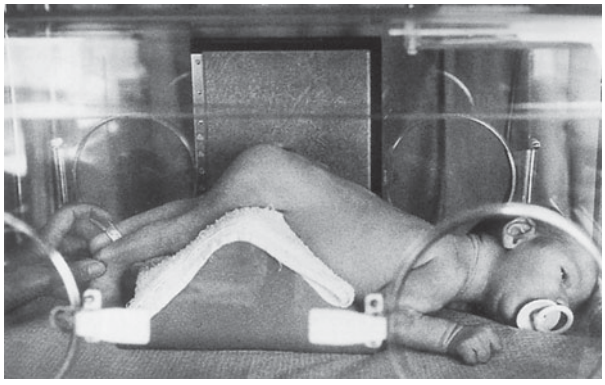


(c)

Figure 15.3 (a) Dorsal decubitus. Position of baby in incubator for horizontal beam exposure. (b) Dorsal decubitus – large amount of free gas. In the dorsal decubitus position, a large amount of free intraperitoneal gas clearly outlines the diaphragm, liver, and bowel loops. (c) Dorsal decubitus – small amount of free gas. Even small amounts of gas may be detected in the dorsal decubitus position, outlining the anterior abdominal wall and adjacent bowel as in this case, (arrowheads) or anterior to the liver.

the infant. A good example of this is that our previous practice of performing inverted lateral radiographs for anorectal anomalies has been abandoned. It is unacceptable that the baby be removed from the incubator and held upside-down by the legs while the exposure is taken. Aside from the trauma to the infant, it is difficult to obtain a good true lateral view centered at the correct level. A prone lateral view with the buttocks elevated and using a horizontal x-ray beam is a far superior technique. The baby can be left comfortably in this position for a period of time to ensure that gas outlines the distal limit of the blind rectal pouch (Fig. 15.4a,b).



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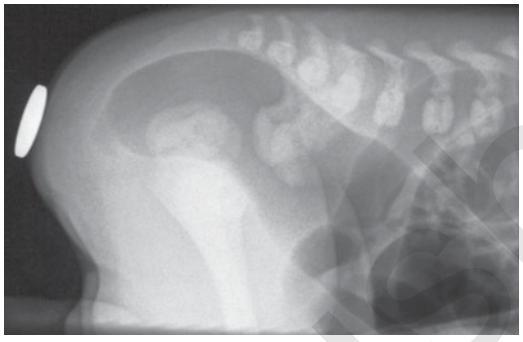


(b)

Figure 15.4 (a) Lateral rectum. Newborn with imperforate anus in prone position in incubator, with buttocks elevated for lateral view with horizontal beam. (b) Lateral rectum. Lateral x-ray of the rectum demonstrating the distal limit of the rectal pouch in this child with anorectal malformation. An assessment of the sacrum can also be made.

FLUOROSCOPIC EXAMINATIONS

For investigations in neonates the fluoroscopy room should be warm, with oxygen and suction outlets readily available. A fully equipped resuscitation trolley should be at hand. Procedures should be carried out quickly but carefully. A satisfactory i.v. infusion should be ensured before commencing any invasive or interventional procedure. The radiologist should concentrate on solving the clinical problem presented and tailor the study accordingly.

Developments in computerized digital fluoroscopy in recent years have resulted in the potential for a marked reduction in radiation exposure, more rapid performance of dynamic contrast studies, and greatly improved recorded images. Digital fluoroscopy units often have the facility to provide a rapid series of exposures at up to 8/second. While this can be very useful in studies of the swallowing mechanism or of the airway, the ability to store and review a 'video-loop' is much more valuable. The use of appropriate reduced rate pulsed fluoroscopy greatly reduces radiation dose. A 'last image hold' facility allows hard-copy images to be obtained with no additional radiation. In most neonates it should be possible to screen without a 'grid', thus further reducing radiation dose and the use of magnification should be minimized. Modern installations provide image enhancement, processing and digital subtraction facilities, which are very useful in angiography.[4]

Non-ionic water soluble contrast media are used for all intravascular studies in children. Such contrast agents can also be used for gastrointestinal examinations. They permit excellent anatomic delineation and may be safely used even where leakage or obstruction is suspected. They are well tolerated even if pulmonary aspiration occurs, though some element of pulmonary edema may develop. If diluted, an iso-osmolar solution can be achieved for even greater tolerance in the airway. A good example of this is shown with a bolus injection in the upper esophagus in H-type tracheo-esophageal fistula (Fig. 15.5).

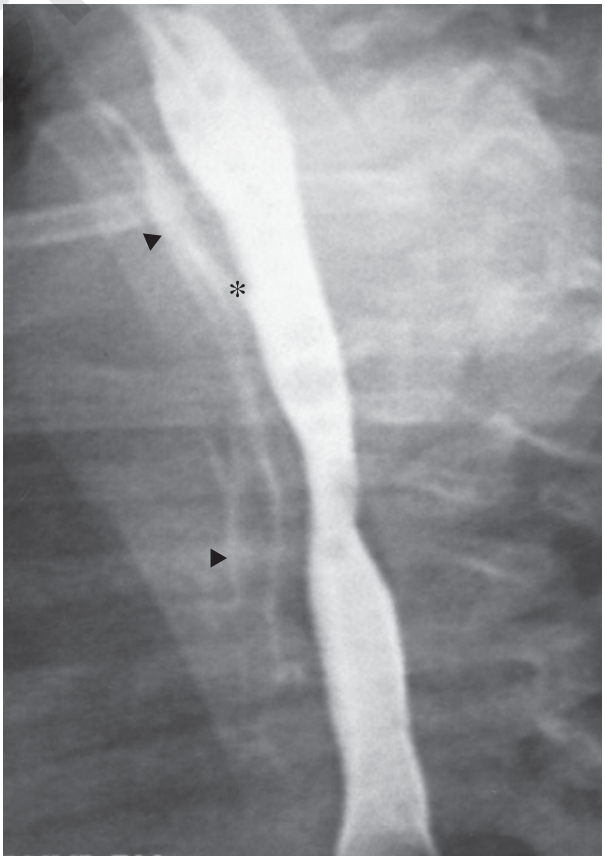


Figure 15.5 H-type tracheo-esophageal fistula. Water soluble contrast fills the esophagus and passes through an H-type fistula (asterix) into the trachea (arrowheads).

Conventional ionic contrast agents, e.g. Urografin (Bayer) 30%, are less expensive and are appropriate for micturating cystourethrography (MCUG) (Fig. 15.6). All infants should have appropriate antimicrobial cover during MCUG to reduce the risk of infection. The contrast agent should be warmed to body temperature and may be diluted with sterile water. Either a 5F or 6F feeding tube is used to catheterize the baby. In males, a steep oblique view of the urethra must be obtained during voiding to exclude the presence of posterior urethral valves. Screening time can be kept to a minimum by observing the flow of contrast from the bottle. When flow stops, the baby is usually ready to urinate.

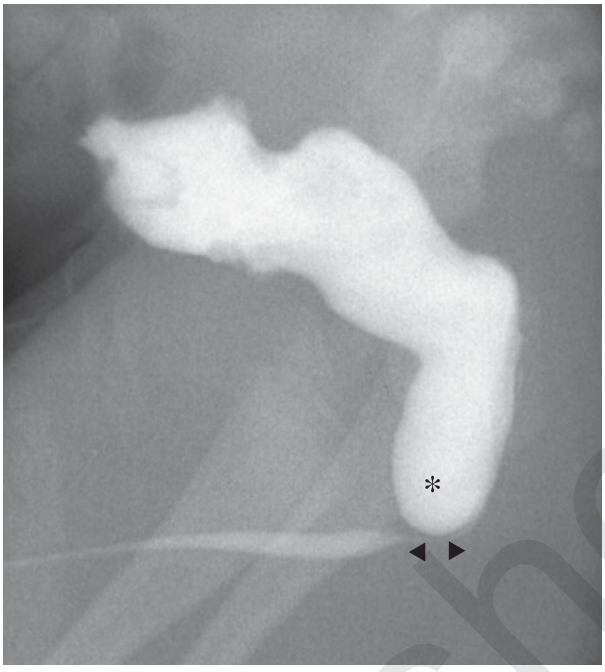


Figure 15.6 Micturating cystourethrography. Lateral image of the bladder and urethra in a male infant taken during micturition. The bladder is abnormal in contour and the posterior urethra is markedly dilated (asterix). The thin filling defect representing the membrane of the posterior urethra valve is visible (arrowheads).

ULTRASONOGRAPHY

This relatively inexpensive and widely available imaging modality has transformed neonatal diagnostic imaging. Lack of ionizing radiation, portability, and the freedom to do serial repeat studies make it especially suitable for this patient population. In premature or severely ill babies, ultrasound (US) scans can be performed satisfactorily without removing the infants from their incubators. The principles of minimal handling and maintenance of body temperature apply. Examinations should be carried out quickly and efficiently, aimed to achieve a diagnosis and not prolonged or repeated just to produce the 'perfect picture'.

Congenital structural abnormalities are being diagnosed with increasing frequency on antenatal scans. Congenital brain malformations, hydrocephalus, and spinal anomalies are easily recognized.[5] Prenatal recognition of anomalies, such as cystic adenomatoid malformation, cystic renal disease or intestinal tract obstructions, alerts the neonatologist to the need for careful postnatal evaluation.

The identification of abdominal wall defects, e.g. exomphalos and gastroschisis or of a diaphragmatic hernia on an antenatal scan, allows the delivery to be arranged in or close to a major pediatric surgical center. *Ex utero* intrapartum treatment or 'EXIT' surgery can be planned if major airway problems are detected *in utero*. Antenatal interventional techniques can be performed under US guidance, e.g. the insertion of stents or drains in obstructed urinary tracts.

Cranial US is now an indispensible facility in any department dealing with newborn patients.[6] Using real-time high frequency probes, images of excellent detail are obtained. Hydrocephalus secondary to intraventricular hemorrhage (IVH) or myelomeningocele can be accurately diagnosed and graded. Serial examinations are helpful in relation to the need for shunting. However, if the cause of the hydrocephalus is not evident, then other imaging, e.g. magnetic resonance imaging (MRI), will be necessary. One of the most important contributions of US is in the diagnosis and grading of IVH. Early diagnosis of minimal lesions can be achieved in infants at risk. The discovery of IVH can influence the decision to operate on a newborn with a congenital malformation if IVH is severe (Fig. 15.7).

There is an increasing use of ultrasound in evaluating suspected anomalies of the spinal cord in infants (Fig. 15.8). The scans can demonstrate the entire spectrum of intraspinal anatomy, both normal and abnormal, and define pathological conditions with a high degree of accuracy.[7] It may obviate the need for MRI.

Sonography plays a significant role in the investigation of mass lesions in the neck and mediastinum. It permits localization, delineation of relationships to surrounding structures, and especially differentiation of cystic from solid lesions (Fig. 15.9). Real-time sonography is very useful in evaluating phrenic nerve paralysis.

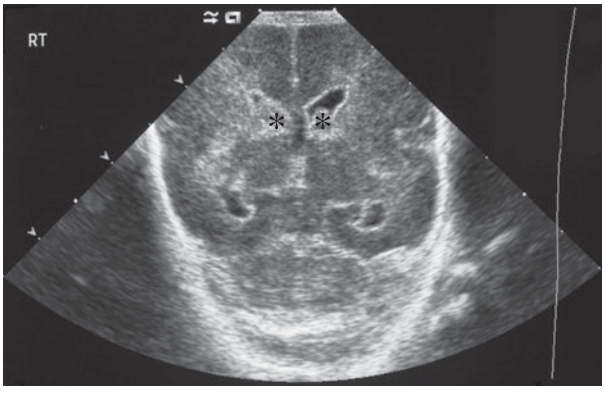


Figure 15.7 Cranial US. Coronal US image of the brain in a premature neonate. Hemorrhage is visible within both lateral ventricles (asterix). The ventricle wall is echogenic. In addition there is increased echogenicity within the periventricular parenchyma on the right, in keeping with infarction, indicating a Grade 4 intraventricular hemorrhage on this side. Note the relatively poor sulcation typical of a premature infant.

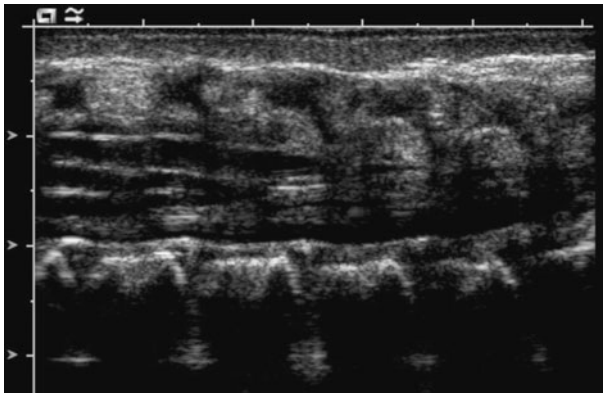


Figure 15.8 Ultrasound spine. US of the spine clearly depicts the cord, conus, and cauda equina. The position of the conus relative to the vertebral elements can be assessed and the presence or absence of spinal anomalies can be confidently determined. Spinal US is best performed before 6 weeks of age, when the relative lack of vertebral ossification allows for good visualization.

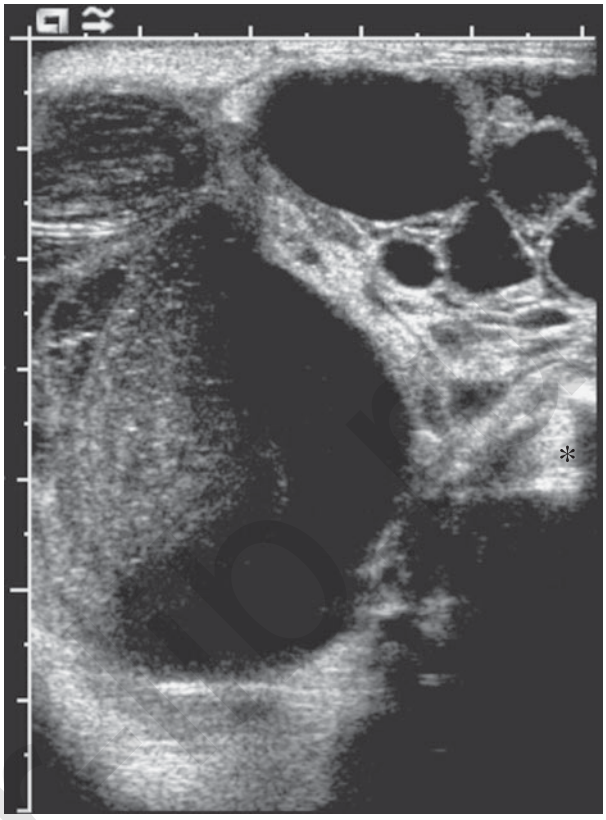
Abdominal US is very frequently carried out in the newborn to diagnose or exclude renal disease. Lesions confined to the kidneys include multicystic dysplastic kidney, polycystic disease, and hydronephrosis. The latter may be due to obstruction at pelvi-ureteric or uretero-vesical level or, in males, to the presence of posterior urethral valves. All these lesions are readily diagnosed with US, and severity of obstruction and renal damage can also be assessed. The kidneys are frequently involved in complex syndromes, e.g. VACTERL syndrome. The spectrum of renal anomalies varies from agenesis to crossed fused ectopic and duplex kidneys.

Ultrasound is well established as the optimal diagnostic tool in the routine evaluation of infantile pyloric stenosis. Whilst pyloric stenosis is rare in the first 2 weeks of life, it has been reported, and the standard US measurement criteria may not be valid in this patient population.[8]

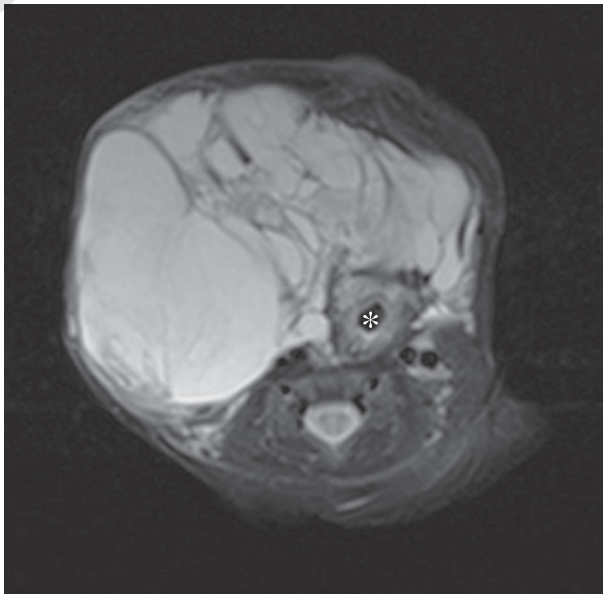
In the evaluation of space-occupying lesions of the neonatal abdomen, US should be the first investigation. It will characterize the lesion, for example differentiating cystic from solid and identifying the organ of origin. Figure 15.10 shows the typical cystic appearance of neonatal adrenal hemorrhage. In comparison, Figure 15.11 demonstrates a solid suprarenal mass, confirmed to be neuroblastoma, stage 4S. US may give the complete diagnosis, e.g. congenital mesoblastic nephroma. Failing that, it should give a clear indication of the next logical investigation.

In neonatal jaundice, US has a key role in defining the anatomy of the biliary tract. Choledochal cyst may be diagnosed with confidence and biliary atresia excluded. It can demonstrate or exclude dilatation of the biliary duct system (Fig. 15.12). Radionuclide imaging may be complementary.

The development of Doppler, including color Doppler, has been a considerable advance with widespread application. The safe placement of vascular access lines is greatly aided by this technique. It can accurately map the vascular anatomy of abdominal masses or of arteriovenous malformations in other sites. It allows noninvasive imaging of hepatic vascular structures.



(a)



(b)

Figure 15.9 (a,b) Ultrasound neck – cystic hygroma + accompanying magnetic resonance imaging (MRI). (a) US and (b) MRI of a cystic hygroma of the neck. US and MRI are complementary modalities. US has superior spatial resolution, for example being able to detect thin septations. MRI, however, allows a more accurate assessment of the overall extent of a lesion and its relation to adjacent structures. In this example, the trachea is visible on both the US and MRI (asterix).

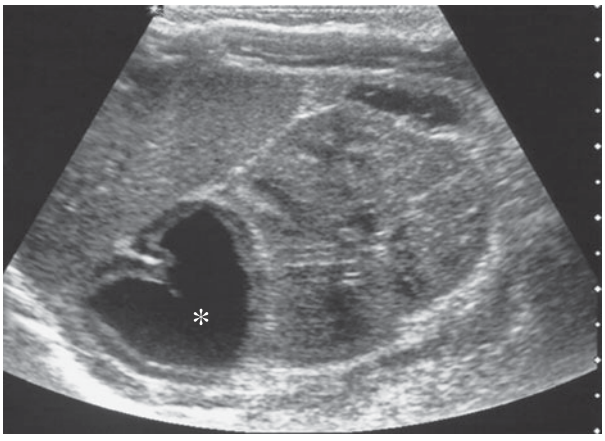


Figure 15.10 Ultrasound adrenal hemorrhage. Cystic enlargement of the adrenal gland typical of an adrenal hemorrhage (asterix). (L = liver, K = right kidney.)

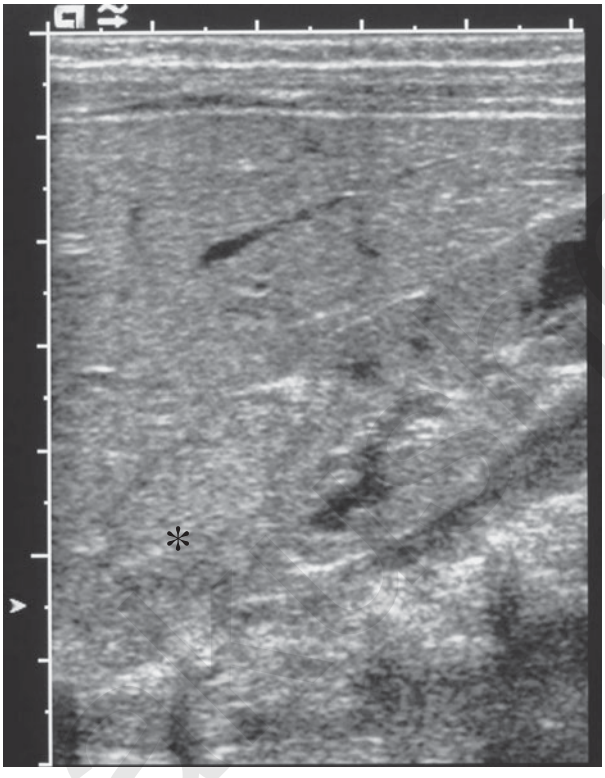


Figure 15.11 Ultrasound neuroblastoma. In contrast, this suprarenal abnormality is clearly solid, representing an adrenal mass in a child with neuroblastoma (asterix). (L = liver, K = right kidney.)

NUCLEAR MEDICINE

With the great advances in US, computed tomography (CT) and MRI, the role of radionuclide examinations is very limited in the newborn period. Functional rather than morphological studies are usually required. Total and individual renal function can be assessed, but, due to functional immaturity, imaging is less reliable than in the older infant or child. Technetium-99m labeled mercaptoacetyltriglycine (MAG 3) is used for assessment of obstruction with technetium labeled dimercaptosuccinic acid (DMSA) employed for static imaging and to demonstrate the functioning renal parenchyma. Either method will give an estimate of relative renal function. Excretory urography or IVU has no place in modern neonatal imaging.

Hepatobiliary scintigraphy is extremely useful in the investigation of neonatal jaundice where biliary atresia is a concern. The infant is given phenobarbital, 5 mg/kg per day divided into two equal doses, given for 3–5 days prior to the scan. Mebrofenin labeled with technetium-99m (Choletec) is preferred in infants because of its greater hepatic extraction. The scan will usually differentiate between biliary atresia and neonatal hepatitis (Fig. 15.13). If the biliary tract is patent, isotope should be detected in the intestine within 60 minutes.

Though uncommon, Meckel's diverticulum may present with rectal bleeding in the newborn period. It can be elegantly demonstrated on technetium pertechnetate scintigraphy (Fig. 15.14).

Isotope bone scanning can be very unreliable in the diagnosis of neonatal osteomyelitis and/or septic arthritis and is rarely employed.

Infants presenting with congenital hypothyroidism and absence of the thyroid gland from its normal location can be scanned using 99m Tc-pertechnetate, looking for an ectopic or lingual thyroid (Fig. 15.15).

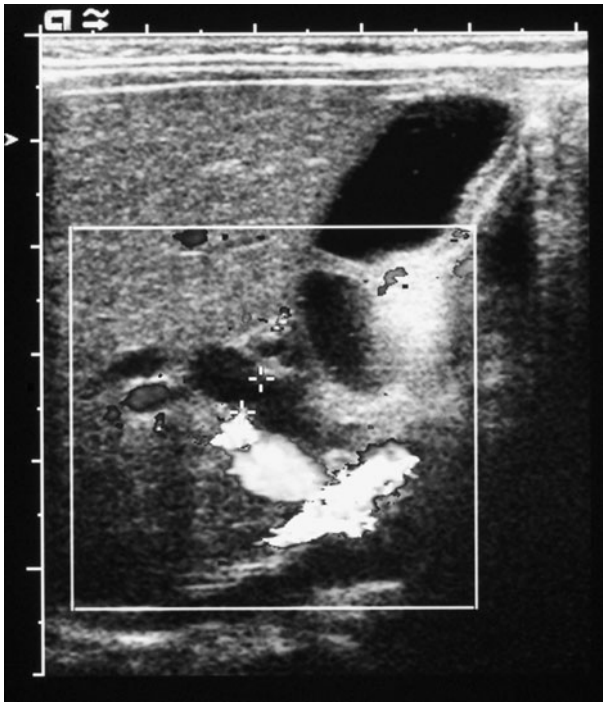


Figure 15.12 Ultrasound bile duct dilatation. US reveals dilatation of the common bile duct (calipers) in this neonate with gallstones. Color Doppler imaging is often used as in this instance to identify vascular structures separate from the bile duct.

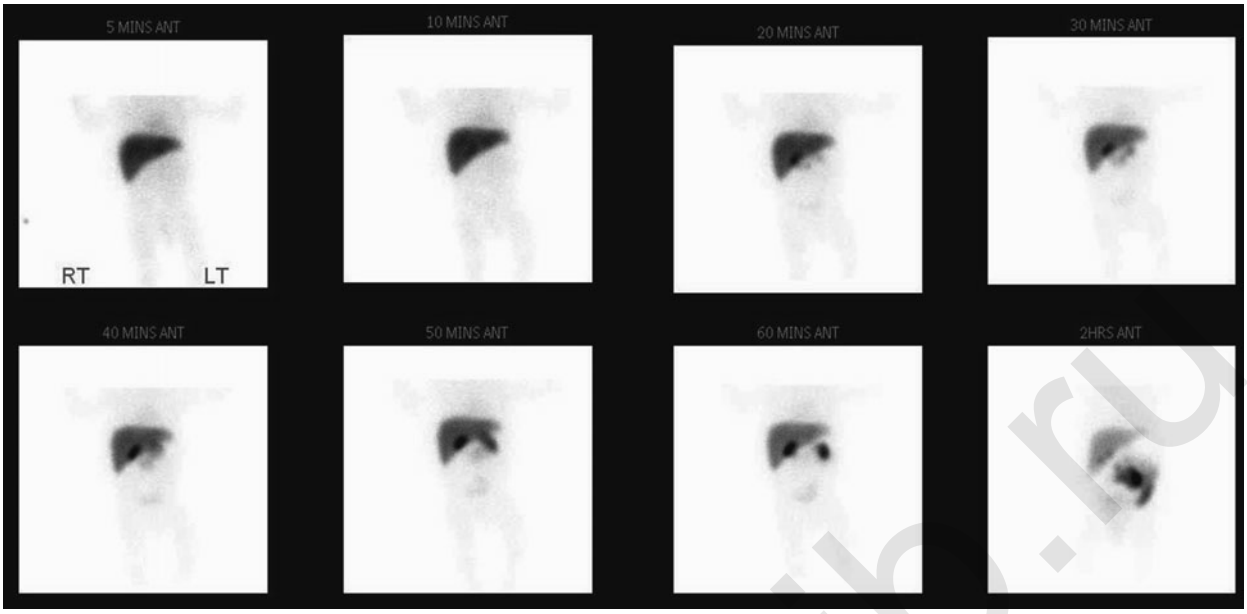


Figure 15.13 HIDA. Radioisotope rapidly appears within the liver. In this normal study, radioisotope is rapidly excreted into the gallbladder (20 min) and proximal small bowel (30 min). The delayed image at 2 hours shows radioisotope having largely passed through the liver and appearing within small bowel loops.

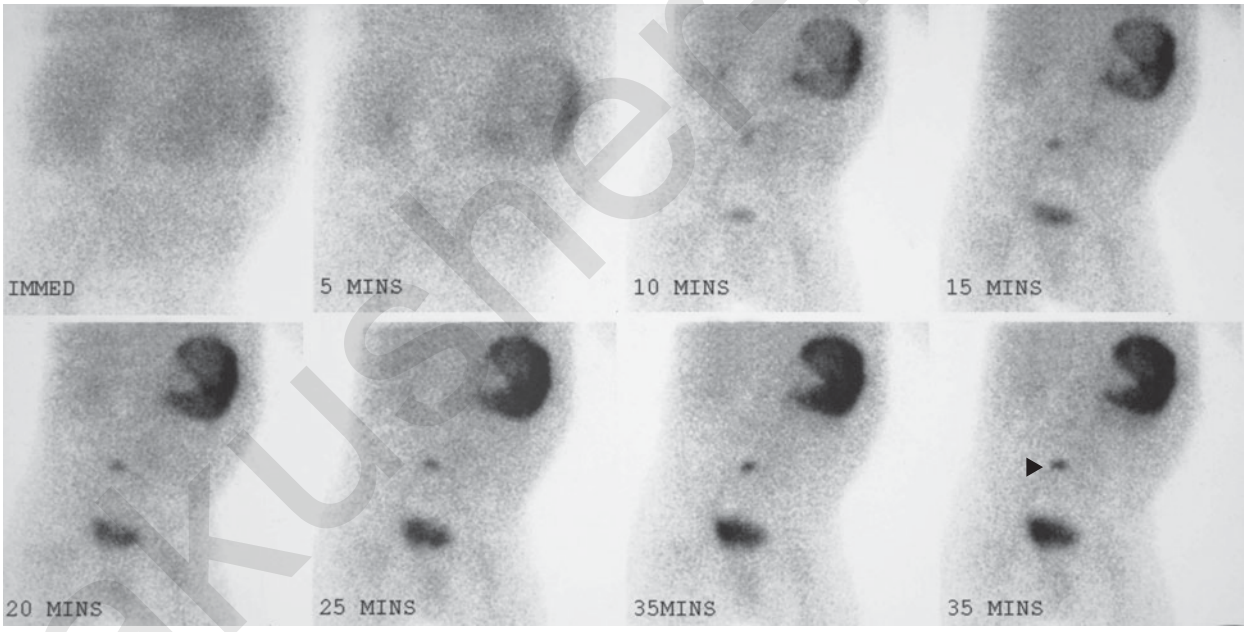


Figure 15.14 Meckel scan. Radioisotope is taken up by gastric mucosa within a Meckel's diverticulum (arrowhead). Note the normal uptake by the gastric mucosa of the stomach. Also note the normal appearance of radioisotope within the bladder, having been excreted by the kidneys.

COMPUTED TOMOGRAPHY

Computed tomography remains an established and vital imaging modality in pediatrics but has relatively limited application in the newborn where US and MRI have many advantages. While CT can be useful in evaluating structural abnormalities in the thorax, such as congenital pulmonary adenomatoid malformations (CPAM) and congenital lobar emphysema (CLE), its usefulness in evaluating the neonatal abdomen is significantly limited by the lack of intra-abdominal fat. In general, abdominal MRI is more useful than CT when US fails to provide the diagnosis. While modern multislice scanning should be available on site in any specialized pediatric unit, radiation dose remains a major concern.[9] CT should be reserved in the newborn for specific indications where other modalities provide insufficient information. These would include cranial CT scans in suspected head trauma, exclusion of intracranial calcification in congenital infection, e.g. TORCH, and assessment of bony abnormality associated with severe choanal atresia

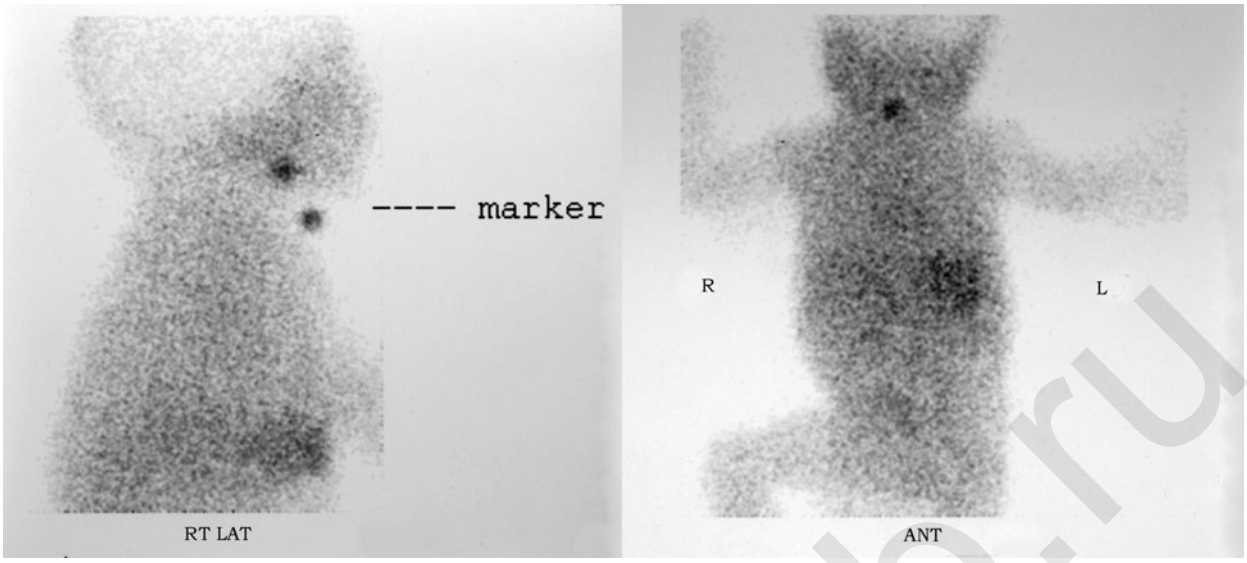


Figure 15.15 Lingual thyroid. Radioisotope accumulates within thyroid tissue which is located at the base of the tongue. Its position can be determined relative to the chin and the marker at the sternal notch. On the anteroposterior view the lingual thyroid has a rounded configuration, as opposed to the typical bilobed appearance expected of a normal thyroid gland.

(Fig. 15.16). In all instances protocols to reduce radiation dose must be in place as per the ALARA principle.[10]

MAGNETIC RESONANCE IMAGING

Increased access to MRI has transformed neonatal radiology. While US remains the mainstay of brain and spinal imaging in the neonate because of portability etc., MRI is used to clarify complex malformations and to provide vital functional and prognostic information. Hypoxic-ischemic brain injury (HIE) is a frequent and significant problem in the neonatal period. Regardless of the type of hypoxic injury, the imaging manifestations are related to the gestational maturity of the infant. Hypoxic injury to the premature brain affects primarily the germinal matrix and periventricular white matter, while in the term infant damage to the cortical tissues and basal ganglia occurs (Fig. 15.17). MRI with spectroscopy is the diagnostic modality of choice in suspected neonatal HIE.[11]

Outside of the central nervous system an increasing use of MRI is also seen. In the evaluation of mass lesions of the neck and mediastinum it offers exquisite anatomical detail. The ability to image in multiple planes facilitates surgical planning. In the abdomen, while US mostly reigns supreme, MRI is increasingly used to evaluate complex masses, to complement US in the biliary tract (MR cholangiography) and to evaluate the renal tract (MR urography). With increasing use and experience this utilization may expand but cost, availability, and motion artifacts remain a barrier, as does the requirement for sedation or anesthesia.

Over the last 25 years, advances in MRI technology have allowed safe and accurate imaging of the fetus. Fetal MR has become a useful adjunct to antenatal ultrasound.[12] It has been shown to detect sonographically occult abnormalities, and may result in changes to pregnancy management. Figure 15.18 shows MR imaging of a fetus with a large cystic hygroma of the neck. Assessment of the extent of the lesion, in particular its relationship to the airway, allowed planning for an *ex utero* intrapartum treatment ('EXIT' procedure).[13]

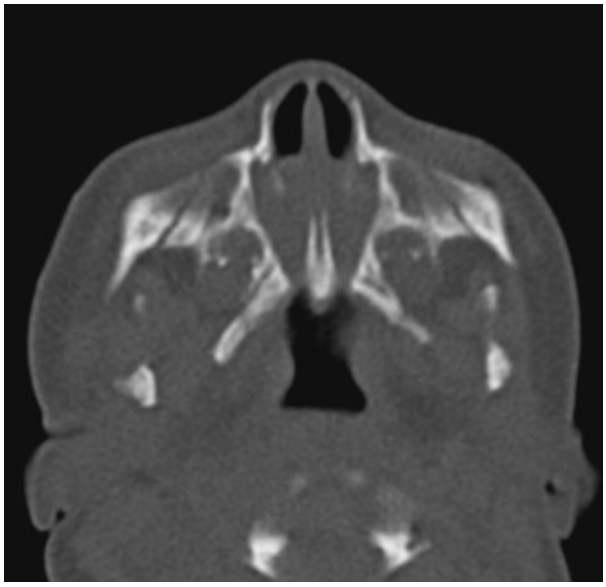
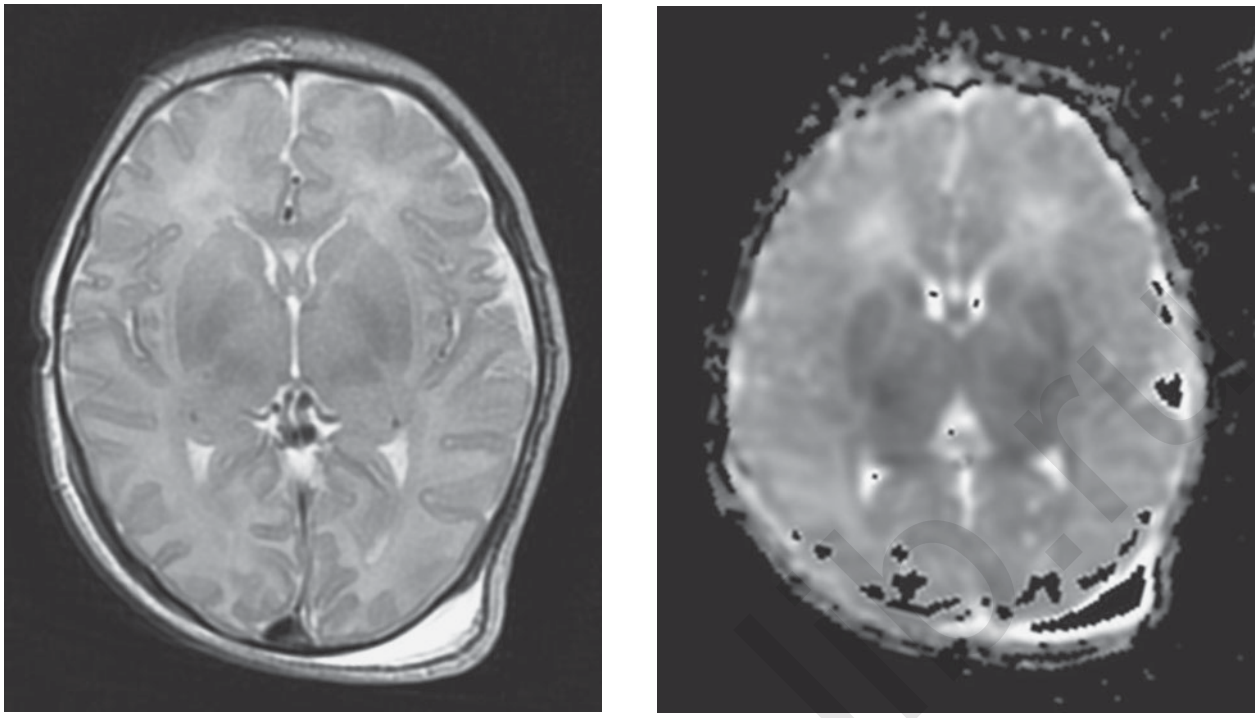


Figure 15.16 Computed tomography (CT) choanal atresia. CT is the best modality for assessing the bony narrowing of the choanae. In this case there is severe bilateral narrowing of the posterior nasal cavity in a patient with bilateral choanal atresia.



(a) (b)

Figure 15.17 (a,b) Magnetic resonance imaging hypoxic-ischemic brain injury. (a) Axial T2 and (b) adjusted diffusion coefficient (ADC) map from the diffusion-weighted imaging (DWI). Signal abnormality in the newborn is often subtle on T1 and T2 imaging, and is influenced by gestation. DWI, when performed within an appropriate timeframe, is helpful in determining the extent of abnormality. In this term infant, extensive restricted diffusion is clearly evident within the basal ganglia (low signal on the ADC) in keeping with a profound hypoxic ischemic event.

INTERVENTIONAL TECHNIQUES

There has been a dramatic increase in recent years in the number, range, and complexity of interventional procedures in pediatric as well as in adult radiology practice. Hospital stay may be shortened and patient outcome improved as these interventional procedures tend to be more cost-effective than the alternative conventional surgical approach. In the gastrointestinal tract, hydrostatic or pneumatic reduction of intussusception is a well established technique. This, however, is a rare condition in the newborn. The non-operative management of meconium ileus by Gastrografin enema is almost universal (Fig. 15.19). However, it must be remembered that complications such as volvulus, peritonitis, and perforation must be excluded before an enema is attempted. The fluoroscopy room should be warm, the infant well hydrated and a functioning i.v. line must be in place. This author advocates the use of diluted Gastrografin, one part contrast and two parts water to reduce the risks of mucosal damage. Several attempts may be made over a period of days if the infant's condition permits.

Balloon catheter dilatation of post-anastomosis esophageal strictures in neonates following repair of esophageal atresia is now established in major centers worldwide. The advantages of balloon dilatation over bougienage relate to the marked reduction in shear force with radial force mainly achieving the dilatation.

Balloon dilatation of colonic strictures complicating necrotizing enterocolitis is another, though infrequent, interventional procedure. Percutaneous gastrostomy and placement of a feeding tube in the jejunum are further useful techniques performed under fluoroscopy.

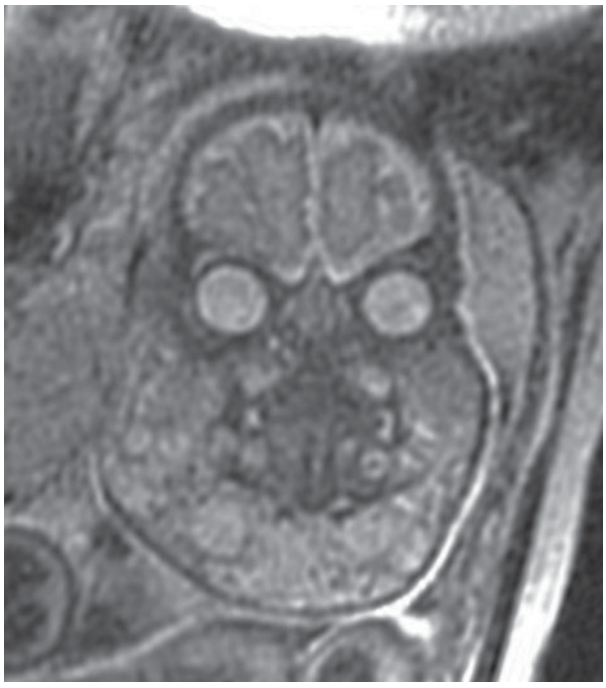
In urinary tract obstruction, percutaneous nephrostomy to relieve obstruction is widely practiced and should be performed under direct US guidance. Either a single stab technique or a modified Seldinger approach may be used and a pigtail catheter is left in place.

Percutaneous biopsy of organs or lesions under US, fluoroscopic, or CT guidance and the aspiration or drainage of abscesses or cysts are all part of the interventional radiologist's workload. The cumulative radiation burden to the infant must be borne in mind, and in general, US is the imaging modality of choice.[14]

In the very low birth weight (VLBW) infants vascular access procedures are amongst the most common indication for radiological intervention and are not without complication.[15]

CONCLUSION

The role of the imaging department and of the pediatric radiologist in the management of the neonatal patient is continuously evolving and expanding. They should be involved as an integral member of the 'team'. Frequent consultation among all carers will avoid inappropriate requests for imaging. It will prevent duplication of examinations and the accumulation of redundant information, thus helping to reduce costs. The application of appropriate imaging techniques will also have the great virtue of reducing the infant's discomfort and morbidity.



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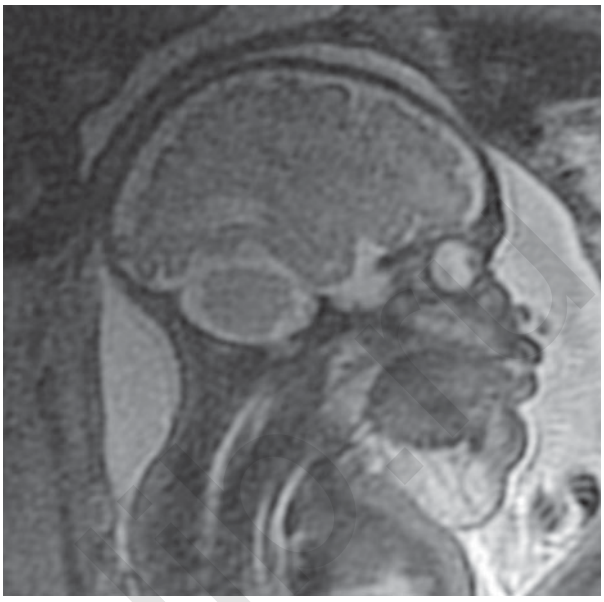

(b)

Figure 15.18 Fetal magnetic resonance (MR) cystic hygroma. Axial and sagittal images of a fetus with a large cystic hygroma. In this case, fetal MRI provided additional information relating to the extent of the mass and its relationship to the airway and allowed planning for an elective EXIT procedure.

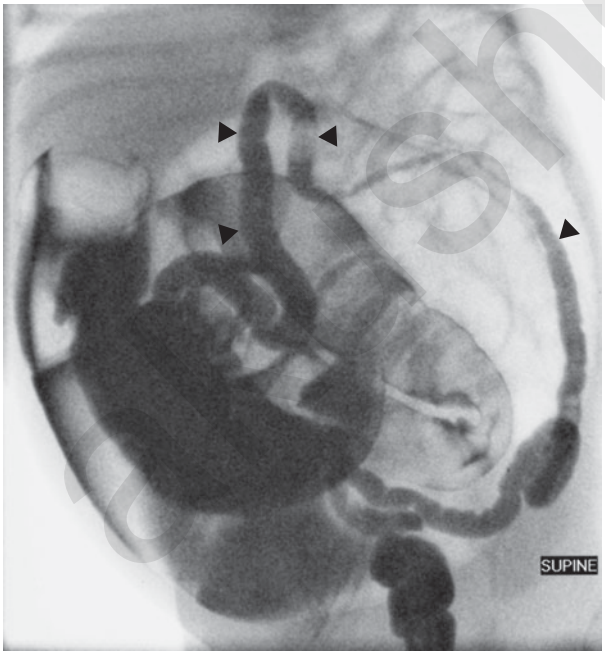

Figure 15.19 Meconium ileus. Contrast enema. Contrast fills a microcolon (arrow heads) before refluxing into markedly distended distal small bowel loops. Filling defects within these dilated loops are due to impacted meconium in this neonate with meconium ileus.

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16

Immune system of the newborn

FIONA O'HARE, DENIS J REEN, AND ELEANOR J MOLLOY

INTRODUCTION

The first line of defense against infection is the innate immune system and activation occurs when a pathogen breaches the host's natural barriers (Fig. 16.1).[1] The innate immune system developed before the separation of vertebrates from invertebrates and is the primary immune response for most multicellular organisms.[2] It responds instantaneously to microbes and is composed of both soluble (the alternative and mannan-binding lectin pathways of the complement system, acute phase proteins, and cytokines) and cellular elements (monocytes, macrophages, neutrophils, dendritic cells, and natural killer cells). Careful modulation of the innate immune system is vital to prevent either uncontrolled microbial growth or devastating inflammatory responses with tissue injury, vascular collapse, and multiorgan failure.

Detection of invading microorganisms is mediated by pattern recognition receptors expressed on the surface of innate immune cells, which recognize structures common to many microbial pathogens and are called pathogen-associated molecular patterns (PAMPs). These include endotoxins (lipopolysaccharide: LPS), peptidoglycan, lipoteichoic acid, lipopeptides, flagellin, mannan, and viral RNA, which are essential for survival of the microorganisms and therefore do not undergo major mutations. Pattern recognition receptors have been evolutionarily conserved not to recognize any self-structure. Any receptor that bound to a self-ligand could lead to death of the organism that expressed such a receptor. Therefore, autoimmunity is prevented when the only available recognition system is the innate immune system.[3]

Several intracellular signaling pathways are activated when a PAMP binds to a pattern recognition receptor, resulting in activation of transcription factors (NF-kB, AP-1, Fos, Jun). These transcription factors control the expression of immune response genes and the release of numerous effector molecules, such as cytokines. Cytokines are chemical mediators with an essential role in orchestrating the innate and acquired immune responses to an invading pathogen.[4]

The acquired immune system has evolved relatively recently and is built upon the phylogenetically older innate immune system, by which it is controlled and assisted. The principal mediators of acquired immunity are the highly evolved lymphocytes, which express an enormous array of recombinant receptors, immunoglobulin (Ig) and T-cell receptors. They can recognize any potential pathogen with which the host may come in contact. This response takes from days to weeks to develop optimally. Newborns acquire passive immunity from their mothers by maternally derived IgG crossing the placenta. Transferable maternal immunologic memory is essential for the survival of the fetus, newborn, and infant. Moreover, the attenuation of infection by transferable maternal immunity permits microbial agents to immunize the child under optimal conditions. This provides protection for up to the first six months of life at which time neonatal acquired immunity has developed.[5]

The hygiene hypothesis states that exposure to allergens in the environment early in life reduces the risk of developing allergies by boosting immune system activity. Conversely, a relatively clean environment in early life would sway the immune system towards allergy-promoting responses. The hygiene hypothesis may explain the rising incidence of allergic diseases and facts such as the lower incidence of allergy in those living on farms or in rural areas (due possibly to more exposure to bacteria); the lower incidence of allergy in younger children of large families with three or more older siblings (due perhaps to repeated exposure to infection); and the lower incidence of asthma and wheezing in children attending day care (with more exposure to infections). The hygiene hypothesis, however, cannot explain the higher rates of allergic asthma among poor African Americans in inner city areas.[6,7]

CLINICAL OUTCOMES IN NEONATAL SEPSIS AND INFLAMMATION

Death and long-term complications are common sequelae of bacterial infections in newborns. Neonates undergoing

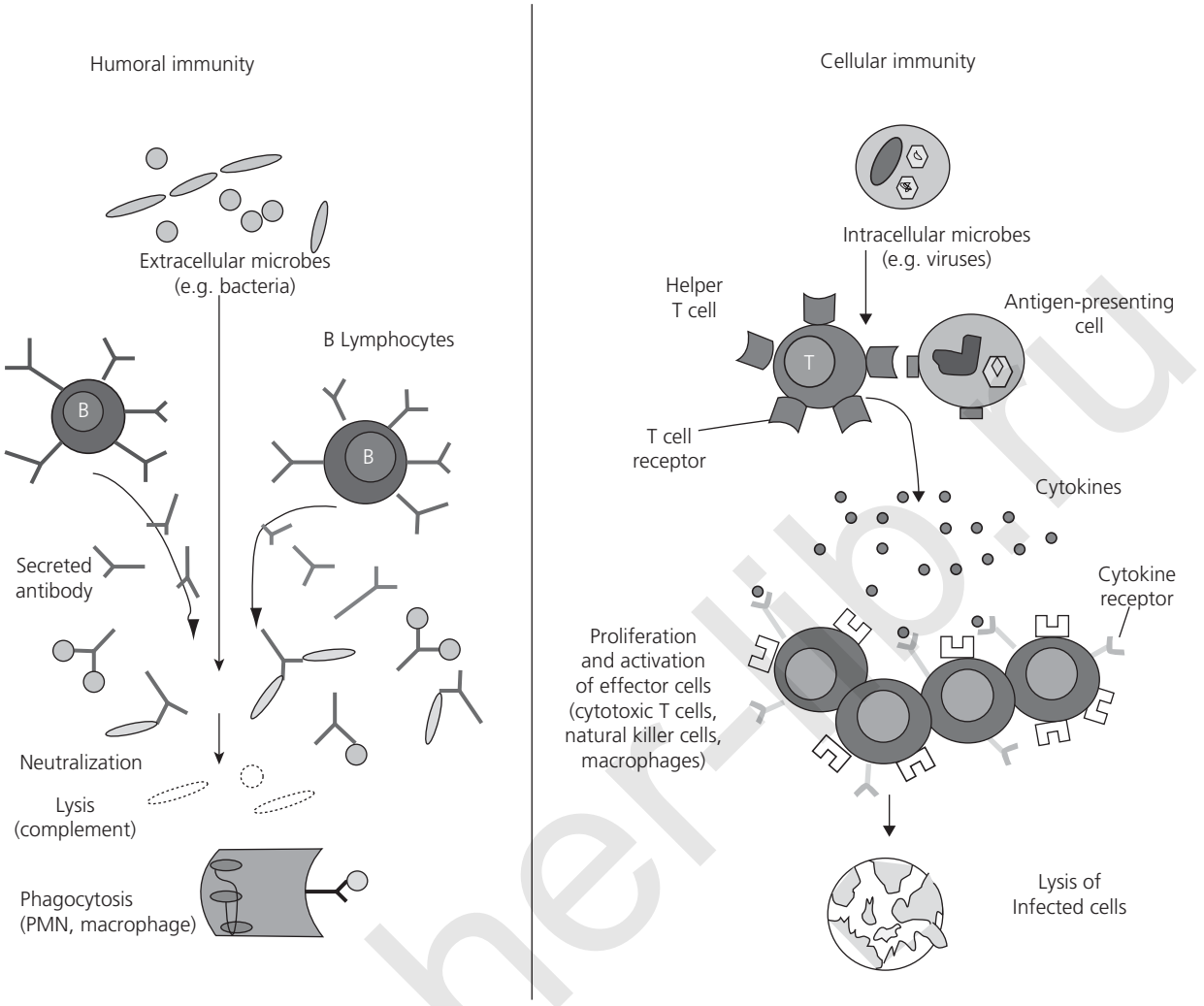

Figure 16.1 Immune function: Humoral and cellular immunity. Humoral immunity is mediated by B-lymphocytes which produce soluble antibody proteins. These antibodies can either: (1) directly neutralize extracellular microbes; or (2) activate complement, neutrophils, macrophages to kill microorganisms. Cellular immunity is mediated by T-lymphocytes. Cytotoxic T-cells directly lyse pathogens. Helper T-cells produce cytokines which stimulate other immune cells to remove microorganisms.

intensive care have infection rates of 25–50%[8,9] and mortality has not changed from 15–20% over the last 20 years. Altered bactericidal mechanisms are responsible for the increased vulnerability to sepsis in this group and mirror the pattern seen in grossly neutropenic patients.[10] Neutropenia commonly develops in neonatal sepsis in contrast to the leukocytosis in septic adults.[11] This may be mediated by a decreased neutrophil storage pool and a limited capacity for increased progenitor production in newborns, especially preterms.[12]

There is increasing evidence that sepsis and inflammation are important in the pathogenesis of perinatal brain injury. In preterm infants episodes of sepsis are associated with poorer neurodevelopmental outcomes.[13] In addition, an association between cerebral palsy and maternal peripartum infection in term infants has been well documented.[14] Elevated proinflammatory cytokines have also been demonstrated in retrospectively reviewed dried neonatal blood spots from children aged three years with cerebral palsy.[15] Activated leukocytes and infection have been implicated in the pathogenesis of neonatal brain damage.[16] Severe disruption of the blood–brain barrier in severe asphyxia may exacerbate neuronal damage[17] allowing infiltration of activated immune cells and cytokines.

NEONATAL INNATE IMMUNITY

Newborns rely on their innate immune system initially following birth as there are deficiencies in the adaptive response due to lack of previous exposure to antigens *in utero*.[7] The intrauterine environment is usually sterile and transition postnatally to the foreign antigen-rich external world starts with colonization of skin and gut with microorganisms. The fetus is considered to be immunologically naive and exists in a state of immune privilege *in utero*, to prevent rejection by the maternal immune cells. The *in utero* defense system is largely unknown although recent evidence hints at a powerful fetal system of innate immunity.[18] The

antibacterial properties of vernix caseosa, the creamy white substance covering the skin of term babies, have also been recognized and in particular the presence of antimicrobial peptides including alpha defensins[19] and inflammatory mediators.[20] Antimicrobial peptides may be an adjunctive compensatory mechanism in the neonate as adaptive immunity evolves.[21] Neonates are immune competent but with a predominant Th2 profile being geared towards immune tolerance instead of towards defense from microbial infections (Th1-skewed).[22] Th1 responses are suppressed by placental products such as progesterone, prostaglandin E2, and cytokines such as IL-4 and IL-10.[23–25]

MONOCYTES

The crucial role of monocytes/macrophages in the immune response resides in their accessory cell and immunoregulatory functions of both humoral and cellular immunity. Human cord blood contains almost three times as many monocytes as adult blood does and major changes occur in the levels of monocytes during the first few weeks of life. Newborn macrophages show poor resistance against facultative intracellular organisms. Newborn monocytes exhibit marked heterogeneity with respect to density. This heterogeneity in density is reflected in functional responses in different populations of newborn monocytes.[26] The most dense population of newborn monocytes appear to have helper function for antibody production, while suppressor function resides in the less dense populations.[27] Neonatal blood monocytes are also characterized as having a much lower frequency of class II molecular expression than adult monocytes, which may be related to the selective incapacity of neonates to secrete significant levels of IFN-γ.[28] The precise role of the monocyte in the newborn's unique susceptibility to infections with various agents remains a challenging area for future study. Dendritic cells are the primary antigen-presenting cells for optimum sensitization of naive T-cells to antigen. Newborn dendritic cells have been shown to be deficient in IL-12 (p35) expression, a key regulator of Th1-type T-cell responses.[29]

Neutrophils

The critical role of the neutrophil in host defenses against microbial infection has long suggested that defects in this particular cell type might be the cause of the increased susceptibility of the newborn to serious bacterial infections. Impaired neonatal neutrophil function at birth has also been implicated in neonatal inflammatory disorders.[11] Recent advances in our understanding of the molecular basis of cell adherence and phagocytosis have provided us with greater insight into the role of the neutrophil in the newborn's defense system. Numerous *in vitro* abnormalities include decreased chemotaxis, leukocyte adherence, bacterial killing, and depressed oxidative metabolism.[30,31] However, most of these neonatal neutrophil functions have been found in cord blood, which contains immature forms of the cells, and therefore care must be taken in interpreting some of the data. Oxidative metabolic function of cord blood monocytes, measured by chemiluminescence, has been shown to be depressed 12–36 hours after birth.[32] Cytoskeletal actin polymerization has also been shown to be altered in neonates.[33]

Decreased adherence of neonatal neutrophils may be caused, at least in part, by the decreased expression of adherence glycoproteins, or by decreased fibronectin content in the plasma membrane of neutrophils.[34] Humoral defects have also been found in neonates, which may help explain the decreased levels of chemotaxis reported in neonatal neutrophils. Such altered humoral factors include decreased levels of complement components and fibronectin.[35,36]

Neonatal neutrophils exhibit normal phagocytosis of opsonized particles as well as particles that required no opsonization. The major opsonic role of neutrophils for the uptake of antibody or complement-coated microorganisms is reflected in their expression of a number of receptors both for antibody (Fc receptors) and complement (CR receptors). In newborn cord blood, the levels of these receptors are similar to those in adult neutrophils.[37–39] The level of expression of Fc receptors is significantly more upregulated in response to *in vitro* stimuli such as f-met-leu-phe (FMLP) on adult neutrophils compared to newborn neutrophils.[33]

Neonatal neutrophils have diminished function[40] and delayed apoptosis (programmed cell death) compared with adults.[41,42] In addition, neonatal neutrophil lipopolysaccharide (LPS) responses are altered,[43,44] which may further increase susceptibility to sepsis in this population. The effects of granulocyte colony stimulating factor (GCSF) and granulocyte macrophage colony stimulating factor (GMCSF) on neonatal neutrophils is altered compared with adults, showing that GCSF may improve neutrophil survival whereas GMCSF augments function.[45]

NETs are lattices of extracellular DNA, chromatin, and antibacterial proteins that mediate extracellular killing of microorganisms and are thought to form via a unique death pathway signaled by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-generated reactive oxygen species (ROS). Neutrophils from term and preterm infants fail to form NETs when activated by inflammatory agonists, in contrast to leukocytes from healthy adults, reflecting a deficit in extracellular bacterial killing.[46]

THE INFLAMMATORY RESPONSE SYNDROMES

One reason for the failure of anti-inflammatory strategies in patients with sepsis may be a change in the syndrome over time (Fig. 16.2). Initially, sepsis may be characterized by increases in inflammatory mediators; but as sepsis persists, there is a shift towards an anti-inflammatory immunosuppressive state.[47,48] If the initial insult is sufficiently severe, the proinflammatory response can become intense and lead to a massive systemic inflammatory response syndrome (SIRS) and disrupt homeostasis.[49] If the delay is prolonged and the resolution of inflammation is blocked, the neutrophil[50] has a very high potential for causing extreme damage to healthy

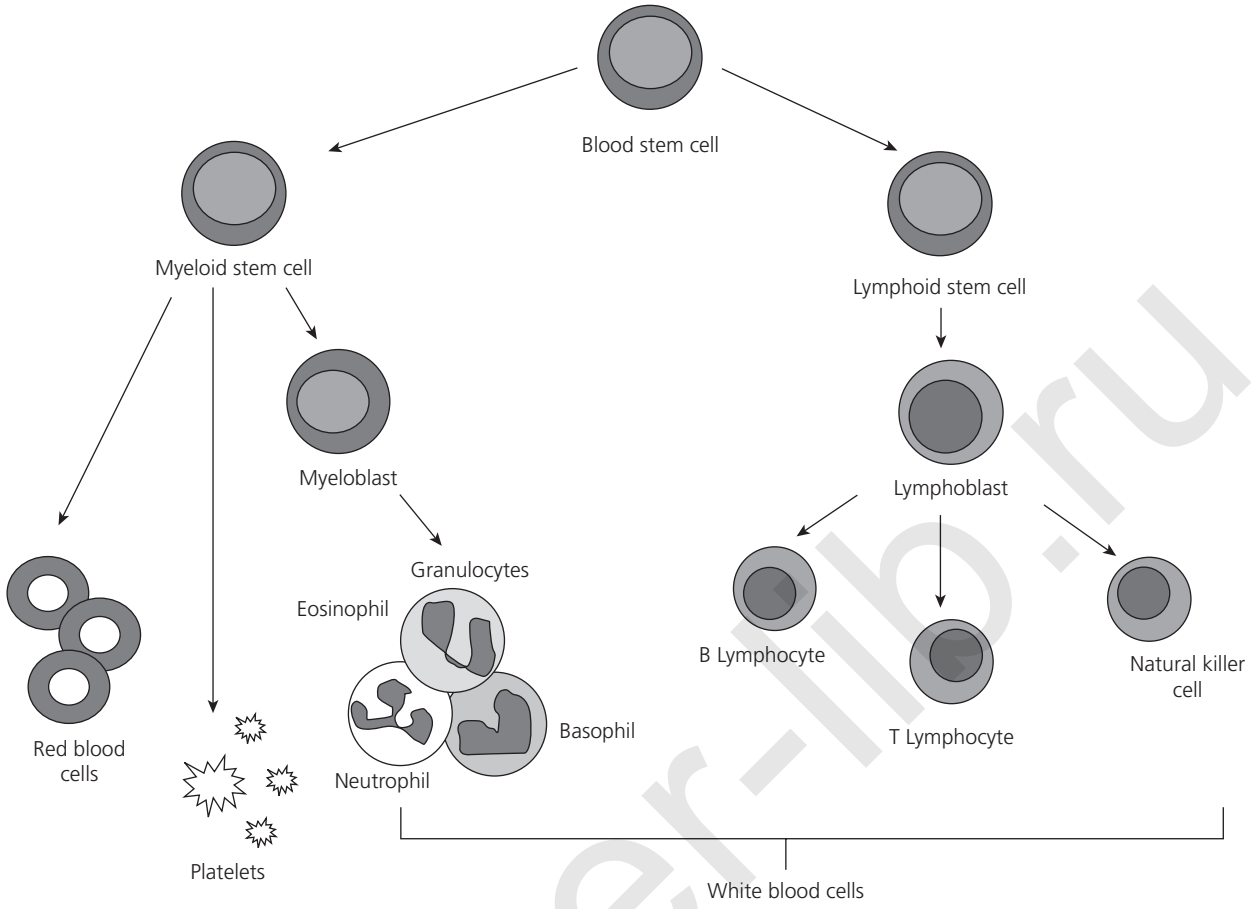

Figure 16.2 Blood cell development. Blood stem cells released from the bone marrow develop into mature blood cells over time. The blood stem cell may become a myeloid stem cell or a lymphoid stem cell. The myeloid stem can further differentiate into either red blood cells, white blood cells, or platelets. The lymphoid stem cell becomes a lymphoblast which then differentiates into one of the following lymphocyte types: B-lymphocyte, T-lymphocyte, or natural killer cell.

tissue due to the concentrated release of ROS and proteases.[51] This then forces the body to produce a massive compensatory anti-inflammatory response syndrome (CARS) that may be inappropriate and result in tissue injury. If this occurs, the body develops 'immune paralysis' and is more susceptible to infection. The final stage occurs when the overwhelming inflammation is not resolved, causing multiple organ dysfunction syndrome and death of the patient.[52] Adjunctive immunomodulatory treatments for sepsis seek to balance these responses and restore homeostasis.[52] However, discovering which inflammatory phase is dominant in the patient at a certain time point remains difficult and hinders appropriate therapeutic immunomodulation. Anti-inflammatory treatment can increase mortality. Following a cecal ligation and puncture model of sepsis in a murine model, mortality was increased in mice pretreated with interleukin receptor antagonist (IL-1ra).[53]

Fetal inflammatory responses (FIRS) and neonatal inflammatory responses (NIRS) have been described. A systemic fetal inflammatory response as determined by increased interleukin-6 is an independent risk factor for severe neonatal morbidity.[54] Preterm neonates with systemic infection have elevated IL-6, IL-10, and TNF-α concentrations. Severe infection is signified by increased IL-10/TNF-α, and IL6/IL-10 ratios. Transiently elevated IL-10 or IL-10/TNF-α levels are not invariably associated with a poor prognosis.[55]

Toll-like receptors

The Toll-like receptors (TLR) provide the critical link between microbial immune stimulants and initiation of host defense. TLR-4 is the transmembrane LPS receptor that initiates the innate immune response to common Gram-negative bacteria.[56] Neonates have an equivalent if not enhanced capacity compared with adult white-blood cell TLR-mediated response to support Th17- and Th2-type immunity, which promotes defense against extracellular pathogens. However, neonates have a reduced Th1-type response, which promotes defense against intracellular pathogens.[57] TLR-4, TLR-2, and CD14 have been shown to be increased on neonatal immune cells and cytokine release is decreased to a greater extent than adults with TLR-4 antagonists.[58] During infections, pathogens bind to TLR-4 and CD14 receptors and induce cytokine release, leading to inflammation. Neonatal IL-10 and TNF-α release depends on LPS binding, not only to CD14/TLR-4 but also to CD14

associated with another TLR.[58] There is a differential expression of TLR-2 but not TLR-4 in the course of neonatal sepsis.[59] Although decreased levels of MyD88 have been described in neonatal monocytes in response to LPS,[60] there have been few studies on neonatal neutrophils. Wynn *et al.* have recently demonstrated improved survival following polymicrobial sepsis induced by TLR-4 agonist pretreatment which enhanced peritoneal neutrophil recruitment with increased oxidative burst production.[61] Similarly, TLR-7/8 agonism also enhanced peritoneal neutrophil recruitment with increased phagocytic ability. However, these outcomes were independent of the adaptive immune system and type I interferon signaling.[61] Labour upregulates TLR-2 and TLR-4 on cord blood monocytes at the protein level suggesting that labor may be immunologically beneficial to normal newborns.[62] Augmenting innate immune function using TLR signaling may be a potential future adjunctive therapy in neonatal sepsis.

MUCOSAL IMMUNITY, HUMAN MILK, AND NECROTIZING ENTEROCOLITIS

Although the intestinal tract of the fetus is considered to be sterile, recent studies suggest that many preterm infants are exposed to microbes found in the amniotic fluid, even without a history of rupture of membranes or culture-positive chorioamnionitis.[63] Infants are colonized during vaginal delivery and subsequent breastfeeding with maternal vaginal and fecal flora. The fecal microbial profile of infants delivered vaginally versus Cesarean section showed no colonization with *Bacteroides* sp. before two months of age in infants in the latter group, and *Bacteroides* colonization that was half that of vaginally delivered infants by six months of age.[64] The common use of antibiotics, type of feeding (human milk versus formula), mode of delivery (vaginal versus Cesarean section), decreased maternal–infant direct skin contact, and various manipulations in the neonatal intensive care unit (e.g. nursing in an incubator versus under radiant warmers) have the potential to alter the intestinal microbiota.[65] In response to pathogenic intestinal microbiota, proinflammatory cytokines can increase barrier permeability, facilitating bacterial translocation with elaboration of the SIRS and multiple organ failure.[66]

Necrotizing enterocolitis (NEC) is one of the most devastating diseases in newborns. It is associated with loss of gut integrity and immune dysfunction. NEC is also characterized by exaggerated TLR-4 signaling and decreased enterocyte proliferation through unknown mechanisms.[67] Delayed bacterial commensal gut colonization is common in preterm infants in intensive care and tends to render bacterial species virulent. This abnormally upregulates TLR-4 and is associated with activation of NF-κ-B, promoting the transcription of genes for inflammation, and increased concentrations of inducible nitric oxide synthase, another potent proinflammatory regulator.[68] Increased intestinal expression of TLRs (especially TLR-2 and -4) and cytokines precedes histological injury in the experimental NEC.[69]

There is a dose-related association of human milk feeding with a reduction of risk of NEC or death after the first 2 weeks of life among extremely low birth weight infants.[70] Human milk influences neonatal microbial recognition by modulating TLR-mediated responses specifically and differentially.[71] Fresh human milk contains many immunoprotective factors, such as Ig, lactoferrin, neutrophils, lymphocytes, lysozyme, and PAF acetylhydrolase (which inhibits PAF). Human milk is also believed to promote intestinal colonization with *Lactobacillus*. The efficacy of banked human milk is less clear because freezing and pasteurization reduce the cellular components and Igs.[66]

NEONATAL ADAPTIVE IMMUNE RESPONSE

The adaptive immune system consists of B-cells, T-cells, and their products. T-cells or lymphocyte clones each bear a unique T-cell receptor (TCR) which recognizes peptides, derived from foreign or self proteins, bound in a molecular complex to the major histocompatibility complex (MHC) proteins on the surface of other cells. T-cells are divided into subsets based on their expression of different proteins which are assigned cluster differentiation (CD) numbers. Killer T-cells express CD8 and are important to kill virally infected cells. Helper T-cells express CD4 and orchestrate the overall immune response by secreting cytokines and providing co-stimulatory signals to $CD8^+$ cells and B-cells.

The basis of an adequate immune response resides in the capacity of individual cells of the immune system to recognize and react to the myriad antigens in the environment. The hemopoietic system of pluripotent stem cells is the source of all the major cell types, which are involved in the immune response. These cells include various lymphocyte subsets, macrophages, natural killer cells, monocytes, and polymorphonuclear leukocytes. These cells are involved in a complex regulatory network of cell interactions which constitute an immune response, and whose function is to eliminate both self-aberrant molecules and cells, as well as to protect the host from microbial attack (Fig. 16.3).

Lymphocyte development occurs along two distinct pathways leading to the production of the two major lymphocyte

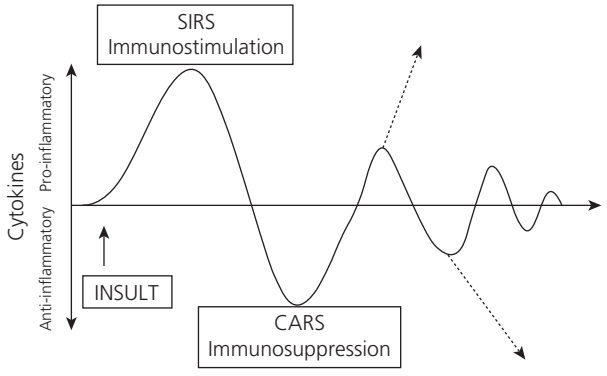

Figure 16.3 Pro-v anti-inflammatory responses. These responses eventually balance to produce homeostasis and recovery. If one or other response predominates it may increase morbidity and mortality. CARS, compensatory anti-inflammatory response syndrome; SIRS, systemic inflammatory response syndrome.

populations, T-cells and B-cells, which have very different biological effector functions. The thymus is the site of development of T-cells, which are responsible for the range of effector functions collectively termed cell-mediated immunity. Cell-mediated immunity ranges from the release of soluble factors such as cytokines, which regulate the activity of all cells of the immune system, to direct cytopathic effect of cytotoxic lymphocytes on viruses or tumor cells. B-lymphocytes, on the other hand, have a more restricted effector function, confined to the synthesis and secretion of humoral antibodies in each of the Ig classes, IgG, A, M, D, and E. More recently, B-lymphocytes have been shown to be capable of presenting antigen to T-cells.[72] In man, the site of synthesis of B-lymphocytes is the bone marrow.

The different regulatory and effector functions mediated by cells of the immune system represent the capabilities of populations of cells that can be recognized by the presence of different patterns of expression of cell-surface antigens. The availability of monoclonal antibody reagents for the recognition of lineage, differentiation stage, activation phase, and effector function of different cell types has contributed enormously to our understanding of the extent of heterogeneity of different cell types within the immune system. This heterogeneity of cell types forms the basis for an international leukocyte typing classification system, utilizing monoclonal antibodies which recognize specific cell-surface markers in order to define individual leukocyte subsets.[73] The more widely used CD antigens, for classifying immune effector cell types, are described in Table 16.1.

It is now well established that T-lymphocytes do not recognize native antigen on any pathogen, but rather a processed form of the antigen, in association with self MHCs, class I (HLA-A,B,C) or class II (HLA-DR/Ia) molecules.[74,75] This important processing of foreign antigen is carried out by one of a group of antigen-presenting cells which include macrophages, dendritic cells, Kupffer cells, and some B-cells. The proper functioning of these accessory cells is therefore as central to an adequate immune response as that of specific effector cells, such as the T-lymphocytes. When antigen becomes localized and processed by the antigen-presenting cell (APC), the complex interaction of APC, T-cells, and B-cells begins, which eventually leads to specific immunological memory, both of T-cells and B-cells as well as to antibody production. Although B-cells can be directly activated by antigen, under experimental conditions, concomitant activation of T-cells is required for the clonal expansion of antigen-specific B-cells, leading to the generation of long-lived memory B-cells and Ig-secreting plasma cells.[76,77]

Table 16.1 Cell surface antigens which identify leukocyte subtypes in the newborn.

Antigen	Function
T-cells	
CD2	LFA-3 receptor (adhesion)
CD3	Associated with cell receptor
CD4	Class II and HIV receptor
CD5	Co-stimulatory
CD7	Unknown
CD8	Class I receptor
B-cells	
CD19	Signal transduction
CD20	Unknown
CD21	C3d and EBV receptor (CR2)
CD72	Ligand for CD5
NK-cells	
CD16	IgG receptor (FcRIII)
CD56	Isoform of N-CAM
CD94	Unknown
Myeloid/monocytic cells	
C14	Unknown
C15	Unknown
CD32	IgG receptor (FcRII)
CD35	C3b receptor (CRI)

T-cell responses

Several studies in the literature have questioned the stage of maturity of circulating lymphocytes in the newborn. Some parameters of T-cell function in cord blood, however, have been shown to be normal or similar to those of healthy older children. These include the quantity and proportion of T-lymphocytes,[78] lymphocyte response to mitogens,[79] and production of certain cytokines such as IL-2.[80] However, other newborn cellular immune functions have been reported to be depressed. These include PHA-induced cytotoxicity, lymphotoxin production, as well as reduced cAMP levels.[81–83] The overall characteristic that distinguishes newborn T-cells from other T-cells at different stages of development is that they are recent thymic emigrants, not long after exiting the thymus.

Lymphocyte phenotype

There has been a reported incidence of up to 25% of cord blood lymphocytes co-expressing both CD4 helper T-cell and CD8 suppressor T-cell surface markers.[84] Cells of this double positive phenotype are common in the thymus, where they are considered to be the precursors of mature helper and suppressor T-cells. However, more recently, using more sensitive flow cytometry-based analytical techniques, workers investigating cord blood samples failed to detect the presence of doubly labeled CD4/CD8-labeled cells.[85] Other markers of an immature phenotype of newborn T-cells have been described. The CD38 antigen, which is a marker of immature thymus-derived T-cells, as well as activated lymphocytes, is present in the majority of newborn cord blood lymphocytes.[86] This thymocyte-like membrane phenotype can be modulated by the influence of thymic hormones *in vitro*.[87] In addition to the presence of CD38 thymocyte-associated antigen, human cord blood contains T-cells of the unusual phenotype which include peanut agglutinin-positive/CD8-positive as well as some CD3-positive CD1a-positive lymphocytes.[88] Like CD38, CD1a is a marker present on early thymocytes.[88] CD1a-positive cells are especially present in

preterm and antenatally stressed infants.[89] While the neonate has adequate numbers of CD4 helper T-cells, cord blood T-cells are deficient in their ability to provide help for antibody production, probably at the level of altered cytokine production.[90,91] The cellular basis for this functional defect is reflected in other phenotypic markers of functional activity. More than 90% of cord blood T-cells carry the $CD45RA^+$ 'virgin' cell phenotype marker, compared with 50% of adult T-cells which express $CD45RA^+$.[92] In contrast, less than 10% of cord blood lymphocytes express the CD45RA 'memory' T-cell marker compared to a 50% level of expression in adult T-cells.[93] This major imbalance in the ratio of $CD45RA^+$/CD45RA, CD4-positive T-cells in the newborn compared to adults may help explain some of the functional differences of newborn cells compared to adult lymphocytes. Regulatory factors contributing to the differences in functional activity and the different phenotypic profiles of newborn T-cells compared to adults require further investigation in order to arrive at a fuller understanding of the mechanisms involved.

B-cell responses

The newborn's capacity to produce antibody is significantly reduced, both quantitatively and qualitatively, compared to that of an adult. Newborn B-lymphocytes poorly differentiate into Ig-producing cells.[94,95] The mechanisms controlling this aspect of B-cell immunocompetence in the newborn are unknown. Many studies have focused on the ability of cord blood lymphocytes to terminally differentiate into IgG-, IgA-, and IgM-producing plasma cells in response to mitogens. However, a delay occurs in B-cell differentiation, resulting in decreased production of plasma cells, markedly diminishing the secretion of antibody, and restriction of secreted antibody to IgM isotype.[96] Cord blood B-lymphocytes, unlike adult B-cells, are usually unable to differentiate into Ig plaque-forming cells when cultured with pokeweed mitogen alone, or with killed *Staphylococcus aureas* Cowan 1 alone.[97] However, it appears that these two stimuli can act synergistically to induce a significant *in vitro* plaque-forming cell response in cord blood B-cells.

The relative inadequacy of IgG and IgA antibody synthesis cannot be attributed to the lack of precursor B-cells, since lymphocytes bearing these Ig classes on the surface are present in the fetus and on cord blood B-cells.[98,99] The impaired capacity to undergo IgG or IgA synthesis has been attributed to immaturity of cord blood B-cells, since their activation by polyclonal activators, like pokeweed mitogen, lipopolysaccharide, or Epstein–Barr virus, generally results in moderate or reduced levels of IgM synthesis with no IgA, IgG, or IgE production.[95] However, the question of T-cell immaturity as a significant factor in the restricted imunoglobulin isotype production of cord blood B-cells has to be taken into account.[100,101] Cord blood mononuclear cells produce normal levels of IgE *in vitro*, when cultured in the presence of IL-4, indicating that the B-cells are mature in their capacity to switch to IgE-producing cells.[100] The defect observed may be associated with the failure of cord blood T-cells to produce detectable levels of IL-4, which has been shown to be responsible for induction of IgE synthesis, both *in vitro* and *in vivo*.[101] An inadequacy of newborn T-cell help for plasma cell isotype switching to IgG and IgA Ig-producing cells is also suggested by the observation that IgG and IgA antibody responses are more dependent upon T-cell help than are IgM responses. In a series of experiments, co-culturing adult T-cells and newborn T-cells with adult or newborn B-cells, the addition of adult T-cells greatly enhanced the pokeweed mitogen-driven responses of newborn mononuclear cells, which included IgG and IgA responses.[102,103] Cord blood T-cells, however, did not show augmentation of B-cell differentiation when co-cultured with non-T-cells from adults. These data, looked at collectively, would indicate that deficient T-cell function, as well as possible deficiencies of B-cell function, exist in the newborn. The defect in Ig production may also be contributed to, of course, by suppressor T-cell activity of newborn lymphocytes or even by enhanced suppressor activity of newborn monocytes. The newborn also possesses a major population of CD5-positive[102] B-cells, which are only commonly found in patients with autoimmune diseases. It appears that these cells, in the newborn, uniquely express the activation antigens 4F2 and CD25.[104] The significance of these activated CD5-positive B-lymphocytes is, however, unclear. A particular function of these cells is the production of natural polyspecific autoantibodies.[105] A possible role for these cells in the newborn may therefore be the influencing of emerging B-cell specificities. Preterm infants are susceptible to viral infection and this is associated with impaired Toll-like receptor-3 and -7 expression on γδ cells compared with term babies and they failed to optimize cytokine production in response to coincident TCR and TLR agonists.[106]

IMMUNOGLOBULINS

The presence of physiological hypogammaglobulinemia has been noted by several investigators in preterm and term infants. Neonates have low levels of IgA and IgM immunoglobulins because of the poor ability of these Ig classes to cross the placenta.[107] Furthermore, all IgG sub-classes are not equally transferred across the placenta, especially the IgG2 and IgG_4 sub-class levels, which are therefore also relatively low in the newborn.[54] The neonate is consequently very susceptible to pyogenic bacterial infections since most of the antibodies that opsonize capsular polysaccharide antigens of pyogenic bacteria are contained in the IgG2 sub-class and IgM immunoglobulin subfraction. Neonates, even during overwhelming sepsis, do not produce type-specific antibodies.[57,108] This impairment in antibody production appears to be secondary to the defect in the differentiation of B-lymphocytes into Ig-secreting plasma cells and T-lymphocyte-mediated facilitation of antibody synthesis. There is a marked limitation in infant antibody responses to most bacterial capsular polysaccharides.[109] This limitation prevents successful infant immunization with Hib polysaccharide vaccines,[110] which fortunately can be circumvented by use of conjugate vaccines shown to be immunogenic in infants.[111]

CYTOKINES

Among the major molecular components of the immune system are the Igs, cytokines, and proteins of the acute phase response and complement system. The term 'cytokine' is used to describe a group of peptides with potent immunoregulatory effects, which are produced and utilized by individual cells of the immune system to communicate with each other and to control the environment in which they operate. A description of some of the major characterized cytokines is listed in Table 16.2.

Present evidence suggests that cytokines are of immense importance in controlling both local and systemic immune responses, inflammation, and the regulation of hematopoiesis.[112,113] Their most important function appears to be at local level, modulating the behavior of adjacent cells in a paracrine fashion,[113] or the cells that secrete them, in an autocrine fashion.[114] In addition, especially in the case of TNF-α, IL-1, and IL-6, cytokines may affect endocrine-like activity on distant organs or tissues.[115] Cytokines have important biological activity which can be of major clinical benefit, such as stimulation of antimicrobial function, promotion of wound healing, and myelostimulation.[116,117] With such diverse biological function, an exaggerated or prolonged secretion of these peptides may be detrimental for the host. Specifically, aberrant secretion of cytokines, such as TNF-α and IL-1, are thought to be responsible for the hemodynamic changes in the host during septic shock and in cachexia of chronic disease.[118,119] The availability of recombinant DNA techniques to produce cytokines in almost unlimited quantities, and the production of specific antagonists such as soluble cytokine receptors and IL-1 receptor antagonists, are leading to new and exciting therapeutic potential for these molecules.

Table 16.2 Cytokines.

Name	Principal cellular source	Principal cellular target
IL-1α + β	Macrophages, fibroblasts, endothelial cells	Thymocytes, endothelial cells, neutrophils, T-cells, B-cells
IL-2	T-cells	T-cells, B-cells
IL-3	T-cells	Multipotential stem cells
IL-4	T helper cells	T-cells, B-cells, mast cells, macrophages
IL-5	T helper cells	B-cells, eosinophils
IL-6	Fibroblasts	B-cells, fibroblasts, hepatocytes
IL-7	Stromal cells	B-cells
IL-8	Macrophages	Neutrophils
IL-10	T-cells, activated monocytes	T-cell subsets, macrophages
IL-12	Macrophages	T-cells, NK cells
IL-13	T helper cells	B-cells
TNF-α	Macrophages, fibroblasts	Many cells type
TNF-β	T-cells	Many cells type
IFN-α	Macrophages, fibroblasts	Many cells type
IFN-β	Fibroblasts	Many cells type
IFN-γ	T-cells, NK cells	Macrophages, T-cells, B-cells
TGF-β	T-cells, macrophages, platelets	Many cell types
GM-CSF	T-cells, endothelial cells	Multipotential stem cells

Chronic lung disease may be associated with impairment in the transition from the innate immune response mediated by neutrophils to the adaptive immune response mediated by T-lymphocytes. Of 1062 extremely low birth weight infants in the Neonatal Research Network of the National Institute of Child Health and Human Development, 606 infants developed chronic lung disease or died. On the basis of results from all models combined, bronchopulmonary dysplasia/death was associated with higher concentrations of interleukin 1β, 6, 8, and 10 and interferon γ and lower concentrations of interleukin 17, regulated on activation, normal T-cell expressed and secreted, and tumor necrosis factor β.[120]

IMMUNOMODULATATION

Neonates, especially those preterm, are particularly vulnerable to sepsis. Transplacental transfer of Igs from the mother to the fetus occurs after 32 weeks of gestation and endogenous production commences at a few months of age. Administration of i.v. Ig provides IgG that can bind to cell surface receptors, provide opsonic activity, activate complement, promote antibody-dependent cytotoxicity, and improve neutrophilic chemoluminescence. Term neonates have low type-specific antibody and opsonin deficiencies.[39,121,122] Preterm neonates also have severe hypogammaglobulinemia[123] and deficient complement activity.[124,125]

Theoretically infectious morbidity and morbidity could be reduced by the administration of i.v. immunoglobulin (IVIg). Meta-analysis of small trials has suggested that IVIg may reduce the rate of neonatal death but the Cochrane review could not recommend routine use of prophylaxis against nosocomial infections or for treatment in proven or suspected infection.[126,127] The International Neonatal Immunotherapy Study (INIS) is an international multicenter randomized controlled trial studying the use of non-specific IVIg in addition to antibiotics in babies with suspected or proven sepsis. This study is designed to confirm or refute the hypothesis that IVIg reduces the rate of mortality and major morbidity and results are awaited.[128]

COLONY STIMULATING FACTORS

Neonates often become neutropenic when septic and therefore the use of GCSF and GMCSF have been studied on this population. The Cochrane meta-analysis of trials has found no significant improvement in outcome when colony stimulating factors (CSFs) were used for prophylaxis or treatment of sepsis.[129]

The PROGRAMS Multicenter RCT of Prophylactic GMCSF to Reduce Systemic Sepsis in Preterm Neonates included 280 infants <31 weeks. When GMCSF 10 μg/kg per day was administered prophylactically for 5 days, neutrophil counts were higher on days 3–12 than controls. There were no significant differences in sepsis-free survival in infants who are neutropenic at recruitment, the number of infants experiencing one or more episodes of culture-positive sepsis or survival to discharge. GMCSF rapidly corrected neutropenia in preterm, growth-restricted neonates. Prophylactic GMCSF and correction of neutropenia, even when severe, did not reduce sepsis or all cause mortality.[130] Kuhn *et al.* recently described a multicenter, randomized, double-blind, placebo-controlled trial of the prophylactic use of GCSF in neutropenic preterm infants <32 weeks ($n=200$) and found no differences in survival free of confirmed infection for 4 weeks after treatment with either rG-CSF (10 mg/kg per day) or placebo for 3 days.[131] However, activated leukocytes may mediate neonatal brain injury.[16] GMCSF stimulates neonatal neutrophil activation, unlike GCSF, and both prolong neutrophil survival.[45] Therefore, the two-year developmental outcomes of the PROGRAMS trial will be awaited with interest. In addition, a randomized controlled trail of CSF use in infants with sepsis is needed to address the use of these agents in neonates.

APC (drotrecogin alfa activated) decreased death from any cause in patients with sepsis (absolute reduction in RR 6.1%) and there was one additional life saved for every 16 patients treated. There was a decrease in coagulopathy: D-dimers and inflammation:IL-6[132] RESOLVE (REsearching severe Sepsis and Organ dysfunction in children: a gLobal perspectiVE) trial evaluated sepsis for safety, pharmacokinetics, and pharmacodynamics of drotrecogin alfa (activated) in children with severe sepsis.[133] The patients studied were from term newborn to 18 years with similar pharmacokinetic profiles, effects on D-dimer levels, other coagulation parameters, and bleeding rates to PROWESS, although there was more Gram-negative sepsis.

PREBIOTICS AND PROBIOTICS

Prebiotics are unique oligosaccharides that are not absorbed but facilitate colonization by probiotic organisms (bifidobacteria and lactic acid-producing bacteria). Use of probiotics has been shown to decrease the duration and severity of rotavirus-induced diarrhea, allergies to cow milk protein, atopic dermatitis, and some inflammatory intestinal diseases. A relative reduction in the risk of NEC, late-onset sepsis, and mortality has been demonstrated with probiotics (*B. infantis*, *Streptococcus thermophilus*, and *B. bifidus* in one study and *Lactobacillus acidophilus* and *B. infantis* in another).[134,135] A multicenter, double-blind, randomized, controlled trial of the probiotics *B. bifidus* and *L. acidophilus* showed a lower incidence of NEC in the study group than controls but sepsis was more frequent,[136] although this difference was not significant on multivariate analyses and none of the affected patients developed sepsis with organisms used as probiotics. There are persistent concerns about the use of probiotics in immunosuppressed infants as there have been reports of preterm infants who had short gut syndrome developing *Lactobacillus* bacteremia while receiving this probiotic bacterium.[137] In adults, another multicenter, double-blind, randomized, controlled trial of probiotics to reduce infections in pancreatitis showed a more than two-fold increase in mortality and no reduction in infections.[138] In addition to these immediate concerns about sepsis, the long-term effects of the use of probiotics, especially in preterm infants in terms of immune modulation in later life, development of immune disorders (such as insulin resistance, diabetes, obesity, and cancer), and neurodevelopmental outcomes are not known.

IMMUNE DEFICIENCY DISEASES IN THE NEWBORN

Although there are many forms of primary immunodeficiency in the newborn there are several well-described clinical conditions, two of which we will mention in this chapter. DiGeorge's syndrome (DGS) usually involves a hemizygous microdeletion in the chromosome 22q11.2 region characterized by the triad of conotruncal cardiac anomaly, thymic hypoplasia, and hypocalcemia. The syndrome encompasses a broad spectrum of congenital defects that have varying degrees of severity, especially in the degree of immunodeficiency, and the incidence is one in 4000 births. Only $<1\%$ of patients have severe immunodeficiency but early identification is essential to prevent and treat life-threatening infections and to plan for immune reconstitution. Immunodeficient DGS patients present with profoundly decreased T-cell numbers ($<50/mm^3$), depressed T-cell function (as measured by lymphocyte proliferation assays, such as with mitogens), and often concomitantly low Ig levels. These patients are at high risk for the development of disseminated and life-threatening infections with organisms that require an intact cell-mediated immune system for eradication, such as cytomegalovirus, adenovirus, or *Pneumocystis jiroveci* (formerly *P. carinii*). Graft-versus-host disease also may be found due to transplacental transfer and engraftment of maternal T-cells, leading to the typical rash and diarrhea seen in other forms of graft-versus-host disease.[139]

Severe combined immunodeficiency (SCID) is a primary immune deficiency with a severe defect in both the T- and B-lymphocyte systems, resulting in serious infections within the first few months of life. Newborn screening for severe combined immunodeficiency is advancing toward pilot trials as early diagnosis improves outcomes and facilitates bone marrow transplantation.[140] Persistent lymphopenia or leukopenia and recurrent infections in neonates warrant further investigation and immunology and infectious diseases involvement.

CONCLUSION

In fetal and neonatal life, many aspects of the immune system are different to older children and adults. The molecular and cellular basis for these abnormalities, while partially explained by many of the observations described in this chapter, remains

relatively unclear. The prospects for more specific and selective immunological intervention as part of the treatment of the immunocompromised neonate undergoing surgery will benefit enormously from ongoing research into the biological basis of immuno-incompetence of the newborn.

Designing new drugs to neutralize microbial products or block their interaction with specific receptor on immune cells is an attractive concept.[141] Potential targets include LPS binding protein, CD14, TLR-4, and MD-2 for Gram-negative sepsis, and CD14, TLR-2, and TLR-6 for Gram-positive sepsis. Monoclonal antibodies against CD14 are being evaluated in phase II studies. Several intracellular signaling molecules, such as MyD88 and mitogen-activated protein kinase, are other possible therapeutic targets. However, inactivating molecules that are pivotal to innate immunity can be harmful, as shown by the increased sensitivity to bacterial sepsis in mice with mutations of the Tlr4 gene.[142] Careful selection of patients with severe infections associated with a high probability of death will therefore be essential.

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17

Neonatal sepsis

JAMES PIERCE, TRACY GRIKSCHEIT, AND HENRI FORD

INTRODUCTION

Neonatal sepsis remains one of the most common and potentially preventable causes of mortality and long-term morbidity in the world. A recent study by the Neonatal Research Network of the National Institute of Child Health and Human Development (NICHD) demonstrated that compared with uninfected infants, those who develop infections in the neonatal period were significantly more likely to have adverse neurodevelopmental outcomes at follow-up. These include cerebral palsy, poor vision, delayed psychomotor development, low Bayley Scales of Infant Development II scores on the mental development index, as well as impaired head growth, a known predictor of poor neurodevelopmental outcome.[1] Similarly, a four-fold increase in the incidence of cerebral palsy was reported in a British cohort,[2] and poor neurodevelopmental outcomes were noted in a large American cohort[3] following neonatal infections.

DEFINITIONS AND CLINICAL FEATURES OF SEPSIS

Sepsis is characterized by an invasive microbial infection and a resulting systemic inflammatory response. Classically, sepsis was described in the adult patient with a Gram-negative infection who subsequently developed fever, hypotension with poor tissue perfusion, and ultimately multiple organ failure. Subsequently, bench and clinical research demonstrated that a number of initial insults, including significant infection, toxin exposure, severe tissue necrosis, and open burn wounds, were capable of inducing these signs and symptoms. Therefore, the term systemic inflammatory response syndrome (SIRS) was introduced to describe this constellation of symptoms. A number of pro-inflammatory as well as regulatory (or anti-inflammatory) cytokines and hormones have been identified in association with the SIRS response. Investigators have grouped various patterns of cytokine response with specific clinical signs and symptoms. Thus, in addition to SIRS, the concept of a compensatory anti-inflammatory response syndrome (CARS) or a mixed anti-inflammatory response syndrome (MARS)[4,5] has also evolved (Fig. 17.1).[6]

Sepsis is defined as the presence of a SIRS response coupled with a causative infection. Historically, group B streptococci (GBS) and associated SIRS accounted for the majority of admissions to the neonatal intensive care unit for sepsis (see Table 17.1).[7,8] Subsequent implementation of perinatal antibiotic therapy has drastically reduced the number of GBS infections; nevertheless, GBS and *Escherichia coli* remain common pathogens in neonates. This is in stark contrast to *Pseudomonas*, *Klebsiella*, and *Bacteroides*, which are significantly more common in the pediatric and adult age groups. In addition, systemic fungal infections, particularly *Candidiasis*, have become increasingly prevalent in the neonatal population.[9,10] Thus, a discussion of sepsis in the neonate – from epidemiology to outcome – cannot be separated from the epidemiology of neonatal infections.[11,12]

Sepsis neonatorum is the presence of systemic symptoms in the setting of an identified microbial infection. Because neonates have a relatively immature immune system and their intestinal microbial flora continues to evolve during the first weeks of life, defining criteria that appropriately identify sepsis and serious bacterial infections in this age group remains challenging. Furthermore, as the phenotype of the neonate's immune system changes rapidly, criteria must take into consideration immunologic differences in preterm, term, or older infants. Therefore, a list of the clinical features of sepsis must reflect both corrected gestational age and chronologic age. There are multiple criteria for defining or diagnosing sepsis. Clinicians can apply these criteria to determine if sepsis is likely, guide subsequent workup and antibiotic therapy, or document the presence of sepsis for outcome analysis (see Table 17.2 for comparison of different sepsis criteria). One of the important early criteria, for example, is the Rochester Criteria.[13,14] These criteria predict serious bacterial infection and high risk of sepsis in a population of healthy term infants, less than three months of age. However, the Rochester criteria neither effectively

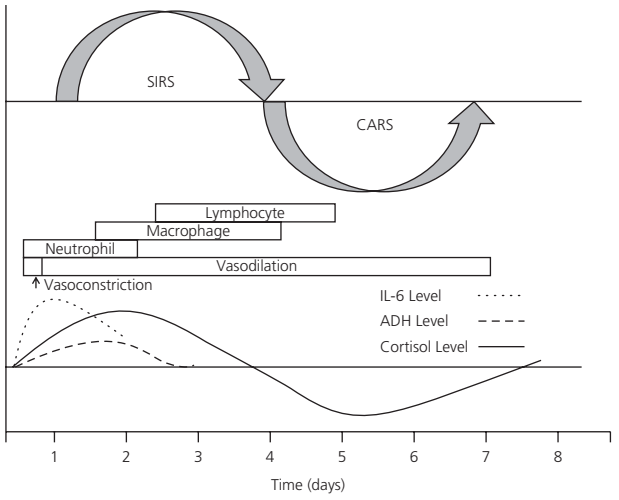

Figure 17.1 Following onset of sepsis, there are predictable phases of systemic inflammatory response syndrome (SIRS) and compensatory anti-inflammatory response syndrome (CARS). This figure is not meant to be comprehensive, but representative of several of the most well-understood components of each phase.

Table 17.1 Major events in the changing epidemiology of bacterial sepsis in the neonatal intensive care unit.

Changing epidemiology of neonatal sepsis	
1930–40s	Majority of infections were Gram-positive cocci
1950s	Balanced frequency of *S. aureus*, *E. coli*
1960s	Rising incidence of group B *Strep*, ongoing *E. coli*
1970s	Peak of group B *Strep*
1980s	Coagulase-negative *Staph* surpassed *Strep*, *S. aureus*, *E. coli*
1990s	Rising incidence of nosocomial infections: CNS and *Candida* sp.
2000s	Multidrug resistant infection

define sepsis nor assist in the management of complicated perinatal or preterm infants.[15] Pediatric criteria,[11] developed from large-scale pediatric databases to parallel adult criteria, are useful in defining sepsis for outcome analysis but lack characteristics that make them applicable to the neonatal population. In addition, some criteria are strictly biochemical[16] rather than clinical, in contrast to the more classic 'Bone' criteria.[17,18] Table 17.2 shows a useful list of criteria that help define the sepsis syndrome in the neonate.[17,19–22]

EPIDEMIOLOGY AND RISK FACTORS

Recent studies have shown an increased incidence of sepsis in the United States[23] and in the world.[24–26] Martin and colleagues reported an 8.7% increase annually in the overall incidence of sepsis between 1979 and 2000.[27] Indeed, a national survey of nearly 1.6 million hospitalized children, ages 19 years or younger, revealed 42 364 cases of sepsis per year.[28]

Overall, bacterial sepsis affects approximately 32 000 infants annually, or 1–8 cases per 1000 live births. Nursery-acquired sepsis has a national incidence of 1.4% and NICU-acquired sepsis ranges from 5 to 30%, depending on the level of acuity of the unit. Well-established independent risk factors for infections can be divided into genetic, prenatal, perinatal, and postnatal causes. In the prenatal period, the presence of maternal–fetal infection, the need for invasive procedures, low maternal age, multiparity, and group B strep colonization have been identified as putative risk factors for sepsis.[29] Perinatal risk factors include prolonged (greater than 12 hours) internal monitoring, documented chorioamnionitis and endometritis, premature and prolonged rupture of membranes,[30] low birth weight, low gestational age, and presence of existing comorbidities.[31,32] Postnatal need for procedures or indwelling catheters, prolonged hospitalization, and overcrowded nurseries have been associated with

Table 17.2 Criteria for diagnosing sepsis in critically ill neonates and children.

Physiologic criteria	Laboratory criteria	Biochemical criteria
Fever (rectal temperature $>38^{\circ}C$), hypothermia ($<35^{\circ}C$), or increased temperature variability in isolette	White blood cell count $>12\,000$ cell/cc or <4000 cell/cc	Elevated C-reactive protein (>3 mg/cc with physiologic symptoms, >10 mg/cc without symptoms)
Tachycardia (heart rate >95th percentile for age)	Bandemia ($>10\%$ bands)	Elevated interleukin >44.4 pg/mL
Tachypnea (respiratory rate >95th percentile for age) or increasing frequency of apneic events with bradycardia	Ratio of immature to total neutrophils (>0.2 for infection, >0.8 for bone marrow depletion)	Elevated procalcitin (PCT >6.1 ng/mL)
Hypotension (mean arterial blood pressure <5th percentile for age)	Thrombocytopenia ($<50\,000$ per cc)	Elevated lipopolysaccharide protein (LBP >25 μg)
Poor peripheral perfusion (delayed capillary refill or central-peripheral temperature disparity)	Metabolic acidosis (pH <7.25 or base excess <-5)	
Oliguria (urine output <1 mL/kg per hour after day of life 1)	Elevated lactate (>4 mmol/cc)	
Poor feeding		

an increased risk of sepsis.[12,33] There is increasing evidence for a genetic,[34] proteomic,[35] and phenotypic role in neonatal sepsis. Consistent with this observation, male gender and African-American ethnicity are independent risk factors for neonatal sepsis.

According to current terminology, preterm neonates are defined as those born before 37 0/7 weeks' gestation and late preterm neonates are those born between 34 0/7 and 36 6/7 weeks (Table 17.3).[36] Extreme prematurity refers to neonates at the limits of viability, specifically between 23 0/7 weeks and 27 0/7 weeks' gestation.[37]

Birth weight is defined relative to gestational age. In particular, an infant is considered small for gestational age if he/she is less than the 10th percentile in weight in an age-matched cohort; by contrast, an infant is large for gestational age if he/she is above the 90th percentile for weight. As birth weight is an independent risk factor for a number of outcomes, including neonatal sepsis, age-matched birth weight is a confounding variable. Thus, definitions for non-age-matched birth weight exist as well. Any newborn less than 2500 g is considered to have low birth weight (Table 17.4). A newborn less than 1500 g is categorized as very low birth weight, while any infant weighing less than 1000 g is considered to be extremely low birth weight. Unfortunately, neither small for gestational age, nor low birth weight captures an additional important variable – the trajectory of intrauterine weight gain. A trajectory of normal weight gain for a small for gestational age fetus is significantly less concerning than a sudden change in the trajectory of weight gain for an appropriate weight fetus. Falling off an intrauterine growth curve can indicate either primary placental insufficiency or increased fetal demand due to maternal–fetal infection.

The NICHD Neonatal Research Network defines early-onset sepsis as a culture-positive systemic infection that occurs within 72 hours of birth, while late-onset sepsis presents after 72 hours from birth (Table 17.4).[38] As a result, infants who develop early-onset sepsis consist of those delivered during active, invasive maternal–fetal infections, and those delivered without significant maternal–fetal infections but exposed to either subclinical uterine infection or maternal vaginal flora.

In recent years, several perinatal study groups have identified maternal and fetal infectious processes as being clinically significant to the fetus and a major cause of preterm delivery.[39] Microbial invasion is evident in up to 40% of preterm neonates' fetal membranes and, similar to sepsis, asymptomatic histologic chorioamnionitis is associated with poor neurodevelopmental outcome.[40] This process has both direct invasive infection and maternal–fetal-systemic effects and has appropriately been termed fetal inflammatory response syndrome (see Fig. 17.2).[41–44] Given that pathologic evaluation of fetal membranes is not always performed and final pathologic results are often not available at tertiary neonatal units, many meconium aspiration and other peripartum sepsis events may represent an underdiagnosed group of peripartum sepsis events. Indeed, respiratory distress syndrome,[45] preterm necrotizing enterocolitis,[44] long-term pulmonary,[43] and neurologic[46] outcome have all been shown to correlate with the presence of invasive infection and cord hypercytokinemia. In brief, early or prolonged rupture of membranes and ongoing vaginitis are associated with higher rates of funisitis and chorioamnionitis. These findings are more common in preterm neonates and the incidence of chorioamnionitis increases sharply with earlier gestational age (from 10% in late preterm neonates to as high as 60% in extreme prematurity). Several maternal biomarkers, including the vaginal presence of fetal fibronectin, have also been associated with increased early onset infection.[47] Appropriate use of antibiotics has been shown to reduce neonatal sepsis secondary to GBS from 78 to 47%, and overall sepsis from 4 to 1.2%.[48]

Early-onset sepsis peaks in the first 24 hours of life (85% of overall cases), and declines in frequency over the next 48 hours. As a result, early-onset sepsis is believed to be related to peripartum events, particularly transplacental infection or

Table 17.3 Rates of early-onset and late-onset sepsis by gestational age at birth.

	Extreme preterm (23–27 weeks, %)	Preterm (<37 weeks, %)	Late preterm (34–36 weeks, %)	Term (>37 weeks, %)
Early-onset sepsis (<72 hours)	Not reported by gestational age	0.56	0.44	0.02–0.35
Late-onset sepsis (>72 hours)	22–48	16	6.3	1.4

Table 17.4 Rates of early-onset and late-onset sepsis by birth weight. This table does not take into account large for gestational age (greatest 10th percentile).

	Extremely low birth weight (<1000 g)	Very low birth weight (1000–1500 g)	Low birth weight (1500–2500 g)	Appropriate birth weight (>2500 g)
Early-onset sepsis (<72 hours)	Not reported by weight	0.19–0.59%	Not reported by weight	0.12–0.66%
Late-onset sepsis (>72 hours)	22–33% mean (38% 750–1000 g, 48% 500–750 g)	16–22% mean (7% 1250–1500 g, 18% 1000–1250 g)	5–16%	1.4–5.6%

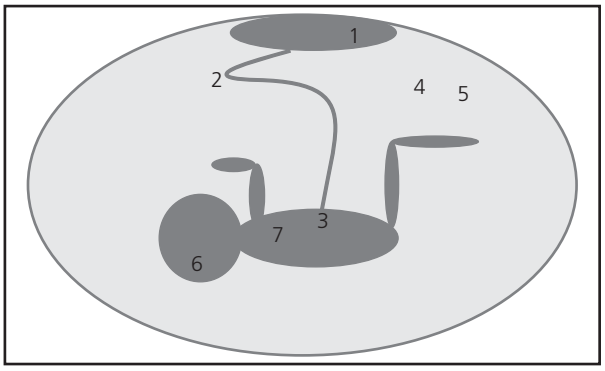

Figure 17.2 Components of fetal inflammatory response syndrome (FIRS) and ascending maternal–fetal infection; not all are present nor is the order of presentation required. 1 – Infection and inflammation of the placenta (chorioamnionitis), 2 – Ascending vasculitis and infection of the umbilical cord (funisitis), 3 – Presence of inflammatory cytokines in the fetal circulation, 4 – Presence of inflammatory cytokines in the amniotic fluid, 5 – Presence of bacteria in the amniotic fluid, 6 – End organ dysfunction and damage due to cytokinemia, including altered blood–brain barrier, 7 – End organ dysfunction and damage due to cytokinemia, including changes in alveolar cellular development and surfactant production.

ascending maternal infection. By contrast, late-onset sepsis, which occurs after the first 72 hours, is almost entirely due to an environmentally acquired (nosocomial) infection. It is important to recognize, however, that some neonatal intensive care units – particularly those referral centers that accept outborn neonates – do have some term and late-preterm neonates with community-acquired infections.

Since the implementation of screening for, and treatment of group B Strep with antibiotics, rates of GBS infection have fallen. The rate of infection, which was estimated at 0.51 cases per 1000 births in the 1990s, is currently around 0.40 cases per 1000 births.[49] Although perinatal practices continue to reduce GBS sepsis, rising Gram-negative resistance to ampicillin is evident.[50] The long-term significance is unclear as it may result in exchanging one infection for another and may require a significant change in the early empiric treatment of suspected sepsis.

Late-onset sepsis, predominantly of nosocomial origin, accounts for the majority of cases of neonatal sepsis. There has been a shift towards rising ampicillin resistant Gram-negative infections. Additionally, candidal infection, which had been rising, may recently have reached its peak with the institution of fluconazole prophylaxis.[51,52] The remainder of late-onset sepsis is predominantly associated with indwelling devices, including central venous catheters, endotracheal tubes, and urinary catheters (see Table 17.5).[53]

Two issues that have recently become more important are the rising incidence of resistant organisms (discussed below) and the management of suspected and culture-confirmed meningitis. Despite relatively high incidences of meningitis following bacteremia, practice surveys and retrospective analyses have shown that there is significant practice variation regarding performance of lumbar puncture for diagnosis of meningitis and management of duration of therapy.[54] While a full discussion of meningitis is beyond the scope of this chapter, it has become increasingly clear that lumbar punctures should be performed more frequently than currently and repeat lumbar punctures to confirm sterilization of the meninges are necessary.[38,48,55]

Table 17.5 National surveillance and rates of nosocomial infection in neonatal intensive care units.

Type of nosocomial infection	PPN (%)	NNIS (%)
BSI/1000 CVC/day	Not reported	8.6
<1000 g	12.8	9.1
>1500 g	4.7	4.1
VAP/1000 Vent-day	Not reported	2.5
<1000 g	4.9	1.5
>1500 g	1.1	1.4
Overall PNA/1000 pt-day	12.9	Not reported
UTI/1000 pt-day	8.6	Not reported

BSI, Blood stream infection; CVC, central venous catheter, PNA, pneumonia; UTI, urinary tract infection; VAP, ventilator associated pneumonia.

PATHOPHYSIOLOGY OF SEPSIS

There are two necessary criteria for the establishment of an invasive infection: significant bacterial virulence and failure of the host defense system. Bacterial virulence factors include ability to adhere to epithelia, invade through the basement membrane into host tissues, and evade the host defense mechanisms. The process of microbial adhesion depends on bacterial fimbriae or pili, which bind to the common peptide sequence Arg-Gly-Asp found in fibronectin, collagen, and other host structural proteins. After adhering, high affinity receptors bind to cellular integrins to promote internalization or invasion.[56] Bacteria then use a number of different enzymes and toxins to neutralize intracellular, cell-mediated, and humoral host responses. These include hyaluronidase, collagenase, lecithinase, and proteinases, as well as exotoxins capable of inhibition of neutrophil and phagocyte function.[57]

The neonatal immune system is profoundly different from that of pediatric patients.[58] While it still consists of both innate and adaptive components, and generates both humoral and cellular responses, the infant's immune system is immature and the transition between fetal and extrauterine life represents a transient period of relative immunosuppression (Fig. 17.3). The humoral innate system at birth lacks significant opsonin function,[59] and complement levels decrease after birth and reach their nadir at 3 weeks. Normal complement levels and opsonization do not occur until approximately six months.[60] The adaptive humoral system is dependent on maternal production of antibodies as infant B-cells have not yet been exposed to a significant antigen load. During the peripartum period placental transfer provides a lopsided supply of maternal antibodies – excellent for antitoxins but poor for enteric somatic antibodies (O antigen).[61] Postpartum antibodies are delivered through maternal colostrum and milk. They reflect primarily the maternal response

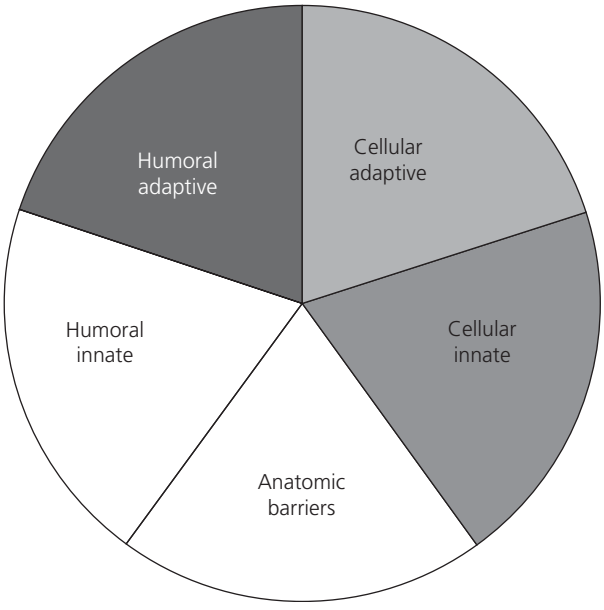

Figure 17.3 The five components of neonatal host defense against pathogens: anatomic barriers including skin and mucosa, innate and adaptive humoral response, and innate and adaptive cell-mediated response.

to gastrointestinal antigenic exposure and thus do not confer protection against NICU pathogens.[61] Cellular innate and adaptive defense mechanisms are present as early as 13 weeks of gestation.[62] However, significant production of leukocytes does not occur until nearly the 30th week, and innate cells like neutrophils continue to represent only 20–30% of the adult pool.[62] Although lymphocytes account for the majority of the leukocyte population at this age, the adaptive immune response remains qualitatively immature until significant antigen exposure leads to development of an appropriately mature helper T-cell population. Only then will T-cell mediated cytotoxicity and B-cell antibody production begin to increase.[63]

Several deficiencies exist in non-immunologic neonatal host defenses as well. External anatomic barriers such as the skin suffer from immaturity or fragility, which results in skin breaks due to injuries during delivery and invasive procedures in the nursery.[64] The gastrointestinal mucosal barrier is also immature and gut colonization with commensal bacteria occurs in several waves before the normal distribution of microflora is achieved.[65] Finally, internal barriers, particularly the meninges and the blood–brain barrier, are immature and allow active translocation of bacteria to normally sterile areas during bacteremia.[54]

Management

Given the profound morbidity and mortality associated with neonatal sepsis, best practice management should begin with prevention. There are two principal targeted approaches to prevent or reduce early-onset sepsis. The first centers on the prenatal and peripartum management of the maternal–fetal unit. The second approach focuses on active management of early postpartum newborns based on their risk profile. Both perinatal and postpartum studies indicate that term neonates without any risk factors do not require systemic antibiotic prophylaxis. Unfortunately, there are no good data on term neonates with risk factors for sepsis.[66] Furthermore, given the significant improvement in perinatal care over the last two decades, the epidemiology of early-onset sepsis has changed greatly.[9,67] Current recommendations from the Centers for Disease Control for intrapartum therapy are penicillin G or ampicillin at loading doses and then every 4 hours until delivery.[68] Postnatal ampicillin should be administered to the neonate every 4–6 hours for moderate to high risk newborns.[69,70] Due to the increase in Gram-negative sepsis, particularly *E. coli*, several postnatal protocols have been developed including the additional administration of an aminoglycoside such as gentamicin or third generation cephalosporin like cefotaxime.[71]

A significant effort has also been made toward prevention of late-onset sepsis in the hospital nursery. Although aggressive skin care, including 3% hexachlorophene bathing, can significantly reduce *S. aureus* and other Gram-positive cocci colonization, the significant skin permeability of the neonate leads to absorption and associated neurotoxicity.[72] The World Health Organization recommends dry skin care in developed countries and antiseptic use in developing countries,[73] although many centers routinely apply small amounts of antimicrobials to the umbilicus and circumcision sites. Indeed, a recent randomized controlled trial investigating umbilical cord care demonstrated superiority and safety of chlorhexidine powder to dry care.[74] Additionally, prevention of colonization and infection in nurseries requires adequate space and personnel. Recommendations of space range from 36 to 100 square feet and nurse to patient ratio of 1:4 to 1:1, depending on acuity. Although good outcome studies of individual interventions are not possible due to power restrictions, quality assurance and intervention bundle studies indicate that combined implementation of infection control techniques reduces the risk of nosocomial infections. This includes frequent hand hygiene, gowns and gloves, care of invasive devices, sterilization of equipment, and epidemic control techniques.[75,76] Despite the success of these environmental techniques, several well-designed Cochrane reviews failed to produce evidence in favor of prophylactic systemic antibiotics in ventilated newborn infants[77] or neonates with central venous[78] or umbilical catheters.[79]

The cornerstone of treatment of established sepsis is combining source control with adequate antibiotic coverage. As described above, early-onset sepsis is caused by ascending or transplacental transmission of infection. Source control consists of clamping and cutting the umbilical cord. Late-onset sepsis, on the other hand, is most commonly related to indwelling vascular catheter-related sepsis, ventilator-associated pneumonias, and urinary tract infections. When considering source control, it is important to consider alternative forms of therapy. These include prompt removal of umbilical catheters, placement of peripherally inserted central catheters, and surgically placed tunneled lines. Similarly, extubation to noninvasive positive pressure ventilator support (such as continuous positive airway pressure) or patient positioning for ventilator associated pneumonias[80,81]

and early removal of indwelling urinary catheters should be considered if possible. However, the systemic inflammatory response syndrome and multi-organ dysfunction often make these maneuvers impossible.

Selection of initial antibiotic therapy can be difficult. The epidemiology of early-onset sepsis continues to change rapidly, and while a penicillin and aminoglycoside appear to be optimal peripartum therapy, integration of individual unit antibiograms and ongoing surveillance are necessary for treating late-onset sepsis. Furthermore, decreasing Gram-negative and Gram-positive sepsis has led to a commensurate rise in anaerobic, fungal, and viral sepsis. There is inadequate evidence from randomized trials to support any particular antibiotic regimen in the initial treatment of suspected late-onset sepsis in the newborn.[82] Although variations on penicillins (such as anti-pseudomonal penicillins or beta-lactamase inhibitors) and low cross resistance between aminoglycosides help individual units develop broad-spectrum strategies, increasing rates of methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant Gram-negative infections make optimal broad-spectrum coverage a moving target. Increasingly, initial therapy includes vancomycin in units highly colonized with MRSA as well as an antifungal agent due to the increased incidence of *Candida* spp. sepsis as well.[83] Indeed, there are randomized controlled trials that support prophylactic,[84] initial, and completion antifungal therapy.[85,86]

Once culture proven sepsis has been documented, it is safe and appropriate to narrow the spectrum of initial antibiotic therapy. The challenge of culture-directed therapy in neonatal sepsis, however, is the optimal duration of treatment. Only one small randomized trial investigated 7-day versus 14-day duration of antibiotics for neonatal sepsis.[87] Unfortunately, small sample size and heterogeneity of enrolled neonates precluded statistical significance. Several randomized clinical trials[88] have examined optimal duration of treatment for meningitis with similar limitations. Indeed, the greatest challenge is the lack of good criteria for response to therapy, as many neonates may appear minimally symptomatic despite positive blood cultures and permeable meninges. For this reason, repeat cultures to ensure site control are mandatory, and antibiotic therapy is often carried on for several days following clearance of cultures and disappearance of symptoms. Although C-reactive protein emerged nearly a decade ago as a useful biomarker of the response to sepsis,[89] subsequent investigation failed to produce a consistent or reproducible pattern to determine those infections that respond to therapy.[90] The negative predictive value of C-reactive protein is significantly more useful than its positive predictive value.[91] No prospective randomized trials exist in neonates regarding the utility of biomarkers in guiding duration of antibiotic therapy. Thus, current practice is to repeat cultures and laboratory values to ensure clearance of bacteremia and then continuing antibiotic therapy specifically tailored for the offending microorganisms for a minimum of 5 days for neonates without central venous catheter, 10 days for infants with indwelling central venous catheters, and up to 2 weeks for documented meningitis. Nevertheless, as more experience with screening and management with biomarkers in neonatal sepsis accumulate, well-powered randomized controlled trials regarding duration of tailored antibiotic therapy will be required.

Because sepsis often leads to shock, adequate resuscitation is imperative in the management of sepsis. Significant improvement in the morbidity and mortality of adult and pediatric sepsis has been achieved through goal-directed resuscitation (see Fig. 17.4).[92] Unfortunately, the 'goal' of resuscitation is not as clear in the neonatal population as it is in adults.[93] At birth, newborns carry a 'backpack' of extra salt and water to carry them through transition.[12] During transition and early life, many hemodynamic parameters such as blood pressure do not have clear 'normal' values.[94] In addition, immature cardiovascular and endocrine systems may blunt the appropriate stress response in newborns, making vasopressor, inotrope, calcium, and hormone replacement necessary.[95] Finally, aggressive fluid resuscitation is associated with a significant risk of reopening the ductus arteriosus and potentially worsening perfusion.[96] Nevertheless, fluid resuscitation, vasopressor use, calcium replacement, and endocrine replacement are key components of the therapeutic armamentarium for achieving adequate tissue perfusion.[97,98]

There are no validated clinical signs of shock or poor tissue perfusion without end organ damage. Clinical signs include urine output, blood pressure, heart rate, color, capillary refill, and central-peripheral temperature discrepancy. Though frequently assessed for management, studies have demonstrated no association between blood pressure and tissue perfusion[99] and weak association between color,[100] capillary refill,[101] and tissue perfusion. Significantly decreased tissue perfusion has several measurable laboratory and biochemical effects on the neonate. In particular, metabolic acidosis, base deficit, and serum lactate can be utilized as markers of poor perfusion.[102] Therefore, improvement in these laboratory markers along with urine output can be used as putative 'goals' for resuscitation.

The first approach to resuscitation should consider volume expansion (Fig. 17.5), remembering that most hypotensive neonates have a normal circulating blood volume. During transition from fetal to extrauterine circulation, evidence suggests that excessive volume resuscitation is associated with bronchopulmonary dysplasia,[103] intraventricular hemorrhage,[104] and reopening or persistence of the ductus arteriosus. Late-onset sepsis in the neonate receiving chronic diuretic therapy requires adequate fluid resuscitation. Therefore, while the surviving sepsis guidelines indicate pediatric patients can be strongly recommended to receive 60 mL/kg within 15 minutes, a more appropriate empiric choice in neonates appears to be incremental 10–20 mL/kg boluses with low threshold for vasopressor use.[95]

The most commonly studied and prescribed adrenergic medications include dopamine, dobutamine, and epinephrine. In addition, milrinone is a frequently used phosphodiesterase inhibitor. Due to the differing proportions of alpha- and beta-adrenergic receptors in the neonate, there has been significant skepticism regarding the utility of alpha-specific medications such as phenylephrine or norepinephrine, although they are used routinely in older patients. Nevertheless, a recent prospective trial evaluating norepinephrine demonstrated improved tissue perfusion and

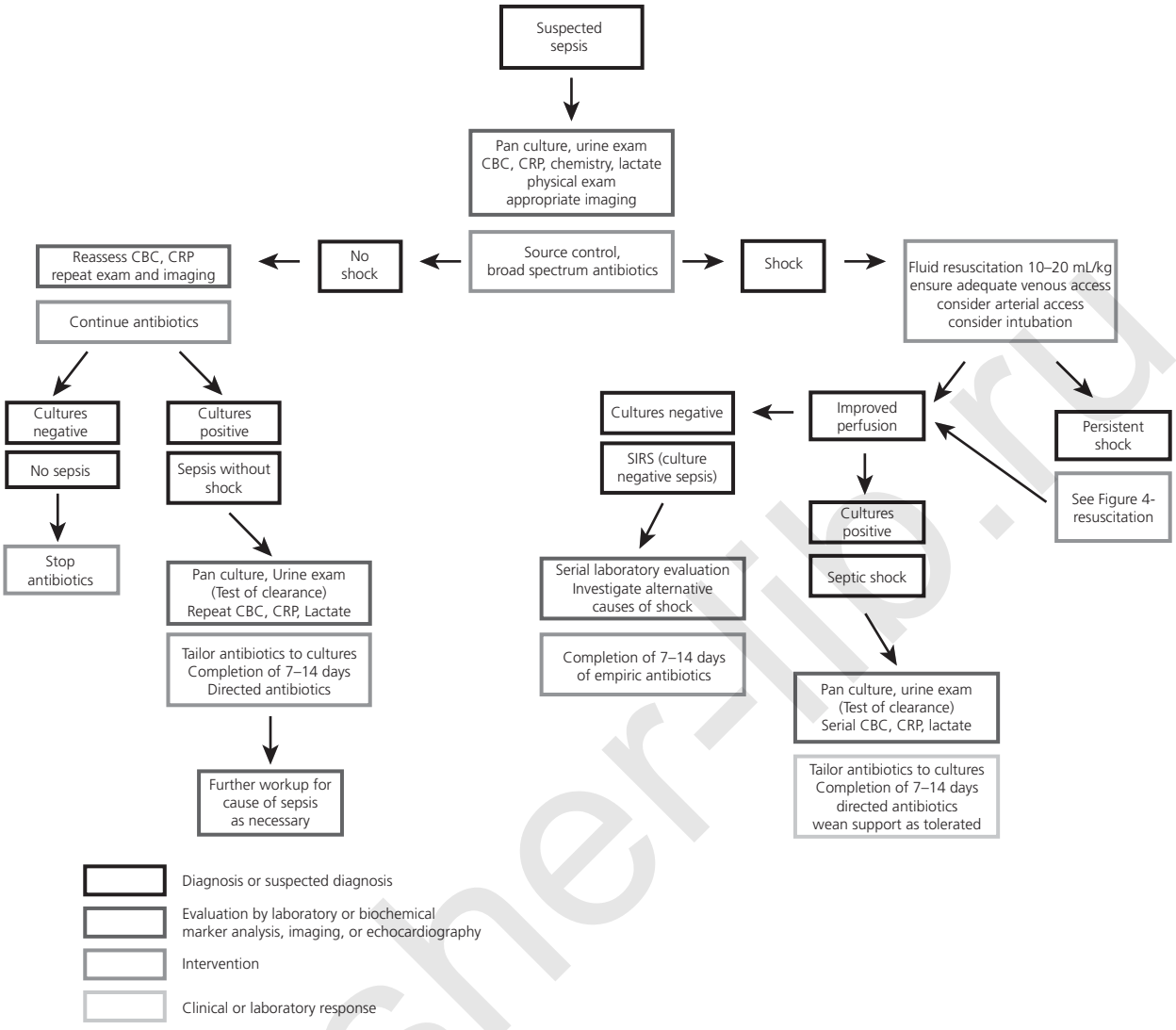

Figure 17.4 Algorithm for management of sepsis.

relative safety in the neonate with shock refractory to fluid and classic vasopressors.[105] Similarly, several reports of neonatal use of vasopressin agonists in refractory shock and post cardiopulmonary bypass stun suggest vasopressin[106] and terlipressin[107] also appear to be effective and relatively safe. Nonetheless, current neonatal guidelines generally favor dopamine over dobutamine as an initial choice of vasopressor, and epinephrine as a rescue medication for dopamine-refractory shock, despite ongoing debate about the optimal pressor for different types of shock.[95] Because neonatal sarcomeres are immature, sarcoplasmic calcium stores are significantly less;[108] this results in a profound dependence on serum calcium for successful contractility of the myocardium and tone of the arteriolar vascular tree. Calcium chloride infusions, along with various forms of calcium replacement, have been strongly advocated in the pediatric and anesthesia communities,[109] but safety and i.v. access issues have not been studied in the setting of calcium infusion for septic shock. Nevertheless, most units prefer to add calcium to i.v. fluid and parenteral nutrition, as well as i.v. calcium boluses to maintain calcium in the normal range.

Recent evidence supports endocrine replacement therapy in the setting of neonatal shock refractory to vasopressor treatment.[110] Although there is inadequate evidence to support empiric corticosteroid use,[111,112] measurement of serum cortisol concentrations and absolute and relative adrenal insufficiency can identify neonates who will benefit from hydrocortisone replacement therapy.[113] Corticosteroids have two main classes of effects: genomic and non-genomic. Late effects, such as alterations in IL-2 production and secretion, are due to changes in leukocyte gene regulation. Early non-genomic effects, on the other hand, are responsible for the efficacy of endocrine replacement in shock. In particular, corticosteroids lead, in a non-genomic, rapid fashion, to the prevention of endocytosis of adrenergic receptors and downregulation of secondary messenger systems that lead to tachyphylaxis to both autologous and extrinsically infused adrenergic vasopressors.[110] Successful response to hydrocortisone therapy generally is immediate (minutes to hours)[114] and requires replacement of stress dose cortisol levels only, or hydrocortisone 1 mg/kg every 6 hours. There are currently no evidence-based guidelines on weaning

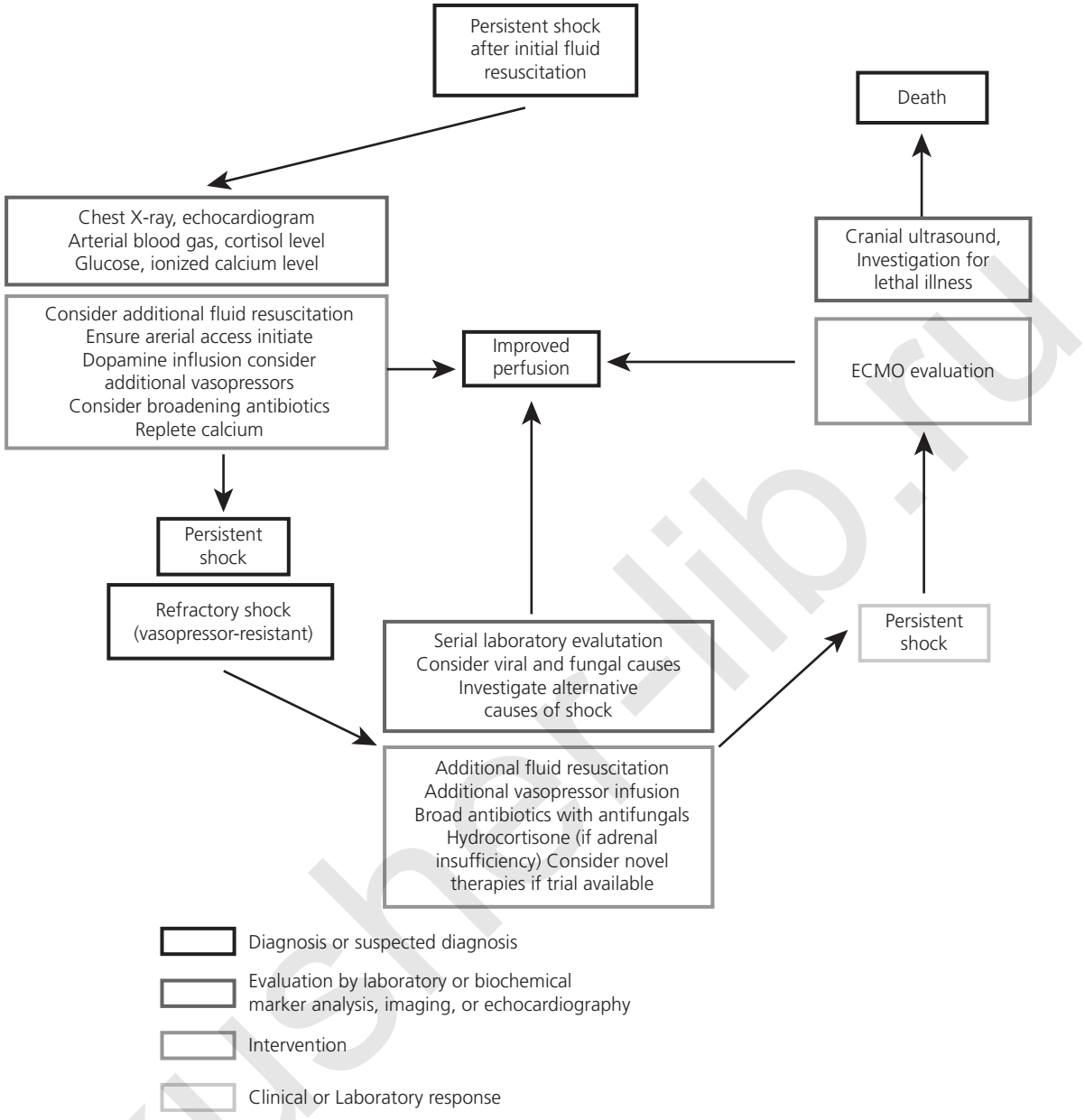

Figure 17.5 Algorithm for management of shock.

hydrocortisone.[115] Of note, extracorporeal membrane oxygenation (ECMO) is a very effective tool for providing cardiopulmonary support for refractory shock in neonatal sepsis.[116–118] A full discussion of ECMO is beyond the scope of this chapter.

Several new therapies have been developed for the management of neonatal sepsis. Polyclonal intravenous immunoglobulin (IVIg), known to be effective in inflammatory neurologic and rheumatologic disorders, has long been hypothesized to be effective in reducing the risk of, and complications from infections. Nondiscriminate use of IVIg in the neonatal population has had anecdotal success, but several clinical trials have failed to demonstrate a benefit in the morbidity and mortality of neonatal sepsis.[119] Restricting IVIg to preterm or low birth weight infants, although successful in reducing the risk of culture proven sepsis by 3%, also failed to demonstrate a benefit in decreasing morbidity or mortality.[120] The heterogeneity of these populations, however, may have obscured the benefit of IVIg in the subset of very low birth weight neonates. Because prior IVIg trials did demonstrate safety, a well-powered randomized, double-blinded, placebo-controlled trial is currently being conducted to examine efficacy in the treatment of neonatal sepsis.[121] In addition to polyclonal immunoglobulin, monoclonal antibodies against several specific targets are currently being studied. Unfortunately, only anti-staphylococcal antibodies have been extensively investigated. They have been found to be safe but did not result in any significant improvement in outcome.[122] Oral immunoglobulins have also been administered in an attempt to mimic breast milk, however, they did not reduce the risk of developing necrotizing enterocolitis or mortality.[123] Secretory IgA, one

of the active components of breast milk, has not yet been evaluated. Several additional interventions, including pentoxyfilline,[124] recombinant activated protein C,[125] and colony stimulating factors,[126] are still awaiting adequate clinical trials before they can be added to our armamentarium.

MULTIDRUG-RESISTANT AND OPPORTUNISTIC INFECTION

Management of systemic infections or sepsis in general has become increasingly challenging because of the emergence of multiple antibiotic-resistant bacteria.[127] Two molecular patterns of antibiotic resistance have been described. First, epidemic outbreaks of drug-resistant infections occur following introduction of new organisms to a nursery. Such outbreaks propagate due to environmental crowding and lapses in inter-patient infection control strategies.[128] In many cases, these epidemics begin with a health-care worker, fomite, or visitor, although molecular genotyping suggests that community-acquired infections may also be transmitted vertically (up to 20% of MRSA).[129] Alternatively, drug resistance can be driven by institutional antibiotic strategies, as has been shown with GBS prophylaxis.[50] Administration of newer broad-spectrum antibiotics can lead to abnormal colonization with saprophytes and yeast, resulting in invasive opportunistic infections.[130]

MRSA is the most common antibiotic-resistant organism in the neonatal intensive care unit and a major cause of neonatal morbidity and mortality.[131] Several molecular phenotypes of community-acquired and nosocomial MRSA make it particularly virulent.[132] A recent National Nosocomial Infections Surveillance System (NNIS) report indicated a more than 300% increase in neonatal MRSA infections between 1995 and 2004, with nearly 59% of *S. aureus* isolates being classified as MRSA.[133] In 2008, 432 MRSA-negative mothers delivered a cohort of term newborns who subsequently developed 11 MRSA infections within 4–23 days of birth.[134] Amazingly, molecular analysis of these MRSA isolated demonstrated hospital patterns of methicillin resistance. With an increasing awareness of endemic and epidemic patterns of neonatal MRSA infection, attention must be paid to prevention of nosocomial spread and containment of outbreaks of MRSA.[135] Countries such as the Netherlands, which apply very aggressive containment procedures, consistently have MRSA rates significantly lower than less aggressive countries such as the USA.[48,136] In brief, infection control bundling should include three components: prevention, management of outbreaks, and quality assurance. While individual preventive interventions such as wearing gloves would be difficult to assess, it is possible to decrease horizontal transmission of infection by bundling of proper hand hygiene, gowns, gloves, masks, with provision of adequate isolette space, isolation of patient care equipment, and screening of infants to detect MRSA and vancomycin-resistant enterococcus (VRE) colonization. Furthermore, it is very effective during outbreaks to isolate or cohort both patients and health-care staff (especially nurses), culture environmental sources in response to a cluster of colonization or infection, and investigate all outbreaks with molecular analysis (pulsed-field gel electrophoresis or a comparable tool) to assess the relatedness of strains found in NICU patients, health-care workers, and the environment. The major challenge is the implementation of patient care practices designed to prevent horizontal transmission of infection and contain outbreaks, rather than the development of new antibiotics.[137]

VRE, like MRSA, is also on the rise. In a predictable fashion, VRE begins to appear after a significant increase in vancomycin use for endemic and epidemic MRSA. Although the pediatric prevention network has not yet published estimates, the CDC-NNIS reported a 12% rate of VRE in *Enterococcus* isolates from neonatal intensive care units compared to 28.5% in all ICUs up until 2004.[138] Two subsequent studies[139,140] demonstrated epidemic clusters of VRE that could be traced to an original hospital site. Much like MRSA, it is the implementation of infection control practices, rather than the introduction of newer antibiotics, that will likely reduce the burden of VRE disease.[137]

Unlike MRSA and VRE, which propagate in epidemic-type outbreaks, prophylactic administration of beta-lactam antibiotics for GBS has resulted in a significant increase in extended-spectrum beta-lactamase (ESBL) producing Gram-negative organisms.[141] Several reports regarding neonatal epidemiologic trends of ESBL *Klebsiella*,[142] *E. coli*,[143] *Serratia*,[144] and *Enterobacter*[145] have demonstrated this pattern as well. More data are required before risk factors and outcomes for ESBL Gram-negative organisms can be effectively assessed. Nevertheless, adjustment of empiric therapy for suspected sepsis in nurseries and neonatal intensive care units with high rates of ESBL Gram-negative organisms has generally been effective.[146]

In addition to inducing multidrug-resistant organisms as described above, broad-spectrum antibiotics also foster the development of opportunistic or unusual infections in the host. This situation is best exemplified by the explosion of invasive candidal infections during the past 20 years.[147] Despite an expanding antifungal armamentarium, chemotherapeutic options work slowly and mortality remains high once fungal infection occurs. Thus, prevention remains the keystone to minimizing fungal sepsis.[148,149] Similarly, bacterial opportunistic infections have been on the rise as well. *Acinetobacter*, a saprophyte with significant natural drug resistance patterns previously unique to burn units, has already appeared in several neonatal intensive care units.[150–152] Saprophytic infections are a marker for significant use of antibiotics and critical illness. Unfortunately, because most of these Gram-negative soil bacteria are nearly pan-resistant, the associated sepsis is often lethal despite aggressive therapy. In this situation, complete containment with unit sterilization following patient loss is the only available mechanism to protect other patients.[153,154]

CONCLUSION

Neonatal sepsis continues to be a major cause of long-term morbidity and mortality. Each advance in the prevention, identification, and therapy of sepsis produces a shift in the

epidemiology and bacteriology of the disease. Thus, the development of systems-based practice organizations has become one of the most important advances during the last 50 years. The World Health Organization and various national organizations such as the National Nosocomial Infections Surveillance System provide ongoing surveillance for the changing epidemiology of early- and late-onset sepsis. Ongoing design of well-organized trials looking at optimizing prenatal and perinatal care, along with future development of trials to investigate prophylactic measures for late-onset sepsis, however, will continue to change the bacteriology of sepsis neonatorum. Hopefully, completion of several large trials investigating novel sepsis therapies and alternative methods of resuscitation of neonatal septic shock will increase the armamentarium available for combating the new distributions of infections. In the meantime, continued hand hygiene, proper neonatal environment design, and early intervention for suspected sepsis will remain the standard of care for minimizing neonatal infections and improving outcomes.

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18

Hematological problems in the neonate

OWEN P SMITH

INTRODUCTION

The neonatal period is a time of rapid flux and hematological problems that present during this period as a result of a genetic defect, immaturity, or stress and present a major diagnostic and therapeutic challenge to the neonatologist and hematologist alike. The recent explosion in molecular biological techniques has allowed the elucidation of the molecular and cellular mechanisms that give rise to the disorders of platelets, coagulation proteins, and red cells that present in the newborn. Because of the space allotted it is hoped that this chapter will give the reader a broad understanding and appreciation of the major hematological disorders seen in the neonatal period, especially those involving platelets and clotting proteins.

PLATELETS

The normal range of the platelet count is similar in fetal life to that seen in adulthood, being in the range of 150×10^9/L to 400×10^9/L. Neonatal thrombocytopenia, defined as a blood platelet count of below 150×10^9/L is common, with a reported frequency to approximate 0.9% in unselected newborns, and 40% in infants in intensive care units.[1–3] The differential diagnosis of thrombocytopenia in the neonatal period is similar to thrombocytopenia in older children with a number of exceptions that include the inherited thrombocytopenia group and those that arise due to pathophysiological events unique to the antenatal and perinatal periods. It is important to remember to confirm that the low platelet count is genuine by careful inspection of the blood sample and smear before initiating further investigations. Once established, the approach to the diagnosis of the thrombocytopenia should be tailored to the individual infant and mother. For example, assessment of the child's general well-being is very important as healthy neonates usually have an immune or an inherited etiology, whereas the presence of lymphadenopathy, hepatosplenomegaly, mass lesions, hemangiomas, bruits, and congenital anomalies will point towards a totally different spectrum of causes. It should also be emphasized that obtaining a detailed maternal history to include bleeding problems, pre-eclampsia, and drug ingestion in the present and past pregnancies and any history of viral infections or connective tissue disease will save time and indeed unnecessary investigations. The causes of thrombocytopenia are divided into two broad categories; inherited thrombocytopenia and congenital thrombocytopenia

INHERITED THROMBOCYTOPENIA

The inherited thrombocytopenias comprise a group of platelet formation abnormalities in which platelet numbers are reduced. In the vast majority of patients the platelet count is only mild to moderately reduced (50×10^9/L and 100×10^9/L) and therefore, significant spontaneous hemorrhage tends not to be problematical. There are however, a small number of notable exceptions where spontaneous bleeding is a prominent clinical feature of the syndrome. These include Wiskott–Aldrich syndrome, amegakaryocytic thrombocytopenia, and thrombocytopenia with absent radii where the platelet count is usually very low and in the Bernard–Soulier and Chediak–Higashi syndromes where there is also a marked platelet dysfunction.[4] Immune-mediated thrombocytopenia is a major differential diagnosis in children with low platelet counts and, therefore, making the correct diagnosis of these conditions is important as it usually prevents the useless and potentially dangerous prescribing of immunosuppressants such as corticosteroids.[4,5]

Bernard–Soulier syndrome

Bernard–Soulier syndrome (BSS) is the best characterized inherited thrombocytopenia which has in association, an abnormal platelet function. Typically, there is moderate to severe thrombocytopenia, a prolonged bleeding time and

platelet morphology usually reveals 'giant' forms. BSS is inherited as an autosomal recessive manner with the underlying molecular defects due to quantitative or qualitative defects in platelet membrane receptors.

Pseudo-von Willebrand's disease

Pseudo-von Willebrand's disease (pseudo-vWD) is an autosomal dominant disorder characterized by mild intermittent thrombocytopenia, mild bleeding, absence of high molecular weight von Willebrand factor (vWf) multimers, and increased ristocetin-induced platelet aggregation. It can be differentiated from type 2B von Willebrand's disease (vWd), where the mutation resides in the vWf protein by spontaneous aggregation of the patient's platelets with normal plasma[4].

Type 2B vWd

This subtype of vWd is clinically and biochemically very similar to pseudo-vWd. Type 2B is usually diagnosed by the increased platelet agglutination induced by low concentrations of ristocetin.[4]

Montreal platelet syndrome

This syndrome is characterized by thrombocytopenia, large platelets, spontaneous platelet aggregation, and a reduced response to thrombin-induced aggregation. It can be distinguished from BSS by its autosomal dominant inheritance and a normal platelet agglutinability response to ristocetin.[4]

Gray platelet syndrome

This is an extremely rare autosomally inherited syndrome characterized by a markedly reduced platelet alpha-granule content but normal dense-bodies and lysosomes. Other features include a prolonged skin bleeding time, morphologically large platelets, and highly variable platelet aggregation profiles. The thrombocytopenia and bleeding symptoms are usually mild.[4,6]

Paris–Trousseau syndrome

This is a recently described autosomal dominant syndrome comprising mild thrombocytopenia, a moderate hemorrhagic tendency, giant alpha-granules in a subpopulation of platelets, bone marrow micromegakaryocytes with enhanced megakaryocyte apoptosis, and a deletion of the distal part of chromosome 11 at position 11q23 (del (11)(q23.3;qter)).[4,6]

Wiskott–Aldrich syndrome

Wiskott–Aldrich syndrome (WAS) is inherited as an X-linked recessive trait and is characterized by eczema, microthrombocytopenia, and combined immunodeficiency. It is often fatal by the early teens due to infection, lymphoreticular malignancy, or bleeding. Hemorrhagic events in this syndrome are common during the first two years of life and the reason for this is multifactorial.[4,6]

WISKOTT–ALDRICH SYNDROME VARIANTS (X-LINKED THROMBOCYTOPENIA)

This is a heterogeneous group of thrombocytopenic disorders with X-linked inheritance. The thrombocytopenia is usually less severe in WAS variants and requires no treatment.[4,6]

OCULOCUTANEOUS ALBINISM – HERMANSKY–PUDLAK AND CHEDIAK–HIGASHI SYNDROMES

Oculocutaneous albinism denotes a group of inherited disorders characterized by reduced or absent pigmentation of the skin, hair, and eyes. While the majority of these patients have an isolated platelet storage pool defect, in some an accompanying low platelet count can occur.[4,6]

Hermansky–Pudlak syndrome is an autosomal recessive disorder with the classic triad of oculocutaneous albinism (tyrosinase-positive), platelet dense-body or combined dense-body and alpha-granule storage pool deficiency, and depositions of ceroid-like material in the monocyte–macrophage system. The bleeding tendency is usually mild (related to the storage pool defect and not thrombocytopenia, as the latter is not a feature syndrome), however, excessive bleeding following tooth extractions and tonsillectomy is the rule.[4,6]

The features of Chediak–Higashi syndrome include partial oculocutaneous albinism, the presence of giant granules in all granule-containing cells, neutropenia, peripheral neuropathy, and platelet storage pool deficiency which usually involves the dense-bodies. Thrombocytopenia usually occurs during the accelerated phase of the disease which involves the development of pancytopenia, hepatosplenomegaly, lymphadenopathy, and extensive tissue infiltration with lymphoid cells.[4,6]

May–Hegglin anomaly

This is an autosomal dominant disorder, characterized by giant platelets, variable thrombocytopenia, and Dohle-like inclusions within granulocytic cells including monocytes. Platelet function has been reported to be normal in some and impaired in others.[4]

Alport variants

Alport syndrome is associated with the findings of sensorineural deafness (usually high tone deafness), hematuria, cataracts, and progressive renal failure. The disorder is a

heterogeneous group with the majority having autosomal dominant inheritance. Many variants of Alport syndrome have been described, the three associated with thrombocytopenia include Epstein's syndrome, Fechtner syndrome, and Sebastian platelet syndrome.[4]

INHERITED BONE MARROW FAILURE SYNDROMES

Thrombocytopenia with absent radii

Thrombocytopenia with absent radii (TAR) is a rare, autosomal recessive disorder that is usually diagnosed at birth as the vast majority of these patients are thrombocytopenic and have the pathognomonic physical sign of bilateral absent radii. Other skeletal abnormalities involving the ulnae, fingers, and lower limbs are also seen but are much less common. TAR differs from Fanconi anemia in several ways: the absent radii are accompanied by the presence of thumbs, the thrombocytopenia is the only cytopenia, there is absence of spontaneous or clastogenic stress-induced chromosomal breakage, and evolution to aplastic anemia and leukemia have not been reported.[4,7] The majority of children with TAR have recurrent significant bleeding episodes in the first six months of life.[4,7] Intracerebral and gastrointestinal hemorrhage are the usual causes of mortality with previously one in four of these children dying by four years of age. The majority of these deaths however, occur in the first year of life. The mainstay of treatment is judicious use of single donor platelet concentrates aiming to keep the platelet count above 20×10^9/L, especially in the first year of life as this is the time of maximum morbidity and mortality.[4,7]

Amegakaryocytic thrombocytopenia

Amegakaryocytic thrombocytopenia (AMEGA) is an extremely rare disorder of infancy and early childhood. The thrombocytopenia is nonimmune, usually severe, and early bone marrow examination shows a normal karyotype, absent or greatly reduced numbers of megakaryocytes. Platelet transfusions are the main therapeutic intervention from diagnosis.[7]

Fanconi anemia

Fanconi anemia (FA) is a premalignant disorder, inherited as an autosomal recessive trait, with genetic heterogeneity and a gene frequency of about one in 600. Thrombocytopenia is usually the first cytopenia to appear but rarely in the neonatal period.[7]

Trisomy syndromes

Moderately severe thrombocytopenia is seen in some cases of trisomy-18 syndrome, trisomy-13 syndrome and, to a lesser extent, in trisomy 21. Both trisomy 13 and 18 are usually diagnosed at birth as the associated abnormalities are usually quite striking. The majority of these cases die in the neonatal period from non-hemorrhagic sequelae.[4]

CONGENITAL THROMBOCYTOPENIA

Congenital thrombocytopenia is defined as a low platelet count at birth not resulting from the association of a specific gene defect and accounts for the majority cases of neonatal thrombocytopenia. Thrombocytopenia is a common finding in sick neonates, however, and since the introduction of automated cell counters it is now considered a relatively common (approximately 1%) finding in apparently normal infants.[8] In the vast majority of cases the thrombocytopenia results from increased platelet destruction which can arise by several mechanisms, the majority of which are not known.

Immune thrombocytopenia

Immune-mediated thrombocytopenia is usually seen in term babies that are clinically well and may be responsible for one-third of cases of thrombocytopenia seen in the general neonate population.[9] There are two broad groups of conditions, those mediated by an alloimmune mechanism and those with associated autoimmune phenomena.

Neonatal alloimmune thrombocytopenia

Neonatal alloimmune thrombocytopenia (NAIT) arises following maternal sensitization to paternal antigens present on fetal platelets. It occurs in approximately one in 1500 to one in 2000 births, with the mother having a normal platelet count and a negative history for bleeding.[9] The maternal alloantibody produced does not react with the mother's platelets but crosses the placenta and destroys fetal platelets. NAIT typically presents as an isolated severe thrombocytopenia in an otherwise healthy child at birth. Severe thrombocytopenia may be present early in gestation and at least 20% of cases suffer intracranial hemorrhage.[8] Widespread petechial hemorrhage is present in more than 90% of cases, while cephalohematomata, hematuria, and gastrointestinal bleeding occur in a significantly smaller number of children.[1,4,9] Typically, the platelet count spontaneously returns into the normal range within 3 weeks after birth. The mainstay of treatment for affected infants is washed, irradiated, maternal platelet concentrates.

Maternal autoimmune thrombocytopenia

Autoimmune thrombocytopenia (AIT) is due to the passive transfer of autoantibodies from mothers with isolated immune thrombocytopenic purpura (ITP), or it may be seen in association with conditions that have immune dysregulatory features such as maternal systemic lupus

erythematosus, hypothyroidism, and lymphoproliferative states.[9] Approximately one in 10 000 pregnancies are complicated by maternal ITP. The risk of significant infant morbidity and mortality is minimal, as the infant platelet count is rarely less than 50×10^9/L, intracerebral hemorrhage (ICH) rarely if ever happens and when it does occur it is not related to birth trauma.[9]

Intrauterine infections (TORCH syndromes)

Intrauterine viral infections rarely produce severe thrombocytopenia ($< 20 \times 10^9$/L) and therefore, therapeutic intervention in the form of platelet concentrate and/or antiviral therapy are only indicated when there is active bleeding or surgical intervention is being considered.[10] In the vast majority of cases the platelet count returns into the normal range within 2–4 weeks after birth but may persist to four months of age.

Giant hemangioma syndrome (Kasabach–Merritt syndrome)

Kasabach–Merritt syndrome (KMS) is the association of giant cavernous hemangiomata and disseminated intravascular coagulopathy. The consumptive coagulopathy which is seen in approximately 25% of cases of KMS is usually low grade and compensated. However, acceleration into the fulminant form, which is characterized by hypofibrinogenemia, raised D-dimers, red cell microangiopathy, and severe thrombocytopenia, is not uncommon. Fortunately, spontaneous regression of these tumors occurs in the majority of patients.

The vascular tumors associated with KMS are usually kaposiform hemangioendotheliomas (KHE) and not the more usual infantile hemangiomas that are seen in early childhood. The KHE lesions tend to affect males and females equally, have a predilection for the trunk, retroperitoneum, proximal extremities, and less frequently the cervicofacial region. Like other tumors, whether benign or malignant, KHE is dependent on the formation of new blood vessels from pre-existing vasculature (angiogenesis) and this complex process is regulated by several proangiogenic (e.g. vascular endothelial growth factor) and anti-angiogenic molecules (e.g. endostatin). Because of their large size and infiltrative nature, complications such as hemorrhage from consumptive coagulopathy, airway obstruction, and congestive cardiac failure are not uncommon in a small subset of these patients and surgical resection or embolization may not be an option. Over the past three decades medical intervention for these potentially life-threatening lesions has included the use of corticosteroids as a single agent or in combination with vincristine and/or interferon-α together with the judicious use of plasma and clotting factor concentrates with variable responses. More recently, because of their role in tumor growth, there has been a move to target the platelet by using antiplatelet agents and withholding of platelet concentrate infusions, even in those patients who have significant thrombocytopenia and are coagulopathic.[4]

Hypercoagulable states

Consumptive thrombocytopenia, mainly secondary to disseminated intravascular coagulation (DIC) following thrombin generation, can be the first manifestation of an acquired or inherited hypercoagulable state.[11]

MISCELLANEOUS CONDITIONS

Other associations of neonatal thrombocytopenia include maternal pre-eclampsia, maternal use of drugs, disseminated intravascular coagulation, primary microangiopathic hemolytic anemias, including hemolytic uremic syndrome, transient abnormal myelopoiesis (TAM) associated with Down syndrome, hemophagocytic lymphohistiocytosis, osteopetrosis, congenital leukemia, metastatic neuroblastoma.

COAGULATION PROTEINS

Plasma levels of many of the hemostatic coagulation factors are lower in newborns than in older children and adults.[12–15] At the end of gestation, a healthy normal newborn should have approximately half the adult values of the vitamin K-dependent coagulant factors (factors II, VII, IX, and X) and contact factors (factors XII and XI, prekalikreinin, and high molecular weight kininogen).[12–15] In preterm infants these levels are even lower. The natural anticoagulants, antithrombin and protein S, are also approximately 50% at term with a similar relationship to gestational age.[12–15] The plasma levels of the procoagulant co-factors, factor V and factor VIII, and fibrinogen are the same in term infants as is in adults. Like the coagulation system the fibrinolytic system is also physiologically immature in the neonate.[12–15]

Inherited bleeding disorders

Hemophilia A (factor VIII deficiency) is the second most common inherited bleeding disorder in man with a frequency of approximately 1:5000 male births.[16] Hemophilia B or factor IX deficiency is approximately one-sixth as common as that of hemophilia A. When there is a family history of hemophilia, newborns are usually picked up early as the condition is usually suspected. However, one-third to one-half of all individuals with hemophilia A and B arise from the *de novo* mutations and it may be some time before a firm diagnosis is made as a significant number of these children will be seen in the general pediatric setting.[16] Hemophilia has a worldwide distribution, and affects all racial groups. Hemophilia A and B are clinically indistinguishable. In the severe form the phenotype is characterized by bleeding into the joints and soft tissues. Both the factor VIII and factor IX genes were cloned over 15 years ago and as a result recombinant factor VIII and factor IX are the treatment of choice.[16]

Hemorrhagic complications in moderate and severe hemophilia A and B may become obvious after birth, especially if the child is circumcised. Severity and type of bleeding is related to the absolute level of circulating plasma VIII:C. A minimal effective level for hemostasis is about 25–30% for hemophilia A and 20–25% for hemophilia B. Those with severe deficiency (less than l%) usually experience repeated and often spontaneous hemorrhages. While muscular skeletal bleeding is by far the most common clinical event, other spontaneous hemorrhagic manifestations frequently occur and may be life threatening. Successful treatment in acute or potentially acute (pre-surgery) bleeding is usually achieved with adequate and prompt factor replacement therapy. The level of factor concentrate required to achieve adequate hemostasis will depend on the type of bleeding.[16]

Other coagulation factor deficiencies

Deficiencies of all coagulation factors have been described. However, it should be remembered that the number of patients with hemophilia A greatly outnumber all of these put together. Common features to these rarer forms of coagulation factor deficiencies have variable bleeding and autosomal recessive inheritance.[16,17]

ACQUIRED BLEEDING DISORDERS

The acquired coagulation disorders are far more common than the inherited disorders and are usually associated with multiple coagulation factor deficiencies.

HEMOPHAGOCYTIC LYMPHOHYSTIOCYTOSIS

Hemophagocytic lymphohystiocytosis (HLH) is a rare autosomal recessive disorder of infancy and childhood that manifests as a hyperinflammatory state resulting from an abnormal proliferation of activated lymphocytes and histiocytes (tissue macrophages). The classic clinical features include fever, hepatosplenomegaly, cytopenias, hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia, lymphadenopathy, skin rash, jaundice, and edema. Although it can occur in all age groups, neonatal-onset HLH is said to be rare, however it should be noted that the classic pentad of fever, big liver and spleen, together with low fibrinogen and high triglycerides, may not all be present and hence mutational analyses for UNC13D and perforin gene should be performed in neonates suspected of having HLH. Early recognition and treatment is necessary to prevent disease progression. Remission can be achieved with the use of etoposide-based chemotherapy regimens in conjunction with immune modulating medications such as ciclosporin A, corticosteroids, and antithymocyte globulin. The only definitive cure, however, is allogeneic hematopoietic stem cell transplantation.

VITAMIN K

Vitamin K is crucial for the function of procoagulant factors II, VII, IX, and X and the natural anticoagulants protein C and protein S. Vitamin K itself is recycled and when this process is blocked, as with warfarin administration, these vitamin K-dependent factors are not produced in adequate amounts.[16,18]

HEMORRHAGIC DISEASE OF THE NEWBORN

This syndrome usually occurs on the second to fourth day of life as a result of decreased synthesis of vitamin K-dependent factors. The etiology of vitamin K deficiency in newborns is multifactorial to include reduction of vitamin K stored in the fetus and neonate, functional immaturity of the liver, lack of bacterial synthesis of vitamin K in the gut, and low amounts of vitamin K in breast milk.[16,18] Most neonates now are given vitamin K at birth. Exceptions to the rule are those children with known glucose 6-phosphate dehydrogenase (G6PD) deficiency in the family as a significant number of these patients will develop frank hemolysis. In those children who present with frank bleeding, vitamin K and infusions of fresh frozen plasma (FFP) can be given to arrest the blood loss.

LIVER DISEASE

The coagulopathy associated with liver disease is complex, involving reduced synthesis of vitamin K-dependent procoagulant factors, non-vitamin K-dependent procoagulant factors, structually abnormal coagulation proteins, and reduced amount of natural anticoagulants.[19] A significant number of these patients are also vitamin K deficient because of an associated malabsorption. It should also be noted that these patients are usually thrombocytopenic and even though the platelets do circulate, they are usually dysfunctional. Correcting the coagulopathy usually involves replacement of vitamin K, addition of fresh frozen plasma and, when volume restriction is imperative, then factor concentrates such as factor VII concentrate, and prothromplex concentrate can be given along with platelets and 1-deamino-8-D-arginine vasopressin (DDAVP).[19]

CARDIOPULMONARY BYPASS

The coagulopathy associated with cardiopulmonary bypass is multifactorial involving activation of the contact pathway, fibrinolytic pathway, tissue factor pathway, and platelets; also these children have significant platelet function defects.[16]

CONGENITAL HEART DISEASE

A significant number of children with congenital heart disease will have coagulation defects. It should be remembered, however, that in children with cyanotic heart disease with associated polycythemia, the elevation in prothrombin time (PT)/activated partial thromboplastic time (APTT) may be spurious, i.e. may be secondary to a sampling defect as there will be an alteration in the plasma anticoagulant ratio, especially when the hematocrit is greater than 60%.[16]

VON WILLEBRAND'S DISEASE

von Willebrand's disease is the most common inherited bleeding disorder in man with a gene prevalence of approximately 1% of the population.[16] There is significant phenotypic heterogeneity even among members of the same family. The majority of individuals have type 1 vWd with type 3 vWd being seen in 1–2 per million of the population. Bleeding tends to be predominantly mucocutaneous, so called 'wet purpura', the most common type being epistaxis, easy bruising, gum bleeding following tooth brushing and, in adolescent girls, heavy menses. Bleeding into joints is rare and typically only seen in individuals with severe type 3 disease where the circulating plasma FVIII levels are usually around 2%.

The main objective of treatment is to correct the two laboratory hallmarks of the disease, namely, the prolonged bleeding time, and the low FVIII level.[16] As most patients have a quantitative defect it is possible to stimulate endogenous release with i.v. DDAVP. While this treatment is inexpensive and infection-free, it does have a number of rare side effects, notably, hyponatremia and seizures, especially in very young children. Failure to respond occurs in approximately 10–15% of patients, and in those who do not respond a significant number become refractory when the drug is given over an extended period of time (tachyphylaxis).[16]

Thrombotic states

The fetus and neonate are less efficient in generating thrombin and thus thrombotic disease in early childhood is rare and when seen is either secondary to an acquired prothrombotic state or indeed the child has inherited gene defects predisposing to clot formation.[12–15,20] When it does occur in childhood it can be fatal or associated with several sequelae such as amputation, organ dysfunction, and post-phlebitic syndrome.[20] The peak incidence for these thrombotic events is undoubtedly the neonatal period where the use of indwelling catheters in the tertiary care pediatrics is almost the norm.[20]

Acquired states

CENTRAL VENOUS CATHETER DEVICES

Central venous catheter devices have revolutionized the intensive care management of neonates requiring indwelling vein or artery catheterization. Unfortunately, thrombosis related to their placement continues to be a therapeutically challenging complication in terms of diagnosis, prophylaxis against thrombosis, and also treatment of established thrombosis within the catheter. Once clot formation occurs, the catheter may be salvaged using either/or antithrombotic or antifibrinolytic agents, however, it should always be remembered that these therapeutics pose special risks in the neonatal age group. It should be remembered that, although very uncommon, death from venous thromboembolic disease in young children does occur. Therefore, early detection of such thrombotic events and adequate treatment are absolutely mandatory in this group of children.

RENAL ARTERY AND VEIN THROMBOSIS

Renal artery thrombosis, especially in the neonatal period, is commonly associated with umbilical artery indwelling on umbilical artery catheters.[20] It may be difficult to diagnose and hypertension and heart failure may be the presenting clinical features. There is usually extension of the thrombus to other vascular beds such as the aorta. Its incidence can be as high as one in six neonates and factors that can reduce its incidence include prophylactic anticoagulants, using a smaller size catheter, and also concentration of fluids infused.[20] Both medical and surgical approaches have been used with variable outcome. Renal vein thrombosis is more common than renal arterial thrombosis in the newborn period. It is associated with birth asphyxia, dehydration, hypotension, cyanotic heart disease, polycythemia, and babies born to diabetic mothers. The most common presenting features are flank swelling followed by hematuria, microscopic hematuria, renal dysfunction, and thrombocytopenia. Usually ultrasound will reveal renal enlargement with or without evidence of venous thrombosis. The use of anticoagulants and thrombolytic agents in this condition continue to be evaluated.[20] Survival rates in babies are as high as 80% and renal status after recovery ranges from normal function to renal atrophy, hypertension, and chronic renal failure.

ACQUIRED PROTEIN C/S DEFICIENCY

Purpura fulminans is a term to describe an acute, often lethal, syndrome of DIC and purpuric skin.[21] Inherited and acquired abnormalities of the protein C pathway, especially protein C deficiency, are mainly responsible for the majority of patients with this clinical syndrome.[21–23] The treatment of choice is protein C replacement.

ACQUIRED ANTITHROMBIN DEFICIENCY

Acquired deficiencies of antithrombin have been associated with a large number of diseases, which in turn have an increased rate of venous and arterial thrombosis. Antithrombin concentrates are available and are the treatment of choice during the acute phase of the disease.[20]

MISCELLANEOUS CONDITIONS

Other associations of neonatal thrombosis include necrotizing enterocolitis, respiratory distress syndrome, heparin-induced thrombocytopenia/thrombosis syndrome (extremely rare in neonates), antiphosolipid antibodies and lupus anticoagulant, extracorporeal membrane oxygenation (ECMO), hemolytic uraemic syndrome, and birth asphyxia.[20]

Inherited thrombotic states

Genetic defects within the protein C pathway account for the majority of cases of inherited thrombophilia.[23]

PROTEIN C AND PROTEIN S DEFICIENCY

Hereditary protein C (PC) and protein S (PS) deficiency (homozygosity or compound heterozygosity) are associated with a high venous thromboembolic risk at birth or in the first few months of life. The first clinical manifestation is usually skin purpura, mainly affecting extremities and in some cases massive large vessel thrombosis can also be a presenting feature. Optimum therapy involves factor replacement (PC concentrate in PC deficiency or fresh frozen plasma in PS deficiency) and heparin in the acute phase and oral anticoagulation in the long term.[23]

ANTITHROMBIN III DEFICIENCY

Reducing functional defects are also associated with a high risk of venous thromboembolic disease. The homozygous state is extremely rare and appears to be incompatible with life. Presentations of antithrombin deficiency in neonates include myocardial infarction at birth, aortic thrombosis, saggital sinus thrombosis, and cerebral thrombosis.[20]

OTHER INHERITED THROMBOPHILIAS

Several other inherited gene defects have been associated with increased propensity to clot formation, the most common being activated protein C resistance (APCR) and factor V^{R506Q}/factor V Leiden, factor II gene variant (prothrombin^{G20210A}), and hyperhomocysteinemia.[20]

Management

The indications for use of anticoagulants in infants and children have changed dramatically over the past 20 years with major advances in tertiary pediatric care such as ECMO, cardiopulmonary bypass, hemodialysis, and the use of intra-arterial and i.v. indwelling catheters.[20,24,25] The choice of anticoagulant is dependent upon the duration of anticoagulation and therefore in the acute phase heparins, either unfractionated or low molecular weight forms are used, while in the longer term oral anticoagulants are the treatment of choice. In more specific disease states, such as inherited or acquired PC or antithrombin deficiencies, factor concentrate replacement as an adjuvant hemostatic support is used more and more. It should be remembered that because the hemostatic system in infancy and throughout childhood is constantly maturing, the anticoagulant effects of unfractionated heparin and warfarin are not predictable and therefore are deemed age dependent.

ANEMIA

There is a gradual decrease in hemoglobin (Hb) level following birth and throughout the first two months. This is termed 'physiological anemia' and it is a direct consequence of changes in red cell production reflecting the increase in oxygenation with adaptation to pulmonary respiration, together with redistribution of blood flow following birth and changes in red cell production.[26] When the level of Hb is below the 'physiological anemic' range then a pathological neonatal anemia is present.[26] While the majority of cases of anemia occurring in the neonatal period are acquired, a number of inherited disorders that involve genes, defects of hemoglobin, red cell membrane, and enzymes also present during this period.[27] Anemia, whether it be acquired or inherited, may present as an incidental finding on a blood count performed for other reasons, with nonspecific signs of pallor, tachypnea and/or tachycardia, failure to thrive, jaundice, splenomegaly, or bleeding. If the anemia is due to a hemolytic process, the jaundice is almost always present.

Acquired anemia

ALLOIMMUNE HEMOLYTIC ANEMIA

Hemolytic disease of the newborn (HDN) is caused by transplacental passage of maternal alloantibodies.[27] The most common allo-antibodies causing severe hemolytic disease of the newborn are: anti-D, anti-c, and anti-Kell which produce hemolysis in fetuses which carry the D, c, and Kell antigens, respectively.[27] The alloantibodies are acquired either as a result of blood transfusion prior to or during pregnancy or as a result of alloimmunization during the pregnancy itself. Alloimmunization due to anti-D affects around 1200 pregnancies per year and causes at least 50 deaths every year in the UK.[27] HDN is usually diagnosed by testing the blood group of the mother and baby together with the presence of maternal alloantibodies and a positive Coomb's test. If HDN is due to Rhesus antibodies the number of circulating nucleated red cells is often very high and thrombocytopenia may be present in those severely affected. In HDN due to ABO incompatibility the Hb is often normal and the nucleated red cell count is rarely elevated; however, there are very large numbers of spherocytes, in contrast to a relative paucity of spherocytes in Rhesus disease.

AUTOIMMUNE HEMOLYTIC ANEMIA

This is a very uncommon cause of neonatal anemia and it arises when autoantibodies produced in the mother are directed against fetal red cell antigens causing hemolysis in a similar fashion to neonatal thrombocytopenia secondary to AIT.[27]

INFANTILE PYKNOCYTOSIS

This transient acquired disorder typically presents with jaundice, mild hepatosplenomegaly, and anemia in a term baby within a few days or weeks of birth.[27] It is not an uncommon cause of moderate anemia in the first few weeks of life in term infants. The cause is unknown but some cases appear to be due to selenium deficiency. The Hb may fall as low as 4 g/dL and many neonates require one or two red cell

transfusions before the condition resolves spontaneously around 4–6 weeks of age.[27]

BLOOD LOSS

Anemia due to blood loss is the most common cause of neonatal anemia in preterm infants. In most cases this is iatrogenic and due to frequent blood sampling. In term infants, blood loss is also not an uncommon cause of anemia and is often occult. This is the most common cause of otherwise unexplained neonatal anemia. Blood loss may occur before or around delivery due to feto-maternal hemorrhage or to twin–twin transfusion; it may occur as a result of bleeding from a ruptured cord or abnormal placenta, or there may be bleeding into the baby.

ANEMIA OF PREMATURITY

Almost all preterm infants have anemia, the etiology of which is usually multifactorial with reduced red cell lifespan and inappropriately low erythropoietin production being the most important contributing factors.[28–31] The best approach is prevention. While blood transfusion is usually carried out especially in babies of less than 28 weeks' gestation or those requiring prolonged mechanical ventilation, the amount of allogeneic red cell exposure can be significantly reduced by reducing blood tests in the child, give folate and iron to all preterms, appropriate use of erythropoietin, and compliance with peer-reviewed transfusion guidelines.

APPROACH TO MANAGEMENT

Only severe or moderate neonatal anemia should be treated with blood transfusion and this decision is made on clinical grounds as well as the Hb in accordance with peer-reviewed guidelines.[31] HDN always resolves, albeit it may take one to two months and in the first couple of weeks of life the hemolytic process may be so brisk that the high bilirubin necessitates phototherapy to prevent kernicterus. Blood transfusion may also be required for infantile pyknocytosis and for neonatal anemia due to blood loss.

Inherited anemia

As stated above, if the anemia is due to a hemolytic process the jaundice is almost always present. When the hemolytic process is secondary to a red cell membrane disorder then jaundice is usually accompanied by mild to moderate splenomegaly. Jaundice is also frequently seen in neonates with inherited red cell enzyme deficiencies, however in G6PD deficiency anemia is not usually present and the hyperbilirubinemia is thought to be most likely of hepatic origin. Most of the hemoglobinopathies, apart from alpha-thalassemia major and hemoglobin-H (HbH) disease, do not cause neonatal jaundice.[27]

RED CELL MEMBRANE DEFECTS

These can be difficult to diagnose in the neonatal period, especially in the case of the most common type, hereditary spherocytosis (HS) where the classic blood film morphology of numerous spherocytes is indistinguishable from that seen in ABO incompatibility. Spherocytes are also seen in the neonatal period with consumptive coagulopathy, birth asphyxia, and when there was significant placental insufficiency. A positive family history of HS is usually the best piece of additional information that is needed to make the diagnosis as osmotic fragility testing in this age group is not reliable and should be postponed until the child is between six and 12 months of age. Hereditary elliptocytosis is straightforward to diagnose from peripheral red cell morphology.

HEMOGLOBINOPATHIES

As globin chain synthesis is in a state of flux between late fetal life and following birth, diagnosing hemoglobinopathy is fraught with difficulty in the neonatal period.

The hemoglobinopathies that cause neonatal anemia include α-thalassemia major (Hb Barts hydrops fetalis) and HbH disease. In sickle cell syndromes the Hb is normal.

RED CELL ENZYME DEFICIENCIES

These usually are straightforward to diagnose in the neonatal period. A G6PD assay should be performed in any cases of prolonged or severe jaundice unless there is an obvious alternative cause. Pyruvate kinase deficiency is also diagnosed by assaying red cell enzyme levels; PK assays should be performed in cases of unexplained hydrops, those with hemolytic anemia of unknown cause, and where there is a family history.

MISCELLANEOUS

Other inherited conditions that can present as anemia in the neonatal period include Diamond–Blackfan anemia,[32] Pearson's syndrome,[33] congenital dyserythopoietic anemia,[34] Aase syndrome,[35] and osteopetrosis.[27]

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19

Genetics in neonatal surgical practice

ANDREW GREEN

NATURE AND STRUCTURE OF A GENE

Genetics is traditionally defined as the science of biologic variation, and has been a scientific discipline for over 100 years. Human genetics makes up a large part of the field of genetics, but the principal laws of genetics are universal, and apply equally to all species, including humans. Mendel's studies in the 19th century were originally felt to have no relevance to humans, and it is only in retrospect that their importance can be seen. Many of the principles of genetics were discovered through the study of smaller organisms, such as bacteria, yeast, and fruit flies. The basic genetic mechanisms of cell division, development, and differentiation happen in the same way in widely divergent species. Therefore it is impossible to look at human genetics in isolation, and there are large amounts of information from lower species which have bearing on human disorders. The study of the genetics of small organisms has had a profound impact on our understanding of human development, and of how human diseases develop. It is likely that such basic science will continue to contribute significantly to the understanding of human genetic disease. This chapter will attempt to outline the basic elements of genetics, describe the types of genetic tests now available to help in neonatal diagnosis, and give an approach to the diagnosis of congenital abnormalities.

The basic unit of inheritance for any species is the gene. The original concept of a gene arose long before the relationship between genes and nucleic acids was ever understood. A gene was considered to be a stable heritable element, which conferred a particular property or phenotype onto an individual organism. This element was passed on to subsequent generations of a particular species, and the nature of the phenotype varied according to the nature of the gene. The concept of dominant and recessive traits, which will be discussed later, was derived from studies of inheritance patterns, long before the molecular basis of the gene was understood.

A gene can also be considered in another way, as a specific length of deoxyribonucleic acid (DNA), which encodes a particular function, in most cases the synthesis of a protein. This also is a stable heritable unit. Each cell in an organism, regardless of its function, has the entire set of genes for that particular organism, but only a proportion of those genes will be active. DNA is found in the nucleus of every cell of an organism as a double helix (Fig. 19.1).

Each strand of the double helix has a backbone of alternating phosphate and deoxyribose sugar molecules, with the sugars attached to the 5′ and 3′ hydroxyl groups of the phosphate group. Attached to the sugar molecule, lying

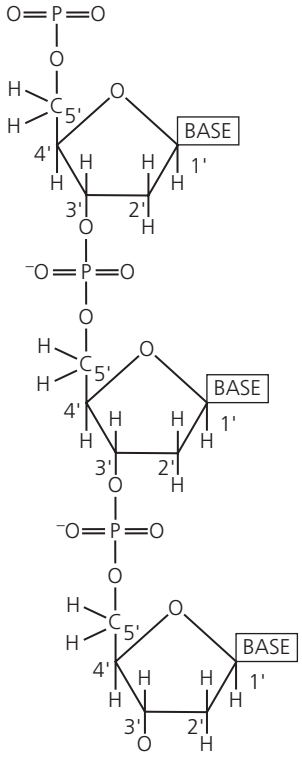

Figure 19.1 Structure of a DNA chain. The deoxyribose and phosphate residues are linked to form the sugar-phosphate backbone of DNA.

within the helix, is one of four nitrogen-containing nucleic acid bases. Two of these bases, adenine (A) and guanine (G), are purines, and two are the smaller pyrimidines cytosine (C) and thymine (T). The A and T bases pair together by hydrogen bonding, and the G and C bases similarly pair by hydrogen bonds (Fig. 19.2). The two strands of the double helix are held together by paired A-T or G-C bases of opposite strands of the double helix. The DNA strand can be read in only one direction from 5′ (left hand) to 3′ (right hand). The two strands of DNA are complementary to each other, and the sequence of one strand can be predicted from its opposite. If one strand reads 5′-CAGCGTA-3′, then the opposite strand must read 5′-TACGCTG-3′. The double-stranded sequence would then be written as follows:

5′-CAGCGTA-3′
3′-GTCGCAT-5′

The simplicity of the double helix structure allows for several important functions for DNA.

First, huge amounts of information can be stored in the strand of DNA. If a molecule of DNA is one million bases long, then there are $4^{1\,000\,000}$ possible sequences for that stretch of DNA. A genome is the complete DNA sequence of an organism. In humans, the estimated genome size is 3×10^9 base pairs (bp). The human genome contains a huge amount of coded information, of which as yet only a small part is known.

Second, the double helix provides a framework for DNA replication. One strand of DNA acts as a template for the synthesis of a new strand of DNA. The double helix unwinds, allowing DNA replication enzymes access to the template strand of DNA. The replication system builds a new strand of DNA based on the template. The new double helix formed as a result will contain one original strand, and a newly synthesized complementary second strand. This is the basic mechanism of DNA replication in all species.

Third, the double helix provides a basis for repair of damaged DNA. A damaged base can be replaced, knowing its complementary base is present on the opposite strand. Damage to the sugar-phosphate backbone can also be repaired using the opposite strand as a template.

Figure 19.2 Double-helix structure of DNA. The double helix of deoxyribose and phosphate molecules is held together by paired purine and pyrimidine bonds.

DECODING THE INFORMATION IN DNA

About 90% of the DNA in the human genome does not code for any specific property. Only about 10% of the genome actually contains coding information in the form of a gene. In simple terms, the genetic code in DNA is transcribed into a molecule called messenger RNA (mRNA). The mRNA is then translated into a protein, which carries out the function encoded by the specific DNA.

A gene has several distinct elements (Fig. 19.3). The major part of the gene is divided into coding regions, called exons, and non-coding regions called introns. Just before (5′) the first exon, there is a promoter which indicates where transcription of a gene should start. There can be several promoters for one gene, and different promoters can be used according to the tissue in which the gene is being expressed, in other words the promoter is tissue specific. Further 5′ of the promoter, there can also be enhancers or suppressors, which can increase or decrease the level of transcription of the gene. Not all of the mRNA will code for protein, as some exons will code for mRNA that does not directly encode protein. These areas, known as untranslated regions, can be either at the start (5′) or the end (3′) of the mRNA.

To express the DNA code, mRNA is used. There are several different types of RNA, but mRNA is the most important in decoding DNA. There are three differences between RNA and DNA. First, the sugar backbone of RNA contains ribose rather than deoxyribose. Second, mRNA exists as a single strand, and remains more unstable. Third, in RNA the base uracil (U) is used instead of thymine (T), whereas the other three nucleic acids remain the same.

The DNA code in most genes is expressed as a protein, which is a peptide made of the building blocks of individual amino acids. Each amino acid is coded for by a sequence of three DNA bases, known as a codon. For some amino acids, there is more than one codon (see Table 19.1). A long series of DNA codons in a gene will thus code for an entire protein. The mRNA codons coding for amino acids are identical to DNA codons, with the substitution of U for T. There is a tightly controlled mechanism for the generation of protein from a DNA template.

To decode a gene into protein, the DNA is first transcribed into mRNA. A strand (the 'sense' strand) of the DNA double helix is used by the enzyme RNA polymerase to synthesize a complementary strand of mRNA. Transcription of mRNA starts from the 5′ end of the first exon of the

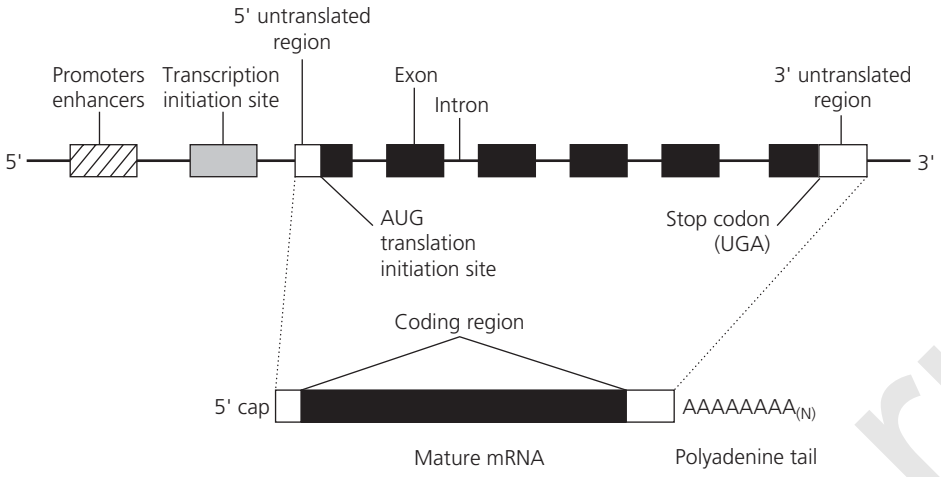

Figure 19.3 An idealized gene.

Table 19.1 The genetic code.

	Second position				
First position	U amino acid	C amino acid	A amino acid	G amino acid	Third position
U	UUU Phe	UCC Ser	UAU Tyr	UGU Cys	U
	UUC Phe	UCU Ser	UAC Tyr	UGC Cys	C
	UUA Leu	UCA Ser	UAA Stop	UGA Stop	A
	UUG Leu	UCG Ser	UAG Stop	UGG Trp	G
C	CUU Leu	CCU Pro	CAU His	CGU Arg	U
	CUC Leu	CCC Pro	CAC His	CGC Arg	C
	CUA Leu	CCA Pro	CAA Gln	CGA Arg	A
	CUG Leu	CCG Pro	CAG Gln	CGG Arg	G
A	AUU Ile	ACU Thr	AAU Asn	AGU Ser	U
	AUC Ile	ACC Thr	AAC Asn	AGC Ser	C
	AUA Ile	ACA Thr	AAA Lys	AGA Arg	A
	AUG Met	ACG Thr	AAG Lys	AGG Arg	G
G	GUU Val	GCU Ala	GAU Asp	GGU Gly	U
	GUC Val	GCC Ala	GAC Asp	GGC Gly	C
	GUA Val	GCA Ala	GAA Glu	GGA Gly	A
	GUG Val	GCG Ala	GAG Glu	GGG Gly	G

gene, until the end of the most 3′ exon. The intervening introns are initially included and the first molecule is known as pre-mRNA. The intronic RNA sequences are spliced out, and a 3′ polyadenine tail is added, producing mature mRNA. The mature mRNA is then transferred from the nucleus to the ribosome to be used as a template for the production of protein. The mature mRNA has both 5′ and 3′ untranslated regions.

Protein synthesis does not begin at the 5′ end of the mRNA, but at the first 5′ AUG codon, which codes for the amino acid methionine. Protein translation stops at the first truncation codon (usually UGA) thereafter (Fig. 19.3). In the ribosome, amino acid-specific RNA molecules, called transfer RNAs (tRNA), bind a free molecule of their specific amino acid. The binding is carried out by an anti-codon in the tRNA, which is complementary to the mRNA that codes for that specific amino acid. Using its anti-codon, the tRNA binds the specific mRNA codon for its amino acid. By complex machinery, the amino acid is then added to a growing peptide chain which will eventually form the mature protein (Fig. 19.4). The 5′ end of the mRNA corresponds to the NH_2 (amino terminus) of the protein, and the 3′ end of the mRNA corresponds to the COOH (carboxyl terminus) of the protein. Many proteins in higher species are modified after translation by the addition of phosphate or lipid groups.

CHROMOSOMES AND CELL DIVISION

The first coiling of DNA is in the form of the double helix. However, there are subsequent higher orders of coiling and packaging of DNA. The first order gives a loop of about 146 bp in size, wound around a histone protein. The complex is known as a nucleosome. The highest order of coiling of a large DNA molecule, with its associated histones and other proteins, is known as a chromosome.

A chromosome consists of one very long double helix of DNA, containing very many genes in millions of base pairs. Humans are diploid, that is to say they have two copies of every chromosome. The normal human chromosome complement is 46, made up of 22 pairs of autosomes (non-sex chromosomes) and two sex chromosomes, either X and Y in a male, or two X chromosomes in a female. Each member of a pair of autosomes contains the same genetic information. The pair of X chromosomes in a female will contain the same genetic information, but X and Y chromosomes in a male only have a small amount of genes in common. A normal human metaphase karyotype is shown in Figure 19.5.

When cells divide, the genetic content must also be duplicated so that the daughter cells have the correct genetic material. Most cell division occurs as mitosis, where one cell divides to give two cells genetically identical to that parent.

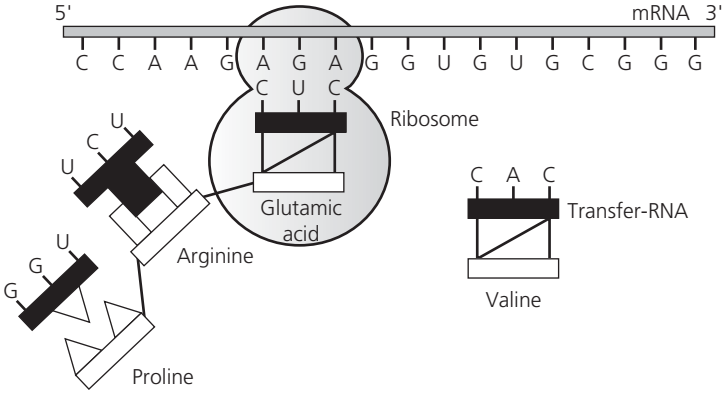

Figure 19.4 Diagram of protein synthesis from mRNA.

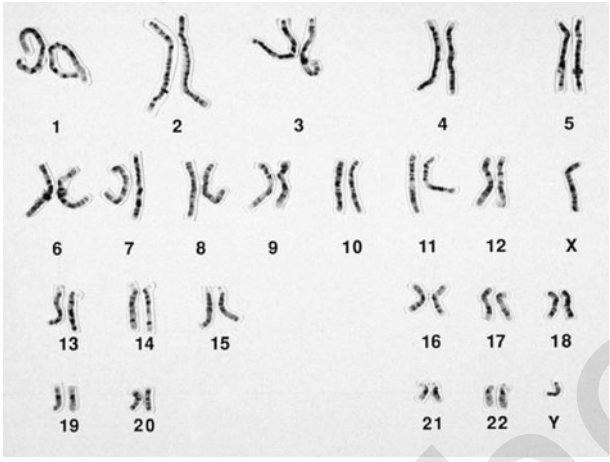

Figure 19.5 A normal male karyotype.

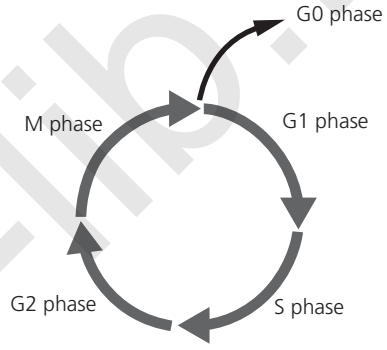

Figure 19.6 Cell cycle.

This is the process which allows the formation of a complete human being from one fertilized embryo, and is also the process by which the cells of many organs are constantly renewed. Mitosis is one short period during a carefully programmed cell cycle (Fig. 19.6). After mitosis, the cell may enter a resting phase (G_0), or go on to divide again (G1). A cell in G1 will then go on to synthesize new DNA as described earlier (S phase). There is then a second gap phase (G2) followed by mitosis (M).

Prior to mitosis the cell can be said to be in interphase, during which the chromosomes are very elongated. Just before mitosis, in S phase, the chromosomes are duplicated, and begin to condense as two (sister) chromatids per chromosome. This condensation phase is known as prophase. In the next phase, metaphase, the condensed chromatids line up along the plane of the cell, and spindle fibers develop between the centromeres (narrow waist of each chromatid), and the polar centrioles. Standard analysis of human chromosomes is carried out in metaphase. The chromatids separate, starting from each centromere, and pass to the new daughter cell, in the step called anaphase. By the telophase, the chromatids have reached to opposite poles of the dividing cell, and division completes.

Meiosis is the form of division required to form gametes (sperm or oocyte). Gametes are haploid, with only one of each chromosome, 23 chromosomes in the case of humans. This allows the formation of a new diploid organism from two haploid gametes. Meiosis occurs in two stages: meiosis I and meiosis II. The first phase of meiosis I, prophase I, is similar to that in mitosis, with the appearance of two condensed chromatids which have duplicated. At this stage, crossing over of genetic material from one chromatid to another can occur. It is estimated that about 1–2 crossovers occurs per chromosome in each meiosis. This introduces further genetic diversity, ensuring that the inherited chromosomes are different from the chromosomes of the parent. Metaphase I then occurs, where chromatids do not separate, but go to the opposite ends of the cell in anaphase I and telophase I. The cells at this stage are still diploid.

The second meiotic division then occurs, where chromatids condense again in prophase II, and line up along the axis of the dividing cell in metaphase II. The chromatids then separate, passing to opposite ends of the cell in anaphase II. The new cells are then haploid, with 23 chromosomes, and the chromatids elongate into thin strands in telophase II.

CHROMOSOME ANALYSIS

To examine chromosomes from a patient (a karyotype), dividing cells in culture must be examined. These cells are usually lymphocytes, amniotic fluid cells, or fibroblasts. Cells

are arrested in the metaphase stage of mitosis, and stained in such a way that the chromosomes are easily visualized. The usual technique used is G-banding (using a Giemsa stain), which gives a characteristic positive and negative banding pattern to each chromosome. Each chromosome has a constriction, called a centromere, dividing the chromosome into a short arm (p) and a long arm (q). Each arm has a number of prominent bands, which can then be subdivided into smaller bands. The gene for the ABO blood group is localized to chromosome 9q34. The gene thus lies in the fourth sub-band from the centromere (q34) of the third band from the centromere (q34) on the long arm (q34) of chromosome 9 (9q34).

Chromosome abnormalities can broadly be classified into abnormalities of chromosome number, or a rearrangement of a normal number of chromosomes. The critical issue in most cases for determining the significance of a chromosome abnormality is whether the abnormality gives rise to an excess or deficiency of the normal diploid state (aneuploidy).

Abnormalities of chromosome number are relatively common, but many are not recognized, as they may result in the early loss of a pregnancy. Triploidy (69 chromosomes) and tetraploidy (92 chromosomes) are relatively common causes of early pregnancy loss. Trisomy, the presence of a single extra chromosome (47 chromosomes), is also a common cause of miscarriage. Specific trisomies can give rise to an affected neonate, the most common being trisomy 21 (Down syndrome), trisomy 13 (Patau's syndrome) and trisomy 18 (Edwards' syndrome). All these trisomies usually occur as a result of autosomal non-dysjunction in meiotic division of the oocyte. In non-dysjunction, the specific chromatids fail to separate, resulting in an extra chromosome in one oocyte, and no chromosome in the opposite gamete. A fertilized embryo from the oocyte with an extra chromosome will therefore be trisomic. The fertilized oocyte with an absent chromosome will be monosomic, and be lost as an early miscarriage. Non-dysjunction tends to occur more frequently with increasing maternal age. Non-dysjunction can occur in the male germline, but rarely produces viable offspring.

There are numerous types of chromosome rearrangements, the most common of which are shown in Figure 19.7. Pericentric and paracentric chromosome inversions are usually balanced, and inherited without any phenotypic effect. Paracentric inversions are usually associated with a low risk of producing a liveborn unbalanced karyotype, but pericentric inversions may carry a higher risk. Insertions, duplications, deletions, isochromosomes, and ring chromosomes are all usually aneuploid and associated with significant clinical abnormalities. Reciprocal translocations occur where there is exchange of genetic material from one arm of a chromosome in return for genetic material from a different chromosome. Reciprocal translocations are usually balanced, without any clinical effect, but may carry a risk of having a child with problems due to an unbalanced karyotype.

Another type of translocation occurs between the acrocentric chromosomes (13–15, 21 and 22), where there is no appreciable coding material on a very small short (p) arm. This is known as a Robertsonian translocation. Robertsonian translocations are one of the most common human chromosome translocations, and in the balanced form have no clinical effect. A Robertsonian translocation involving chromosomes 14 and 21 is shown in Figure 19.8. Those who carry a Robertsonian translocation involving chromosome 21 may be at significantly higher risk of having a child with Down syndrome as an unbalanced product of the translocation. The same applies to a lesser extent for those carrying a

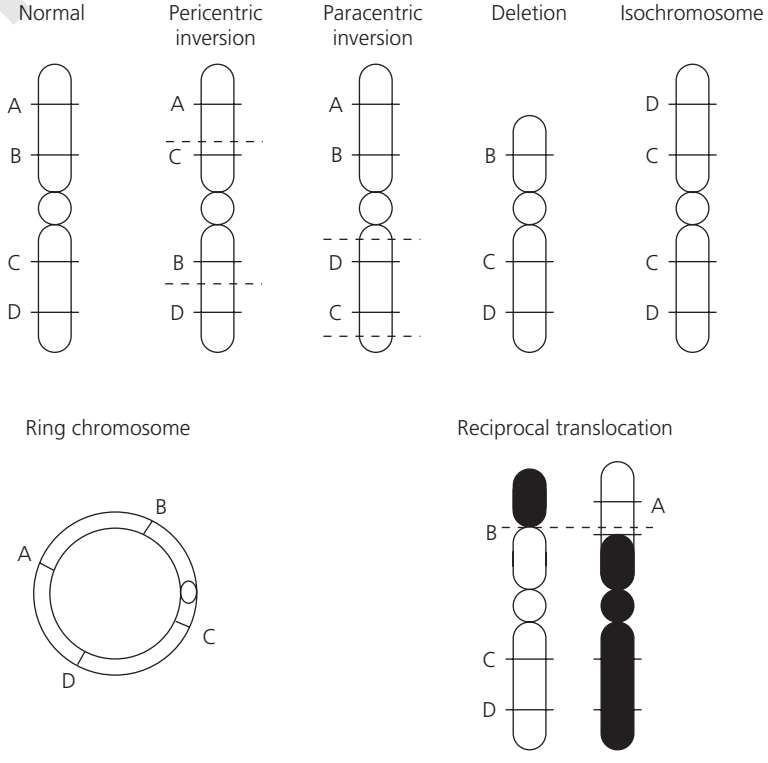

Figure 19.7 Different types of chromosome anomaly. A–D represent notional chromosomal loci.

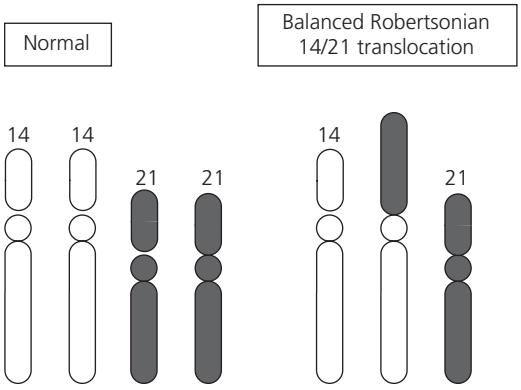

Figure 19.8 Robertsonian translocation.

Robertsonian translocation involving chromosome 13, and a subsequent risk of a child with Patau's syndrome.

The nomenclature for reporting a chromosome analysis is strict, and needs to be read carefully. A karyotype is reported initially as the number of chromosomes, regardless of whether those chromosomes are normal or not. The sex chromosomes are then described. If there is no further abnormality, the report is then complete. Any further abnormality is added after the sex chromosomes. A normal male karyotype is thus 46,XY. A male with non-dysjunctional Down syndrome will have the karyotype 47,XY,+ 21, an extra unattached chromosome 21. A male with Down syndrome due to a Robertsonian translocation between chromosomes 14 and 21 will have the karyotype 46,XY,t(14;21), and his carrier mother will have a karyotype 45,XX,t(14;21).

A standard laboratory chromosome analysis will be performed on G-banded chromosomes, which will detect many common and less common chromosome abnormalities, and in most cases no further laboratory work is required. However, recombinant DNA technology has allowed new techniques for chromosome analysis, based on the hybridization of fluorescently labeled fragments of DNA to the DNA of chromosomes, prepared in a standard fashion, immobilized on a glass slide. The slides can then be visualized by eye using a fluorescent microscope, or indirectly by generating an image of the hybridization on computer. This technique is known as fluorescent *in situ* hybridization (FISH). The information which can be gained from this technique depends on the origin of the fragments of DNA hybridized to the chromosome preparation. Labeled whole chromosome 'paints', consisting of DNA exclusively from one chromosome, are now commercially available. For example, whole chromosome paints can be used to identify the origin of extra chromosomal material which cannot be identified using G-banding techniques. Whole chromosome paints are also helpful in determining the origin of subtle complex translocations. It is also now technically possible to use a chromosome 21 paint on uncultured cells in interphase, to look for trisomy 21. A cell would show three fluorescent nuclear dots, representing three chromosomes 21, as opposed to two in the normal situation.

Fluorescently labeled small DNA fragments, corresponding to 40–50 kb of DNA from a specific chromosomal region, can also be hybridized to metaphase chromosomes. Chromosomal deletions which cannot be detected within the resolution of conventional cytogenetic analysis can be detected by the FISH method. A normal karyotype will give two hybridization signals: one from the same part of each chromosome. A karyotype containing a submicroscopic chromosomal deletion involving the segment of the chromosome corresponding to the 50 kb DNA fragment will only give one hybridization signal. An example would be the submicroscopic deletion of chromosome 22q11 which occurs in most cases of the Di George spectrum, which can only be seen by FISH analysis of chromosomes.

GENOMIC ARRAY ANALYSIS

A new technological development is the ability to immobilize thousands, and more recently millions, of distinct recognizable pieces of DNA on slides of silicone or glass as ordered microarrays, colloquially known as DNA microchips. This genomic array technology can permit analysis of thousands of individual loci simultaneously, and gives chromosome analysis at a resolution at least 100 times greater than conventional G-banded chromosome analysis. Genomic array technology will identify pathogenic chromosomal anomalies in 20–25% of infants in whom no underlying diagnosis had been identified previously. There is a drawback in that genomic array technology will often find genetic variants of unknown significance, and the current understanding of the role of such variants in disease pathogenesis is limited. Genomic array technology is now becoming available in an increasing number of diagnostic cytogenetic laboratories. Genomic array technology is likely to replace standard G-banded chromosome analysis for a wide variety of indications over the next few years.

PATTERNS OF INHERITANCE

Single-gene disorders have one of three principal modes of inheritance: autosomal dominant, autosomal recessive, and X-linked recessive. Other rare forms of inheritance include X-linked dominant, and mitochondrial disorders, as well as disorders due to abnormalities of genetic imprinting. Disorders caused by inheritance of unstable elements of DNA are now increasingly being recognized (see Other forms of inheritance).

Autosomal dominant inheritance

Autosomal dominant disorders are characterized by vertical transmission from parent to child, and the hallmark of these conditions is male-to-male transmission of the disease (Fig. 19.9).

Those affected with an autosomal dominant disorder have an alteration in one or other copy of their two genes responsible for that condition. Each child of a person with an autosomal dominant disorder has a 50:50 chance of inheriting the gene responsible for the condition from its parent.

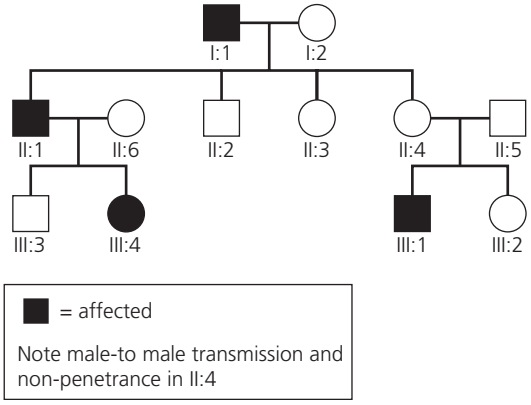

Figure 19.9 Autosomal dominant inheritance.

There are many examples of autosomal dominant disorders, including neurofibromatosis 1 and 2, familial adenomatous polyposis coli, myotonic dystrophy, and Huntington's disease. There can often be variability in both expression and penetrance of autosomal dominant disorders. For example, neurofibromatosis 1, an autosomal dominant condition, will almost always manifest in someone who has an altered neurofibromatosis 1 gene. This means that the condition has almost complete penetrance. However, different people can manifest the condition in different ways, with some people showing mild skin lesions, and others with severe intracerebral complications. This means that the expression or expressivity of the condition is very variable. In contrast, only 80% of those who have a single altered gene for the rare hereditary form of retinoblastoma will actually develop an eye tumor. The penetrance in this situation is 80%, but the expression of the altered gene is consistent, as manifested by a retinoblastoma.

Autosomal dominant disorders are not commonly seen in neonatal surgical practice. A list of the more frequent conditions is outlined in Table 19.2.

Table 19.2 Autosomal dominant disorders in neonatal surgical practice.

System affected	Condition
Gastrointestinal	Hirschsprung's disease (some cases)
	Beckwith–Wiedemann syndrome with exomphalos (some cases)
	Pyloric stenosis (some cases)
Genitourinary	Vesico-ureteric reflux
Skeletal	Stickler's syndrome
	Most craniosynostosis syndromes
	Achondroplasia
	Osteogenesis imperfecta
	Limb reduction defects (some cases)
Cardiac	Holt-Oram syndrome
	Noonan's syndrome
	22q11 microdeletion syndrome
Other	Retinoblastoma

Autosomal recessive inheritance

When a child is diagnosed with an autosomal recessive disorder, then both copies of a particular gene responsible for the condition are altered. Both its parents are therefore carriers for that condition, with one normal and one altered gene. Two of the child's four grandparents are also carriers, and it is likely that many of the child's relatives are also unknowingly carriers (Fig. 19.10). In most cases, being a carrier for an autosomal recessive condition has no effect on that person.

When both parents are carriers for an alteration in the same gene, then there is a 25% or one in four chance for each of their children to be affected by the condition. The risk of a healthy carrier sibling of having a child with the same condition depends on the chances of that sibling's partner also being a carrier. A child of a person with an autosomal recessive disorder will automatically be a carrier. The child's chances of being affected will depend upon whether its unaffected parent is a carrier for an alteration in the same gene.

Autosomal recessive disorders are commonly encountered in neonatal practice, and the nature of the disorder depends on the population being seen. Each regional population has its own recessive disorder, where the frequency of carriers for that disorder is highest. For instance, cystic fibrosis is a very common autosomal recessive disorder in Western Europe, whereas sickle cell anemia is the most common autosomal recessive disorder in West Africa. Common examples of autosomal recessive conditions include cystic fibrosis, sickle cell anemia, several of the mucopolysaccharidoses, beta-thalassemia, spinal muscular atrophy, and congenital adrenal hyperplasia (Table 19.3). Prenatal diagnosis is available for many of these conditions.

X-linked recessive inheritance

In X-linked recessive inheritance, the condition affects almost exclusively males, and females can be carriers (Fig. 19.11). The classic examples of such conditions are hemophilia A and B, Duchenne and Becker muscular dystrophy, and Hunter syndrome.

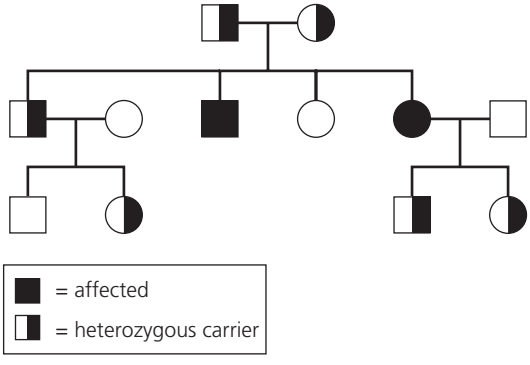

Figure 19.10 Autosomal recessive inheritance.

Table 19.3 Autosomal recessive disorders in neonatal surgical practice.

System affected	Condition
Metabolic	Cystic fibrosis
	α-1-antitrypsin deficiency
Skeletal	Short-rib polydactyly syndrome
	Jeune's syndrome
	Robert's syndrome
Genitourinary	Infantile polycystic kidneys
	Meckel–Gruber syndrome
Endocrine	Congenital adrenal hyperplasia

The daughters of a man with an X-linked recessive condition are all obligate carriers. The sons of a man with an X-linked condition are all normal, as they inherit his Y chromosome, and not his X chromosome. When a woman is a carrier of an X-linked condition, each of her sons has a 50:50 chance of being affected, and each of her daughters has a 50:50 chance of being a carrier. There can be a relatively high mutation rate for some X-linked recessive conditions, and affected boys may not have any family history of the condition. About one-third of cases of boys with Duchenne muscular dystrophy occur as a result of new mutations. Prenatal diagnosis is available for a wide range of X-linked recessive diseases. The more common X-linked disorders in neonatal practice are shown in Table 19.4.

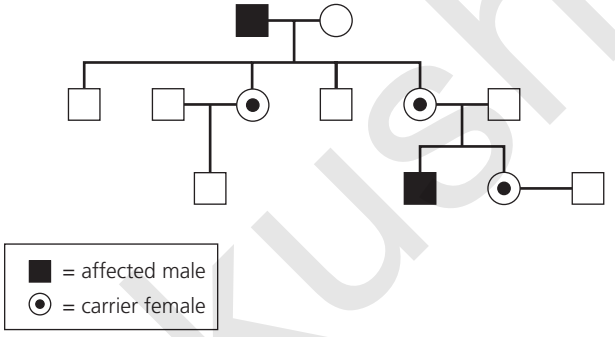

Figure 19.11 X-linked recessive inheritance.

Table 19.4 X-linked recessive disorders in neonatal surgical practice.

System affected	Condition
Neurological	Hydrocephalus with aqueduct stenosis (some cases)
Hematological	Hemophilia
Skeletal	Amelogenesis imperfect
Endocrine	Androgen insensitivity syndrome
Metabolic	Adrenoleukodystrophy

Polygenic inheritance

Many congenital conditions do not have a clear mode of inheritance, and can be classed as polygenic or oligogenic, where a disease may arise as a result of the effects of several genes. A good example is cleft lip and palate, which usually occurs in the absence of a family history. However, monozygotic twins have a high concordance for cleft palate, suggesting a genetic influence. A similar model applies to the genetics of neural tube defects, which arise as a result of the combination of several environmental and genetic factors.

Other forms of inheritance

There are also much rarer forms of inheritance, including X-linked dominant, which can be hard to tell apart from autosomal dominant, except that females will be more mildly affected, and there is no male-to-male transmission. An example of an X-linked dominant condition is hypophosphatemic rickets.

Mitochondrially inherited diseases show a very unusual pattern of inheritance. Most of the proteins in the mitochondria are encoded for by nuclear genes, but the mitochondria also contain their own small genome of 18 kb, with many copies per cell. The mitochondrial genome replicates independently and far more frequently than the nuclear genome. Several important mitochondrial proteins are encoded by the mitochondrial genome. Mitochondria are only inherited via oocytes, and not sperm. Therefore, where a gene alteration is in the mitochondrial genome, it will pass exclusively down the female line, but both males and females can be affected. The children of an affected male will not inherit his mitochondrial gene alteration. Children with mitochondrial disorders can present with many varied symptoms, including myoclonic seizures, acute acidoses, muscle weakness, deafness, or diabetes. A number of point mutations and deletions in the mitochondrial genome have been described in patients with a wide variety of conditions, including MELAS (myoclonic epilepsy with lactic acidosis and stroke-like episodes) or MERRF (myoclonic epilepsy with ragged red fibers on muscle biopsy). To complicate matters further, Leber's hereditary ophthalmopathy is a mitochondrially inherited condition, with a characteristic mitochondrial mutation, but the expression appears to have an X-linked recessive influence.

Some conditions show a phenomenon known as genetic imprinting. An imprinted gene has been marked during meiosis, to indicate the parent from which it comes. For some genes, it appears to be important not only to inherit two copies of that gene, but to inherit one from each parent. Some genes may be silenced, depending upon which parent has passed on that gene. A good example is the presence of a small deletion of chromosome 15q, which has a different effect, depending upon which chromosome 15 is deleted. If the deletion occurs on the chromosome inherited from a child's normal father, the child will develop Prader–Willi syndrome. If the deletion occurs on the chromosome inherited from a child's normal mother, the child will develop a completely different clinical condition, Angelman's syndrome. The genes

in this area of chromosome 15 are therefore imprinted. In addition, if a child has two maternal copies of chromosome 15 (maternal disomy), but no paternal copy, he or she will also develop Prader–Willi syndrome. Other conditions which show imprinting effects include Russell–Silver syndrome, Beckwith–Wiedemann syndrome, and the rare condition of transient neonatal diabetes mellitus.

A new molecular mechanism for genetic disease has been described, of inherited unstable triplet repeat expansions. At least nine different conditions are caused by this phenomenon. In one of these genes, a normal person has a stable number of a repetitive element of three bases of DNA (for example 20 copies of a CAG repeat) in a particular gene. In that case the gene functions normally and the children of that person have the same number of repeats in their gene. An affected person has an increased number of repeats (say 100 copies) in that gene, and the affected children of that person have more serious disease, with perhaps 200 repeats in the gene. The molecular genetic findings appear to be the genetic correlate of the phenomenon of anticipation, where a condition appears to worsen from generation to generation. The most extreme example is that of congenital myotonic dystrophy, where a minimally affected mother can have a profoundly affected infant. In this case, there is a small repeat expansion of say 150 repeats in the mother, increasing to many hundreds of repeats in her affected infant.

This molecular mechanism is responsible for Fragile X syndrome, Huntington's disease, Friedreich's ataxia, several forms of spinocerebellar ataxia, and probably several other conditions.

MOLECULAR GENETIC ANALYSIS FOR SINGLE-GENE DISORDERS

Laboratory tests for single-gene disorders have been available for a considerable amount of time. Hemoglobin electrophoresis for sickle cell anemia and thalassemia, and enzyme assays for Tay–Sachs' disease, are very effective in resolving clinical issues in individual families. However, an increasing number of specific DNA-based tests can now be used in diagnosis and prediction of single-gene disorders.

The two major techniques used in molecular genetic analysis are the polymerase chain reaction (PCR) and Southern blotting techniques. PCR is a technique which allows amplification of a specific genetic region in large quantities from a small amount of DNA template (Fig. 19.12). The DNA sequence of the region to be amplified must be known, so that synthetic pieces of single-stranded DNA (oligonucleotide primers) corresponding to the region can be designed and manufactured. The oligonucleotide primers are added in great excess to the DNA template, along with a thermostable DNA polymerase, and free nucleotides (A,C,T,G). The mixture is heated up to cause the two strands of template DNA to separate, and then cooled. As the DNA cools, the oligonucleotides bind to the template sequence, and are extended by the polymerase. A new copy of the template DNA is thus produced. The cycle is repeated 30–40 times, with an exponential increase in the amount of the target sequence.

DNA generated by PCR can be used in many different ways to detect an abnormality in the sequence. If the test is aimed at detecting a known sequence abnormally, such as the common three base pair deletion on the cystic fibrosis gene Phe508del, the PCR product can be analyzed using mutation-specific oligonucleotide primers, or a DNA restriction enzyme test. If the search is for an unknown DNA mutation, such as those seen in hereditary breast and ovarian cancer, then many pieces of DNA generated by PCR from the patient can have their sequence analyzed using a semi-automated DNA analyzer.

Southern blotting is a more protracted procedure involving the digestion of a relatively large amount of DNA by a restriction enzyme. The digested DNA is then electrophoresed through an agarose gel, giving a smear of DNA of different sizes. The DNA is then transferred (blotted) and fixed to a membrane. The fixed DNA is then hybridized to a labeled DNA probe specific for the gene to be analyzed, and the specific sizes of DNA to which the probe binds allows determination of the 'genotype' (Fig. 19.13). This test is often superseded by PCR technology.

There are different degrees to which molecular genetic tests can contribute to clinical diagnosis. Some specific molecular genetic tests can be used to detect a known pathogenic DNA mutation, and give a diagnosis, even without any knowledge of the patient's clinical status. For instance, the PCR detection of the Phe508del deletion in both copies of a person's cystic fibrosis (CFTR) gene immediately gives a diagnosis of cystic fibrosis. Such direct mutation tests are possible where both the gene responsible for a condition has been isolated, and specific pathogenic mutations have been identified. Similarly, a PCR test detects a deletion of exons seven and eight in both alleles of a gene called SMN on chromosome 5q in almost all children with spinal muscular atrophy. Southern blot analysis of DNA from infants with congenital myotonic dystrophy shows a very large expansion in a triplet repeat DNA sequence in the myotonin kinase gene

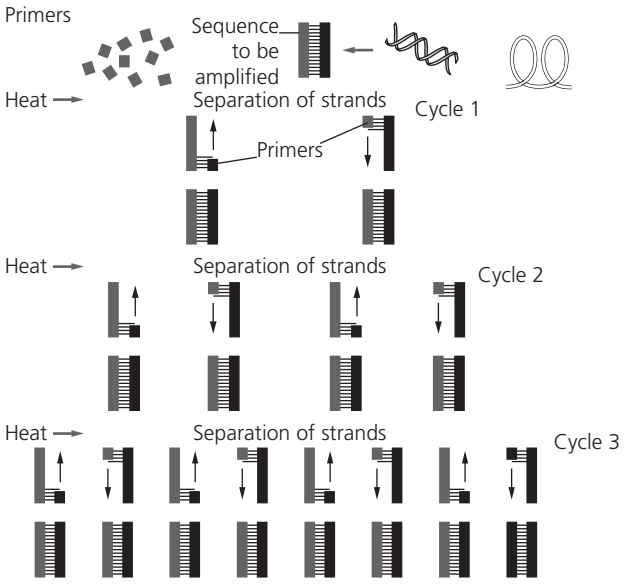

Figure 19.12 Polymerase chain reaction (PCR).

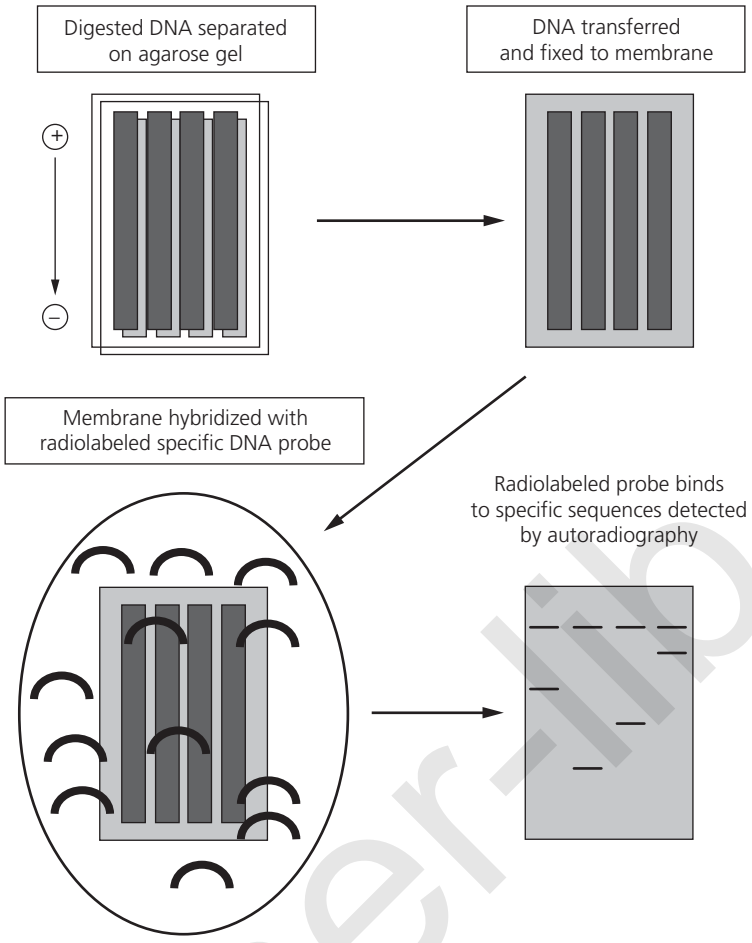

Figure 19.13 Southern blotting and hybridization.

on chromosome 19, as described earlier under Other forms of inheritance.

In other cases, molecular genetic diagnosis can point towards a diagnosis, without confirming it. For instance, the presence of a single Phe508del CFTR gene mutation in a child with a history suggestive of cystic fibrosis increases the likelihood of the child being affected.

In some cases, where either a gene is not known, or very few gene mutations have been identified in a known gene, gene tracking studies can be performed in a family to predict whether a person in that family is affected. This is known as linkage analysis. Such a study requires careful clinical examination of several family members, to establish whether they are affected or unaffected. Where their clinical status is clear, DNA samples are then obtained.

Gene tracking analysis in the family uses the property of normal variation in a gene between different people. Some genetic areas show wide variation between individuals, and a DNA marker from such an area, which can detect many variations, is described as being polymorphic. Each variant of a polymorphic marker is known as an allele. There are now thousands of polymorphic markers covering most of the human genome, and such markers can be found very close to most known genes. There are several types of polymorphic DNA markers, including markers characterized by different numbers of specific DNA-cutting enzymes recognition sites or restriction fragment length polymorphisms (RFLPs). Other markers detect the variation in number of anonymous elements of repetitive DNA and are called microsatellites or minisatellites.

If the two alleles of a polymorphic marker can be distinguished to discriminate between the two copies of that particular chromosome from where the marker comes, then the marker is informative in that individual. Where a gene location is known but the actual gene has yet to be found, the alleles of informative markers which lie on either side of the gene will be inherited along with each copy of the gene in question. This can be used to predict a child's clinical status.

If one set of alleles is found in the affected members of the family, but not in those unaffected, then the presence or absence of these alleles in the at-risk individual can be used to predict their chances of being affected. An example of linkage analysis for an autosomal recessive disorder is shown in Fig. 19.14. This form of linkage analysis is often used in families with X-linked recessive conditions such as Duchenne muscular dystrophy, to predict whether a woman is a carrier. Such linkage analysis can also be used in prenatal diagnosis.

Of its nature, linkage analysis is more prone to error than direct mutation testing. This can be due to difficulties in assessing a person's clinical status, and because of the possibility of recombination between the polymorphic

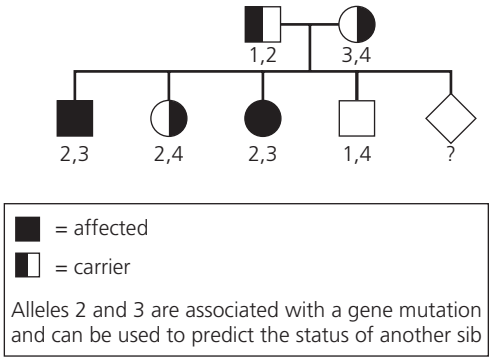

Figure 19.14 Linkage analysis in an autosomal recessive disorder using an intragenic polymorphic marker.

markers. However, with the rapid advances in molecular genetics, many more mutations are being found in many different genes, and linkage analysis is often superseded by direct mutation testing.

The rapid advances in genetic technology will alter how genetic testing will be used in clinical diagnosis. Present DNA sequencing technology allows analysis of several thousand DNA bases over a period of weeks. New short high density oligonucleotide DNA sequencing technology, called collectively next generation sequencing, can now permit the analysis of millions of DNA bases over a much shorter period of time. With this technology, many genes can be analyzed in a short clinically relevant period of time at reasonable cost. Thus in children with specific sets of malformations, direct sequencing of multiple genes in a short period of time will soon be available to provide rapid clinical information for clinicians and families.

A CLINICAL GENETIC APPROACH TO DIAGNOSIS OF MALFORMATION SYNDROMES

Definitions

One child in 40 (2.5%) is born with a significant congenital anomaly and 20–25% of perinatal and childhood mortality is accounted for by congenital anomalies. Only a small number of these anomalies will occur as part of a specific genetic syndrome. A list of common congenital anomalies and approximate birth incidence is shown in Table 19.5.

Awareness of the possibility of a genetic or syndromal association for anomalies is very important for management of the patient, and for advising the whole family. A distinction has also to be drawn between several different forms of abnormality, with appropriate definitions.

A 'disruption' can be defined as an anomaly which is caused by an interference in the structure of a normally developing organ. A good example would be the digital constrictions and amputations caused by amniotic bands.

A 'deformation' can be defined as an anomaly which is caused by an external interference in the structure of a normally developing organ. An example would be talipes equinovarus caused by chronic oligohydramnios, perhaps from an amniotic leak.

Table 19.5 Examples of major congenital anomalies.

Type	Birth incidence (per 1000 births)
Cardiovascular	10
Ventricular septal defect	2.5
Atrial septal defect	1
Patent ductus arteriosus	1
Fallot's tetralogy	1
Central nervous system	10
Anencephaly	1
Hydrocephalus	1
Microcephaly	1
Lumbosacral spina bifida	2
Gastrointestinal	4
Cleft lip/palate	1.5
Diaphragmatic hernia	0.5
Esophageal atresia	0.3
Imperforate anus	0.2
Limb	2
Transverse amputation	0.2
Urogenital	4
Bilateral renal agenesis	2
Polycystic kidneys (infantile)	0.02
Bladder extrophy	0.03

A 'malformation' can be defined as an anomaly which is caused by an intrinsic failure in the normal development of an organ. Common examples would be congenital heart disease, cleft lip and palate, and neural tube defects.

A 'dysplasia' is an abnormal organization of cells in a tissue, often specific to a particular tissue. For example, achondroplasia is a skeletal dysplasia caused by a mutation in the FGFR3 gene. Most dysplasias are single-gene disorders.

A 'sequence' can be defined as a group of anomalies which arise due to one single event. An example would be Potter's sequence. Potter's sequence (Fig. 19.15) is the group of anomalies consisting of pulmonary hypoplasia, oligohydramnios, talipes, cleft palate, and hypertelorism. All of these anomalies arise as a result of the failure of urine production in the fetus. The cause of Potter's syndrome and failure of urine production could be posterior urethral valves, dysplastic or cystic kidneys, or renal agenesis, all of which can have genetic, non-genetic, or chromosomal origins. Pierre Robin sequence is the grouping of cleft palate, micrognathia, and glossoptosis, which can have at least 30 different causes. A sequence therefore does not have a specific cause or inheritance pattern.

An 'association' can be defined as a clustering of anomalies, which is not a sequence, and which occurs more frequently than by chance, but has no prior assumption about causation. A good example is the association of VATER (vertebral anomalies, anal abnormalities, tracheo-esophageal fistula, and radial or renal anomalies). There is no clear cause for VATER, although it can rarely occur in people with chromosome 22q11 microdeletions, and can also rarely be mimicked by Fanconi's anemia.

A 'syndrome' is a description of a group of symptoms and signs, and a pattern of anomalies, where there is often a

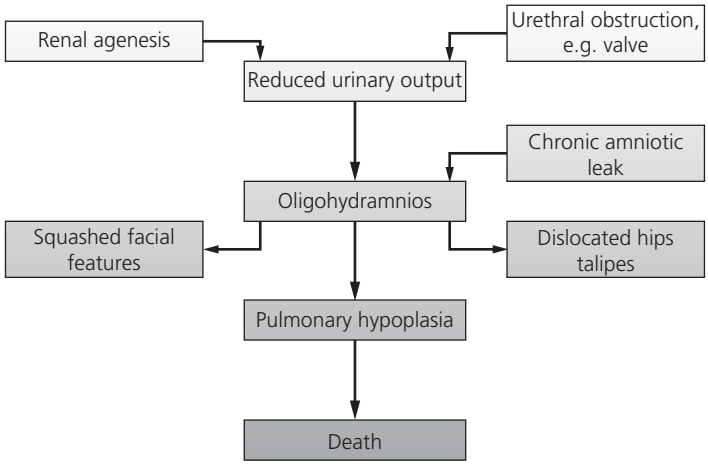

Figure 19.15 Potter's sequence.

known cause or an assumption about causation. The looser definition of 'syndrome' to describe an anomaly should be avoided. The term can include chromosomal disorders such as Down syndrome, or single-gene disorders such as van der Woude syndrome, which can cause cleft lip and palate with lower lip pits.

An approach to diagnosis

When a child is born with a congenital anomaly, several particular aspects of the history need to be explored. A good family history must be taken, with reference not only to a history of the same anomaly, but other anomalies as well. A family history must include documentation of pregnancy losses, stillbirths, and neonatal deaths. Any history of potential teratogens in the pregnancy should be looked for, considering the likely embryological timing of the anomaly. Teratogens can include medications, recreational drugs, maternal diabetes, and prolonged maternal hyperthermia.

If a child has one congenital anomaly, a very careful examination should be carried out to check for any other more subtle abnormalities or for dysmorphic facial features, e.g. to check for hydrocephalus in an infant with a spinal meningomyelocele. If there is more than one malformation or significant dysmorphology, a chromosomal analysis should be requested, as chromosomal aneuploidy is a well-recognized cause of multiple malformations. A clinical genetic opinion should also be sought, as a clinical geneticist can often help greatly in achieving a diagnosis, as well as in counseling parents about the likelihood of recurrence of similar problems in other family members.

A diagnostic approach to congenital anomalies is outlined in Figure 19.16. Deformations and disruptions need to be excluded first. If the pattern of malformations fits into a well-described sequence, then a cause for that sequence should be sought. If the anomalies do not fit into a sequence, then a syndrome or association diagnosis should be attempted. If a syndrome diagnosis is achieved, it is important to remember that syndromes can be caused by chromosomal disorders, single-gene (monogenic) disorders, or by environmental agents (teratogens).

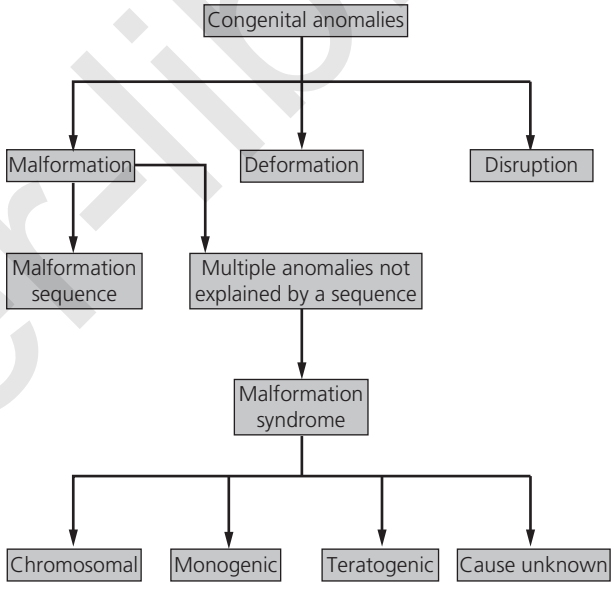

Figure 19.16 A diagnostic approach to congenital anomalies.

Table 19.6 Causes of congenital anomalies.

Type	Relative frequency (%)
Genetic	
Chromosomal	6
Single gene	7.5
Multifactorial/polygenic	20–30
Environmental	
Drugs, infections, maternal illness	5–10
Unknown	50
Total	100

The majority of congenital anomalies have a polygenic or multifactorial origin, and most are isolated (non-syndromal). The causes of congenital abnormalities are outlined in Table 19.6, and it is important to note that about 50% do not have a clear cause. Nonetheless, parents and families want

an explanation as to the origin of their child's anomaly, and it is therefore worthwhile to pursue a diagnosis wherever possible.

This chapter is an introduction to the concepts and principles of genetics in neonatal surgical practice. It is not intended to be a comprehensive review of syndromes. Further information can be obtained from the bibliography later, and from many Internet sources.

GLOSSARY

3-prime Distal end of a gene, as indicated by the bond at the 3rd hydroxyl group of the deoxyribose sugar

5-prime Proximal end of a gene, as indicated by the bond at the 3rd hydroxyl group of the deoxyribose sugar

Acrocentric A chromosome with effectively only a long arm – chromosomes 13,14,15,21, and 22

Allele A genetic variation of a gene or DNA marker

Aneuploidy An excess or deficiency of chromosomal material

Anti-codon An element of transfer RNA which binds a specific amino acid

Autosomal dominant Inheritance pattern characterized by transmission through several generations, male-to-male transmission, and a 50:50 risk to the children of any affected person.

Autosomal recessive Inheritance pattern characterized by several affected members of the same generation, with carrier parents and a 1:4 recurrence risk where both parents are carriers

Base pair Unit of double-stranded DNA

Centromere Element of chromosome involved in chromosome replication, found as a constriction in the chromosome

Chromatid Condensed chromosome found just before mitosis

Codon Three base pair element of DNA encoding an amino acid

Diploid A complement of two copies of each chromosome per cell

DNA marker A piece of DNA corresponding to a specific gene or chromosomal segment

Enhancers Elements of DNA which are involved in increasing gene transcription

Exon A part of a gene which is transcribed into mRNA

Expression The way in which a gene fault manifests clinically

FISH Fluorescent *in situ* hybridization – a new and powerful technique for studying specific chromosomes or regions of chromosomes

Gamete A germ cell – sperm or oocyte

Genetic imprinting The marking of a gene according to which parent has passed the gene to its child

Haploid A complement of one copy of each chromosome per cell (as in sperm or oocyte)

Haplotype A pattern of alleles of DNA markers representing one of the two copies of a chromosomal region

Histone A DNA-binding protein important in chromosomal folding

Interphase Phase of mitosis in which the chromosomes are very elongated

Intron The part of a gene between the exons which is not transcribed into mRNA

Isochromosome An abnormal chromosome made up of two long or two short arms of a normal chromosome

Karyotype An analysis of the chromosome complement of a cell type

Linkage analysis The use of polymorphic DNA markers to perform gene tracking studies within a family

Meiosis The process of cell division to give haploid germ cells

Metaphase Phase of mitosis in which the chromosomes are very condensed and easier to analyze

Microsatellite marker A DNA marker which detects variation in number of an anonymous small repetitive element of DNA

Minisatellite marker A DNA marker which detects variation in number of an anonymous medium repetitive element of DNA

Mitosis The normal process of cell division to give two diploid copies of a cell

Non-dysjunction A failure of meiosis, giving two copies of a chromosome in one gamete, and no copy of a chromosome in the other gamete

Nucleosome The combination of a histone and its bound DNA

Oligonucleotide primers Small lengths of synthetic single-stranded DNA of a specific sequence

Paracentric inversion A rearrangement of chromosomal material within one arm of a chromosome

PCR Polymerase chain reaction – a method of generating large amounts of specific DNA from a small amount of target sequence

Penetrance The number of people known to carry a gene mutation who manifest the condition

Pericentric inversion A rearrangement of chromosomal material around the centromere of a chromosome

Promoter Element of a gene which is necessary to activate gene transcription

Prophase Phase of the cell cycle where condensation of the chromosomes occurs, just before metaphase

Reciprocal translocation Exchange of chromosomal segments between different chromosomes

Restriction enzyme An enzyme which cuts double-stranded DNA at a specific unique short DNA sequence

Restriction fragment length polymorphism A genetic variation between two copies of the same gene, where one gene may have one copy of a restriction enzyme recognition site, and the other has two copies. This variation can be detected using PCR or Southern blotting

Ribosome Area of the cell where mRNA is converted into protein

Ring chromosome An abnormal chromosome in which the tips of the long and short arms have fused

Robertsonian translocation A fusion of two acrocentric chromosomes

Southern blotting A process of immobilizing DNA to nylon membrane for genetic analysis

Suppressor A DNA element which reduces the expression of a gene

Telophase The last phase of mitosis

Telomere The end of a chromosome

Transcription The process of converting DNA into mRNA

Translation The production of protein from a DNA sequence

Triploidy Three of each chromosome, i.e. 69 chromosomes in man

Trisomy One extra chromosome, i.e. 47 chromosomes in man

X-linked recessive Inheritance characterized by affected males in several generations, and by female carriers

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20

Ethical considerations in newborn surgery

JACQUELINE J GLOVER AND DONNA A CANIANO

INTRODUCTION

In caring for the extremely premature neonate with surgical disease or the infant with multiple, life-threatening congenital anomalies, pediatric surgeons often encounter difficult ethical decisions about the use of advanced, life-sustaining treatments and operative interventions. The imperative to utilize new technology is tempered with concerns about quality of life, informed parental decision making, and access to scarce medical resources. Pediatric surgeons, families, and communities ask the difficult ethical question: 'We can do this particular intervention, but, should we?' This chapter provides the pediatric surgeon with ethical guidelines to utilize in clinical situations in which therapeutic decisions contain uncertainty or conflict and the next steps in the management of an infant that pose challenges for the parents and physicians.

DEFINING THE BEST INTERESTS STANDARD

Since neonates and infants cannot make decisions about the appropriate use of technology based on their own personal values, the central ethical question is framed in pediatrics as, 'What is in the best interests of this infant?' An answer requires a unique and complex ethical framework that combines a concern for who makes the decision and what decision is appropriate.

In the United States, parents are presumed to be the appropriate decision makers for their infants,[1] but they are not unqualified decision makers. Parents and pediatric surgeons must work together to make decisions that are in the 'best interests' of infants.[2,3] The term 'best interests' is meant to capture a balancing of the benefits and burdens to this infant of a particular intervention.[4]

In the mainstream medical culture in the US, the term 'best interests' was developed to focus attention on the need to assess the benefits and burdens of treatment for a particular infant from the infant's perspective. In an effort to be as objective as possible, only the direct pain and suffering associated with an infant's condition and/or proposed treatment was to be considered in conjunction with the benefit of continued life. The standard was proposed as a very strict one, regarding treatment as beneficial and in the infant's best interest unless the infant was dying, the treatment was medically contraindicated, or continued life would be worse for the infant than an early death. A central feature of this narrow understanding of best interests includes its child-centeredness, understood to mean the exclusion from consideration of the negative effects of an impaired infant's life on other persons, including parents, siblings, and society.

A second key feature is its emphasis on the infant's concrete experience of burden in the form of pain and suffering. In addition to the difficulties associated with assessing the burdens experienced by an infant, a narrow best interests standard cannot be applied to neonates and infants with neurological deficits so severe as to exclude the possibility of experience of any sort. Infants who are not responsive to outside stimuli, for example, cannot experience pain and therefore cannot be burdened in the same way as conscious infants.

Some ethicists have appropriately pointed out that absence of pain is not the only morally relevant feature.[5] A 'relational potential' standard is necessary to augment a best interests standard. It is not morally obligatory to sustain life without any capacity for human relationship, even though life is not burdensome per se. Just as the presence of pain unable to be relieved can preclude the attainment of those basic human goods that make life worth living, so the absence of fundamental human capacity can render a life devoid of the same basic human goods.[6]

For the last few decades, the best interests standard has enjoyed prominence in pediatric ethics in the US, although its limitations have also been clearly articulated. Critics argue that an infant's interests are unknowable, that an interests appeal can yield counterintuitive results, and others' interests also deserve consideration.[7] For those who favor a best interests standard, it is a way to focus attention on the patient as the primary loyalty of the health care professional, to

maximize benefit to the patient,[8] to insure that the lives of the disabled are not undervalued, and to guarantee that justice in the form of principles of nondiscrimination are applied.[5] However, reliance on a narrow best interests standard fails to take into account other moral features that are a necessary part of ethical decision making in pediatrics. The term has been used to oversimplify a distressingly complex set of moral problems. The more one can render an ethical decision unidimensional, and the more factors one can exclude from consideration beforehand, the easier the choice becomes.[6]

An expanded understanding of best interests must take into consideration several competing ethical values. One value is respect for family autonomy or self-determination. Families ought to have the freedom to make important choices about family welfare independent of others. It is not so much that families have a right to make important decisions for their infants, as it is that families have the responsibility to make decisions and provide the necessary financial and other types of support. Families are an essential unit of care that are both valuable in themselves, and instrumentally valuable to meet the social goal of caring for children. Since families are presumed to love their children and desire to do what is best for them, they have a unique claim to the decision-making role. Also, families have to live with the consequences of the health care decisions that are made.[9]

In a very real sense, the families interests are linked with the interests of the neonate or infant.[10] An attempt to starkly separate infant and family interests is artificial and diminishes rather than enhances an understanding of the infant's well-being. One can understand how the best interests standard developed in the context of imperiled newborns, where there is great uncertainty and no one has a longstanding relationship with the infant. The objectivity sought is comprehensible only because the infant is a stranger to all. Yet even in the case of newborns, most authors agree that parents should be the primary decision makers.[11] If family interests were irrelevant, it would be difficult to make sense of such a presumption. Given this presumption in favor of parental decision making, and the fact that most infants are not strangers to their parents, a best interests standard would be better understood to include a more comprehensive understanding of a child-centered decision, one made by a family whose daily lives involve the love and care of their infant.

Additionally, the search for the 'best' interests of the infant apart from the family has several negative consequences. First of all, it can antagonize parents and turn all parties into adversaries. It can also cut off discussion and planning rather than improve it. Families may not feel free to discuss difficulties, and important needs may go unmet. Rather than search for some artificial 'best' interest, all parties should acknowledge the complex goal of promoting the infant's well-being and the necessary interdependence of families in that endeavor. To exclude the family in a concept of child-centeredness is to reduce the infant to only a physiological organism and well-being to pathophysiological function.

Another value that is in tension with respect for family decision making is respect for professional integrity. Since 'best interests' also contains an important focus on the uniquely medical interests of the infant, professional judgment plays an important role in describing and evaluating the benefits and burdens of health care interventions.[12] Pediatric surgeons have independent obligations to the infants who are their patients, to promote their well-being and protect them from harm. They have a professional obligation to promote life and quality of life, and to avoid such harms as killing, premature death, pain and suffering. Yet even based on so-called medical facts, decisions are a complex amalgam of what the infant's alternative futures will be like, how likely it is that these futures can be gained, and what the infant has to endure to get there. An infant's present interests in being free from undue burdens must be weighed against all future interests.[13]

A third important value is that of justice as nondiscrimination.[5] How do we understand the interests of a child in himself or herself, independent of how others may value him or her? What does society owe its children as a matter of justice? Infants do not only belong to their families, but they also are members of their community. Communities have an obligation to protect the most vulnerable among them, especially if they are vulnerable to the neglect and abuse of their families. All infants deserve a certain level of health care, independent of what their families might choose for them.

The principle of justice also has another important component that is in direct conflict with the highly individualistic interpretation of 'best interests'. In fact, a 'best interests' standard is an attempt to narrowly focus decisions on the patient him/herself and to avoid greater issues of the just distribution of health care resources, but this is impossible. Families and communities struggle to consider what they owe each child, but also to consider what is fair for this child and all children together. Resources of time, effort, services, and money are limited within families and communities. Each must consider the impact of choices on the availability of resources for others. There is no doubt that questions of distributive justice are among the most difficult ethical issues that families, professionals, and communities must face, but they will never be resolved if they are simply ignored in the decision-making process. The authors agree that allocation decisions are best made at levels other than at the bedside, as in the formulation of insurance plans and governmental policies, but these corporate allocation decisions will always have implications for bedside care, and must not be ignored.

An expanded 'best interests' standard is an attempt to balance the benefits and burdens of a health care intervention according to the values of the parents, pediatric surgeons, and the larger society. It should be clear that the model described represents its application in the dominant medical culture in the US. First, other cultures and countries may have a different understanding of what constitutes family and necessarily include others besides parents. Perhaps others, such as family elders, are the persons designated as decision makers. Second, this particular model is based on Western notions of the importance of informed consent and respect for the autonomy (self-determination) of the patient, and the family in the case of pediatrics. In other cultures and countries, families may not see their role as decision makers at all, but only in terms of doing what the doctor orders. Also, other cultures

and countries may emphasize other core values such as responsibility to the larger family and community rather than autonomy (self-determination). Finally, the model described presumes a certain access to technology that is primarily available in developed nations. A concern for quality of life is different in developed nations where the issue may be the result of technology that is able to save life of diminished quality, as opposed to developing nations where diminished quality of life may be primarily a consequence of inadequate access to basic health care services.

APPLYING THE BEST INTERESTS STANDARD

How does the best interests standard work in practice? It must be remembered that the term is just a place holder for a complex structure of values that must themselves be interpreted and applied. It is not possible to use the label 'best interests' and expect it to do the moral work for us. It is always necessary to discuss the particular benefits and burdens of an intervention, according to the evaluations of all the parties involved. No one party has a privileged view of the best interests of the infant.

Consider for example, an infant born with an intestinal atresia. There are no associated anomalies and the infant cannot survive without operative correction. The pediatric surgeon recommends surgery to the parents because surgery would be in the best interests of their infant. The pediatric surgeon means by the use of the term, that the possible benefits to the infant (life, restoration of function, reduction of pain and suffering) outweigh the possible burdens (time in the hospital away from family, risk of death associated with anesthesia, pain and suffering associated with testing and interventions, and risk of compromised function). The calculation of best interests is based on the infant's diagnosis, prognosis, available treatment options, and the likelihood of their success. The anomaly is fatal without intervention, and the surgery is relatively low risk with a high likelihood of success. The pediatric surgeon wishes to preserve professional integrity by fulfilling the ethical obligations to promote the infant's welfare by saving the infant's life and restoring function, and protecting the infant from harm. The pediatric surgeon is acting upon the values of what it means to be a 'good physician'.

Most parents would agree that surgery for an intestinal atresia is in the best interests of their infant. Out of their values to be 'good parents,' they strive to promote their infant's welfare and cope with the burdens placed on their infant and upon themselves. Most parents would agree that the outcome is good (life and restored function), and the surgery has a high likelihood of success with minimum burden (surgery, recovery time, and associated costs). Parents who refused such surgery in the US would most likely be accused of medical neglect, and the power of the state would most likely be used to insure that the infant received the necessary care.

In other situations, a pediatric surgeon and parents may agree that stopping life-sustaining treatment would be in the best interests of a particular infant. For example, consider the case of a 23-week-old infant weighing 600 g who develops necrotizing enterocolitis (NEC). Following an operation that leaves 15 cm of jejunoileum, the infant develops a grade IV intraventricular hemorrhage, worsening lung disease, renal failure, and ongoing sepsis. In this case, the mortality rate of the condition is very high, and the infant's quality of life is affected by the associated neurological, renal, and pulmonary complications. A pediatric surgeon and parents would be justified in withdrawing life support and instituting comfort care for this infant. It could be argued that it would be inappropriate to subject this already vulnerable infant, with little or no potential to interact with the environment, to the substantial burdens of life-sustaining technology for devastating bowel disease and compromised pulmonary and renal function. None of the treatments for devastating bowel disease, such as further surgery, the use of total parenteral nutrition (TPN), or a bowel transplant, would improve the infant's neurological condition. With little or no opportunity to experience things such as pleasure or comfort that we regard as benefits, inflicting pain or separation from family could be viewed as disproportionally burdensome or not necessary according to a relational potential standard.

Although most health care professionals and parents would agree that further interventions are not in this infant's best interests, some parents would disagree and insist that 'everything possible be done'. In the US, it is a very difficult matter both ethically and legally to stop life-sustaining treatment over the objections of the parents.[14] Conflict resolution depends on a trusting relationship between the pediatric surgeon and the family. The family must be able to trust the pediatric surgeon so that they can rely on the pediatric surgeon's judgment. This trust begins with the pediatric surgeon's honesty: the commitment to disclose all relevant information, to insure that families understand what is being said and to respond to the questions and concerns of the family. Pediatric surgeons must also be compassionate, feeling for the infant and with the family as they endure this critical illness. The family needs to know not only that the pediatric surgeon cares for and about them and their infant, but that the pediatric surgeon will not abandon them on this difficult journey. It is vital in these so-called 'futility' cases, to understand just what the family means when they say 'everything possible is being done'. The conflict may be a matter of misunderstanding the diagnosis and prognosis and such false expectations can be often corrected with open, ongoing communication. However, sometimes there is a real conflict between the values of the pediatric surgeon, the entire neonatal healthcare team, and the values of the family.[14–17]

Because families may differ in how they make value judgments about what constitutes an acceptable quality of life for their infants, it is essential to be able to elicit information about values and preferences from families. The authors have found the following questions useful. The questions are intended as subject guides only; each clinician must translate the questions into his or her own style:

1. What is your understanding of your baby's current condition?
2. How has your baby's illness affected your family?

3. What is most important in the care of your baby?
4. What do you fear the most? What would you like to avoid?
5. What are your family's sources of strength and support?

GUIDELINES FOR ETHICAL DECISION MAKING

Ethical dilemmas most often arise when parents and pediatric surgeons disagree about what constitutes an acceptable quality of life or what constitutes the best interest of the infant. Whose judgment should prevail?

Pediatric surgeons can help insure that their ethical judgments are reliable through the application of an organized process.[18] There are multiple versions available in the ethics literature, but they generally all contain the following components:

1. Identify the decision makers. Are the parents involved? Are there non-parental legal guardians? Do the parents have the capacity to make a decision? Who are the involved clinicians?
2. Gather the relevant medical facts. What is the diagnosis? What is the prognosis? Are additional tests necessary for further clarification? Is there necessary information to be gathered from other clinicians?
3. Solicit value data from all involved parties. Do conflicts exist among the values of the parents, other family members, and the physicians? Has the basis for the conflict been identified?
4. Define the available treatment options. With each option, what is the likelihood of cure or amelioration? What are the risks of an adverse effect? What is a minimum level of professionally acceptable treatment?
5. Evaluate possible treatment options and make a recommendation. Justify your choice according to the values of various parties.
6. Achieve a consensus resolution. Have all parties articulated their viewpoint? Would more factual information help to resolve any disputes? Would a mediator (ethics consultant, ethics committee, or other trusted third party) be helpful?

Most of the time, ethical conflicts between pediatric surgeons and parents can be resolved with further communication, negotiation, and accommodation, but sometimes the conflict is so severe that the pediatric surgeons should consider appealing to an outside resource such as an ethics committee or withdrawing from the case based on conscientious objections.

The threshold is high for involving the courts in a decision about surgery for a neonate or infant. Pediatric surgeons should invoke the power of the state to secure treatment for an infant only when that treatment is universally regarded as beneficial and the appropriate standard of care, making parental refusal equivalent to medical neglect, as in the previously cited case of the infant with an intestinal atresia.[19] The classic case for court intervention involves treatment for a life-threatening condition in which the benefits are substantial and the burdens minimal, such as court-ordered blood transfusions for pediatric patients.[20] Courts are also not the appropriate venue when parents demand treatments that the pediatric surgeon regards as not being in the best interests of the infant. Conflicts are resolved best at the bedside among the parties who know the infant and the circumstances, and those who will live with the consequences of the decision.

BEST INTERESTS AND CLINICAL RESEARCH

The best interest standard with its balancing of benefits and harms for individual patients and their families rests on the assumption of good information about the best proven surgical care in a shared decision-making process. Good information relies on clinical research to validate the best approach, and in the current environment of cost containment, to validate the approach that brings the best outcome with the least costs, including financial costs. There is strong support for a professional and ethical obligation of pediatric surgeons to be involved in clinical research. According to the Committee on Pediatric Research of the American Academy of Pediatrics, all subspecialists, including surgeons, should be encouraged and supported to pursue research activities.[21] The needs of newborns are unique and cannot be extrapolated from other research involving older children and/or adults.

However, there are barriers to participation in research for pediatric surgeons as well as for parents and their newborns. Caniano has noted elsewhere 'that surgery, in contrast to other areas in medicine, has been historically free to develop new operations and treatments without the stringent requirements of animal testing and rigorous, prospective multi-institutional clinical trials in humans. The boundaries are often blurred between an operation that should be evaluated by a clinical trial before it is recommended for general implementation and an operation that is considered to be a refinement of an accepted procedure, and therefore not needing rigorous testing.'[22] Other barriers include a misunderstanding of the meaning of 'equipoise', a concept necessary for the ethical conduct of research.[23] Equipoise requires that the researcher believe that one surgery or treatment is no better or worse than another or even the use of placebo, because there is no evidence supporting one over the other. Surgeons treating critically ill newborns are often in a position of rescue and believe that doing something, even if it is not proven, is better than doing nothing and better than enrolling a newborn in a trial where they may not get the proposed treatment.[24]

Even though there is support for this obligation of pediatric surgeons, and even patients, to be involved in research, there may be great hesitation because of the obvious vulnerability of the family and the infant.[25,26] Researchers struggle to apply the standard of best interests by expanding the evidence base for pediatric practice for future patients on the one hand, while also protecting the vulnerable patients in their care on the other hand. It is quite difficult to obtain parental permission that is informed and voluntary under conditions of duress and within a short therapeutic window.[26]

It is also very difficult to balance the risks and potential benefits of the research itself.[26] Research standards in both the US and Europe state that any child should only be enrolled in research when it is absolutely necessary to answer an important scientific question.[26] An important issue in both the US and Europe involves whether and how pediatric research has to provide benefit to the participating children. In the US, children can be involved in research that offers no direct benefit, but only if the risks of participation are minimal. Children may also participate in research that involves a minor increase over minimal risk, but only if there is a reasonable expectation of future benefit to those with the same condition.[27] Research guidelines from the Ethics Working Group of the Confederation of European Specialists in Paediatrics (CESP) state that 'Children should not be involved in research that serves only scientific interests and does not provide any benefit to them.'[28] In a discussion of the ethical principles and legal requirements for pediatric research in the EU, Pinxten and colleagues state, '... the principle of beneficence requires that biomedical interventions contribute to the welfare of these persons (in research). This can be achieved in two ways. First, biomedical interventions can generate benefits in the research subjects themselves. Second, the drawbacks of biomedical interventions can be balanced with a newly generated benefit, either directly to the minor research subject or to another beneficiary.'[29] A requirement for direct benefit has serious implications for the selection of control groups and research designs that include a placebo. For the regulations in the US, determining what counts as minimal risk, or a minor increase over minimal risk, is very complex.[30] If protecting children in research is not to be translated into excluding children from research, special protections must be put in place.

In general, what are the requirements for ethical research? Emanuel and colleagues have proposed seven requirements for determining whether a research trail is ethical.[31]

1. Social or scientific value
2. Scientific validity
3. Fair subject selection
4. Favorable risk-benefit ratio
5. Independent review
6. Informed consent
7. Respect for potential and enrolled subjects.

Because of the special vulnerabilities of children, and especially newborns, three procedures have been proposed to improve protection of pediatric research participants.[27]

1. Pediatric data and safety monitoring committees
2. Robust assent processes
3. Decision monitoring that could verify the 'informed' nature of the consent.

A final issue for consideration is what special protections should be in place for research in developing countries, as an increasing amount of research is, in fact, multinational. Emanuel and colleagues have proposed an eighth principle – Collaborative Partnership – to be added to the seven requirements listed above.[32] This principle emphasizes the need to develop partnerships among researchers, makers of health policies, and communities. It recognizes the importance of respecting the community's values, culture, traditions, and social practices, and, perhaps most importantly, this principle seeks to ensure that the recruited participants and communities receive benefits from the conduct and results of the research. Raising the issue of research in developing countries also raises the more general question of the role of culture in decision making in practice, as well as in research.

ROLE OF CULTURE IN DECISION MAKING

The ethical concept of best interests that has been articulated is largely dependent upon the authors' own experiences in the medical culture in the US. Some of the most difficult ethical issues that the authors have personally faced involve a conflict between this Western medical notion of best interests and families making decisions for their infants from other cultures. The following case illustrates how culture may affect parental decisions and the patient–physician relationship.

Case study

MS is a 25-day-old infant born at 26 weeks' gestation, weighing 650 g. He was stable on 50% oxygen and minimal ventilatory settings. He was on continuous feedings using a premature formula. At 25 days of age the infant developed acute abdominal distention, intolerance to feedings, and bloody stools. Urgent consultation with the pediatric surgeon was requested. A radiograph showed diffuse pneumatosis. He was mottled, acidotic, and hypotensive. His laboratory values showed a white blood cell count of 2000, hemoglobin of 7 g/dL, and a platelet count of 6000. He received packed red cells and platelets. Blood cultures were drawn and he was started on triple antibiotics. The parents agreed to bedside peritoneal drainage. After 12 hours, MS remained clinically unstable and the pediatric surgeon advised laparotomy. The parents refused the operation.

MS's parents are from Nigeria and are in the US on student visas. They have two other healthy children, aged three and five. They plan to return to their native country in six months. Both parents visit daily and are concerned about their son. Both the father and mother speak English, but the father's English is slightly better than the mother's. Sometimes the father has to translate information for the mother and translate the mother's statements for the doctors. They ask appropriate questions and seem to understand their son's medical condition, prognosis, and alternatives for treatment. They desire that their son live, but are strongly opposed to TPN, especially since this technology is not available in their village in Nigeria.

They acknowledge that MS is gravely ill and are accepting of his probable death. They say that they agreed to the use of all the previous medical technology because they thought it would save their son's life, but a life dependent on medical

technology is too burdensome. They were expecting that their son would be able to live normally once he got out of the hospital. The parents explain that they have a strong faith in God, and God will decide if their son lives or dies and they will accept whatever happens. They believe that it is not in their power to alter God's will by the continued use of technology to support a life 'that was not meant to be' and that if the boy is not able to eat like a normal infant, then it is better that he go to God. They are supported in this belief by their Nigerian minister and congregation. They have clearly stated their intention to return to Nigeria where life-sustaining technology, such as TPN and specialized nutritional formulas, are unavailable. In addition, they will not have access to pediatric specialists when they return to their native country, and worry about how they will secure medical and surgical care for an infant with a poorly functioning intestine and other chronic disabilities. What should the pediatric surgeon do?

Some may be tempted to resolve this conflict in a very legalistic fashion dependent on Western notions of medical neglect and their attendant professional obligations to turn to the courts for proper resolution. Simply stated, 'You are in the USA – our cultural norms get to override your cultural norms.' In that sense, this case is no different from any other case that raises the issue of the limits of parental discretion in medical decision making. A narrow best interests standard would seem to require overriding the parents' decision and forcing the operation. According to informed medical judgment, the infant will most likely die without the surgery, while there is a reasonable probability that the infant's life can be saved by resection of the diseased bowel. To say that the infant is better off dead is to substantially undervalue the lives of persons with disabilities, including this infant. Some would argue that this case is similar to the case of the infant with an imperforate anus or an infant needing a blood transfusion. To allow this family to choose non-treatment would violate the principle of justice as nondiscrimination.

However, there is something particularly compelling about such cases that call participants to value and respect cultural differences. Both the parents and pediatric surgeons are struggling to fulfill their role-specific obligations to be good parents and good physicians, but they literally see their roles quite differently. It is culture that provides the 'lens' for each of us to view the world. One definition of culture states:

> Culture is a set of guidelines (both explicit and implicit) which individuals inherit as members of a particular society, and which tells them how to view the world, how to experience it emotionally, and how to behave in it in relation to other people, to supernatural forces or gods, and to the natural environment. It also provides them with a way of transmitting symbols, language, art, and ritual. To some extent, culture can be seen as an inherited 'lens', through which individuals perceive and understand the world that they inhabit, and learn how to live within it. Growing up within any society is a form of enculturation, whereby the individual slowly acquires the cultural 'lens' of that society. Without such a shared perception of the world, both the cohesion and the continuity of any human group would be impossible.[33]

It seems obvious from this definition that there is no way to talk about best interests from outside a cultural perspective. All of our discussion, then, is in some sense cross-cultural. The narrow explication of best interests represents the perspective of the US, and perhaps predominantly the powerful status of its medical and legal culture.

A Nigerian anthropologist commenting on this case might point out that the US has several unique cultural features. People in the US tend to think that there is nothing worse than death – at least for a child or young person. Children are to be viewed as little adults – as individuals first and then only secondarily as members of a family or community, essentially independent of their families rather than dependent. Their right to grow up and to ultimately make their own choices is primary. US culture is very action oriented: when in doubt – act. The US is also obsessed by the development and perceived power of technology. Technology and knowledge are primary goods.

However, the central question is not really whether or not we have a cultural perspective, but whether we can judge some perspectives as better than others. This raises the difficult ethical question of cultural relativity. Cultural relativity refers to the following claims: (1) all moral judgments are relative to the culture in which they arise; (2) moral judgments across cultures are significantly different; and (3) there is no way to rank moral judgments across cultures.[34]

The well-respected physician–ethicist, Edmund Pellegrino, accepts that culture is essential in the context of medical and ethical decisions, but that there are also features of human beings as human beings according to which we can judge among cultures.[35] It can be argued that there are some universal features that all cultures either should or would accept. An example would be that moral communities must allow democratic processes and cannot be oppressive.[36] The philosopher, Sara Ruddick, identifies three universal maternal interests that are applicable regardless of the particular form they take in a culture. These maternal interests include: (1) preservation; (2) growth; and (3) acceptability.[37] Other ethicists identify universal moral principles that underlie our commitments to be tolerant of cultural diversity.[38,39] Without some principle of respect for persons, for example, there would be no reason to prefer tolerance of cultural differences.

A cultural perspective is particularly important to ethical theorists, who support the inclusion of context and relationship in an ethical analysis, and to those of us working in clinical settings. As Carl Elliot writes:

> Ethical concepts are tied to a society's customs, manners, tradition, institutions – all of the concepts that structure and inform the ways in which a member of that society deals with the world. When we forget this, we are in danger of leaving this world of genuine moral experience for the world of moral fiction – a simplified, hypothetical creation less suited for practical difficulties than for intellectual convenience.[40]

The authors wish to support an ethical analysis that includes culture as an important feature, but also acknowledges

the role of the application of universal ethical principles. Like Pellegrino, the authors accept that there are some ethical principles that apply to all humans based on their humanity. Culture is necessary to understand what these principles mean and how they are applied with respect to each of the parties in the conflict. It is possible to be respectful of cultural differences and at the same time acknowledge that there are limits. What remains critical is the perceived degree of harm; some cultural practices may constitute violations of fundamental human rights.[41] It is useful to return to the above case and apply the process for ethical decision making, with special attention to its cross-cultural features.

The ethical question in this case is: what should the pediatric surgeon do for MS? What role should culture play in the deliberations?

The family in this case clearly value their son's life and his quality of life. They also value the impact of this infant's life on their other children, the life of the family as a whole, and their plans to return to their native country. They accepted the initial use of technology in the care of their premature son, in the hope that it would deliver a 'normal' infant, free of future dependence on medical technology. They are clear that for them, in a cultural and religious sense, a life dependent on TPN, specialized nutritional feedings, and the prospect of bowel transplantation is unacceptable.

For the pediatric surgeon and the other members of the health care team, the preservation of this infant's life is a goal, but the quality of his life is also a consideration. The laparotomy will allow the pediatric surgeon to assess the severity of the NEC, the amount of diseased bowel, and the prognosis for MS to have functional intestine without the need for prolonged TPN.

There are basically three options available in this situation. First, the pediatric surgeon can go forward with all the care that it takes to save this infant's life. This would include surgery, the use of TPN for as long as necessary, and all efforts to preserve the life of MS, including the possibility for bowel transplantation. This would more than likely include going to court to force the parents to consent to the operation and having a guardian appointed to make medical decisions for MS. This option could result in the permanent loss of parental rights and placement of the infant in the care of the state. In the second option, the pediatric surgeon performs the operation in the hope that there is sufficient residual bowel without the need for long-term TPN and bowel transplantation. If there were clearly not enough viable bowel, MS would be provided with comfort care and allowed to die. If there were sufficient residual bowel, care would proceed as appropriate. A difficulty arises if there is a questionable amount of bowel and a trial of TPN would seem to be appropriate. The pediatric surgeon could resect the diseased bowel and proceed with a trial of TPN, discontinuing the use of TPN when it is clear that the bowel is not going to function normally. The third option is not to perform the operation. The infant could be maintained on current levels of support to see whether his bowel will heal on its own, or a comfort care plan could be initiated that would allow the infant to die sooner rather than prolonging the dying process.

The authors think that the first option is outside the range of moral justification and should not be recommended. The infant is critically ill with a disease that carries high rates of mortality and morbidity. Non-treatment for MS does not rise to the standard of medical neglect. The strongest argument for insisting on treatment rests on the claim that this infant is a member of the community, not only a member of his family. If families will not or cannot take proper care of their children, then we will step in to do so, but who is this 'we'? If there is no such community support, or insofar as the broader community fails in this responsibility, then the community's claim on the family's choice is diminished.

In this case, the Nigerian community (here or in Nigeria) does not make demands on the parents' choice. They do not see themselves as able, or obligated, to provide these services to MS. But in what sense is MS and his family a member of the US community? An argument can be made that they are community members by virtue of their residence, yet they are planning to return to Nigeria. The argument that treatment must be forced because of community obligations seems diminished by their departure. We will not be around to provide the support we claim is necessary, but will we provide the necessary support even if they stay? Is it possible for them to stay? Our community claims also seem diminished insofar as the family's student visa is not renewed, or access to health and social services is limited based on their foreign status. To claim that we are discharging our community obligations only by saving the child's life, seems to greatly distort the notion of community.

A final consideration needs to be mentioned. Couldn't we discharge our community responsibility by keeping the child here and placing him up for adoption? Then he certainly would become a full member of our community and the concerns raised earlier would no longer apply. Such an action could clearly state that we believe the only appropriate parental choice is to try and save the infant's life. To choose anything else is to act as bad parents who should be replaced. Yet are they really bad parents? Such a judgment clearly raises serious concerns about cultural norms of parenting, and fails to take culture into consideration. From the parent's cultural perspective, good parents would not choose surgery and neither would good physicians. This is not standard of care in Nigeria.

How should culture figure into the deliberations of the pediatric surgeon? It obviously cannot simply be ignored in a grand act of medical and parental imperialism. Also, we should not pay lip service to cultural perspectives, accepting the unusual and exotic only when it also fits into our own value framework. For example, this family could make the choice based on their cultural values only if there were a much higher mortality rate associated with the infant's condition. Finally, respect for different cultures cannot simply be some kind of ultimate trump. Automatically deferring to any choices based on cultural differences is to ignore the central values of our own culture. Ironically, it would be a violation of respect for cultural diversity in that our own cultural values are ignored. An attempt at negotiation and compromise is to be preferred.

The authors think that the pediatric surgeon should recommend surgery under the second scenario, saving the

infant if possible, letting the infant die if appropriate, and negotiating a trial of TPN if necessary. But if this is not acceptable to the parents, the pediatric surgeon should respect the parents' decision not to have surgery and proceed with a plan of care aimed at keeping the infant comfortable until he either improves or dies. A decision by a pediatric surgeon to conscientiously withdraw from this patient's care out of concern for his or her own central values should be respected.

The second option is supported by the health care professionals' and the family's values. Surgery could save the infant's life, which all parties value, but it would do so under conditions of a quality of life that are acceptable to the family. Some health care professionals may have problems with this option if a trial of TPN is necessary. It is difficult to establish how long a trial of TPN should last. This difficult negotiation must consider what is medically feasible and also acceptable to the family. Also, many believe that there is a distinction between decisions not to start treatments (withholding) and decisions to stop treatments (withdrawing). Although this distinction is psychologically powerful, it is not ethically or legally valid in the US.[41] If health care professionals and parents have sufficient justification based on the balance of benefits and burdens not to start a treatment, then they have the same justification to stop a treatment once begun. There is a hidden danger in maintaining this distinction between not starting and stopping medical and surgical treatments. Sometimes trials of therapy are not initiated when they are appropriate out of fear that the therapy cannot be stopped once it has begun.

Others argue that the provision of nutrition and hydration is different than other medical interventions, such as ventilators and dialysis, which are 'extraordinary' and ethically can be withheld or withdrawn. According to this view, the provision of nutrition and hydration is ordinary and is always morally required. The attempt to classify categories of interventions independent of their application to the care of an individual patient is misguided. So-called 'ordinary' treatments, such as antibiotics and the medical provision of hydration and nutrition, can be disproportionally burdensome to certain infants and may be ethically forgone (withheld or withdrawn).[42,43] Many physicians and parents have particular values around the importance of feeding, regarding feeding tubes and TPN as morally equivalent to bottle or breast feeding an infant or to sharing a meal. Yet the provision of TPN is not readily comparable to feeding an infant or to a shared family meal. There are important differences. When hydration and nutrition are provided through medical means, they must be assessed according to the same principles used to evaluate any medical intervention. Decisions must be based on a careful evaluation of the proportionality of the possible benefits and burdens. For this family, TPN is not only burdensome because of the risk of frequent infections and the likelihood of progressive liver disease, but because of what feeding through technology means in their culture, and the financial and social burdens to the entire family. The health care team in the US cannot allocate this family's scarce resources for them, or for their country of origin.

SUMMARY

The best interests standard is a complex amalgam of the values of pediatric surgeons, families, and broader societies. As health care itself becomes increasingly multicultural and international, the need for cross-cultural ethical dialogue increases. There are no ultimate trump cards, just a genuine need for what one philosopher calls 'communitarian perspectivalism.'[34] Any healthy, growing and self-renewing culture continually subjects itself to self-evaluation and evaluation by others. In this regard, the authors wish to point to the need for greater attention to the value of justice in the provision of health care around the globe. This chapter represents a tendency to look at the developed nations and evaluate the issue of not providing the most that can be done. This is obviously an ethical problem for the rich. What about the bigger ethical problem of not providing the basic minimum to infants everywhere – the ethical problem of not providing what poor parents want for their children and cannot afford? Certainly ethical dialogue needs to include what children around the globe are owed as a matter of justice – of fundamental human rights. Access to global health care resources is a problem that affects all persons. The contribution of the medical marketplace to the disproportionate allocation of health care that exists cannot be ignored. Medicine must take responsibility for the emphasis on expanding new technologies in the market rather than meeting basic public health needs, and the disproportionate burden it may place on the economies of developing nations or nations committed to universal access to health care. A global cross-cultural perspective is essential to help expand the concept of 'best interests' to include a necessary public health focus.

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Minimal invasive neonatal surgery

RICHARD KEIJZER, OLIVER J MUENSTERER, AND KEITH E GEORGESON

INTRODUCTION

The first reports on minimal invasive surgery in adults were published by gynecologists and stem from the first half of last century. By then, it was mainly used for diagnostic procedures, due to the limitations in visualization and instrumentation. When chip cameras were introduced in the late 1980s, the surgeon and assistant were able to watch a screen and perform surgery at the same time, instead of holding a telescope and looking through a lens close to the patient. This, and the development of better endosurgical instruments, enabled surgeons to perform a variety of laparoscopic procedures including appendectomies, cholecystectomies, fundoplications, and more advanced operations. However, due to the lack of instruments, endoscopes, and trocars of appropriate size, the acceptance of minimal invasive surgery in the pediatric population in general, let alone in neonates, took longer than in adults. Recently, the development of smaller, shorter, and more durable instruments along with improved optical equipment has allowed pediatric surgeons to perform more complex endosurgical procedures in young children and newborns.[1]

This chapter reviews the current practice of minimal invasive neonatal surgery and reflects upon potential future developments in this field.

THORACOSCOPY

The first experience with thoracoscopic procedures in children was published 30 years ago.[2] Biopsies of pulmonary lesions, both primary and metastatic in origin, are the most frequently performed thoracoscopic surgical procedure in children (reviewed in Ref. 3). However, with the advancement of experience and, again, better equipment, more sophisticated procedures such as pulmonary resections and the repair of esophageal atresia with or without tracheoesophageal fistula have been embraced by the pediatric surgical community. Compared to open thoracotomy, the potential advantages of a thoracoscopic approach are the muscle-sparing nature of the procedure, decreased risk of nerve injury, and less secondary scoliosis in the long term.[4]

Physiology and anesthetic considerations

The introduction of automatic carbon dioxide (CO_2) insufflation in the early 1960s created the necessary working domain during endoscopic surgical procedures. In most thoracoscopic cases, gentle insufflation of CO_2 to a maximum pressure of 4–5 mmHg using a low flow of 1 L/min compresses the lung enough to grant access to most structures in the chest. Single-lung ventilation, which is more easily established and used in adult thoracoscopy, is rarely necessary in young children and neonates. In neonates, methods for single lung ventilation are very limited, since the smallest size double-lumen tube available cannot be used in children under 30 kg. In those cases where single lung ventilation is desired, a small Fogarty catheter has been placed into the ipsilateral main stem bronchus and gently inflated, blocking gas exchange to that lung.[5] Excellent communication between the surgeon and anesthetist is mandatory, as the establishment of an artificial capnothorax may change physiologic parameters. If anticipated, a higher endtidal CO_2 can be overcome by increasing the ventilatory rate, and decreased venous return can be counteracted by appropriate volume replacement.[6] Although described in adults, the development of CO_2 embolism is extremely rare in the pediatric population.

Diagnostic thoracoscopy and biopsy or resection of pulmonary lesions

Improvement in the resolution of diagnostic imaging techniques, such as computed tomography (CT) scanning and magnetic resonance imaging (MRI), along with the capability to produce multiplanar reconstructions in any three-dimensional plane, has made thoracoscopy almost obsolete for the mere assessment of intrathoracic anatomy. However,

the good visualization and excellent access to almost all intrathoracic lesions has resulted in the replacement of most open lung biopsies by the thoracoscopic technique. In fact, thoracoscopic lung biopsy and the resection of pulmonary lesions are the most commonly performed thoracoscopic operations in neonates. In many cases, small pulmonary lesions are easily identified and isolated from the rest of the lung using a Roeder loop (Endoloop, Ethicon San Angelo, TX, USA). After placing the suture tightly around the base of the lesion, the tissue is excised sharply peripheral to the loop and retrieved through one of the trocar sites. In children above 10 kg, a stapler can be used to transect the lung central to the lesion. Larger pulmonary lesions, such as congenital cystadenomatoid malformations and congenital lobar emphysema, should be resected by respecting the lobar or segmental anatomy. Most of the time, this entails identifying the proprietary vessels and bronchus to the affected part of the lung, and using a vessel sealing device such as the endoscopic Ligasure (Covidien, Dublin, Ireland) or Enseal (Ethicon, Cincinnati, OH, USA) to divide the vessels.[4] The bronchus can be stapled, sutured, or clipped. The authors usually leave a chest tube in place through one of the trocar sites for 24 hours after the procedure, although others do not.

Mediastinum

The thoracoscopic approach to mediastinal masses such as esophageal duplication cysts, bronchogenic cysts, and extralobar sequestrations is very useful for several reasons. Visualization of adjacent anatomical structures is usually excellent due to magnification of the video image (Fig. 21.1). Furthermore, the anatomy of the mediastinum is usually well defined, and some lesions tend to be well vascularized.

During esophageal duplication cyst resection, opening of the esophagus is common since the cyst and the esophagus

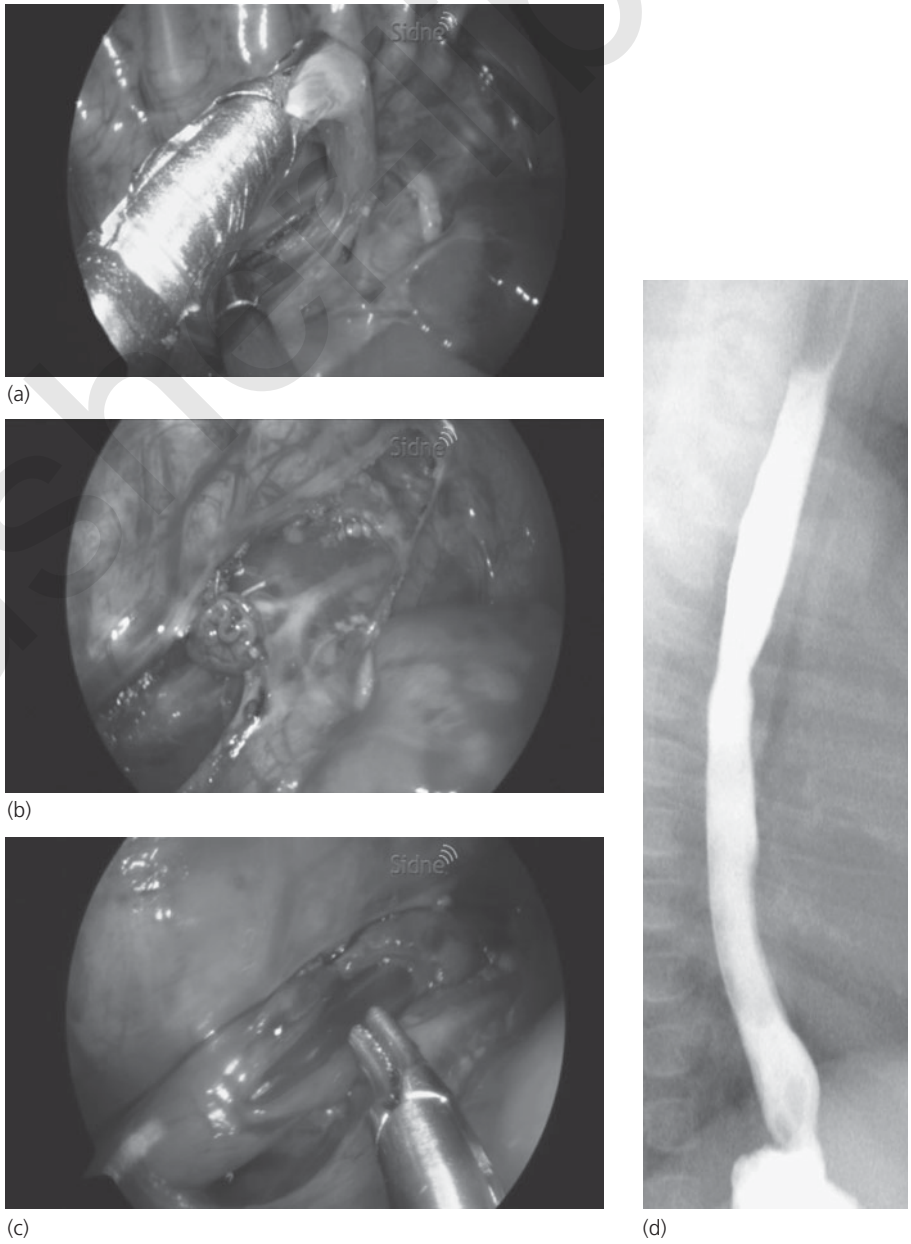

Figure 21.1 Repair of esophageal atresia with distal tracheo-esophageal fistula. The fistula is identified, dissected (a), ligated, and divided (b). Subsequently, the anastomosis is performed over an orogastric tube (c). Postoperative results are generally excellent and comparable to those of the open technique (d).

often share a common wall. Therefore, the esophageal defect should be closed or reinforced using interrupted absorbable sutures. A dilator or endoscope can be placed inside the esophagus to decrease the risk of esophageal injury.

Closure of patent ductus arteriosus and aortopexy

The first reports on thoracoscopic closure of patent ductus arteriosus (PDA) originate from the early 1990s.[7] Improvement in technique and instruments has made it possible to safely perform closure of a PDA thoracoscopically in neonates with a birth weight as low as 1500 g. However, potential complications with the thoracoscopic approach and the safety and excellent outcome of open PDA ligation have prevented both the thoracoscopic and interventional approaches from being universally accepted.

Tracheomalacia, an intrinsic weakness of the tracheal wall causing the airways to collapse during expiration, is usually a benign, self-limiting condition that improves as the infant matures. In some cases, especially when associated with other intrathoracic lesions such as esophageal atresia, the gas exchange is compromised and the tracheomalacia should be treated with an aortopexy. It is important to rule out a vascular cause for the patient's stridor (such as a vascular ring or sling) by esophagram or angiography. Once all other causes are ruled out, a thoracoscopic aortopexy can be performed using triangular position of the camera and instruments in the anterior mid- and anterior axillary lines. The surgeon generally uses three interrupted sutures to pexy the aorta to the sternum.[8]

Esophageal atresia

Thoracoscopic repair of tracheo-esophageal fistula and esophageal atresia is considered one of the most technically demanding minimal invasive procedures in pediatric surgery due to the limited domain inside the neonatal thorax, and the technical difficulty of making a good and trustworthy anastomosis between the proximal pouch and the distal fistula. Consequently, complications observed following thoracoscopic repair are often related to the anastomosis, such as anastomotic leakage and stricture.[9] In contrast, advocates of the thoracoscopic approach acclaim the excellent visualization of the anatomy and warn against the long-term disadvantages of repair using a thoracotomy, such as asymmetry of the chest wall, scoliosis, or a winged scapula as the consequence of nerve injury.[10] To date, however, both techniques have not been compared against each other in a randomized clinical trial, (RCT) and therefore, the question of which technique is superior remains to be answered. Since the learning curve of the thoracoscopic repair is considered to be lengthy, this type of study may be difficult to complete.

For esophageal atresia and fistula repair, echocardiography is used to determine whether there is a right- or left-sided aorta. The esophagus is approached from the contralateral side. The patient is positioned in a lateral decubitus position, slightly prone, to allow gravitational retraction of the lungs away from the posterior mediastinum. Three triangulated trocars are used, with an additional access site if needed for retraction. In most cases, the Azygos vein is divided, and the pleura is opened over the fistula. The fistula is suture-ligated or clipped, both ends of the esophagus are mobilized just enough to facilitate the anastomosis, and the anastomosis is performed (Fig. 21.1a–d).

Congenital diaphragmatic hernia

In contrast to tracheal-esophageal fistula repair, repair of congenital diaphragmatic hernia (CDH) (most frequently Bochdalek hernias) has gained more popularity among pediatric surgeons during the past few years. Whereas the first reports of both laparoscopic and thoracoscopic repairs were mainly anecdotal and described the procedure in older infants and children, the indication for thoracoscopic repair has shifted to symptomatic CDHs in newborns.[11] Even repair of the diaphragmatic defect using a patch has been well described with good results.[12] Most likely, the positive outcomes in the latest studies reflect the completion of learning curves by those pediatric surgeons who perform the procedure frequently. Again, at present, no RCT has compared the classic repair via a laparotomy against the minimal invasive thoracoscopic approach. Outcomes of such an RCT might be difficult to compare, since congenital diaphragmatic hernia is such a heterogeneous, complex disease. Due to the associated persistent pulmonary hypertension and pulmonary hypoplasia, many logical outcome measures to test the superiority of either technique, such as ventilation days or length of stay, will be mainly influenced by the degree of any associated conditions.

The thoracoscopic approach is generally preferred over a purely laparoscopic repair of CDH. In some cases, we have used simultaneous thoracoscopic and laparoscopic cameras to aid with the anatomic reduction of the viscera, and to rule out injury to the intra-abdominal organs during suturing. The patient is positioned in a contralateral decubitus position, and an axillary triangulated trocar configuration is used. The most lateral suture often has the most tension, and a transcostal suture placed through a small stab incision through the lower chest is helpful in facilitating a complete and secure closure of the defect. Figure 21.2 illustrates a standard diaphragmatic hernia repair.

LAPAROSCOPY

Physiology of pneumoperitoneum

While CO_2 insufflation into the thorax may be associated with considerable changes to the physiology, CO_2 insufflation to establish a capnoperitoneum is often very well tolerated by most neonatal patients. Still, the pressures and flows should be kept at the minimum necessary to guarantee adequate working space and visualization. In neonates, we generally

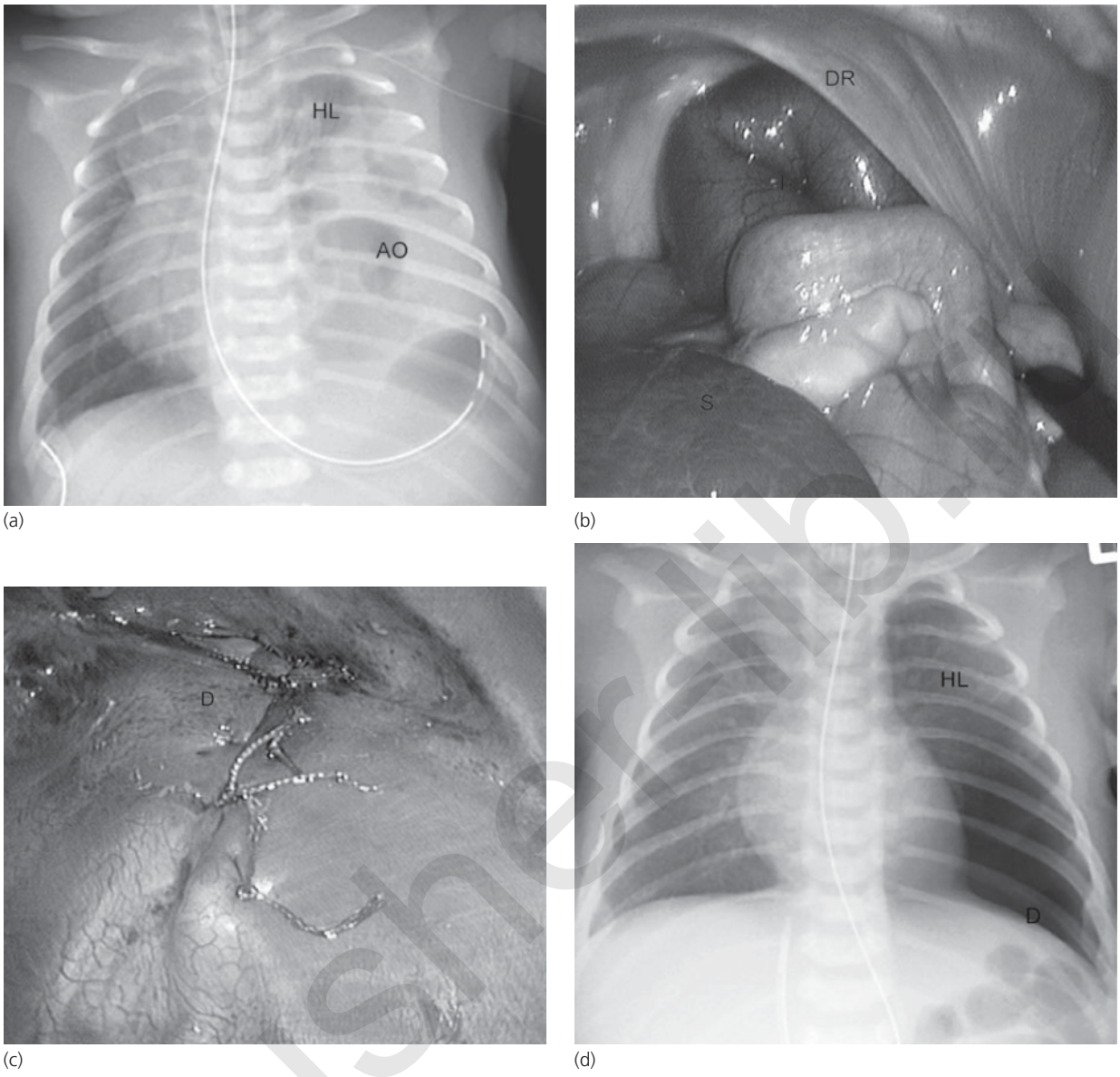

Figure 21.2 Closure of congenital diaphragmatic hernia (CDH): Preoperative chest x-ray of an infant with left-sided CDH (a). Thoracoscopic intraoperative view looking down on the abdominal organs (intestines and spleen) that herniated through the diaphragmatic defect into the thorax (b). Diaphragmatic defect has been closed using interrupted sutures (c). Postoperative chest x-ray. Note the hypoplastic lung in the top of the thorax and the reconstructed dome of the diaphragm (d). AO: abdominal organs; D: diaphragm; DR: diaphragmatic rim; HL: hypoplastic lung; I: intestines; S: spleen.

use pressures of 6–8 mmHg and flows between 1 and 2 L/min. Furthermore, the insufflated CO_2 may be absorbed into the bloodstream of neonates more readily, mainly due to smaller diffusion barriers and an increased peritoneal absorptive surface area in comparison to body weight. Subsequently, hypercapnia and respiratory acidosis may result and can usually be overcome by increasing minute ventilation during the laparoscopic procedure.[6]

Potential negative side effects of increased intra-abdominal pressure include compression of the inferior caval vein resulting in a decrease in the venous return, as well as upward displacement of the paralyzed diaphragm. This can result in pulmonary atelectasis that may only become clinically relevant after resumption of spontaneous breathing. Some of these patients may require prolonged positive pressure ventilation in order to recruit the collapsed pulmonary alveoli.

Abdominal access

There is no evidence that either the Veress needle technique or the Hasson technique is safest for initial access to the abdomen in children. As long as one adheres to the basic principles of safe insertion, damage to intra-abdominal contents, including the large vessels, is rare. As in adults, abdominal access for laparoscopic procedures is usually obtained through the umbilicus. The umbilicus might be a

potential source of infection if the umbilical cord has recently separated. Some surgeons therefore prefer a circumbilical incision instead. Following the installation of local anesthetic, and after vertically incising the skin in the umbilical scar, we prefer to enter the abdomen using the naturally occurring small umbilical hernia defect to place a 5 mm radially expanding trocar. Reusable trocars can subsequently be inserted safely under direct vision where required. When placing the trocars, the surgeon should keep the triangulation principle in mind: left hand instrument, camera and right hand instrument should form a triangle with the target organ in one axis with the surgeon and the camera.

Dislodgement of the trocars can be a major problem and nuisance during laparoscopic surgery in neonates and small children.[13] To prevent this, we place radially expanding 5 mm trocars through small incisions that hold them in place. Non-expanding trocars are secured in place using a red rubber cuff around the shaft of the trocar, secured to the skin with a silk stitch. If necessary, the trocar can then be moved in and out relative to the cuff using a mosquito clamp.

Pyloromyotomy

Laparoscopic pyloromyotomy is one of the few laparoscopic operations that have recently been demonstrated in a large multicenter RCT to be superior to the open classical approach.[14] The conclusion of the hallmark study by Hall *et al.* was that both open and laparoscopic pyloromyotomy are safe, but that time to achieve full enteral feeding was better in the laparoscopic group. The authors therefore recommend laparoscopic pyloromyotomy in centers with suitable laparoscopic experience. Interestingly, this trial was stopped by the data monitoring and ethics committee because of significant treatment benefit in the laparoscopy group at interim analysis.

Another prospective randomized trial concluded that the laparoscopic approach does not affect the length of recovery or complication rate.[15] However, the laparoscopic operation was associated with less pain and fewer episodes of emesis. In addition, the authors mentioned the cosmetic benefit of the laparoscopic approach, when compared to a right upper quadrant incision.

Although the laparoscopic approach is associated with a considerable learning curve[16] that may have resulted in more incomplete pyloromyotomies in the first published patients series, recent RCTs have failed to show a difference in this regard. In summary, advantages of laparoscopic versus open pyloromyotomy appear to result in less postoperative discomfort, a faster recovery, shorter length of stay, and better cosmesis. Recently, a single-incision laparoscopic approach has been described.[17]

Gastrostomy

Gastrostomy placement to provide either total or supplemental nutrition is a common procedure in infants and children. In many centers, gastroenterologists (sometimes in close collaboration with the pediatric surgeons) perform most of these feeding tube placements using the percutaneous endoscopic gastrostomy tube. The procedure combines flexible esophagogastroscopy with percutaneous puncture of the stomach to place a gastrostomy tube that can later be replaced by a gastrostomy button device. However, the percutaneous endoscopic technique has significant drawbacks and a relatively high complication rate, including bowel perforation. Therefore, we prefer a laparoscopic, single-incision technique for gastrostomy tube placement that was developed in our center in 1993.[18,19] This procedure allows visualization of the stomach and abdominal wall during the entire procedure, avoiding injury to adjacent viscera. It also permits primary placement of a gastrostomy button device, which is generally preferred by the caregivers.

Fundoplication

The laparoscopic Nissen fundoplication quickly gained popularity for treatment of symptomatic gastro-esophageal reflux disease (GERD). Good intraoperative visibility of the hiatus, excellent postoperative cosmesis, less pain, and reduced length of stay, as well as good efficacy combined with a low morbidity and mortality, has made this operation the standard of care. In our practice, indications for a laparoscopic Nissen fundoplication are failure of medical therapy for GERD and inability to tolerate gastric bolus feeds, either via the orogastric route or through an existing gastrostomy. The laparoscopic technique for gastrostomy placement described above assures that it is in a good location on the anterior aspect of the stomach, close to the greater curvature, and about two-thirds down from the fundus to the antrum. In such cases, a later laparoscopic fundoplication is easily achieved if necessary.

Generally, we perform a 360° wrap around the lower esophagus and gastro-esophageal junction with minimal dissection of the hiatus, as this has been shown to decrease failure rate.

Endorectal pull-through

Following a biopsy proven diagnosis of Hirschsprung's disease, a primary one-stage laparoscopic endorectal pull-through in the neonatal period is currently considered the standard of care by most pediatric surgeons.[20] Naturally, significant comorbidities or severe enterocolitis should be absent in this circumstance. The procedure is performed using three to four small abdominal ports, either in a triangular configuration or through the same skin incision in the umbilicus for a single-incision approach.[21] The transition zone is estimated by its morphology and laparoscopic seromuscular biopsies are obtained. In patients with a rectosigmoid colon transition zone, the intra-abdominal portion of the aganglionic bowel is devascularized using a hook electrocautery. In patients with longer segments of aganglionic colon, a pedicle preserving the marginal artery is fashioned as far proximal as necessary to bring the colon pedicle down without tension to form the neorectum. The rectal mobilization is performed transanally using an endorectal sleeve technique. The anastomosis is performed transanally 0.5 cm above the dentate line. Successful

techniques for performing laparoscopy-assisted Duhamel and Swenson pull-through procedures have also been reported in neonates. The laparoscopic-assisted endorectal pull-through has several advantages over a purely perineal approach. For one, the transition zone is histologically proven before the diseased bowel is resected. Furthermore, mobilizing the colon helps preserve a normal anorectal angle, which is important for later continence.

Using similar principles, a minimal invasive technique for the correction of intermediate and high anorectal malformations (ARMs) has been developed in our institution, namely the laparoscopically assisted anorectoplasty (LAARP). Taking maximal advantage of the good visualization of the pelvic musculature from the inside using the laparoscope, the distal colon and fistula are dissected and divided. An expanding trocar is then placed through the muscle complex, which is identified using the electric nerve stimulator. Placement of the trocar is further aided by transillumination of the endoscope's light.[22] In comparative studies, functionality and continence for both the perineal and laparoscopic operation are comparable.[23]

Malrotation

Incomplete rotation or malrotation of the intestines results in a malposition and non-fixation of the duodenum and terminal ileum and this situation predisposes the patient to midgut volvulus. Principles of the laparoscopic approach are similar to the open and include counterclockwise derotation of the intestines in case of a volvulus and release of the Ladd's bands starting distal to the pylorus and continuing distally until the mesenteric stalk is widened and the whole duodenum as well as the jejunum are located on the right side and the cecum is allowed to fall over to the left side of the abdomen.[24] This operation is usually performed with an incidental appendectomy as described by Ladd.

Duodenal atresia

Smaller laparoscopic surgical instruments have enabled pediatric surgeons to perform more sophisticated laparoscopic procedures, such as duodenal atresia repair. First reports of successful laparoscopic duodenal atresia repair were published at the beginning of this century. Using intracorporeal suturing, a diamond-shaped anastomosis is performed similar to the open approach to open duodenal atresia repair. We prefer to use a running suture for the back wall, and interrupted sutures in the front. Only a few small case series have been published so far, and a number of complications have been described. Therefore, this procedure should be reserved for very experienced pediatric endosurgeons and a low threshold for conversion in our view is warranted.

Billiary pathology

A large series of laparoscopic choledochal cyst excisions have been published in the literature, with excellent results comparable to the open approach. The surgical principles

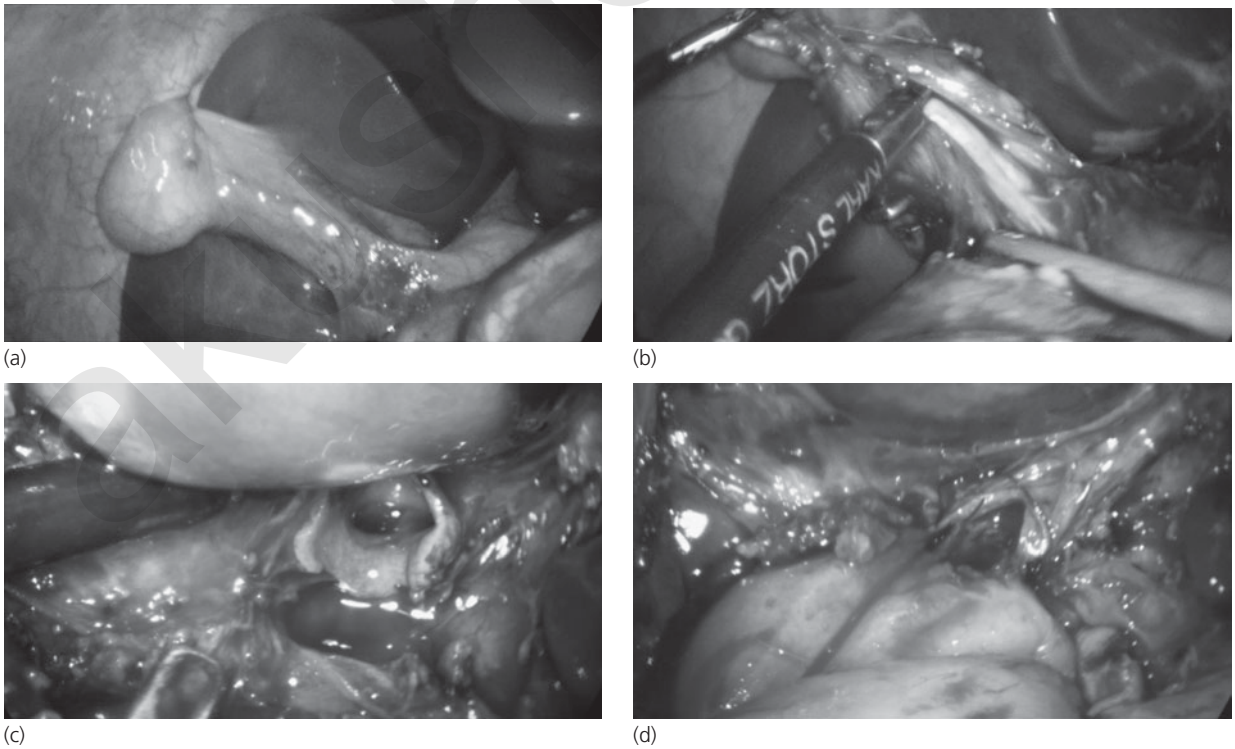

Figure 21.3 Resection of type 1 choledochal cyst: The gallbladder is restricted by a transabdominal suture, exposing the common bile duct below (a). The common bile duct is transected proximally (b) and then the cyst itself is resected (c). After creation of a Roux-en-Y limb, an enterobilliary anastomosis is performed (d).

are equivalent to those of the open procedure. Retraction of the gallbladder using a transabdominal suture in the right upper quadrant aids with the dissection. After resection of the cyst, a Roux-en-Y loop of bowel is created either intracorporeally or by exteriorizing the proximal small bowel through the umbilical incision. The anastomosis between the Roux-loop and the proximal common bile duct is performed using an intracorporeal suturing technique (Fig. 21.3a–d).

Although laparoscopic and robot-assisted Kasai procedures have been performed and reported, the higher failure rate has been reported compared to the open operation.[25] The reason for these findings is still unclear. In a sentinel vote at the 2007 IPEG meeting in Buenos Aires, the attending endoscopic pediatric surgeons agreed to perform minimally invasive Kasai operations only in well-controlled study protocols until more information is available.

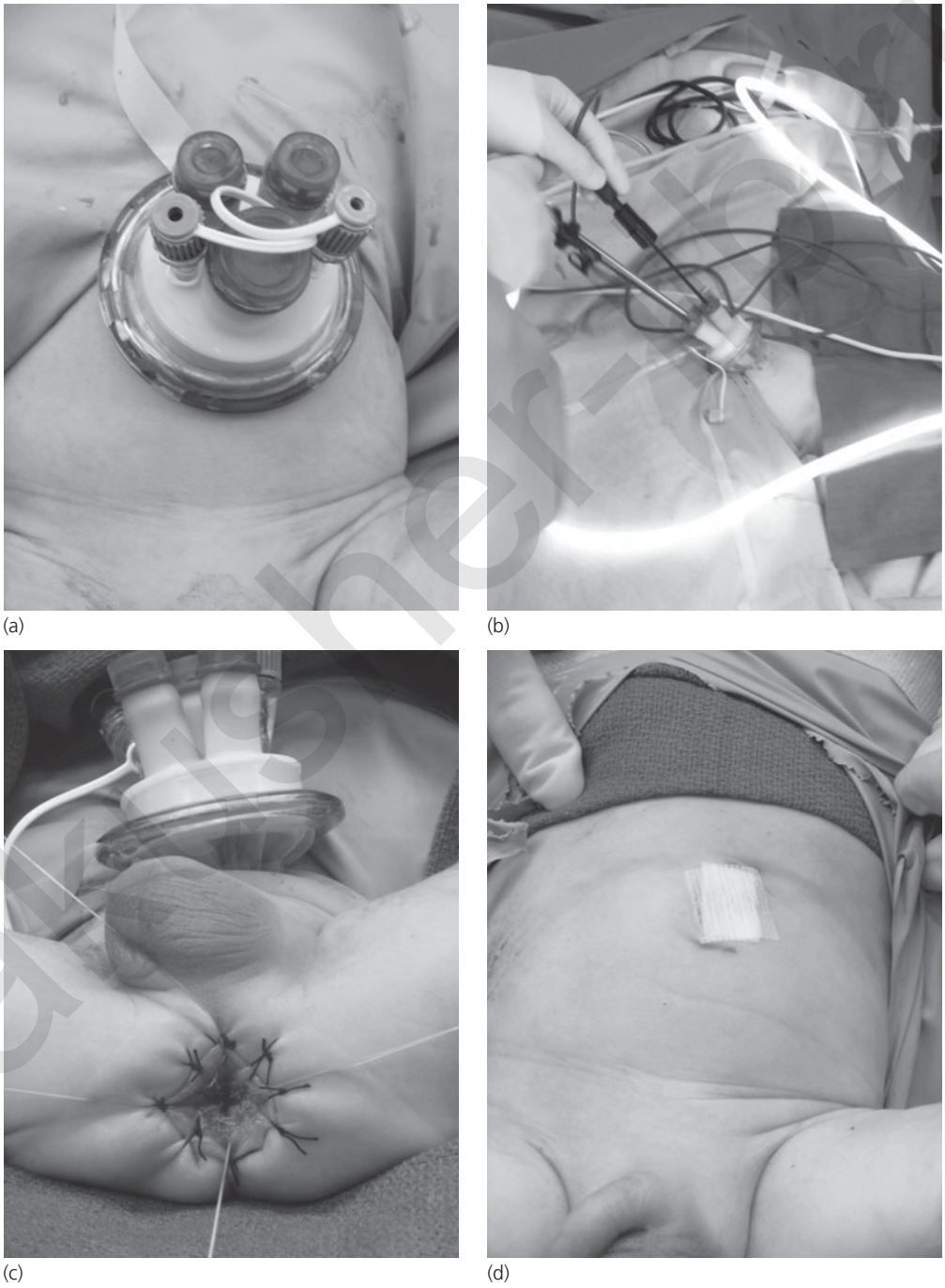

Figure 21.4 Single incision pediatric endoscopic surgery (SIPES) endorectal pull-through for Hirschsprung's disease. Single incision port introduced through the umbilicus (a). Intra-abdominal phase of operation via the umbilical port (b). Peri-anal phase of operation while umbilical port is still *in situ* (c). Umbilical incision leaves hardly any scar after surgery (d).

Pelvic pathology

With the improvement of prenatal ultrasound screening, pediatric surgeons see more neonates with enlarged ovarian cysts these days. In general, cysts with a complicated or complex ultrasound pattern, and those over 4 cm in diameter that do not resolve spontaneously after several weeks of life, warrant surgical exploration.[26] This is preferably done using laparoscopy. Serum AFP and beta-HCG levels should be checked preoperatively, and sound oncologic principles should be applied during surgery. Benign simple cysts may be drained by needle aspiration to facilitate removal through a trocar site. All other lesions can be resected in an endoscopic retrieval bag through the umbilicus or a separate, Pfannenstiel-type suprapubic incision.

Another pelvic pathology that can benefit from a laparoscopically assisted intra-pelvic or intra-abdominal dissection is the resection of a sacrococcygeal teratoma.[27,28] More than 50% of the tumors have such an intra-corporeal portion of the tumor and dissection can be facilitated by the magnified view of the laparoscope. Control of the presacral veins can be achieved laparoscopically and the intra-abdominal portion of the tumor can be mobilized off surrounding structures. Again, strict observance of oncologic principles is mandatory.

Future directions

In a period of only less than 20 years, minimal invasive surgery has become a major part of the practice of many pediatric surgeons. Many open procedures have been replaced or supplemented by comparable or even better minimal invasive procedures. It is hard to imagine that new developments in the field, such as natural orifice translumenal endoscopic surgery (NOTES) or single incision pediatric endosurgery (SIPES), are going to bring the same revolutionary advancement to general pediatric surgery as laparoscopic and thoracoscopic surgery have done. Although the first large series of NOTES procedures (cholecystectomies through the vagina) in adults have been published recently, NOTES is still suffering from the technological difficulty of perfect closure of the access organ that is used as the natural orifice.

In contrast, SIPES is slowly gaining more popularity, and series on several operations such as appendectomies, cholecystectomies, splenectomies, and pyloromyotomies have been published.[17,21,29–34] Introducing the camera and work instruments through the umbilicus, occasionally supplemented by a 2 mm percutaneous grasper in another location, we have been able to safely perform over 300 such procedures, including appendectomies, Nissen fundoplications, cholecystectomies, splenectomies, pyloromyotomies, and endorectal pull-throughs for Hirschsprung's disease (Fig. 21.4). However, our experience demonstrates that the procedures are more technically demanding because of the loss of triangulation, instrument clashing, and limited visualization. RCTs testing SIPES versus laparoscopic surgery in terms of complications, postoperative recovery, length of stay, and postoperative pain should be awaited before this technically more demanding technique can be recommended universally.

CONCLUSION

Minimal invasive neonatal surgery has become an established tool in the palette of the modern pediatric surgeon. Although the number of RCTs testing this relatively new approach is low, more and more publications are showing the benefit of the minimal invasive approach with regards to postoperative recovery, pain, and cosmesis. Whereas costs of minimal invasive surgery have always been a concern, the equipment has become less expensive over the past few years. In fact, when costs are considered on a macro-economical scale, shorter length of stay after a minimal invasive procedure may level or offset the balance in favor of minimal-invasive surgery. Eventually, it is likely that most intra-cavitary surgical conditions in neonates will be corrected using these techniques.

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22

Fetal surgery

SHINJIRO HIROSE AND MICHAEL R HARRISON

INTRODUCTION

This chapter is an overview of fetal intervention. In reality, birth defects have a long and interesting history. As Samuel Taylor Coleridge said, 'The history of man for the nine months preceding his birth would be far more interesting and have events of far greater moment than all three-score and ten years that follow'. In this chapter, we will present general principles of fetal surgery, methods of fetal access, diseases that are amenable to fetal intervention, and a brief discussion of the future.

The impetus to try to help the fetus came from two sources. First, are the obstetricians, perinatologists, and prenatal diagnosticians who developed the technical tools that allow detection before birth. They could see the problems and say 'why don't we fix them?' Second were the pediatricians who were seeing newborn infants with terrible problems which looked as though they were not fixable unless they were treated earlier. When these two groups got together, things started to happen.

GENERAL PRINCIPLES

Fetal intervention is complicated by not only the risk to the unborn patient, but by risk to the mother as well. Our heaviest responsibility is to the mother and her family. It is obvious that she is really an innocent bystander in the calculation of risk and benefit for her baby.

In her capacity, the mother stands nothing to gain in terms of health benefits from fetal surgery, yet she undergoes significant risk or morbidity in fetal surgery. To date, there have been no reported maternal deaths due to fetal surgery, although significant short-term maternal morbidity has been reported.[1] Complications include endotracheal intubation, blood transfusion, premature rupture of membranes, chorio-amniotic separation, chorioamnionitis, and placental abruption. In this light, fetal surgery is considered only if there is a severe, life-threatening or debilitating anomaly in the fetus that has been thoroughly investigated in animal models, and has been shown to be improved by fetal surgery.

Initially, fetal surgical experiments were carried out in a variety of animal models: rat, rabbit, sheep, and non-human primate. In these experiments, it was shown that *in utero* surgery could be performed safely and was subsequently attempted in humans. The first open fetal surgical procedure was performed at the University of California, San Francisco (UCSF) and was reported in 1982.[1] Since that time, we have performed over 380 fetal interventions over the past 27 years with no maternal mortalities. The main morbidity has been and remains preterm labor and premature delivery with gestational ages at delivery following fetal surgery ranging from 25 to 35 weeks.[2] Notably, after review, subsequent fertility following fetal intervention has been good.

A crucial component contributing to the success of a fetal treatment program is a multidisciplinary approach, utilizing the skills of various specialists working in concert. At UCSF, all fetal referrals are discussed at a large, open weekly meeting at which the patients are discussed, imaging studies are reviewed, and a consensus is reached regarding workup and treatment. This group consists of perinatologists, anesthesiologists, neonatologists, cardiologists, radiologists, geneticists, and pediatric surgeons. In addition, specific subspecialists are involved for certain cases, such as pediatric neurosurgeons for fetal myelomeningocele repair. The weekly discussion not only covers medical and surgical aspects of the patients' care, but also includes the ethical and social aspects of each case. Finally, a special institutional fetal treatment oversight committee reviews all fetal interventions on a monthly basis. This group serves as a quality control mechanism as well as an ethical review.

FETAL ACCESS

There are three general methods of accessing the fetus: percutaneously, with ultrasound guidance; minimally invasive fetoscopically; and open hysterotomy. In all three methods, preoperative and intraoperative ultrasound is

crucial in order to define the anomaly or anomalies, to delineate the placental anatomy, determine the position of the fetus, detect the presence of maternal blood vessels, and to monitor the fetal heart rate during the procedure. In percutaneous and fetoscopic procedures, ultrasound is of particular importance because of the lack of direct exposure of the fetus and uterus.

Maternal positioning is usually supine, with the left side down to minimize compression of the vena cava by the gravid uterus. Anesthesia is either spinal or general, depending on the nature and duration of the intervention. Fetal anesthesia is given when operating directly on the fetus. This is given as an intramuscular injection of opiate and non-depolarizing neuromuscular blocking agent.

Ultrasound-guided, percutaneous procedures are performed via small skin incisions in the maternal skin. These procedures require real-time ultrasound, as the only visualization of the fetal and maternal anatomy is via ultrasound images.[3] Through this type of access, catheters and shunts can be deployed in the fetus, draining cystic structures or ascites or pleural fluid into the amniotic space. In addition, using the same access technique, radio frequency ablation (RFA) probes can be deployed into the amniotic space in order to treat various twin gestational complications. The needles used to place catheters as well as the RFA device are approximately 1.5–2 mm in diameter, resulting in minimal morbidity to the mother during these procedures.[4,5]

Fetoscopic or 'FETENDO' procedures are generally performed via a 3 mm fetoscope, or less frequently, via standard 3 and 5 mm laparoscopic ports. For many fetoscopic procedures, the 3 mm fetoscope with its 1 mm working channel is sufficient to perform interventions on the fetus. For these procedures, it is important to identify a 'window' in the uterus that is devoid of placenta in order to reduce the risk of maternal bleeding, placental abruption, and fetal morbidity. When using the fetoscope, we can usually identify an access point on the mother's abdominal wall and use a 3 mm skin incision and access the uterus without a maternal laparotomy. When using multiple ports and more standard laparoscopic instruments, we prefer to perform a maternal laparotomy and direct uterine closure. Occasionally, the amniotic fluid is not clear enough for a good image via the small endoscopes. In these cases, we perform amnio-exchange, using warmed crystalloid solutions in order to clear the operative view.

Open fetal procedures require general anesthesia and a combination of preoperative indomethacin and high MAC inhalational agents in order to maintain uterine relaxation.[6–8] The incision is a low, transverse incision with a vertical or transverse fascial incision, depending on the exposure needed. Preoperative and intraoperative ultrasound is again crucial in order to avoid the placenta. Specific uterine staplers with absorbable staples were developed specifically for fetal surgery and allow for a hemostatic hysterotomy with minimal blood loss. Fetal monitoring is via ultrasound and continuous pulse oximetry. The uterus is stabilized within the maternal abdomen and herniation of the uterus is avoided to reduce tension on the uterine blood vessels. In addition, fetal exposure is limited to the specific body part in question. The majority of the fetus is left inside the uterus, and great care is taken not to handle or stretch the umbilical cord as this can cause fetal ischemia due to injury or vasospasm. After the fetal procedure is completed, the fetus is returned to the uterus, fluid is replaced, and the uterus is closed in multiple layers, using absorbable sutures. Postoperatively, the mother and fetus are monitored continuously for uterine contractions and heart rate, respectively. Often, the uterus is irritable and contractions require control with tocolytic regimens. Notably, open fetal surgery requires lifelong Cesarean section for future pregnancies due to the potential for uterine rupture in subsequent births.

Complications can occur after all types of fetal access. Bleeding can originate from the fetus, the placenta, the uterine wall, or the maternal abdominal wall. The uterine vessels are specifically avoided and identified with ultrasound to minimize bleeding. Premature rupture of membranes and preterm labor remain the main problem and limiting factor following fetal surgery. This complication is contributed to by inadequate membrane closure, chorioamnionitis, chorioamniotic separation, and uterine contractions.

ANOMALIES AMENABLE TO FETAL SURGERY

Congenital diaphragmatic hernia

Despite advances in neonatal methods of respiratory support, survival for children born with congenital diaphragmatic hernia (CDH) remains at only 60–70% throughout the United States. Additionally, survival for all fetuses diagnosed with CDH may be as low as 20–27% due to *in utero* demise or death of infants with unrecognized CDH.[9–11] We have theorized that *in utero* intervention may allow increased antenatal lung growth and increased pulmonary function and survival postnatally and have studied fetal lung development extensively.[12,13] In a fetal lamb model, compression of the lungs during the last trimester, either with an intra-thoracic balloon or by creation of a diaphragmatic hernia, results in fatal pulmonary hypoplasia. In addition, removal of the compressing lesion allows the lung to grow and develop sufficiently to permit survival at birth.[14]

Fetal surgery for CDH initially involved *in utero* diaphragmatic hernia repair. Analysis of this initial group of patients proved that open fetal surgery for CDH was feasible, but did not show an increase in survival.[15] However, the subset of fetuses with severe lung hypoplasia continues to have poor prognosis and are identifiable prenatally by ultrasound and magnetic resonance imaging (MRI). The factors associated with poor outcome that can be assessed prenatally by ultrasonography are: (1) the presence of liver herniation into the chest; and (2) a low lung-to-head ratio (LHR). In our experience, survival was 100% in fetuses with CDH without liver herniation and 56% in fetuses with CDH with liver herniation into the chest. The LHR is calculated as the area of the contralateral lung at the level of the cardiac atria divided by the head circumference. This LHR value has been shown to correlate in a statistically significant fashion with survival: 100% survival with an LHR greater than 1.35, 61% survival with an LHR between 0.6 and 1.35, and 0% survival

with an LHR less than 0.6.[16] Ultrasound is also critical in identifying other anomalies associated with CDH, particularly cardiac anomalies as those portend extremely poor prognosis. Magnetic resonance volumetric imaging of the lung for CDH is a promising modality for prognostic purposes.[17]

Over the last 20 years, we have been able to stratify risk for fetuses with CDH. Over this same time period, extensive animal studies and observation in fetuses born with congenital high airway obstruction have proven that lung growth may be driven by tracheal obstruction or occlusion leading to pressurized fluid accumulating in the airway. This has led to the study of lung distension by tracheal occlusion.[18,19] Our group has focused on *in utero* tracheal occlusion as a method of augmenting lung growth in fetuses with CDH. Our preliminary study examined the effect of extrinsic tracheal occlusion by the placement of an obstructing clip *in utero* using both open and FETENDO techniques.[20,21] We found in a small number of patients that survival was increased in the FETENDO but not the open group as compared to the control group, which consisted of patients undergoing standard postnatal care. This led to an NIH-funded trial comparing *in utero* tracheal occlusion using FETENDO to standard postnatal care using minimal access techniques for fetuses diagnosed with severe left-sided CDH and no other detectable anomalies. Results of the trial showed survival of 75% with no difference between the tracheal occlusion group and the standard postnatal care group. The survival in the postnatal care group was considerably greater than as compared to historical controls.[22] Although this study did not demonstrate a difference in survival between the prenatal intervention group and the postnatal one, the results of this trial demonstrate the tremendous importance of proper randomized controlled trials for novel fetal surgical procedures.

Refinement of tracheal occlusion techniques have progressed from tracheal clipping to percutaneous, fetoscopic placement of a detachable, intratracheal balloon. Animal studies demonstrated complete occlusion with this technique, and it has now become the current method of choice for fetal tracheal occlusion. Further data regarding tracheal occlusion have suggested that temporary, short-term reversible tracheal occlusion may be preferable to longer duration occlusion. Animal models of tracheal occlusion have demonstrated that long-term tracheal occlusion can be deleterious to type II pneumocytes: the cells that secrete surfactant, and that this effect is not seen in shorter durations of tracheal occlusion. In addition, other studies demonstrated the efficacy of short-term, reversible tracheal occlusion on lung growth in animals. A recent report from Cannie *et al.* demonstrated improved lung volumes following temporary balloon tracheal occlusion in human fetuses. In 36 of 40 patients, the tracheal balloon was removed prenatally, limiting the duration of occlusion. In this group of patients, improved lung growth was associated with improved postnatal survival.[23] Finally, reversal of tracheal occlusion requires a second maternal and fetal intervention for the removal of the fetal intratracheal balloon; however, it obviated the need for an *ex utero* intrapartum treatment (EXIT) procedure at birth for these patients. The EXIT procedure is a controlled surgical delivery method for these fetuses and was initially developed to reverse tracheal occlusion in this cohort of patients. After reversal of tracheal occlusion, standard delivery plans are possible for these patients with CDH.[24,25]

Based on these data, as part of an FDA-sponsored trial, our group is currently offering reversible, fetal tracheal occlusion for fetuses with liver herniation in the chest and lung to head ratio of less than 1.0, as these patients continue to have greater than 60% mortality. We perform the initial procedure between 24 and 26 weeks' gestation, and remove the balloon between 32 and 34 weeks.

Tumors

In general, fetal tumors are rare. When they do occur, most are benign. However, if they become large enough to either impede venous return to the heart or create high output heart failure via arteriovenous shunts, they can cause non-immune hydrops in the fetus. Hydropic changes include polyhydramnios, placentomegaly, fetal skin, and scalp edema, and pleural, pericardial, and peritoneal fluid accumulation. Left untreated, fetal hydrops is nearly always fatal.[26,27] The two most common prenatally diagnosed tumors that cause non-immune hydrops are congenital cystic adenomatoid malformation (CCAM) and sacrococcygeal teratoma (SCT).

Congenital cystic adenomatoid malformations

Congenital cystic adenomatoid malformations are pulmonary lesions with a broad range of clinical presentations. They are characterized by an overgrowth of respiratory bronchioles with the formation of cysts of various sizes. Classification of CCAM has classically been based on pathologic findings regarding the size of the cysts.[28–31] Most fetuses diagnosed with a CCAM *in utero* develop normally, and can be monitored with serial ultrasound studies. These asymptomatic patients can undergo standard, postnatal resection. A small percentage of patients with a prenatal diagnosis of CCAM will develop non-immune hydrops.[30,31] Various measurements have been developed in order to predict which fetuses are at risk for developing hydrops. The most accepted measurement is the CCAM volume ratio (CVR), defined as the product of the three longest measurements on ultrasound, multiplied by the constant 0.52, divided by the head circumference. In a recent paper, Crombleholme *et al.* identified a CVR 1.6 as a cut-off for an increased likelihood of developing hydrops.[32]

Interestingly, CCAMs that are predominantly microcystic have a more predictable course than the macrocystic ones. Microcystic CCAMs undergo steady growth and tend to plateau at 26–28 weeks' gestation. In contrast, macrocystic CCAMs can have abrupt enlargements in size due to rapid fluid accumulation in a large cyst. For these reasons, patients with microcystic CCAMs can be followed closely up to 26–28 weeks' gestation, and then the interval between ultrasound examinations can be lengthened, while macrocystic CCAMs require close follow-up throughout the duration of the pregnancy.[29,33]

If the fetus is of a viable gestational age in the presence of hydrops, early delivery should be considered. In instances where one dominant macrocystic lesion is present in a previable fetus, thoracoamniotic shunt may reverse the hydrops fetalis. Needle drainage has not proven to be an effective option as rapid re-accumulation of fluid occurs. Fetal thoracotomy with resection is an option in the previable fetus with a microcystic CCAM or one without the presence of a dominant cyst. The fetal thoracic space is exposed through a fifth intercostal space thoractomy after maternal hysterotomy. The lobe containing the CCAM is identified and brought out through the wound. The pulmonary hilar structures are then mass ligated using an endoloop or a vascular endostapling device. The thoractomy is then closed in layers.[34–36]

The experience with CCAM at the UCSF and the Children's Hospital of Philadelphia (CHOP) was reviewed. One hundred and thirty-four women pregnant with fetuses with CCAM were diagnosed *in utero*. Of this group, 120 elected to continue their pregnancies. Seventy-nine fetuses had no evidence of hydrops. Of these, 76 were followed expectantly and all survived. Three fetuses without evidence of hydrops with large dominant cysts underwent thoracoamniotic shunt placement and all three of these fetuses survived. Twenty-five hydropic fetuses were followed with no intervention. All mothers delivered prematurely and all fetuses died perinatally. Sixteen fetuses with hydrops underwent intervention: 13 underwent open fetal surgery while three underwent thoracoamniotic shunt placement. Two of three survived in the group that underwent shunt placement while eight of 13 survived in the open fetal surgery group.

Recently, it has been shown that fetuses with large CCAMs and hydrops can be treated by the administration of maternal steroids. This finding was discovered serendipitously at UCSF after several hydropic fetuses were identified and, in preparation for fetal surgery, maternal steroids were administered to enhance fetal lung maturity.[37] Subsequent ultrasound surveys showed the resolution of hydrops. These findings were later identified in similar patients at CHOP.[38] A multicenter, prospective trial is now underway in order to investigate the role of steroids in the treatment and management of hydrops in large fetal CCAMs.

Sacrococcygeal teratoma

Sacrococcygeal teratoma is a rare tumor that is being diagnosed with increasing frequency *in utero*, allowing for observation of the prenatal natural history of the disease and appropriate perinatal management. As with CCAM, fetuses with SCT are susceptible to *in utero* demise. SCT tumors can grow to a tremendous size in relation to the fetus, resulting in a vascular shunt, and, in the extreme form, high output cardiac failure and non-immume hydrops. Rarely, tumors bleed either within the tumor or externally and may cause fetal anemia and hypovolemia. Other potential problems with a fetus with a large SCT are those of dystocia and preterm labor. Delivery can be particularly difficult when the diagnosis has not been made prenatally. Traumatic delivery may result in hemorrhage or tumor rupture. Most clinicians would favor Cesarean delivery for fetuses with large SCTs. Thus, prenatal diagnosis and careful obstetrical planning are critical in the appropriate management of the fetus with an SCT.

The UCSF experience with prenatally diagnosed SCT included the management of 17 fetuses and mothers. Of the 17 fetuses, 12 developed hydrops while five did not. All five of the non-hydropic fetuses delivered near term and survived. Of the 12 hydropic fetuses, seven underwent fetal intervention with three survivors. Five hydropic fetuses were followed without fetal intervention and none of this group survived.[39] Hydrops in fetuses with SCTs has been shown in other groups to correlate with an exceedingly high rate of fetal demise. The group at CHOP recently published their experience with 30 fetuses with SCT. In their patient cohort, there were 14 survivors. Four fetuses were terminated. Fifteen fetuses had solid tumors, and of those, four developed signs of hydrops and underwent fetal debulking operations. Three of four survived.[40]

The most common method of fetal intervention is hysterotomy with resection or debulking of the tumor. A predominantly cystic lesion may be amenable to percutaneous drainage or placement of a shunt. Effectively debulking the tumor with percutaneous coagulation, such as with radiofrequency ablation or laser coagulation to decrease the vascular shunt, are minimally invasive alternatives to open resection that warrant further investigation.[27,41]

ABNORMALITIES OF TWIN GESTATIONS

Twin–twin transfusion syndrome

Twin–twin transfusion syndrome (TTTS) is the most common complication of monochorionic twin pregnancies, complicating approximately 10%.[42] In monochorionic twin pregnancies, the two fetuses share one placenta, and there are normal vascular connections between them. TTTS occurs when there is net flow from one twin to the other. As a result of the transfusion of blood from the donor twin to the recipient twin, hemodynamic compromise can occur in both or either twin. The donor twin suffers from a low flow state and can sustain injuries to the brain and kidneys. Conversely, the recipient twin has fluid overload, and may develop congestive heart failure and hydrops. The hallmark of TTTS is oligohydramnios in the donor twin and polyhydramnios in the recipient. In addition, often there is size discordance between the twins with the donor being smaller than the recipient. Advanced disease is evidenced by progressive discordance in fluid volumes with the donor becoming 'stuck' in its amniotic sac due to a complete lack of fluid. In addition, worsening cardiac changes in the recipient portend a grave prognosis. If left untreated, TTTS carries 80–90% mortality for both twins. In addition, in monochorionic twins, if one twin dies, the other is at risk of neurologic injury due to a sump phenomenon in the placenta and demised fetus and from embolism.[43–45]

Clinicians have attempted a variety of treatments aimed at achieving improved outcome in one or both twins. The most commonly used treatment is high-volume amnioreduction of the fluid of the polydramniotic sac. Because polyhydramnios may incite labor, the initial aim of amnioreduction was to

reduce uterine volume to decrease the risk of preterm labor. High-volume amnioreduction resulted in the survival of 58% of twins from the International Amnioreduction Registry.[46]

Several groups have used fetoscopic guidance to laser ablate intertwin vascular connections. This can be done either nonselectively, by ablating all intertwin connections, or selectively, by ablating only AV connections with flow in the causative direction. Fetoscopic laser ablation can be performed either percutaneously using 1.0–2.0 mm endoscopes or by maternal laparotomy with 3.0–5.0 mm endoscopes. A maternal laparotomy is favored with use of the larger scopes in order to close the uterine defect created by placement of these devices. All scopes are placed through ports that have side channels for irrigation and placement of the laser. Recently, two large prospective trials have been published comparing amnioreduction to laser ablation of intertwin vessels. The European trial enrolled 70 women in the amnioreduction arm and 72 women in the laser ablation arm. The trial was stopped early after interim analysis showed a clear survival advantage to laser therapy: 76 versus 51% single survivor and 36 versus 26% for dual survivor.[47] The North American trial was also stopped early after randomizing 42 mothers: 20 in the amnioreduction arm and 22 in the laser ablation one. There was no survival benefit to either intervention, but their study was underpowered due to the early termination of the trial. This trial was complicated by the reluctance of referring physicians to send their patients to the various centers in order to be randomized.[48]

Twin reversed arterial perfusion

Twin reversed arterial perfusion (TRAP) sequence is a rare disease of monochorionic twins that occurs when one normal twin acts as a 'pump' for an acardiac, acephalic one. The normal twin is put at risk for high output heart failure and hydrops as it has to maintain blood flow throughout the entire placenta as well as to the acardiac twin. The blood flow in the acardiac twin is characteristically reversed, and thus the acronym TRAP was coined to describe this anomaly. The natural history of TRAP is greater than 50% mortality in the pump twin due to hydrops.[49,50] The risk of hydrops increases as the mass of the acardiac twin increases relative to the normal twin. Generally, we choose to intervene when there is evidence of hydrops in the pump twin, or when the estimated fetal weight of the acardiac twin is 50% or more relative to the pump one.

Multiple techniques have been used to separate the vascular supplies in TRAP pregnancies: open hysterotomy and delivery, fetoscopic ligation, bipolar cautery, harmonic scalpel division, thermal coagulation, and laser coagulation. At UCSF, we have been using RFA to coagulate the umbilical cord insertion site on the abdomen of the acardiac twin.[51–53] These devices were originally designed for ablation of solid tumors, but their small size and effective coagulation has been ideal for this application.[54] We recently published our results with RFA for TRAP, identifying 29 patients who underwent RFA between 18 and 24 weeks' gestation. Survival was 86% percent overall, with 92% survival in monochorionic, diamniotic pregnancies.[5]

Myelomeningocele

Myelomeningocele (MMC), or spina bifida, is characterized by an open neural tube and exposed spinal canal elements. MMC can occur anywhere along the spine, but most commonly occurs in the lumbar or cervical vertebral levels. Complications include neurologic deficits with motor and somatosensory abnormalities which correspond to the level of the spinal defect. In addition, autonomic function is also commonly deranged with an inability to control bladder or bowel function. Finally, nearly all patients with MMC develop the Arnold–Chiari II malformation of the hindbrain and most will require ventriculo-peritoneal (VP) shunting for hydrocephalus. Unlike previous patients considered for fetal intervention, fetuses with MMC are generally born alive and healthy, but the attendant morbidity from neurologic abnormalities is severe, and up to 30% of patients die before reaching adulthood due to respiratory, urinary, or central nervous system complications. Current therapy for MMC is postnatal repair of the spinal defect and extensive rehabilitation.[55]

The rationale for fetal intervention in MMC is the 'two-hit' hypothesis, where the first hit is the original neural tube defect that results in the open spinal canal. The second hit is postulated to be due to direct trauma to the exposed neural elements while the fetus is *in utero*.[56,57] It is this second hit that could potentially be ameliorated by fetal surgery.[58] Various animal models for fetal MMC were created in rats, lambs, rabbits, and non-human primates in order to test this hypothesis. The data from these experiments showed improved distal neurologic function as well as correction of the Arnold–Chiari II malformation.[57,59]

These animal data led to pilot studies in human fetuses. Initial attempts at human MMC repair were performed via open hysterotomy and fetoscopic techniques.[60,61] A review of initial results demonstrated no improvement in distal neurologic function, but did show improvement in the Arnold–Chiari II malformation with reduced hind-brain herniation, as well as a possible decrease in the need for VP shunting when compared with historic controls.[62–64] MMC is unique as it is the first nonlethal anomaly for which fetal surgery has been undertaken. However, it is associated with significant morbidity, and refinement of techniques have minimized the risk to the mother as much as possible during these open fetal operations. Based on these data, as well as animal studies, the NIH has sponsored a prospective, multicenter, randomized controlled trial to investigate the efficacy of fetal surgery for MMC.

THE FUTURE

The requirements for intervention to correct a fetal defect remain the same:

- experimental work to prove the pathophysiology of the defect;
- careful study of the natural history of the untreated disease; and
- ability to select the fetus that will benefit from prenatal treatment.

Stem cells and gene therapy

Gene therapy for prenatally identifiable diseases is currently experimental, and is being actively pursued for specific disorders. The rationale behind *in utero* therapy with stem cells and/or virally directed genes include avoiding the progression of disease in the fetus during gestation as well as taking advantage of the developing immune system of the fetus, thus potentially avoiding issues of tolerance, rejection, and graft versus host disease.[65]

Specific issues for *in utero* treatment of genetic diseases include timing of diagnosis, timing of therapy, delivery of stem cells or genes, sources for stem cells, and durability of treatment. With the advent of chorionic villus sampling, genetic diseases can be identified in the first trimester. Timing of potential treatments is crucial in order to take advantage of the possible 'pre-immune' status of the fetus, making fetuses potentially more receptive to exogenous genes or cells. Several investigators have utilized hematopoetic stem cells (HSC) as a vector to attempt to induce chimerism in order to treat the disease. Others have investigated the use of retroviral vectors in order to insert genetic material into fetal animals. This approach reduces the problem of obtaining the large numbers of stem cells needed to create even a modest amount of chimerism. Other approaches include the use of maternal stem cells or genetic material as studies have demonstrated early cross-trafficking of maternal cells in the fetus. Candidate diseases include hematologic, immunologic, metabolic, and neurologic abnormalities (Box 22.1). To date, there have been over 30 reports of *in utero* therapy with HSCs; however, the only durable treatment has been in patients with pre-existing immunologic defects.[66,67] Currently, *in utero* gene therapy and stem cell therapy are in their infancy but remain an active topic of research and investigation.

Box 22.1 Candidate diseases for fetal gene therapy and stem cell therapy

- Hematologic
  - Alpha-thalassemia
  - Fanconi anemia
  - Chronic granulomatous disease
  - Hemophilia A
- Immunologic
  - SCID
  - Wiscott–Aldrich syndrome
- Metabolic
  - Wolman disease
  - Type II Gaucher disease
  - Pompe disease
  - Osteogenesis imperfecta
  - Cystic fibrosis
- Neurologic
  - Lesch–Nyhan syndrome
  - Tay–Sachs
  - Sandhoff disease
  - Niemann–Pick disease
  - Leukodystrophies
  - Generalized gangliosidosis
  - Leigh disease

SUMMARY

Fetal surgery has progressed from an investigational therapy to an accepted mode of therapy for selected fetal diseases. Multidisciplinary teams are critical for the success of a fetal treatment program, and regular, weekly meetings are necessary to keep all members of the team abreast of developments and new patients. Diseases that historically have a high perinatal mortality rate have shown improved survival with fetal surgery. NIH-funded, prospective trials have been performed for CHD and TTTS. Current clinical trials include those for MMC, hydrops, and CCAM, and reversible tracheal occlusion for CDH. Initially, fetal interventions were reserved for fetuses with lethal anomalies in order to maximize the fetal benefit balanced with minimizing maternal risk. Myelomeningocele is the first nonlethal anomaly that has been treated with fetal surgery.

As minimal access techniques improve, and maternal risks are further reduced, indications for fetal surgery will continue to broaden. New areas of investigation include tissue engineering, stem cell therapy, and gene therapy. Maternal safety must remain paramount, and the risk to the mother should be minimized at all times. The study of these new techniques and areas of investigation should take place initially with animal models, and then in humans under the rubric of prospective, clinical trials and, as many of these disease are rare, they will likely require multicenter input.

Over the years, the progress seen in fetal intervention is directly related to the investigation process, i.e. the understanding of the pathophysiology in the laboratory, the documentation of the natural history in the human fetus, and the push for less and less invasive procedures. Many people have contributed to this development but it is also important to acknowledge the important contribution of the patients and their families to this enterprise. Families who chose to undergo fetal therapy have been able to understand the benefits and risks of unproven treatment, be tough enough to withstand the pressures and disappointments, and dedicated enough to appreciate their own contribution to helping other families in the future.

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23

Liver transplantation

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INTRODUCTION

One of the prime stimuli for the development of liver transplantation was the inevitable mortality from infant liver disease and many of the advances in liver transplantation techniques were prompted by the need to tailor the procedure for the pediatric patient. The first ever human transplant was attempted in 1963 by Starzl on a three-year-old child with biliary atresia.[1] The infant did not survive the operation and it was not until four years later that he obtained 'success' in achieving survival for 400 days in an 18-month-old girl with a malignant liver tumor. She died from disseminated metastases. Over the next decade one-year mortality remained high at around 50% and it was not until cyclosporine was introduced in 1980 that survivals dramatically increased. Eleven of the first 12 recipients receiving cyclosporine and prednisone immune suppression therapy lived more than one year and seven survived at least 12 years.[2,3] In June 1983 at the National Institutes of Health Consensus Development Conference liver transplantation was declared a valid treatment for end stage liver disease. The introduction a decade later of tacrolimus, a similar but more powerful drug, pushed the boundaries of success even further.[4] Further technical advances included reduced size liver transplantation,[5] split liver transplants,[6] and living related transplants.[7,8]

Advances in patient selection, organ preservation, surgical technique, anesthetic management, pre- and postoperative care and refinements in immunosuppression and management of the immune suppressed patient over the last four decades has resulted in a much improved outcome with an ever-increasing list of indications being identified and indeed a changing pattern of indications (Box 23.1).[9]

In infancy, the most frequent reasons for liver transplantation are infantile liver failure due to hemochromatosis and biliary atresia.

Current expected five-year survival is now greater than 90% and one-year survival of 100% has been achieved.[10,11] Excellent quality of life is the rule rather than the exception but does to some extent depend on pretransplant morbidity, particularly from the nutritional deprivation which occurs with chronic liver function impairment and cholestatis leading to neurodevelopmental delay.[12] The longest survivor is well 40 years after transplantation. Current anxieties remain over organ donor scarcity militating against timely transplant, the long-term side effects of the immunosuppressive therapy, financial implications, and some ethical issues. The focus of attention has now shifted from an initial target of early post-transplant survival to quality of life in the long term. Shortage of donor organs has been tackled in an imaginative way with increasing use being made of size reduction of the donor liver even into a single segment, splitting the liver into two functioning units for two recipients, as well as the use of living related donors and non-heart beating donors.

INDICATIONS

Liver disease has been generally underestimated as a cause of death in infants and children.[11] This is probably because many liver conditions in children have led to rapid deterioration and death in the past. Almost all forms of liver disease in children can be complicated by hepatocellular failure.[13,14] These would include acute and subacute liver failure from metabolic, toxic, or viral insults and chronic parenchymal disease of varying causes of which biliary atresia, biliary hypoplasia, autoimmune hepatitis, viral hepatitis, and some metabolic diseases are the most common.[14–19] The widespread introduction of hepatitis B virus (HBV) and hepatitis A virus (HVA) vaccines have significantly reduced the incidence of acute hepatic failure in some countries. In some metabolic diseases, the manifestation is in hepatocellular disease and in others there may be more widespread effects such as with tyrosinemia, Wilson's disease, hyperglycoproteinemia, some glycogen storage diseases, and hyperoxaluria (Box 23.1). New treatments for acute liver failure from neonatal hemochromatosis using antenatal i.v. immunoglobulin (IVIG) for the mother and

Box 23.1 Indications for which liver transplantation has been performed in children

I Metabolic (inborn errors of metabolism)
- Alpha-1 antitrypsin
- Tyrosinaemia
- Glycogen storage disease type III and IV
- Wilson's disease
- Perinatal hemochromatosis
- Hypercholesterolemia
- Cystic fibrosis
- Hyperoxaluria (pre-emptive or + renal transplant)
- Hemophilia A + B
- Protein C deficiency
- Crigler-Najjar syndrome
- Urea cycle defect

II Acute and chronic hepatitis
- Fulminant hepatic failure (viral, toxin or drug induced)
- Chronic hepatitis (B, C, etc. toxin, autoimmune, idiopathic)

III Intrahepatic cholestasis
- Neonatal hepatitis
- Alagille syndrome
- Biliary hypoplasia
- Familial cholestasis
- Primary sclerosing cholangitis

IV Obstructive biliary tract disease
- Biliary atresia
- Choledochal cyst with cirrhosis

V Neoplasia
- Hepatoblastoma
- Hepatocellular carcinoma
- Sarcoma
- Hemangioendothelioma

VI Miscellaneous
- Cryptogenic cirrhosis
- Congenital hepatic fibrosis
- Caroli's disease
- Budd–Chiari syndrome
- Cirrhosis from prolonged parenteral nutrition

exchange transfusion and IVIG for the newly diagnosed neonate may reduce the need for liver transplantation in this group of patients.[20,21]

In infants with hyperoxaluria, an innovative strategy may be that of early liver transplantation followed by later renal transplantation.[22]

Hemangioendothelioma in infancy is an occasional indication if medical treatment with steroids, propranolol, and surgical treatment with resection hepatic artery ligation or embolization fails, but outcome is guarded.[23,24]

More recently, liver transplantation has been successfully used in infants with short bowel syndrome and parenteral nutrition-associated liver failure, where adaptation can be expected, and in patients with cystic fibrosis and liver disease.[25]

Re-transplantation is less frequently required in the early post-transplant period but will become a more frequent indication as greater numbers of transplant recipients live long term and achieve adult status.

ASSESSMENT

In general, liver transplantation should be considered as a therapeutic option in all cases of chronic liver disease before the condition of end stage liver disease is realized,[26,27] and in acute liver failure with defined parameters indicating a poor prognosis.

There are indeed few reasons for refusal for transplantation (Box 23.1).[26,27] These include uncontrolled systemic bacterial, viral or fungal infections, malignancy outside the liver, cyanotic pulmonary arterio-venous shunting with pulmonary hypertension, active chronic hepatitis B, HIV/AIDS not controlled with anti-viral treatment, as well as other major cardio-respiratory and/or neurological disease which would be incompatible with quality long-term survival.[28] To a certain extent these are all relative contraindications. Psychosocial factors may be a reason for refusal. Parental substance abuse, severe psychiatric problems and poor preoperative compliance with therapy are factors that need to be carefully examined. In developing countries, the socioeconomic factors such as poor sanitation and lack of access to adequate medical follow-up are often contraindications to transplantation.

Compliance is more difficult to predict in families of children with acute hepatic failure, as time from presentation to decision to transplant is much shorter. Good adherence is one of the factors thought to contribute to the slightly better outcome after living donor transplantation as the bond and responsibilities between donor and recipient is that much greater.

As the outcome of the operation is so much better in recent years, indications for early transplant in patients with chronic liver disease would be evidence of impaired synthetic function, including prolonged prothrombin time, reduced serum cholesterol levels and low serum albumin. Clinical indicators include presence of ascites, bleeding from esophageal varices not controlled by sclerotherapy/banding, and poor response to nutritional resuscitation. Those with acute hepatic failure who develop encephalopathy, hypoglycemia, a prothrombin time of greater than 50 seconds, and a factor V level of less than 20% should be considered for transplant, as almost all of these children die without transplantation.

All patients require initial confirmation of the diagnosis, intensive medical investigation, nutritional resuscitation, and active treatment of the complications of the liver disease, portal hypertension, and nutritional deprivation (Box 23.2). Immunization status must be reviewed and supplemented with hepatitis A and B immunization, *Hemophilus influenzae*, pneumococcal, varicella, and meningococcal vaccine in most cases. Blood group identical or compatible donors are much preferred as the long-term survival with blood group incompatible donors has been significantly less but there have been recent reports of excellent outcomes with blood group incompatibility, particularly in infants under one year

Box 23.2 Summary of common postoperative problems

1. Biliary tract
   a Stenosis or stricture
   b Anastomotic leak – often associated with hepatic artery thrombosis
   c Infection
2. Rejection
   a Acute
   b Chronic (vanishing bile duct syndrome)
3. Infection – bacterial, viral, (CMV, EBV, herpes zoster, hepatitis B), fungal (Candida, Aspergillus), parasitic (pneumocystis)
   a Abdominal (peri- or intrahepatic abscess)
   b Biliary tree
   c Pulmonary
   d Reactivated virus
   e Gastrointestinal tract
   f Catheter associated (i.v., urinary tract)
4. Vascular (thrombosis, stenosis)
   a Hepatic artery
   b Portal vein
   c Inferior vena cava (supra and infrahepatic)
   d Hepatic vein (left lateral segment grafts), Budd–Chiari recurrence
5. Renal dysfunction
   a Calcineurin inhibitor or other drug-induced injury
   b Tubular necrosis due to hypoperfusion
   c Pre-existing disease (hepato-renal syndrome)
   d Hypertension
6. Miscellaneous
   a Encephalopathy (cyclosporin, tacrolimus, hypertensive, metabolic)
   b Bowel perforation (steroid, diathermy, hypoxia)
   c Diaphragm paresis/paralysis
   d Gastrointestinal hemorrhage (peptic ulceration, variceal)
   e Obesity (steroids)
   f Other drug side effects

of age. Patients are generally listed according to urgency on a UNOS score from 1 to 4 with 1 being the most urgent or according to the pediatric end stage liver disease (PELD) score. Young age (less than six months), creatinine clearance (<90 mL/1.73 m^2), pretransplant hospitalization, pretransplant ventilation, retransplantation, and transplant for reasons other than cholestatic disease have been associated with a reduced survival.[29]

Blood group compatibility of the donor with the recipient should be respected but in infants better results have been achieved if circumstances militate for urgent transplant and only an incompatible ABO blood group donor organ is available. There are also specific strategies to reduce the potential adverse immune consequences of a blood group incompatible organ including the use of a CD20 monoclonal antibody, i.v. immunoglobulin, and plasma exchange.[30]

SURGICAL TECHNIQUE

Donor organ suitability and function is difficult to predict. Increasingly marginal donors are being used with a surprisingly low incidence of primary poor or nonfunction. Age limits are being extended.[31] However, stable donors aged under 45 years with a short intensive care unit stay (less than 3 days), little requirement for inotropic support, and normal or near normal liver function are preferred, with an expected $<5\%$ incidence of impaired function after transplant. Liver biopsy is useful if steatosis is suspected. Greater than 50% fatty infiltration would preclude the use of the liver in most centers. Viral screening of the donors is essential. This would include hepatitis B (HBsAg, HBV IgG core Ab) and C, cytomegalovirus (CMV), Epstein–Barr virus (EBV), and human immunodeficiency virus (HIV) screening. HBV IgG core antibody and HCV positive donors would only be considered in selected viral infected recipients and, if appropriate, post-transplant hepatitis B prophylaxis could be given.

Surgical techniques used for donor retrieval and recipient liver removal and engraftment have evolved over the last 40 years.[32,33] The majority of donor livers are removed as part of a multi-organ procurement procedure, which would include various combinations of kidneys, liver, heart or heart and lungs, small bowel and pancreas. University of Wisconsin solution and histidine-tryptophan-ketoglutarate (HTK) solution are both widely used as the preservation solutions of choice.[34]

The principal two techniques are a careful dissection and excision technique or the so-called rapid technique described by Starzl.[33,35]

DONATION AFTER CARDIAC DEATH

Donation after cardiac death has been established practice for many years for renal transplantation but recently, in an effort to expand the donor pool, this has been extended to other organs. The concept of cardiac death may be more acceptable to some and could increase the number of potential donors. Although there are considerable logistic problems to overcome, some success has been achieved with acceptable graft function even in segmental liver transplantation using a 'super-rapid' technique and keeping both cold and warm ischemic times to a minimum.

The graft should be of an appropriate size both to provide adequate function but not too large to compromise abdominal compartment domain. A minimum graft size should be $>0.8\%$ of body mass (normal $\sim 2\%$), i.e. 40% of estimated standard liver volume. Grafts of smaller size have a poorer outcome from graft failure due to 'small-for-size' syndrome due in part to excessive portal flow.

The recipient operation is commenced so that the estimated hepatic graft ischemic time is less than 12 hours. Much longer preservation times have been recorded, but this leads to an increased incidence of cholestasis and graft dysfunction.

Careful dissection is required when split liver transplantation is being used; that is when the liver is divided into two functional units for two recipients; and decisions must be

made as to which porta hepatis structures will go with which graft. It is advisable to perform a portable cholangiogram to confirm bile duct anatomy as there are many variations in biliary anatomy. Depending on local preference, many centers opt to export the right-sided graft with the full complement of structures of bile duct, portal vein, and hepatic artery, keeping the left lateral segment for the local graft in much the same way as a living donor transplant. Where a reduced size liver is used, the caudate lobe is always excised. The division of liver tissue may be performed using the standard forceps clamp or bipolar diathermy technique with titanium clip and/or suture and ligation of vascular and biliary structures. The ultrasonic dissector (CUSA), Ligasure R, or Harmonic Scalpel may also be used. The cut edge of the liver is then sprayed with two layers of tissue glue. If the recipient inferior vena cava is to be preserved, this is simplest done by carefully excising the diseased liver clear of the cava and when the liver has been removed, individually suturing closed all small areas of leakage from divided direct caudate lobe hepatic veins. The IVC is prepared for the donor liver by dividing the bridges between the separate hepatic veins. This creates a wide orifice for the hepatic vein to cava anastomosis. The inferior vena cava should be incised distally for approximately 1–2 cm to make a triangular orifice for the 'piggy-back' graft.[36]

Engraftment should begin with the upper caval anastomosis taking into account the need to rotate the liver anticlockwise 60° with reduced size liver grafts. Split grafts and living donor segmental grafts may need to lie in an orthotopic anatomical position and a number of techniques of stabilizing the graft have been used so as to avoid torsion at the hepatic vein to caval anastomosis and to facilitate vascular anastomoses without using interposition grafts. Prior to completion of the anastomosis, the liver is flushed of preservation solution via the portal vein with recipient blood, normal saline, or a colloid solution. It is important for the portal vein to be of adequate size and length and it should lie without tension. If the recipient vein is too narrow and sclerotic, interposition of a donor iliac vein is indicated.[33] Likewise with the arterial anastomosis, if the recipient vessel is too small or the donor artery too short, an interposition graft is placed onto the supraceliac or infrarenal aorta. The bile duct is trimmed back and spatulated in pediatric donors such that there is good bleeding from the cut edge and a wide anastomosis is obtained. With reduced and variant size grafts, a Roux-en-Y choledochojejunostomy is always performed using fine absorbable sutures.[37–41]

Occasionally in pediatric cases, a duct-to-duct anastomosis may be performed with a whole liver graft in a recipient with a normal extrahepatic biliary system or for infants with short bowel syndrome undergoing isolated liver transplant. Stents or T tubes are optional but less used as there is some evidence of an increased incidence of biliary complications associated with their use.

SPLIT LIVER TRANSPLANTATION AND LIVING RELATED DONATION

In split liver transplantation a whole cadaver donor organ is divided into two functional units. Segments 2 and 3 are used for an infant and the right liver for an adult recipient. The graft can be further reduced in size by removing segments 2 or alternatively segment 2 is used as the graft and segment 3 is resected and discarded. The disadvantage of using a segment 3 graft is the greater anterior posterior dimension, which may be difficult to accommodate in an infant abdomen (Fig. 23.1).[42] Living related donation of the left lateral segment, first successfully performed by Strong, has become widely accepted as a method of acquiring a liver graft in the face of severe donor shortages, particularly in countries with cultural or religious reticence to accept brain death in a ventilated heart-beating donor.[42,43] There are clear advantages in the planned nature of the procedure, preferably before end stage liver disease in the recipient, the excellent quality of the graft, and short ischemic time. In general, the use of a living donor also increases the availability of donor organs for other patients on the waiting list. The only advantage to the donor is a psychological one and there is a current morbidity of around 10% (wound sepsis, hernia, bile leak, and adhesive bowel obstruction). There is also a reported mortality of around 0.2%, although in one center in Japan more than a 1000 of these operations were carried out without donor mortality.[44] There are ethical concerns, which appear justified, as with more widespread transplant activity increasing mortality and morbidity has been recorded in adult-to-adult donation but adult-to-child donation has a very low morbidity and mortality. The donor should first undergo a thorough screening, both clinical and psychological, without coercion and be given an option to withdraw from the procedure at any time before the

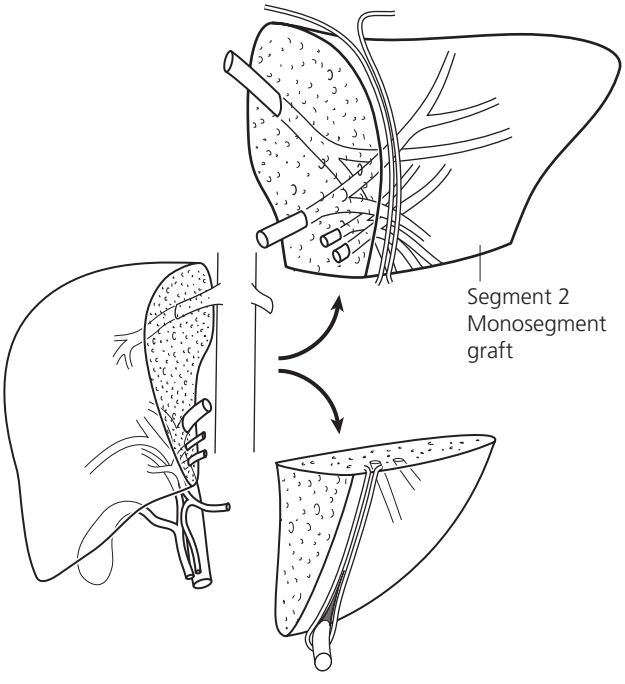

Figure 23.1 Left lateral segment transplant from a living donor or split liver, further reduced in size to a monosegment graft by resection of segment 3.[42]

transplant.[45,46] This process may have to be accelerated where donation is for fulminant hepatic failure. Cholangiography is essential as there is considerable variety in the intrahepatic biliary anatomy.[47] Angiography is desirable but not essential. MR imaging has made interventional radiographic techniques obsolete.

MEDICAL MANAGEMENT

Immunosuppression

Most protocols employ triple therapy with cyclosporine/tacrolimus, azathioprine, or mycophenolate mofetil (MMF) and methylprednisolone. Both tacrolimus and cyclosporine are effective in preventing acute rejection but tacrolimus is more likely to prevent steroid-resistant rejection (94 versus 70%).[48] Increasingly, particularly for small children, tacrolimus is used as primary immunosuppression. In addition, there are a number of other strategies in place to reduce the amount of nephrotoxicity, which is a toxic side effect of both calcineurin inhibitors. Thus, mycophenolate mofetil, an inosine monophosphate dehydrogenase inhibitor, may be used instead of azathioprine and a monoclonal interleukin-2 (IL-2) receptor antibody may also be used with some steroid-sparing.[49,50] Rapamycin, an mTOR inhibitor and mostly used as the synthetic compound sirolimus, is structurally similar to tacrolimus, and prevents proliferation of T cells, but acts at a different stage of T-cell activation than either cyclosporine or tacrolimus. Rapamycin does not interfere with transcription and production of IL-2, rather it antagonizes the action of IL-2 on its receptor. It has the advantage that it is not nephrotoxic but can be hepatotoxic and may be synergistic with cyclosporine. It may cause proteinuria and increases serum triglyceride levels. It may cause hepatic artery thrombosis and delay wound healing and is thus not recommended in the early postoperative period.

Regular monitoring of the renal function is essential as renal-sparing regimens are more effective if started before irreversible renal dysfunction occurs.[51]

IL-2 antibodies such as dacluzimab and basiliximab, which selectively block IL-2 receptors on activated T cells, are particularly useful in children with renal impairment as lower doses of calcineurin inhibitors can be used.[52]

Tacrolimus is increasingly used as primary immunosuppression in pediatric transplantation in place of cyclosporine because of less hirsutism, soft tissue overgrowth, and gingival hyperplasia. Balanced against this is the neurotoxicity in the form of leukoencephalophathy, not infrequently seen in children.

Use of anti-CD25 monoclonal antibodies given before and during the first week of the transplant in conjunction with calcineurin inhibitors has reduced the incidence of acute rejection in the first three months by around 30%, but long-term graft survival is essentially the same as when these agents have not been used. The other polyclonal anti-lymphocyte immunoglobulins are rarely used but have been used with low dose calcineurin inhibitors in tolerance inducing techniques.

Postoperative care

Patients are monitored intensively postoperatively and usually require ventilation for a period of 24–48 hours. Liver ultrasound with color flow Doppler is performed frequently to confirm vascular patency and the absence of biliary dilatation. Liver biopsies are performed if indicated by increasing serum liver enzyme activity or by bilirubin levels, using the Menghini technique (Hepafix needle (Braun), diameter 1.4 mm), unless biliary dilatation is observed on ultrasonography. Biopsies are routinely assayed for viral and bacterial activity.

Diagnosis of rejection can be made on the basis of clinical, biochemical, and histologic changes and usually presents in the first few weeks after transplant with fever, malaise, a tender graft, and loose stools. The grade of rejection is assessed according to established histological criteria according to the Banff schema.[53]

Acute cellular rejection can usually be managed by either switching from cyclosporine to tacrolimus or maintaining adequate trough tacrolimus levels (10–15 ng/mL). If necessary, mycophenolate mofetil can be used instead of azathioprine. If there is ongoing rejection, pulsing with i.v. methylprednisone can be used; four doses of methylpredisnolone at 10 mg/kg for the first three doses on successive days and the fourth on the fifth day after commencing treatment. Monoclonal antibodies and antilymphocyte globulin are very rarely used for steroid-resistant rejection. Once rejection is under control and liver function tests have returned to normal, the tacrolimus dosage can be reduced to a maintenance dose, obtaining trough levels of around 5 ng/mL.

Immunosuppression naturally leads to susceptibility to bacterial, fungal, protozoal, and viral infections. Antibiotics are given as prophylaxis and according to culture and sensitivity of blood, sputum, and body fluid. In infants there is a low threshold for antifungal therapy with either amphotericin or fluconazole. Antiviral prophylaxis for CMV is advisable in all CMV naive recipients and when the donor is CMV IgG positive. There is some debate about the efficacy of prolonged ganciclovir or valganciclovir for EBV control.[54] Trimethoprim/sulfamethoxazole is routinely given for pneumocystis prophylaxis.

Anti-tuberculosis prophylaxis is given only if the reason for transplant is a reaction to anti-tuberculosis drugs with fulminant hepatic failure, where evidence of tuberculosis is found before surgery and if a close family contact has tuberculosis.

Ofloxacin, rifampicin, ethambutol, or pyrazidamide may be used in addition to isoniazid but very careful monitoring of liver function tests is required because all of these drugs may be hepatotoxic and, particularly rifampicin, may result in a decrease in the levels of cyclosporine or tacrolimus levels due to enzyme P450 induction with increased drug metabolism.

Acute postoperative hypertension is almost universal in pediatric transplantation and persists in 25% of recipients.[55] It is usually initially managed with nifedipine sublingually in conjunction with diuretic agents. Subsequently, long-acting oral calcium channel blockers or ACE inhibitors may be

given in appropriate dosage. Aspirin, 3 mg/kg, given on alternate days is used as prophylaxis against arterial thrombosis and a proton pump inhibitor is given for gastric mucosal protection.

Nutritional and vitamin supplementation should be commenced within 72 hours of surgery and may be supplemented by nasogastric feeding or parenteral nutrition in the early phase if there is a delay in restoration of bowel function. Phosphate and magnesium deficiency is common and requires replacement therapy in nearly all patients.

Surgical complications

Surgical complications may be reduced to an absolute minimum with meticulous technique.[56–58] These may present early and late. Biliary complications continue to be a significant problem with an overall incidence of between 10 and 20%, particularly in living related left lateral segment grafts.[59] A proactive management approach is taken with close monitoring of vascular patency using Doppler ultrasound scanning and CT or MR angiogram if there is any doubt. Radiological intervention techniques have been used successfully for later complications of biliary strictures and portal vein stenosis.

Medical follow-up and late complications

Most patients can be discharged from the intensive care unit within the first week after transplantation. The majority of infections can be prevented. However, should the patient require excessive immunosuppression for persistent rejection, almost inevitably they will develop some opportunistic infections.[60–74]

In this situation, not only must specific therapy be directed at the pathogen but also immunosuppression must be reduced. CMV and EBV is best monitored with quantitative polymerase chain reaction (PCR) measurement of the virus.

Post-transplantation lymphoproliferative disorder (PTLD) presents from the first few weeks after transplant to several years later, with a mean time of onset around nine months. Risk of PTLD relates to the intensity of immunosuppression (5–7% in liver transplant recipients) and pretransplant EBV status. Regular EBV PCR monitoring and appropriate reduction in immunosuppression reduces the risk. A typical presentation is initially with acute membranous tonsillitis and associated cervical lymphadenopathy, which is resistant to antibiotic therapy. However, the disease may be widespread and gastrointestinal and central nervous system involvement is common.

Management strategies include reduction of immunosuppression, which may require complete withdrawal along with chemotherapy, anti-CD20 monoclonal antibodies, and adoptive immunotherapy, particularly with the monoclonal PTLD.[75] Mortality varies from 20 to 70% or more. Prophylactic i.v. ganciclovir, given for a prolonged period (100 days), may be effective in preventing EBV activation, which is the promoter of PTLD in most cases.[54]

Hepatitis B infection has been a problem, particularly if hepatitis B IgG core antibody positive donors are used in the absence of prophylaxis where HBV in the graft occurs in up to 80% of cases. There is frequently progression to chronic hepatitis and cirrhosis although antiviral therapy using lamivudine along with hepatitis B immunoglobulin may be effective in controlling the virus, which is monitored with regular HBV DNA levels. Newer antivirals such as tenofovir and entecavir are not licensed for pediatric use.

Children are frequently hypertensive and require antihypertensive therapy for a period of time post-transplant. A degree of renal impairment is almost inevitable in those patients suffering from chronic liver disease with cholestasis. With the additional burden of the use of nephrotoxic immunosuppressive drugs such as cyclosporine and tacrolimus, many have significant impairment of renal function in the long term. The importance of renal sparing strategies in immunosuppression is becoming increasingly evident as 4–5% long-term survivors present with drug-induced renal failure requiring renal replacement therapy.[51]

Chronic rejection is an irreversible phenomenon, which is chiefly intrahepatic and ductular rather than a vascular phenomenon in contrast to other organ transplants. This is usually manifested by disruption of bile duct radicals with development of the vanishing bile duct syndrome. The incidence seems less frequent with tacrolimus-based immunosuppressive regimens as opposed to cyclosporine, where an incidence of up to 10% has been recorded. Late chronic rejection may also be associated with a vasculopathy affecting larger arteries.

RE-TRANSPLANTATION

Ten to 20% of patients may suffer graft failure at some time and need re-transplantation. Early indications may be primary nonfunction, early hepatic arterial thrombosis, severe drug-resistant acute rejection, and established chronic rejection. Early re-transplantation is technically a much less traumatic procedure than the original transplant, although the patient may be in a poorer condition. Outcome largely depends on the indication for re-transplantation and is quite good for technical causes but less satisfactory for rejection and infection. An increasingly poorer outcome can be expected after third and fourth re-transplants and the efficacy and ethics of these interventions are in question.

LONG-TERM SURVIVAL AND QUALITY OF LIFE

One-year survival of >95% is being achieved in the best centers with predicted 10-year survivals of around 70–75%.[76–80] Patients grafted for acute liver failure have done less well with a higher early death rate, usually associated with cerebral complications and multi-organ failure. Excellent quality of life can be achieved and most children are fully rehabilitated.

However, it is increasingly evident that prolonged cholestatic jaundice and malnutrition in infancy may have late

effects and despite good physical rehabilitation evidence of significant cognitive deficits, which present during early schooling as learning difficulties and attention deficit disorder, are common.[81]

Catch-up growth post-liver transplant improves if steroids are reduced, used on alternate days, or withdrawn.[82,83] However, steroid withdrawal comes with the risk of development of chronic rejection or *de novo* hepatitis.[84–86] As with any immunosuppressed patient, the incidence of neoplasia in a lifetime is greatly increased (12% skin and other malignancies).[87] Renal function impairment aggravated by hypertension and calcineurin and antibiotic toxicity is frequent with up to 25% developing chronic renal failure at ten years post-transplant.[88]

Fibrosis on histology is an increasingly recognized phenomenon which seems to be more related to factors at the time of the transplant (cold ischemic time, young age, donor:recipient weight ratio, use of partial grafts) rather than immunological or infective factors.[89]

At a workshop on long-term outcomes, the following factors were identified as requiring further research: risk factors associated with long-term immunosuppression complications; development of tolerance-inducing regimens; definition of biomarkers that reflect the level of clinical immunosuppression; development of instruments for the measurement of health wellness; identification of risk factors that impede growth and intellectual development before and after liver transplantation, and identification of barriers and facilitators that impact non-adherence and transition of care for adolescents.[90]

In the unusual indication of isolated liver transplant for short bowel and intestinal failure-associated liver disease (IFALD), liver transplantation is a lifesaving option. Revised criteria are proposed: progressive IFALD; 50 cm functional bowel in absence of the ileocecal valve (ICV) or 30 cm with ICV; 50% daily energy intake tolerated enterally for 4 weeks with satisfactory growth; and children with dysmotile bowel should be assessed for combined liver/bowel transplant unless the dysmotility is resolved and associated with minimal line infections. Non-transplant surgery may be required to facilitate full adaptation but a >50% long-term survival can be expected.[25]

ADOLESCENCE

Non-adherence in adolescent transplant recipients (~20%) is a particular concern.[91,92] In addition to coping with the usual issues of autonomy, peer pressure with regard to alcohol, recreational drugs, and sex, the transplant teenager has to cope with the cosmetic side effects of immunosuppression, regular medical monitoring, and strict adherence to drug regimens. These issues often occur at the time of transfer to an adult unit. It is important to actively involve teenagers in the decision making, discuss issues of sexuality, risks of pregnancy, and appropriate contraception. A planned transfer to an adult program is essential as the risk of noncompliance and graft loss is great during this period. Use of mobile phone text messaging has been shown in one study to reduce non-adherence among teenagers.[93]

Transplantation in infancy appears to result in a reduced incidence of non-adherence in adolescence compared with later transplantation.

CONCLUSION

Careful planning, extensive preparation of personnel and a broad base of skills along with good teamwork between health professionals are required for the development of a successful pediatric transplant program. Surgical technique, anesthetic skills, and medical care of the highest order are essential. Size of the recipient is only important in so far as making the graft fit the recipient abdomen but long-term outcomes are excellent.

A patient with a liver transplant is a patient for life and requires complete commitment from the transplant medical and surgical team, which cannot be abrogated after discharge from hospital.

The need for pediatric liver transplants has been assessed at approximately 1–2 children per million per year. Thus transplant activity should be concentrated in specific centers with pediatric surgical and medical expertise. The shortage of donor organs will continue and future efforts must be focused on maximum use of cadaver donors and increasing living related donation. No child with end stage liver disease should be denied the opportunity of receiving appropriate treatment.

These challenges must be met to offer any infant or child requiring liver replacement a chance of a life. The ultimate aim is to restore the child to normal health such that he/she can grow up into a productive healthy adult who can make his/her contribution to society and develop all of his/her human potential.

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PART II

HEAD AND NECK

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24

Choanal atresia

STEPHEN M KIERAN AND JOHN D RUSSELL

INTRODUCTION

Choanal atresia is a congenital abnormality in which the nasal cavity does not open into the nasopharynx (Fig. 24.1). The malformation was first described in 1755 by Roederer.[1] The condition may be either unilateral or bilateral. Bilateral choanal atresia presents acutely in the neonatal period with respiratory distress, in view of the fact that the neonate lacks the ability to mouth breathe. A unilateral defect may go undetected for months or even years prior to diagnosis. Treatment involves surgical repair of the defect and has evolved from transmaxillary, transeptal, transpalatine, and sublabial intransal approaches to modern endoscopic techniques. Despite the acceptance of the endoscopic approach as the current gold standard, controversies still exist in how to best manage patients with this condition, particularly regarding the use of adjuvant topical medications following the surgical repair and the use and duration of postoperative stenting.[2]

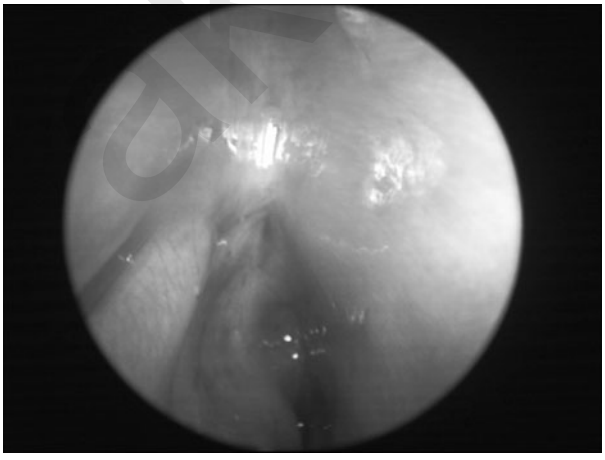

Figure 24.1 Endoscopic view of a right sided choanal atresia as viewed from the nose.

EPIDEMIOLOGY

Choanal atresia occurs in one of 5000–8000 live births and is twice as common in females as in males.[3] Unilateral choanal atresia is more common than bilateral malformations and accounts for 65–75% of cases. Approximately 50% of all patients have other associated congenital abnormalities, which rises to approximately 75% in patients with bilateral disease.[4] The atretic plate may be either mixed bony or membranous in nature. A 90% rate of bony stenosis and 10% membranous stenosis rate was classically reported, but modern imaging suggests a mixed bony/membranous obstruction in 70% and a pure bony obstruction in 30%.[5] Associated syndromes include CHARGE, Crouzon, Pfeiffer, Antley-Bixler, Marshall-Smith, Schinzel-Giedion, and Treacher Collins.

EMBRYOLOGY AND ANATOMIC CONSIDERATIONS

The nasal placodes derive from the ectoderm and appear during the third week of gestation. Around the fifth week, these placodes invaginate into pits that extend posteriorly to form the nasal cavity, which is separated from the oral cavity by a thin nasobuccal membrane. This eventually ruptures at approximately 6 weeks forming the posterior choanae.

In choanal atresia, the abnormality is complex, representing more than just an obstruction membrane across the posterior choanae. The lateral nasal wall and medial pterygoid plates form part of the obstruction and need to be addressed during the surgical repair.[6] The boundaries of the atretic plate are composed of the undersurface of the sphenoid body superiorly, the medial pterygoid laterally, the vomer medially, and the horizontal portion of the palatine bone inferiorly.

A number of embryological theories as to the development of choanal atresia have been proposed; persistence of the buccopharyngeal membrane; failure of perforation of the

nasoubuccal membrane of Hochstetter; or more recently misdirection of neural crest migration.[7] Choanal atresia has also been associated with abnormalities of vitamin A metabolism and maternal use of thionamides (methimizole or carbimazole) during pregnancy.[1]

The CHARGE association (Coloboma, Heard defect, Atresia Choanae, Retarded growth, Genital hyoplasia, Ear anomalies) is associated with choanal atresia in approximately 30% of cases.[8] All patients diagnosed with choanal atresia should have a systematic examination for other features of the CHARGE association.

CLINICAL FEATURES

Clinical presentation depends on whether the malformation is unilateral or bilateral and whether other congenital abnormalities are present. Unilateral atresia may be picked up in the newborn period during routine nasal catheter screening. However, if the catheter rolls up in the nasal cavity, choanal atresia may not be diagnosed until later when the child presents with unilateral nasal obstruction (no misting of mirror) and an associated thick unilateral foul smelling nasal discharge.

Bilateral choanal atresia presents in the neonatal period with respiratory distress, since neonates lack the capacity for mouth breathing.[9,10] The infant presents with airway obstruction and paradoxical cyanosis (the infant turns pink when crying as they breathe through an open mouth). Examination reveals no misting of a mirror placed in front of the nares and failure to pass a nasal catheter. The diagnosis is usually confirmed using a fiberoptic nasendoscope, which after suctioning of mucous, reveals the atretic plate at the posterior choanae. Acute airway stabilization can require an oral airway, a McGovern nipple (a nipple from a feeding bottle with the end opened to allow respiration), or even intubation.

RADIOLOGICAL INVESTIGATIONS

Traditional plain radiography in the supine position with the nasal cavity filled with radiopaque contrast has been replaced by computed tomography (CT). CT of the paranasal sinuses and skull base is recognized as the investigation of choice, but is not necessary until after the patient has had their airway stabilized. Thin section (1–2 mm) axial images provide the best view of the obstruction, but coronal reconstructions should also be provided to identify intraoperative landmarks. Ideally, the nasal cavity should be suctioned prior to the scan as thick mucus can be hard to differentiate from a membranous atretic plate.[5] Imaging provides details as to the nature (bony versus membranous) and thickness of the obstructing segment.[11,12] Imaging will also differentiate choanal atresia from other conditions that present with bilateral nasal obstruction such as pyriform aperture stenosis and bilateral nasolacrimal duct cysts. In unilateral cases, CT again confirms the diagnosis as well as differentiating the condition from others that make up the differential diagnosis of unilateral nasal obstruction; nasal foreign body, large nasal polyp, or nasal tumor.

MANAGEMENT

Infants with bilateral choanal atresia will require airway stabilization with at least an oropharyngeal airway as outlined above. Such devices need to be carefully kept in place and an orogastric tube passed to facilitate feeding until definitive surgical repair can be attempted. Surgical repair should be performed early (even in the first week of life) in patients with bilateral atresia. The only contraindication being medical ones associated with other congenital abnormalities (i.e. cardiac abnormalities in those patients with the CHARGE association). Those with unilateral atresia, however, can generally wait until one year of age, when the risk of general anesthetic has diminished. Occasionally, patients with unilateral atresia have significant airway difficulties and will require earlier intervention.

A number of surgical techniques have been described since the first reported repair of choanal atresia by Carl Emmert in 1854. Transnasal puncture of the atretic plate using urethral sounds was initially performed blindly.[13] However, this technique has now largely been superseded by endoscopic resection using powered instruments.[1]

Endoscopic resection

This approach is preferred by the authors as it allows excellent visualization of the operative field. A tonsil (Boyle–Davis) mouth gag is inserted and a suture is placed through the uvula and clipped to provide retraction of the soft palate. A 120° 4 mm endoscope is passed through the mouth into the nasopharynx and a view of the poster surface of the obstructed choanae obtained (Fig. 24.2). The nasal cavity is decongested with 1:10 000 adrenaline patties and the atretic plate injected with 1% lignocaine with 1:200 000 adrenaline. The atretic plate is perforated with a small urethral sound using the 120° telescope which is passed

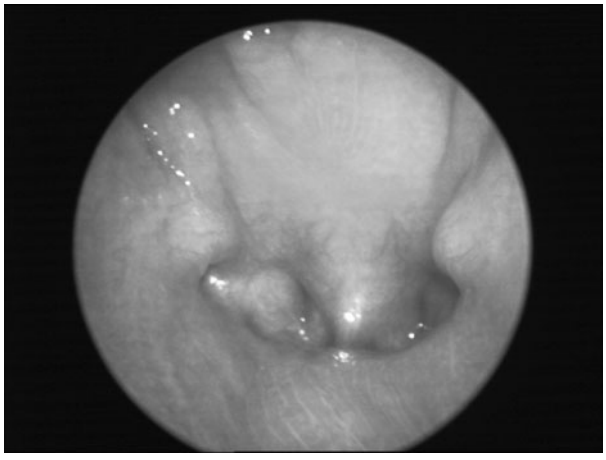

Figure 24.2 Endoscopic view of choanal atresia from the nasopharynx as viewed through a 120° telescope.

through the mouth to view the atretic plate at the time of perforation (Fig. 24.3). The sound is passed to the medial and inferior aspect of the atretic plate to avoid inadvertent injury to the skull base or sphenoid. Even with thick atretic plates, the sound can usually be passed without much force being required. Progressively larger sounds are introduced until the sound can no longer pass through the anterior choana. The drill is then inserted through the nose until it reaches the nasopharynx. We use a specialized drill (Medtronic) which has a protective sheath over the shaft preventing trauma to the nasal cavity. The drilling is performed medially over the vomer and laterally over the medal pterygoid plates. The posterior aspect of the vomer is then removed using a back biting forceps into the nasopharynx and removing the posterior half of the vomer. This creates a common cavity posteriorly which minimizes the chance of restenosis. We insert stents for 6 weeks. An oval shape is cut from the centre of an endotracheal tube. The tube is then inserted in the right and left nasal cavities, through the posterior choanae, and the cut oval section placed over the columella to allow nasal breathing. These are secured in place using a suture. Postoperatively, the stents are kept patent with saline drops. Beclamethasone drops, although unproven, are applied to the nasal cavities to minimize edema. The child is brought back to the operating theatre 6 weeks postoperatively and the stents are removed. Any granulations present are removed at this point with a microdebrider.

Multiple procedures for further microdebridement and dilitations are often required with one large series reporting an average of 4.9 procedures.[14] A number of variations of the endoscopic technique are reported,[1] the most common variation from our technique is a complete transnasal approach using the 0° 4 mm (or 2.7 mm in neonates) telescopes. We find the sole use of the transnasal approach is associated with difficulty using two instruments in the same nasal cavity, particularly with limited space available in the newborn. Similarly, mucosal sparing flaps are advocated by some surgeons in an attempt to improve re-epithelialization.[15,16] However, the authors experience is that these flaps are difficult to perform in the newborn's nose and are generally not viable at the end of the procedure. CT-based image guidance systems are now widely used in pediatric endoscopic nasal surgery.[17] While not mandatory, we advocate its use in this procedure if available.

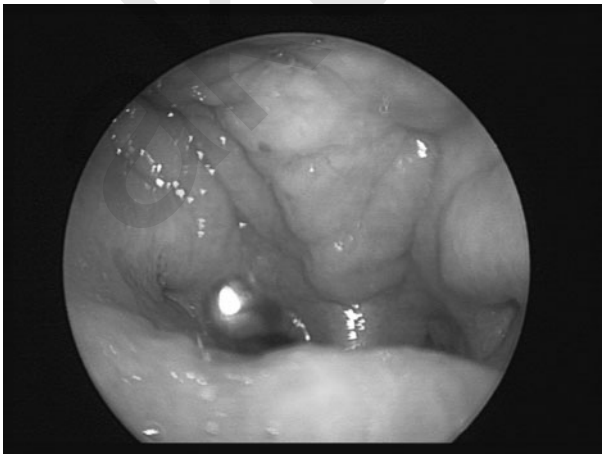

Figure 24.3 Endoscopic view of urethral sound being passed through an atretic plate as viewed from the nasopharynx using a 120° telescope.

Transpalatal resection

The transpalatal approach was the first approach to the choanal abnormality that provided good exposure of the operative field. Alongside simple blind dilatation it remained the mainstay of surgical repair until the advent of endoscopic techniques. A U-shaped incision on the hard palate is made 5 mm from the dental arch. A posteriorly based superiosteal flap is raised to gain access to the nasopharynx. The inferior vomer is encountered and removed prior to drilling of the lateral atretic plate. This technique remains useful in patients with a small nasopharynx and low skull base, such as infants with Treacher Collins syndrome or where an endoscopic approach has failed. The transpalatal approach is associated with a higher complication rate than endoscopic techniques. Potential complications include postoperative pain, palatal fistula, and reduced midface face growth leading to a high arched palate and associated dental malocclusion which occurs in approximately 50% of patients.[18]

ADJUVANTS TO SURGERY

Mitomycin C

Mitomycin C is an aminoglycoside which is produced by the bacteria stremptomyces, and crosslinks DNA inducing apoptosis. When applied to healing tissue, it has an antiproliferative effect that inhibits fibroblast growth and proliferation. Mitomycin C is widely used in laryngeal and ophthalmic surgery to prevent scar formation and was thus proposed as an agent to reduce restenosis following choanal atresia resection. However, several small studies have not shown mitomycin C to be effective in improving long-term outcomes following choanal atresia repair and there are concerns about using a potentially oncongenic medication in children.[19] Therefore, this is not routinely used following initial choanal atresia repair.

Stents

The use of postoperative nasal stents is traditional yet controversial. Despite the absence of evidence of efficacy in reducing restenosis,[19] the majority of pediatric otolaryngologists employ stents in the postoperative period.[20] However, recent reports are emerging that suggest that stents are not always necessary after endoscopic surgery and there seems to be a current trend away from their use, particularly in older patients.[21–23] However, most surgeons still use stents in those

patients who have high restenosis rates such as neonates. Stents are not without potential side effects with necrosis of the external nose, septum, and palate reported. Furthermore, stents have a tendency to become blocked with secretions, requiring lavage and suctioning on a routine basis by both the parents and nursing staff. When stents are used, the optimum duration of use is unclear with the literature reporting a range of 24 hours to 12 weeks.[1]

OUTCOMES

The primary outcome measure is restenosis as evidenced by a need for reoperation. Reported revision rates for endoscopic resection vary from 0 to 36%.[1,7] Restenosis appears more likely to be required in patients who undergo surgery in the neonatal period for bilateral disease and suffer from gastro-oesophageal reflux. Favorable outcomes may be predicted by the absence of associated facial anomalies, higher weight at the time of surgery (>2.3 kg), and larger stent size.[19,24] One long-term study has demonstrated moderate hyposmia in adults who underwent bilateral choanal atresia repair as a child.[25]

A considerable array of surgical techniques (including adjuvant therapies) exist for the management of choanal atresia in the newborn. To date, no randomized control trials exist to determine optimum treatment protocols, even for the more controversial questions such as the postoperative use of stents. Unfortunately, due to overall rarity of the condition, this absence of evidence is likely to remain unchanged and management guidelines will continue to be based on personal reports and case series.

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25

Pierre Robin Sequence

UDO ROLLE AND ROBERT SADER

INTRODUCTION

Pierre Robin Sequence (PRS) is still considered a 'surgical' cause of neonatal airway obstruction and some of the affected patients truly require surgical procedures to achieve appropriate airway and nutritional management. The various features of clinical presentation and the respective conservative or surgical treatment of Pierre Robin Syndrome will be displayed within the following chapter.

HISTORY

The condition is named after the French dental surgeon Pierre Robin (1867–1950). He described micrognathia, glossoptosis, and respiratory distress in his first paper (1923).[1] In a later publication, Pierre Robin added cleft palate to the list of symptoms.[2] There had been previous reports describing the triad of micrognathia, cleft palate, and glossoptosis resulting in dyspnoea and cyanosis.[3–5] Pierre Robin introduced the term 'glossoptosis' to describe the tendency for the tongue to fall back and cause pharyngeal obstruction.

The condition was traditionally called 'Pierre Robin Syndrome'. After 1975, a series of nosologic changes took place, including Robin anomalad,[6] Robin malformation complex,[7] and then Robin sequence.[8]

The term 'sequence' is used to reflect the hypothesis that the three cardinal symptoms develop sequentially, though it is still not proven what the correct sequence is. The traditional hypothesis states that a mandibular anomaly leads to an anomalous palate (cleft palate) and subsequent airway obstruction.[9] Even if this concept seems to be supported by animal experiments,[10] actual functional therapy results also support the opposite hypothesis that a malpositioned tongue leads to altered mandibular growing patterns.[11–13]

ETIOLOGY, PATHOPHYSIOLOGY, INCIDENCE

The etiological hypothesis is as follows: hypoplasia or abnormal development of the mandible around 7–11 weeks gestational age displaces the tongue high within the nasopharynx. The tongue, unable to descend because of either the lack of mandibular growth or severe retropositioning of the mandible, obstructs the palatal shelves from fusing. The cause of the growth insult to the mandible is uncertain and, presumably, is of heterogeneous etiology. Reported possible causes included: (1) positional or mechanical deformation, as in oligohydramnios, which can be caused by a number of factors; (2) intrinsic mandibular hypoplasia, as in numerous congenital malformation syndromes; (3) neurological or neuromuscular abnormalities, such as myotonic dystrophy or arthrogryposis; and (4) connective tissue disorders, such as Larsen syndrome.

In all these cases, sequential events would lead to the changes seen in Pierre Robin Sequence. A logical assumption is that a variety of factors may lead to persistent mandibular hypoplasia with the resulting postnatal manifestations.[11,14] Since mandibular abnormalities might have numerous causes, PRS cannot be regarded as a specific disease entity. A differentiation should be made between isolated PRS and patients in which PRS is part of a recognized syndrome, part of a complex of multiple anomalies, or part of an unrecognized syndrome.

The proportion of number of cases with isolated PRS varies in different studies from 40 to 74%.[6,15] There are more cases in females, with a male:female ratio of 3:2,[16] which is equal to the ratio comparing male and female children with cleft palate.[17]

The most common PRS syndromes are Stickler syndrome (20–25% of all cases) and velocardiofacial syndrome (15% of all cases). Nager syndrome, spondyloepiphyseal dysplasia congenital, and other recognized syndromes comprise the rest of the syndromic PRS cases (Fig. 25.1).

The severity and persistence of the clinical pathology is probably related to the nature of the insult, as illustrated by the difference in outcome between 'syndromic' and 'non-syndromic' micrognathia.[18–20]

The reported incidence of PRS varies from one in 2000 to one in 30 000 live births.[21,22] The reported differences in the prevalence of PRS at birth are due to the variations of the case definitions.

CLINICAL FEATURES

PRS consists of three essential components:

1. Micrognathia or retrognathia
2. Glossoptosis, possibly accompanied by airway obstruction
3. Cleft palate (usually U-shaped, but V-shape also possible).

It should be mentioned that cleft palate does not have a complete penetrance and can only be seen in about 80% of the Pierre Robin patients.[9,16]

The airway obstruction in PRS requires early and proper management, since it may lead to hypoxia, cor pulmonale, failure to thrive, and cerebral impairment. Generally, syndromic cases are more severe and have worse prognosis than non-syndromic PRS.

Generally, it is expected that patients with non-syndromic PRS will show catch-up growth of the mandible.

AIRWAY MANAGEMENT

Airway obstruction due to glossoptosis can occur at or immediately after birth, but may take much longer (up to 3 weeks) to become apparent.[23] Most neonates present with an isolated PRS and not one of the syndromes, which typically present more significant clinical problems, i.e. airway and feeding difficulties. The airway obstruction in PRS is due to the narrowing or complete obstruction of the pharyngeal space by the posteriorly displaced tongue. This airway obstruction could be intermittent. Most of the complications and unfavorable outcomes of PRS are directly related to delayed or inappropriate airway management.[24–26] Therefore, special vigilance is required, even in patients with only minor defects. Typical clinical signs of upper airway obstruction are increased respiratory effort, stridor, subcostal retractions, and cyanotic or apneic spells. In an otherwise asymptomatic child, choking attacks, cyanosis during feeding, or repeated aspiration events may be due to intermittent airway problems.

Every child with symptoms of airway obstruction should be nursed prone with the head to one side. The head should be maintained in a level position to prevent either glossoptosis or gastroesophageal reflux. Usually, affected children can be successfully fed by mouth in this position.

Persistence of airway difficulties requires further intervention.

Nasopharyngeal tube

The nasopharyngeal airway bypasses the oral pharynx and the obstruction due to the glossoptosis. A regular Portex endotracheal tube (Portex., Wilmington, MA, USA), cut to the appropriate length, is inserted by nasal route and securely strapped in place. The nasopharyngeal airway is a very effective, temporary form of airway management within the intensive care unit (ICU). Usually, patients with nasopharyngeal tubes in place would not be sent home, as dislodgement of the tube can result in an acute airway obstruction.

Endotracheal tube

Endotracheal intubation serves as a short-term support if the nasopharyngeal airway is not successful or during resuscitation or anaesthesia.

Tongue–lip adhesion/glossopexy

Essentially, in this technique, the tongue is sutured to the lower lip. After the child has demonstrated catch-up growth, the tongue–lip adhesion can be released. The efficacy of the tongue–lip adhesion technique remains a controversial issue.

Glossopexy consists of suturing the tongue base to the mandible. Due to the relatively soft consistency of the mandible, a permanent glossopexy is difficult to achieve, therefore this technique is also controversial.

Tracheostomy

Tracheostomy should be avoided if possible, and it should only be employed if all other techniques fail. Tracheostomy should be performed by an appropriately skilled surgeon who is familiar with infantile airways. Tracheostomy requires closed monitoring but enables oral feeding. Tracheostomy could be removed after the child's airway obstruction has resolved, which usually happens within the first year of life.

Distraction osteogenesis of the mandible

Distraction osteogenesis comprises a relatively new technique. The mandible needs to be cut near the angle of the mandible on both sides. A specialized mechanical device distracts these two portions every day by approximately 1.5–2 mm. Using this technique, the mandible gradually elongates over a period of 2–3 weeks. Timing of performing a mandibular distraction can be in newborns to prevent tracheostomy or at a later stage to remove a tracheostomy tube.

Distraction osteogenesis has been carried out only during the last 5–10 years. Therefore, long-term follow-up results of this promising technique are not available. Nevertheless, the distraction osteogenesis technique should be reserved for severe cases of non-syndromic Pierre Robin and syndromic PRS, since in most cases of non-syndromic PRS physiologic catch-up growth of the mandible occurs.

Tongue positioning and stimulation plate

During the last decade, a new, nonsurgical technique was developed by orthodontists that guarantees, in most cases, a free airway space and treats the hypoplastic mandible causally. Immediately, a palatal plate is produced, similar to the feeding plate for cleft palate newborns, but with a dorsal spur that goes shortly to the epiglottis (Figs 25.2–25.4). Sometimes endoscopic control is necessary during positioning to avoid irritation of the epiglottis. To accomplish this, the tongue is positioned anteriorly and the airway is kept

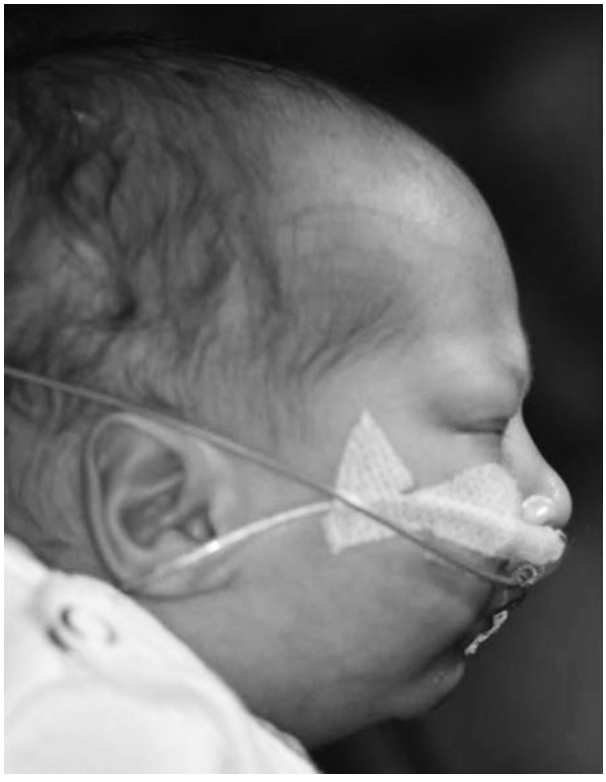


Figure 25.1 Typical Pierre Robin Sequence facies with receding chin.

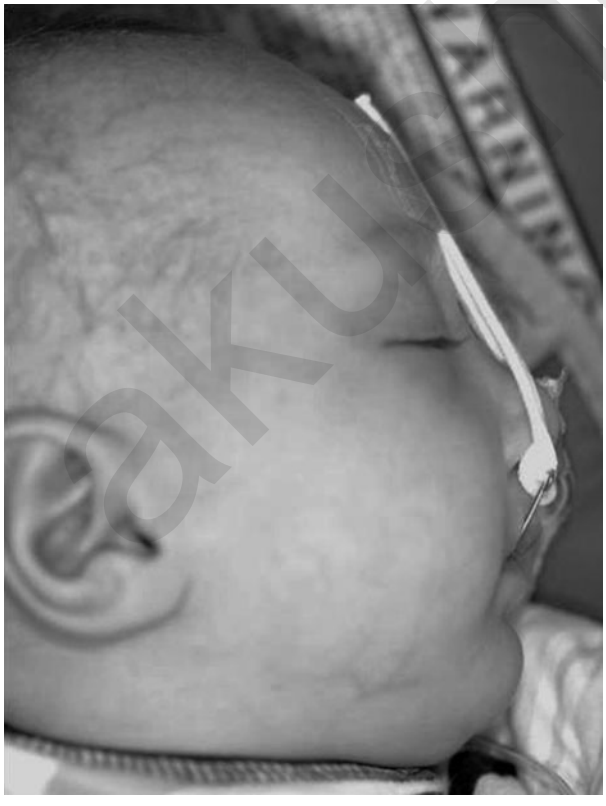


Figure 25.2 Pierre Robin Sequence patient with stimulation plate.

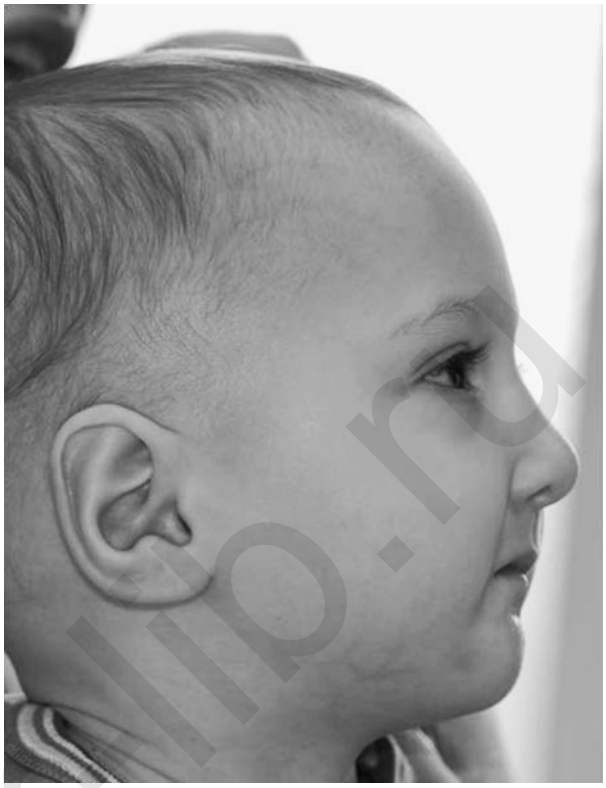
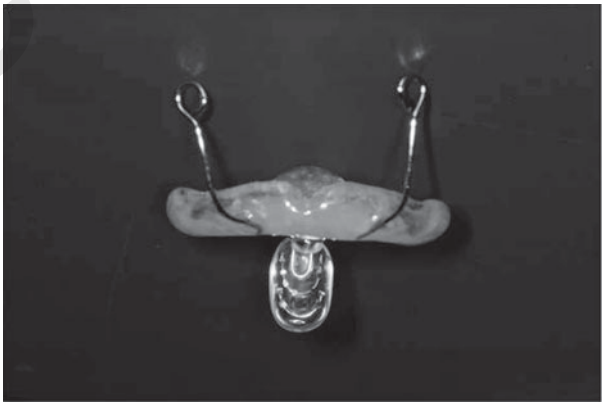
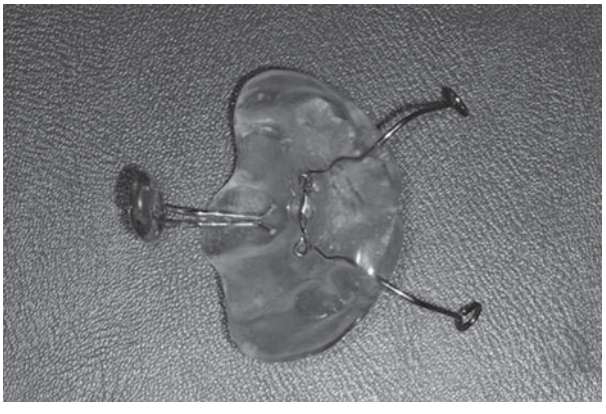


Figure 25.3 Result of stimulation plate after 15 months.



(a)



(b)

Figure 25.4 (a and b) Stimulation plate with dorsal spur.

patent. Moreover, via functional stimulation of the tongue, the mandible starts to grow during the following months and will be quite normal when the palatal closure is performed at the age of about six months. Feeding is also supported, but problems remain in some cases.[13,27]

NUTRITIONAL MANAGEMENT

Most of the children with PRS have feeding difficulties. Initial treatment consists of bottle-feeding in a prone position with the head slightly elevated. This method of feeding is appropriate in children with catch-up growth of the mandible.

If this is not satisfactory, gavage or feeding tubes can be used temporarily to improve nutrition. If the feeding is still not successful, the child might need a gastrostomy, which could be removed after gaining the ability to be feed orally.

It has been shown clearly that infants with PRS require adequate caloric intake. It is important to achieve the maximum growth rate of the mandible since the resolution of the airway problems is directly related to mandibular growth. Only recently has increased work of breathing been appreciated as an important component of calorie consumption. It may be necessary to provide these children with several times the normal caloric requirement of an infant to compensate for up to a ten-fold increase in respiratory work.[28] Indeed, failure to gain weight despite maximum nutritional intake should suggest the need for more aggressive airway management.[29] The availability of total parenteral nutrition should prevent any instances of failure to thrive, but it is rarely needed if other aspects of the condition are managed correctly.

CLEFT PALATE

Cleft palate is present in at least 80% of patients with PRS. Cleft palates are typically repaired while patients are infants. A palatal plate can be used in patients with a cleft of the hard palate to improve feeding. The plate also corrects the tongue position by moving it anteriorly. In patients with a cleft of the soft palate alone, a palatal plate has no positive effect on feeding, but it can improve the tongue position and stimulate mandibular growth. To enhance this effect, the plate can be modified by an anterior stimulus according to Castillo-Morales.[30]

Surgical protocols differ from center to center, and cleft closure is performed not only by different techniques (i.e. Langenbeck, Furlow, Wardill), but also at different ages, ranging from four to 36 months.

It is currently assumed that early surgery will provide a better chance of normal palatal function and speech development.

MICROGNATHIA/RETROGNATHIA

The first described functional therapy for micrognathia was the use of the orthodontic palatal plate to achieve growth stimulation of the mandible. It was not clear until today whether the growth potential of the mandible after this stimulation is sufficient to achieve the normal dimensions. However, it has been shown, based on physical examinations until age five, that the mandible can barely regain its growth in relation to a normal population.[31] A retrospective longitudinal study by cephalograms and lateral photographs of American patients with PRS and cleft of the soft palate showed that the mandible achieved only partial catch-up growth and, in adults, a smaller maxilla, mandible, and a narrow respiratory airway space persisted.[32] Studies in the Finnish population showed the same result.[33–35] An increased mandibular growth was seen during the first two years of life, but normal craniofacial dimensions were never achieved. At the young adult stage, even if the patient's profile appeared less retrognathic due to masking by the overlying soft tissues or the patient's teeth showed neutral occlusion, cephalograms revealed retrognathia and caudal-dorsal rotation of the mandible. Thus, it seems in accordance with today's knowledge that the microgenia in PRS can be balanced only partially by growth processes. Frequently, orthodontic therapy is necessary in childhood. In severe cases, surgical advancement of the mandible combined with a genioplasty can be beneficial, as well.

SKELETAL ANOMALIES

Around 11–21% of children with PRS have limb defects.[17,36] Common anomalies are talipes equinovarus, syndactyly, short, or absent digits and hypoplastic long bones. Occipito-atlanto-axial instability has also been described, emphasizing the need for very experienced clinicians to undertake the intubation of such patients. Orthopedic and radiological consultation should be sought in children with suspected skeletal problems. Rare neuromuscular defects can also occur, resulting in a tendency for glossoptosis to persist despite mandibular growth.[11]

EAR PROBLEMS

Malformations of the ear have a frequency of 10.5% and consist of defects in the auditory capacity and anomalies of the shape of the ear. One main concern is the frequently recurring infections of the middle ear, which also occur in patients with a cleft palate and are based on disturbed function of the Eustachian tube. Therefore, a hearing screening has to be performed at birth. At a later date, control of the middle ear tube function has to be achieved and grommets placed, if necessary.[37,38]

CARDIOVASCULAR ANOMALIES

Intrinsic cardiac defects are found in up to 20% of infants with PRS.[17,36,39] Septal defects are common, but more complex lesions can also occur. A thorough cardiovascular

examination should be performed in PRS babies, particularly since airway difficulties may aggravate the cardiac status.[40]

OCULAR ANOMALIES

Retinal detachment and micrognathia occur as part of Stickler syndrome,[41] but 10% of infants with non-syndromic PRS also have eye defects, such as strabismus, ptosis, and microphthalmia. More severe defects, such as cataract and congenital glaucoma, have also been reported, and ophthalmologic consultation is recommended in all cases.[17,36,42]

NASAL OBSTRUCTION

Choanal atresia is a rare accompaniment of PRS,[43] but it may complicate the respiratory difficulties in small infants who do not mouth-breathe. It is important to ensure nasal patency, especially if one nostril is to be utilized for a nasogastric feeding tube. Choanal obstruction by itself can lead to glossoptosis, with consequences identical to those of PRS.[44]

COMPLICATIONS AND OUTCOME

In isolated PRS, the long-term outcome is directly related to the quality of the management at the onset of symptoms. With adequate nutrition, mandibular growth will achieve normal or near-normal proportions, and the glossoptosis will resolve.[14,45,46] One study has suggested that there is no significant difference in proportional mandibular growth during the first year of life between PRS infants and controls[46] but, in the majority of affected infants, symptoms are relieved within a few months. Airway protection during this period is vital. The previously documented high incidence of mental retardation in PRS patients was almost certainly due to unrecognized episodes of hypoxia, and with good airway management this complication is uncommon.[17,36]

Undiagnosed hypoxia may also lead to pulmonary vasoconstriction, with resultant pulmonary hypertension and cor pulmonale.[40] Some instances of sudden death in PRS were likely due to this problem. The presence of cardiomegaly on a chest x-ray should alert the physician to the possibility that hypoxic episodes have been overlooked, and appropriate steps should be taken immediately.

Although airway patency improves with growth, there remains a potential for obstruction, particularly after invasive procedures such as intubation or cleft palate repair.[47] In some children, obstruction may occur during sleep, causing occasional apnea with potentially hazardous consequences.[44,48,49] A degree of mandibular hypoplasia may persist for several years, resulting in malocclusion and the need for dental treatment.[50,51]

The overall mortality rate in infants with PRS is approximately 25%. The majority of deaths (70%) occur in children with associated anomalies, particularly those with cardiac defects or an underlying syndrome.[17,36,51] These facts must be considered when counseling parents of affected children. With good medical and nursing care, the prognosis for children with isolated PRS should be excellent.[52]

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26

Macroglossia

GEORGE G YOUNGSON

INTRODUCTION

Macroglossia (primary form) is defined as a resting tongue which protrudes beyond the teeth, or in the case of the neonate, the alveolar ridge.[1] Pseudo-macroglossia arises when the tongue itself is normal, but relative protrusion occurs because of a small mandible, as is seen in Down syndrome or in Pierre–Robin syndrome (see Chapter 25, Pierre Robin Sequence).[2]

ETIOLOGY

The causes of primary macroglossia include hypothyroidism, lymphangioma, hemangioma, idiopathic hyperplasia, and chromosomal abnormalities. Macroglossia is one of the most constant features of the Beckwith–Wiedemann syndrome, which is characterized by an omphalocele or umbilical hernia, with associated visceromegaly, somatic gigantism, or hemi-hypertrophy and hypoglycemia.[3] When displaced because of adjacent pathology such as cystic hygroma, cysts in the lingual thyroglossal duct, neurofibromatosis, or tumors such as rhabdomyosarcoma, then the term secondary macroglossia can be used. Heterotopic or ectopic tissue will rarely contribute to enlargement and intraoral and intralingual enteric duplication cysts have been detected *in utero*.[4–6] The differential diagnosis of such intralingual anomalies also includes dermoid cyst, hemangioma, and ranula.

PATHOLOGY

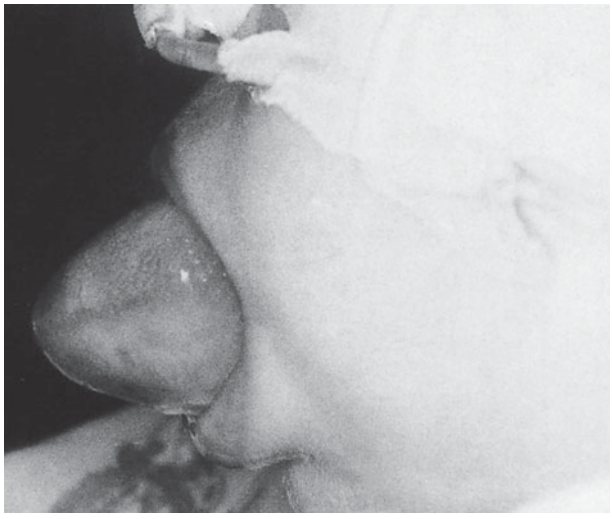
The histological features depend upon the underlying disorder. In addition to the conditions mentioned above, macroglossia can also be found in the triad of intrauterine growth retardation, transient diabetes mellitus, and macroglossia.[7] It is also seen in a number of syndromes including Behmel, Hurlers, Laband, and Tollner syndrome.

PRESENTATION

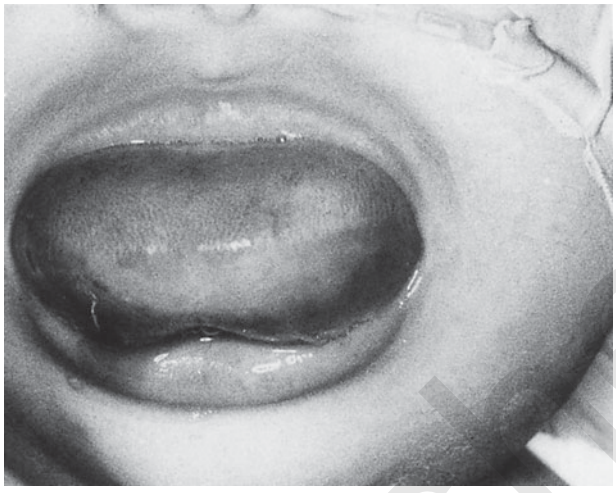
Lymphangioma is the most common cause of macroglossia to present in the neonatal period (Fig. 26.1a,b) and prenatal diagnosis by ultrasound is possible when associated with Beckwith–Wiedemann syndrome[8] and some of the intraoral cystic lesions discussed above. The clinical presentation includes noisy breathing and drooling, as well as the obvious physical features and, when difficulties in feeding occur, then failure to thrive and poor weight gain develop. Moreover, when lymphangioma is the cause, verrucous lesions may appear on the surface and these can ulcerate and exude a serous discharge.

If unrecognized or untreated in the neonatal period, the lesion may become more problematic in infancy or later in childhood when it may present with minor trauma, for example a lingual lymphangioma. This can then result in intralesional hemorrhage and/or sepsis (usually cellulitis from group B hemolytic *Streptococcus*). In this event, abrupt enlargement may compromise the airway and produce a life-threatening emergency necessitating tracheostomy and gastrostomy until definitive tongue reduction can be carried out (Fig. 26.2).

If treatment is inappropriately delayed, protracted dental defects develop including prognathism, anterior open bite, and an increased angle between the ramus and body of mandible.[9] Speech defects occur and articulation is subsequently defective, especially expression of consonants which are precluded by inadequate tongue movement as a consequence of the increased bulk in a limited cavity. Regression of macroglossia is not a regular feature when due to lymphangioma and a conservative approach to the lesion has no merit.



(a)



(b)

Figure 26.1 (a, b) Lymphangioma of the tongue occluding the oral cavity in a 4-week-old neonate.

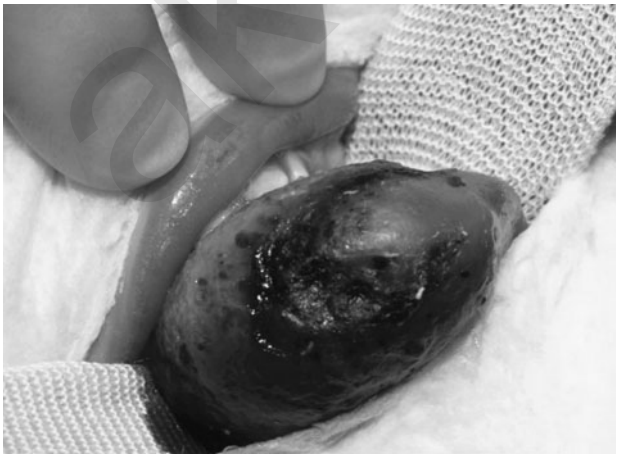


Figure 26.2 Intralesional hemorrhage into a lingual lymphangioma producing respiratory obstruction.

DIAGNOSIS

Investigation, following thorough physical examination for secondary causes of macroglossia, comprises thyroid function testing, echocardiography, and karyotype analysis. Magnetic resonance imaging to detail the extent of tongue involvement is indicated, particularly when the volume of lingual tissue affected is not clinically apparent.

MANAGEMENT

Preoperative

Multidisciplinary involvement is, as ever, helpful, with speech therapists, dieticians, and pediatric dentists valuable contributors to patient and parental management. If airway occlusion with associated respiratory distress exists, then airway management requires involvement of anesthetists/intensivists. Biopsy is rarely indicated with histology becoming available on the resected specimen. However, needle aspiration of intralingual cystic lesions may be a useful temporizing procedure,[5] but requires confident exclusion of vascular anomalies by pre- or postnatal imaging.

When the tongue is particularly large, nursing the infant in the lateral or prone position assists in airway management and skin care, especially if drooling is a prominent feature. In cases of Beckwith–Wiedemann syndrome, the tongue is seldom grossly enlarged and treatment must be seen in the context of the care requirements of the infant in relation to the other features of this condition. Similarly, surgical intervention is inappropriate if hypothyroidism is the primary diagnosis. However, massive enlargement may precipitate the need for early intervention and the challenge of anesthesia and endotracheal intubation point towards the need for tracheostomy and close collaboration with a pediatric otolaryngologist.

Alternatives to reduction glossectomy include intravascular photocoagulation[10] and embolism of vascular tongue anomalies,[11] but early surgery (preferably before seven months of age)[12] confers optimal opportunity for rehabilitation of tongue movement and avoiding complications, such as glossitis, hemorrhage, and secondary speech and maxillofacial abnormalities. Clearly, postponing surgery in the newborn period is preferable for avoidance of unnecessary morbidity but the timing thereafter is a matter of individual clinical judgment.

Steroid treatment may confer temporary benefit during management of the acute airway obstruction and penicillin-based antibiotic therapy is indicated for the treatment of septic complications. These problems, however, are usually seen later in infancy and childhood rather than the neonatal period and result from inappropriate delay of surgery.

Operative

Reduction glossectomy is the mainstay of treatment and options include central wedge resection, circumferential

wedge resection, or a combined transoral and transcervical approach for a massive infiltrative lymphangioma.[13]

The aims of reduction are to allow intraoral position of the tongue in the floor of the mouth to restore normal tongue movement and to permit speech and deglutition. Implicit in these objectives is the fact that surgery should be conservative and a repeat tapering procedure is preferable to removal of excess tissue.

V-shaped resection of the anterior tongue has been previously described.[14,15] The principles involve careful hemostasis by use of a tourniquet or, alternatively, by use of a YAG laser, CO_2 laser,[16] or harmonic scalpel.

Nasal intubation or tracheostomy secures airway protection. The head is placed in a silicone ring and the neck extended. A suture placed on the apex of the tongue and two hemostatic/traction sutures tied over silicone rubber dams at the base of the tongue provide the requisite traction (Fig. 26.3).

Traction on these three sutures delivers the necessary exposure and hemostasis sufficient for central wedge resection. The resection should not usually extend into the posterior one-third where the extrinsic muscles of the tongue are inserted. The lateral margins of the incision extend from the level of the anterior gum, with the tongue in a resting position, to the apex, and this incision is beveled such that more ventral than dorsal tissue is removed. This recreates the natural concavity of the central tongue (Fig. 26.4). A straight needle is a useful adjunct to creating this bevel.

The divided lingual arteries are ligated. Restoration of the tongue flaps and the midline is performed incorporating mucosa and a few mm of muscle (Fig. 26.5).

The opportunity to place a percutaneous gastrostomy should be taken if protracted delay in feeding is anticipated.

Postoperative

Antibiotics should be continued into the postoperative period to provide prophylaxis against sepsis in the floor of the mouth. Oral hygiene is maintained with chlorhexidine or saline oral toilet. The appropriate tracheostomy care, if required, is given and secondary orthodontic and speech therapy follow up arranged.

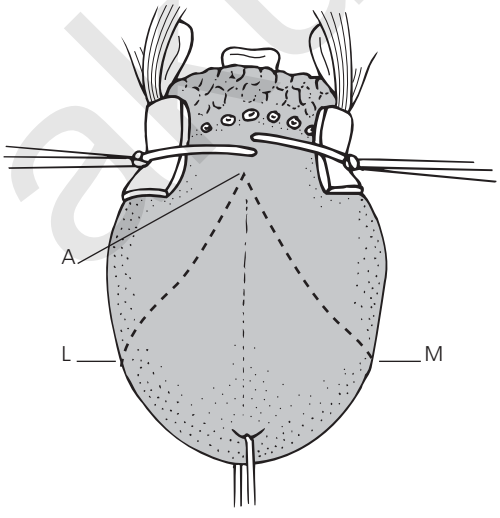


Figure 26.3 Traction sutures allow good exposure and good hemostasis during reduction glossectomy.

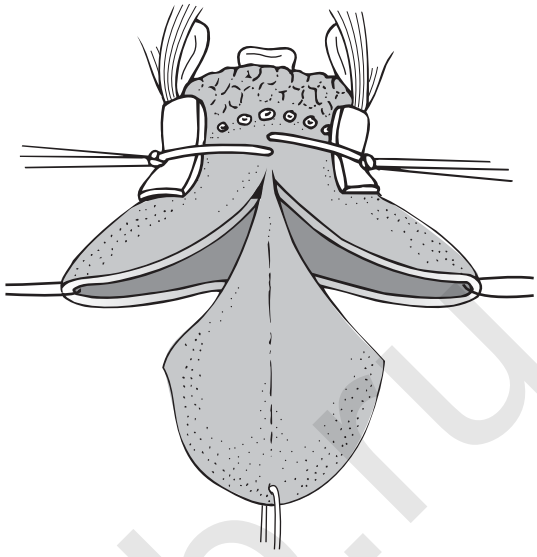


Figure 26.4 Wedge of tissue incorporating more of the ventral than the dorsal aspect of the tongue is removed.

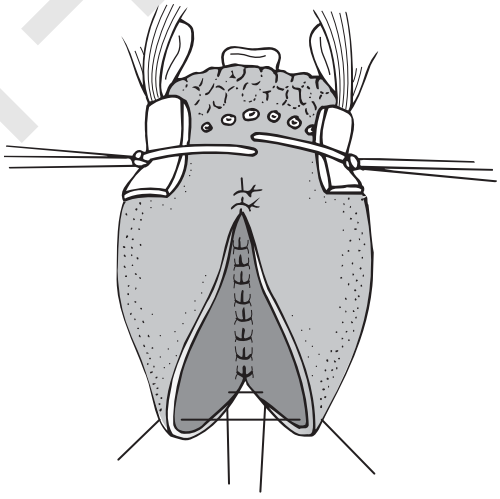


Figure 26.5 The remaining lateral segments of the tongue approximated in the midline.

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27

Tracheostomy in infants

THOM E LOBE

INTRODUCTION

Neonatology and technology have made great strides over the last few decades. Pulmonary disease remains the primary indication for tracheostomy in preterm infants. However, in general, because of the routine use of surfactant and steroids, it is now less common to see infants dependent on a ventilator for lung disease alone, and it is neither unusual nor unsafe to leave an infant on a ventilator with an endotracheal tube in place for months on end. Term infants who need a tracheostomy do so because of an inadequate airway. These infants otherwise are ready to go home or to a facility for technologically dependent children, but still require ventilatory assistance.

This chapter will discuss the indications and techniques for insertion and maintenance of a tracheostomy in infants.

INDICATIONS FOR TRACHEOSTOMY

The indications for tracheostomy in infants fall into five main categories: (1) airway immaturity, (2) obstructing congenital anomalies, (3) acquired obstructions, (4) tumors, and (5) trauma.

The immature airway manifests itself as laryngomalacia, tracheomalacia, or a combination of the two conditions. These infants present with inspiratory stridor and some degree of nasal flaring and chest retractions. Other related conditions are congenital vocal cord paralysis, which is usually due to a central nervous system deficit, phrenic nerve injury, which may be associated with a difficult delivery, and recurrent laryngeal nerve injury, which may occur after ligation of a patent ductus arteriosus.

Some patients with choanal atresia and Pierre Robin syndrome may be candidates for tracheostomy. Other craniofacial deformities such as Freeman Sheldon syndrome, Cerebro-costo-mandibular syndrome, arthrogyposis multiplex congenital, and others also may require a tracheostomy for airway maintenance.

Patients with a congenitally stenotic airway or tracheal agenesis are special cases. In the case of agenesis, an emergency tracheostomy may be necessary where the trachea re-establishes distally. Usually, however, these patients can be ventilated best using a mask because the bronchi come off the esophagus and an esophageal tube can cause obstruction. Technology today allows bedside bronchoscopy in such infants with tenuous airway status so that proper decisions can be made before one risks transporting the infant to the operating room. There are several acquired conditions that require tracheostomy including infection, papillomatosis, neuromuscular failure, chronic aspiration, and subglottic stenosis.

Occasionally, the management of a tumor such as a cervical teratoma or sarcoma in infancy will mandate a tracheostomy. More likely a hemangioma or lymphangioma will compromise the airway to the extent that a more stable airway is needed. Infants with congenital high airway obstruction (CHAOS) are often diagnosed *in utero* today and an EXIT procedure (trachesotomy performed with maternal–fetal circulation intact), may be required.

Rarely, trauma will prompt the surgeon to perform a tracheostomy. This can be related to birth trauma, child abuse, or accidents.

PREOPERATIVE EVALUATION

Most infants who need a tracheostomy already have an endotracheal tube in place. Infants suspected of laryngotracheomalacia may require direct laryngoscopy and/or bronchoscopy to assess the situation.

The surgeon should make certain of the coagulation status, hemoglobin level, and electrolytes as indicated by the patient's condition. The nutritional status of the patient should also be taken into consideration. Poor nutrition will complicate nearly any condition in infancy and may weigh in favor of an earlier tracheostomy than would be indicated otherwise.

When an infant is not intubated but is under consideration for tracheostomy, the extent to which the child maintains oxygenation and demonstrates adequate ventilation, as judged by the PCO_2 measured by transcutaneous monitoring, will determine the need for a more direct assessment before a decision for tracheostomy is made.

Finally, patients with persistent aspiration, despite correction of any gastroesophageal reflux, may necessitate a tracheostomy to prevent severe pulmonary consequences.

TECHNIQUE

The infant is placed supine on the operating table, sufficiently toward the foot of the table so that the surgeon can access the infant's neck easily, but not so far down on the table that the anesthesiologist cannot reach the patient to manipulate the endotracheal tube when required.

These cases should be performed under a general anesthetic unless the infant is so ill as to be unable to tolerate the drugs. Even so, an anesthesiologist or anesthetist should maintain control of the airway while the surgeon is exposing and manipulating the trachea.

The patient's cardiorespiratory status should be monitored during the case. This should consist of a cardiac monitor for heart rate, a blood pressure monitor, and ideally a pulse oximeter to assess the infant's oxygenation.

If there is any question as to the status of the airway, bronchoscopy should be performed to assure that the tracheal lumen will accept a tracheostomy without difficulty. Special issues, such as a tracheostomy to stent an airway for severe tracheomalacia, can be assessed by bronchoscopy to determine the proper length of the proposed cannula, which may have to be specially ordered. In some cases, it may be necessary to use an ordinary endotracheal tube placed through the cervical incision and secured to the skin of the neck until this temporary tracheostomy cannula can be replaced with the specially ordered device.

When positioning the infant on the operating table, the neck should be extended sufficiently to allow complete access to the neck. Sometimes, on chubby infants, it is still difficult to see the entire neck, despite the best attempts. A roll should be placed under the infant's shoulders to facilitate proper positioning (Fig. 27.1).

The endotracheal tube should be secured so that the anesthesiologist can easily remove the tube at the appropriate time. This means that any tape should be loosened beforehand. If there is a feeding tube in place, it should be removed so that it does not interfere with endotracheal tube manipulation.

When the infant is properly positioned and monitored, the entire neck from the lower lip to below the nipples should be prepped with a suitable surgical prep and draped.

The superiormost surgical drape should allow easy access to the patient by the anesthesiologist.

Once prepped and draped, the surgeon should carefully palpate the infant's neck to locate the trachea that hopefully is in the midline. The surgeon must remember that the infant's trachea is quite mobile and compressible, and may be difficult to palpate. The anesthesiologist can jiggle the endotracheal tube from above to assist with its location.

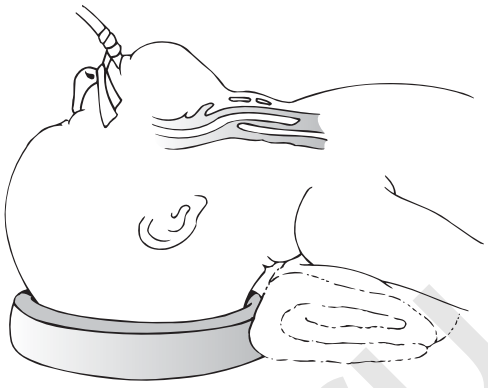

Figure 27.1 Position of infant for tracheostomy. The shoulders are elevated on a roll; the head is hyperextended on the neck and supported by a doughnut-form support.

A transverse skin incision is best. We make our incision in the lower neck crease, about the width of one finger above the jugular notch. If the incision is too low, the endotracheal tube will end up in the mediastinum and the cannula will be placed too low in the trachea. We first score the skin with a scalpel, then use a needle-point electrocautery device to deepen the incision, taking care not to burn the skin. This incision is extended through the subcutaneous fascia and platysma muscle, which is quite thin in the small infant. It is helpful to insert two right-angled retractors in the corners of this incision to better expose the operative site.

Next, we use two atraumatic forceps to grasp the anterior cervical fascia on either side of the midline and open it vertically in the midline. We extend this incision inferiorly to the jugular notch and superiorly to the thyroid gland.

The strap muscles, immediately beneath the anterior cervical fascia, are similarly separated in the midline. Usually, there are few to no blood vessels in the dissection thus far. Occasionally, the surgeon will encounter a few small vessels that cross the midline. These should be cauterized and divided as they are encountered.

Once these muscles are separated, we place the two retractors deep to the muscle edges and gently retract laterally to better expose the trachea below. Sometimes it is necessary to free the muscle edges sufficiently to allow room for the blade of the retractor to gain a secure purchase.

The trachea should be visualized easily. If not, then palpation in the wound with manipulation of the endotracheal tube by the anesthesiologist will help locate the trachea.

The proposed tracheostomy cannula should be selected, opened, and its outer diameter visually checked against the exposed trachea to judge the correctness of its size. If it seems that the initial selection was incorrect, then a tracheostomy cannula of a more appropriate size should be selected.

The pretracheal fascia should be lightly scored with the cautery to coagulate any tiny vessels on the surface of the trachea in the midline. Again, the blades of the retractors should be deep in the wound on either side of the trachea for optimal exposure.

A suture of 4-0 Prolene or its equivalent should be placed on either side of the midline scored anterior trachea (Fig. 27.2). Each suture incorporates one or two tracheal rings. These sutures are not tied onto the tracheal wall, but can be tied at their ends and should be left 6–8 cm in length. At the end of the case, these sutures should be taped securely to the anterior chest wall and used to locate the tracheal incision in the event of a postoperative emergency in which the newly placed tracheostomy cannula dislodges. These sutures can also be used to hold open the edges of the tracheal incision for ease of placement of the tracheostomy cannula at operation.

The surgeon should request that the endotracheal tube be loosened and prepared for removal. Using a No. 11 blade, a vertical incision is made through the tracheal wall along the score mark (Fig. 27.3). Two or three tracheal rings should be divided, usually rings 2, 3, and 4. Rarely, it is necessary to divide the isthmus of the thyroid gland for proper tracheostomy positioning. A transverse tracheal incision or removal of a tracheal ring is likely to result in a tracheal deformity and thus should be avoided. Similarly, unless one is dealing specifically with a localized stenosis or deformity, tracheal wall resection is to be avoided.

Suction should be available in case blood or secretions interfere with the surgeon's view of the tracheal lumen. The tip of the cannula to be inserted should be lubricated with a water-soluble surgical lubricant and positioned over the incision, poised for insertion when the endotracheal tube is withdrawn.

The surgeon should then ask the anesthesiologist to withdraw the endotracheal tube sufficiently to clear the lumen so that the tracheostomy cannula can be inserted and directed caudally toward the carina.

One way to avoid misplacement is to insert a suction catheter through the lumen, beyond the tip of the cannula (Fig. 27.4). The suction catheter then can be inserted into the tracheal lumen first and serve as a guide over which the cannula can be passed. This technique is also useful should the cannula become dislodged after the procedure.

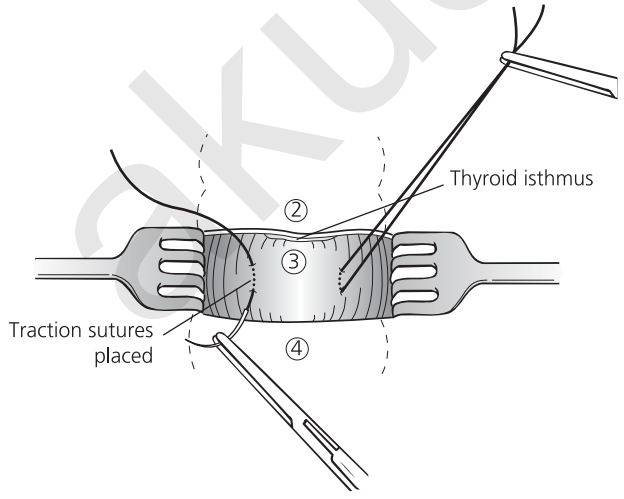

Figure 27.2 Traction sutures of fine silk are placed around the third tracheal ring to stabilize the trachea before incision. The sutures are tied in loose loops and later taped to the anterior chest wall. The sutures are left in place for 4 days as a precaution against accidental decannulation postoperatively.

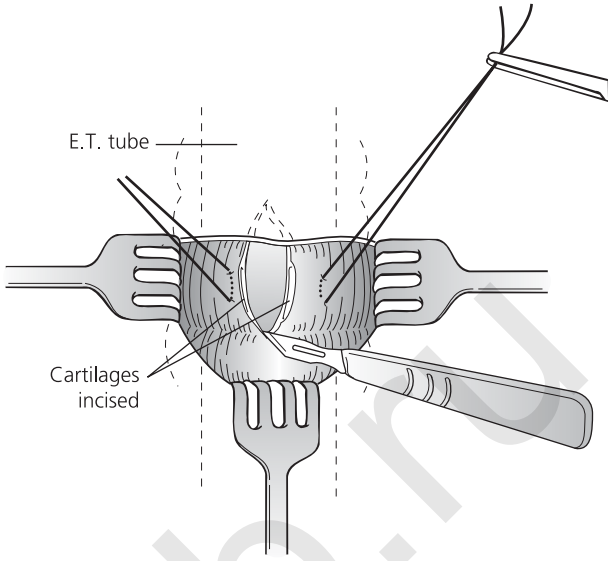

Figure 27.3 The trachea should be opened through a midline vertical incision across 2–3 tracheal rings. The incision must be long enough to avoid excess tube pressure against the cartilages. A tight tube can result in pressure deformity and reabsorption of cartilage.

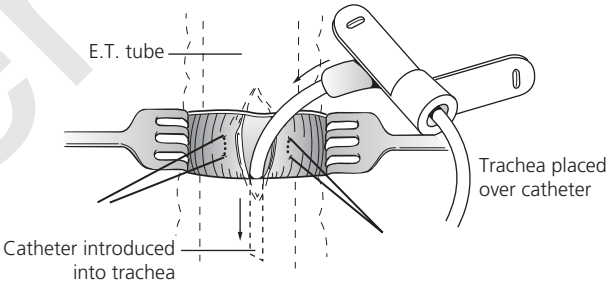

Figure 27.4 Tube insertion into the trachea is accomplished by shifting the endotracheal tube up to the cephalad margin of the new stoma, inserting a tracheal suction catheter into the trachea through the newly established opening, and then advancing the tracheostomy tube over the catheter in the trachea. This is safer than using the tube obturator, the short tip of which sometimes slips out of the stoma and allows the tracheostomy tube to pass anterior to the trachea and into the mediastinum.

If, for any reason, the tracheostomy cannula does not fit easily into the trachea, it should be removed and the endotracheal tube advanced beyond the tracheal incision so that ventilation will not be compromised. This might occur if the diameter of the tracheal lumen has been overestimated and the previously selected tracheostomy is too large to fit into the trachea. In the latter case, a smaller cannula should be selected.

As soon as the cannula is in place, the obturator or suction catheter should be removed and the anesthesiologist should disconnect the ventilator hose from the endotracheal tube

and connect it to the tracheostomy cannula. Once that is done, the anesthesiologist should administer several deep breaths to the patient to confirm that the cannula is in the proper place and that the infant can be ventilated satisfactorily. If it appears that although the cannula width is appropriate, the cannula is too long and its tip rests on the carina, then several pieces of gauze can be used to build up the gap between the neck and the tracheostomy collar, thus backing the tip of the cannula away from the carina. Once adequate ventilation is confirmed, then the endotracheal tube can be removed completely.

Once the cannula is connected to the ventilator, the cervical wings of the body of the cannula need to be secured to the patient. We do not rely on a tie placed around the neck, but accomplish this with the aid of sutures.

For each wing, a suture of 3-0 silk or its equivalent is passed through the skin of the neck, then through the upper edge of the wing of the cannula (midway between the midline and the end of the wing), through the lower edge of the wing, then again through the skin. When this suture is tied, the skin will be drawn over the wing and usually will cover it. After these sutures are placed, both wings will be securely fixed to the skin of the neck.

The two ties that were placed in the anterior tracheal wall should now be taped securely to the anterior chest wall in such a fashion that ensures that their ends are easily accessible in case they are needed in an emergency to reinsert the cannula (Fig. 27.5).

Finally, the umbilical tape or tie that usually comes with the cannula is passed through the holes in the end of the wings and tied around the neck to further secure the cannula. This should be tied at the back of the neck. A simple gauze dressing with antibiotic ointment applied is placed underneath the wings of the cannula over the cervical incision to complete the procedure.

We send our infants to the intensive care unit after a fresh tracheostomy in case of emergency.

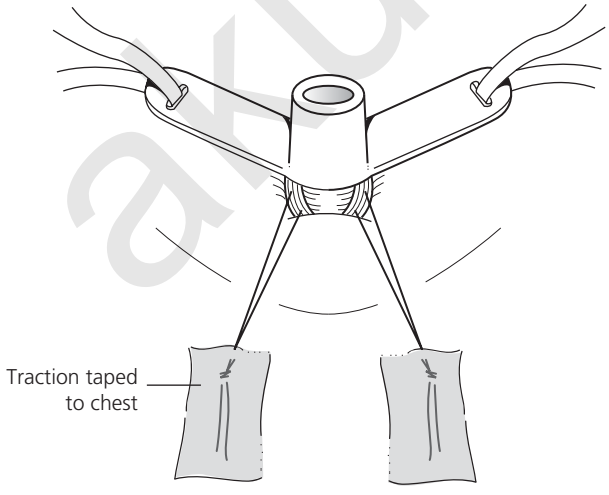

Figure 27.5 Prevention of accidental decannulation is the surgeon's responsibility. The tube should be taped to the anterior chest for 4 days in case an unexpected tube change should become necessary.

PERIOPERATIVE MANAGEMENT

If the skin of the patient's neck is infected with a bacterial or fungal infection, this should be cleared before any operation is undertaken unless emergency tracheostomy is required to save an infant's life.

In patients with short, fat necks, it may be necessary to place the infant in a position of neck extension to facilitate clearing any skin infection or breakdown that is due to chronic moisture. Simply exposing the infant's neck to air for drying is often sufficient to clear any problem.

Immediately after the tracheostomy is secured, the roll under the patient's neck should be removed and an x-ray of the chest should be reviewed before the patient is removed from the operating room. This is important to make certain that the tip of the cannula is sufficiently clear of the carina and will not become obstructed as the patient's neck is manipulated.

The fresh tracheostomy should be left in place for about 10 days before it is disturbed. At least once each day the site should be cleaned with a cotton applicator soaked in a solution of hydrogen peroxide, and an antibiotic ointment should be applied to the incision site.

The sutures securing the tracheostomy should be left untouched for the initial 10-day period, after which they can be cut. The sutures to the edges of the tracheal incision should be left until the tracheostomy is changed successfully for the first time.

If the patient is unusually agitated or the ventilator tubing is so heavy that dislodging the cannula is highly likely, then sedation or paralysis may be helpful until the wound has matured and reinsertion can be done more safely.

After the cannula is free and the umbilical tape is untied, the cannula can be removed and replaced. Ideally, the parents or ultimate caretakers should observe the exchange, particularly if the patient is close to discharge.

If a temporary endotracheal tube is being replaced with a specially ordered tracheostomy cannula, the new cannula should be inserted as described earlier.

Once it is obvious that the cannula can be changed with ease, is in its proper position, and that the patient can be ventilated, it is safe to remove the sutures to the edges of tracheal incision.

Suctioning of the newly placed tracheostomy should be carried out as often as necessary, particularly immediately after the procedure. Care must be taken, however, to restrict the passage of the suction catheter to no further than the tip of the cannula. Routine suctioning beyond the tip of the cannula promotes the development of granulation tissue that may obstruct the airway later on.

HOME INSTRUCTION AND CARE

Patients should be discharged home with an extra tracheostomy cannula in case a problem occurs. The caretakers should be instructed and checked out on tracheotomy change and cardiopulmonary resuscitation (CPR). They should know how to suction the cannula and be sent home with a suction

machine. They should know how to use an Ambu bag for ventilation in conjunction with suctioning.

An air filter should be attached to the tracheostomy cannula if a ventilating device or some other humidification device is not connected. Of course, the family or caretakers must know how to use and troubleshoot in case of problems with using any of the devices chosen, especially the cannula and its attachments.

It is often helpful to arrange for home nursing visits until the family becomes familiar and comfortable with the new devices; this is especially true when it comes to the first scheduled tracheostomy change if it is to be done at home.

The physician may choose to do the first tracheostomy change in the office and take the opportunity to further instruct and reassure the family or caretakers.

COMPLICATIONS

Hemorrhage is an unusual complication that can occur at the time of operation or as a delayed event. When hemorrhage occurs at operation, it can be controlled easily with electrocautery or vessel ligation. Rarely, especially in the smaller newborn, the thyroid gland is near the incision site on the anterior trachea and is inadvertently divided or lacerated. The resultant hemorrhage can usually be controlled with sutures or electrocautery.

Late hemorrhage is often more problematic and can be more serious. First, it must be ascertained whether the hemorrhage is from the tracheal lumen or from the incision. This can be accomplished by suctioning the cannula and inspecting the wound. Occasionally, a small skin vessel will bleed briskly but can be easily seen and controlled with a simple suture or even with an injection of 1% lidocaine containing 1:100 000 epinephrine.

More problematic is the possibility of hemorrhage from one of the great vessels, such as the innominate vein or artery. This can occur from erosion of the vessels when the cannula fits too snugly in the thoracic inlet and partially compresses the vessels against the manubrium or clavicle. This type of hemorrhage often presents with a so-called 'herald bleed', which starts briskly but stops, and usually requires a trip to the operating room to repair the damaged vessel.

Aside from hemorrhage, the cannula can become dislodged. We are compulsive about securing the cannula in place using the techniques described earlier in order to avoid this complication. Even so, despite our best efforts, a suture will pull loose or one of the plastic wings will tear, allowing the cannula to dislodge.

We prefer to keep our infants in the intensive care unit during the immediate postoperative period. We anticipate that if the cannula becomes dislodged, it will be noticed immediately. Replacing the cannula in the immediate postoperative period can be a treacherous ordeal that under ideal circumstances should be performed by someone familiar with cannula insertion. If a surgeon or intensivist is readily available, then one of them should replace the cannula and resecure the device. The sutures to the tracheal incision should be taped in such a manner as to be easy to access, untape, and retract to expose the tracheal lumen. Good lighting is essential to see well and either the obturator should be inserted into the cannula before reinsertion is attempted or a suction catheter should be used as a guide.

It is very undesirable to force the cannula outside the trachea. Proper positioning is assured by administering a deep breath or two with an Ambu bag once the cannula is in place. If the chest does not rise immediately, it is possible that the cannula is not in the proper place and should be replaced. A chest x-ray should be taken to assure proper cannula position.

It is not usually necessary to use instruments to insert the cannula because the sutures attached to the edges of the tracheal incision should lead directly to the opening in the trachea. If difficulty arises, two small right-angled retractors should be sufficient to complete the job. In the event that the cannula cannot be reinserted, then the ventilation using an Ambu bag and mask can be used to maintain oxygenation until the infant can be returned to the operating room.

Infection is an unusual complication and should be treated with the appropriate antimicrobials according to culture results.

Injury to the vagus nerves or, more likely, the recurrent laryngeal nerves can occur. In experienced hands with a surgeon well versed in the anatomy of the infant's neck, this injury should be rare.

While unlikely, it is possible to place the cannula into the esophagus. This can occur if the trachea is retracted laterally, out of the field, and the esophagus is entered in error. If this occurs, the esophagus should be repaired primarily and a drain should be left in place. The trachesotomy cannula can then be inserted properly.

Endotracheal granulation tissue can result from the chronic irritation of the tip of the tracheostomy cannula against the tracheal wall or from the repeated suctioning of the trachea. It is common for granulation tissue to develop at the stoma. This can be exophytic at the level of the skin, or can be intralumenal. The exophytic granulation tissue at the skin should be cauterized with silver nitrate during an outpatient visit. This may need to be carried out every month or so if bothersome hemorrhage or chronic irritation with infection is present.

If the granulation tissue develops immediately within the trachea at the stoma, it usually can be left alone until it is time for decannulation. Only if the granulation tissue is so bulky that it interferes with routine tracheostomy changes or causes significant hemorrhage should it be removed before decannulation is contemplated.

The development of granulation tissue at the tip of the cannula can present with obstruction, sometimes resulting in a 'ball-valve' effect, with trapped air and difficulty with ventilation. This can be diagnosed by slipping a flexible bronchoscope through the cannula to visualize the tracheal lumen beyond the tip of the cannula. If the results of this diagnostic maneuver are unclear, rigid bronchoscopy may be necessary.

We believe that this type of granulation tissue is best removed with laser. Our preference is for the KTP/532 laser or an equivalent wavelength that operates using a flexible fiber. The technique for laser vaporization of granulation tissue is beyond the scope of this discussion.

The mortality in infants with tracheostomy is near 40%; however, the tracheostomy-related mortality is between 0 and 6%.

SPECIAL SITUATIONS

Occasionally, there exist special circumstances which require careful thought and planning. Such is the case with tracheal stenosis. Simple acquired subglottic stenosis can be easily managed with a tracheostomy inserted as described, except for the size of the endotracheal tube. A small endotracheal tube may be difficult to palpate, however, thus locating the trachea may be difficult.

With a particularly stenotic airway, mask ventilation may be the only way to maintain ventilation. The most difficult part of the case is locating the trachea without an endotracheal tube.

For patients with distal tracheal stenosis, tracheostomy insertion may be inappropriate. While beyond the scope of this discussion, the infant should be carefully studied if this diagnosis is suspected. Usually, plain radiographs of the chest may lead one to suspect the diagnosis. Computed tomography or bronchoscopy may be required for confirmation. When the distal trachea is stenotic in an infant who is difficult to ventilate, a conventional tracheostomy cannula is inappropriate and may interfere with tracheal reconstruction.

Patients who are candidates for congenital heart surgery, and in whom the ultimate need for a tracheostomy is anticipated, may be best managed by completing the cardiac surgery before tracheostomy is performed. Otherwise, the sternal incision is so close to the tracheostomy site that the risk of cardiac infection is greatly increased.

DECANNULATION

Decannulation is usually anticipated well in advance. Its timing depends largely on the indication for the tracheostomy. Patients with severe subglottic stenoses may have their tracheostomy removed at the time of their laryngoplasty. The timing of this procedure, then, depends on the surgeon and may occur any time between four to six months and two years, or later.

In patients whose tracheostomy was placed because of tracheomalacia, it would be unusual to attempt decannulation before the infant is one year of age. The infant should undergo periodic bronchoscopic examination to assess the status of the malacia. Once it is certain that the airway is sufficiently mature as to be able to maintain its patency, decannulation can be attempted.

The first step is to make certain that the airway is mature and free of any potential obstructing lesions such as granulation tissue. This is best accomplished with rigid bronchoscopy. Any residual malacia or granulation tissue can be documented and dealt with as needed.

At the time of attempted decannulation, we bring the patient to the operating room, positioned as described earlier for insertion of the cannula with the neck extended, and perform the bronchoscopy. In order to assess whether malacia is present, the patient should not be paralyzed and the anesthesia should be light. This is to determine whether the airway remains patent, with the patient breathing spontaneously.

Once committed to decannulation, the bronchoscope and neck roll should be removed and the patient is observed for any difficulty, such as severe chest retraction or deoxygenation, that would suggest the continued need for the tracheostomy. If, on the other hand, the patient ventilates with ease, then the patient should be fully awakened and allowed to recover in a unit that permits careful observation.

We usually keep these patients in the hospital overnight, or longer if there is any concern, to assure that the tracheostomy is no longer required.

Once the cannula is removed, a snug dressing of plain or petroleum jelly-saturated gauze is secured over the tracheostomy stoma to occlude it. The caretakers or parents should be instructed on how to change this dressing until the stoma closes completely.

Occasionally, we encounter a stoma that does not close spontaneously. If the stoma remains open after several months, then operative closure of the stoma can be performed as an outpatient procedure. Usually, this is simply a matter of excising the stoma and placing a simple stitch or two in the anterior trachea. A larger persistent opening may require an anterior wedge excision for proper repair. This may necessitate admission to the hospital.

If after the patient leaves the operating room decannulated, the infant becomes fatigued or demonstrates other signs of respiratory distress, the dressing can be removed and another cannula should be reinserted. A smaller cannula size can be inserted if desired.

This technique is often used to serially wean a patient to progressively smaller-sized cannulae until decannulation is certain to be successful.

If, after decannulation, it is necessary to reinsert a tracheostomy, the procedure should be carried out in the operating room. While this is usually done with an endotracheal tube in place, there are some patients for whom it may be undesirable to insert an endotracheal tube. This avoids airway irritation and prevents restenosis. That being the case, the surgeon can inject a local anesthetic around the stoma, dilate the stoma with Hegar dilators (or possibly make a small incision with a No. 11 scalpel blade), and reinsert a cannula of an appropriate size. This maneuver should only be attempted if the anesthesiologist can maintain an adequate airway during the procedure.

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28

Congenital cysts and sinuses of the neck

YOUSEF EL-GOHARY AND GEORGE K GITTES

INTRODUCTION

Cervical masses in infants and children are frequently encountered by pediatric surgeons with intriguing clinical presentations. Some can be easily diagnosed with a good history and physical examination, such as the thyroglossal cyst. Others require more extensive investigation and imaging to accurately diagnose and treat. The vast majority are benign in origin, however rarely they can be malignant.[1] They frequently form residual structures from embryologic development that have failed to resorb completely or mature. Knowledge of the embryological origins of these cysts and sinuses, along with the detailed neck anatomy, is essential for proper management and for ultimately a successful dissection and excision. In this chapter, we will discuss the embryology of the neck, followed by a brief review of the common neck cysts and sinuses, along with their management.

EMBRYOLOGY

During early embryonic stages, the primitive gut tube, which is derived from the endoderm germ layer during gastrulation, is divided into the foregut, midgut, and hindgut domains, each of which will give rise to specialized regions due to the regional specification of the gut tube.[2] The foregut, which includes the pharyngeal (branchial) apparatus, extends between the bucco-pharyngeal membrane and ends at the origin of the liver bud.

The pharyngeal apparatus, which consists of arches, pouches, and clefts, will eventually give rise to the various muscles, nerves, bones, and cartilages in the head and neck region as illustrated in Fig. 28.1 and Table 28.1. There are six pharyngeal (branchial) arches, each consisting of a core of mesoderm, with its own nerve and arterial supply, surrounded by an outer ectodermal and inner endodermal lining. The mesoderm of the second pharyngeal arch proliferates and causes the arch to grow caudally, overlapping the third and fourth arches, and in the process burying the second, third, and fourth pharyngeal clefts and creating a temporary cervical

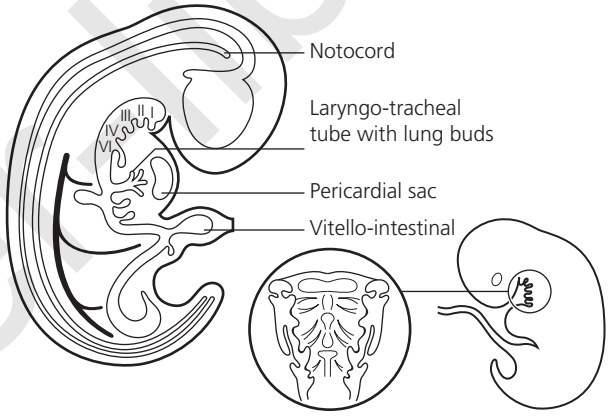

Figure 28.1 Schematic illustration of the embryo with the pharyngeal arches (I–VI).

sinus, which normally disappears (Fig. 28.2). The first pharyngeal cleft will give rise to the external auditory meatus and the fifth arch disappears. It is the incomplete closure or obliteration of these ectodermal portions of the second, third, and fourth pharyngeal clefts that leads to the various neck anomalies, including cartilaginous remnants, that pediatric surgeons encounter today. The remnants of these clefts form the cervical sinus which remains connected to the surface via a narrow canal called the 'external' branchial fistula, which may drain a branchial cyst. Rarely does the branchial fistula connect to the pharynx, near the tonsil area, via the 'internal' branchial fistula.

INCIDENCE

Branchial clefts and fistualae represent about 23% of cervical masses in children.[3] The 'rule of 80' is often applied in adults, which states that 80% of non-thyroid neck masses in adults are neoplastic and that 80% of these masses are malignant. A neck mass in a child, on the other hand, has a 90% probability of being benign.

Table 28.1 Summary of the derivatives of the pharyngeal arches.

Arch	Muscles	Nerve	Cartilage, bone, and ligament
I	Muscles of mastication	Mandibular division of trigeminal nerve	Malleus, incus, spheno-mandibular ligament
II	Muscles of face and scalp	Facial nerve	Stapes, styloid process, styloid ligament, lesser horn and upper part of body of hyoid bone
III	Stylopharyngeus	Glossopharyngeal nerve	Greater horn and lower part of body of hyoid bone
IV	Crico-thyroid	Superior laryngeal branch of vagus nerve	Thyroid cartilage
VI	Intrinsic muscles of larynx	Recurrent laryngeal branch of vagus nerve	All laryngeal cartilages except thyroid cartilage

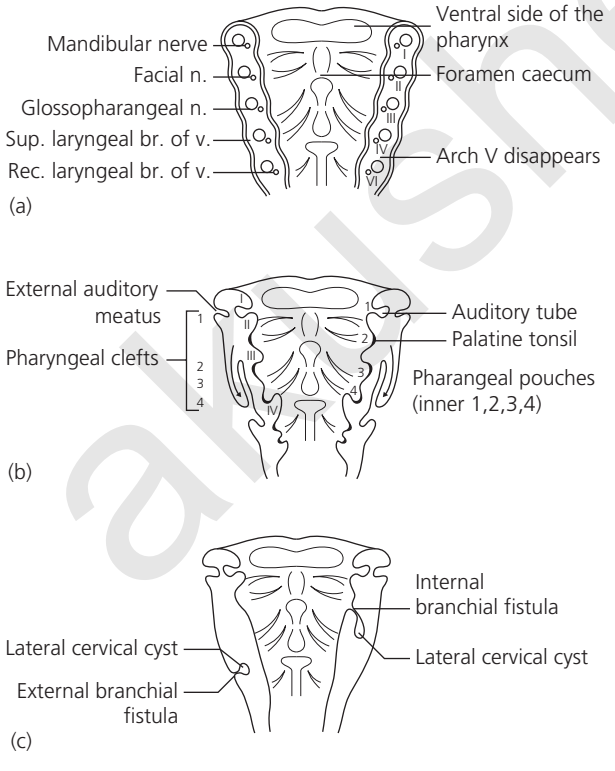

Figure 28.2 Illustration of the pharyngeal arches (I–IV) with their own nerve supply. The mesoderm of the second pharyngeal arch grows downwards, burying in the process the second, third and fourth pharyngeal clefts (a,b). Incomplete closure of these pharyngeal clefts leads to the formation of branchial anomalies such as a cyst or fistula (c).

BRANCHIAL ANOMALIES

First branchial cleft anomalies account for less than 10% of all branchial cleft defects.[4] They have a wide range of presentations, manifesting in a sinus, fistula, or cyst anywhere between the floor of the external auditory meatus and the submandibular region (Fig. 28.3). Clinically, they can present with either a persistent purulent discharge from the ear, pre-auricular swelling in the parotid area, or fistula in the neck above the hyoid bone. However, they are most commonly associated with an infection, often being initially treated with a course of antibiotics or unnecessary repeated incision and drainage of an abscess.[4,5] The relationship of the facial nerve to the anomaly is variable, with careful and meticulous surgical dissection needed to avoid nerve paralysis. In a series of 39 patients with first branchial cleft anomalies reported, six patients developed temporary facial nerve paralysis and only one (2.5%) patient developed permanent damage.[6] Diagnosing first cleft anomalies can be challenging, with the anomaly often closely related to the parotid gland. Examining the external auditory meatus may reveal a fistula; thus linking the parotid swelling or lateral neck mass to a first cleft anomaly. Preoperative imaging with magnetic resonance imaging (MRI) allows assessment of the extent of the anomaly, especially in the parotid area, and high-resolution computed tomography (CT) imaging shows its exact relationship with the external auditory canal and the middle ear.[6] Complete surgical excision is the treatment of choice, which often necessitates a superficial parotidectomy, with careful preservation of the facial nerve. Methylene blue injection into a draining tract prior to excision may facilitate removal. Recurrent infections or previous surgical interventions will increase the morbidity of the operation. That is why it is essential for an adequate preoperative work up prior to any surgical intervention.

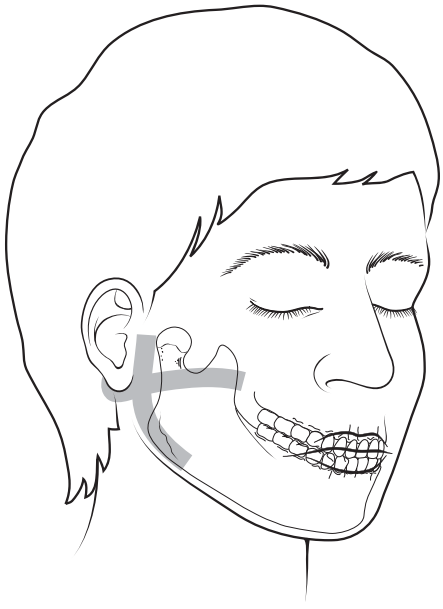

Figure 28.3 Shaded area on the face represents locations where first branchial cleft anomalies would be generally located.

Second branchial cleft anomalies are the most common (95%),[7] often presenting along the anterior border of the sternocleidomastoid muscle as a sinus, fistula, or cyst, typically at the junction of the upper two-thirds and lower third. The fistula goes deep to the platysma muscle along the carotid sheath between the external and internal carotid artery, above the hypoglossal and glossopharyngeal nerves and ends near the tonsillar fossa (Fig. 28.4). Deep fistulas or sinuses would generally necessitate two or three 'step-ladder' or McFee incisions in order to completely remove the entire tract. However, the majority of the anomalies manifest as cysts[8] and rarely present as a full fistula tract.[7]

Bailey[9] described four types of cysts. Type 1 is superficial and lies beneath the platysma and cervical fascia but anterior to sternocleidomastoid process. Type 2 cysts, which are the most common, characteristically lie on the great vessels and may be adherent to the internal jugular vein. Type 3 cysts course between internal and external carotid artery and extends to the lateral wall of the pharynx. Type 4 cysts lie against the pharyngeal wall. Complete surgical excision is the treatment of choice, with recurrence being the most common postoperative surgical complication. A large series of 208 cases showed recurrence in 21% of those with a history of prior surgical intervention, 14% with a history of infection, and 3% with a history of neither.[10]

Third and fourth branchial cleft anomalies are rare, accounting for 2–8% and 1–2% of all branchial anomalies, respectively.[4,11] Clinically and radiologically, it can be difficult to distinguish between the two, as both types begin at the pyriform sinus and end blindly in the paratracheal or thyroid regions. Ninety-seven percent of the lesions occur on the left side.[10] Although rare anomalies, they can have devastating respiratory consequences presenting as an acute stridor[12,13] or acute thyrioditis.[14,15] Diagnoses can be quite challenging, as these cysts are generally subjected to repeated incision and drainage, being mistaken for a simple abscess. A plain film showing air or fluid levels within the cyst can help differentiate a branchial anomaly from other causes of pediatric neck masses. The pharyngeal opening may be visualized by flexible fiberoptic nasopharyngoscopy or demonstrated using a barium meal.[16] In a series of 43 patients with acute suppurative thyroiditis, nearly 88% of the patients were documented to have a pyriform sinus fistula.[15] Therefore, it should be a consideration for any patient presenting with acute thyroiditis to have a potential third or fourth branchial anomaly as an underlying cause, and promote a search for it. The only definitive way of distinguishing an anomaly as being a third or fourth arch is through surgical dissection, which is the treatment of choice ensuring that the tract is completely excised to avoid risk of recurrence. This is done by demonstrating the relationship of the tract to the recurrent and superior laryngeal nerves. A tract that goes inferior to the superior laryngeal nerve (fourth arch) and superior to the recurrent nerve (sixth arch) is derived from the fourth pouch. However, if the tract passes superior to the superior laryngeal nerve (fourth arch) then a third pouch origin is likely. Vocal cord paralysis is a potential complication as a result of the dissection.

CT scan and MRI are the imaging modalities of choice to assess the extent and depth of any branchial cleft cysts.

THYROGLOSSAL DUCT CYSTS AND SINUSES

Thyroglossal duct anomalies are the most common congenital anomalies of the neck, constituting nearly 70% of all cervical neck masses in children.[17] They represent remnants from the embryological migration of thyroid tissue from the foramen caecum to the thyroid fossa. Clinically, they usually present as a palpable, non-tender midline neck mass that elevates with swallowing or protrusion of the tongue (see Fig. 28.5). It is

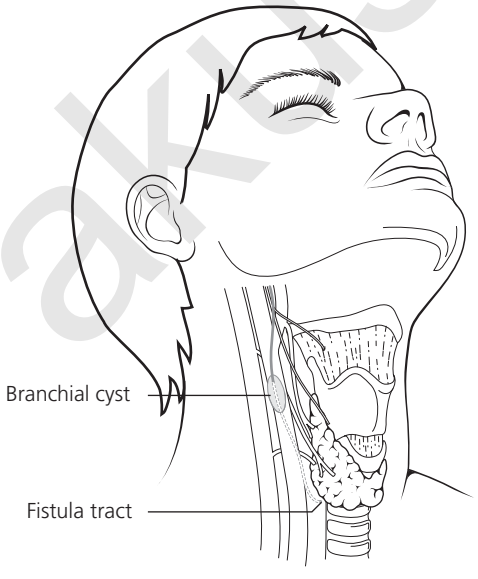

Figure 28.4 Second branchial cleft cyst and fistula tract coursing between the internal and external carotid arteries, above the IX and XII nerves, ending near the tonsillar fossa.

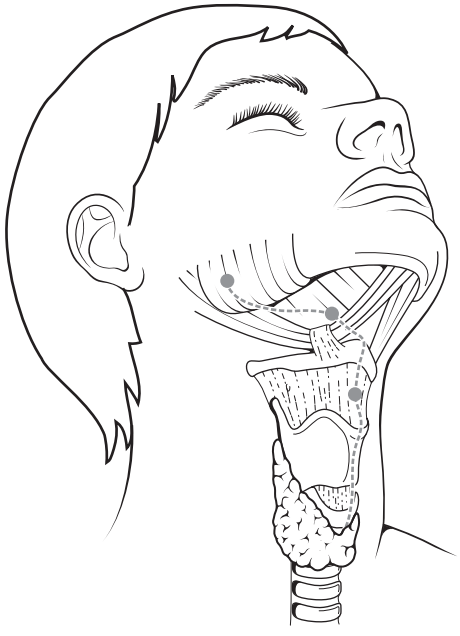

Figure 28.5 Illustration of the thyroglossal duct tract.

important to note that 10–24% of these cysts are located laterally, often to the left.[18]

Ultrasonography is the imaging technique of choice for these lesions, especially to rule out thyroid ectopia. The reported incidence of an ectopic thyroid being misdiagnosed as a thyroglossal cyst is 1–2%.[19]

Sistrunk's procedure, with dissection of the tract up to the hyoid bone, including its midportion, is accepted as the main operation of choice with the lowest recurrence rate.[20,21] Malignancy of the thyroglossal duct cysts is rare (1%)[19,22] with the majority (80%) of histological examination revealing a papillary adenocarcinoma.[23,24]

CONGENITAL MIDLINE CERVICAL CLEFTS

Congenital midline cervical clefts are rare developmental anomalies with differing severities from patient to patient with various length and width.[25] The embryological origin has not been fully elucidated, but it is thought to be a result of failed mesodermal fusion along the distal branchial arches in the midline.[26] The common characteristic features include midline fissure of atrophic skin, subcutaneous fibrous cord, and a thickened nipple-like projection at the superior aspect of the lesion.[27] It can occur anywhere along the midline of the neck from the symphysis of the mandible to the suprasternal notch. Midline cervical clefts are generally excised because, if left untreated, the cleft will cause cicatrical skin contracture. It is recommended to excise the cleft between 10 and 12 weeks of age before tethering of the anterior skin occurs.[28] Simple linear closure has been reported to result in hypertrophic scarring and recurrent neck contracture.[29] As a result, Z-plasty closure is the preferred surgical management of this congenital abnormality as it provides a superior cosmetic result compared to linear closure, and adds the lengthening effect on the anterior neck skin that aids in preventing recurrent contracture.[28]

DERMOID CYSTS

Cervical dermoid cysts are benign tumors that are frequently mistaken for a thyroglossal cyst due to similar presentation and distribution. They are of ectodermal and mesodermal origin, and a definitive diagnosis is usually made during histologic examination revealing hair follicles, smooth muscle, sebaceous glands, and connective tissue elements.[30] They are thought to arise due to trapping of epithelial rests during midline fusion of the first and second branchial arches.[31] Surgical excision is the treatment of choice.

PREAURICULAR SINUSES AND CYSTS

Preauricular sinuses are congenital malformations, usually noted during physical examination as small pits adjacent to the external ear, usually at the anterior margin of the ascending limb of the helix.[32] The incidence varies between different races, with the reported incidence ranging between 0.02 and 5%, with higher incidence among African-American and Asian populations.[33–36] They are mostly unilateral with usually an asymptomatic presentation, however they can present as a purulent discharge from the sinus opening resulting in facial cellulitis or abscess formation, which is the most common indication for a fistulectomy. Surgery should be performed once the infection has resolved, whenever possible, with the recurrence rate after surgery being reported between 3.7 and 36%, with the rate much higher if infection preceded surgery.[32,36,37] In the process of excising the sinus tract, various techniques can be used to identify its extension, but it is recommended to combine the use of dye injection with probing using a fine lacrimal duct probe at the time of surgery as it is associated with the least incidence of recurrence.[34,36]

RANULA

Ranulas are divided into simple and plunging ranulas. Simple ranulas are either mucus retention cysts that are restricted to the oral cavity floor, or mucus extravasation pseudocysts, whereas plunging ranulas are mucus extravasation pseudocysts that originate from the sublingual gland, herniate through the mylohyoid muscle to present as a cervical neck swelling, which may be confused with a submandibular mass when there is no intraoral component.[38] The ideal management for both of these lesions remains controversial, ranging from injecting sclerosing agents to different surgical techniques. Although most would agree to surgically excise them, the general consensus for the ideal technique and approach still remains unknown.

Injecting oral and plunging ranulas with OK-432 (a mixture of a low virulence strain of *Streptococcus pyogenes* incubated with benzylpenicillin) has a reported success rate of 74 and 100%, respectively, however this was achieved after multiple injections.[39,40] Most advocate marsupialization of the oral ranula, as illustrated in Fig. 28.6, which is associated with a recurrence rate of around 20%.[41] Others advocate surgical excision of the cyst alone, which has a recurrence rate of 12%.[41] Some authors prefer to remove the sublingual gland, seen as the definitive treatment with the least recurrence rate, along with the cyst. However, this is associated with a low morbidity of lingual nerve and submandibular duct damage due to the more invasive intervention. Others simply excise the sublingual gland transorally along with evacuation of the ranula, which is seen as the modality yielding the lowest recurrence (1–2%) and complication rates for both oral and plunging ranulas.[41,42] A transoral approach for plunging ranulas is associated with a lower morbidity and complication rate compared to the cervical approach, as the latter places the marginal mandibular and hypoglossal nerves at risk of damage.[43,44] Removing the origin of the disease, usually the sublingual gland, is the key to successful treatment of simple and plunging ranulas.

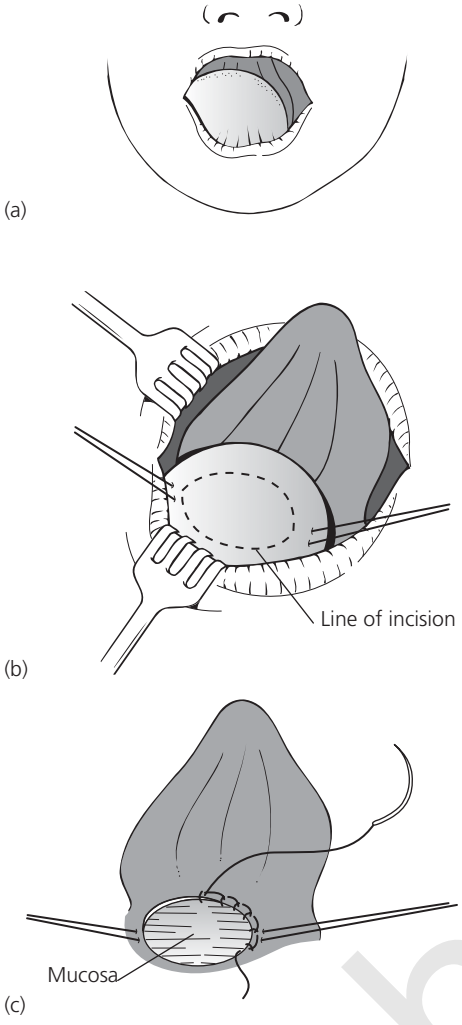

Figure 28.6 (a) Large ranula occupying the floor of the mouth. (b) Line of incision. (c) Continuous 4-0 Vicryl stitch to complete marsupialization.

CYSTIC HYGROMA

Cystic hygroma or lymphangiomas are non-malignant cystic (uni- or multilocular) abnormalities of the lymphatic system, mostly occurring in the cervicofacial region with a predilection to the left side, and has a prevalence of one in every 6000 live births.[45] It can occur in the axilla, mediastinum, retroperitoneum, and rarely in the extremities with variable sizes, ranging from a few centimeters in diameter to large masses, potentially filling a large portion of the thorax.[46,47]

The term 'hygroma' is derived from Greek meaning moist or watery tumor and has equal sex distribution. They rarely self-resorb with aspiration of the cystic fluid, which is usually clear or amber-colored, and are occasionally hemorrhagic,[47] usually resulting in rapid reaccumulation. They can present as a congenital birth defect or be acquired at a later stage in life, with the majority (80–90%) presenting by two years of age.[48,49]

They are thought to arise due to the failure of lymph vessels to communicate with the venous system, with abnormal budding and/or sequestrations of primitive embryonic lymphatic tissue.[50] Lymphangiomas are often classified into three types based on histology: capillary lymphangioma or lymphangioma simplex, composed of small thin-walled lymphatics; cavernous lymphangioma, consisting of larger lymphatic channels with advential coats; and cystic lymphangioma (hygroma) made up of larger macroscopic lymphatic spaces.[51,52] Immunocytochemical staining for CD31 (platelet-endothelial cell adhesion molecule-1), a stain that is intended to reveal the endothelium of small vessels, confirms the diagnosis.

Diagnosis can be made with a good history and clinical examination due to the characteristic clinical appearance, usually soft, compressible, and transilluminating with light. In a series of 168 patients with lymphangiomas, 41% were diagnosed based on clinical examination alone. Ultrasonography is a useful aid in diagnosis revealing a cystic structure rather than solid, however CT or MRI can show the full extent of the lesion and its relationship with the surrounding structures.[48,53] The radiologic characteristics of cystic hygroma are consistent with a fluid-filled, multiseptate mass with enhancing septal walls.[46]

Malignant transformation has not yet been reported, however complete surgical excision is the surgical treatment of choice. It is generally recommended to remove the mass due to its potential large size, which can compromise the airway if in the cervicofacial area, as well as disfigurement and recurrent bouts of inflammation, which unfortunately does not induce regression.[54] Aspirating the lesion may be useful for emergency decompression. Complete surgical resection can be difficult in the infiltrative form. They can be complicated with recurrences after surgical excision, which is reported to be 12% in patients who have undergone complete excision for neck lesions,[48] as well as with lymphangitis and cellulitis, which can lead to sepsis, prompting the need for i.v. antibiotics. It is advised that the initial approach for patients with recurrences after complete excision is to observe and wait, as spontaneous regression has been reported in up to 12% of patients after surgery. Other alternative treatments include intralesional injection with bleomycin or OK-432 with a reported response rate of 55–60%,[55,56] and argon beam ablation and laser treatment. These modalities maybe useful in patients with complex diffuse lesions when surgical therapy may be difficult to achieve a complete cure, or when vital structures are engrossed with the lesion.[57–59]

TORTICOLLIS

Torticollis or sternocleidomastoid tumor results from shortening of the sternocleidomastoid muscle, which may lead to limitation of neck movement and craniofacial deformity. The term 'torticollis' is derived from two Latin roots, 'tortus' meaning twisted and 'collum' which means neck.[60] It is considered one of the most common congenital musculoskeletal anomalies after developmental dysplasia of the hip and clubfoot, with an incidence rate of 0.3–2%.[60–62] Although various theories have been proposed with regard

to its etiology, such as birth trauma, intrauterine malposition, infectious myositis, and compartment syndrome, an exact cause has not yet been identified.[60] Diagnosis is usually established on clinical examination of a firm, spindle-shaped mass within the sternocleidomastoid muscle. Ultrasonography is the imaging modality of choice to confirm the diagnosis, usually hypoechoic compared to muscle.[63] This unilateral contraction of the muscle results in the head tilting toward the affected side and the face rotating to the opposite side, as seen in Fig. 28.7. This therefore can induce plagiocephaly and facial asymmetry at presentation. Treatment includes physical therapy, which is the primary treatment modality, with over 95% of achieving passive cervical rotation after physiotherapy.[64] This involves stretching the affected muscle to an over-corrected position by gentle, even, and persistent motion with the infant lying in a supine position. The head is flexed forward and away from the affected side and the chin is rotated toward the affected side. Some use botulinum toxin injection as an adjunct to physical therapy in those who have not responded to three months of conservative management.[65] Failure to respond to conservative treatment after the age of one year may necessitate the need for surgical intervention. Surgical options include unipolar or bipolar release, release with Z-plasty, transaxillary endoscopic release, and muscle resection. The transaxillary subcutaneous endoscopic approach has recently been developed to avoid the potential for poor cosmesis from neck scars.[66] The overall outcome from all these treatment modalities is excellent.

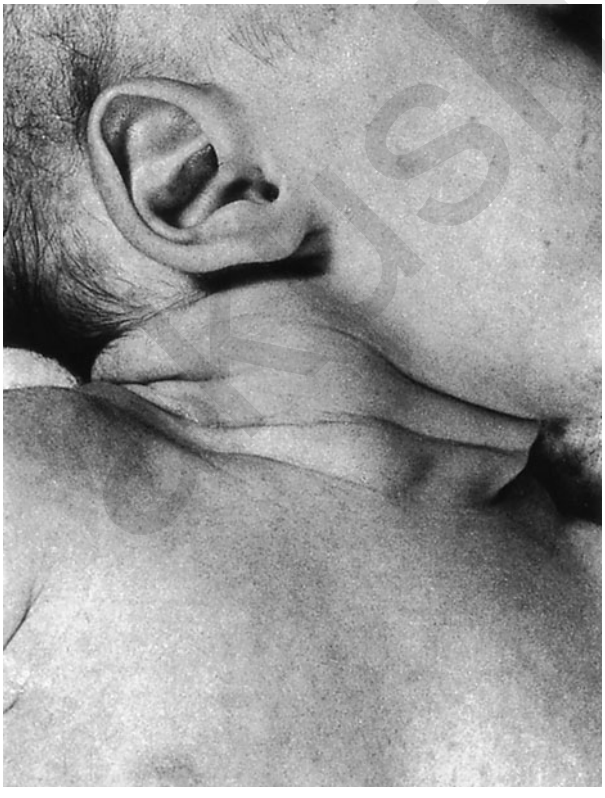

Figure 28.7 Right sternomastoid tumor in a 3-week-old infant.

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PART III

CHEST

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29

Congenital thoracic deformities

KONSTANTINOS PAPADAKIS AND ROBERT C SHAMBERGER

INTRODUCTION

Congenital thoracic deformities present a wide spectrum of abnormalities. They include a myriad of complete and incomplete sternal defects: thoracic ectopia cordis, thoraco-abdominal ectopia cordis (Cantrell's pentalogy), and bifid sternum. The most frequent are the deformities of the ribs – including pectus excavatum, pectus carinatum, and Poland's syndrome. Asphyxiating thoracic dystrophy (Juene's syndrome) and spondylothoracic dysplasia (Jarcho–Levin syndrome) pose the greatest surgical challenges.

ECTOPIA CORDIS

The first description of an exposed heart through a split sternum was described in 1671–1672, by N Stensen.[1] Later reports, by Weese in 1818[2] and Todd in 1836,[3] proposed classifications of this disorder.

Infants with this anomaly are classified by the precise location of the heart: cervical (3%), cervicothoracic, thoracic (60%), thoraco-abdominal (7%), and abdominal types (30%).[3,4] In cervical ectopia cordis, the heart protrudes at the base of the neck and occurs in association with other severe deformities of the fetus. The cervical type is not compatible with life.

Thoracic ectopia cordis includes infants with an entirely bare heart which is outside the thorax with cephalic orientation of the cardiac apex. It protrudes through a central sternal cleft and lacks a parietal pericardium and overlying skin. This condition may be associated with separate epigastric omphalocele or upper abdominal wall defect. Thoracic ectopia cordis must be distinguished from cleft sternum, in which the heart is covered by normal skin in an orthotopic intrathoracic position and is anatomically normal.

In thoraco-abdominal ectopia cordis, also known as Pentalogy of Cantrell, the heart is covered by skin or an omphalocele-like membrane. It is associated with a constellation of anomalies. The classic pentalogy includes: (1) a midline, supraumbilical abdominal wall defect; (2) a defect of the lower sternum; (3) a deficiency of the anterior diaphragm (absence of septum transversum); (4) a defect in the diaphragmatic pericardium; and (5) congenital intracardiac defects. All five anomalies may not be present, and there can be an incomplete expression of the syndrome.[5] In contrast with thoracic ectopia cordis, the heart is covered and lacks severe anterior displacement and cephalic orientation. The world literature on ectopia cordis has been extensively reviewed previously.[6]

Ectopia cordis is diagnosed by prenatal ultrasound from early stages of gestation, which facilitates perinatal preparation.[7,8] Associated intrinsic cardiac anomalies and other anomalies can be defined by *in utero* studies in order to facilitate parental discussion regarding prognosis. The cause is unknown. There has been a weak association with trisomy 18,[9,10] triploidy, and familial X-linked inheritance.[10–13] The incidence is 5.5–7.9 per one million live births.[13]

Thoracic ectopia cordis

The presentation of the heart, naked and beating upon the chest wall, has stimulated many case reports (Fig. 29.1). Surgical repair has been described,[14,15] but long-term successes are limited by a combination of associated intrinsic cardiac malformations and abnormal rotation of the heart with the apex pointing cephalad.[16] The first successful repair of ectopia cordis was achieved by Koop in 1975, as reported by Saxena (Table 29.1).[17] An infant with a normal heart had skin flap coverage at 5 hours of age, with inferior mobilization of the anterior attachments of the diaphragm. At seven months of age, an acrylic resin of Dacron and Marlex mesh was inserted to widen the sternal cleft with primary skin closure. Necrosis of the skin flaps complicated the post-operative course; the infection of the prosthetic material required its subsequent removal. The child's long-term survival has been reported.[18] Lillehei (as reported by Hornberger) achieved successful repair of the only infant with an intrinsic cardiac anomaly, tetrology of Fallot with pulmonary atresia.[19] A combination of thoracic ectopia cordis and separate omphalocele with an intervening bridge

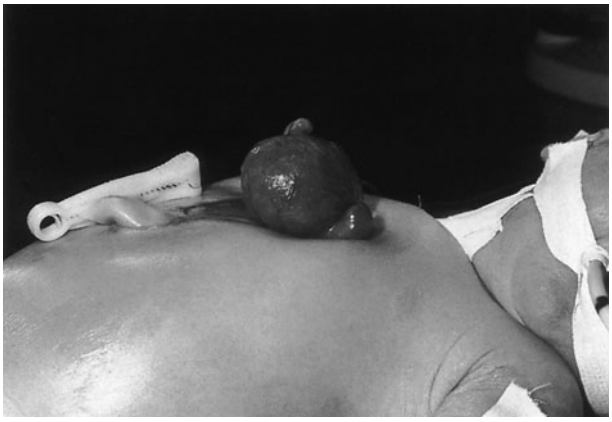


Figure 29.1 Infant with thoracic ectopia cordis. Heart lies anterior to the thoracic cavity and apex is directed cephalad.

Table 29.1 Successful repairs of ectopia cordis.

Author	Year	Cardiac lesion	Method of sternal closure
Koop	1975	None	Skin flap closure at 5 hours. Acrylic resin applied to sternal cleft at seven months (Saxena[17])
Dobell *et al.*[76]	1982	None	Perinatal skin closure in one stage. Second-stage repair with autologous rib grafts
Amato *et al.*[35]	1988	None	Skin flaps mobilized, diaphragm moved inferiorly. Gortex membrane used to close defect with skin flaps over it. Child survived but died of aspiration at 11 months of age
Lillehei	1996	Tetralogy of Fallot	Perinatal skin flap closure (Hornberger *et al.*[33]), Blalock–Taussig shunt at 4 days of life and complete repair at two years of age. No prosthetic tissue coverage

of normal skin can be particularly difficult to manage. In this group of patients, adequate skin and abdominal wall components to cover both areas is lacking and no survivors exist. The unifying theme of successfully managed cases is construction of a partially anterior chest cavity surrounding the heart and avoidance of attempts to return the heart to an orthotopic location.

For a successful outcome in infants with thoracic ectopia cordis, early definition of the associated cardiac malformation is necessary. Prenatal work up with echocardiography and magnetic resonance imaging (MRI) is often more successful than postnatal attempted ultrasonography, which is complicated by direct motion artifact of the heart and interference by air. Cardiac catheterization with angiography may be required in infants not diagnosed by antenatal studies. If the cardiac malformation is correctable, the infant should be taken from the catheterization laboratory directly to the operating room for cardiac repair. Some form of cardiac enclosure must then be provided. Use of prosthetic materials is associated with a high incidence of sepsis and death, especially when prosthetic materials have been used inside the cardiac repair.

Thoraco-abdominal ectopia cordis (Cantrell's pentalogy)

In 1958, Cantrell and coworkers[20] reported a series of a previously described congenital syndrome characterized by: (1) a midline, supraumbilical abdominal defect; (2) a defect of the lower sternum; (3) a deficiency of the anterior diaphragm; (4) a defect in the diaphragmatic pericardium; and (5) congenital intracardiac defects (Fig. 29.2). All five anomalies may not be present, and there can be an incomplete expression of the syndrome.[21] The pathogenesis of the defects present is unclear, but the occurrence of this syndrome is likely sporadic.[22] X-chromosome recessive inheritance has been postulated.[23] There have been associated cases with trisomy 13, 18, and 21.[24,25] Multiple etiologies, including viral infection,[26] maternal abuse of beta-amino-propionitrile,[27] and chlorine inhalation,[28] have also been implicated. The survival rate is less than one in 100 000 live births, and affects males 2:1, while affected females have more severe symptoms.[29] Due to the variable nature of expression, Toyama suggested further subclassification of this syndrome: class 1, definite diagnosis with all five defects present; class 2, probable diagnosis with four defects noted (including intracardiac and ventral abdominal wall abnormalities); and class 3, incomplete expression.[30]

The successful management of thoraco-abdominal ectopia cordis necessitates a multispecialty approach from the establishment of the antenatal diagnosis to the completed staged repairs. Immediate neonatal intervention is required in patients with a large upper omphalocele and lower sternal cleft (Fig. 29.3). In a staged repair, primary closure,

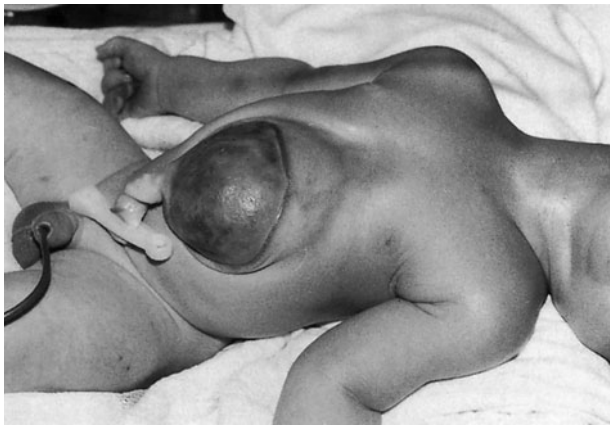


Figure 29.2 Newborn male with Cantrell's pentalogy. Flaring of the lower thoracic cavity is present with a large epigastric omphalocele. The septum transversum and the inferior portion of the pericardium were absent (From Welch[75] by permission of WB Saunders Co., Philadelphia).

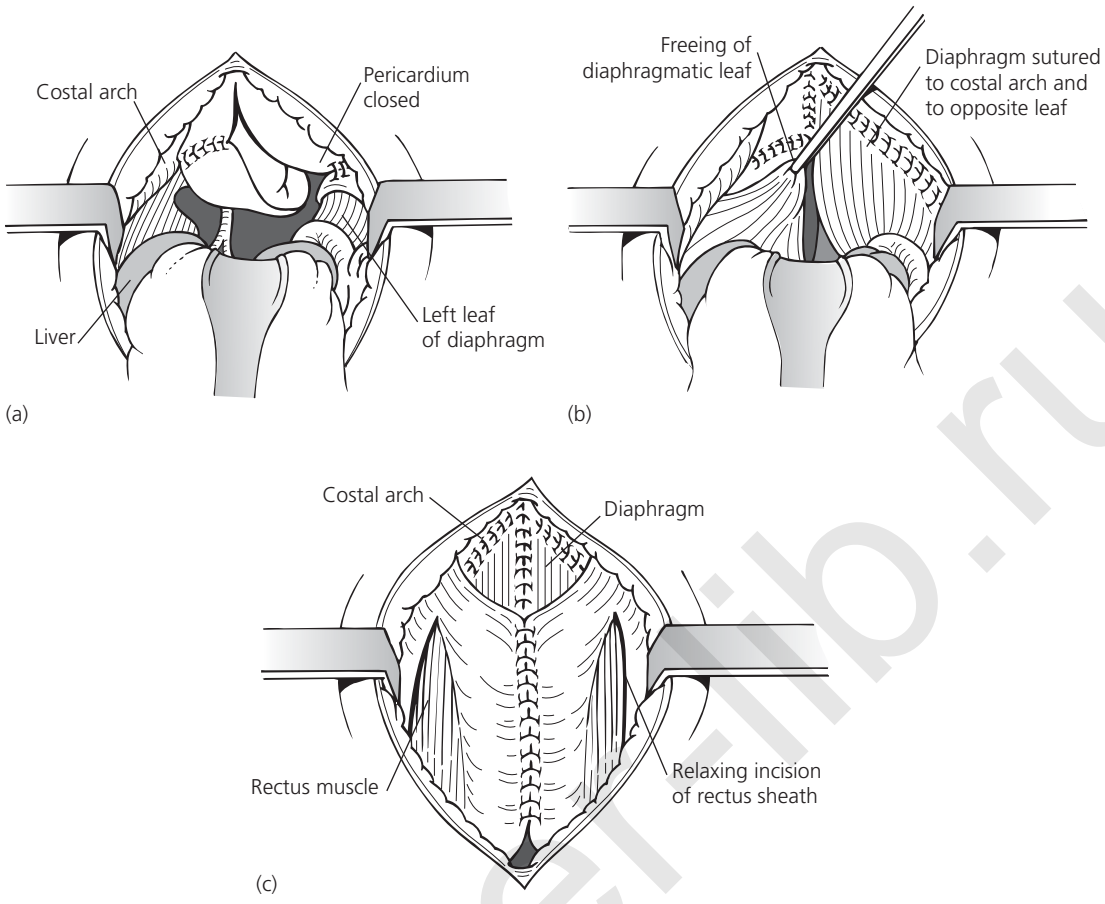


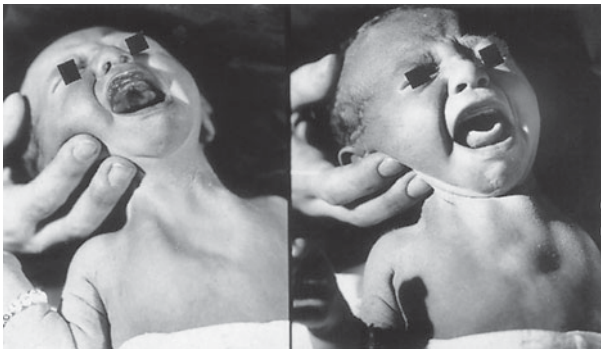
Figure 29.3 Repair of pentalogy of Cantrell is depicted. (a) The pericardium is closed after appropriate lateral and inferior dissection to the vena cava. The right and left dorsal leaves of the diaphragm which are widely separated are identified. The liver is retracted inferiorly after division of the falciform ligament. (b) Pedicles of the diaphragm are developed from each side and transposed medially. They are sutured together and to each costal arch. (c) After diaphragmatic closure, the falciform ligament is reconstructed. Closure continues by advancement of the anterior sheath of the rectus muscle to the midline. Lateral relaxing incisions are often required. Parietal repair can be accomplished at the time of cardiac correction. Prosthetic material may be required to obtain closure of the abdominal component of the repair (From Welch[75] by permission of WB Saunders Co., Philadelphia).

split-thickness skin graft, cadaveric skin graft or prosthetic material sutured to the skin edges[31–33] must be achieved to prevent fluid losses, cardiac dessication, or trauma to the heart. Subsequent stages may be needed to gradually reduce the heart to a more anatomic position.[32] Multiple procedures have been suggested to try to accommodate the heart; these include partial or total thymus excision, repair of the diaphragmatic defect, plication of a hemidiaphragm, or division of the costal cartilages. Some have even advocated a left lower lobectomy be performed in order to better accommodate the heart in the left pleural space.[34] In all procedures care must be taken to prevent kinking of the great vessels and to avoid phrenic nerve damage.[35] Other options include the use of alloplastic materials, such as creation of methyl methacrylate struts shaped as ribs and spaced to allow for future growth of ribs and thorax.[36]

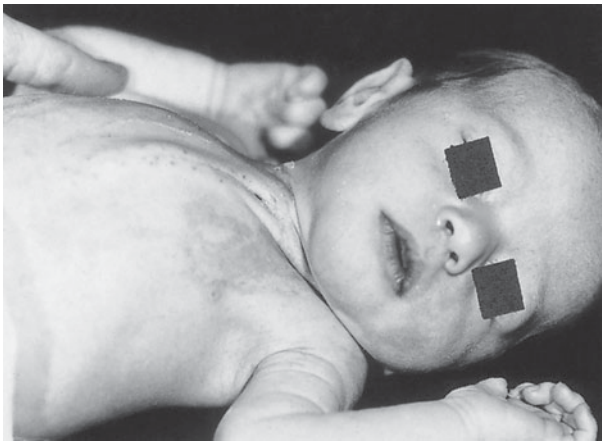
BIFID STERNUM

Sternal clefts are malformations caused by the failure of fusion of the sternal elements. The etiology of sternal cleft deformity is unknown. There are studies on ventral body development in mice that indicate impairment in Hoxb gene expression as a possible factor.[37] Cleft sternum may be complete or incomplete and results from failure of the mesenchymal plate fusion process at the eighth week of gestation. No familial predisposition has been described. Alcohol intake and methylcobalamine deficiency have been implicated. There is a slight female predominance. Sternal clefts can be associated with cervicofacial hemangiomas (vascular dysplasia)[38] and PHACES syndrome.[39,40]

In all cases, there is a sternal separation and skin coverage of the midline defect, intact pleural envelopes, and a normal diaphragm. Omphalocele does not occur in association with this anomaly and the condition causes little difficulty other than a dramatic increase in the deformity with crying or valsalva maneuver (Fig. 29.4). The sternal defect involved an upper cleft in 46 patients, an upper cleft to the xiphoid in 33 patients, and a complete cleft in 23 patients. The cleft involved the lower sternum in only five reported cases. A total of 69 repairs has been reported, 25 with primary closure.[6] None of the infants and children had intrinsic congenital heart disease.



(a)



(b)

Figure 29.4 Newborn infant with a bifid sternum. (a) Vigorous crying produces retraction at the defect with inspiration (left) and protrusion with exhalation or Valsalva maneuver (right). (b) Following repair, normal configuration of the sternum is present.

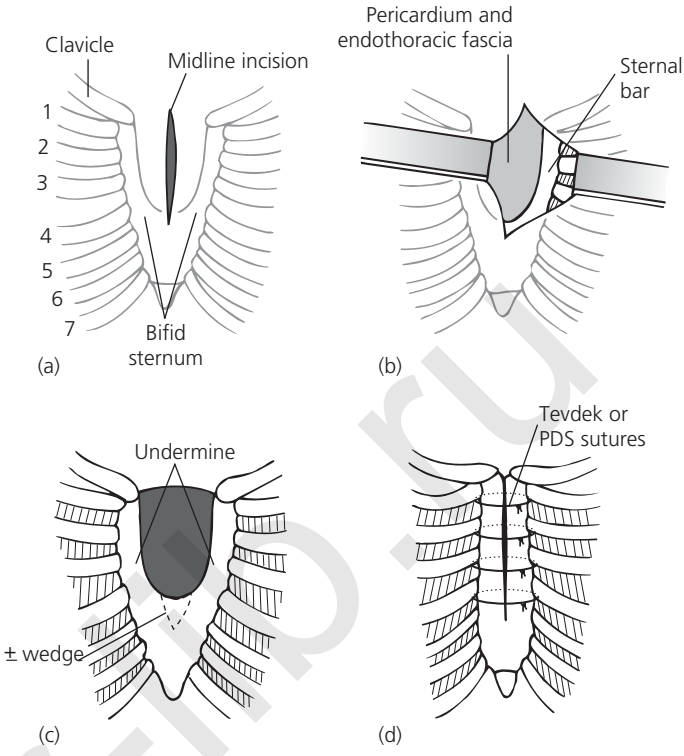


Figure 29.5 (a) Repair of bifid sternum is best performed through a longitudinal incision extending the length of the defect. (b) Directly beneath the subcutaneous tissues, the sternal bars are encountered with pectoral muscles present lateral to the bars. The endothoracic fascia and pericardium are just below these structures. (c) The endothoracic fascia is mobilized off the sternal bars posteriorly with blunt dissection to allow safe placement of the sutures. Approximation of the sternal bars may be facilitated by excising a wedge of cartilage inferiorly. Repair is best accomplished in the neonatal period because of the flexibility of the chest wall. (d) Closure of the defect is achieved with 2-0 Tevdek or PDS sutures (From Shamberger and Welch[6] by permission of Springer-Verlag, Heidelberg, Germany).

Most authors now recommend surgical treatment in the newborn period when all such malformations can be dealt with by simple direct closure without producing compression of the heart and avoiding the use of prosthetic materials (Fig. 29.5).[41,42] No reports of recurrence or delayed healing have been encountered. In older children, reconstruction of the anterior chest wall using multiple oblique sliding chondrotomies leaving the perichondrium intact was reported by Sabiston[43] and subsequently by others. This technique is useful in older infants and children with a less flexible chest wall and a wide defect. Closure employing composite cartilage grafts from the costal arch or prosthetic materials such as Marlex or Teflon mesh have also been reported, but these methods can be avoided with repair of the infants in a timely fashion.

Shamberger and Welch[6] reviewed their experience with sternal defects at the Children's Hospital Boston, MA, USA. A total of 16 patients with sternal defects were identified, five with ectopia cordis, eight with thoraco-abdominal ectopia cordis, and three with cleft sternum.[6] Thoracic ectopia cordis was uniformly fatal in their series; thoraco-abdominal ectopia cordis was fatal in five of eight cases and bifid sternum was successfully repaired in all three cases in infancy.

PECTUS EXCAVATUM

Pectus excavatum (funnel chest or trichterbrust) is a depression of the sternum and lower costal cartilages. It is generally identified within the first year of life (in 86% of patients) and in many infants it is noted at birth.[44] The extent of sternal and cartilaginous deformity is quite variable, but generally consists of posterior displacement of the sternum below the insertion of the second costal cartilage. The first and second costal cartilages are generally normal in contour, whereas the third to seventh are curved posteriorly to join the sternum. The ossified portion of the rib is normal in configuration in infancy. In infants, the extreme flexibility of the costal cartilages results in remarkable changes in the deformity with vigorous respiration or crying. Self-limited deformities are either gone or vastly improved by three years of age. Repairs should be avoided in all infants younger than two years of age or later if they have continued sternal flexibility. We generally delay open repair until children have achieved much of their chest wall growth to avoid the reported

occurrence of acquired thoracic dystrophy in younger children following repair.

Pectus excavatum may occur as frequently as one in 300–400 live births.[45] The etiology of pectus excavatum is unknown. A family history of some type of anterior thoracic deformity is present in 37% of patients.[44] Scoliosis is identified in up to 15% of patients with pectus excavatum, usually in children with an asymmetric thoracic deformity, but it is generally not seen in infancy. Patients with Marfan syndrome have a high incidence of associated chest wall deformities, often in the most severe form and usually accompanied by scoliosis.

PECTUS CARINATUM

Pectus carinatum, the anterior protrusion deformity of the chest, is much less frequent than pectus excavatum, comprising 16% of our combined series.[46] A spectrum of protrusion deformities exists and these are often divided into four types. The most frequent type consists of anterior displacement of the sternum with symmetric concavity of the costal cartilages laterally. Asymmetric deformities with anterior displacement of the costal cartilages on one side and a normally positioned or oblique sternum and normal cartilages on the contralateral side are less common. 'Mixed' lesions have a carinate deformity on one side and a depression or excavatum deformity on the contralateral side, often with sternal obliquity. Most unusual are the upper 'pouter pigeon' or chondromanubrial deformities, with protrusion of the manubrium and second and third costal cartilages and relative depression of the body of the sternum.

The etiology of pectus carinatum is unknown. There is overgrowth of the costal cartilages, with forward buckling and anterior displacement of the sternum. As with pectus excavatum, there is a clear-cut increased family incidence, suggesting a genetic basis. In a recent review, 26% of patients had a family history of chest wall deformity and 12% had a family history of scoliosis.[46] It is much more common in boys than girls, with a ratio of 4:1. Only the upper 'pouter pigeon' deformity is associated with congenital heart disease in 18% of cases.[47]

In contrast to pectus excavatum, patients with pectus carinatum have a much later appearance of the deformity. In a recent review, only one-sixth of the patients were noted to have a carinate deformity within the first year of life and, in almost half it was noted after the onset of the pubertal growth spurt at 11 years of age.[46] The deformity, which may be mild at birth, often worsens rapidly during puberty. Because of mild deformity at birth and flexible costal cartilages, this deformity is rarely repaired during the first two years of life and is probably best repaired in the early teenage years.

POLAND SYNDROME

In 1841, Poland described congenital absence of the pectoralis major and minor muscles, associated with syndactyly.[48] This is a diverse syndrome, often involving chest wall and breast deformity, as well as serious ipsilateral hand and arm anomalies. The extent of thoracic involvement may range from hypoplasia of the sternal head of the pectoralis major and minor muscles with normal underlying ribs, to complete absence of the anterior portions of the second to fourth ribs and cartilages, often called the second to fourth rib syndrome. Breast involvement is significant in females, ranging from mild degrees of breast hypoplasia to complete absence of the breast (amastia) and nipple (athelia). Hand deformities are frequent and occurred in the patient described by Poland. They may include hypoplasia (brachydactyly), fused fingers (syndactyly), and mitten or claw deformity (ectromelia).

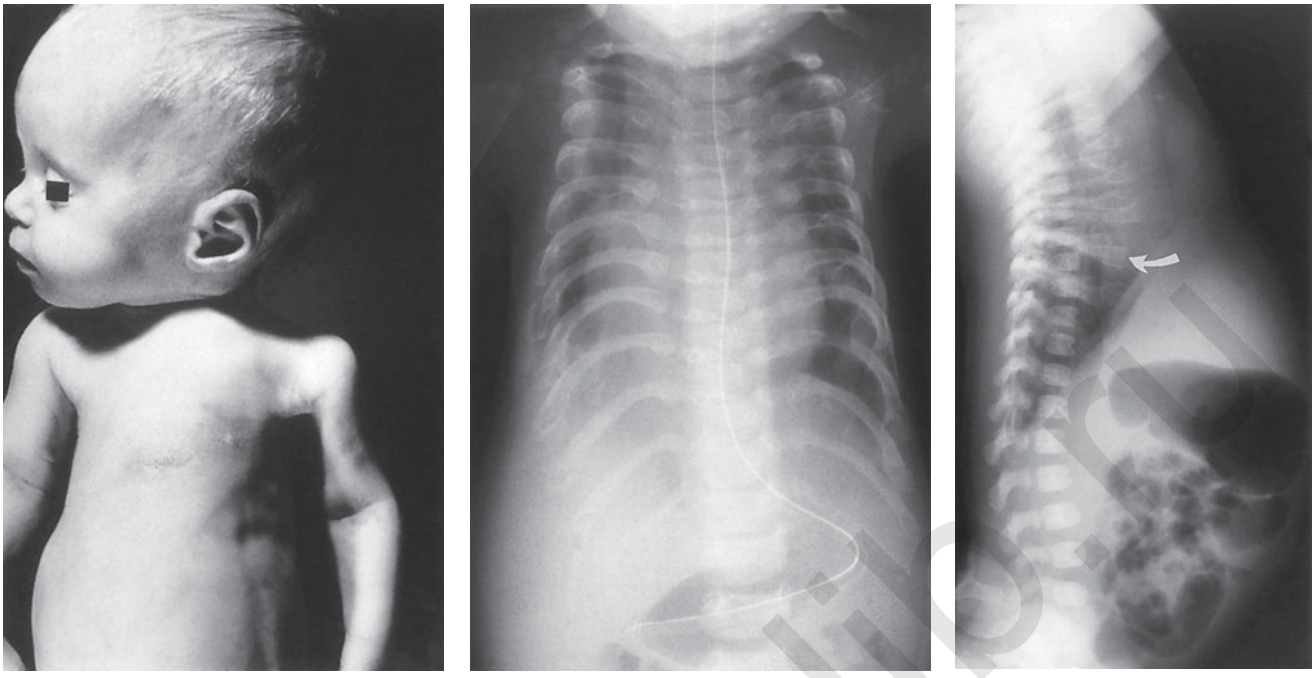
This condition is present at birth and has an estimated incidence of one in 30000–32000.[49] The etiology of this deformity is unknown, but it affects the developing somatic tissue for the entire limb bud and chest wall. Abnormalities in the breast can be recognized at birth by the absence of the underlying breast bud and hypoplastic, often superiorly displaced, nipple. Males predominate by at least 3:1 and show a right-sided predilection. Females show less sidedness. Familial cases, in either gender, occur equally on the left or the right.[50] In our series, chest wall reconstruction was required in 10 out of 41 cases, but never in infancy.[51]

THORACIC DEFORMITIES IN SKELETAL DISORDERS

Congenital asphyxiating thoracic dystrophy (Jeune's disease)

In 1954, Jeune *et al.*[52] first described a pair of siblings with a narrow rigid chest and multiple cartilage anomalies. The syndrome is also known as asphyxiating thoracic dysplasia (ATD) and thoracic-pelvic-phalangeal dystrophy.[53] This is a rare autosomal recessive disorder.[54] Other manifestations include dwarfism with short ribs and short limbs, with radiographic changes in the ribs and pelvis. There is some association with abnormalities of the kidneys, liver, pancreas, and retina.[55] Variable skeletal and radiographic severity occurs in this syndrome. Its most prominent feature is a narrow 'bell-shaped' thorax and protuberant abdomen. The thorax is narrow in both the transverse and sagittal axis and has little respiratory motion due to the horizontal direction of the ribs (Fig. 29.6). The ribs are short and wide and the splayed costochondral junctions barely reach the anterior axillary line. The costal cartilage is abundant and irregular like a rachitic rosary. Microscopic examination of the costochondral junction reveals disordered and poorly progressing endochondral ossification, resulting in decreased rib length.

The syndrome has variable expression and extent of pulmonary involvement. Lung hypoplasia is due to a restricted thoracic cage and may be the cause of death in infancy. The most common presentation is hypoventilation, caused by impaired chest expansion. Frequency of the condition is approximately one per 100000–130000 live births.[56] Reports have described the ability to diagnose fetuses suspected to have Jeune's syndrome with prenatal



(a) (b) (c)

Figure 29.6 Infant with asphyxiating thoracic dystrophy (Jeune syndrome). (a) Clinical photograph demonstrates small size of thorax relative to infant. (b) X-ray shows the short horizontal ribs and narrow thorax with limited lung volumes. (c) Lateral x-ray demonstrates the endings of the bony ribs at the mid-axillary line and the abnormal costochondral junctions (arrow).

ultrasonography.[57,58] The pathological findings in autopsy cases are variable and show a range of pulmonary development; in most cases the bronchial development is normal and there is a variable decrease in alveolar divisions.[59]

There have been many surgical attempts to treat this disorder. The main goal of surgery is to expand thoracic volume and allow improved lung expansion. Early surgical interventions were reported by Barnes and colleagues, Karjoo and coworkers and Mustard.[60–62] Early repairs reported attempts at thoracic enlargement by splitting the sternum, which was then held apart by a variety of graft materials. Authors used either autologous tissue, such as rib grafts or iliac crest bone, or synthetic materials including methyl methacrylate, and stainless steel wires. There are multiple reports of initial improvement in lung ventilation, but subsequent growth failure of the chest resulted in recurrent respiratory distress.[63,64] In 1995, Davis and coworkers described a new lateral thoracic expansion technique for ATD.[65] New bone formation is documented 3 weeks after the procedure. Long-term follow up for this procedure has not been reported.

Campbell and coworkers have described a vertical expandable titanium rib (VEPTR) procedure for use in a variety of pediatric conditions of 'thoracic insufficiency syndrome'.[66] Vertically oriented titanium struts are attached to ribs and or transverse processes of the spine and progressively lengthened, with a series of surgical procedures to allow progressive expansion of the chest cavity. Computed tomography (CT) imaging studies have documented postoperative increase in chest volume, however, improvements in pulmonary function tests (PFTs) have not been demonstrated. Few patients with Jeune syndrome[67] have had VEPTR procedures. In one series, 9% of those treated with VEPTR had Jeune syndrome and all died within two years of the procedure, two from respiratory complications, one from renal failure, and one from liver failure.[68] The ultimate results of all surgical attempts will depend on the degree of underlying pulmonary parenchymal impairment of the infants.

Spondylothoracic dysplasia (Jarcho–Levin syndrome)

Spondylothoracic dysplasia is an autosomal recessive deformity characterized by short trunk dwarfism associated with multiple vertebral and rib malformations.[69] The ribs have a crab-like appearance (Fig. 29.7). Death occurs early in infancy from respiratory failure and pneumonia.[70] Patients have multiple alternating hemi-vertebrae which affect most of the thoracic and lumbar spine. The ossification centers rarely cross the midline. Multiple posterior fusions of the ribs, as well as remarkable shortening of the thoracic spine, result in a 'crab-like' radiographic appearance of the chest. One-third of the patients with this syndrome have associated malformations including congenital heart disease and renal anomalies. Its occurrence has been reported primarily in Puerto Rican families (15 out of 18 cases).[71] Bone formation is normal in these patients. Successful prenatal diagnosis can be established by sonographic examination.[72] Thoracic deformity is secondary to the spinal anomaly which results in close posterior approximation of the origin of the ribs. Although most infants with this syndrome succumb before

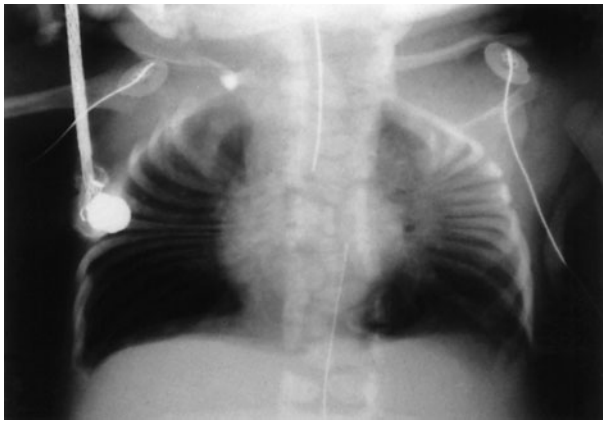


Figure 29.7 X-ray of infant with spondylothoracic dysplasia (Jarcho–Levin syndrome). Severe abnormality of the spine is apparent with multiple hemivertebrae and the 'crab-like' ribs with close approximation posteriorly and splaying out anteriorly.

15 months of age, no surgical efforts have been proposed or attempted.[73] Spondylothoracic dysplasia has a mortality rate approaching 50% from respiratory complications due to thoracic insufficiency syndrome. In spite of severe restrictive respiratory disease, adult survivors of spondylothoracic dysplasia appear to do well clinically for unknown reasons.[74]

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30

Mediastinal masses in the newborn

STEPHEN J SHOCHAT

INTRODUCTION

Mediastinal masses in the newborn represent a wide variety of congenital and neoplastic lesions which can present interesting diagnostic and therapeutic challenges. However, despite the heterogeneous make up of this group of lesions, an accurate preoperative diagnosis can usually be established on the basis of the location of the mass. While the subject of this chapter deals with the treatment of masses in the newborn, it is helpful to discuss differences between various age groups when dealing with mediastinal masses in the childhood population.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of mediastinal masses in infants and children is simplified if the mediastinum is arbitrarily separated into three compartments (Fig. 30.1). For the purpose of this discussion, the mediastinum will be partitioned as follow: the anterior mediastinum lies anterior to the heart and lung roots and contains the thymus, anterior mediastinal lymph nodes, and rarely a substernal extension of the thyroid and parathyroiod; the middle mediastinum contains the trachea, bronchi, mediastinal lymph nodes, heart, and great vessels; the posterior mediastinum lies behind the heart and lung roots and contains the esophagus and intercostals sympathetic nerves. Anterior mediastinal masses include teratomas; thymic cysts, hyperplasia, or tumors; cystic hygromas and lymphomas. Masses within the middle mediastinum include the lymphomas, bronchogenic cysts, and granulomatous infections within the mediastinal lymph nodes. Posterior mediastinal lesions include the tumors of neurogenic origin, enterogenous cysts, and the undifferentiated sarcomas.

The age of the patient at the time of diagnosis is extremely important, since certain masses have a predilection for younger infants and others are predominantly seen in older children and adolescents. In newborns and children under two years of age, the most common mediastinal is the neuroblastoma within the posterior mediastinum. In addition, thymic hyperplasia and bronchogenic cysts are seen predominantly in children less than two years of age. The various lymphomas are the most common mediastinal masses seen in children greater than two years. The mean age of children with mediastinal Hodgkin's disease is approximately 13 years of age and the mean age of children who present with non-Hodgkin's lymphoma is 11 years of age.

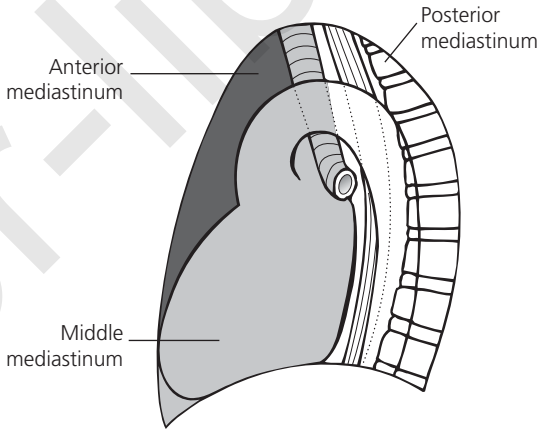

Figure 30.1 Compartments of the mediastinum.

The presenting signs and symptoms in infants and children with mediastinal masses vary depending upon age:

- acute respiratory distress;
- fever;
- cough;
- shortness of breath;
- cervical adenopathy;
- superior vena caval syndrome;
- Horner's syndrome;
- asymptomatic.

Infants under two years of age frequently present with signs of tracheal compression and acute respiratory distress. This is

due to the smaller, softer, more pliable tracheobronchial tree in infants, as well as the fact that they do not have a fixed mediastinum so that large mediastinal masses can cause a significant shift of the mediastinum with compromise of the contralateral hemithorax. Older children will present with symptoms of fever, cough, and shortness of breath. Approximately half the children with mediastinal lymphomas will present with cervical adenopathy. Superior vena caval obstruction is rare in children, but is occasionally seen. Horner's syndrome may be the presenting finding in infants with neuroblastomas or neurogenic tumors of the posterior mediastinum. Asymptomatic mediastinal masses are seen in children of all ages and are frequently noted on a chest x-ray performed for a mild upper respiratory infection or are discovered incidentally following imaging studies for symptoms unrelated to the mediastinal mass.

DIAGNOSIS

A systematic approach to the diagnosis of a mediastinal mass in the newborn is imperative:

- posteroanterior–lateral chest x-ray;
- barium swallow;
- ultrasonography;
- computed tomography (CT) scan;
- magnetic resonance imaging (MRI);
- bone marrow – lymph node biopsy;
- skin test – complement fixation;
- serum markers – AFP, HCG;
- urinary catecholamines.

The most helpful diagnostic technique in this age group is still the chest x-ray in the posteroanterior and lateral projections, in order to localize the position of the mass. Vertebral anomalies associated with a medistinal mass in an infant should raise the suspicion of the so-called neuroenteric variety of enterogenous cyst, which communicates with the meninges. Calcification within a posterior mediastinal mass suggests the presence of a neuroblastoma and anterior mediastinal teratomas frequently contain calcification. In cases of suspected enterogenous and brochogenic cysts, the esophagogram may be of value. Ultrasonography of the chest can be quite helpful in defining complicated mediastinal lesions and has been especially helpful in infants with suspected thymic hyperplasia. Echocardiography should be performed to delineate the heart and great vessels if lesions of these structures are suspected. A CT scan should be reserved for difficult diagnostic dilemmas and for delineating anatomical boundaries in preparation for tumor resection. MRI may be of help in differentiating masses of vascular origin from other mediastinal structures and may be helpful in infants with suspected thymic hyperplasia. In addition, MRI should be considered in cases of posterior mediastinal masses in order to detect intraspinous extension of tumor (dumbbell tumors).

Cervical lymph node biopsy should be considered in children with middle mediastinal lesions and suspected lymphoma. A bone marrow aspiration and biopsy should also be performed prior to other invasive studies in children suspected of having non-Hodgkin's lymphoma. Skin testing and complement fixation titers should be considered in infants with middle mediastinal masses to rule out granulomatous infections. Alpha fetoprotein determination and HCG titers should be performed in children with anterior mediastinal masses if malignant teratomas are suspected. Urinary catecholamine metabolites should be evaluated in infants with posterior mediastinal masses, both for diagnosis and for postoperative follow up in children with suspected neuroblastomas.

ANTERIOR MEDIASTINUM

Thymic hyperplasia is the most common anterior mediastinal mass seen in infants (Fig. 30.2). This diagnosis is usually not difficult as there is frequently a characteristic 'sail' sign on routine chest x-ray. Recently, ultrasonography has been very helpful in differentiating thymic hyperplasia from other mediastinal masses and should be considered in difficult cases. The use of steroids to help with the diagnosis of thymic hyperplasia in infants as listed below is rarely necessary and has not been required in our institution for some time. Benign teratoma is the most frequent anterior mediastinal neoplasm seen in children under two years of age (Fig. 30.3). These masses are usually well encapsulated and can be treated by total excision through a posterolateral thoracotomy. Cystic hygromas are also observed in infants, but usually have a cervical or axillary component which makes this diagnosis obvious. Thymic cysts are extremely rare in children and only 20 thymomas have been reported in childhood. Germ cell tumors of the anterior mediastinum are usually seen in older children and adolescents and many have an endodermal sinus or yolk sac component with an elevated serum alpha fetoprotein. AFP and HCG levels should be performed in all older children with anterior mediastinal masses as these markers are helpful not only in diagnosis, but in following response to therapy.

These tumors are highly malignant lesions and total resection rarely is possible. Evaluation of these patients requires a multidisciplinary approach with consultation between surgeon, pediatric oncologist, and radiation therapist.

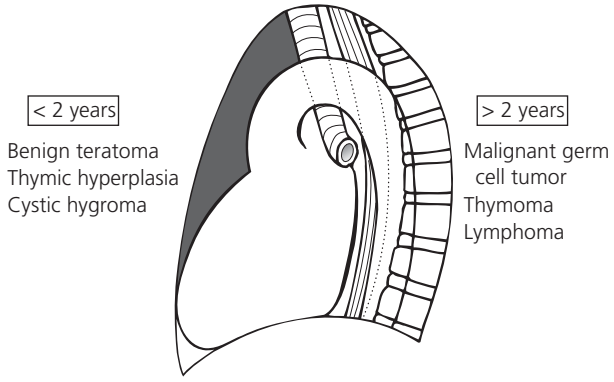

Figure 30.2 Anterior mediastinum.

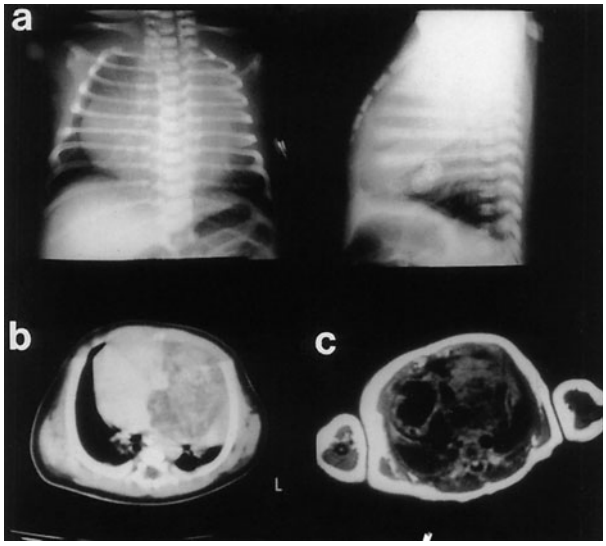

Figure 30.3 Cardiac teratoma with anterior mediastinal mass: (a) posteroanterior–lateral chest x-ray; (b) CT scan; (c) MRI.

In the rare case where total excision is possible, this should be carried out and followed by multi-agent chemotherapy. However, radical resection is not indicated. When the tumor is non-resectable, a biopsy rather than partial resection is followed by chemotherapy and delayed primary excision. While isolated lymphomas of the thymus do occur, the majority of lymphomas of the anterior mediastinum will also have a major middle mediastinal component which makes diagnosis straightforward.

MIDDLE MEDIASTINUM

Bronchogenic cysts may be seen in all age groups, but are the most frequent mass seen within the middle medistinum in infants and children under two years of age (Fig. 30.4). Bronchogenic cysts are located in the subcarinal region and are frequently associated with a characteristic expiratory stridor due to accentuation of the obstruction of the lower trachea during expiration. Bronchogenic cysts are frequently difficult to diagnose on routine chest x-ray, but there is usually a characteristic displacement of the esophagus on barium swallow (Fig. 30.5). Bronchogenic cysts occasionally are intimately attached to the membranous trachea and if this is the case a small portion of the cysts should be left attached to the trachea.

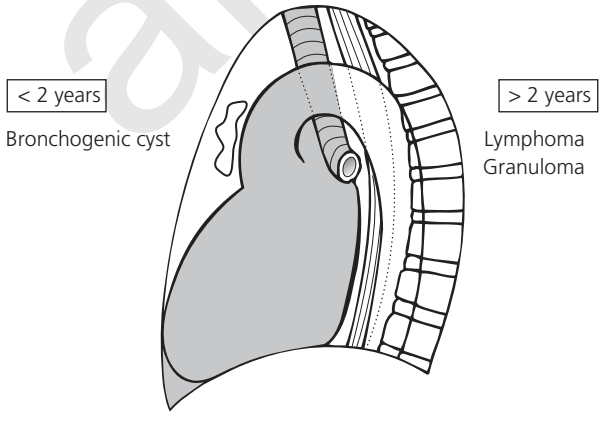

Figure 30.4 Middle mediastinum.

The most common mediastinal mass in individuals over two years of age is Hodgkin's or non-Hodgkin's lymphoma. Lymphomas are also the most frequent tumors involving the middle mediastinum.

The initial diagnostic work up in children with suspected lymphoma should include cervical or supraclavicular lymph node biopsy, as well as bone marrow biopsy. Mediastinoscopy, anterior mediastinotomy, or CT-guided needle biopsy are the procedures of choice to establish a tissue diagnosis in the absence of cervical adenopathy. A formal thoracotomy is rarely indicated for diagnosis or treatment in children with lymphoma. Children who present with a large middle mediastinal mass and respiratory distress and a suspected diagnosis of non-Hodgkin's lymphoma may be treated initially with steroids prior to biopsy because of the dangers of acute respiratory decompensation on induction of anesthesia. However, every attempt should be made to safely establish a diagnosis prior to the use of steroids since even a brief course of therapy can make subsequent diagnosis difficult. A multidisciplinary approach (surgeon, oncologist, radiotherapist) to the child with suspected mediastinal lymphoma is imperative and tissue obtained at the time of biopsy should be placed in saline so that immunologic surface marker studies can be performed. These studies are extremely important in the classification, and hence therapy, of the various non-Hodgkin's lymphomas.

Granulomatous infections of the paratracheal, subcarinal, or hilar lymph nodes are occasionally seen and can usually be diagnosed by appropriate skin tests and complement fixation titers. In the Midwest of the USA and other endemic areas, histoplasmosis seems to have a predilection for the azygous node which is characteristically enlarged in children with this infection. Diagnosis is confirmed by mediastinoscopy, mediastinotomy, or rarely thoracotomy.

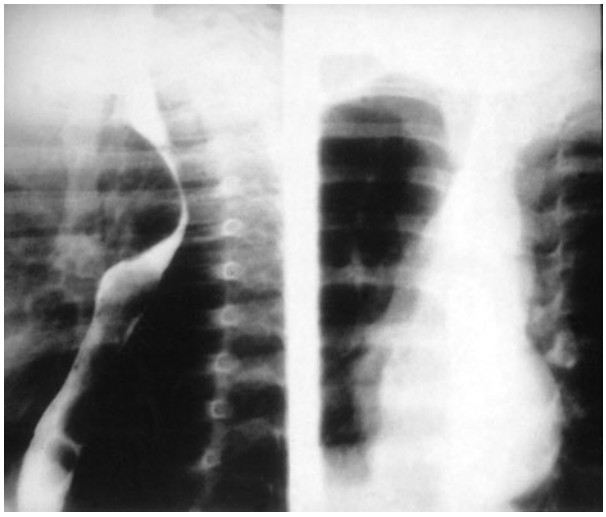

Figure 30.5 Bronchogenic cyst showing displacement of esophagus. Normal appearing chest x-ray.

POSTERIOR MEDIASTINUM

The most common mass of the posterior mediastinum, and in fact the most common mass in newborns, is a posterior mediastinal neuroblastoma (Fig. 30.6). Mediastinal neuroblastomas are interesting in that they seem to have a different biological behavior than intra-abdominal tumors. The majority of mediastinal neuroblastomas are localized or low-stage disease and have a favorable outcome following resection. These tumors are more often occult and are diagnosed on x-ray examination for other complaints. Respiratory distress due to compression or deviation of trachea is a feature in some cases. Thoracic neuroblastomas with dumb-bell extension may present with neurological symptoms due to spinal cord compression. While the treatment of mediastinal neuroblastomas in children is total excision if at all possible, this does not mean radical chest wall resection. In the rare case of a massive mediastinal neuroblastoma, that cannot be resected without a radical operation, a biopsy to establish the diagnosis is followed by chemotherapy and delayed primary excision. While this clinical situation is unusual, we have found that a tissue diagnosis can usually be obtained by a percutaneous core needle biopsy avoiding formal thoracotomy. In children with disseminated neuroblastoma, thoractotomy and resection should be carried out only after all metastatic sites are controlled with multi-agent chemotherapy. Despite impressive shrinking of tumor following chemotherapy and complete delayed primary excision, the prognosis continues to be discouraging.

Children with posterior mediastinal neuroblastoma can also present with unusual symptoms. The case in Figure. 30.7 presented with a three-month history of diarrhea. The mass turned out to be a large neuroblastoma that extended up into the cervical region. The tumor contained high concentrations of prostaglandin E which was the etiology of the diarrhea. Vasoactive intestinal polypeptide secreting neuroblastomas have also been described in children with profuse watery diarrhea. Ratner and Pelton reported an infant who presented with progressively worsening labored respirations and was found to have a neuroblastoma extending from the mediastinum, through the thoracic inlet, and into the neck.

Enterogenous cysts, while rare, represent an interesting spectrum of lesions. They may be intimately associated with

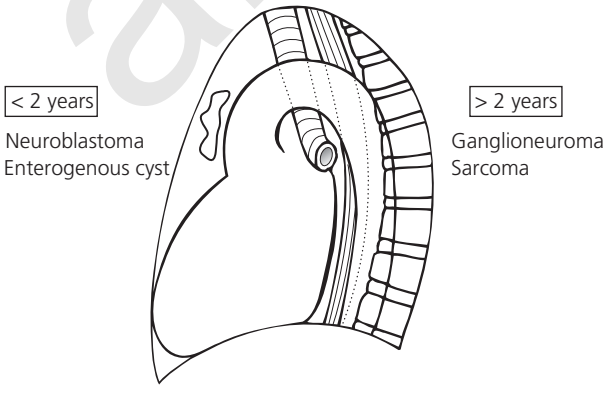

Figure 30.6 Posterior mediastinum.

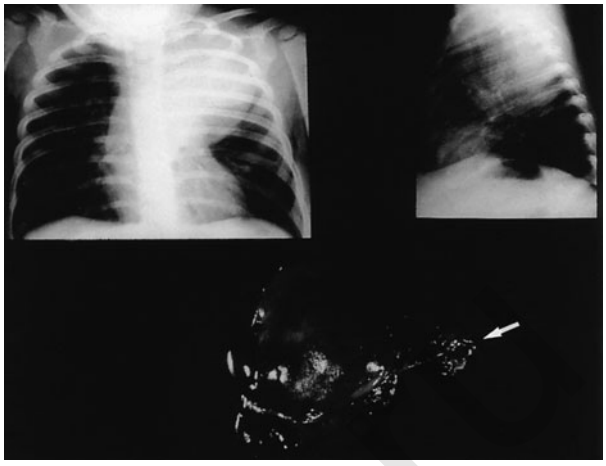

Figure 30.7 Posterior mediastinal neuroblastoma treated by total excision. Note cervical extension (arrow).

the esophagus and cause dysphagia or they can contain gastric mucosa which has been associated with peptic ulceration, perforation, and bleeding. Large cysts can have abdominal extensions and communicate with an intestinal duplication.

An interesting but rare variant is the so-called neurenteric cyst that communicates with the meninges through an intraspinous component. These infants present with a large mediastinal mass, respiratory distress, and rarely neurological symptoms. Characteristic deformities of the lower cervical and upper thoracic spine are always present on routine chest x-ray. During resection of these masses through a posterolateral thoracotomy, the communication between the thoracic and infraspinous component must be identified and ligated to prevent a spinal fluid leak and meningitis. These patients should be evaluated by MRI as the infraspinous cystic component may require laminectomy and excision.

ANESTHETIC MANAGEMENT OF INFANTS WITH A MEDIASTINAL MASS

Respiratory compromise on induction of general anesthesia in children with large mediastinal masses is a well-recognized complication that must be considered in the preoperative evaluation of any child with a mediastinal mass. Infants and small children have a small compressible airway, which is associated with significant increased airway resistance with even a modest degree of narrowing. In addition, infants do not have a fixed mediastinum and large masses can easily displace the mediastinal structures with compression of the tracheobrochial tree, superior vena cava, or right ventricular outflow tract. Cardiac output may also be diminished due to pressure on the great vessels. Induction of anesthesia is associated with a decrease in the functional residual capacity, decreased lung capacity, and an increase in lung retractile force. The above alterations are extenuated with the addition of paralysis. Narrowing of the trachea will also become smaller when the patient changes from spontaneous to positive pressure ventilation. All of the above factors lead

to the sometime critical condition that is associated with general anesthesia in these patients.

The most important factor in preventing anesthetic complications in children with mediastinal mass is recognition of the above problems and the anticipation of a possible airway problem. A very thorough radiologic evaluation should be performed and CT examination to determine the tracheal cross-sectional area may also be of help. Once the preoperative evaluation is completed, the anesthetic of choice can be determined depending upon the procedure that will be performed. Preoperative radiation therapy or chemotherapy may be required prior to primary excision or biopsy. Incisional biopsies can be performed under local anesthesia in older children and needle biopsy with local anesthesia can be performed in younger children and infants. In children with benign lesions, one lung anesthesia with placement of the endotracheal tube beyond the obstruction has been found to be helpful and occasionally ventilation through a rigid bronchoscope is necessary. While cardiopulmonary bypass of extracorporeal membrane oxygenation (ECMO) may be required, these techniques are usually not necessary in the majority of patients. A high index of suspicion, meticulous preoperative evaluation, and a multidisciplinary action plan decided upon by surgeons, anesthesiology, radiation therapist, hematology/oncologist, and pathologist can usually avert the potential catastrophe associated with general anesthesia in children with critical mediastinal masses.

OPERATIVE TECHNIQUE FOR REMOVAL OF MEDIASTINAL NEUROBLASTOMA

The tumor is usually approached through a standard posterolateral thoracotomy at the approximate level of the tumor. The lung is retracted medially to reveal tumor covered with pleura arising from the sympathetic trunk and an assessment made of it and obvious lymph node involvement in the vicinity. The pleura is incised around the tumor approximately 1 cm from it and the fascia and pleura mobilized towards the tumor. A plane of dissection can usually be developed superficial to endothoracic fascia. The tumor is now mobilized from the ribs by sharp dissection and intercostals vessels entering the tumor will need division. If the tumor extends far enough anteriorly, the azygos vein on the right side will need division between ties. Care is taken to avoid damage to the first thoracic nerve passing laterally across the first rib to join the brachial plexus. The superior intercostals artery normally descends between the first nerve and the sympathetic trunk. Other intercostal nerves may be sacrificed if they are intimate with the tumor.

Depending on how far the tumor has extended anteriorly, it will need to be dissected off the main structures in the superior mediastinum. This is most likely to be the esophagus and the closely applied vagus nerve, but in a large tumor the trachea may be involved. It may prove useful to have a large size tube in the esophagus to aid dissection. On the left side, the thoracic duct, arch of aorta with subclavian, and carotid branches along with the vagus will need protection.

It should now prove possible to dissect the tumor off the bodies of the vertebra and any extension into the intravertebral foramen should be carefully dissected out. Titanium clips may prove useful to control hemorrhage in small vessels, and these will not interfere with subsequent CT scanning. They may also be used as markers if all the tumor is not excised and radiation therapy is being considered. Any suspiciously involved lymph nodes locally should be taken for biopsy (staging). The chest is closed after leaving a chest drain.

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31

Congenital airway malformations

RICHARD G AZIZKHAN

INTRODUCTION

Congenital airway malformations include a wide spectrum of pathology that occurs at various anatomic levels. Presentation varies widely, and is influenced both by the level at which obstruction occurs and the severity of obstruction. In view of the distinct anatomy of the pediatric airway and the possibility of airway symptoms quickly progressing to life-threatening airway compromise, early detection, diagnosis, and treatment are imperative. The aim of this chapter is to briefly discuss anomalies extending from larynx to the distal airway, highlighting symptomatology, patient assessment, and primary management strategies.

PATIENT ASSESSMENT

Medical history

Evaluating an infant with respiratory compromise should begin with a meticulous review of the infant's history of airway symptoms. Clinicians should explore circumstances that may elicit the onset of symptoms and should question parents regarding the duration of symptoms and symptom progression. They should also explore possible swallowing or feeding problems, the nature of the child's cry, and the possibility of foreign-body aspiration. Additionally, any history of endotracheal intubation, trauma, or previous cardiac surgery should be carefully reviewed. All of this information may provide important clues as to the underlying etiology, and may determine or affect management strategy.

Signs and symptoms

Patients with mild airway compromise may present with subtle symptoms such as irritability, restlessness, and feeding difficulties. Those with more severe obstruction frequently present with severe suprasternal and intercostal retractions, tachypnea, lethargy, and cyanosis. Stridor, defined as a harsh sound caused by turbulent airflow through a partially obstructed airway, can manifest during the expiratory or inspiratory phases of the respiratory cycle or can be biphasic. Inspiratory stridor usually indicates an airway obstruction in the extrathoracic airway, whereas expiratory stridor usually indicates a problem in the intrathoracic airway. Biphasic stridor typically signifies a fixed glottic or subglottic lesion. The pitch of stridor, as well as its relationship to the respiratory cycle, is generally helpful in establishing a differential diagnosis and in establishing priorities for patient assessment. Clinicians should be mindful of the fact that the degree of stridor does not necessarily reflect the severity of airway obstruction. More specifically, even minimal stridor can reflect the lack of airway movement across a critical airway.

Diagnostic studies

The most critical component of the airway assessment after physical examination is endoscopic evaluation. Depending on the type of suspected airway lesion, either flexible or rigid bronchoscopy or both are performed. To adequately assess the dynamic aspects of some suspected airway lesions (e.g. tracheomalacia), endoscopy should be performed with the patient spontaneously breathing. Seventeen percent of patients have a synchronous airway lesion; evaluation of the entire airway is thus required. Given that up to 45% of children with congenital airway obstruction also have significant non-airway anomalies, all patients require a thorough overall evaluation.

Imaging studies are helpful in diagnosis as well as patient management. Computed tomography (CT) and magnetic resonance imaging (MRI) studies provide a rapid and precise way of assessing and measuring the extent and length of airway narrowing or displacement. These investigations are also helpful in detecting associated mediastinal and pulmonary anomalies. Specifically, MR angiography is valuable in assessing the relationship of mediastinal great vessel anomalies

(e.g. vascular rings, pulmonary artery slings) to the airway. Newer computer software allows for three-dimensional image reconstruction and is helpful in planning surgical procedures. Echocardiography is valuable in identifying intracardiac defects and most associated great vessel anomalies. Contrast swallow studies are valuable in assessing esophageal motility, aspiration, and some mediastinal lesions that affect the airway. Fiberoptic endoscopic evaluation of swallowing (FEES) is performed to evaluate structural and functional disorders of swallowing and to identify functional problems of the larynx, pharynx, epiglottis, and proximal esophagus.

CONGENITAL LARYNGEAL ANOMALIES

Laryngomalacia

Laryngomalacia is the most common congenital laryngeal anomaly, accounting for up to 75% of laryngeal disorders in neonates. This condition is characterized by laxity of both the glottic and supraglottic tissues, which causes the epiglottis, arytenoids, and aryepiglottic folds to collapse and partially obstruct during inspiration. The reported incidence of secondary airway lesions in infants with laryngomalacia varies, with some authors documenting rates as high as 50[1] and 64%.[2]

Laryngomalacia is also the most common cause of stridor in neonates. This symptom is usually evident soon after birth or within the first few days of life. It is generally mild, but can be exacerbated by feeding, crying, or lying in a supine position. Fifty percent of children with laryngomalacia experience a worsening of stridor during the first six months of life, though in virtually all affected children, symptoms resolve by one year of age. When the disorder is severe, however, children may exhibit apnea, cyanosis, severe retractions, and failure to thrive, and thus require surgical intervention. In extremely severe cases, cor pulmonale can develop.

Flexible transnasal fiberoptic laryngoscopy is used to confirm the diagnosis. Pathognomonic findings include short aryepiglottic folds, with prolapse of the cuneiform cartilages. Collapse of the supraglottic structures is seen on inspiration, and inflammation indicative of reflux laryngitis is also frequently seen (Fig. 31.1). In some patients, a tightly curled (omega-shaped) epiglottis is observed.

The decision as to whether to intervene surgically is based more so on symptom severity than on the endoscopic appearance of the larynx. For patients with severe symptoms, supraglottoplasty (also termed epiglottoplasty) is the preferred operative procedure, with a reported surgical success as high as 94%.[3–5] Both aryepiglottic folds are divided and one or both cuneiform cartilages may be removed. If the aryepiglottic folds alone are divided, postoperative intubation is usually not required. Patients should be observed overnight in the intensive care unit. Antireflux management is advisable for helping to minimize laryngeal edema. This is especially important in patients with a synchronous airway lesion, as these patients are known to have a higher incidence of gastroesophageal reflux disease (GERD) than those without a synchronous lesion.[1,3] Synchronous airway lesions

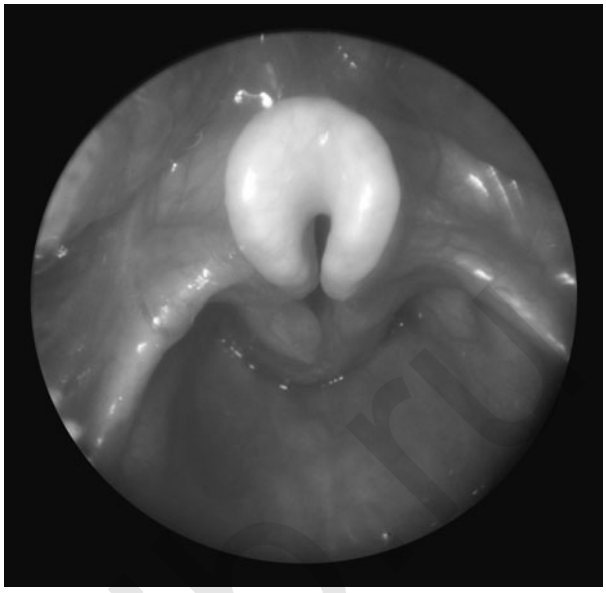


Figure 31.1 Endoscopic view of laryngomalacia in an infant showing partial collapse of the supraglottic structures during inspiration.

as well as neurologic conditions and pre-existing laryngeal edema can adversely affect operative outcomes.[6] Occasionally, an infant's obstructive symptoms continue despite an adequate postoperative appearance of the larynx. These infants may have an underlying neurologic problem that may become more evident over time. As such, they are much more likely to require tracheotomy placement.

Subglottic stenosis

Subglottic stenosis (SGS) is an anomaly that involves a narrowing of the subglottic lumen. It can be either congenital or acquired; however, the latter is seen far more frequently and is generally a sequela of prolonged intubation of the neonate. In the premature infant, SGS is considered present when this lumen measures 3.0 mm or less in diameter at the level of the cricoid, whereas in the full-term neonate, SGS is defined as a lumen of 4.0 mm or less in diameter at this level. Congenital SGS is thought to be caused by failure of the laryngeal lumen to recanalize during embryogenesis. It may occur as an isolated anomaly or may be associated with other congenital head and neck lesions and chromosomal anomalies such as a small larynx in patients with Down syndrome.[7]

Levels of SGS severity range from mild to severe, and are graded based on the Myer–Cotton grading system (Table 31.1). Patients with mild SGS (no obstruction–50% obstruction) may present with recurrent upper respiratory infections, often misdiagnosed as croup. In a young child, the greatest obstruction is usually 2–3 mm below the true vocal cords.[8] Patients with more severe narrowing (71–99% obstruction) may present with acute airway compromise and require endotracheal intubation or tracheotomy placement at delivery (Fig. 31.2). However, many of these infants, even those with grade III SGS (71–99%), may not be symptomatic for weeks or months. When stridor is present,

Table 31.1 Myer–Cotton grading system for subglottic stenosis.

Classification	Level of airway obstruction	
	From	To
Grade I	No obstruction	50% obstruction
Grade II	551% obstruction	70% obstruction
Grade III	771% obstruction	99% obstruction
Grade IV	No detectable lumen	

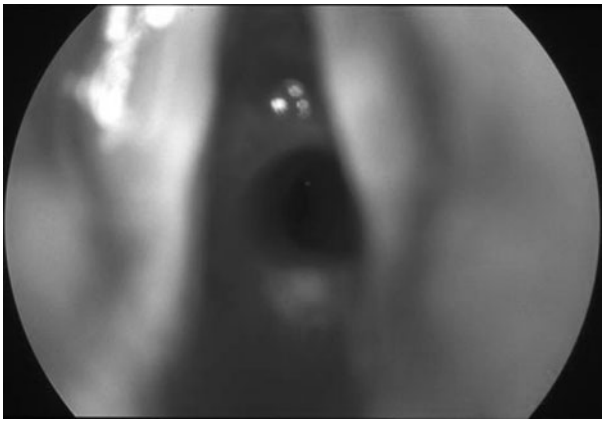


Figure 31.2 High-grade subglottic stenosis in a symptomatic neonate.

it initially occurs during the inspiratory phase of respiration. As SGS severity increases, stridor becomes biphasic.

Radiologic evaluation of the non-intubated airway can provide information regarding the site of the stenosis and its extent. Chest x-ray, inspiratory and expiratory lateral soft-tissue neck films, and fluoroscopy are helpful in revealing the dynamics of the trachea and larynx. High-kilovoltage airway films identify the classic steeple-like configuration seen in patients with SGS, as well as possible tracheal stenosis, and are therefore of utmost importance. Flexible and rigid endoscopy are used in a complementary fashion for airway evaluation and are both essential. Flexible endoscopy provides critical information regarding the structural dynamics of airflow in the hypopharyngeal and laryngeal airways. Rigid endoscopy provides an assessment of the entire laryngotracheobronchial airway.

In children with mild to moderate disease (grades I or II), congenital SGS improves with age. Children with a minor degree of SGS who experience mild symptoms, may, nevertheless, benefit from endoscopic intervention. Endoscopic options include radial laser incisions through the stenosis and laryngeal dilatation.[9] Outcomes are improved when mitomycin C is used concomitantly with this approach.[10] Less than 50% of these patients require tracheotomy placement to maintain their airway. Children with more severe disease are best managed with open subglottic airway reconstruction. Costal cartilage grafts can be placed through either the anterior or posterior lamina of the cricoid cartilage or both. This may be carried out as a single-stage laryngotracheoplasty[11,12] or as a two-stage procedure, requiring stenting and placement of a temporary tracheostomy.[13] For severe SGS, good results have been achieved by performing partial or complete cricotracheal resection and reconstruction; however, this is a demanding procedure with considerable risks. Successful outcome depends on the management of comorbidities such as GERD, eosinophilic esophagitis, and low-grade tracheal infection.

Vocal cord paralysis

Vocal cord paralysis can be congenital or acquired and can occur either unilaterally or bilaterally. Unilateral paralysis is usually an acquired condition caused by damage to the recurrent laryngeal nerve (RLN). Because of the length and course of the left RLN, this is far more likely to be damaged than the right RLN. Acquired paralysis thus generally affects the left vocal cord. Unlike unilateral vocal cord paralysis, bilateral paralysis is usually evident at birth. It is generally idiopathic, but often is seen with central nervous system conditions, such as hydrocephalus and Chiari malformation of the brainstem. Although most children with bilateral paralysis present with significant airway compromise, they have an intelligible voice and do not aspirate. In contrast, most children with unilateral vocal cord paralysis have an acceptable airway, but are at a slightly higher risk of aspiration and have a breathy voice.

The diagnosis is made by flexible laryngoscopy with the patient awake. Investigation aimed at finding the underlying cause is then carried out. Stabilization can be achieved with intubation, continuous positive airway pressure (CPAP), or high-flow nasal canula as an alternative temporizing measure. Almost all infants with bilateral paralysis require tracheotomy placement to ensure a safe and adequate airway. However, up to 50% of children with congenital idiopathic bilateral paralysis experience spontaneous resolution of their paralysis by the age of one.[14] In view of possible resolution, decannulation is almost always delayed to allow time for this to occur. Children with acquired bilateral paralysis may also experience spontaneous recovery, provided that the RLN was stretched or crushed but otherwise intact.

Because no single surgical approach offers a universally acceptable outcome, a number of surgical approaches have been used for children with bilateral paralysis. These approaches include laser cordotomy, partial or complete arytenoidectomy, and vocal cord medialization or lateralization (open or endoscopically guided).[15,16] The aim of each of these procedures is to achieve an adequate decannulated airway while maintaining voice and preventing aspiration.

Posterior laryngeal cleft

Posterior laryngeal cleft is a rare congenital anomaly that results from failure of the laryngotracheal groove to fuse during embryogenesis. This anomaly comprises five anatomic subtypes that differ with respect to involvement of the larynx and/or trachea (Fig. 31.3). Patients frequently have coexisting anomalies, many of which affect the airway. Associated airway anomalies include tracheomalacia (almost always present in varying levels of severity), tracheoesophageal

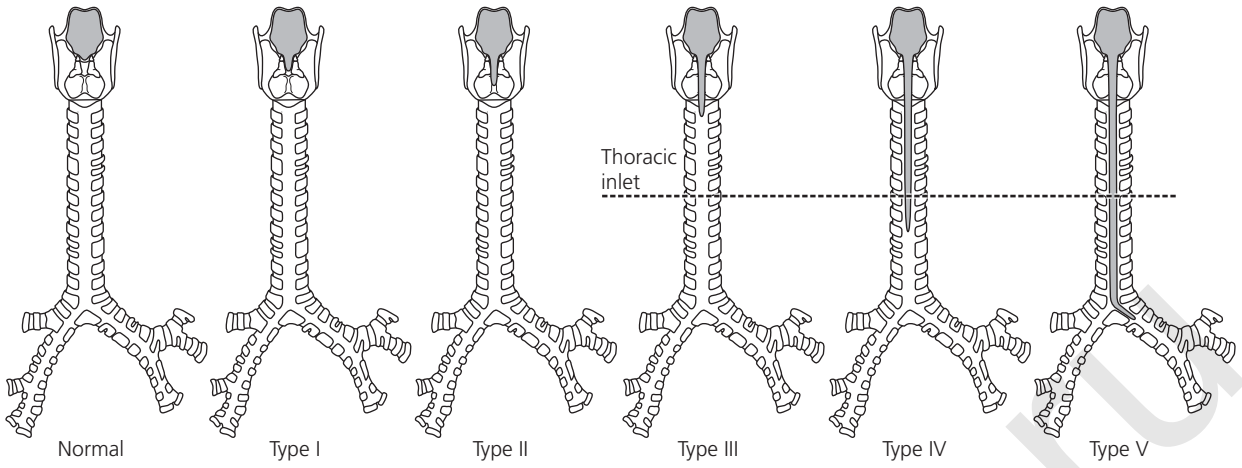


Figure 31.3 Posterior laryngeal cleft classification.

fistula formation (20%), laryngomalacia, vocal cord paralysis, SGS, and innominate artery compression. Associated non-airway conditions include anogenital anomalies, cleft lip and palate, congenital heart defects, and GERD, which affects most children. The most common associated syndrome is Opitz–Frias syndrome, which is characterized by hypertelorism, anogenital anomalies, and posterior laryngeal clefting.

Diagnosis can be extremely difficult, as presenting symptoms vary greatly. In type I and type II clefts, symptoms are often subtle, and may mimic those of other disorders such as GERD. Nonetheless, aspiration is a hallmark clinical feature of this spectrum of disease. With more severe clefts, gross aspiration may occur with associated apnea, cyanosis, and even pneumonia. For milder clefts, the symptoms are those of microaspiration, with choking episodes, transient cyanosis, and recurrent chest infections.[8,17] Airway obstruction manifested by stridor may also be present and is caused either by redundant mucosa on the edge of the cleft or a small cricoid ring. In patients with severe tracheomalacia, especially those with an associated tracheoesophageal fistula, the airway may be significantly compromised. Contrast swallow studies may demonstrate aspiration; however, rigid laryngoscopy and bronchoscopy are essential for definitive diagnosis. The interarytenoid area is specifically probed to determine if a posterior laryngeal cleft is present.

In children who are symptomatic and do not have other more severe anomalies, repair of the posterior laryngeal cleft should be performed as soon as possible to prevent chronic microaspiration with long-term pulmonary sequelae. Depending on the extent of the airway anomaly, tracheotomy and gastrostomy tube placement may be required before definitive surgical repair of the airway. Because of the high incidence of GERD, fundoplication is often required, and is preferably performed prior to surgical repair. Most type I and some type II clefts are amenable to endoscopic surgical repair, whereas clefts that extend into the cervical or thoracic trachea require open repair. A transtracheal approach is advised, as it provides optimal exposure of the cleft while protecting the recurrent laryngeal nerves. A two-layer closure is recommended, with the option of performing an interposition graft if warranted. Type V clefts, which extend to the carina or beyond and are often associated with multiple congenital anomalies, are exceedingly difficult to repair and are prone to anastomotic breakdown.[17] Success rates for cleft repair vary significantly (50–90%) depending on both the severity of the cleft and the presence of comorbidities.

Laryngeal atresia

CONGENITAL HIGH AIRWAY OBSTRUCTION SYNDROME

Congenital high airway obstruction syndrome (CHAOS) is a rare, life-threatening, prenatally diagnosed condition caused by complete or near-complete obstruction of the larynx and trachea. Fetal lung fluid becomes trapped, causing the lungs to become abnormally distended. This creates massive lung expansion that characteristically everts the hemi-diaphragms.

This type of fetal airway obstruction may be caused by multiple etiologies, including laryngeal atresia, laryngeal web, tracheal atresia, and laryngeal cyst.[18] Airway atresia is sometimes an isolated anomaly, but often is seen in association with genitourinary, vertebral, and cardiac anomalies as well as with hydrocephalus malformation of the Aqueduct of Sylvius, bronchotracheal fistula, esophageal atresia, tracheoesophageal fistula, and syndactyly. Regardless of the etiology, the clinical features and presentation of CHAOS are the same. Prenatal findings on ultrasound (US) include diffuse and enhanced echogenicity of the lungs, dilated airways, and flattened or everted diaphragms with associated fetal ascites and non-immune hydrops (Fig. 31.4). A fetus identified with these sonographic features is at significant risk of intrauterine death and faces a high likelihood of mortality should the pregnancy progress to delivery. Although US provides a good initial assessment of CHAOS, MRI is clearly superior in identifying severity and the level of airway obstruction, and optimizes planning for airway management at delivery.[19] These patients all require delivery by the *ex utero* intrapartum technique (EXIT) procedure. This procedure maintains placental circulation to the fetus while securing the airway at the time of delivery.[18] Securing the airway may include a full endoscopic diagnostic assessment and tracheostomy.

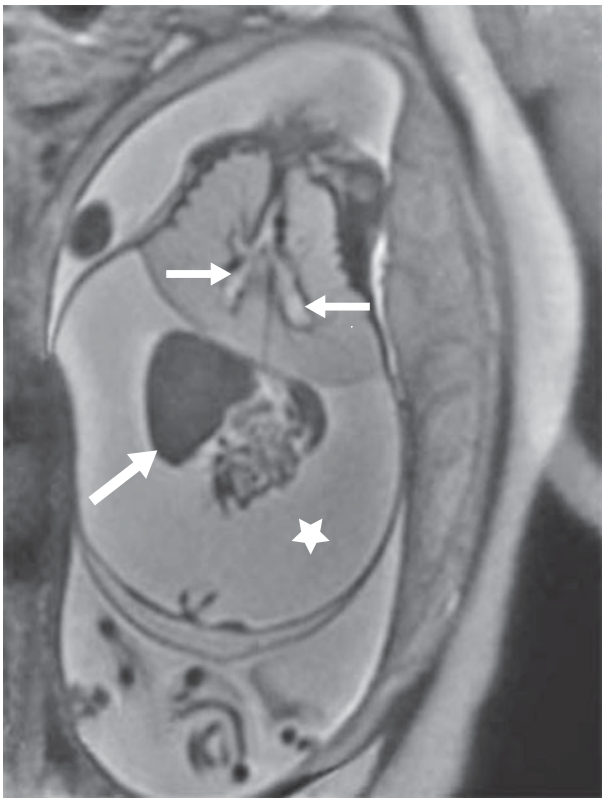


Figure 31.4 Fetal ultrasonography at 27 weeks' gestation demonstrating findings consistent with the diagnosis of congenital high airway obstruction: enlarged echogenic lungs, dilated airway (white arrow), flattened or everted diaphragms, and fetal ascites (white star) and hydrops. Fetal liver and intestines marked with a black arrow.

For the newborn diagnosed with CHAOS, securing and maintaining the airway is the highest priority. These patients are almost always extremely ill and require a prolonged period of critical care and ventilatory support. Once the infant's cardiorespiratory status is stable and other critical or potentially life-threatening anomalies are ruled out, careful endoscopic evaluation of the airway precedes elective laryngotracheal reconstruction; however, consensus has not been reached as to optimal timing of airway reconstruction. Although a functional airway can be constructed, patients do not always attain intelligible speech capabilities.

Diagnosis in the middle of the second trimester generally correlates with a poor perinatal outcome. A fetus presenting in the third trimester with CHAOS in the absence of associated anomalies or hydrops is likely to have incomplete obstruction, and is therefore more likely to survive.

ANOMALIES OF THE TRACHEA AND BRONCHI

Tracheal agenesis and atresia

Tracheal agenesis is a rare developmental anomaly that almost always results in death. Patients who are prenatally diagnosed and in whom the atresia involves only the proximal trachea occasionally survive by using an EXIT procedure and eventual tracheal reconstruction. In another form of tracheal agenesis, the entire trachea is absent and the bronchi come directly off the esophagus. Neonates present at birth with severe respiratory distress, attempting ventilation through bronchoesophageal communications. Temporary ventilation may be possible with esophageal intubation of the esophagus, but this is typically unsustainable. If there is no communication between the airway and the esophagus, CHAOS will result.[18]

Tracheal stenosis and webs

Tracheal stenosis encompasses a broad spectrum of rare tracheal anomalies. Affected segments of the trachea differ in the degree and extent of stenosis, which can range from extremely thin webs to more severe long segments of stenosis affecting the entire airway.

TRACHEAL WEBS

Tracheal webs involve an intraluminal soft-tissue stenosis of the trachea. These webs may be membranous or consist of thick, relatively rigid tissue. Patients typically present with biphasic stridor or expiratory wheezing, and the severity of these symptoms depends on the degree of the stenosis. Thin webs can be easily managed by hydrostatic balloon dilatation.[20] For thicker webs that are not associated with underlying cartilage deformity, laser ablation is often used.[21] The carbon dioxide (CO_2) or potassium-titanyl-phosphate (KTP) laser is beneficial for treating lesions in the proximal trachea. Lesions in the distal airway are best managed with the KTP laser, which can be used through small fiberoptic cables. For children with a web greater than 1 cm in length or those in whom the airway cartilage is thought to be structurally deficient or anomalous, operative treatment with segmental tracheal resection or slide tracheoplasty is usually carried out.

CARTILAGINOUS RING APLASIA

Cartilaginous ring aplasia is an extremely rare anomaly in which only a small region of the trachea lacks cartilage, creating a distinct anatomic area that is both malacic and stenotic. The remainder of the trachea is unaffected, and most children do not have coexisting congenital anomalies. Management entails segmental resection of the trachea, which successfully restores the airway.

TRACHEAL CARTILAGINOUS SLEEVE

Tracheal cartilaginous sleeve is also extremely rare. In children with this anomaly discrete cartilaginous rings are replaced by a fused cartilaginous cylinder, with or without a membranous portion. It is typically seen in children with craniosynostosis syndromes such as Pfeiffer, Apert, Crouzon, and Goldenhar.[22–24] Neonates usually exhibit respiratory illness. Patients presenting in early infancy often experience acute respiratory symptoms, which may include biphasic stridor with respiratory distress, cough, and frequent

respiratory infections. Because of tracheal rigidity, the mechanism for clearing secretions is impaired.

On endoscopy, the anterior tracheal wall appears smooth, though the membranous posterior tracheal wall may be normal, stenotic, or absent. CT and MRI are sometimes useful in determining the extent of the lesion. Tracheotomy placement may be used as a temporizing measure; however, resection and repair are imperative to achieve normal function.

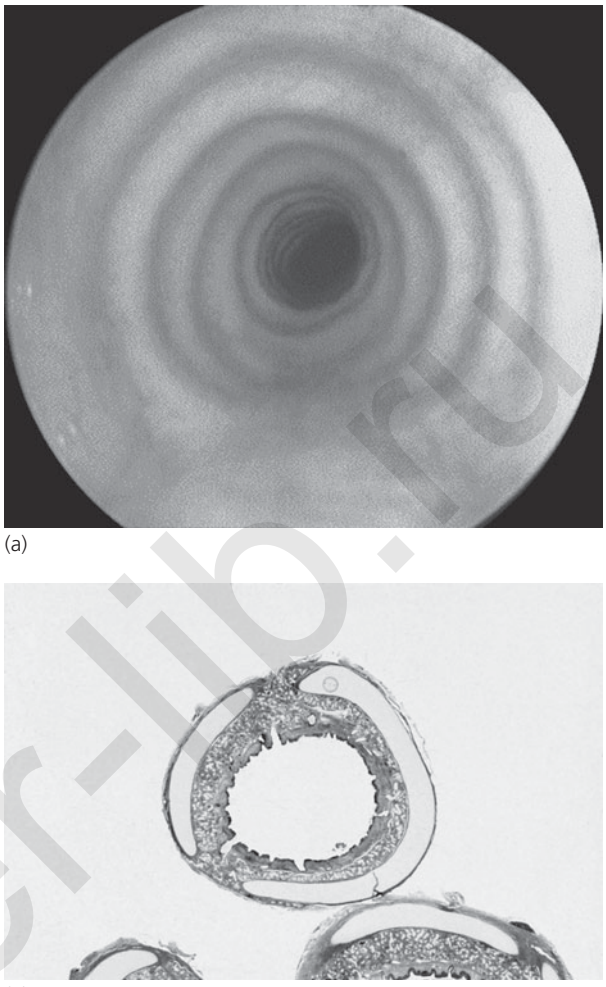
COMPLETE TRACHEAL RINGS

Although rare, complete tracheal rings are the most common congenital tracheal stenosis. With this spectrum of potentially life-threatening anomalies, either the trachea alone or both the trachea and bronchi are significantly narrowed. The tracheal cartilage in these patients is abnormally shaped and forms complete rings (Fig. 31.5). More than 50% of infants have a segmental stenosis. The clinical manifestations of complete tracheal rings vary from life-threatening respiratory distress during the perinatal period to subtle symptoms of airway compromise in older children. Most symptomatic infants exhibit deterioration of respiratory function over the first few months of life. Symptoms include stridor, retractions, cough, and alterations of cry. Atypical and persistent wheezing and rhonchi and sudden death can also occur. More than 80% of children with complete tracheal rings have other, and often multiple, congenital anomalies;[8] 50% specifically have congenital heart disease with or without great vessel anomalies.

In some patients, placement of an endotracheal tube may further exacerbate respiratory distress by causing acute swelling and inflammation of the mucosa. Partially obstructing tracheal lesions also may become life threatening following the onset of a respiratory infection. In an infant or child with an abnormal trachea, the cross-sectional area of airway can be significantly decreased with as little as 1 mm of edema. This accounts for the rapid worsening of symptoms in some children with acute inflammatory conditions and coexisting tracheal narrowing.

Prompt diagnostic evaluation to define tracheobronchial anatomy is essential. An initial high-kilovolt airway film may indicate stenosis; however, bronchoscopy is required to reveal the precise location and extent of the stenosis. Bronchoscopy should be performed with extreme caution, using the smallest possible telescopes, as any airway edema in the region of the stenosis may turn a narrow airway into a critical airway.[8] CT scans provide a rapid and precise method of measuring the extent and length of airway narrowing or displacement. Three-dimensional reconstruction of the airway and its relationship to the great vessels aids in operative planning. Furthermore, with new software enhancements, virtual bronchoscopic images can be obtained. These images are particularly useful in assessing the airway distal to the obstruction (Fig. 31.6). MRI is also valuable in evaluating the relationship of the mediastinal great vessels to the airway. Echocardiography is used mainly to determine whether intracardiac defects are present, and can identify most coexisting pulmonary artery slings.

About 10% of patients with complete tracheal rings are minimally symptomatic and can be managed non-operatively,



(a)

(b)

Figure 31.5 Congenital tracheal stenosis. (a) Endoscopic view demonstrating complete tracheal rings. (b) Histology showing cartilaginous rings that are circumferential.

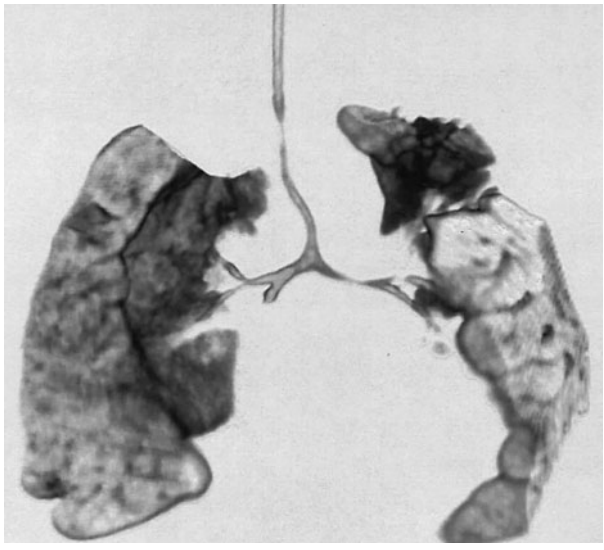


Figure 31.6 CT scan with three-dimensional reconstruction to demonstrate anatomy of the trachea in a patient with congenital tracheal stenosis involving the majority of the tracheal length.

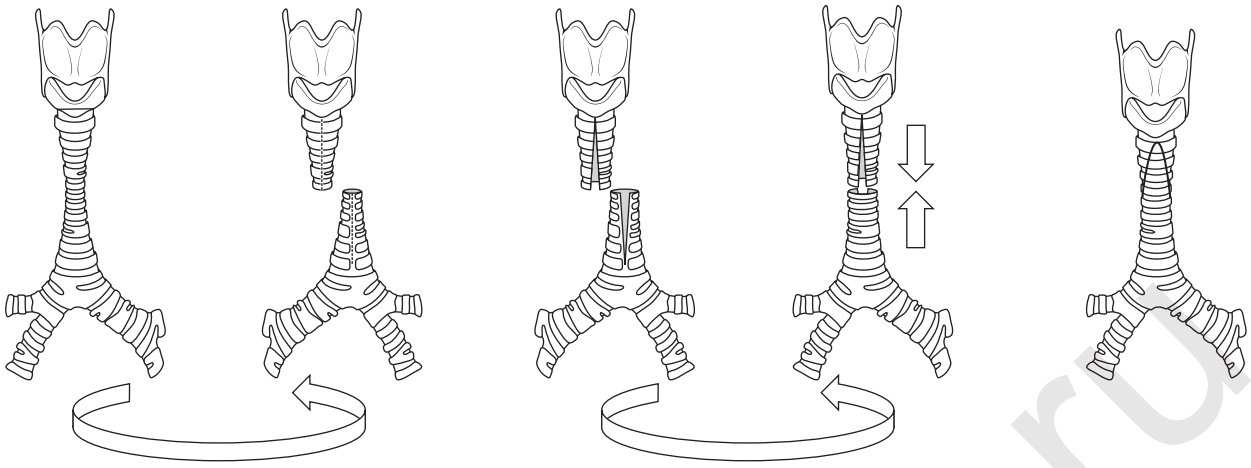


Figure 31.7 Slide tracheoplasty. The trachea is transversely divided at the midpoint of the tracheal stenosis. After proximal and distal tracheal mobilization, the posterior portion of the cephalic trachea segment and the anterior portion of the caudal tracheal segment are incised. The two tracheal segments are then overlapped and obliquely sutured together.

though they require ongoing observation.[25] Most children must undergo tracheal reconstruction.[25] Repair of coexisting anomalies, such as pulmonary artery sling or vascular ring, should be carried out concurrent with the tracheal repair. Although patch tracheoplasty was historically the preferred procedure for long segments of narrowing, slide tracheoplasty is now the procedure of choice for both short-and long-segment stenosis (Fig. 31.7).[26] This approach results in significantly less morbidity than other tracheal reconstruction techniques and is adaptable to all anatomic configurations of complete tracheal rings. Slide tracheoplasty uses only autologous tracheal tissue and is performed by transecting the trachea into two equal segments. The anterior wall of the lower half of the trachea and the posterior wall of the upper trachea are incised. These segments are then slid over each other and anastomosed with 5-0 monofilament and absorbable sutures. Postoperatively, the cross-sectional area of the airway has a four-fold increase and the length of the involved airway decreases by half. Airflow is increased 16-fold.

Postoperatively, endotracheal intubation is generally required for 1–2 days, though some patients with parenchymal pulmonary disease require longer ventilatory support. During the perioperative period, unnecessary movements of the endotracheal tube or unplanned extubation must be avoided so as to minimize the risk of damage to the newly reconstructed airway. Nasotracheal intubation is preferred, as the endotracheal tube can be more securely stabilized. Patients require continuous monitoring, careful pulmonary toilet, and endoscopic removal of any obstructing granulation tissue. Immediately prior to extubation, the integrity and patency of the reconstructed airway are assessed by flexible fiberoptic endoscopy through the endotracheal tube, thus ensuring a safe extubation.

Although airway configuration following slide tracheoplasty may resemble a figure eight, this does not indicate airway obstruction. The trachea generally remodels to a normal oval shape within one year of reconstruction. Long-term survival is currently 90% in our institution. Mortality is usually associated with severe comorbidities, such as cardiac disease rather than airway complications.

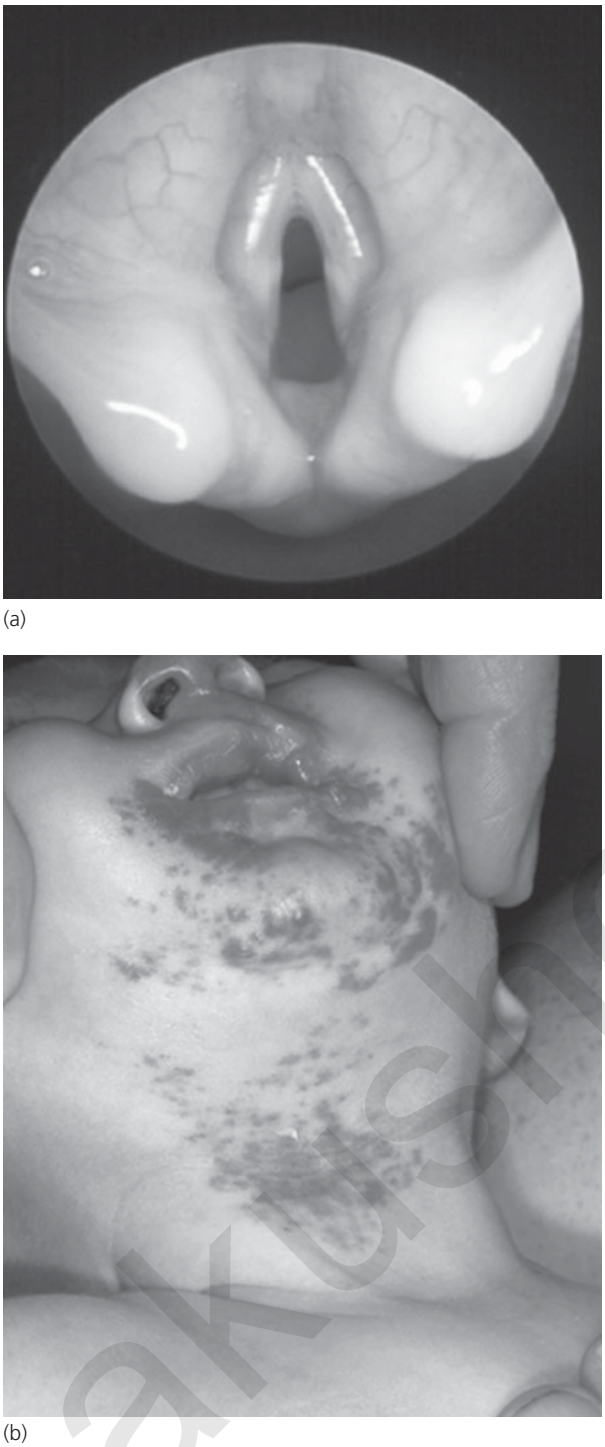
Tracheal diverticulum and tracheal bronchus

Tracheal diverticulum and tracheal bronchus are relatively common embryologic abnormalities of early tracheal budding. Tracheal diverticulum resembles a bronchus, though it originates from the trachea and ends blindly or communicates with a rudimentary lung. Tracheal bronchus most often affects the right upper lobe bronchus and may connect to an isolated intrathoracic lung segment or the apical segment of an upper lobe. Both anomalies frequently occur along with other tracheal, esophageal, and pulmonary anomalies. Diagnosis is established by airway endoscopy. Most children are asymptomatic and do not require treatment. Pneumonia and respiratory distress may be the presenting symptoms during the neonatal period. These symptoms are almost always associated with stenosis of a bronchus or other lung anomalies. Resection of involved lobe and bronchus in these patients is generally curative.

The most common cause of tracheal diverticulum is iatrogenic, following division of a tracheoesophageal fistula where a small remnant of the esophagus is left on the tracheal side. These defects can be readily managed with endoscopic resection.[27–29]

Airway malacia

Airway malacia is a condition in which the structural integrity of either the trachea or bronchi or both are weakened, and the cartilaginous rings of the airway lack the rigidity required to avoid airway collapse during expiration. Malacia may be localized or occur diffusely throughout the airway. Tracheomalacia is the most common congenital tracheal anomaly. This condition may occur in isolation or



(a)

(b)

Figure 31.8 (a) Endoscopic view of a subglottic hemangioma in a patient with infantile hemangioma in (b) bearded distribution.

in conjunction with other congenital anomalies. Tracheoesophageal fistula, esophageal atresia, and posterior laryngeal clefts are particularly common associations.[30] Premature neonates and children with chronic lung disease are at high risk for developing combined severe tracheobronchomalacia.

Presenting symptoms vary depending upon the severity, duration, and region of airway involvement. Most children are either asymptomatic or minimally symptomatic and most cases involve posterior malacia of the trachealis, with associated broadening of the tracheal rings. Presenting symptoms may include a honking cough, stridor, wheezing, respiratory distress when agitated, and cyanosis. Some children are misdiagnosed with allergic asthma and unsuccessfully treated with bronchodilators. Diagnosis is best established by bronchoscopy, with the patient breathing spontaneously; this demonstrates dynamic distortion and compression of the trachea. In children who are minimally symptomatic, symptoms often resolve by the age of three. These children are managed with observation alone. Children who experience symptom progression require medical or surgical intervention.[30] For some patients, respiratory monitoring with nasal CPAP may be sufficient to effect improvement.

Segmental tracheal involvement is managed with endoscopic or open aortopexy, with thymectomy and anterior suspension of the ascending arch of the aorta to the posterior periosteum of the sternum.[31] More diffuse malacia may require tracheotomy placement with positive pressure ventilation over a long duration. For patients with severely problematic tracheobronchomalacia that is unresponsive to nonoperative therapy or unsuitable for surgical treatment, intratracheal stents are placed. This approach is, however, associated with serious complications, such as stent collapse, stent dislodgement, or rarely, stent erosion into the great vessels. Additionally, stent removal can cause tracheal tearing or major hemorrhage.

Esophageal bronchus

Isolated bronchial connection between the esophagus and the airway is extremely rare and occurs more frequently in females (2:1). Associated cardiac, genitourinary, vertebral, and diaphragmatic anomalies are common. Esophageal bronchus is thought to develop from a supernumerary lung bud arising from the esophagus. Most commonly, a lower lobe is aerated by this ectopic bronchus; however, an entire main bronchus and lung may be affected. As in pulmonary sequestration anomalies, the pulmonary vasculature may be abnormal, with the arterial supply coming off the aorta and venous drainage going into either the systemic or pulmonary veins.

Inadequate bronchial drainage usually results in recurrent pulmonary infection and parenchymal damage.[32] Nonetheless, some patients remain undiagnosed until adolescence or adulthood despite recurring pneumonias and persistent x-ray abnormalities. Although x-ray findings vary with the segment of the lung affected by the anomaly, collapse, consolidation, cavitation, and cyst formation within the pulmonary parenchyma are commonly seen. The diagnosis is confirmed by a contrast study of the esophagus, though false-negative results sometimes occur. Excision of the abnormal lung and closure of the bronchoesophageal fistula is the treatment of choice in patients beyond the neonatal period. Prognosis depends on early diagnosis and treatment and the severity of associated anomalies. Bronchotracheal reconstruction has been successfully accomplished in neonates diagnosed with esophageal bronchus.[33]

Tracheobronchial–biliary fistula

A congenital tracheobronchial-biliary fistula is an anomalous tract that connects the respiratory tree with the biliary tree. This is an extremely rare developmental anomaly that is thought to arise from the distal trachea or either mainstem bronchus. To date, only 25 cases have been reported in the English language literature.[34] An association with other foregut anomalies also has been reported.[35] Children usually present with recurrent pneumonias, respiratory distress, and failure to thrive, often starting early in the neonatal period; however, the cardinal symptom is bile-stained sputum. Symptom severity varies and primarily depends on whether the bile from the left lobe of the liver has normal drainage channels to the duodenum or only drains through the bronchobiliary fistula.[35–37] The diagnosis is established either by bronchoscopy or endoscopic retrograde cholangiopancreatography (ERCP); however, a recent case report offers optimism for using contrast-enhanced CT of the chest and abdomen as a method of diagnosis.[34] Surgical interruption of the fistulous tract is the only effective therapy for this malformation.

Subglottic hemangioma

Hemangiomas of infancy (also referred to as infantile hemangiomas) are the most common vascular tumors, affecting one in ten white infants in North America[38] and occurring with a three-fold female preponderance. These benign lesions usually follow a predetermined phase of growth (proliferation) and later tumor regression (involution). The involutive phase occurs at 12–18 months and is generally complete by the first decade of life.

Hemangiomas generally present cutaneously but can occur in any organ or anatomic site. Lesions within the tracheobronchial tree most commonly occur in the subglottis. Their natural history generally mirrors that of cutaneous lesions. More than 50% of patients with a subglottic hemangioma also have cutaneous lesions. The latter may therefore provide an indication of the possible presence of a subglottic lesion. The highest risk (65%) patients are those with a hemangioma occurring in a beard distribution[39] or those with PHACE association, which is characterized by posterior fossa abnormalities, hemangiomas of the cervicofacial region that are usually plaque-like and segmental, arterial defects, cardiac and aortic arch defects, and eye abnormalities.[40,41]

As a subglottic hemangioma undergoes proliferation, progressive worsening of the airway usually occurs. Presenting symptoms include biphasic stridor with retractions. The degree of obstruction varies and can be exacerbated by certain positions or crying, both of which increase venous pressure and lead to vascular engorgement. When airway narrowing is severe, apnea, cyanosis, and 'dying spells' may result.

The diagnosis is based on medical history and findings on airway endoscopy. Lesions are typically asymmetric and may be covered by a normal smooth mucosa (Fig. 31.8a). Because of the risk of hemorrhage, biopsy is not advised. Most patients require treatment and combining various treatment modalities is often essential. Depending on both the severity of the obstruction and the expertise of involved clinicians, early symptoms are managed with systemic steroids and, recently, with propranolol. Important to note, dramatic results have been achieved with propranolol, and these results have already changed the paradigm of both pharmacologic and surgical treatment.[42–45] For critical airways, some surgeons advocate laser fulguration or translaryngeal resection, whereas others place a tracheotomy below the lesion, with the expectation of removal following involution of the hemangioma.[40,46]

Bronchogenic cyst

Bronchogenic cysts stem from aberrant embryogenesis of the bronchial tree in which a segment of the lung bud develops independently. The walls of the cyst often contain fibrous tissue and cartilaginous remnants, while the internal surface consists of ciliated columnar epithelium.[47] Lesions usually expand, causing extramural compression of the airway. The most commonly seen symptom in infants is respiratory distress. Coughing, wheezing, or chest pain also may be present. A plain chest x-ray may suggest the presence of a bronchogenic cyst. A CT scan or MRI is valuable in establishing a definitive diagnosis (Fig. 31.9a). Patients are successfully managed by open or thoracoscopic resection (Fig. 31.9b).[48,49]

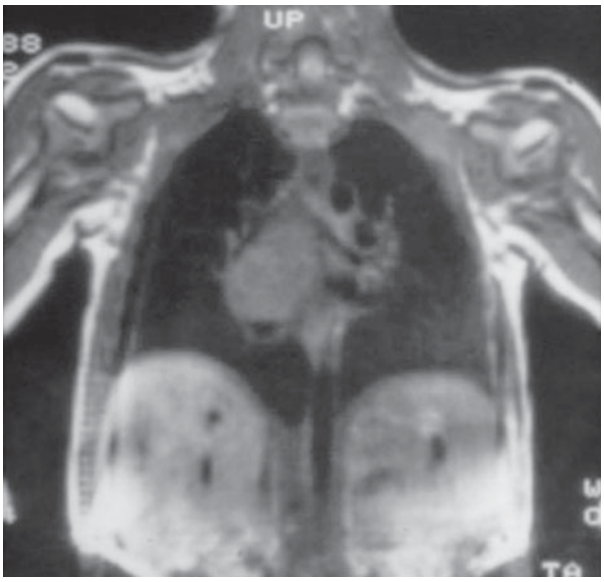
Bronchial atresia and bronchial lobar agenesis

BRONCHIAL ATRESIA

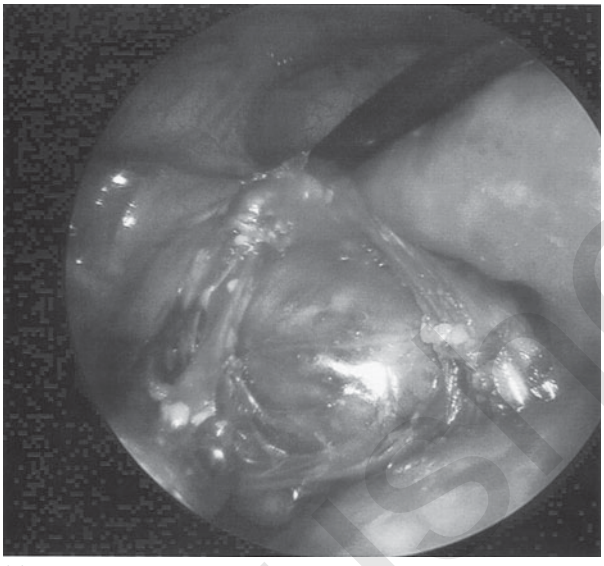
Localized bronchial atresia is a rare abnormality in which the atretic bronchus impedes the flow of secretions and air from the distal lung to the main tracheobronchial tree. This condition may mimic lobar emphysema or a mediastinal mass.[50] At birth, the affected lung retains fluid. Eventually, however, the anomalous lobe or segment becomes hyperaerated as air enters through the pores of Kohn. Secretions accumulate proximal to the atresia, resulting in the formation of a mucocele.[51] Emphysema of the segment may cause atelectasis of the normal lung tissue, which may be manifested by wheezing and stridor. Plain chest films may reveal a hilar mass with radiating solid channels surrounded by hyperinflated lung. A CT chest scan may show a cystic central mucocele and is valuable in distinguishing bronchial atresia from a bronchogenic cyst or lobar emphysema. Although children may initially be asymptomatic, secretions trapped in the lung may result in serious pulmonary infection. Surgical resection of the affected lobe restores normal lung function.

BRONCHIAL LOBAR AGENESIS

Bronchial agenesis is more commonly seen than tracheal agenesis and, unlike tracheal agenesis, it is compatible with life.



(a)



(b)

Figure 31.9 (a) MRI demonstrating a right-sided bronchogenic cyst just below the right main bronchus. (b) Thoracoscopic view of a bronchogenic cyst. The parietal pleura has been opened in the process of removal.

Several anatomic forms have been described; these include lobar, bronchial, and parenchymal agenesis. In the most severe form, complete agenesis of the lung and its bronchus and blood supply may occur.[50] Also, there may be a rudimentary bronchus and aplasia of the lung. As with most airway malformations, children may have coexistent congenital anomalies; most commonly these anomalies involve the skeletal, cardiovascular, gastrointestinal, and genitourinary systems. Diagnosis is established by chest x-rays and airway endoscopy. Most patients can be managed non-operatively. These abnormalities are important to identify in that they may mimic other airway anomalies requiring treatment (e.g. bronchial stenosis or extraluminal airway obstruction by tumors or masses).

Bronchial stenosis

Isolated congenital bronchial stenosis is extremely rare, with causality including compressive vascular, cardiac, and congenital cystic lesions or soft tissue cartilaginous stenoses. Symptoms and treatment vary, depending on both the severity and anatomic location of the lesion. Surgical management includes resection and reconstruction of the bronchus and slide bronchoplasty.[52,53]

Acquired bronchial stenosis is more common than its congenital manifestation, and is a significant cause of morbidity and mortality in infants who have undergone prolonged intubation and respiratory support. Most such cases can be managed with endoscopic balloon dilatation or laser resection.[21]

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32

Vascular rings

BENJAMIN O BIERBACH AND J MARK REDMOND

INTRODUCTION

Vascular rings are unusual congenital anomalies that occur early in the development of the aortic arch and great vessels. The primary symptoms associated with vascular rings relate to the structures that are encircled by the ring, namely, the trachea and esophagus.

DEFINITION AND HISTORY

A vascular ring is a rare congenital condition in which an anomalous configuration of the aortic arch or associated vessels surrounds the trachea and esophagus, to form a complete compressing ring around them. Several other related vascular anomalies involving aortic arch vessels do not form complete rings but have been grouped descriptively with vascular rings because they can produce similar symptoms related to compression of the trachea and or esophagus. In common usage, however, the definition of a complete vascular ring is extended to include pulmonary artery slings which do not completely surround the trachea and esophagus but may compress them. Both complete and incomplete rings and slings are discussed in this chapter.

The first vascular ring described was that of a double aortic arch by Hommel in 1737.[1] Subsequently, Bayford reported a retroesophageal right subclavian artery in 1794 after performing an autopsy on a woman who had experienced dysphagia for years and died of starvation. Maude Abbott described five cases of double aortic arch in 1932 and made the suggestion that surgical intervention should be undertaken in such cases.

The term 'vascular ring' was first used by Dr Robert Gross in his report describing the first successful division of a double aortic arch in 1945.[2]

In 1954, Potts and Holinger coined the term 'pulmonary artery sling' when they reported the first successful repair of this anomaly in a five-month-old infant with wheezing and intermittent episodes of dyspnea and cyanosis.[3] This anomaly was, however, first reported by Glaevecke and Döhle in 1897 in a post-mortem study in a seven-month old infant with severe respiratory distress.[4]

Although innominate artery compression syndrome and pulmonary artery sling are not complete anatomic rings, they have been traditionally classified with classic vascular rings because of the similarities in patient presentation, diagnosis, and surgical therapy.

FREQUENCY

Vascular rings are uncommon anomalies and make up less than 1% of all congenital cardiac defects. They occur with about equal frequency in both sexes. No geographical or racial predominance exists. Some vascular rings are associated with other congenital heart defects, while others may be isolated malformations.

The two most common types of complete vascular rings are double aortic arch and right aortic arch with left ligamentum arteriosum. These make up 85–95% of cases. Two other complete vascular rings that are extremely rare (<1%) include right aortic arch with mirror-image branching and left ligamentum arteriosum, and left aortic arch with retroesophageal right subclavian artery, right-sided descending aorta, and right ligamentum arteriosum.

Other anomalies that produce symptoms but do not form a complete anatomic vascular ring make up the remainder and include the anomalous innominate artery and the anomalous right subclavian artery with left-sided aortic arch and left ligamentum arteriosum.

The anomalous left pulmonary artery or pulmonary artery sling makes up about 10% of cases, and, although it is not associated with anomalies of the aortic arch or its branches, it arises from an abnormality of the sixth branchial arch and produces a complete ring. This anomaly is associated with intracardiac defects in 10–15% of cases.

EMBRYOLOGY

In 1922, Congdon reported his extensive experience with the study of the embryogenic development of the human aortic arch system (Fig. 32.1).[5] Edwards developed a schematic model with a double aortic arch system and bilateral ductus arteriosus.[6]

Vascular rings are a group of congenital anomalies caused by different regressions and involutons from the embryonic aortic arch system. Several recent papers report the close association of band 22q11 deletion with anomalies of the aortic arch, as well as other congenital cardiac abnormalities. In the embryonic aortic arch system, the ventral and dorsal aorta are connected by six primitive aortic arches. The embryo then utilizes the mechanism of programmed cell death, so called apoptosis, to eliminate redundant and unnecessary components. The multiple branchial arches in the human embryo are an excellent example. They represent the blood supply of gill breathing organisms which lie in our phylogenetic past. They are transiently present during human development but, either partially or completely, disappear as the pulmonary circulation develops and connects with the heart. Only a few segments usually remain. In case unnecessary segments persist, anomalies such as vascular rings result.

The paired right and left dorsal aortae, one of which will eventually become the descending thoracic aorta, are present in the embryo by approximately the 21st day of intrauterine life. Subsequently, the first to sixth branchial arteries form bilaterally, each with its own aortic arch communicating from the aortic sac to the dorsal aortas.

At this point in development, therefore, multiple vascular rings are present. The first and second arches largely resorb and contribute only to minor facial arteries, while the third arches form the carotid arteries. The left fourth arch forms distal aortic arch and aortic isthmus from the origin of the left common carotid artery to the origin the descending thoracic aorta, which itself represents a persistence of the left dorsal aorta. So, if the right fourth arch involutes, a normal left arch is formed, which means that the aorta passes from the anterior to posterior mediastinum to the left of the trachea and esophagus. If the left fourth arch involutes, a right aortic arch is formed. In this case, the aorta courses to the right of the trachea and esophagus from the anterior to the posterior mediastinum.

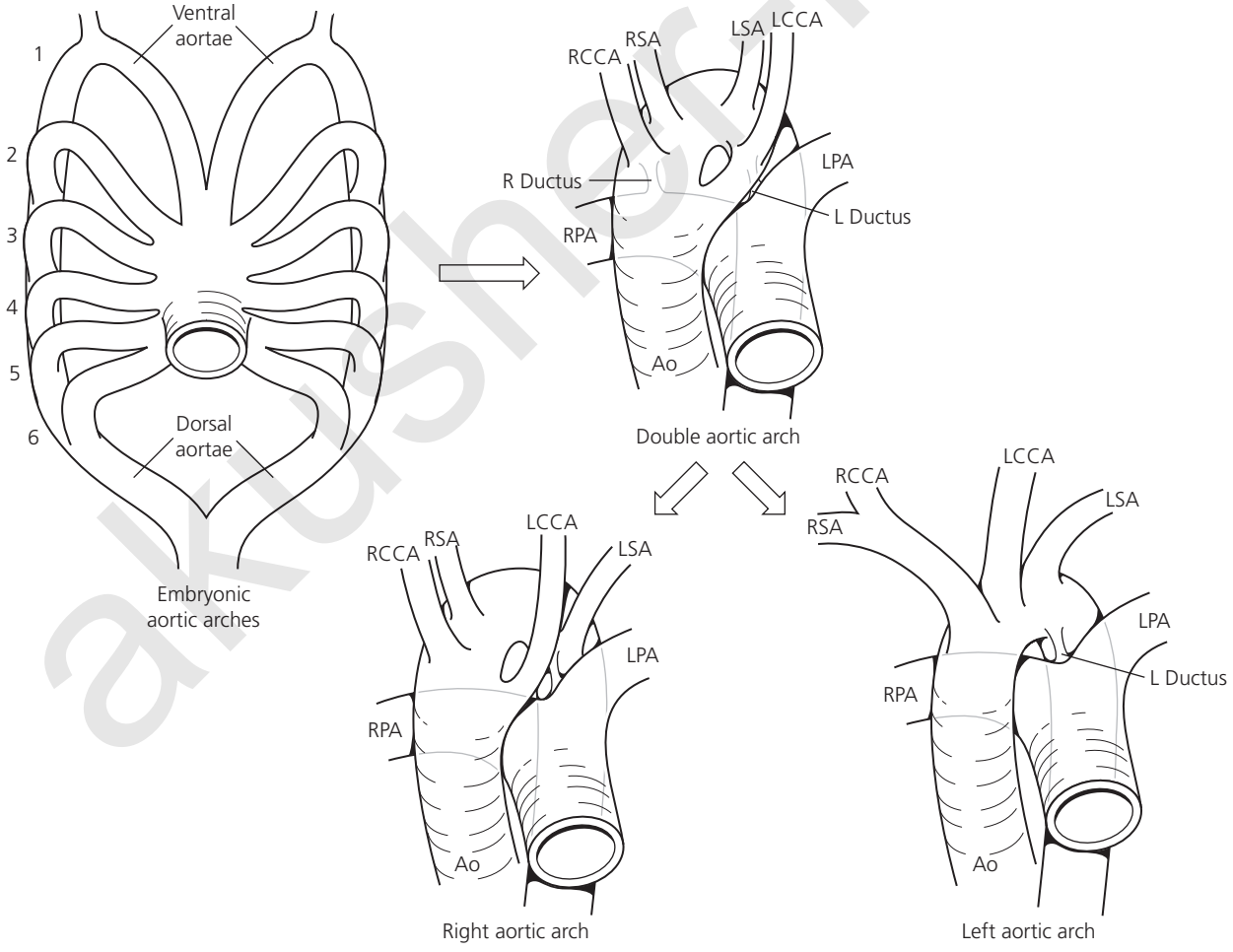

Figure 32.1 Diagram of the embryonic aortic arches. Six pairs of aortic arches originally develop between the dorsal and ventral aorta. The first, second, and fifth arches regress completely. Preservation or deletion of different segments of the rudimentary arches results in a double aortic arch, a right aortic arch, or the normal left aortic arch. Ao, aorta; LCCA, RCCA, left or right common carotid artery; LPA, RPA, left or right pulmonary artery; LSA, RSA, left or right subclavian artery.

Proximally, septation of the conotruncus produces the ascending aorta, which joins with the fourth left arch. The right dorsal aorta ultimately contributes to the right subclavian artery. The first, second, and fifth arches involute to form Edward's classic double aortic arch.

Stewart *et al.* summarized these pathologic, embryologic, and roentgenographic correlations of the lesions contributing to anomalies of the aortic arch.[7]

FORMS

Different variations of vascular anomalies exist (listed by incidence):

1. Double aortic arch
2. Right aortic arch
3. Pulmonary artery sling
4. Vascular rings associated with left aortic arch
5. Cervical aorta

Double aortic arch

Double aortic arch is an anomaly in which both right and left arches are present and may be one of several variations (Fig. 32.2):

- both arches widely patent;
- hypoplasia of one arch (usually the left);
- atresia of one arch (usually the left).

Double aortic arch represents a persistence of both right and left embryonic fourth branchial arches joining the aortic

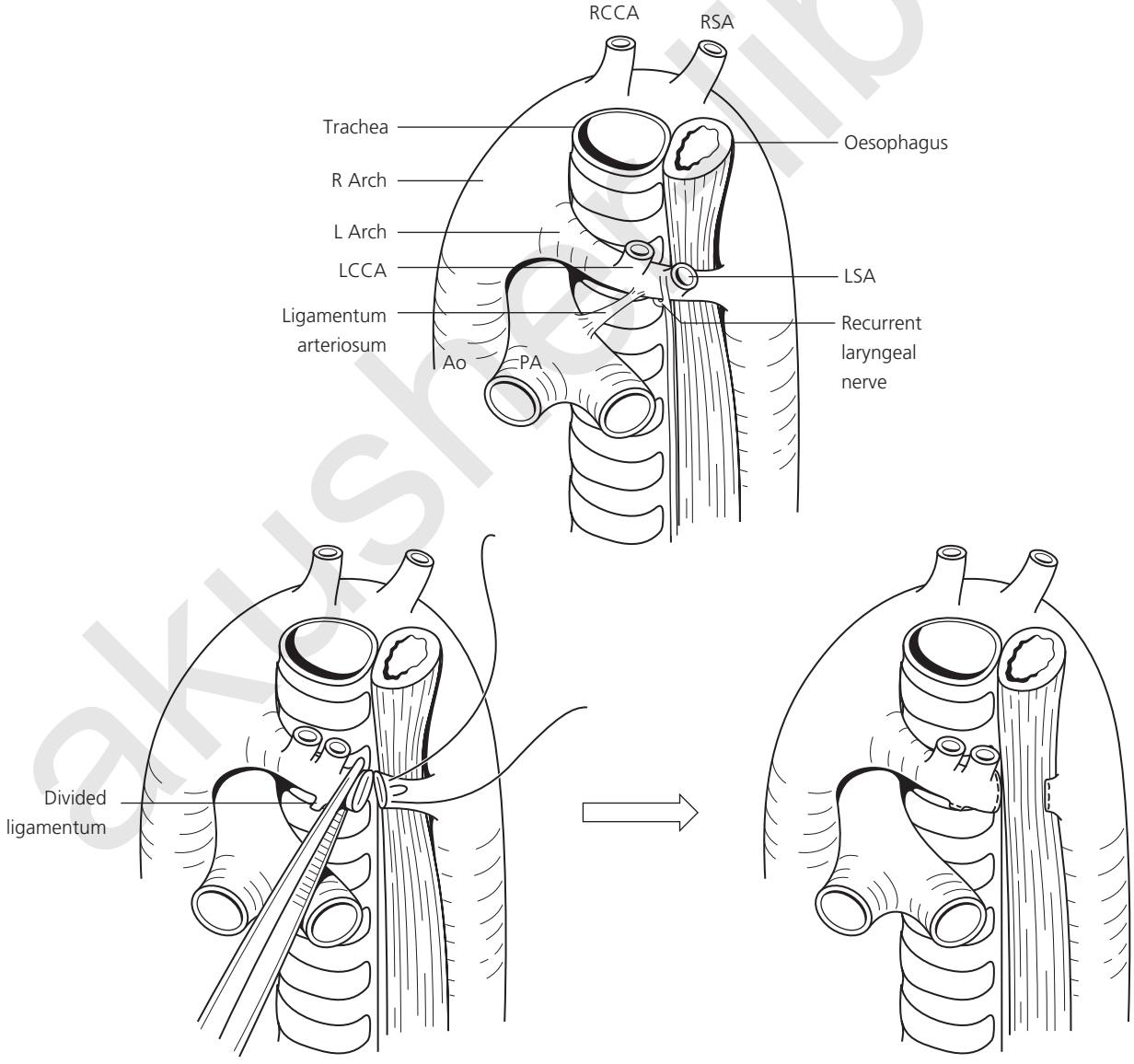

Figure 32.2 Division of a double aortic arch (from left to right). Double aortic arch with a dominant right aortic arch. The lesser left aortic arch is divided between two applied vascular clamps. The stumps are oversewn and this opens up the desired space for trachea and esophagus. Ao, aorta; LCCA, RCCA, left or right common carotid artery; PA, pulmonary artery; LSA, RSA, left or right subclavian artery.

portion of the truncoaortic sac to their respective dorsal aorta. The ascending aorta bifurcates anterior to the trachea and each arch course either to the left or to the right of the trachea or esophagus. The larger of the two arches usually crosses posterior to the esophagus and joins with the other arch in the posterior mediastinum to form the unified descending aorta. Thus a complete vascular ring is formed. Note that the right recurrent laryngeal nerve has to pass around the right aortic arch, rather than being in its usual position around the right subclavian artery. Double aortic arch is rarely associated with congenital heart disease but, when present, tetralogy of Fallot and transposition of the great vessels are most common.

Right aortic arch

In cases of individuals in whom the left fourth branchial arch involutes and the right remains, a right aortic arch is present (Fig. 32.3). Right aortic arch occurs less frequently than one in 100 000 times in the general population and may exist in the absence of any other anomalies. Its presence is suggestive of the existence of an associated anomaly. About 30% of patients with Tetralogy of Fallot have an associated right aortic arch. Persistence of the right arch with involution of the left creates a situation in which the origins of the left subclavian artery and ductus arteriosus can vary. Several of these configurations can produce a vascular ring.

RIGHT AORTIC ARCH WITH ABERRANT LEFT SUBCLAVIAN ARTERY AND LEFT LIGAMENTUM ARTERIOSUM

In this anomaly, the right arch first gives off the left carotid artery, which travels anterior to the trachea. It then gives off the right carotid, followed by the right subclavian artery, and, lastly, the left subclavian artery, which courses in a retro-esophageal position and gives rise to the ligamentum arteriosum from its base. The ligamentum arteriosum connects the left subclavian or descending aorta to the left pulmonary artery. The trachea and esophagus are surrounded by the ascending aorta anteriorly, the aortic arch on the right, the descending aorta posteriorly, and the ligamentum arteriosum and left pulmonary artery on the left. Almost 10% of these defects are associated with an intracardiac defect.

RIGHT AORTIC ARCH WITH MIRROR-IMAGE BRANCHING AND RETROESOPHAGEAL LIGAMENTUM ARTERIOSUM

In these cases, only partial resorption of the distal left fourth arch occurs. The first brachiocephalic vessel originating from the right arch is the left innominate artery, which, in turn,

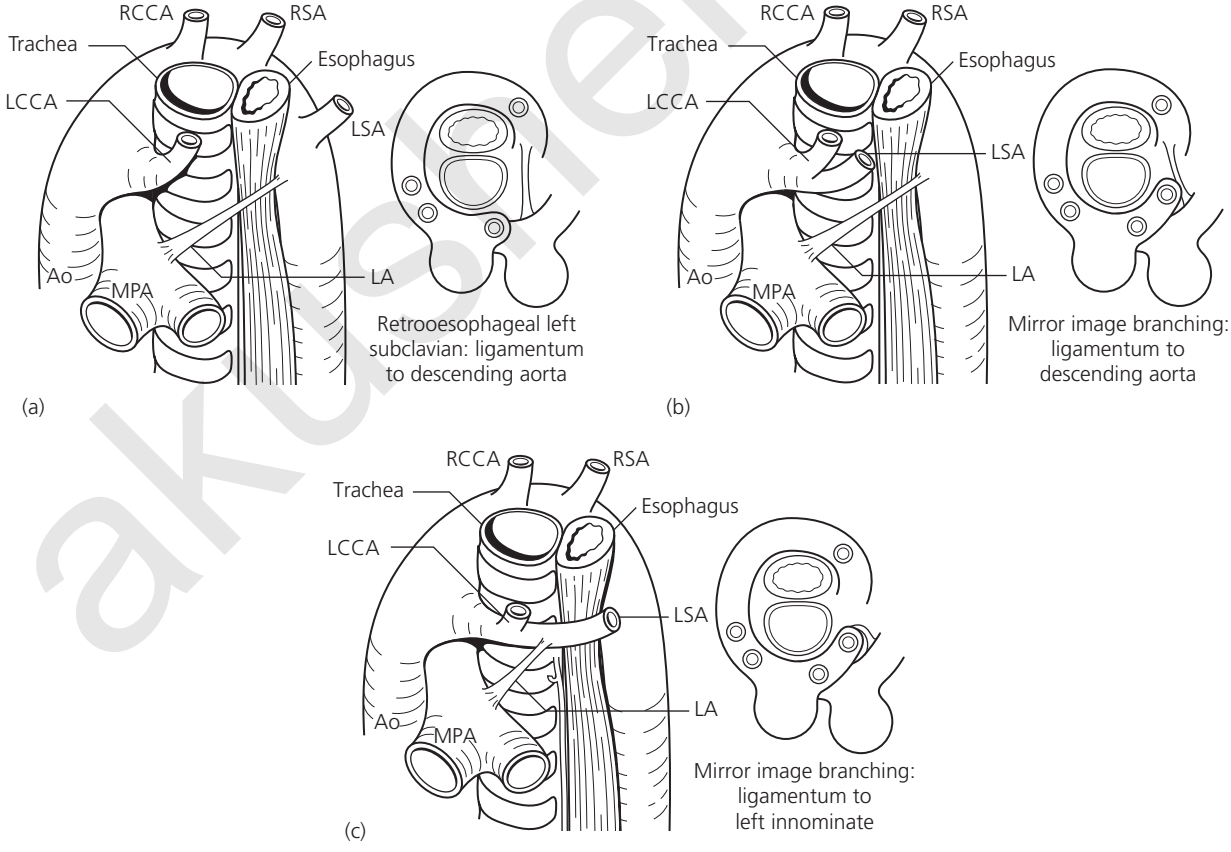

Figure 32.3 Right aortic arch types. (a) Retroesophageal left subclavian artery, ligamentum arteriosum to descending aorta. (b) Mirror image branching, ligamentum arteriosum to descending aorta. (c) Mirror image branching, ligamentum arteriosum to the left innominate artery. Ao, aorta; LCCA, RCCA, left or right common carotid artery; MPA, main pulmonary artery; LSA, RSA, left or right subclavian artery.

branches into a left carotid and left subclavian artery. These vessels course anterior to the trachea. Following these, a right carotid artery and then a right subclavian artery arise. The ligamentum arteriosum is the final structure arising from the arch in this sequence. It originates from an area called Kommerell diverticulum, which represents the nonresorbed remnant of the left fourth arch and is situated at the point of merger between the right arch and the proximal descending thoracic aorta. The ligamentum passes leftward and behind the esophagus and then travels anteriorly to join with the left pulmonary artery and complete the ring.

More commonly, in cases of right aortic arch with mirror-image branching, the ligamentum arteriosum travels from the mirror-image innominate or left subclavian artery to the left pulmonary artery. A complete ring is not present in these cases. Most importantly this type of vascular ring has a more than 90% association with intracardiac defects.

Pulmonary artery sling

Typically, the left pulmonary artery arises directly from the right pulmonary artery and passes leftward between the trachea and the esophagus (Fig. 32.4).[8] The ligamentum arteriosum passes posteriorly from the origin of the right pulmonary artery where it arises from the main pulmonary artery to the undersurface of the aortic arch and thus creating a vascular ring surrounding the trachea but not the esophagus. The left pulmonary artery is often relatively hypoplastic. In opposition, the right pulmonary artery appears larger than normal and almost like a direct extension of the main pulmonary artery. The small caliber of the left pulmonary artery may explain the high incidence of anastomotic problems that have been observed in the past with attempts to reimplant the vessel at the main pulmonary artery.

This lesion is often associated with hypoplasia and other abnormalities of the tracheal and bronchial cartilages. Most patients are symptomatic by one month after birth. Respiratory symptoms predominate, as the most severe compression is on the trachea. More than 50% of infants also have severe tracheobronchial anomalies, such as absence of the posterior membranous component, tracheomalacia, stenosis, webs, or complete tracheal rings. Although the presence of complete rings does not imply that high graded stenosis will be observed, the trachea is often narrower than normal. The complete rings may be localized at the region where the sling passes around the trachea, although in some cases the entire trachea consists of complete ringed cartilages. Severe stenosis can involve the carina and extend for a considerable distance into one or both mainstem bronchi.

Intracardiac defects are also seen in 20% of these infants.

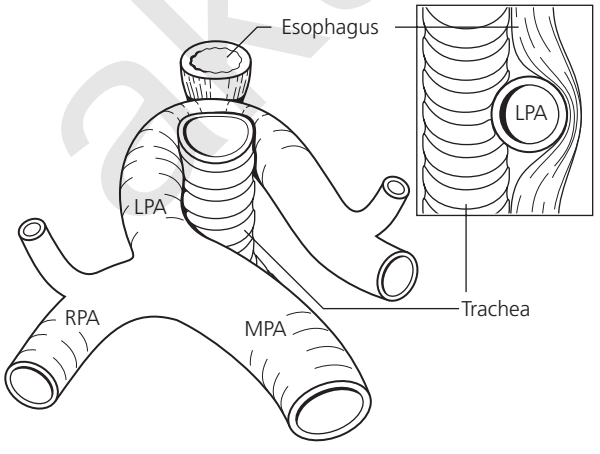

Figure 32.4 Pulmonary artery sling. MPA, LPA, RPA: main pulmonary artery, left pulmonary artery, right pulmonary artery; Inset: Lateral view of anterior compression of the esophagus.

Vascular rings associated with left aortic arch

Two extremely rare complete rings occur in the presence of a left aortic arch, and both are associated with a right-sided descending thoracic aorta.

LEFT AORTIC ARCH WITH RIGHT DESCENDING AORTA AND RIGHT LIGAMENTUM ARTERIOSUM

The first arch vessel to exit the left aortic arch is the right common carotid, which passes anterior to the trachea. The left carotid is next, followed by the left subclavian artery. The right subclavian artery arises more distally as a branch of the proximal right-sided descending aorta. The ligamentum arteriosum arises from the base of the right subclavian artery or a nearby diverticulum and travels to the right pulmonary artery.

LEFT AORTIC ARCH, RIGHT DESCENDING AORTA, AND ATRETIC RIGHT AORTIC ARCH

The brachiocephalic vessels arise from the left-sided arch in a normal arrangement. The left arch passes behind the esophagus to join a right-sided descending aorta. An atretic right arch is present and completes the ring.

LEFT AORTIC ARCH AND LEFT LIGAMENTUM ARTERIOSUM WITH RETROESOPHAGEAL RIGHT SUBCLAVIAN ARTERY

This is the most common of the arch vessel anomalies, occurring in about 0.5% of the population (Fig. 32.5). In these cases, the right subclavian artery does not arise from an innominate trunk with the right carotid artery but originates as the last brachiocephalic branch from the descending aorta and takes a retroesophageal route to its destination, as depicted in the image below. A normally positioned ligamentum arteriosum is present on the left. If a right ligamentum arteriosum were present instead of one on the left, its course would proceed from the base of this anomalous right subclavian artery to the right pulmonary artery and a complete ring would exist. Instead, no true vascular ring is present in these cases. Most patients are symptomatic, but the occasional patient may present with dysphagia.

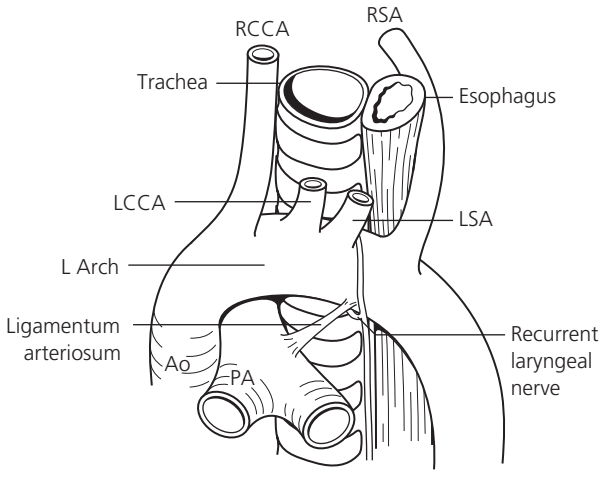

Figure 32.5 Left aortic arch with aberant right subclavian artery compressing the esophagus. Ao, aorta; LCCA, RCCA, left or right common carotid artery; PA, pulmonary artery; LSA, RSA, left or right subclavian artery.

LEFT AORTIC ARCH WITH ANOMALOUS ORIGIN OF THE INNOMINATE ARTERY

The actual prevalence of this abnormality is widely debated. This is because, in as many as 90% of cases in which symptomatic tracheal compression is produced by the innominate artery, the vessel is noted angiographically to have a normal origin from the aorta (Fig. 32.6). When an anatomic abnormality is noted in these cases, the innominate artery appears to originate from a more distal and leftward position on the arch than normal. As it takes its course from left to right, it crosses the trachea anteriorly and in doing so may produce compression of the trachea.

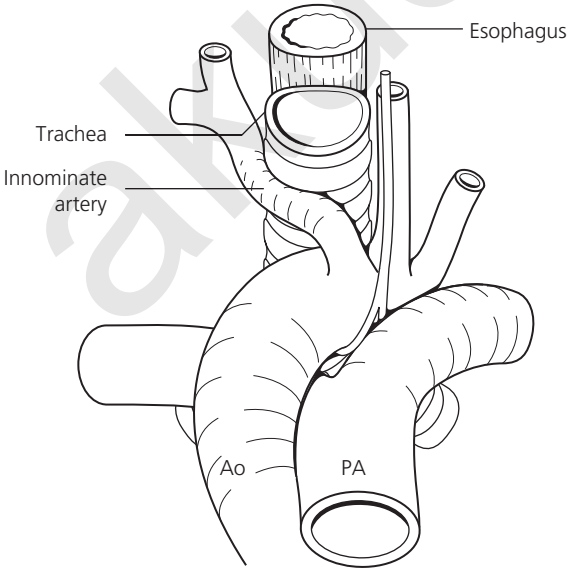

Figure 32.6 Innominate artery compression of the anterior trachea. Ao: Aorta; PA: pulmonary artery.

CERVICAL AORTA

This a rare anomaly in which the aorta ascends into the neck on the right or left side, forming a pulsatile mass in the supraclavicular region. Several morphological types have been described according to side of the aortic arch (contralateral or ipsilateral) and the origin of the head and neck vessels.[9]

CLINICAL FINDINGS

Clinical manifestations are related to the nature of malformation and tightness of the ring. Most children with vascular rings present with symptoms in the first few months of life and require surgery within the first year of life.[10] The classic symptom of a child with a vascular ring is the 'seal-bark' cough. In addition, noisy breathing may be heard both during inspiration and expiration (biphasic stridor), while in asthma, the noise is mainly at the end of expiration. A common finding in all forms of vascular rings is the fact that recurrent respiratory infections occur.

In children with double aortic arch if both arches are widely patent, the rings are tight and patients present with biphasic stridor in the first weeks of life. In case one arch is hypoplastic or atretic, the rings are usually looser, with presentation at 3–6 months of age. Rarely does double aortic arch present in adulthood. Children with double aortic arch are often small, poorly developed, and hold their head in hyperextension. Repeated severe respiratory infections may occur.

Children with a pulmonary artery sling and or complete tracheal rings often have severe respiratory distress requiring emergent intubation and ventilation.

Children with the innominate artery compression syndrome often present with apnea as initial symptom.

Feeding difficulties occur when solid food is introduced to the infant. This results in dysphagia and only tends to occur in older children. Gastroesophageal reflux with concomitant pain or fear of food intake is observed. Cyanotic spells in these young patients may have caused episodes that are termed apparent life-threatening events (ALTE) or death spells, in which acute apneic or severe obstructive events are accompanied by cyanosis.

Physical examination may be within normal limits, but one may see coughing, dyspnea, drooling, or dysphagia. Infants will feed poorly due to respiratory distress and may have life-threatening episodes of apnea and cyanosis.

Cardiac examination will most often be normal. Lung examination may or may not show evidence of pneumonia.

ASSOCIATED SYNDROMES AND NON-CARDIAC CONDITIONS

Double aortic arch is associated with a chromosome band 22q11 deletion in approximately 20% of patients. Band 22q11 deletion is responsible for DiGeorge, velocardiofacial, and conotruncal anomaly face syndromes, which are often

referred to using the unified terms CATCH-22 syndrome or chromosome band 22q11 deletion syndrome. In patients with double aortic arch, the frequency of phenotypes satisfying the clinical criteria for these various syndromes is not known. Rather, the important point is that double aortic arch may be associated with band 22q11 deletion, which has various other possible manifestations. These include, but are not limited to, palatal abnormalities, laryngotracheal anomalies, speech and learning delay, characteristic facial features, hypocalcemia, abnormalities of T-cell-mediated immune function, and neurologic defects.

Occasionally, patients with double aortic arch may have anomalies consistent with either vertebral, anal, cardiac, tracheal, esophageal, renal, and limb (VACTERL) or posterior coloboma, heart defect, choanal atresia, retardation, genital, and ear (CHARGE) associations. Double aortic arch has also been reported in association with other chromosomal anomalies, such as trisomy 21 and other syndromes.

One of the more important non-cardiac features that sometimes is found in association with double aortic arch is esophageal atresia, insofar as an undiagnosed arch anomaly may complicate repair of the esophageal atresia, which is usually recognized earlier than the double aortic arch.

Another non-cardiac anomaly that may be associated with vascular rings is a congenital laryngeal web, which may present with the same symptoms and signs as a vascular ring. Accordingly, patients with persistent stridor or upper airway obstruction after repair of a vascular ring, particularly those with a chromosome 22q11 deletion, should be evaluated for the presence of a congenital laryngeal web.

LABORATORY STUDIES

No laboratory screening or diagnostic study exists for this abnormality.

IMAGING STUDIES

Chest x-ray

Children usually present with symptoms of respiratory difficulty, therefore chest x-ray is always the first and most commonly performed test. Look for the position of the aortic arch, which is usually identifiable on the plain chest x-ray. The identification of a right aortic arch on chest x-ray in a child with airway difficulties, respiratory distress, or dysphagia should alert the clinician to a higher likelihood of a vascular ring. An ill-defined arch location is often observed in patients with double aortic arch. Such a finding should raise the suspicion of an arch anomaly in a symptomatic child. Other x-ray findings that may be noted with vascular rings include compression of the trachea and hyperinflation and/or atelectasis of some of the lobes of either lung. A specific finding associated with anomalous left pulmonary artery is hyperinflation of the right lung. In general, chest x-ray is not very sensitive in the diagnosis of vascular rings.

Barium esophagram

Most authorities consider barium esophagram to be the most important study in patients with a suspected vascular ring, and it is diagnostic in the vast majority of cases. Double aortic arch (Fig. 32.7) produces bilateral and posterior compressions of the esophagus, which remain constant regardless of peristalsis. The right indentation is usually slightly higher than the left, and the posterior compression is usually rather wide and courses in a downward direction as it goes from right to left. Patients having anomalies in which the right subclavian artery takes a retroesophageal course have a posterior defect slanting upward from left to right. The posterior defect in these cases is usually not as broad as that found in double aortic arch. In opposition, in patients with left aortic arch and aberrant subclavian artery the oblique filling defect is mirror imaged. An experienced radiologist can usually distinguish a double aortic arch from the retroesophageal subclavian artery based on the esophageal impression.[11]

An anterior indentation of the esophagus is, however, typical of an anomalous left pulmonary artery or so-called pulmonary artery sling. No posterior compression is present with this anomaly. Cases of abnormally located innominate artery causing tracheal compression have normal findings on esophagram.

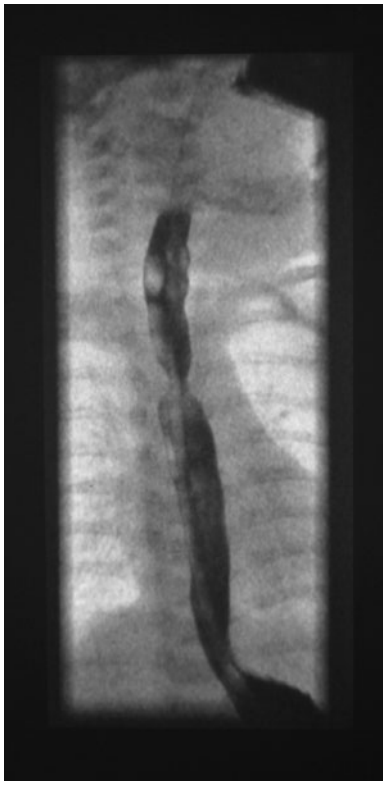

Figure 32.7 Barium esophagram in antero-posterior projection in a patient with double aortic arch.

Echocardiography and color-flow Doppler

Echocardiographic studies have been increasingly used for the diagnosis of a vascular ring. This study has replaced

pulmonary angiography at many centers to determine the presence of an anomalous left pulmonary artery. It is essential in the diagnostic work up of associated congenital cardiac defects. Some limitations in diagnosis using this study exist. Structures without a lumen, such as a ligamentum arteriosum or an atretic arch, have no blood flow and are difficult to identify with color-flow echocardiography. Also, identification of compressed midline structures and their relationship to encircling vascular anomalies may be difficult to detect, especially for the less experienced echocardiographer.

Computed tomography scan, magnetic resonance imaging, and digital subtraction angiography

Computed tomography (CT) scan, magnetic resonance imaging (MRI) (Fig. 32.8), and digital subtraction angiography (DSA) can be useful diagnostic tools because they reveal the positions of vascular, tracheobronchial, and esophageal structures and their relationships to one another. Although these modalities provide excellent delineation of all of the associated structures, they should be reserved for cases in which the results of barium esophagram do not provide a clear diagnosis. MRI has been proposed as an excellent substitute for angiography. All of these studies have drawbacks. CT scan and DSA expose the patient to radiation and require i.v. contrast. MRI requires patients to remain very still, so very young patients who are unable to understand verbal instructions require sedation. This may be particularly risky in young children with existing airway compromise. The expense encountered with these investigations must also be considered.

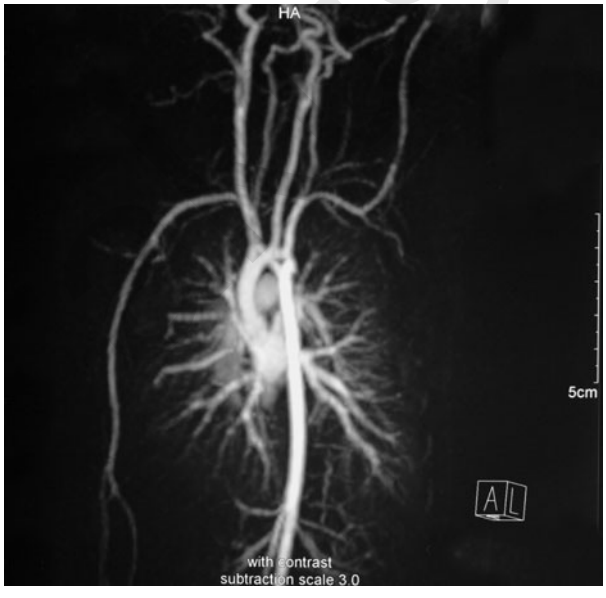

Figure 32.8 Magnetic resonance imaging in left anterior oblique projection in a patient with double aortic arch. Both aortic arch segments are of equal calibre and widely patent.

Aortic angiography and cardiac catheterization

In the past, diagnostic aortography was performed in selected cases to delineate the anomalous arch vasculature. It is generally agreed at present that, in the vast majority of cases, this study adds very little to the information obtained from a barium esophagram. If additional studies are required, echocardiography, CT scan, or MRI can usually provide the required information. However, reported cases exist of rare arch anomalies in which aortography was the only study from which the correct anatomic configuration was identified.[12] This study may be required in cases in which the diagnosis and arch configuration remains in question after other less invasive studies fail to provide a definitive answer.

Cardiac catheterization is useful in cases in which associated cardiac abnormalities are known or suspected.

Bronchoscopy

This diagnostic study has been used in the evaluation of children with symptoms of airway obstruction or compression. It is an essential part of the work up for congenital tracheal stenosis. It is rarely required in the diagnosis of the various types of complete vascular ring. In case a simple vascular ring was diagnosed by other tests, a bronchoscopy should not be performed due to the added risks and costs.

In the presence of a vascular ring, pulsatile external tracheal compression is easily observed. Note that compression of the airway by a vascular structure in the pediatric patient does not represent an unyielding obstruction and should not pose a problem for passage of the bronchoscope. In cases of an abnormally placed innominate artery, obvious pulsation is observed in the anterior wall of the trachea corresponding to the area of compression.

INDICATION FOR INTERVENTION

Surgical division of the vascular ring is indicated in any patient who is symptomatic with airway or esophageal compression.

MEDICAL THERAPY

No medical therapy exists for the definitive treatment of vascular rings. Preoperatively, the patient should be given adequate nutritional support, as well as general respiratory care and appropriate treatment of any respiratory tract infection. Surgery should not be delayed in the presence of a respiratory tract infection, because the division of the ring allows more adequate and complete clearing of respiratory secretions.

SURGICAL THERAPY

Surgical division of symptomatic vascular rings is the only appropriate form of therapy (see Box 32.1). Surgery should be performed promptly after the diagnosis is made, especially in patients with stridor, apnea, or other symptoms of respiratory

Box 32.1 Surgical management

Double aortic arch
- Left thoracotomy inmuscle sparing technique – fourth interspace
- Division of lesser of the two arches at insertion with descending aorta
- Preserve blood flow to head and neck arteries
- Ligate and divide ligamentum arteriosum
- Leave pleura open

Right aortic arch with left ligamentum arteriosum
- Left thoracotomy in muscle sparing technique – fourth interspace
- Ligate and divide ligamentum arteriosum
- If present, resect Kommerell's diverticulum and transfer left subclavian to left carotid artery
- Lyse adhesive bands
- Leave pleura open

Pulmonary artery sling
- Median sternotomy
- Commence extracorporeal circulation
- Resect left pulmonary artery (LPA) at its origin at the right pulmonary artery (RPA)
- Oversew resulting defect in RPA
- Reimplant LPA into main pulmonary artery anterior to trachea
- Tracheal sliding plasty to for affected segment of tracheal stenosis

Innominate artery compression syndrome
- Right anterolateral thoracotomy (left sided thoracotomy also possible) – third or fourth interspace
- Resect right lobe of thymus
- Suspend innominate artery to posterior sternum
- Postoperative bronchoscopy

distress. Delay in operative intervention can result in complications of a serious nature. Left thoracotomy is the surgical approach of choice for the division of a vascular ring in the majority of cases. In the past, anomalous left pulmonary artery has been corrected using the left thoracotomy approach. More recently, the use of median sternotomy and cardiopulmonary bypass has been shown to produce better long-term results. The extremely rare configurations associated with left aortic arch and right descending thoracic aorta are the lesions that should be approached via a right thoracotomy for division of the ring. General anesthesia with a single lumen nasotracheal or orotracheal tube is used for infants and small children. Bilateral radial arterial lines and a femoral arterial line together with oxygen saturation probes on all extremities is ideal.

Division of a double aortic arch

TRADITIONAL THORACOTOMY APPROACH

The surgical approach to a double aortic arch is through a left thoracotomy in the fourth intercostal space with a muscle-sparing technique, and the components of the vascular ring are visualized. The pleura overlying the vascular ring should then be opened and careful dissection performed to clearly identify all the pertinent vascular structures (Fig. 32.9). The right, or posterior, arch does not require mobilization unless it is the lesser of the two arches and is to be divided. In such cases, the proximal descending aorta should be reflected anteriorly to visualize the area where the right arch enters.

The goal of surgical therapy is to divide the smaller of the two arches at a site that does not compromise the blood flow to the head vessels. A likely site for division of the minor, or atretic, arch is at its point of juncture with the descending aorta. Identify and avoid the recurrent laryngeal and vagus nerves. Before dividing the arch, it should be temporarily occluded and the anesthesiologist asked to check right and left radial and carotid pulses. Arch division should always be done between vascular clamps with oversewing of the divided stumps with non-absorbable sutures. Simple ligation and division has been associated with ligature slippage and subsequent catastrophic hemorrhage. The divided stumps typically separate by 1.5 to 2 cm, and disappear into the posterior mediastinum making precise hemostasis quite important. The operative repair is completed by freeing up all adhesive bands surrounding the esophagus in the area of the divided ring (Fig. 32.10).

Closure of the mediastinal pleura is not performed to avoid the development of adhesive scarring in the already affected area of the trachea and esophagus. The thoracotomy incision is closed without a chest tube by evacuating air from the plural space with a small suction catheter. It may take up to one year for the child's noisy breathing to disappear as the tracheo-bronchomalacia caused by the ring resolves.

VIDEO-ASSISTED TECHNIQUE

A couple of groups advocate this technique as the method of choice for treatment of vascular rings, unless preoperative studies suggest that a patent segment of a double aortic arch is present.[13–15]

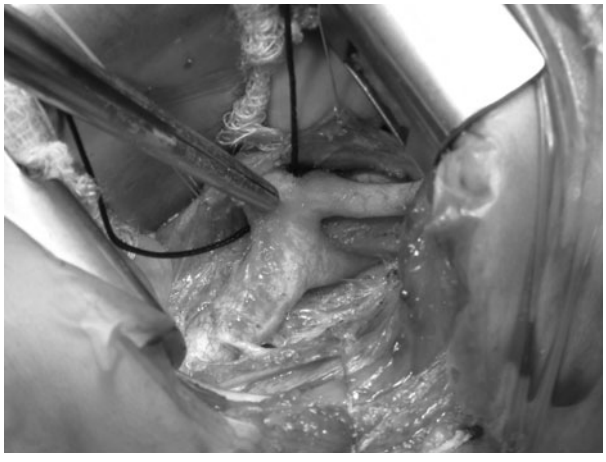

Figure 32.9 Operative photograph taken during dissection after postero-lateral thoracotomy in a patient with double aortic arch. The parietal pleura is opened and the vascular structures are dissected. The left-sided ductus arteriosus is looped by a silk tie.

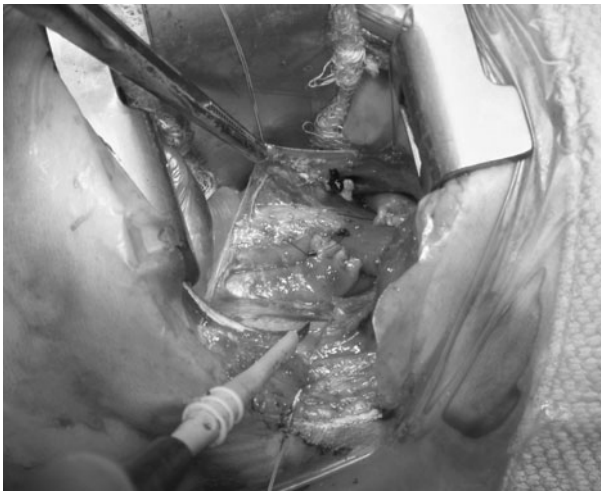

Figure 32.10 Operative photograph taken after division of a double aortic arch via postero-lateral thoracotomy. The parietal pleura is opened and the anterior arch is divided and oversewn. The left-sided ductus arteriosus is tied and only the aortic component is still visible. Note the resulting gap between the two stumps of the anterior aortic arch.

The patient is placed in the right lateral decubitus position following single lumen endotracheal intubation. Four small stab incisions are made in the posterolateral chest wall to admit, from medial to lateral, a grasping forceps, a lung retractor, a video scope, and an L-shaped cautery probe. Exposure is achieved by retracting the inflated left upper lobe inferiorly and medially. The mediastinal pleura is incised over the left subclavian artery which leads to the other components of the vascular ring. The ring is dissected free from the esophagus and surrounding structures. The atretic segment of the vascular ring and ligamentum are identified. Clips are placed and the ring and the ligamentum are divided between clips. Fibrous bands over the esophagus are also freed. A small chest tube is placed under direct vision and the wounds are closed with steri strips.[13,16]

Right aortic arch

Surgical treatment of this condition also consists of dividing the ductus arteriosus or the ligamentum arteriosum. Division of the left subclavian artery is not generally necessary for relieving tracheal compression. Patients with an anomalous left subclavian artery and Kommerell's diverticulum[17] are at risk of developing severe tracheal compression. Backer *et al.* have recommended resection of the diverticulum and reimplantation the left subclavian artery to the left carotid artery as a primary operation.[18,19] Surgery is performed through a muscle sparing left lateral thoracotomy in the fourth intercostal space. After dissection of the vascular structures and division of the ligamentum arteriosum, the patient is anticoagulated. Any adhesive bands are lysed, and the recurrent laryngeal and phrenic nerves are carefully identified and protected. The base of the Kommerell's diverticulum is taken in a side-biting clamp and the distal subclavian artery is occluded with a vascular clamp prior to its division. The diverticulum is resected and its base oversewn. The left subclavian artery is then anastomosed to the origin of the left carotid artery.

Pulmonary artery sling

Although the traditional approach has been through a left-sided thoracotomy with reimplantation at the original site of the left pulmonary artery, as performed in 1953 by Potts,[3] and then reimplantation of the left pulmonary artery on the left side of the main pulmonary artery, as described by Hiller and MacIean in 1957,[20] currently the preferred method is to undertake repair via median sternotomy. With this approach and utilizing cardiopulmonary bypass, reimplantation of the left pulmonary artery onto the left side of the main pulmonary artery without application of a side biting clamp is carried out without aortic cross-clamping. Then tracheal repair can be performed. This technique was introduced in 1986 by Kirklin and Barrat-Boyes.[21] Different techniques are utilized for tracheal repair depending on the length and site of the tracheal stenosis. Over recent years, many different types of repair have been undertaken, ranging from simple end-to-end repair,[22,23] various forms of patch tracheoplasty,[24,25] tracheal homograft implantation,[26,27] and slide tracheoplasty.[28–33]

A review of these methods is beyond the scope of this chapter, but more comprehensive reviews are available.[33,34]

Left aortic arch with anomalous origin of the innominate artery

The surgical treatment of this anomaly is based on the suspension of the innominate artery to the posterior aspect of the sternum. This operation can be performed from either side.[35,36] The thymus lobe of the corresponding side is resected and the pericardium opened respecting the phrenic nerve. The ascending aorta or the innominate artery is approximated to the posterior aspect of the sternum by two or three interrupted pledget-supported heavy sutures. Bronchoscopy is then performed to confirm the tracheal relief. In order to relieve the compression of the trachea, it is essential not to dissect a plane between the great vessels and the trachea, so the tension applied by the suture on the vessels is transferred to the trachea's anterior wall.

Other authors have described using a median sternotomy with division of the innominate artery and reimplantation into the ascending aorta at a site more rightward and anterior to the native site.[37] This technique sacrifices the active suspending mechanism on the tracheal wall provided by the classical suspension maneuver. In addition, there seems to be some risk of cerebrovascular accident, although Grimmer *et al.* report no cerebrovascular injury in a long term follow-up study.[38]

Results

TRADITIONAL THORACOTOMY APPROACH

One of the largest reports of vascular anomalies causing tracheoesophageal compression is a report by Backer *et al.* from the Children's Memorial Hospital in Chicago, USA published in 1989[10] and updated in 2005.[19] The authors described 204 infants and children with a mean age of 13 months who had undergone surgical procedures for tracheoesophageal obstruction. Of these, 113 patients had a vascular ring, 61 with a double aortic arch, and 52 with a right aortic arch and left ligamentum. The operative mortality rate was 4.9% with a late mortality rate of 3.4%. However, there were no operative deaths within the last 28 years. At a mean follow up of 8.5 years, 92% of the patients were essentially free of symptoms.

In 1994, Cordovilla Zurdo *et al.* reported on a series of 43 patients with one hospital and one late death.[39] Over a mean follow up of 11 years, 90% of the patients were asymptomatic. Similarly, Anand *et al.* reported on 44 patients operated on for vascular ring or pulmonary artery sling from 1977 to 1990.[40] In this series, three deaths due to cardiac failure after repair of complex anomalies were reported.

Further studies report on good long-term results with low operative mortality. Mortality seems to be limited, and only occurring in patients with complex cardiac anomalies.[41–44]

VIDEO ASSISTED TECHNIQUE

Only a limited number of publications are currently available reporting on results after throcoscopic division of vascular rings.[13–16] In these series, no mortality was observed. However, stay on ICU and in hospital was no different from the conventional technique. It should be taken into account that this technique offers only a limited amount of control and in addition the surgical times are much longer than the conventional procedures. In addition, the video-assisted technique is only applicable if the vascular structures to be divided are obliterated.

Pulmonary artery sling with tracheal repair

Kocyildirim *et al.*[45] reports in his study on 34 patients with long-segment tracheal stenosis (21 patients with pulmonary artery sling). Cardiopulmonary bypass was used in all operations. Before the establishment of the multidisciplinary tracheal team, pericardial patch tracheoplasty was performed in 15 of 19 patients. Twelve patients had a suspended pericardial patch tracheoplasty, two (17%) of whom died late after the operation. Of the three patients who had had a simple unsuspended patch, two (67%) died early after the operation. Four patients were operated on with the tracheal autograft technique, two (50%) dying early in the post-operative period. After multidisciplinary tracheal team formation, in the era between 2001 and 2004, 15 patients were operated on with slide tracheoplasty, and there were two (13%) early postoperative deaths. A significant reduction in cost and duration of stay has been shown both in the intensive care unit and the hospital.

Backer *et al.*[46,47] reports on 28 infants after pericardial tracheoplasty for long-segment tracheal stenosis. Seven of these infants required reoperation or stenting for residual or recurrent tracheal or bronchial stenosis. Revisions were performed 2–6 months after the original procedure with cardiopulmonary bypass and bronchoscopic guidance. Two patients underwent repeat pericardial patch tracheoplasty, and four patients underwent insertion of a rib cartilage graft. Two of these patients required Palmaz wire expandable stents and one other patient also underwent stent placement. There was one late death one year after cartilage graft insertion. The authors identified three risk factors for reoperation after tracheoplasty; younger age at initial surgery and associated pulmonary artery sling or tracheal right upper lobe bronchus. Good intermediate results are possible in this difficult group of children using a selective and inclusive strategy for tracheal enlargement that includes repeat pericardial tracheoplasty, autologous cartilage grafts, and expandable wire stents.

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33

Pulmonary air leaks

PREM PURI AND JENS DINGEMANN

INTRODUCTION

Pulmonary air leaks include urgent life-threatening neonatal emergencies like pulmonary interstitial emphysema, pneumomediastinum, pneumothorax, or pneumopericardium.[1–4] The incidence of pulmonary air leaks in the neonates has increased in recent years, possibly because an increasing number of sick infants with respiratory distress on assisted ventilation are now surviving to develop this complication.[5] The sequence of events in the occurrence of pulmonary air leaks is similar regardless of whether it is caused by uneven alveolar ventilation, air trapping, and high transpulmonary pressure swings. The rupture of terminal air sacs causes air to escape into the pulmonary interstitium, resulting in pulmonary interstitial emphysema. The air tracks along the sheaths of pulmonary blood vessels to the lung hilum and air may then rupture into mediastinum, pleura, or pericardium.[6] It has also been suggested that air directly enters the pleural cavity following a rupture of a subpleural bleb.[7] Rarely, systemic air embolism may be a terminal event of pulmonary air leaks.[8,9]

PULMONARY INTERSTITIAL EMPHYSEMA

Pulmonary interstitial emphysema (PIE) is predominantly seen in preterm infants with respiratory distress syndrome (RDS) who are on assisted ventilation.[10] Occasionally, it follows vigorous resuscitative efforts. The lesion represents air that has dissected along perivascular sheath within pulmonary interstitium. The compression caused by interstitial 'air conduits' interferes with ventilation and reduces pulmonary perfusion leading to CO_2 retention and hypoxemia.

The incidence of PIE increases with low birth weight and prematurity. In one series, 20 out of 303 ventilated low birth weight (LBW) babies developed PIE,[11] but significantly high incidences of 32 and 42% have been reported in other series.[12,13]

Presentation and diagnosis

Pulmonary interstitial emphysema may be diffuse or localized. It is a radiological diagnosis found on the chest x-ray of an ill neonate. The radiological features consist of hyperinflation and multiple cyst-like lucencies that appear to radiate outward from the hilum of the lung (Fig. 33.1). Suspect

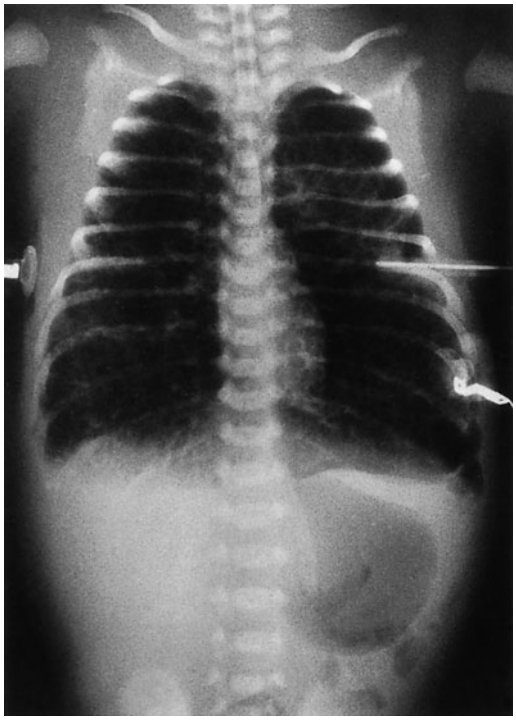


Figure 33.1 Diffuse pulmonary interstitial emphysema in a baby weighing 1200 g and requiring prolonged positive pressure ventilation for hyaline membrane disease. The lungs are grossly hyperinflated with a diffuse cystic pattern in this film at 7 days of life. Note narrow heart shadow due to tamponade effect of the distended lungs. A shallow pneumothorax is present in the left upper zone and a left chest drain has been inserted.

neonates should be monitored by daily chest x-ray for an earlier diagnosis of PIE.

Treatment

PIE, diffuse or localized, makes ventilatory management difficult. It is mandatory to use appropriate ventilation strategies to prevent PIE or its deterioration, respectively. Ventilatory pressures should be kept at a safe minimum while aiming for acceptable blood gas values of PaO_2 >6–7 kPa, pH >7.25, and $PaCO_2$ <8 kPa.[14]

No specific surgical treatment is indicated for diffuse PIE. Benefit has been demonstrated for both high frequency positive pressure ventilation (HFPPV) and triggered ventilation with regard to a reduction in air leak and a shorter duration of ventilation.[14] Also, the prophylactic application of surfactant has been shown to be beneficial for the outcome of preterm infants with PIE.[15] An aggressive approach of decompressing the lungs and creation of artificial pneumothorax has been described for patients in whom conservative management fails. This approach has been shown to successfully remove interstitial gas and, after re-evacuation of the pneumothorax, ventilation could be discontinued shortly.[16]

If the disease is unilateral or localized, selective partial or complete atelectasis of the desired segment can be achieved by selective bronchial intubation[17,18] or by placing the infant with his hyperinflated lung dependent in the lateral decubitus position at all times.[19] Localized pulmonary interstitial emphysema cases have also been successfully treated by resection of the diseased lobes.[20,21]

Prognosis

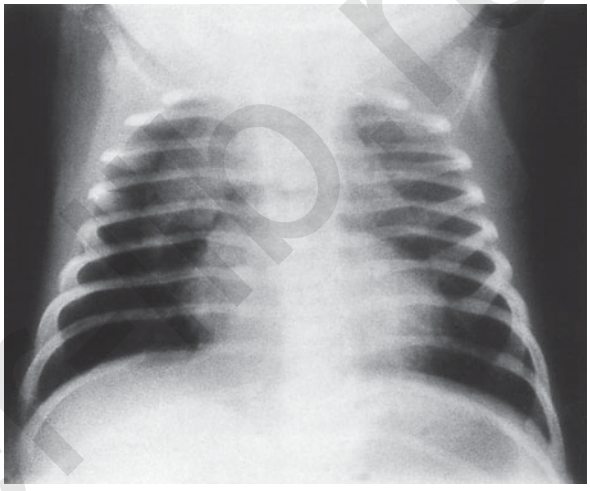
The mortality rate from diffuse PIE has been reported to be from 24% to as high as 60%.[11,22] There have been no significant differences in neonatal parameters between infants who died or survived. However, the survivors had a significantly lower maximal peak inspiratory pressure and FiO_2 on the first day of ventilation.[22]

PIE is invariably fatal in the group of neonates with RDS who weigh <1600 g at birth and who develop bilateral PIE within the first 48 hours of life, needing FiO_2 above 0.6 on the first day. High positive inspiratory pressure on day 1 was found to be the most significant parameter associated with fatal pulmonary interstitial emphysema. A cut-off level of 26 cm H_2O was found to be discriminant.[23] These criteria may be useful in selecting neonates who might benefit best from the new modes of ventilation. In preterm infants, additional application of surfactant significantly reduces mortality of PIE.[15]

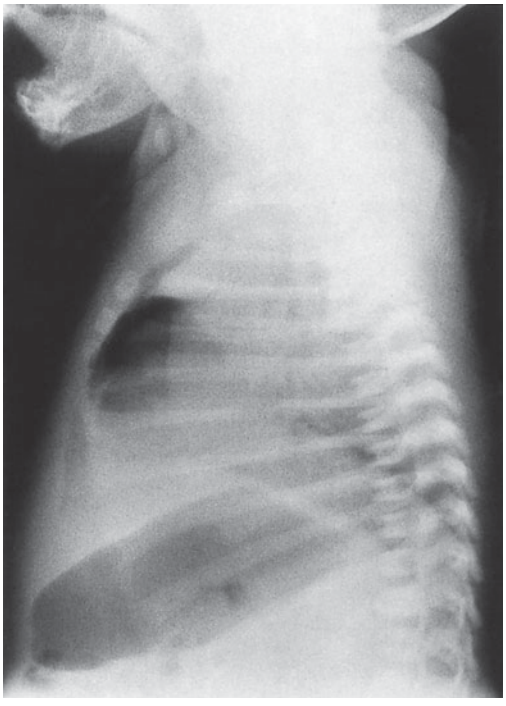
PNEUMOMEDIASTINUM

Pneumomediastinum develops when interstitial air in PIE migrates to the mediastinum. Also, spontaneous pneumomediastinum without any history of mechanical ventilation or concomitant lung disease has been reported.[4,24] If the collection of air is small, it remains asymptomatic. However, large collections of mediastinal air may produce respiratory distress.[24] Heart sounds are muffled and the sternum may appear bowed.

The diagnosis is made on chest x-ray. The antero-posterior views may show the characteristic 'angel-wing' sign produced by air elevating the thymus gland (Fig. 33.2a). It has also been described as having a crescentic configuration resembling a 'spinnaker sail'.[4] Lateral x-ray of the chest shows marked hyperlucency in the anterior mediastinum (Fig. 33.2b). Ultrasound can be used to diagnose pneumomediastinum. It has been reported to be superior to x-ray under certain



(a)



(b)

Figure 33.2 Pneumomediastinum. (a) Anteroposterior view demonstrates the characteristic 'angel wing' sign produced by air elevating the thymus from the heart. (b) Lateral view confirms air in the anterior mediastinum.

conditions and should be considered if a pneumomediastinum is clinically suspected and x-ray shows no typical findings.[25]

Retrocardiac pneumomediastinum has a strong association with other manifestations of extra-alveolar air leaks such as PIE, pneumothorax, dissection of air into the soft tissues of the neck, and pneumoperitoneum.[26] Tension pneumomediastinum has also been described to cause isolated left ventricular inflow obstruction.[27]

Symptomatic pneumomediastinum is managed by ultrasound-guided needle aspiration of the anterior mediastinal compartment.[28] In asymptomatic cases, air is absorbed spontaneously and no treatment is indicated.

PNEUMOTHORAX

Pneumothorax is far more frequent in the newborn period than in any other period of life – symptomatic pneumothorax occurs in 0.08% of all live births[29] and in 5–7% of infants with birth weight of $\leq$1500 g.[30,31] It is bilateral in about 20% of cases.[32] Pneumothorax in the newborn predominantly occurs in patients with hyaline membrane disease, meconium aspiration syndrome, pulmonary hypoplasia, and infants requiring vigorous resuscitation at birth.[32–34]

In ventilated preterm infants, it has been shown to be attributed to high peak inspiratory pressure low FiO_2, pulmonary hemorrhage and high arterial CO_2 while a decreased risk was associated with high positive end-expiratory pressure.[35]

The overall incidence of pneumothorax in the newborn with respiratory difficulties has been reported to be as high as 34% of those who are ventilated.[36] Pneumothorax can also be caused as a complication of deep endotracheal tube suction[37] and by other iatrogenic perforation of the bronchus.[38] A rare association of spontaneous pneumothorax with congenital cystic adenomatoid malformation[39] and early spontaneous pneumothorax with common pulmonary vein atresia[40] have been reported. The 'surgical' cases of pneumothorax and/or pneumomediastinum at the Liverpool Neonatal Surgical Centre included infants with gross renal anomalies, large exomphalos, a rare type of vascular sling, and spontaneous perforation of esophagus. In half of the cases, the etiology was less obvious.[41]

Presentation and diagnosis

Pneumothorax should be suspected in infants with respiratory distress who suddenly deteriorate. Tachypnea is a uniform finding and is often accompanied by grunting, chest retractions, and cyanosis. Physical findings in unilateral pneumothorax include a shift of the cardiac impulse to the unaffected side, diminished or absent breath sounds, and a hyperresonant percussion note on the affected side. In tension pneumothorax, arterial hypotension, apnea, and bradycardia are usually the initial signs.

A large pneumothorax can be diagnosed by transillumination using a high-intensity light with fiberoptic probe.[42] The advantage of this method is the rapidity with which large life-threatening pneumothoraces can be diagnosed and treated. The gold standard for diagnosis is x-ray of the chest. A large pneumothorax is easily recognizable in infants by identification of the visceral pleural line, which is most readily seen over the apex and along the costal surface of the lung (Fig. 33.3). Other important observations in pneumothoraces are a mediastinal shift and absence of lung markings. Small volume pneumothoraces are more difficult to identify and, in these cases, lateral decubitus cross-table views are very helpful in showing the rise in pleural air to the lateral or medial side of the hemithorax (Fig. 33.4).

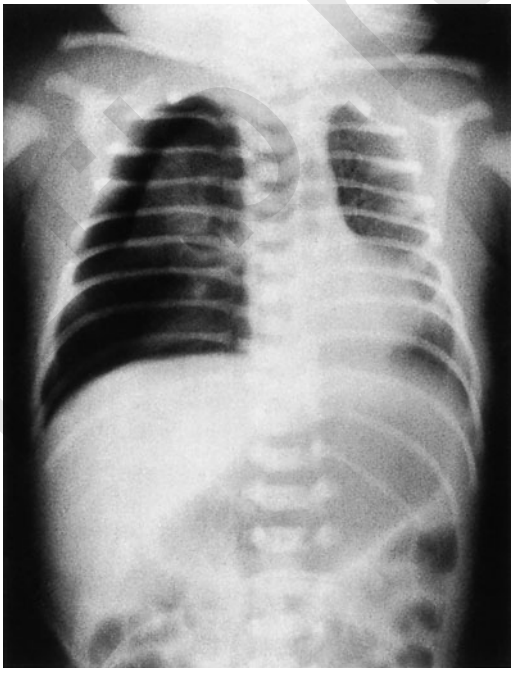


Figure 33.3 Right pneumothorax complicating interstitial emphysema in an infant with hyaline membrane disease. Note air lucency around right lung with absence of lung markings. The mediastinum is shifted to the left, indicating tension.

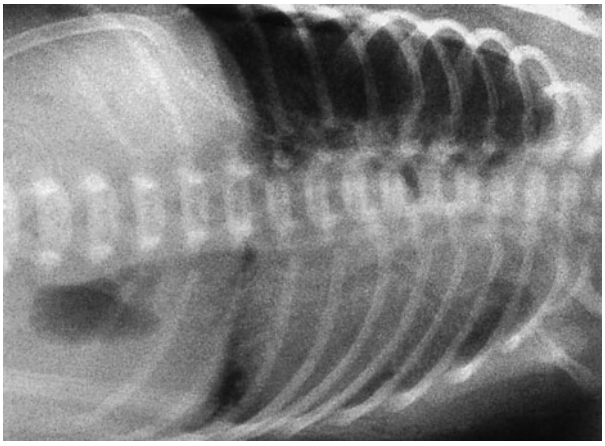


Figure 33.4 Small-volume pneumothorax demonstrated in the lateral decubitus view with the right side raised.

Treatment

Most small pneumothoraces with no symptoms need only close observation and monitoring in a neonatal intensive care unit.[43] The ventilatory management should aim to keep pressures at lower acceptable values including the use of patient triggered ventilation and high frequency positive pressure ventilation,[14] such as adjuvant neuromuscular paralysis of the infant.[44] A pneumothorax should be drained in the following situations:

- radiological signs of tension pneumothorax;
- cardiorespiratory symptoms;
- infants on intermittent positive pressure ventilation (IPPV), even if asymptomatic.

The infant should be temporarily disconnected from the ventilator during the introduction of a chest drain or aspiration of a pneumothorax to avoid the risk of lung damage.[45]

In a desperately ill neonate, a life-saving emergency needle aspiration of a tension pneumothorax can be done before formal insertion of a chest drain. A butterfly (18-gauge) or i.v. cannula with a three-way tap and a 20 mL syringe can be used for decompression. Aspiration is performed through the second intercostal space in the mid-clavicular line. The insertion of the needle is oblique through the muscle plane to avoid entry of air once the needle is removed. Occasionally, a single aspiration may be enough but all these babies must be closely observed and monitored clinically and radiologically as nearly all of them require a tube thoracostomy on follow-up.

Tube thoracostomy is required in the majority of cases. A chest drain (10–14 French gauge) is inserted through the second intercostal space in the mid-clavicular line or the sixth space in the mid-axillary line under local anesthesia. Some surgeons prefer to leave a purse-string stitch around the site of the catheter insertion, even though this is not absolutely necessary in neonates. The tip of the chest tube should be placed anteriorly retrosternally for better drainage.[46] After fixing the catheter firmly, it is connected to an underwater seal drain with or without a low-grade suction of 5–10 cm H_2O. Once the lung is expanded and stable, the tube can then be removed. A chest x-ray after removal of the tube to ensure that a pneumothorax has not recurred should only be carried out if this is clinically suspected.

Use of conventional chest drains is not free from complication as they can cause lung perforation[45] or phrenic nerve injury related to abnormal location of the medial end of the chest tube.[47]

There are pigtail pleural drainage catheters available which have been designed to prevent iatrogenic damage of intrathoracic organs.[48] However, even these catheters made from softer material can be the cause of pulmonary injury in premature infants.[49] In the majority of cases, a properly sized ordinary chest drain with an underwater seal or with a vacuum-control unit should be adequate. The Heimlich flutter valve, though useful clinically, adds to the resistance of the system, especially if fluid accumulates in the valve.[50]

Prognosis

Cases with pneumothoraces without underlying lung disease have a good prognosis. The mortality, though not the incidence, varies with birth weight and is in general double that of babies who have RDS but no airleak.[51] In one series of infants presenting with pneumothoraces within the first 24 hours of life, the overall mortality rate was 52%.[52] The mortality rate is inversely proportional to the infant's birth weight: 53% in infants with birth weights <1 kg.[53] The incidence of grades 3 or 4 intraventricular hemorrhage in infants with pneumothoraces associated with arterial hypotension is 89% as compared with neonates with pneumothoraces associated with normal blood pressure, which is only 10%.[54] This can have a detrimental effect on the neurological outcome. Ventilatory parameters may be helpful in making a prognostic assessment. The survivor group respond well to a fraction of inspired oxygen of less than 70% and a PEEP of 6 cm or less. A CO_2-retention associated with pneumopericardium and PIE is an unfavorable sign.[52]

PNEUMOPERICARDIUM

Pneumopericardium is the least frequent pulmonary air leak. However, recently it has been occurring with increasing frequency as a complication of ventilatory therapy. Pneumopericardium can develop while the patients are on high-frequency ventilation respiratory support.[55] Neonatal pneumopericardium has also been reported during nasal CPAP ventilation[56] and in a full-term neonate following a forceps delivery and mild asphyxia.[57] The exact etiology of pneumopericardium is not known; it is probably interstitial pulmonary air, secondary to alveolar rupture, which dissects into the mediastinum and then enters the pericardial space at the reflection of the pericardium onto the great vessels.

The pneumopericardium may be asymptomatic or symptomatic. Asymptomatic infants do well without any treatment. The clinical signs in symptomatic patients are those of cardiac tamponade, i.e. a sudden onset of bradycardia, muffled heart sounds, cyanosis, and hypotension. Changes in ECG axis and/or voltage may be observed. The classical radiological finding is a continuous radiolucent band of air that conforms to the cardiac outline and does not extend beyond the level of the great vessels (Fig. 33.5). Extra ventilatory air (PIE and pneumomediastinum) is present in over 90% of patients.

Simple needle pericardiocentesis is the appropriate therapy for most cases with cardiac tamponade. However, a few babies with pneumopericardium uncontrolled by needle aspiration require placement of a pericardial catheter for continuous drainage of air. The mortality rate in infants with pneumopericardium is high, especially in preterm infants.[2,51]

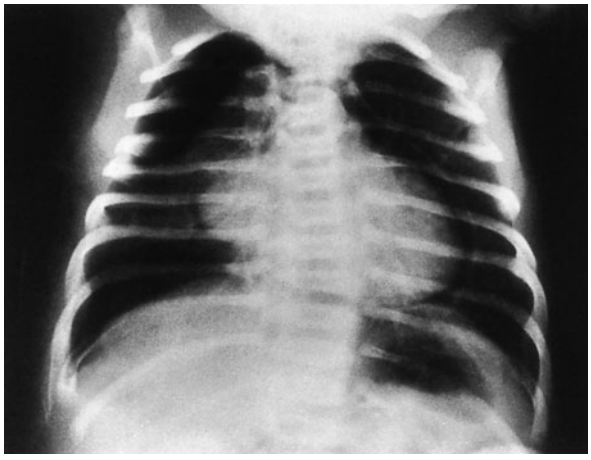


Figure 33.5 Pneumopericardium in a 2-day-old full-term infant with complicating meconium aspiration. Note right pneumothorax also.

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34

Chylothorax and other pleural effusions in neonates

RICHARD G AZIZKHAN

INTRODUCTION

Chylothorax results from the leakage of chyle from the thoracic duct into the pleural cavity. Although it is rare, it is a well-established clinical entity and is the most common cause of pleural effusion in the fetus and neonates.[1–3] Whether chylothorax is congenital or acquired, it frequently resolves with nonoperative measures aimed at optimizing ventilation and maintenance of nutrition. Relatively new on the horizon, somatostatin and its synthetic analog octreotide lend optimism to the possibility of adding new therapies to the current nonoperative treatment armamentarium.[4] When these measures fail to effect spontaneous healing, operative management becomes imperative. For patients in whom resolution does not occur, persistent chylothorax can become a life-threatening disorder, with profound respiratory, nutritional, and immunologic consequences.[1,5–7] While early diagnosis, aggressive initiation of nonoperative management options, and a number of alternative surgical procedures have significantly decreased the mortality rate from 50% before the 1950s[8,9] to current estimates ranging from 6 to 21%,[10–15] significant morbidity continues. This chapter presents an overview of key clinical aspects of fetal and neonatal chylothorax. A basic description of the anatomy and embryology of the lymphatic system and the pathophysiology of chyle provide the foundation for understanding this disorder. Other pleural effusions, including empyema and hemothorax, will also be briefly discussed. Since malignant effusions rarely occur in neonates, they have been omitted from the discussion.

ANATOMY AND EMBRYOLOGY OF THE LYMPHATIC SYSTEM

Lymph is collected in the cisterna chyli and reaches the venous system via the thoracic duct, which ascends in the posterior mediastinum between the azygos vein and the descending aorta. This duct crosses to the left at the level of the fifth thoracic vertebra, continues its ascent into the neck on the left of the esophagus, and opens into the venous system at the confluence of the internal jugular and subclavian veins. In the thorax, it receives lymph from the parietal pleura of both sides via several collecting trunks. Lymphatic branches from structures in the posterior mediastinum and from the left lung and its pleura join to form the left bronchomediastinal trunk; this trunk opens into the thoracic duct or directly into the great veins. There are also several potential lymphovenous communications that may function when the main duct is traumatized or blocked (Fig. 34.1).

The lymphatic system, a diffuse network of endothelial channels, appears during the sixth week of development. The growth of this system is a phenomenon of consecutive centrifugal budding from original lymph sacs. In the early 1900s, Sabin[16] demonstrated that these sacs originated from the endothelium of the adjacent veins, establishing venous endothelium as the primordial structure of the lining of the lymphatic system. She further recognized that all lymphatic channels are developed as outgrowths of the venous endothelium in six original lymph spaces: two jugular lymph sacs, two iliac sacs, a single retroperitoneal sac, and the cisterna chyli. These sacs invade the tissues by continuous growth and branching. The lymphatic system arises by confluence of perivenous mesenchymal spaces to form larger spaces. These in turn join to form continuous vessels that eventually drain into the venous system.

While the thoracic duct is usually a singular structure, its embryology underscores the potential for anatomic variations and congenital anomalies. It may develop in different anatomical patterns with several lymphaticovenous anastomoses. Variation in lymphatic pathways and the presence of accessory lymphatic channels can account for chylous effusions resulting from surgical procedures that do not expose the main thoracic duct.[4] Trauma to the duct in the posterior mediastinum can produce a unilateral or bilateral chylothorax. Increased intraductal tension leads to drainage of chyle into the thorax. A lesion to the thoracic duct below the level of the fifth lumbar vertebra will result in a right-sided chylothorax; a left-sided chylothorax occurs with lesions above this level.

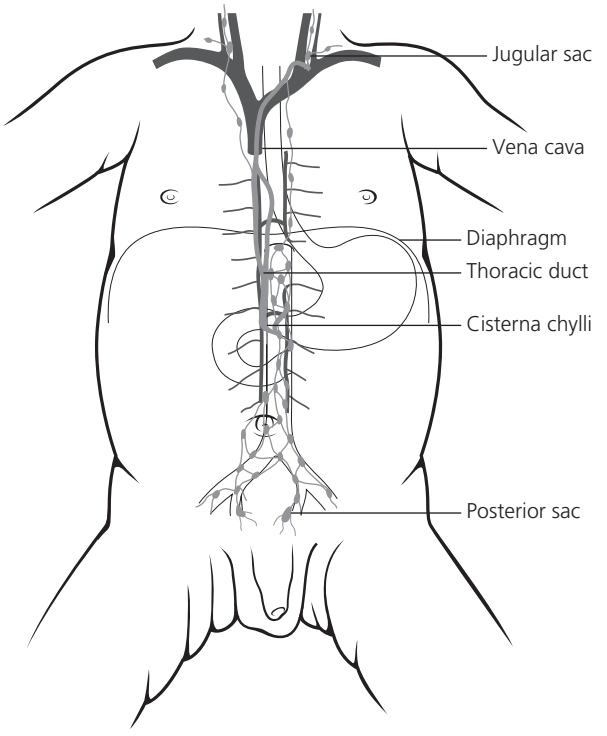

Figure 34.1 Anatomy of the lymphatic system.

PATHOPHYSIOLOGY OF CHYLE

At birth, chyle is clear and straw colored; soon after milk feeding begins, chylomicrons (emulsified fat globules) render it milky white. Depending on the amount of milk ingested, the fat content of the fluid varies from 0.4 to 4.0 g/100 mL, with a triglyceride content of >500 mg/100 mL.[17] Although the protein and electrolyte contents of chyle are similar to those in plasma, chyle is rich in T-cell lymphocytes, with a lymphocyte count of 80–100%. The volume of chyle loss per day can exceed 1.7 times the patient's blood volume, resulting in a serious state of depletion characterized by hyponatremia, hypoproteinemia, metabolic acidosis, and lymphocytopenia.[3] Untreated chylothorax is associated with severe respiratory compromise due to pulmonary parenchymal compression.

The thoracic duct drains most of the body lymph, including the entire intestinal lymph (chyle), into the venous system in the neck. Basal flow of the lymph from the duct averages 1.4 mL/kg per hour and varies with meals. Fatty meals may increase lymph flow up to ten times the basal rate, while lesser increases in the rate of flow are affected by the ingestion of proteins, carbohydrates, and even by oral intake of water.

ETIOLOGY OF CHYLOTHORAX

Congenital chylothorax

Congenital chylothorax is a common cause of neonatal pleural effusion and is classically a disorder of infants at or near term. Males are affected twice as frequently as females and 60% of cases involve the right side of the chest.[18] The occurrence of chylothorax in the absence of other demonstrable disease suggests the existence of congenital malformations of the lymphatic system. Congenital atresia of the thoracic duct or congenital fistulas due to failure of peripheral lymphatic channels to communicate with the major lymphatic network have moreover been assumed on the basis of diffuse chyle leakages seen during surgery.[2]

Congenital defects of the lymphatic system that may become evident with chylothorax are well documented in the literature, presenting clinically as lymphangiomatosis[19–24] or congenital pulmonary lymphangiectasis.[25–27] Congenital chylothorax is also associated with hydrops fetalis[28–32] and various syndromes, such as trisomy 21,[33–35] Turner syndrome, and Noonan syndrome.[36,37] The occurrence of chylothorax in combination with other uncommon disorders, such as autosomal recessive lymphatic anomalies, mediastinal neuroblastoma in neonates, and neonatal thyrotoxicosis, also has been documented.[38–40]

Acquired chylothorax

Acquired chylothorax results primarily from surgical or traumatic insult to the thoracic duct, and virtually every intrathoracic surgical procedure has been associated with it. Recent studies suggest an increase in the prevalence of postoperative chylothorax from the previously reported 1% or less[11,12,14,41] to 2.5–4.7%.[12,42,43] This has been attributed to the increased complexity of the surgery being performed and possibly to the earlier reintroduction of feeding after surgery.[42,43] Iatrogenic injury can occur during surgery in the region of the aortic arch for conditions such as patent ductus arteriosus, coarctation of aorta, vascular ring, and other congenital cardiovascular anomalies[42,44,45] as well as during esophageal repair or repair of congenital diaphragmatic hernia.[46–48] Acquired chylothorax also manifests as a complication of both subclavian and internal jugular venous cannulation and/or obstruction, superior vena caval obstruction secondary to central venous catheters, or elevated central venous pressures,[28,49–54] chest tube insertion,[55] and traumatic delivery.[56] Additionally, there have been anecdotal reports of chylothorax resulting from a blunt blow to the abdomen due to child abuse. (Rodgers, verbal communication, 2000) Chylothorax/chylopericardium is a rare complication, occurring primarily following surgery for congenital heart diseases.[15]

CLINICAL FEATURES OF CHYLOTHORAX

Presenting symptoms

Tachypnea, dyspnea, retraction of chest, and cyanosis mark the onset of chylothorax, with dullness and diminution of breath sounds on the affected side and displacement of the heart and mediastinum to the opposite side. In cases of congenital chylothorax, symptoms of respiratory distress may be noted shortly after birth or at any time up to 2 weeks of life. In contrast, the interval between surgery and the

occurrence of acquired chylothorax can vary from 1 to 25 days. The time is shortest when there is a direct injury to the duct (5–7 days) and longest when there is high pressure or thrombosis of the vena cava (10–14 days). Chyle may accumulate in the mediastinum for several days before extravasating into the pleural space.

Consequence of continuous chylous flow

The loss of large quantities of chyle over a period of time produces nutritional failure, sepsis, metabolic acidosis, and renal failure. Considerable loss of protein and large numbers of lymphocytes may result in immunodeficiencies, including hypogammaglobulinemia and abnormal cell-mediated immune responses.

DIFFERENTIAL DIAGNOSIS

X-rays of the chest typically show opacification of one or both hemithoraces, with compression of lung and displacement of mediastinal structures in unilateral chylothorax (Fig. 34.2). X-ray diagnosis in premature infants may, however, be difficult. Most of these infants already have significant pulmonary disease, and chest x-rays may appear to have areas of increasing consolidation rather than the more typical layering of pleural fluid seen in older children. Sonography is a reliable method of detecting chylothorax in these cases, and its use in obstetric practice as the primary method of imaging the fetal chest has led to the increasing frequency with which fetal chylothorax is being diagnosed[57–61] (see below under Fetal chylothorax (hydrothorax)).

Diagnosis is confirmed after analysis of the pleural fluid drained by thoracentesis or chest tube placement. Initially, this fluid is serous; it turns chylous only after milk feedings have begun. Chyle is characterized by elevated total protein and albumin levels, a specific gravity of >1.012, the presence of white blood cells with a predominance of lymphocytes (80–100%) and elevated triglycerides, cholesterol, and total fat levels if the infant is milk fed.[62] In the unfed neonate, the fat content of the chylothorax may be quite low and the fluid does not have the characteristic milky appearance. The protein content is somewhat less than that of serum and the electrolytes approximate those of serum.

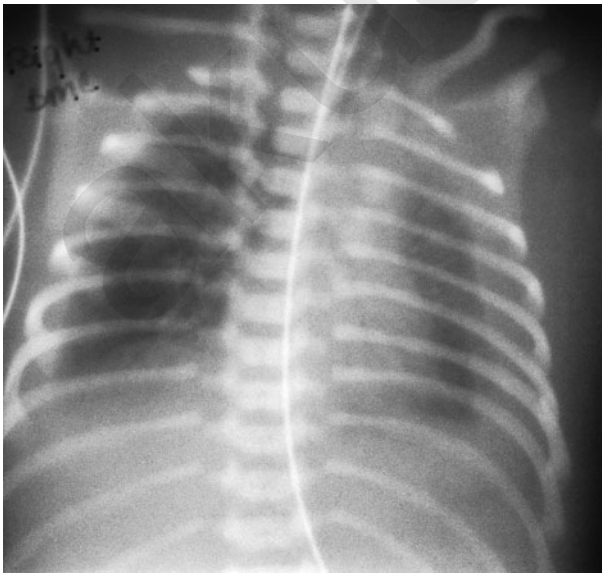

Figure 34.2 Chest x-ray in a term neonate demonstrating bilateral chylothorax.

MANAGEMENT OF CHYLOTHORAX

Historical overview and current consensus

Because chylothorax is associated with a wide array of disorders and accompanying clinical circumstances, the management of patients with this condition varies considerably. Historically, there has been a lack of consensus regarding nonoperative and operative treatment approaches, and to date there is no commonly accepted treatment protocol. The timing and type of operative intervention have been particularly controversial. A critical and unresolved issue is the early identification of babies for whom the morbidity of medical therapy will exceed that of early surgical therapy.[12,63] Differences regarding this issue are reflected in reported preoperative periods of medical therapy ranging from days to weeks.[64] Despite the differences, it is generally agreed that initial thoracentesis is diagnostic and may provide immediate relief of respiratory failure. If failure persists, mechanical ventilation may be required. A course of therapy that avoids the serious nutritional, metabolic, and immunologic sequelae known to the disease should then be chosen.[65]

If the infant is able to tolerate enteral feeding, initial nonoperative management generally consists of enteral feeding with medium-chain triglycerides (MCT). In recalcitrant or severe cases, patients may require total parenteral nutrition (TPN) or a combination of both modalities. This protocol is often successful in mitigating the most serious complication of chylothorax – protein-calorie malnutrition. More than 60% of ingested fats travel to the bloodstream via the thoracic duct. MCTs, which have a 6- to 10-carbon backbone, are the only fats to be absorbed directly via the portal system, bypassing the lymphatics.

There is general consensus that if lymphatic drainage does not resolve within a 2-week period with nonoperative management or if a patient's nutritional or metabolic status declines measurably during that time, surgical intervention should be undertaken.

General management principles

The general principles of management for chylothorax include the following:

- Thoracentesis is performed to provide immediate relief of respiratory failure and to confirm the diagnosis through chemical analysis of pleural fluid specimen.
- Supportive ventilation is instituted as required.

- Thoracostomy tube drainage is carried out if pleural fluid reaccumulates after one or two thoracenteses. (Repeating this procedure carries a risk of producing pneumothorax and introducing infection; chest tube drainage keeps the lungs fully expanded, which is necessary for sealing chyle leakage.)
- Nutritional losses are replaced through a high protein diet, rich in MCTs that are absorbed directly into the portal venous system.
- Parenteral feeding is instituted. (When superior vena caval thrombosis is present with chylothorax, TPN may need to be delivered via a peripheral vein.)
- The albumin, gammaglobulin, and fibrinogen that are contained in chyle, as well as fat-soluble vitamins, are adequately replaced.
- Full expansion of the lungs is maintained by continuous chest tube drainage of chyle. (These tubes may become obstructed and require replacement as necessary.)
- Prophylactic antibiotics are given when chest tubes are in place, since many of these infants have an acquired immune deficiency caused by lymphocytopenia. Some infants may also need salt restriction, diuretics, and digoxin.
- Somatostatin or octreotide may be used for cases recalcitrant to other medical therapies.
- Surgical intervention is warranted when medical therapies fail to significantly diminish chylous drainage for more than 14 days or if there is obvious deterioration in the patient prior to that period of time (Fig. 34.3).

Nonoperative management

As cited earlier, an initial trial of nonoperative management relying on adequate drainage of chyle, coupled with nutritional

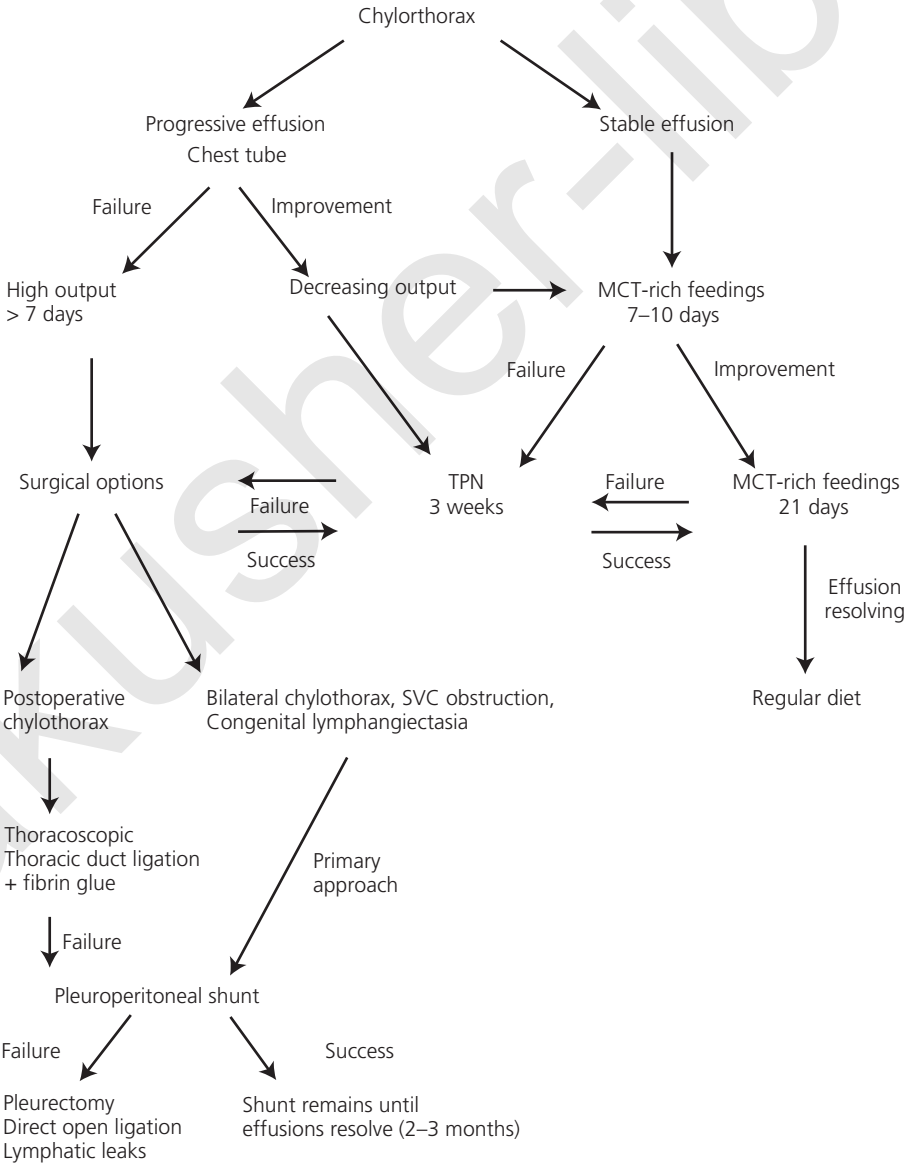

Figure 34.3 Algorithm of management principles. MCT, medium chain triglycerides; SVC, superior vena cava; TPN, total parenteral nutrition.

supplementation via MCT-enriched diets and/or TPN should be given in order to optimize the chance of recovery without surgery. Using this regimen, the majority of cases of congenital chylothorax and up to 77% of cases with traumatic chylothorax (postoperative) resolve spontaneously.[10,66,67]

Some investigators have observed no difference in MCT or TPN in regard to duration or amount of drainage.[15,66] Others have found that for patients with superior vena caval obstruction and congenital lymphatic malformation, MCT alone is not as effective; they thus recommend the rapid administration of TPN.[68]

Growing evidence from numerous uncontrolled case studies suggests that somatostatin (SST) and octreotide (OCT) exert a positive effect on persistent congenital and postoperative chylothorax.[69] At some institutions, these agents are gradually being integrated into treatment algorithms. SST is a polypeptide with mainly inhibitory actions on the release of various hormones (e.g. growth hormone and insulin) and lymph fluid excretion.[70,71] OCT is a synthetic SST analog with anti-secretory properties similar to those of SST. It is thought that octreotide may act directly on somatostatin receptors in the splanchnic circulation to reduce lymph fluid production.[72,73] Thoracic duct lymphatic flow depends on splanchnic vascular tone as well as gastric motility.[74] Octreotide decreases the volume of gastric, pancreatic, and biliary secretions, thus reducing the volume and protein content of fluid within the thoracic duct.

Current research suggests that OCT is well tolerated, even at the highest dosing ranges used (i.e. 80–100 μg/kg per day) for as long as 3 weeks, and that the earlier use of higher doses may be preferable to gradual upward tapering of the dose.[75] Potential adverse effects include cholelithiasis, liver impairment, renal impairment, transient glucose intolerance,[76,77] hypothyroidism,[78] and necrotizing enterocolitis.[79] It is thus prudent for patients to undergo routine monitoring of liver function, blood glucose, and thyroid parameters during the course of treatment.

Positive attributes of SST and OCT include a shorter duration of intensive care treatment, a reduction of recurrent thoracocentesis, and fewer fluid and plasma infusions, thereby reducing the risk of infection.[69] To date, however, no consensus has been reached as to the optimal route of administration, dose, duration of therapy, or strategy for discontinuation of therapy. Unfortunately, specific pharmacokinetic data are not yet available regarding these agents in infants and children.

Another novel though controversial medical treatment alternative is the use of OK-432 (Picibanil®) therapy. OK-432 is a lyophilized incubation mixture of the group A *Streptococcus pyogenes* of human origin. It is presently used to treat adults with chylothorax, though several authors have recently reported its successful use in treating fetal chylothorax and congenital cases resistant to OCT.[80] To date, information is sparse and reports emanate primarily from centers in Japan, where OK-432 is manufactured and readily available.

Operative management

The percentage of neonates requiring surgery and the timing of surgical intervention vary widely among reported series and are dependent upon the patient population being studied, etiology, and the clinical status of individual patients. Operative management has, however, been the mainstay of treatment for a number of clinical conditions that have a high failure rate with standard nonoperative management; these include postsurgical cases in which there is injury to the thoracic duct and massive lymph leakage, caval obstruction, or elevated central venous pressures.[13,15,68,81,82] Congenital chylothorax associated with superior vena caval thrombosis in the premature neonate is also particularly refractory to standard nonoperative therapy.[49] Since failure is associated with a high mortality rate, some investigators maintain that surgical intervention should be considered early in the management strategy of such cases.[69,83–85]

Several surgical options exist and they are often used in combination. They include pleuroperitoneal shunting, thoracic duct ligation (open thoracotomy or thoracoscopy), pleurodesis with different agents, pleurectomy, and intrapleural fibrin glue.

PLEUROPERITONEAL SHUNTS

Pleuroperitoneal shunts, first used by Azizkhan *et al.* in 1983[86] to treat five ventilator-dependent infants with persistent chylothorax, are currently used as a surgical treatment option at a number of major pediatric centers across North America. The procedure avoids the risks associated with a more complicated, open surgical procedure in high-risk infants and is considered safe, highly effective, and easy to perform. Nonetheless, it is associated with several drawbacks. These include having to manually press a pumping chamber several times a day and having the valve and pumping chamber become dysfunctional after several weeks due to an accumulation of fibrin and protein in the valve mechanism. It thus is ideal for patients who require a relatively short or stabilizing procedure.

A postoperative chest x-ray is obtained to make certain that the pleural catheter is properly placed. During the immediate postoperative period, the pumping chamber is compressed 50–100 times per hour in order to completely clear the hemithorax of chyle. As the infant's clinical status improves, a gradual decrease in the frequency of shunt compression is begun. Noninvasive transcutaneous oxygen saturation monitoring, arterial blood gas determination, and serial chest x-rays are used to assess shunt efficacy (Fig. 34.4). Manual compression of the shunt valve is discontinued when it is clear that chylothorax is resolved. This often occurs within 2–3 weeks. However, some infants require a more prolonged period of manual compression, lasting 6–8 weeks.

A high-flow, externally located valve reservoir designed to avoid some of the discomfort and positioning problems associated with a subcutaneous valve reservoir is available. Once the chylous effusion clears, parents are taught the technique of pumping the chamber and the patient is discharged from the hospital. Over the ensuing 2–3 months, the frequency of pumping is further reduced. When the chylous effusion completely resolves, the catheter is removed. This approach offers less interruption of the sleep cycle and

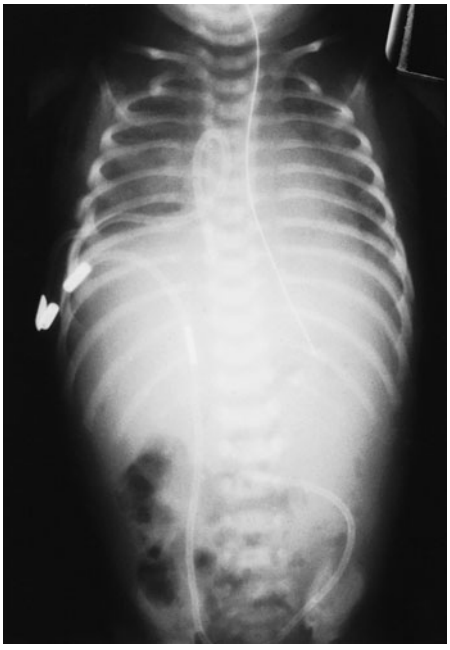

Figure 34.4 Chest x-ray showing resolution of a chylothorax after pleuroperitoneal shunt placement.

may facilitate a shorter hospital stay. Although this approach carries an increased risk of infection, this risk has not been documented in clinical studies.

While there has been some concern that elevated right atrial pressures transmitted to the venous and lymphatic bed of the peritoneal space may impair absorption of shunted pleural fluid, the successful use of pleuroperitoneal shunting with this patient population, even in the face of moderate elevations in right atrial pressure, has been reported.[84] Failure to resolve chylous effusions is associated with occlusion of the shunt catheter or significant intra-abdominal chylous ascites. When the latter occurs, a pleuroperitoneal shunt and a peritoneovenous shunt combination have been successfully used in some cases.

The same principle has been applied in the management of patients with chylopericardium. Case reports indicate that pericardial–peritoneal shunting provides an easy and effective alternative to prolonged pericardial draining, thoracotomy, or thoracic duct ligation in patients with chylopericardium of various etiologies.[87]

OTHER SURGICAL ALTERNATIVES

Although thoracic duct ligation has historically been the most common surgical therapy and has indeed been successful in resolving chylous leak, it requires an already compromised, frail, and often premature neonate to undergo a major surgical procedure. Despite this drawback, it remains an option when pleuroperitoneal shunting fails to resolve the chylous leak or when chylothorax is due to penetrating trauma. Giving cream through the nasogastric tube several hours before operations helps to identify the sites of leakage of the milky white fluid. Major leaks from the thoracic ducts can be closed by direct suturing or by ligating the duct above and below the leak. Pleurodesis and parietal pleurectomy have been used when there is generalized weeping of chyle from parietal pleura. However, these are extensive surgical procedures that may increase the possibility of pulmonary lymphedema, fibrosis, and further pulmonary compromise. Fibrin glue applied to the leakage site after patent ductus arteriosus ligation has been reported to successfully manage chylothorax in both a 3.5-month-old infant,[88] and a premature infant weighing 600 g.[89] The choice of either an open or thoracoscopic approach to thoracic duct ligation depends on the experience of the surgeon.

Video-assisted thoracoscopic procedures are being used with increasing frequency. These procedures offer the advantage of access to the entire hemithorax, with excellent visualization of the mediastinal structures. This approach allows application of clips to the thoracic duct at the hiatus or to the thoracic duct injuries or pleural defects. It also facilitates mechanical or chemical pleurodesis and application of fibrin glue. Despite its advantages, its use is limited by an infant's size and pulmonary status. Also, it may be difficult to correctly visualize leaks in the presence of a massive chylous effusion.

FETAL CHYLOTHORAX (HYDROTHORAX)

Primary fetal chylothorax (also known as hydrothorax), is the most common fetal effusion. It is a complication that occurs in one in 15 000 pregnancies,[60] and with the growth in sonography over the past several decades, it is being diagnosed with increasing frequency – from as early as 17 weeks' gestation to an average of 30 weeks gestation.[32] In contrast to chylothorax diagnosed at birth, primary fetal chylothorax is associated with a mortality rate as high as 50%.[60] Its clinical course varies considerably, ranging from complete resolution with a positive outcome to hydrops fetalis and perinatal death. Survival depends on multiple factors, including the presence of associated anomalies and the gestational age at which diagnosis is first made. The prognosis of small volume, unilateral, isolated fetal pleural effusion is usually good, with spontaneous resolution sometimes observed.[60,90–92] Prognosis is poor when effusion is associated with chromosomal aberrations, multiple malformations, and fetal hydrops.

The management of fetal chylothorax has been controversial and the optimal treatment approach remains unclear. Dissension is primarily focused on the following issues: (1) whether treatment should be attempted *in utero* or the infant should be delivered and treated after birth; (2) under what clinical circumstances antenatal intervention should be carried out; and (3) whether pleurocentesis or pleuroamniotic shunting should be used for thoracic decompression.

Most authors agree that fetal chylothorax with rapid progression warrants intervention. While reports of successful management with pleurocentesis or pleuroamniotic shunting have appeared in the literature,[60,61,93–95] pleurocentesis has been associated with rapid reaccumulation of the effusion and is therefore unlikely to be advantageous.[96–100] Thoracoamniotic shunting has been effective in selected

patients with progressive pleural effusions, especially when there is evidence of intrathoracic hypertension.[101] Most commonly, a Harrison double-pigtail catheter is used. Both techniques are associated with serious pregnancy risks, including preterm labor, prerupture of the membranes, intrauterine infection, bleeding, and maternal or fetal organ trauma. Additionally, technical failures such as shunt displacement and blockage are common.[96]

From a broad perspective, antenatal diagnosis is significant not only in that it can often identify the need for potentially helpful intrauterine intervention and facilitate preparation of appropriate postnatal outcome, but also in that it is a reliable predictor of fatal outcome. As such, it facilitates the communication of a more accurate prognosis to parents. Since most large pleural effusions discovered *in utero* lead to hydrops and pulmonary hypoplasia, such effusions have a high mortality rate. Retrospective studies show that the absence of hydrops predicts 100% survival; fetuses that initially present without hydrops and subsequently develop it have only a 38% survival.[32]

OTHER PLEURAL EFFUSIONS

Hemothorax

Although massive hemothorax is uncommon, accidental injury to the intercostal artery during thoracentesis or closed intercostal drainage can result in intrapleural bleeding.[102] Hemothorax has been reported as a complication of a variety of congenital malformations (e.g. sequestration, patent ductus, and pulmonary arteriovenous malformation) and of subclavian vein catheters.[103] It is also an occasional manifestation of intrathoracic neoplasms and blood dyscrasias, and bleeding diatheses. Additionally, it can occur spontaneously in neonates, sometimes in association with a pneumothorax. Symptoms reveal respiratory embarrassment similar to that seen in tension pneumothorax. However, the percussion note is dull and chest x-rays show opacification. More importantly, the infant may show signs of hypovolemic shock. Blood transfusion and urgent tube thoracostomy generally provide adequate control of bleeding. To avoid sudden circulatory collapse, transfusion should precede intercostal drainage. If massive blood loss continues, urgent thoracotomy and identification and securing of the bleeding site is required.[103]

Empyema

Owing primarily to improved antibiotic treatment of chest infections, empyema (purulent effusion) has become a rare condition in infants. The most common cause of empyema is a pneumonia caused by organisms such as *Staphylococcus areus*, *Pneumococcus,* and *Haemophilus influenzae*. It may, however, be incurred through the introduction of skin bacteria during thoracentesis or thoracotomy. Empyema may also be accompanied by anaerobic infection. Symptoms include indications of respiratory distress in addition to abdominal distension, lethargy, and at times, a septicemic state. Diagnosis is suspected by chest x-rays in which the effusion and pneumonic process is identified. Ultrasonography during diagnostic thoracentesis is helpful in localizing the fluid, if loculated. Prior to beginning a course of antibiotic therapy, a fluid specimen taken during thoracentesis is sent for a Gram stain and aerobic and anaerobic culture. Although most cases resolve with effective intercostal tube drainage and a prolonged period of systemic administration of antibiotics, anaerobic infection tends to be multi-locular and may thus require debridement, and in rare instances, decortication.

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35

Congenital malformations of the lung

LI ERN CHEN AND KEITH T OLDHAM

INTRODUCTION

Congenital lung abnormalities are uncommon and diverse in their presentations. However, all those who care for infants and children must have an appreciation for the diagnosis and treatment of these anomalies because the potential consequences can be life threatening. In order to understand the pathophysiology of these malformations, one must have a basic understanding of the embryology of lung development, as well as lung anatomy and respiratory physiology, which are presented below. Classical lesions including lobar emphysema, congenital pulmonary airway malformation (CPAM), pulmonary sequestration, and congenital lung cysts will be discussed below, along with a number of the less common anomalies.

EMBRYOLOGY

During the third week of gestation, the human embryo develops a diverticulum of the ventral foregut which forms the primordium of the respiratory system. This is mainly of endodermal origin; however, cartilaginous and muscular elements will be derived from the splanchnic mesoderm that surrounds the primitive foregut. As the respiratory diverticulum grows caudad, it becomes separated from the foregut by the lateral esophagotracheal ridges which fuse to form a septum at the end of the fourth gestational week. Thus, the dorsal esophagus and the more ventral trachea and lung buds are defined. The larynx, which is formed from the fourth and sixth branchial arches, maintains communication between the pharynx and the trachea.

The lung buds penetrate the coelomic cavity by caudal growth, resulting in the formation of pleuroperitoneal canals on either side of the foregut. The expanding lung buds eventually come to nearly fill these canals, with the small residual spaces becoming the primitive pleural cavities. The right lung bud divides into three lobes, whereas the left forms two by the mid-portion of the embryo's sixth week. The bronchi continue successive dichotomous division, and by the end of the sixth month of gestation, 17 generations of subdivisions have formed. This period is also the time at which terminal bronchioles and alveoli are forming. An additional six divisions of the terminal airways will occur during early postnatal life, however, lung development probably does not cease until about eight years of age.[1] Thus, development of conductive airways is essentially complete by the end of the second trimester while terminal airways and alveoli, which are the site of gas exchange, continue to develop in late fetal life and indeed during infancy and early childhood. As one considers the various clinical lesions and their therapeutic options, this perspective is critical.[2,3]

The pulmonary vasculature begins to develop in the mesoderm around the primitive lung buds at 7–8 weeks of gestation. By the seventh gestational month, pulmonary blood flow has matured to the point where gas exchange is possible.

ANATOMY

A brief discussion of clinically relevant anatomy is appropriate; several excellent references are available for a more detailed review.[4,5] As seen in early gestational development of the lungs, the mature right lung is composed of three lobes in contrast to the two lobes of the left. The carina is positioned at the level of the fourth thoracic vertebral body in the term infant. The mainstem bronchus of the right lung follows a straighter, more caudad course and is usually shorter and larger in diameter than that of the left. This accounts for the preference of aspirated material to enter the right lower lobe or the posterior segment of the right upper lobe, as well as for right mainstem bronchus intubation during endotracheal tube placement.

The vascular supply of the trachea, bronchi, and lung parenchyma is systemic in origin and separate from the pulmonary arterial circulation which is dedicated to gas exchange. The trachea is supplied by branches of the paired inferior thyroid arteries, which anastomose with the bronchial

blood supply derived from the aorta on the left, and the third intercostal artery on the right. Venous drainage is via the azygous and hemiazygous systems. This systemic arterial supply and its accompanying venous drainage generally follow the segmental architecture of the lung and bronchi.[4–6]

CONGENITAL LOBAR OVERINFLATION OR CONGENITAL LOBAR EMPHYSEMA

Congenital lobar overinflation, also known as congenital lobar emphysema, is among the most common of the congenital lung anomalies. It is characterized by air trapping and overdistention of one or more lobes which are otherwise anatomically normal. This distention causes compression of adjacent normal lung parenchyma and can result in mediastinal shift and cardiorespiratory compromise (Fig. 35.1).

Although a specific etiology of this disorder cannot be demonstrated in up to half of reported cases,[7] it is believed to result most commonly from structural deficiency or absence of supportive cartilage in the affected lobar bronchus, thereby causing expiratory collapse of the conducting airway with impedance to expiratory flow.[8] Other reported etiologies include extrinsic compression from anomalous or enlarged blood vessels, congenital heart disease, mediastinal lymphadenopathy, bronchogenic and enteric cysts, and tumors.[9] Partial obstruction from a reversible endobronchial source, such as mucous plugging, inflammation, or aspirated materials, is a possible cause and should be ruled out by rapid and judicious bronchoscopic evaluation in order to avoid unnecessary lung resection.

Polyalveolar morphology mimics lobar emphysema in its clinical presentation. This is a descriptive histologic term that refers to unusual and abnormal anatomic findings characterized by an increase in the number of alveoli in a particular lobe, resulting in expiratory air trapping and lobar overdistension with respiratory compromise. This is in contrast to lobar emphysema where alveolar histopathology is normal except for overdistention. The diagnosis and treatment of polyalveolar morphology are not different than for congenital lobar emphysema.

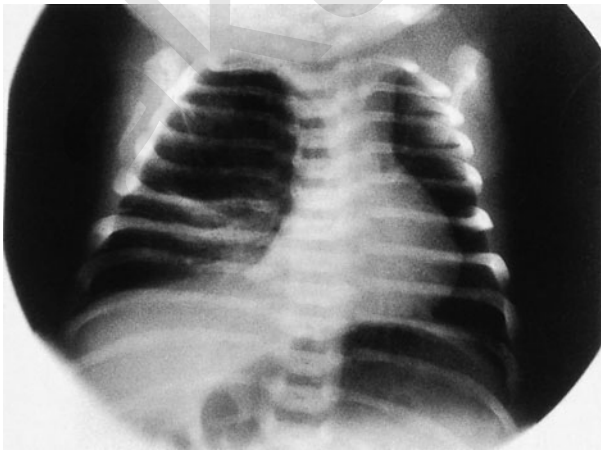


Figure 35.1 Congenital lobar emphysema. Chest x-ray in a 3-day-old infant who presented with respiratory distress, showing marked hyperinflation of right upper lobe.

Congenital lobar emphysema is most often seen in the Caucasian population with a two or three to one male predominance. It is most common in the left upper lobe (40–50%), with other sites affected less frequently; right middle lobe (30–40%), right upper lobe (20%), and lower lobes (1%).[10,11] In 15% of infants, lobar emphysema is associated with congenital heart disease or abnormalities of the great vessels;[12,13] therefore, routine echocardiography is recommended in the screening evaluation of these patients.

Presentation and diagnosis

While the structural characteristics of congenital lobar emphysema do not lend the lesion to easy detection by routine prenatal sonography, there have been several reports of prenatal diagnosis of this lesion.[14–16]

Contrary to its moniker, congenital lobar emphysema patients do not demonstrate respiratory problems immediately at birth, rather they develop symptoms as lobar distention progresses over time with expiratory air trapping in the course of postnatal breathing. Severity is usually related to age of presentation; the most threatening presentations typically occur in newborns. Approximately half of patients develop respiratory distress within the newborn period while the remainder with this symptom present around 4–6 months of age[7] or later. Presenting signs are those of respiratory embarrassment, including dyspnea, tachypnea, agitation, and wheezing. Depending upon the severity of adjacent lung compression, cyanosis and respiratory failure can result. Therefore, the surgeon must be available for emergent decompressive thoracotomy, particularly when positive-pressure ventilation is employed at procedures such as anesthesia induction or bronchoscopy. Older children may present with milder symptoms such as recurrent respiratory infections or cough, or may be asymptomatic altogether.

On examination, the patient with congenital lobar emphysema will demonstrate signs consistent with a hyperinflated lobe, including thoracic and respiratory asymmetry, decreased breath sounds and percussive hyperresonance of the ipsilateral chest. Findings of mediastinal shift such as tracheal deviation and displacement of the cardiac apical impulse are relatively late clinical signs.

Chest roentgenography is the initial and often the sole diagnostic maneuver of choice (Fig. 35.1). There is increased radiolucency over the affected side, with accompanying atelectasis of adjacent compressed parenchyma and a flattened ipsilateral hemidiaphragm. Mediastinal displacement to the contralateral side may also be apparent. The chest x-ray should be inspected closely to differentiate between congenital lobar emphysema and tension pneumothorax which may have similar presentation and appearance, but vastly different management. Contrary to congenital lobar emphysema, tension pneumothorax has no peripheral lung markings. In the first hours after birth, the affected lobe may still be filled with fetal lung fluid and therefore have the appearance of a mass with fluid density. Some authors

advocate ventilation-perfusion radioisotope scanning as a useful adjunct to the chest x-ray.[17] Others advise the use of computed tomography (CT) or magnetic resonance imaging (MRI). However, these studies are generally reserved for situations in which the diagnosis is in doubt.

Treatment

If a source of endobronchial obstruction cannot be found and corrected, then the often-progressive nature of this lesion as well as the risk of respiratory failure dictate lobectomy of the affected lobe in infants. This is done via either muscle sparing thoracotomy or thoracoscopy. For the older child without symptoms, this approach can be reasonably tempered. Reconstructive procedures such as bronchoplasty or segmental bronchial resection are generally not appropriate as the bronchial defects may not be focal or readily localized. In addition, lobectomy in the infant population is very well tolerated[18,19] and bronchial reconstruction in the newborn is fraught with technical limitations.

CONGENITAL PULMONARY AIRWAY MALFORMATIONS

CPAM are a rare group of cystic lobar hamartomatous lesions, also referred to as cystic adrenomatoid malformations. These represent up to 50–70% of the bronchopulmonary foregut malformations in some reports.[20] The lesions are generally large, firm, multicystic masses that are composed of terminal respiratory structures, usually bronchiolar in origin. CPAM are thought to result from developmental arrest in terminal bronchiole maturation, resulting in marked overgrowth of these structures in relation to alveoli. This lesion is characterized by a mass of interconnected and disorganized cysts on gross inspection. Because of the histopathology and associated disorders of organogenesis, it has been proposed that the pathogenic event occurs at 3–7 weeks' gestation, although the precise pathogenesis is unknown. Involvement is usually unilobar, with a slight predilection for the lower lobes; right and left sides are affected equally.

Histology demonstrates ciliated cuboidal or columnar cells lining the cysts, with a lack of organized architecture; usually no cartilage is present (Fig. 35.2). These malformations typically communicate with the normal bronchial tree and have a normal vascular supply, although aberrant systemic vasculature, sometimes derived from the aorta, has been described.[21] The classification of CPAMs has undergone constant modification in the past four decades. Adzick and colleagues described macrocystic and microcystic or solid lesions based on prenatal ultrasound imaging. The contemporary classification scheme proposed Stocker and colleagues grouped CPAM into five distinct pathologic types (Table 35.1).[22,23] This classification system, which is based on the presumed site of development of the malformation, carries both descriptive and prognostic significance.

With regard to outcomes, type 0 is composed of multiple small cysts less than 0.5 cm and the patients have a relatively poor prognosis. Type 1 CPAM accounts for about 65% of cases, and affected patients usually present with respiratory distress in the neonatal period. Patients usually have a good prognosis with lobectomy. Type 2 lesions have multiple smaller cysts (<2.5 cm), and are associated with other congenital anomalies (cardiovascular, genitourinary, and

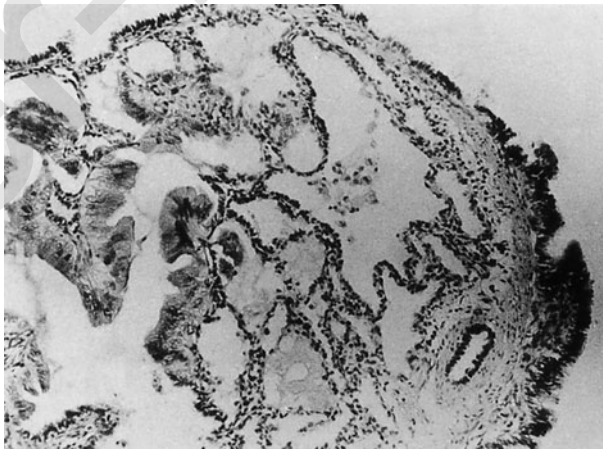


Figure 35.2 Type 1 CPAM. Histology specimen of lung showing mucinogenic cells, papillary epithelium, and disorganized, irregular alveoli.

Table 35.1 Pathologic features of CPAM (from Shimohira *et al.*[23] with permission).

Stocker's type	0	1	2	3	4
Approximate frequency (%)	1–3	>65	20–25	8	2–4
Cyst size (max, cm)	0.5	10.0	2.5	1.5	7.0
Epithelial lining (cysts)	Ciliated; pseudostratified; tall columnar with goblet cells	Ciliated; pseudostratified; tall columnar	Ciliated; cuboidal or columnar	Ciliated; cuboidal	Flattened; alveolar lining cells
Muscular wall thickness of cysts (in μm)	100–500	100–300	50–100	0–50	25–100
Mucous cells	Present in all cases	Present in 33%	Absent	Absent	Absent
Cartilage	Present in all cases	Present in 5–10%	Absent	Absent	Absent
Skeletal muscle	Absent	Absent	Present in 5%	Absent	Absent

musculoskeletal) in up to 40% of patients. Type 3 lesions are more solid than cystic in nature. Both type 2 and type 3 lesions have a poor clinical outcome, presumably because they tend to be relatively large and noncompressible, thus limiting normal maturation and development of unaffected but adjacent lung. Malignant degeneration can occur in all congenital cystic lung lesions, including CPAM. Although this is rare, it is clearly a long-term risk to be considered as management decisions are made.[24]

Presentation and diagnosis

Since the advent of routine ultrasound in obstetric practice, the majority of cystic lung lesions are now discovered prenatally in many institutions. The location of the stomach aids in differentiation between CPAM and congenital diaphragmatic hernia (CDH), although prenatal MRI may be needed for definitive diagnosis in difficult cases.[25] Serial ultrasonographic exams may demonstrate shrinkage or even spontaneous resolution in up to 40% of fetal CPAMs.[19,26] Physiologic consequences of CPAM can be seen antepartum and occur secondary to mediastinal shift and compression of normal lung tissue. Large masses, especially those involving type 2 or type 3 lesions can result in nonimmune hydrops fetalis and fetal demise. The polyhydramnios is thought to result from esophageal compression, preventing fetal swallowing of amniotic fluid; the hydrops results from mediastinal shift from the mass effect, diminishing cardiac output by vena caval obstruction.[19] Either finding during pregnancy is associated with poor outcome.

In the neonatal period, some infants will demonstrate tachypnea, dyspnea, cyanosis, or impending respiratory failure. Although this can be dramatic, only a third of patients present in this manner. Of the remaining patients, most will present within the first few years of life with recurrent or persistent respiratory infections, pulmonary abscesses, or reactive airway disease due to the inability to effectively clear secretions from the abnormal lobe. Chronic pulmonary problems may also lead to failure to thrive.

As with all bronchopulmonary foregut malformations, the plain chest x-ray is the best initial diagnostic test in the neonate (Fig. 35.3). Nasogastric tube position is often helpful to distinguish CPAM from CDH as an intrathoracic stomach is quite common with left CDH. The x-ray findings are variable; x-rays taken early in the neonatal period may demonstrate fluid within the lesion, whereas later films may show air-filled cysts. Mediastinal shift, an ipsilateral flattened diaphragm, and compressed adjacent normal lung may also be present, depending on the severity of disease. It is advisable to obtain an axial imaging study, either a CT scan with i.v. contrast or MRI, in all patients with cystic lesions of the chest in order to establish a diagnosis, as well as delineate anatomic relationships prior to elective resection (Fig. 35.4). Even those who have had spontaneous intrauterine resolution of an apparent CPAM demonstrated by serial prenatal ultrasound should be evaluated with axial imaging following birth, as residual parenchymal abnormalities may be present.[26,27]

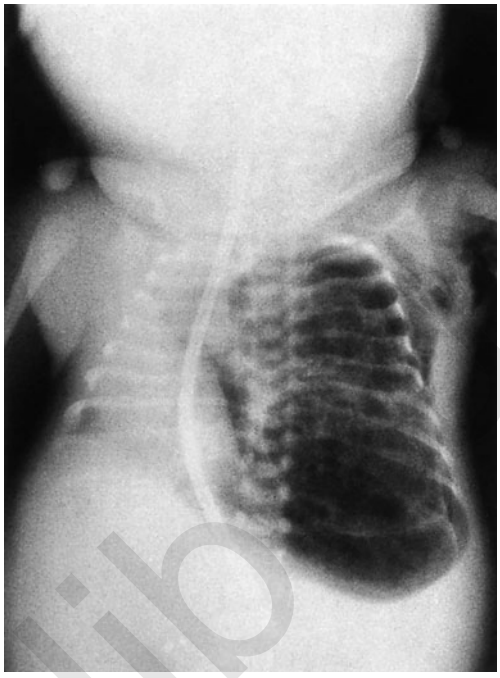


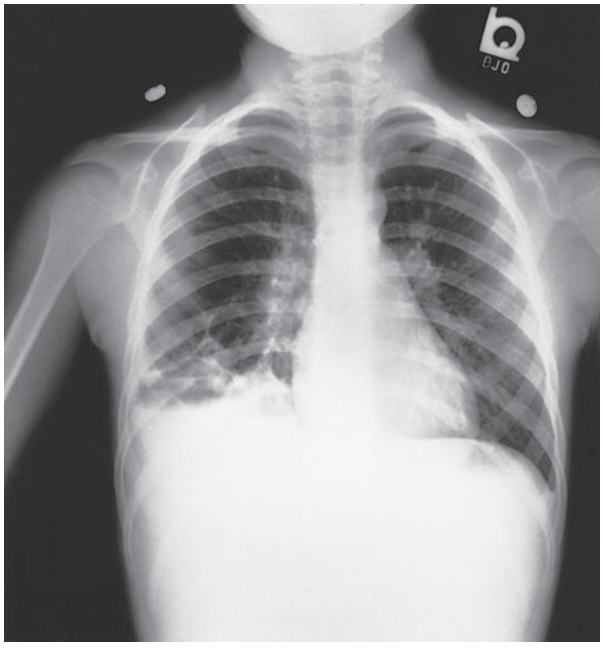
Figure 35.3 Congenital pulmonary airway malformation of the left lung with gross expansion of the lung, marked mediastinal shift to the right and downward displacement of diaphragm. Note surgical emphysema of left axilla and chest wall, indicating rupture of a cyst.

Treatment

The cornerstone of treatment in patients with CPAM is complete resection of abnormal tissue, which usually requires lobectomy. Again this is done via either open, muscle-sparing thoracotomy, or thoracoscopy. Patients with multilobular disease may benefit from segmental resection if possible, and total pneumonectomy is occasionally required.[28] Prenatal diagnosis of CPAM should prompt referral to a tertiary care center where critical care support and emergent pediatric surgical care are available. Like infants with congenital lobar emphysema, the postnatal phenomenon of breathing or positive pressure ventilation may rapidly precipitate a crisis in CPAM patients if there is progressive distention of the affected lobe. Older children who present with pulmonary infection may be managed acutely with antibiotics, then undergo subsequent elective lobectomy. Long-term expectant medical management is not appropriate due to the frequency and severity of recurrent infectious complications and the risk of malignant degeneration.[24]

As noted above, there are a number of reports of spontaneous regression and/or resolution of fetal CPAMs, and serial ultrasounds in the fetus are recommended to document findings. Even if asymptomatic at birth, these patients should undergo axial imaging at one month of age. Should persistent parenchymal abnormality be demonstrated, the infant should undergo elective resection, although this point is somewhat controversial.

A recent meta-analysis demonstrated significantly fewer operative complications when resection is performed prior to onset of symptoms.[29] Additionally, operation in a presymptomatic patient is associated with potentially parenchyma



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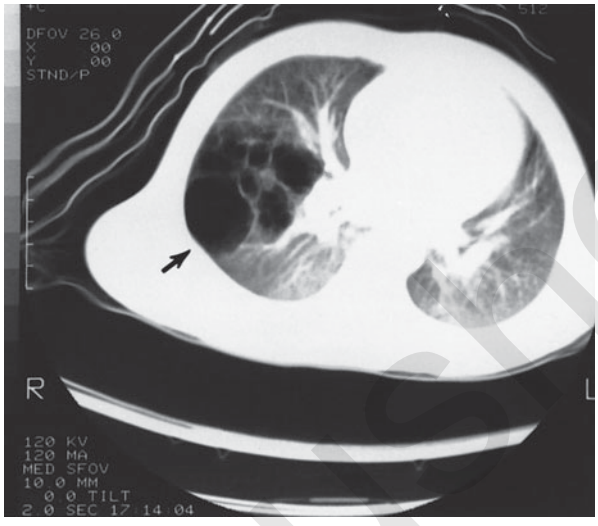


(b)

Figure 35.4 (a) Plain chest x-ray of a nine-year-old child who presented with fever, pleuritic chest pain, and cough. The lesion is an infected type 1 CPAM of the right lower lobe. (b) The lesion in (a) is shown on chest CT scan after treatment with antibiotics and before surgical resection of the right lower lobe (with permission from Coran AG, Oldham KT, The pediatric thorax. In: Greenfield LJ, Mulholland MW, Oldham KT *et al.* (eds). *Surgery: scientific principles and practice*. Philadelphia: JB Lippincott, 1993: 944).

sparing resection such as segmentectomy with better long-term lung function.[30]

In the last decade and a half, various fetal interventions for CPAM have been described. The approaches have included thoracoamniotic shunting in lesions with a single predominant cyst, and resection in those with more complicated type 2 and type 3 CPAM.[31] It appears that difficulty with proper patient selection and technical hazards make the risk of maternal–fetal complications relatively high. The issue of appropriate prenatal patient selection is critical since many of these fetuses do well without intervention and a number of the lesions resolve entirely. However, CPAM associated with fetal hydrops or polyhydramnios carries a high mortality and fetal intervention at specialized centers may be an option in some of these cases. The subject remains controversial.[32]

An additional strategy to manage the fetus in whom significant respiratory distress is anticipated at birth is *ex utero* intrapartum therapy (EXIT). This involves resection of the CPAM via thoracotomy while maternal–placental–fetal circulation is maintained, followed by delivery of the infant.[33]

More recently, maternal administration of betamethasone has been a subject of investigation in the fetal treatment of CPAM. While the exact mechanism is unknown, steroids are thought to impair CPAM growth. Though the response of CPAM to steroids is variable, this treatment appears to have a role in improving survival in select fetuses.[34–36] This is currently the subject of further study.

PULMONARY SEQUESTRATION

Pulmonary sequestrations make up 10–30% of the cystic bronchopulmonary foregut malformations in most reports.[28,37] They are classified by whether the sequestration resides within the visceral pleura of the normal lung (intralobar sequestration) or is invested by its own visceral pleura (extralobar sequestration). In both types of pulmonary sequestration, however, there is no bronchial communication between the sequestrum and the normal tracheobronchial tree. In addition, the malformation receives its blood supply from aberrant systemic arterial vessels (Table 35.2).[38]

Intralobar sequestrations make up the majority (up to 75%) of pulmonary sequestrations and most commonly involve the posterior and basal segments of the left lower lobe.[39] As mentioned, these intralobar lesions are surrounded by normal lung parenchyma and pleura. The arterial supply is usually derived from aberrant branches of the descending thoracic aorta, although occasionally intercostal, brachiocephalic, or abdominal aortic aberrant vessels are encountered. Venous drainage is usually via the associated pulmonary vein. Although sequestrations are by definition nonfunctional and sequestered from the respiratory tree, intralobar sequestrations may communicate with neighboring alveoli in normal lung via abnormal air spaces, allowing some ventilation and air-trapping within the intralobar lesions.

Extralobar sequestrations are completely separated from the normal lung invested by an individual pleura. They are completely separate from the functional airways. They are found in the left lower chest most commonly, but may occur anywhere; rarely, subdiaphragmatic locations are reported.[39,40] A 3:1 male predominance is reported in most series for extralobar sequestrations. These sequestrations also derive arterial blood supply from the descending aorta, with up to 20% having an aberrant vessel traversing the diaphragm. Venous drainage into systemic veins, such as the azygous, hemiazygous, or the portal system, is typical for extralobar sequestrations. There is an association of extralobar pulmonary sequestrations with CPAM and congenital

Table 35.2 Characteristics of pulmonary sequestrations (from Shamji *et al.*[38] with permission).

Characteristic	Intralobar	Extralobar
Incidence	Uncommon	Rare
Incidence ratio	3	1
Sex	Equal	Male 80%
Side	60% left	90% left
Location	Usually in the posterior basal segment	Above the diaphragm, rarely below
Age at presentation and symptoms	Adolescent to young adults, 50% >20 years, recurrent pulmonary infections	Neonate 60%, <1 year, respiratory distress
Associated anomalies	Uncommon	Frequent (>50%), e.g. congenital diaphragmatic hernia (30%)
Diagnosis at neonatal autopsy	None	Frequent
Arterial supply	Systemic – from aorta, large vessels, often a single vessel	Systemic – from pulmonary or aorta, usually small vessels
Venous drainage	Pulmonary – inferior pulmonary vein	Systemic – azygos or hemiazygos vein; rarely portal vein
Anatomical relations	Not separate, within and part of normal lobe	Separate, has its own investment – visceral pleura
Connection with foregut	Very rare	More common
Bronchial communication	Present, small	None

diaphragmatic hernia, as well as a variety of other congenital defects.[6,28,41] Aberrant air space connections are not present, rather extralobar sequestrations are prone to hemorrhage or arterial-venous shunting and the patients may present with high output congestive heart failure.

The embryologic origin of pulmonary sequestrations is unclear, but they are thought to result from either abnormal budding of the tracheobronchial tree or accessory budding of the foregut, or a combination of the two. The stimulus is not known. Extralobar sequestrations are clearly congenital in origin. This conclusion is drawn by the frequent association with other congenital anomalies, their presence in neonatal autopsies, and the now routine discovery of these lesions on prenatal ultrasound.

Presentation and diagnosis

Although diagnosis of intralobar sequestration is improving, patients with intralobar sequestration often present with pulmonary infections due to abnormal air-space connections with inadequate drainage, or from compressive atelectasis of adjacent parenchyma. This pathophysiology explains why diagnosis is uncommon in infancy, and presentation occurs later in childhood or adulthood with complaints of recurrent or refractory pneumonias, lung abscesses, or hemoptysis.

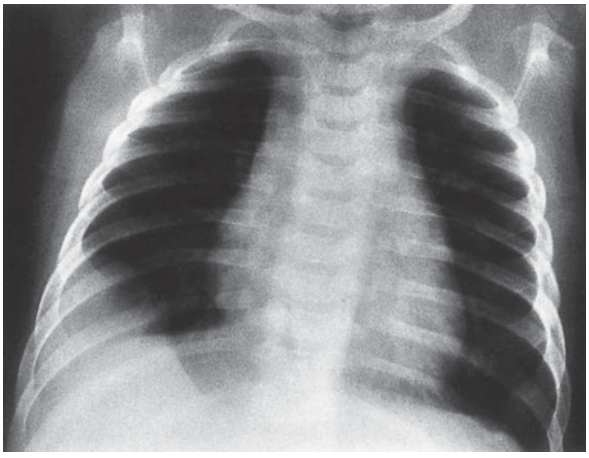
Extralobar sequestrations, on the other hand, are frequently seen on prenatal ultrasound. The infants are often asymptomatic at birth, however, these lesions can be associated with arterial-venous shunting and even congestive heart failure. The pathognomonic aberrant arterial blood supply may be identified prenatally if the ultrasound has Doppler capability. If the mass is large, shift of mediastinal structures, fetal hydrops, and fetal demise can occur. Due to the frequency of associated anomalies, extralobar sequestrations are often diagnosed early in infancy during evaluation for these other problems.

Plain x-rays of the chest will usually demonstrate an intralobar sequestration as a non-aerated, atelectatic mass, or as a cyst with an air-fluid level (Fig. 35.5a). Extralobar sequestrations most often appear as a left posterior mediastinal mass or triangular retrocardiac density on chest x-rays, although they may occur on the right as well.

In most infants and children with pulmonary sequestration, additional imaging beyond the initial radiographs is recommended. Ultrasound with Doppler (Fig. 35.5b), CT angiogram (Fig. 35.5c), or MRI provide good anatomic detail and demonstrate relationships to neighboring structures. Importantly, all delineate the aberrant arterial vessels for purposes of both diagnosis and preoperative planning. Preoperative upper gastrointestinal contrast study may assist in identifying the 10% of patients who have anomalous foregut communication with their sequestration, but some experienced pediatric surgeons do not routinely do this, relying instead on intraoperative discovery.

Treatment

Treatment for pulmonary sequestrations consists of excision of the abnormal tissue. Although extralobar sequestrations may be asymptomatic, the cumulative risks of hemorrhage, infection, arteriovenous shunting, and late malignancy have generally been considered an indication for resection when diagnosed. In patients with extralobar sequestration, this is a relatively straightforward procedure performed via thoracotomy or by thoracoscopy. Intralobar sequestration is treated with lobectomy via thoracotomy or thoracoscopy, although in selected cases, segmentectomy may be appropriate.[42] Segmentectomy may be more feasible in situations where prenatal discovery offers an opportunity for resection prior to the onset of infectious complications.



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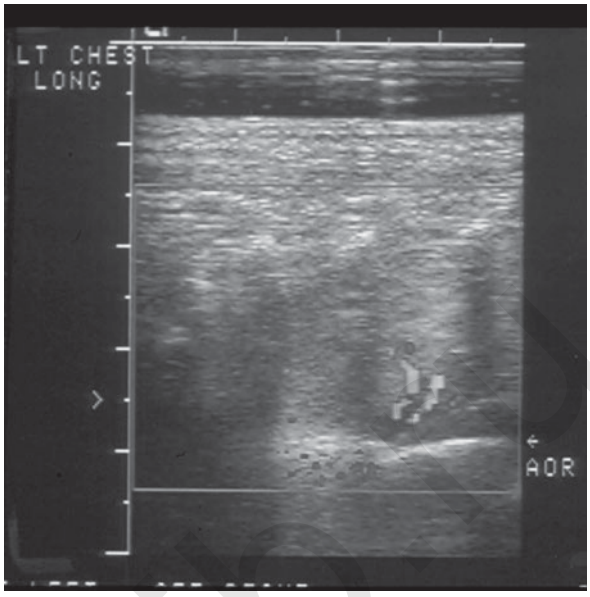

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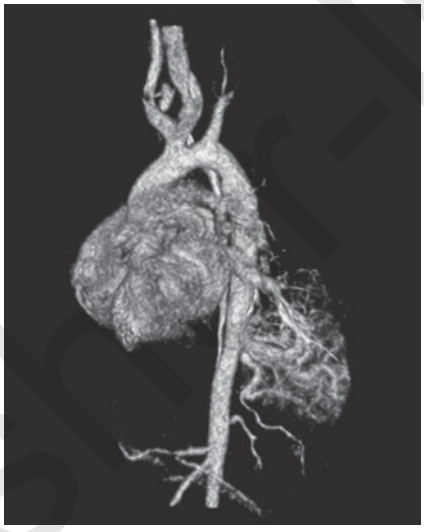


(c)

Figure 35.5 Pulmonary sequestration. (a) Chest x-ray demonstrates a well-defined mass at base of right lung. (b) Prenatal Doppler ultrasound demonstrating two aberrant arterial vessels to extralobar sequestration (arrow). (c) CT angiogram demonstrates an enlarged bronchial artery arising from the distal descending thoracic aorta, supplying an intrapulmonary sequestration.

A critical element in resection of a pulmonary sequestration is the identification and control of the anomalous systemic arterial blood supply. Reports of unrecognized or uncontrolled hemorrhage from accidental division of the aberrant arteries emphasize this point.[43] This is especially true of vessels with a subdiaphragmatic origin that course through the inferior pulmonary ligament and are prone to retraction into the abdomen when severed or avulsed. Current imaging techniques allow preoperative assessment of the arterial and venous anatomy associated with these lesions and assist the surgeon in operative planning.

Other important technical points include particular care in identification of the phrenic nerve, which may travel adjacent and lateral to an extralobar sequestration. Abnormal foregut communications, whether diagnosed preoperatively or not, must be carefully sought and controlled appropriately intraoperatively. Although controversial, fetal interventions such as thoracoamniotic shunting and drainage may be helpful in certain cases of tension hydrothorax and hydrops fetalis.[19]

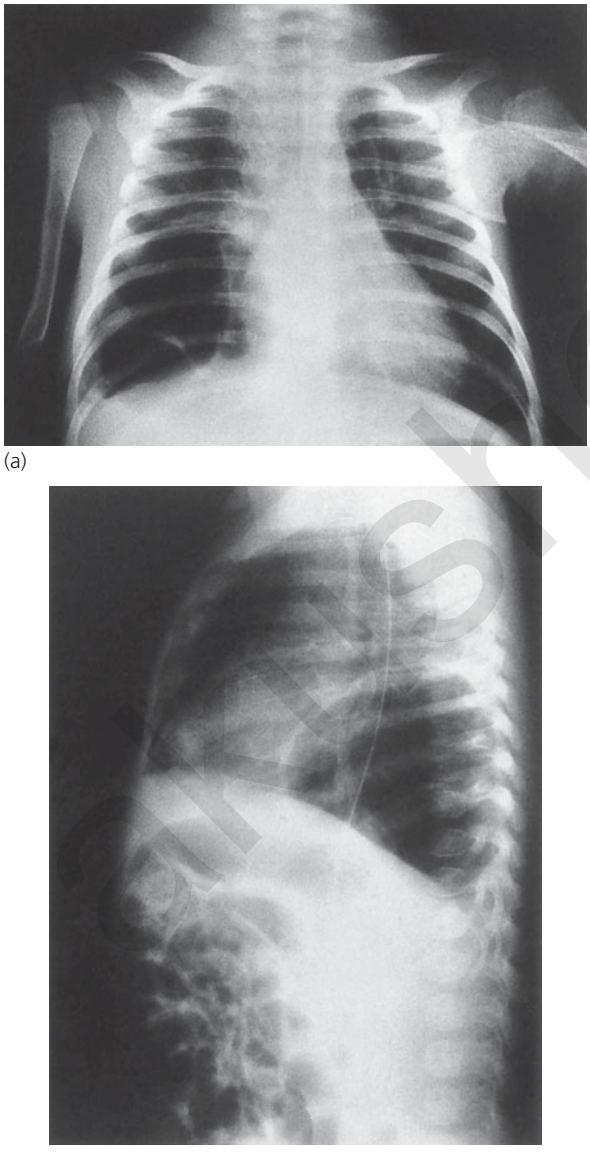
Due to the risk of infection and malignant degeneration, surgical resection is recommended for patients with pulmonary sequestration. In contemporary pediatric surgical practice, the outcome for affected infants and children should be excellent.[44,45] Similar to the CPAM population, resection is recommended before symptoms develop, and before the age of one year, when possible.

CONGENITAL BRONCHOGENIC LUNG CYSTS

Congenital lung cysts comprise up to one-third of bronchopulmonary foregut malformations in some reports.[46,47] The

most common of these lesions are bronchogenic cysts. Bronchogenic cysts are typically thick walled, unilocular lesions which are comprised of smooth muscle, cartilage, and mucous glands lined by pseudostratified ciliated columnar epithelium. It is believed that they become separated from the tracheobronchial tree during development but remain adjacent, which is where they are found clinically. Congenital lung cysts may develop at any time between the third and sixteenth weeks of gestation as the lung buds begin their initial segmental divisions and subsegmental dichotomous divisions progress.

Bronchogenic cysts arise from the trachea, bronchus, or other conducting airways but have usually lost their connection with the parent structure (Fig. 35.6). They are usually simple and contain mucus. However, air-fluid levels and infection may be seen if there is continuity with the tracheobronchial tree. Because these lesions result from abnormal development of bronchi, they may contain any of the cellular elements of the respiratory tract. In contrast to sequestrations, bronchogenic cysts have a normal bronchial blood supply. Although bronchogenic cysts may reside anywhere in the respiratory tract, including paravertebral, paraesophageal, subcarinal, and cervical areas, the majority are found in the lung parenchyma or mediastinum.[8,28,48,49]



(a)

(b)

Figure 35.6 (a) Chest x-ray showing a large cyst occupying the lower half of the right thorax. (b) Lateral view localized the cyst to the lower lobe.

More rare than the bronchogenic cysts are parenchymal lung cysts, which are thought to arise from abnormal budding of distal airways and other respiratory structures. Some consider these among the spectrum of bronchogenic cysts, however most consider them separate because of a more peripheral location and their origin from pulmonary parenchymal structures rather than a conducting airway. Regardless, the histology is variable but resembles that of the structure of origin. The general features of presentation and principles of management for peripheral lung cysts are similar to those of bronchogenic cysts, unless the anomalous structure is lymphatic in origin. In these cases, pulmonary lymphangiectasis may be present; this is manifested by diffuse bilateral cystic lung involvement and a poor clinical prognosis.[6]

Presentation and diagnosis

Some patients with bronchogenic cysts are asymptomatic. Of those with symptoms, the most common presentations are wheezing, tachypnea, or dyspnea, all related to compression of the adjacent conducting airway with partial obstruction or associated tracheomalacia. If there is a patent connection between the tracheobronchial tree and a bronchogenic cyst, patients may develop infection and present with productive cough, fever, chills, and hemoptysis. Rarely, the cyst may enlarge to the point where the mass effect leads to mediastinal displacement, airway compression, compression of normal lung, and cardiorespiratory failure.

Plain chest x-rays typically demonstrate a smooth, spherical, paratracheal, or hilar solid mass without calcifications. If airway communication or infection is present, an air-fluid level may be seen. Displacement of adjacent airway structures is commonly observed. While these cysts are generally unilocular, a honeycomb appearance can be seen in some forms of this lesion.

As with other congenital cystic lesions, axial imaging with CT or MRI will demonstrate anatomic relationships. Contrast esophagram and bronchoscopy are additional modalities by which to identify foregut communication or extrinsic compression.

Treatment

Acute respiratory decompensation from a large tense bronchogenic or lung cyst may necessitate needle or chest tube thoracostomy as a temporizing measure. Pre-existing pneumonias should be treated with preoperative antibiotics. Thereafter, or in patients with stable cysts, simple cystectomy should be performed with oversewing or stapling of any anomalous bronchial communications (Fig. 35.7). If a

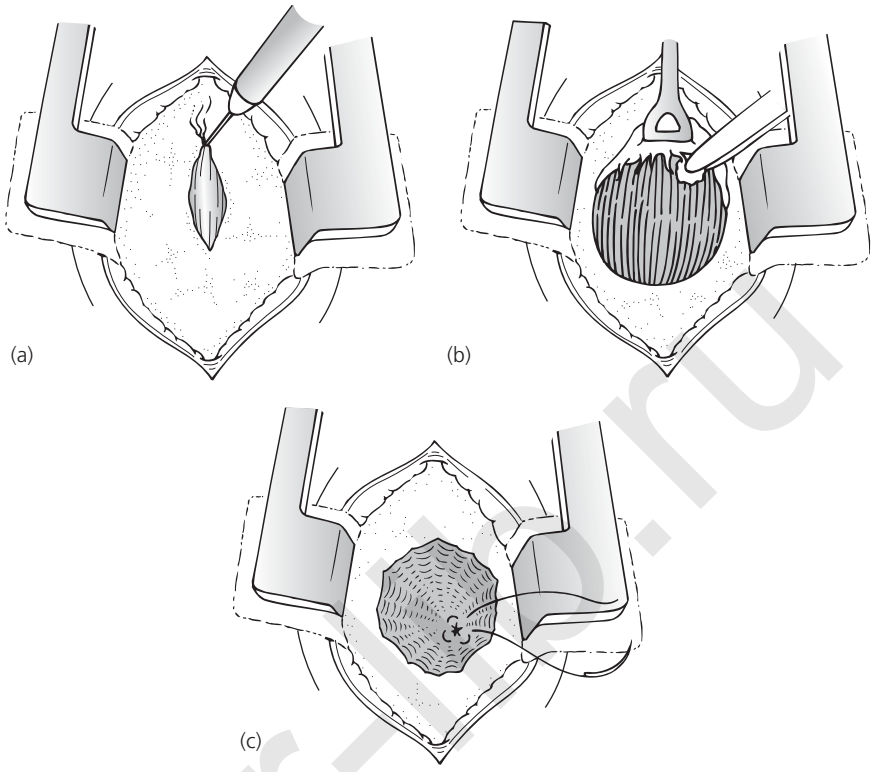


Figure 35.7 Operative technique of lung cystectomy. (a) Cyst wall exposed after incising lung tissue just above the cyst. (b) Dissection in the plane between the cyst and lung tissue. (c) Showing a small bronchus opening into the cyst – the opening is closed by oversewing it.

bronchogenic cyst cannot be removed in its entirety, remaining portions of cyst wall may be destroyed with electrocautery in this situation. For a parenchymal cyst, lobectomy, segmentectomy, or wedge resection may be necessary if simple cystectomy is judged inadequate. The principle in this circumstance is to preserve as much normal lung parenchyma as possible. Generally, lateral thoracotomy or thoracoscopy is employed for management of these lesions, although median sternotomy may be appropriate for certain central lesions. The thoracoscopic approach has been used successfully in recent years, and may be associated with shorter duration of thoracostomy drainage and hospital stay.[50]

PULMONARY HYPOPLASIA, APLASIA, AND AGENESIS

Pulmonary hypoplasia refers to the abnormal development of an entire lung or both lungs, resulting in a diminutive and potentially dysfunctional gas exchange organ. This occurs most commonly as a consequence of extrinsic compression during gestational development, although primary hypoplasia does occur. While a number of intrathoracic mass lesions may cause extrinsic compression of the lung, the most common are CDH and CPAM. Pulmonary aplasia results from developmental arrest during organogenesis some time after the sixth gestational week, resulting in a reduction in the number of alveoli. This may be marked. The physiologic consequences of both derangements can be severe and include pulmonary hypertension, persistent fetal circulation, and respiratory failure. Extraordinary measures of clinical support are frequently required,[37,51] including high-frequency oscillation, the use of inhaled nitric oxide, and extracorporeal membrane oxygenation.

Pulmonary agenesis is the complete absence of one or both lungs. The specific cause of this accident of embryogenesis is unknown, however, there is apparent failure of organogenesis at about the time the trachea divides into the two lung buds, early in the fourth week of gestation. Bilateral pulmonary agenesis is exceedingly rare and is inevitably incompatible with life. Unilateral pulmonary agenesis may be asymptomatic, however symptomatic patients may pose difficult neonatal management issues, not only from the standpoint of respiratory insufficiency, but also because of a high incidence of associated anomalies.[52–54] Older children may be asymptomatic or demonstrate non-specific respiratory symptoms including a history of failure to thrive, exercise intolerance, recurrent respiratory infections, and chest asymmetry or scoliosis. A shift in the location of heart tones and absent ipsilateral breath sounds are demonstrable on physical examination. Chest roentgenograms will demonstrate hyperinflation of the contralateral lung and possibly a fluid-filled ipsilateral hemithorax in the setting of marked displacement of the mediastinum. Absence of the ipsilateral mainstem bronchus or the pulmonary artery is a definitive finding and this can be established by endoscopy, echocardiography, axial imaging, or angiography.

LUNG SURGERY IN NEWBORNS

Although a full discussion of thoracic surgery in children is beyond the scope of this chapter, a brief description of surgical technique in neonates is relevant. A number of comprehensive texts are available.[55,56] Lung surgery in

neonates is generally similar to that in adults except that the diminutive size, the associated lesions, and the unique pathologic entities require certain special considerations. Of course, the smaller the child, the more care must be taken in order to avoid technical injury. As with all lung surgery, technical problems may result in serious and irreversible consequences. Collaboration with pediatric anesthesiologists familiar with the unique circumstances of pediatric chest surgery is essential.

Lobectomy

The patient is positioned in the lateral decubitus position, with the upper arm extended and placed over the head (Fig. 35.8a). Rolled towels and other positioning devices may be placed in order to optimize stabilization and exposure of the operative field. As always in pediatric surgery, heat loss is a concern, and insulating coverings should be placed over exposed areas without interference to the surgical site. Convective and radiant warmers should also be employed.

Optimal exposure is gained by transverse or oblique incision over the fourth or fifth intercostal space, below and lateral to the nipple to avoid cosmetic and functional damage to the breast tissue. There should be some space between the tip of the scapula and the posterior extent of the incision. This becomes important during closure of the muscle layers, especially if the incision must be extended posterolaterally. Underlying muscle and subcutaneous tissue is divided along the line of incision (Fig. 35.8b) by electrocautery. To limit postoperative morbidity from scoliosis, it is desirable and usually possible to employ a muscle sparing approach, which involves retraction of the serratus anterior and latissimus dorsi muscles, but leaves them intact. The scapula is elevated off the chest wall by retractor to gain exposure, and palpation is used to count the ribs to the correct interspace. In most situations in infants, the highest palpable rib is the second. Generally, the fourth interspace is used for a lobectomy although the fifth can be used effectively as well. The incision is then continued with electrocautery just superior to the lower rib of the selected intercostal space to avoid damage to the neurovascular bundle that runs along the inferior border of each rib (Fig. 35.8c). Care must be taken when entering the pleura to avoid injury to the lung parenchyma. A rib spreader is then placed to facilitate retraction (Fig. 35.8d). The incision may then be extended anteriorly or posteriorly if further exposure is needed. It is clear that thoracoscopic techniques in practiced hands yield similar good results, as do open techniques.

The following technique and illustrations are described for left upper lobectomy, however, the principles are the same for any lobe resection. Gentle lateral and inferior traction on the lobe exposes the hilum. The visceral pleura is carefully incised circumferentially, exposing the hilar structures (Fig. 35.9). Meticulous dissection reveals the left main pulmonary artery as it courses under the aortic arch (Fig. 35.10) and crosses the left upper lobe bronchus. Important structures to note are the left phrenic nerve anteriomedially along the mediastinum, and the recurrent laryngeal nerve branching from the vagus under the aortic arch. A review of segmental anatomy of the lung describes four main arterial branches supplying the left upper lobe, however this can be variable. These are individually encircled, ligated, and divided. This is typically done with heavy silk and using double proximal ligatures. Clips or stapling devices are suitable if appropriately sized.

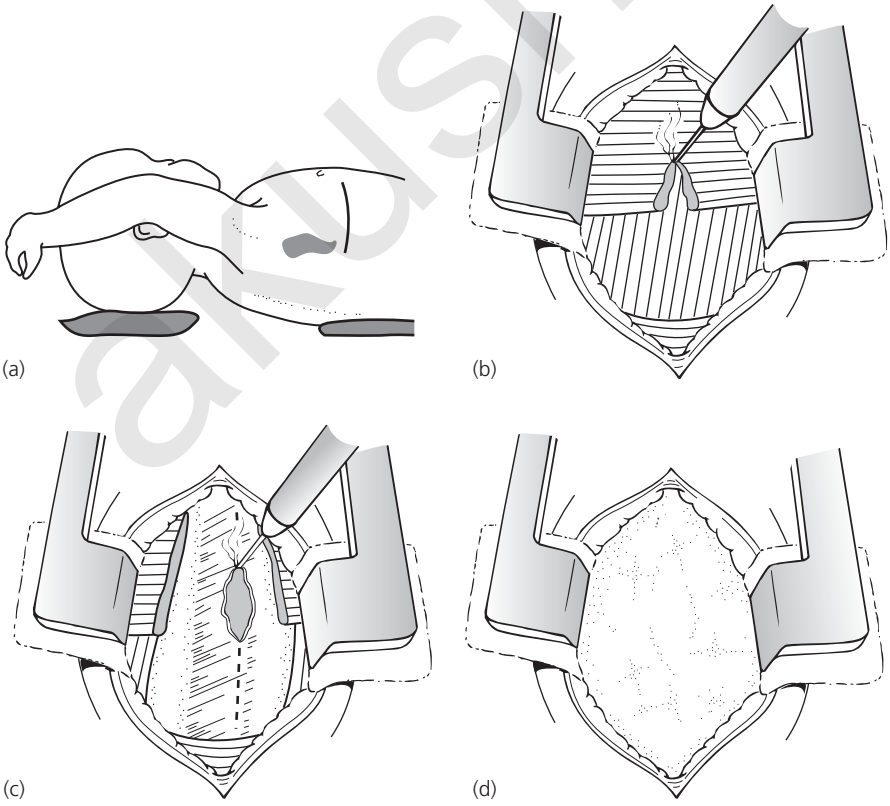


Figure 35.8 Operative technique of thoracotomy: (a) Transverse lateral incision; (b) division of external intercostal muscles; (c) division of intercostal muscles along the upper border of the lower rib; (d) retraction of ribs to expose the lung.

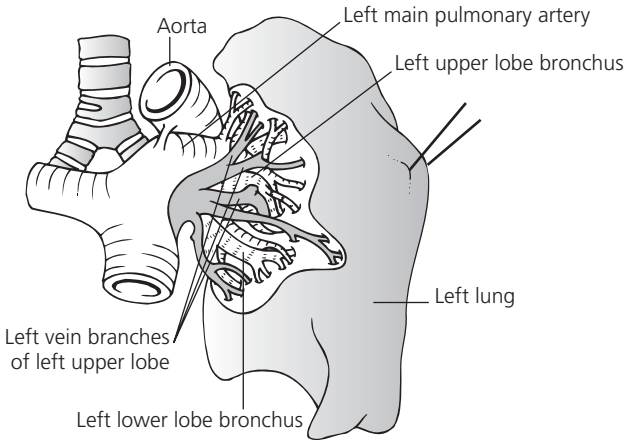


Figure 35.9 Normal anatomy of the left lung hilum containing the pulmonary artery, veins and bronchus.

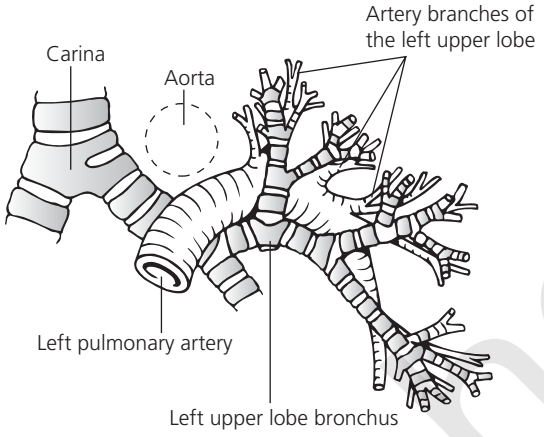


Figure 35.10 The main segmental pulmonary artery branches to the left upper lobe.

The bronchial blood supply traveling with the left upper lobe bronchus is likewise identified, controlled, and divided. Attention is then directed to the left upper lobe venous drainage. Again, individual branches are circumferentially dissected and ligated using the same approach as for the arterial circulation (Fig. 35.11). The bronchus is then dissected, clamped, and divided. Closure of the bronchial stump with commercial surgical stapling devices is appropriate in older children; however, size and other technical limitations may make this undesirable or impractical in infants. If so, a simple sewn closure is best (Fig. 35.12). Air leaks may be identified for suture repair by filling the chest with warm saline coincident with inflation of the residual lobe by the anesthesiologist. The inferior pulmonary ligament should be divided at this time to facilitate expansion of the left lower lobe, or it may be done early in the dissection to facilitate exposure. A tunneled chest tube is placed within the pleural space for drainage, and the wound or port site is closed in anatomical layers using absorbable suture. Postoperatively, the chest tube can be removed when there is no demonstrable air leak and output is minimal. Thoracoscopic

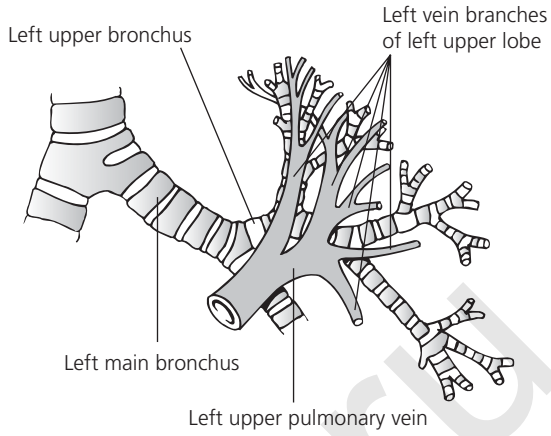


Figure 35.11 The segmental vein branches of the left upper lobe.

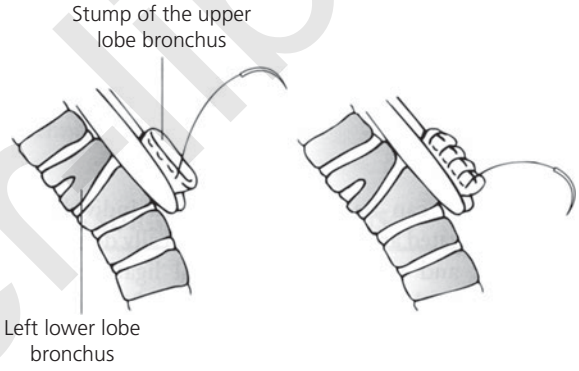


Figure 35.12 Vascular clamp placed across the left upper bronchus and the bronchus oversewn.

lobectomy employs the same surgical principles and anatomic approach, with access through three or four appropriately positioned ports.

Wedge resections and lobectomies are remarkably well tolerated in the pediatric population, although age at resection is a factor. Older children demonstrate less compensatory growth than infants. Even so, most children will have little or no functional deficit after these procedures.[18,19,57]

The need for pneumonectomy is much more limited in infants and children, but functional outcomes are still generally good. Postpneumonectomy syndrome, which is characterized by severe mediastinal shift, bronchial stretching and respiratory failure can complicate pneumonectomy. Placement of an expandable intrathoracic prosthesis has been described as a strategy to manage this potential problem.[58]

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36

Congenital diaphragmatic hernia

PREM PURI AND TAKASHI DOI

INTRODUCTION

Congenital diaphragmatic hernia (CDH) is a common malformation characterized by a defect in the posterolateral diaphragm, the foramen of Bochdalek, through which the abdominal viscera migrate into the chest during fetal life. Recent population-based studies have reported the prevalence of CDH to be between 1 in 2600 and 1 in 3700 live births.[1,2] Approximately 80% are left sided, less than 5% are bilateral, and 15% are right sided.[1,2] The size of the defect varies from small (2 or 3 cm) to very large, involving most of the hemidiaphragm. Despite advances in neonatal resuscitation and intensive care, newborn infants with CDH continue to have high mortality. Current survival rates in population-based studies are around 55–70%.[1,2] Highly specialized centers report 80% and more, but discount the hidden mortality, mainly in the antenatal period. The high mortality and morbidity in CDH are mainly attributed to pulmonary hypoplasia and persistent pulmonary hypertension.[3,4]

EMBRYOGENESIS

The etiology of CDH is still not clearly understood. Although it is generally considered to be sporadic, there are reports of familial cases including known chromosomal aberrations, as well as autosomal recessive inheritance of unknown chromosomal origin.[5,6] The embryogenesis of CDH has been described as a failure of the pleuroperitoneal canals in the posterolateral aspect of the diaphragm to fuse during gestational week 8.[7] Consequently, the abdominal viscera including liver and bowel migrate into the thorax, which is thought to cause pulmonary hypoplasia by compression of the growing lungs. The pulmonary hypoplasia associated with CDH extends to all aspects of the lung, resulting in fewer alveoli, thickened alveolar walls, increased interstitial tissue, and markedly diminished alveolar air space and gas-exchange area.[8] Parallel to airway changes, pulmonary vasculature is abnormal with a reduced number of vessels, adventitial thickening, medial hyperplasia, and peripheral extension of the muscle layer into the smaller intra-acinary arterioles.[9] The morphology of the CDH lung furthermore has an immature appearance.[8,9] The ipsilateral lung is the most severely affected, but the changes usually extend to the contralateral lung, as well.

Recently, experimental studies have suggested that the classical view of embryogenesis of CDH may have to be revised. A toxicological nitrofen model of CDH has shown that abnormalities in the contralateral lung as well as the ipsilateral side are present even before the diaphragm starts to develop.[10] Keijzer *et al.*[11] proposed the dual-hit hypothesis to explain the observations on pulmonary hypoplasia in this model. This hypothesis proposes that the early retardation in lung development that occurs before the development of the diaphragmatic defect is caused by nitrofen, whereas the late-gestational increase in lung hypoplasia is caused by mechanical compression from herniated viscera. Kluth *et al.*[12] have shown that pleuroperitoneal canals are not wide enough to allow herniation of gut loops in rats. Several groups have shown an aberrant gene/protein expression of different growth factors and transcription factors in experimental models, as well as in infants with CDH.[13–15] Retinoid signaling pathway has been shown to be disrupted in the nitrofen model of CDH.[16,17] Vitamin A-deficient rats display pulmonary hypoplasia with CDH.[18] Furthermore, the lungs in experimental models of CDH exhibit a response to retinoic acid differing from normal lungs.[19–21] Recently, it has been reported that prenatal treatment with retinoic acid (RA), the active metabolite of vitamin A, in late gestation promotes pulmonary alveologenesis in the nitrofen model of CDH in rodents.[22] Furthermore, prenatal RA treatment has been shown to upregulate pulmonary expression levels of genes involved in lung morphogenesis in the nitrofen-induced hypoplastic lung.[23,24] Although prenatal use of RA has been controversial, these experimental data suggest that prenatal RA treatment may have a therapeutic potential to revert pulmonary hypoplasia associated with CDH.

PATHOPHYSIOLOGY

The onset and severity of symptoms depends on the amount of abdominal viscera in the chest and the degree of pulmonary hypoplasia. Postnatally, the most severely affected babies present with respiratory distress (cyanosis, tachypnea, and sternal recession) at birth. Although the major cause of this is pulmonary hypoplasia, the resulting hypoxia and hypercarbia will result in pulmonary vasoconstriction and pulmonary hypertension. This, in turn, will cause reversal to right-to-left shunting through the ductus arteriosus and the foramen ovale, and the infant enters a vicious, self-perpetuating cycle.

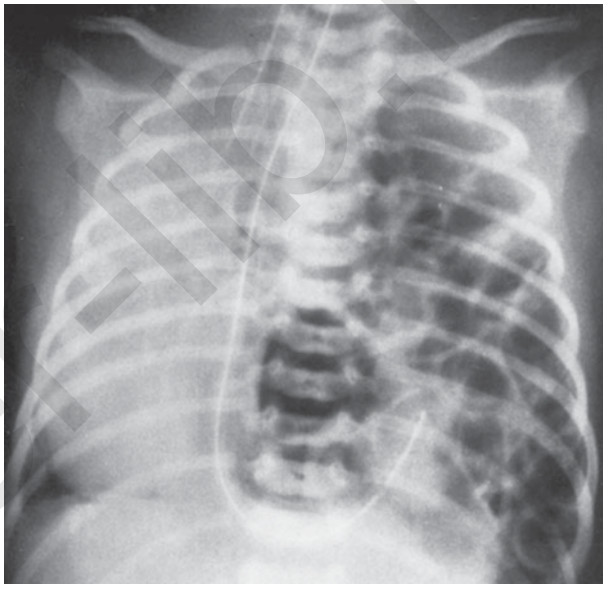
Several additional factors have been known to contribute to the severe pulmonary hypertension in CDH. The pulmonary vascular bed is abnormal, with increased muscularization of arterioles in a manner similar to infants with idiopathic persistent pulmonary hypertension of the newborn (PPHN).[9] Increased thickness of the media as well as the adventitia of arteries of all sizes has also been demonstrated.[25] Furthermore, vasoactive substances, such as endothelin-1 seem to be increased in infants with CDH. Kobayashi and Puri found increased blood levels of endothelin, as well as increased expression of endothelin-1 in endothelial cells in the pulmonary vasculature.[26] Endothelin-1 causes pulmonary vasoconstriction by binding to the endothelin A (ETA) receptor. The ETA receptor is ubiquitously present in the smooth muscle cells of the pulmonary vasculature,[27] and the increased endothelin-1 levels may thus adversely affect pulmonary vasoconstriction.

Hypoxia and hypercarbia may be further aggravated by a reported immaturity of the surfactant system in experimental animals and infants with CDH.[28] Others could, however, not confirm this deficiency,[29] and it has been postulated that the apparent surfactant deficiency may in fact be secondary to respiratory failure, rather than to a primary deficiency.[30]

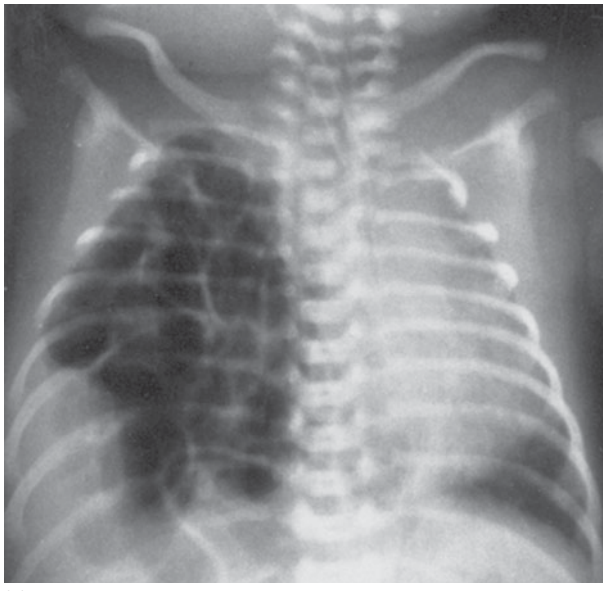
DIAGNOSIS

CDH can be reliably diagnosed prenatally by ultrasonography at about 20 weeks of gestation. The diaphragm can be visualized and its absence is indirectly suggested by the intrathoracic presence of abdominal viscera and compression of thoracic organs.[31] An important feature to look for is the presence of the liver in thorax, if necessary using Doppler interrogation of the umbilical vein and hepatic vessels.[31] Differential diagnosis with other intrathoracic pathologies, including congenital cystic adenomatoid malformation (CCAM), bronchopulmonary sequestration, diaphragmatic eventration, and bronchogenic cyst, needs to be made. It is also of vital importance to exclude the presence of other anomalies, including neural tube defects, cardiac malformations, and chromosomal aberrations, e.g. trisomy 18 and 21. Furthermore, the degree of pulmonary hypoplasia should be assessed. The presence of liver in the chest in left-sided CDH indicates severe pulmonary hypoplasia.[32] The lung-to-head ratio (LHR – the area of the right lung at the level of the four-chamber view divided by the head circumference) has been shown to be a predictable estimation of the degree of pulmonary hypoplasia.[33] Currently, intrauterine lung measurement by magnetic resonance imaging (MRI) is being investigated as a means of estimating lung size.[34]

Postnatally, CDH should be suspected in infants with severe respiratory distress at birth or within the first few hours of life. Physical examination reveals a scaphoid abdomen, an increased anteroposterior diameter of the thorax, and mediastinal shift. Breath sounds are absent on the affected side. Associated congenital anomalies may also be seen or revealed on further examination. The definitive diagnosis is made by plain x-ray of the chest and abdomen by demonstration of air-filled loops of the bowel in the chest and a paucity of gas in the abdomen (Fig. 36.1). There is a



(a)



(b)

Figure 36.1 (a) Left congenital diaphragmatic hernia (CDH) with viscera visible in the left chest, pulmonary hypoplasia, and significant mediastinal shift to the right. (b) Right CDH with viscera visible in the right chest and mediastinal shift to the left side.

mediastinal shift to the opposite side, and only a small portion of lung may be seen on the ipsilateral side.

TREATMENT

An infant with respiratory distress requires endotracheal ventilatory support. Mask ventilation should be avoided as it will distend the stomach and further compromise respiratory status. A baby with CDH should be paralyzed and have a nasogastric tube placed to prevent distension of the stomach and bowel. CDH was previously considered a surgical emergency, where prompt surgery with reduction of the abdominal viscera allowed the lungs to expand. The increased knowledge of the pathophysiology of CDH has led to a different approach, where prolonged preoperative stabilization has proven useful. Most centers now prefer delayed surgery, with a delay of sometimes several days, waiting for the stabilization of the pulmonary circulation before surgery.[35] Surgery in CDH should be based on the optimization of clinical parameters, such as initial blood gases, to improve outcome.[36]

Preoperative treatment

An infant with respiratory distress requires endotracheal ventilatory support. Although previously aggressive hyperventilation and hypocarbia were widely used, a different approach, using gentle ventilation and permissive hypercarbia, has proven more useful in decreasing the mortality rate.[37,38] Without this approach, a high mortality rate from barotrauma can be expected.[39,40] Currently, more than 90% of international CDH registry centers cite the use of permissive hypercapnia, accepting higher $PaCO_2$ during the early course, rather than targeting low $PaCO_2$ to estimate viability and lower pulmonary vascular resistance, as a primary therapeutic guideline.[38] Several centers have shown improved survival as compared to historical controls, using a combination of gentle ventilation and delayed surgery.[38,39]

High-frequency oscillatory ventilation (HFOV) is a valuable tool in the treatment of infants with respiratory distress, since it provides effective ventilation while decreasing barotrauma. However, in CDH, HFOV has not been shown to improve the mortality or morbidity rates.[41,42] The impact of changes in HFOV settings must be monitored carefully, as high airway pressures may cause lung hyperinflation, with adverse effects on venous return, pulmonary vascular resistance, and ultimately in cardiac output.[38] In many CDH cases, the constant distending airway pressure associated with use of HFOV may be more detrimental than helpful.

Inhaled nitric oxide (iNO), which provides selective pulmonary vasodilatation without systemic hypotension, seemed to be a promising therapy,[43] but more recent conclusions seem to be that although selected infants may respond well to iNO, this response seems to be variable or temporary.[44,45] In consequence, iNO is usually used as an adjunct to conventional mechanical ventilation and HFOV while preparing for extracorporeal membrane oxygenation (ECMO) cannulation.

ECMO is a life support system used in the treatment of CDH when conventional mechanical ventilation fails. ECMO employs partial heart–lung bypass providing rest to the lungs for long periods of time during which it is hoped that the lung and pulmonary vasculature will mature. The evidence supporting the use of ECMO is conflicting,[46] although some evidence seems to support the use of ECMO in selected cases.[47,48] Several centers advocate the use of ECMO only in patients with evidence of a 'honeymoon period', i.e. patients with adequate gas exchange for a period preceding the deterioration in respiratory status. Others use preductal blood gases, where only patients with a period of normal preductal pO_2 and pCO_2 will be considered for ECMO.[38] It has recently been suggested that the late implementation of ECMO may lead to reperfusion injury, which causes reduced survival, and that ECMO intervention prior to reaching the cut-points may improve survival in CDH patients.[46]

Since some studies suggest surfactant deficiency in CDH infants, surfactant replacement has been tried as an adjunct to conventional mechanical ventilation or ECMO. The only randomized clinical trial using surfactant in CDH tested 17 infants >34 weeks' gestation who were already on ECMO.[49] The results suggest that postnatal surfactant deficiency may be more persistent in CDH infants than non-CDH infants on ECMO; however, the study showed no improvement with surfactant treatment. Thus, surfactant administration may not be without risk and the benefits still remain unclear.[38]

Several novel therapies of ventilation are in evolution, some of which have been tried in CDH infants. Partial liquid ventilation has been shown to be beneficial in some cases, and some preliminary promising results have been obtained by the use of intratracheal pulmonary ventilation (ITPV).[50] Both of these methods provide efficient ventilation, while apparently protecting the lung against barotrauma. However, none of these methods can improve the fundamental problem with the CDH lung, i.e. hypoplasia, and therefore share the shortcomings of ECMO treatment.

Appropriate fluid management, as well as the use of inotropic agents, is crucial in the treatment of CDH. Adequate sedation and pain management should be used, but the use of paralysis is controversial. Surgery should be performed when the infant is stable with minimal ventilator settings, is diuresing well, and the chest x-ray is improving.

Operative repair

The most straightforward part of the management of CDH is operative repair of the diaphragmatic defect (Fig. 36.2). The most commonly preferred approach is abdominal, offering good exposure, easy reduction of the abdominal viscera, and recognition and correction of associated gastrointestinal anomalies.[50] The contents of hernia are gently reduced in the abdomen. On the right side, the small intestine and the colon are first reduced and the liver is withdrawn last. After the hernia is reduced, an attempt is made to visualize the

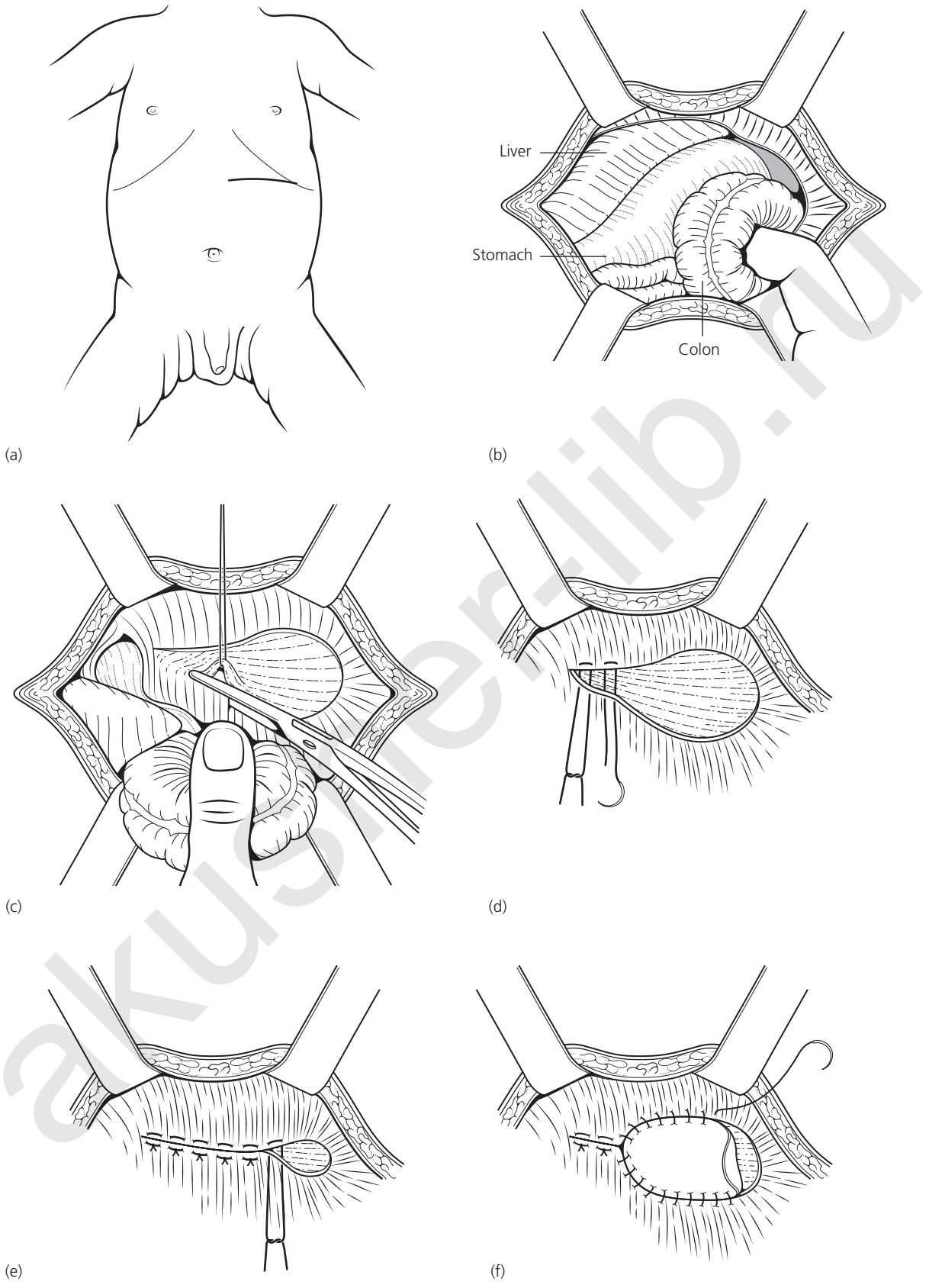


Figure 36.2 Operative repair of congenital diaphragmatic hernia (CDH). (a) A subcostal transverse muscle cutting incision is made on the side of the hernia. (b) The contents of hernia are gently reduced in the abdomen. (c) After inspecting diaphragmatic defect, posterior rim of the diaphragm is mobilized by incising the overlying peritoneum. (d, e) The defect is then closed by interrupted non-absorbable sutures. (f) Large diaphragmatic defect is closed by using Surgisis soft tissue graft.

ipsilateral lung. Most diaphragmatic defects can be sutured by direct sutures of the edges of the defect. Although the anterior rim of the diaphragm is usually quite evident, the posterior rim may not be immediately apparent and may require dissection for delineation. There is usually a layer of peritoneum running from the retroperitoneum over the lower edge of the defect. Division of this tissue usually allows visualization of the posterior edge of the diaphragm. The defect is closed by interrupted non-absorbable suture.

Sometimes, the posterior rim is absent altogether, in which case the anterior rim of the diaphragm is sutured to the lower ribs with either periosteal or pericostal sutures. In some cases, the defect is too large for primary closure, and prosthetic material is used. Currently, the most commonly used prosthetic material is Surgisis® soft tissue graft, which is incorporated into the adjacent tissue (Fig. 36.2f). An alternative to this approach is a muscle flap taken from the transversus abdominus, leaving the outer abdominal muscle layers intact. This technique should not be performed on patients on ECMO, or at risk of ECMO treatment, because of the risk of hemorrhagic complications. It also should be noted that the operations involving muscle flaps are too long and complex for critically ill patients and can lead to unsightly chest deformities. If the abdominal cavity is small, gentle stretching of the abdominal wall will enable safe closure in most patients. Whether a chest drain should be inserted prior to closure is controversial. The argument against the use of chest drain is in avoidance of barotraumas as it increases the transpulmonary pressure gradient.

Minimally invasive surgery has been argued to reduce the trauma and physiological disturbance of surgery. As endosurgical repair of CDH gains popularity, a systematic review and meta-analysis have recently observed that neonatal thoracoscopic CDH repair has greater recurrence rates and operative times, but similar survival and patch usage compared with open surgery.[51]

Postoperative treatment

Postoperative care should be performed in the same manner as preoperatively, with a close watch on fluid management, ventilatory support, and hemodynamic monitoring.[52] Some infants show improvement in oxygenation in the 'honeymoon period', but usually deteriorate 6–24 hours later. This deterioration is due to pulmonary hypertension and persistent fetal circulation with an increase in pulmonary artery resistance, elevated pulmonary artery pressure, and right-to-left ductal and preductal shunting leading to hypoxemia. Pulmonary hypertension is probably caused by multiple factors, such as increased abdominal pressure with impaired visceral and peripheral perfusion, limited diaphragmatic excursion, overdistension of the alveoli in the hypoplastic lungs with diminished alveolar-capillary blood flow, release of vasoactive cytokines, and deterioration in pulmonary compliance after surgical repair. Sudden deterioration in the patient's oxygenation status should raise the suspicion of pneumothorax. Infection complications including pneumonia and septicemia are not uncommon.

PRENATAL TREATMENT

A prenatal intervention that can reverse the lung hypoplasia might theoretically improve prognosis. Fetal surgery, with primary repair of the defect, was shown to be a promising way of dealing with pulmonary hypoplasia in experimental and initial clinical studies.[53,54] However, clinical application of anatomical fetal CDH repair was abandoned once it became clear that it was not possible in fetuses with liver herniation and that those without did not benefit from the intervention.[53,54]

A fetoscopic tracheal occlusion (FETO) was then developed as it became clear from experimental studies that lung growth can also be triggered by tracheal occlusion. The effect on lung growth by tracheal occlusion and retention of pulmonary fluid seems to be exerted by pulmonary stretch itself, which in turn causes upregulation of different growth factors.[55] Vascular endothelial growth factor (VEGF) has been shown to be upregulated by pulmonary stretch, and may contribute to pulmonary growth by increasing angiogenesis.[56] Insulin-like growth factor-I (IGF-I) gene expression is reduced in the lung parenchyma of lambs with surgically created CDH. IGF-I is, however, restored to normal or increased levels after tracheal ligation or postnatal lung distension.[57] A similar method of pulmonary stretch has been tried as a means of inducing postnatal lung growth in CDH infants. The lungs are then continuously distended with perfluorocarbon during ECMO treatment. Experimental as well as initial clinical results are promising.[58]

Sustained tracheal occlusion leads to a decreased number of type II pneumocytes and deficient surfactant production.[59] In sheep, cycles of 47 hours of tracheal occlusion and 1 hour of release yielded sufficient lung growth with normal morphology and type II cell count.[59] As yet, it is impossible to achieve this clinically, but the study proves that timing and duration of the occlusion period are crucial for the quality and response of airways and pulmonary vessels. All this leads us to the concept of tracheal occlusion in the late cannalicular phase with prenatal reversal.[60] Additional interventions such as corticosteroid or surfactant administration may improve postnatal lung function.

FETO has undergone further evolution, and currently a technique using one port, and the endoscopic placement of a tracheal balloon, is used.[61,62] In Europe, Deprest *et al.*[62] have performed FETO procedure percutaneously under epidural anesthesia in an average time of 20 minutes, and they have achieved survival rates of 50% compared to 9% for concurrent non-randomized patients with similar prognostic criteria. In their report, none of the patients has delivered before 37 weeks of gestation, a marked improvement compared to the 33 week average in a previous randomized controlled study in the United States reported by Harrison *et al.*[61] Interestingly, the European group has achieved the best results using balloon deflation by repeat tracheoscopy at 34 weeks gestation.[62] Prenatal release of the occlusion permits vaginal delivery and facilitates delivery closer to home, using standard neonatal therapy. The most common complication of FETO procedure is preterm premature rupture of the membranes (PPROM), which is probably iatrogenic in

nature.[63] PPROM does have an impact on gestational age at delivery and complicates balloon removal.[63] As FETO has the potential of increasing survival and reducing morbidity, this needs to be investigated in prospective randomized trials.

In order to deliver infants with fetal tracheal occlusion, a special method of delivery had to be developed, the *ex utero* intrapartum treatment procedure (EXIT). Cesarean section is performed with maximal uterine relaxation, and while keeping the infant on placental support, the upper airway can be instrumented. This method is useful as a means of delivering infants with other conditions affecting the upper airway as well, e.g. cystic hygroma of the neck or laryngeal atresia.[64]

PROGNOSIS

Although several centers have reported an increased survival rate using novel therapies, including ECMO,[35,44] the fact remains that the hidden mortality rate is high.[65] Since most centers are only aware of the cases that reach their center alive, pre- and perinatal mortality is usually not included. Recent population-based studies have reported that survival rates in CDH are around 55–70%.[1,2] Highly specialized centers report 80% and more, but discount the hidden mortality, mainly in the antenatal period. The high mortality and morbidity in CDH are mainly attributed to pulmonary hypoplasia and persistent pulmonary hypertension.[3,4]

It is of vital importance to recognize variables that predict pre- and perinatal mortality, since they will influence the information given to the family, as well as deciding eligibility to prenatal intervention. First, other lethal malformations, as well as chromosomal aberrations, should be excluded. In isolated left-sided CDH, herniation of the liver into the chest has been shown to be a predictor of high mortality, whereas survival is highly likely if the liver is not herniated into the thorax.[29,66] Furthermore, the LHR has been shown to adequately predict outcome in left-sided, 'liver-up' CDH. In a prospective series, an LHR <1.0 was associated with 100% mortality, whereas all patients with an LHR >1.4 survived.[30] Fetal MRI is a useful tool to measure lung volume and thereby to predict the severity of pulmonary hypoplasia.[31]

Several centers use preductal PaO_2 as a predictor of survival.[35] A study of computer-assisted analysis of the postoperative chest x-ray has been shown to predict pulmonary hypoplasia.[67] However, accurate preoperative predictors are needed in order to avoid placing patients with lethal pulmonary hypoplasia on ECMO.

LONG-TERM OUTCOME

Recent improvement in the treatment of infants with CDH has increased the survival of more severely affected infants. Long-term follow up of those patients has led to the recognition of pulmonary and extrapulmonary morbidities that were not previously recognized. Pulmonary morbidity is the most common and significant problem in CDH infants surviving beyond the neonatal period. Patients treated with ECMO or requiring patch repair of the diaphragmatic defect appear to have a higher risk of developing pulmonary morbidity.[68]

In CDH survivors, the severity of chronic lung disease may require prolonged ventilator support and tracheostomy.[68,69] Several follow-up studies have reported that CDH survivors suffer from recurrent respiratory tract infections in infancy and early childhood.[70,71] Neurodevelopmental abnormalities have been frequently described in CDH survivors. Developmental delay, motor, cognitive and behavioral disorders have been reported in patients with CDH.[72,73] Sensorineural fearing loss (SNHL) represents a peculiar form of neurological sequel in CDH survivors.[72,73] SNHL is found in CDH survivors treated with ECMO and without ECMO, suggesting that the use of ECMO is not the only predisposing factor for SNHL.[74] Because CDH survivors are exposed to a number of other potential predisposing factors, including the use of ototoxic medications and prolonged mechanical ventilations with high oxygen tensions, they are at high risk of developing SNHL.

A significant number of CDH survivors have shown gastrointestinal symptoms, including gastro-esophageal reflux (GER), failure to thrive (FFT, defined as weight <25th or 5th centile), and late bowel obstruction.[75,76] A review of the incidence of GER among CDH patients in different studies has suggested that nearly 40% of babies operated on for CDH will have symptomatic GER, half of which require antireflux surgery.[77] The most frequently reported predictor of antireflux surgery is the need of diaphragmatic patch repair.[68,78] Recurrence is more common in patients repaired with a prosthetic patch. Although most survivors beyond the neonatal period are able to lead a normal life, children with CDH should be followed up and assessed for respiratory status until adolescence.

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Extracorporeal membrane oxygenation for neonatal respiratory failure

JEFFREY W GANDER AND CHARLES JH STOLAR

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a life-saving technology that uses partial heart/lung bypass for extended periods of time. It is a supportive modality, rather than a therapeutic tool, that provides gas exchange and perfusion for neonates with an acute, reversible respiratory or cardiac condition. During the time on ECMO, the patient's cardiopulmonary system is allowed to 'rest', thus being spared from the potentially deleterious effects of high FiO_2, high airway pressure, traumatic mechanical ventilation, and perfusion impairment. ECMO was first used in newborns in 1974. Since then, the Extracorporeal Life Support Organization (ELSO) has recorded approximately 28 000 newborns who have been supported with ECMO for a variety of cardiorespiratory disorders. The most common disorders in the newborn treated with ECMO are meconium aspiration syndrome (MAS), persistent pulmonary hypertension of the neonate (PPHN), congenital diaphragmatic hernia (CDH), sepsis, and cardiac support. Depending on the indication for ECMO, the outcome is varied, but overall, a survival rate of 80% has been reported for newborns treated in this high (>80%) mortality group.[1] This chapter discusses the selection criteria for ECMO in neonates and the management of these babies while on ECMO. It goes on to discuss ECMO for use in difficult clinical scenarios, such as CDH, and finally review outcome and follow up of neonates treated with ECMO.

SELECTION CRITERIA FOR NEONATAL ECMO

The selection criteria for newborns are based on historic experience from multiple institutions, patient safety, and mechanical limitations related to the biomedical devices.

Gestational age

The gestational age should be at least 34 weeks. In the early experience with ECMO, premature infants (<34 weeks' gestation) who were offered ECMO developed significant morbidity and mortality related to intracranial hemorrhage (ICH).[2] Despite refinement of ECMO techniques in the 1980s, premature infants continue to be at risk for ICH. This may be due to the fact that ependymal cells within the brain may not be fully developed in preterm infants, thus making them susceptible to intracranial bleeding. The incidence of ICH appears to be directly related to gestational age. Hardart *et al.*[3] reported a 22% incidence of ICH at 32 weeks versus 12% at 36 weeks. The systemic heparinization necessary to maintain a thrombus-free ECMO circuit also increases the risk of bleeding complications.

Birth weight

The birth weight should be nearly 2000 g as children under this weight present unique anatomical challenges to cannulation due to the limitation of cannula size. The smallest single-lumen ECMO cannula is 8 French (Fr) gauge. Flow through the tube is inversely related to length of the tube as well as directly related to the radius of the tube by a power of 4. If the vein is small, then the cannula will be small, resulting in flow that will be reduced by a 4th power. From historic experience, if the baby weighs less than 2 kg, then the difficulty of the placement of the cannula in conjunction with the inadequate flow from small catheters make ECMO in these small babies challenging.

Bleeding complications

The baby should have no active bleeding or major coagulopathy. Patients with uncorrectable coagulopathy, ongoing

uncontrollable bleeding, or sepsis and its associated coagulopathy are at high risk of bleeding complications while on ECMO. The need for continuous systemic heparin therapy while on ECMO adds to this risk of bleeding.[4] Therefore, prior to initiating ECMO, bleeding should be controlled.

Intracranial hemorrhage

The infant should not have an intracranial hemorrhage. ECMO candidates with a pre-existing intracranial hemorrhage may exacerbate the problem secondary to the use of heparin and altered cerebral blood flow while on ECMO. Infants with small interventricular hemorrhages (grade I–II) may be considered for ECMO on an individual case basis, but these cases should be closely monitored for worsening bleeding. Patients with previous intracranial bleeds, cerebral infarcts, and other risk factors (prematurity, coagulopathy, ischemic central nervous system injury, or sepsis) are particularly at high risk for severe neurologic consequences.[2,5] Pre-ECMO discussion with parents in this circumstance is especially important.

Reversible disease process

The baby should have a reversible lung disease and be supported by aggressive mechanical ventilation for no longer than 10–14 days prior to ECMO. Babies who have had prolonged exposure to high-concentration oxygen and positive-pressure ventilation develop bronchopulmonary dysplasia (BPD).[6] Recovery from this type of irreversible lung injury may take from weeks to months to occur, if at all. Support with ECMO can be beneficial for reversible lung disease over a relatively short period of time (2–3 weeks). However, even a lengthy ECMO course is unlikely to be sufficient to permit recovery of the irreversible fibrotic changes that occur to the lung following sustained barotrauma and/or oxygen toxicity. In addition, with a longer ECMO run, the chance of infection, bleeding complications, thromboembolic events, and mechanical failure increase.

In a retrospective case–control study which reviewed the records of ECMO patients over 66 months, patients with oxygen dependency at one month of age and radiographic evidence of BPD were compared to patients without these findings.[7] Patients with BPD were placed on ECMO at an older mean age than non-BPD patients (135 versus 50 hours old). The BPD group had longer mean ECMO courses as well (203 versus 122 hours). The authors suggest that risk of BPD from high levels of ventilatory support occur with as little as 4 days of assisted ventilation.

Coexisting anomalies

The baby should have no lethal congenital or chromosomal anomalies such as trisomy 13 or 18. ECMO is not intended to delay an inevitable death. Other treatable conditions, such as total anomalous pulmonary venous return (TAPVR) and transposition of the great vessels (TOGV), may initially manifest with respiratory failure. If possible, an echocardiogram should be rapidly obtained to determine the need for ECMO or cardiac surgery.

Bridge to diagnosis

Every effort should be made to establish a clear diagnosis before the initiation of ECMO. However, if that is not possible, then the diagnosis can be established during the course of ECMO. For example, pulmonary vein misalignment, a uniformly fatal anomaly of deficient alveolar capillaries and anomalous veins within the bronchoarterial bundles, presents with symptoms of persistent pulmonary hypertension unresponsive to treatment.[8] These children are often placed on ECMO. If the pulmonary hypertension is intractable despite support by ECMO, then the diagnosis of alveolar capillary dysplasia should be entertained.[9] The diagnosis is made via an open lung biopsy while on ECMO. If alveolar capillary dysplasia is confirmed, then withdrawal of ECMO support should occur. In addition, some important cardiac conditions such as TAPVR, TOGV, and intact septum, may present as respiratory failure, as mentioned above under Coexisting anomalies. These patients are occasionally placed on ECMO before an accurate diagnosis can be made. Once this is established, appropriate therapy should be instituted.

Failure of medical management

The baby must have first failed optimal medical management. This is often the most difficult criterion to elucidate. Different institutions have varying specialties, capabilities, and expertise. 'Optimal' medical management is a subjective term which may vary widely. Current optimal medical management may include pharmacologic support with vasodilator or vasoconstrictive agents, inotropic agents, sedatives, and analgesics. Ventilatory support usually begins with conventional strategies, but may change to include exogenous surfactant administration, induced respiratory alkalosis, hyperoxia, high positive expiratory-end pressure (PEEP), inverse I:E ratios, or high-frequency ventilation. Early use of steroids in the management of respiratory distress syndrome (RDS) has been proposed to decrease pulmonary inflammation, and achievement of metabolic alkalosis may be preferred to respiratory alkalosis.[10] The merits and demerits of all these treatment strategies are beyond the scope of this chapter.

Innovations in medical management have been developed, which have prevented ECMO in patients who otherwise meet the criteria for ECMO support. These innovations in management include high-frequency oscillatory ventilation, permissive hypercapnea with spontaneous ventilation and nitric oxide. In 1985, Wung *et al.*[11] used a non-traditional approach to the management of patients with persistent pulmonary hypertension. Hyperventilation and hyperoxia were not emphasized, and muscle relaxants were not used.

Permissive hypercapnea in conjunction with spontaneous ventilation was employed. In the series of 15 patients, a $PaCO_2$ of 50–80 mmHg and a PaO_2 of 40 mmHg were tolerated and low-pressure ventilator settings were employed to provide adequate chest wall excursion. These patients, who met institutional criteria for ECMO, survived with this medical approach alone.

Other, more objective criteria, have been established to quantify respiratory failure and aid in determining which infants should be placed on ECMO. High-pressure ventilator settings (peak inspiratory pressure (PIP) >40 cmH_2O, PEEP >7 cmH_2O, intermittent mandatory pressure (IMV) >100 and FiO_2 of 1.0) have correlated with mortality. In addition, studies have examined arterial oxygen pressure (PaO_2 <40 mmHg), alveolar-arterial oxygen gradient (A-aDO_2 >625 mmHg for 4 hours), and oxygenation index (OI >40) as predictors of mortality as well.[12–15] However, some have argued that the alveolar–arterial oxygenation gradient and oxygenation index should not be heavily weighted because these factors can be manipulated by ventilator settings.

CLINICAL MANAGEMENT OF NEONATES ON ECMO

Veno-venous versus veno-arterial ECMO

A decision is first made whether the infant would best be served with veno-venous (VV) or veno-arterial (VA) support. VV support delivers oxygen for respiratory indications. VV ECMO can be performed through a double-lumen catheter which is placed in the right internal jugular vein. The double-lumen catheter both drains deoxygenated blood and returns oxygenated blood to the right atrium. Double-lumen catheters of 12–15 Fr gauge are commonly used in the newborn. Bi-caval dual lumen cannulas have recently been designed for neonates. Deoxygenated blood is drained both proximally and distally on the cannula from the superior vena cava and inferior vena cava, respectively, and oxygenated blood is delivered through a single opening directed towards the tricuspid valve. These cannulas are constructed with Elast-Eon®, a combined polyurethane elastomer and silicone gel, which makes them resistant to kinking and thus improves flow characteristics. This is the primary advantage over the traditional VV cannulas which are prone to kinking. However, clinical outcomes between these two cannulas have not been studied.

As opposed to VV ECMO, VA ECMO not only delivers oxygen for respiratory failure but also provides circulatory support in the event of cardiac failure, difficulty weaning from cardiopulmonary bypass, or occasionally CDH anatomy. In these cases, VA support is provided by venous drainage of the right atrium through a cannula inserted in the internal jugular vein (Fig. 37.1). Oxygenated blood is returned through a cannula in the carotid artery. Patients who present with profound lactic acidosis, hypoxic ischemia, and end organ failure often have a component of cardiovascular collapse and may also require the circulatory support of VA as opposed to VV ECMO.

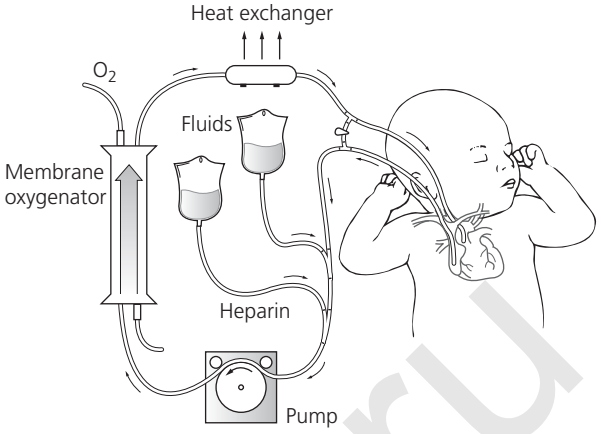

Figure 37.1 Schematic of completed veno-arterial extracorporeal membrane oxygenation (ECMO) circuit. Extrathoracic cannulation of the right atrium and ascending aorta allows venous drainage to a servo-controlled valley pump and arterial return directly to the heart and brain. Oxygenation and CO_2 removal is provided by a non-porous silicone membrane oxygenator. The blood is rewarmed before returning to the infant. All parenterally administered substances, such as heparin, fluids, blood products, and drugs are given directly into the circuit.

Cannula management

The preferred site for cannula placement is in the vessels of the right neck. The reason for this is that the femoral vessels are too diminutive for cannulation in a neonate. The internal jugular vein is accessed via an open procedure. During the open procedure, muscle relaxants are given to prevent the inadvertent aspiration of air into the vein. In the event of VA ECMO, the carotid artery is dissected and identified for catheter placement. After placement of the catheters and initiation of ECMO flow, the catheters are carefully secured with sutures to the blood vessel and skin (Fig. 37.2).

The position of the catheter is confirmed in two ways. First, a chest radiograph is performed, which can grossly demonstrate catheter position. The tip of the venous cannula should be located within the right atrium, while the tip of the arterial cannula should be located in the ascending aorta. The second mode of confirming cannula placement is cardiac echocardiography. The double-lumen catheter should be visualized within the right atrium, venting the return oxygenated blood through the tricuspid valve to minimize recirculation. If there is persistent difficulty maintaining flow due to poor venous withdrawal, the possibility of a catheter problem must be entertained and further imaging should be performed to confirm the proper position.

Prime management

The tubing of the ECMO circuit is initially circulated with carbon dioxide gas. This is followed by the addition of crystalloid and 25% albumin solution. The albumin coats the tubing to decrease its reactivity to circulating blood. The carbon dioxide gas dissolves into the fluid. Approximately 2 units of packed red blood cells are required for initial priming

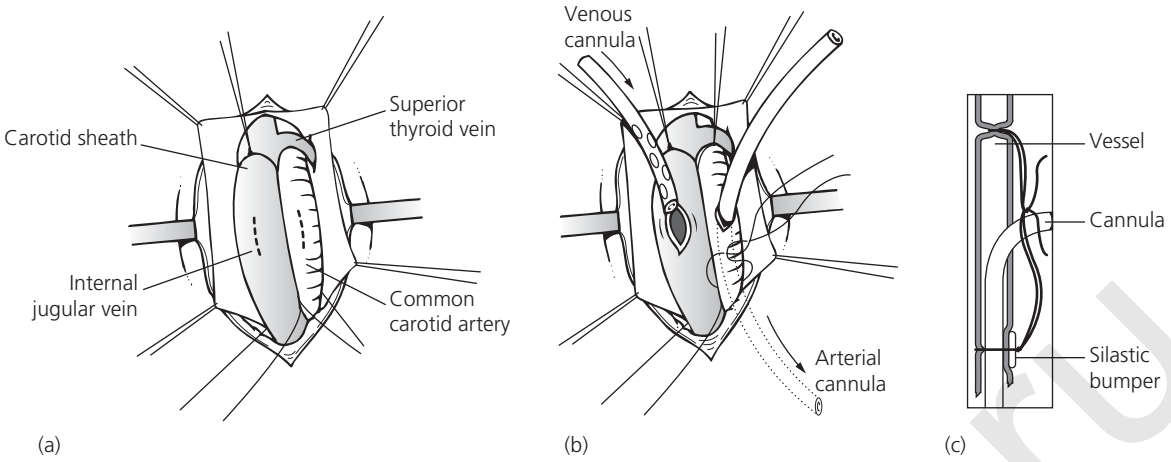

Figure 37.2 Details of the cannulation procedure. (a) The carotid sheath is opened with the sternocleiodomastoid muscle retracted laterally. This exposes the common carotid artery and internal jugular vein. (b) The infant is anticoagulated after the vessels are dissected and then ligated cephalad. A 10 Fr arterial cannula is passed into the ascending aorta by an arteriotomy. A 12–14 Fr venous cannula is passed into the right atrium by the venotomy. (c) The cannulas are fixed in position by ligation over a Silastic® bumper to facilitate removal. The two ligatures on each vessel are then tied together. After the incision is closed, the cannulas are also sutured to the mastoid process and connected to the ECMO circuit.

of the pump, which displaces the crystalloid and colloid in the circuit. One gram of calcium gluconate is added to minimize arrhythmias once going onto ECMO. Sodium bicarbonate and heparin are added to the circuit as well.

The initial pH, oxygen content, and carbon dioxide content of the circuit are then measured and adjusted to physiologic parameters. If the prime blood is acidotic, this may exacerbate the infant's condition; or, if the primed circuit has a low carbon dioxide content, this may cause metabolic problems for the neonate. Additionally, a heat exchanger warms the prime to normal body temperature. In summary, the primed circuit must be physiologically compatible with life prior to initiating ECMO to maximize support and prevent initial worsening of the child's condition.

Pump management

The goal of ECMO is to maintain adequate pump flow, which will result in good oxygen delivery to the tissues and organs. Oxygen delivery to the infant is dependent on the speed or rotations per minute (r.p.m.) of the roller pump as it non-occlusively propels the volume of blood in the 'raceway' (tubing within the roller pump housing). With VA ECMO, adequate perfusion and oxygen delivery can be monitored by the pH and PO_2 of a 'mixed venous' blood sample (pre-oxygenator blood sample). The flow of the roller pump should be adjusted to maintain a mixed venous PO_2 of 37–40 mmHg and saturation of 65–70%. With VV ECMO, the 'mixed venous' sample may not be a reliable indicator of perfusion as recirculation may produce a falsely elevated PO_2. Therefore, other indicators of poor perfusion should be followed: persistent metabolic acidosis, oliguria, seizures, elevated liver function tests, and hypotension. If oxygen delivery is found to be inadequate, then the r.p.m. of the pump may need to be increased to improve perfusion.

Roller pumps roll against the tubing to propel the blood towards the oxygenator. This area of contact is at risk for tubing rupture over time. To reduce the risk of rupture, the 'raceway' is advanced regularly after temporarily stopping the pump flow. Tubing rupture is a rare event, less than 1% of ECMO runs per year, due to modern materials such as Supertygon® (Norton Performance Plastics Corporation, Akron, OH, USA), a chemically altered polyvinyl chloride (PVC).[1]

Oxygenator management

The silicone membrane (envelope) oxygenator (Avecor, Minneapolis, MN, USA) is critical to the success of ECMO and long-term bypass. The mechanism of gas exchange occurs when blood in the tubing enters a manifold region and is distributed around the envelope of a silicone membrane lung. Oxygen flows through the inside of the membrane envelope in a countercurrent direction to the flow of blood. Oxygen diffuses across the silicone membrane into the blood as carbon dioxide is eliminated. The oxygenated blood drains into a manifold and is returned to the infant via a heat exchanger.

A thrombus may form in the oxygenator over time. As a thrombus extends, the membrane surface area is decreased, resulting in decreased oxygen and carbon dioxide transfer. This can lead to increased resistance to blood flow. The gaseous portion of the oxygenator may also develop obstructions, which may lead to air emboli. Long-term use may wear the silicone membrane, resulting in blood and water in the gas phase.

Most ECMO circuits measure a pre- and post-oxygenator pressure. The difference in these two pressures, the ΔP, can help determine when an oxygenator is failing. An elevated pre-oxygenator pressure with a stable post-oxygenator pressure, thus elevated ΔP, likely means that there is an obstruction to

blood flow in the oxygenator, often from thrombus. There is no absolute ΔP value that mandates replacement of an oxygenator. However, a rapid increase in this value with the anticipation of continued ECMO support should alert the practitioner to the need for replacement of the oxygenator. In addition, a larger oxygenator may also be required if the gas and blood flow rating of the old oxygenator are exceeded in order to maintain adequate perfusion.

Some centers have begun to use hollow-fiber oxygenators, such as the QuadroxD® oxygenator (Jostra Medizintechnik AG, Hirrlingen, Germany) for neonates. The oxygenator uses less priming volume (250 mL) and has a smaller surface area. The decreased surface area allows for more efficient gas exchange and reduces the potential for thrombus formation.[16] In addition, the resistance across the oxygenator is smaller than the silicone oxygenator, less than 100 mmHg. This may cause less disruption of red blood cells.

Volume management

While on ECMO, maintenance fluids for a term newborn under a radiant warmer are estimated to be 100 cc/kg/day. Water loss through the oxygenator may approach 2 cc/m^2/hour. For a baby weighing 3 kg, this would be about 10 cc/day. Fluid losses from urine, stool, chest tubes, nasogastric tubes, ostomies, mechanical ventilation, radiant fluid loss, and blood draws should be carefully recorded. Fluid management may become difficult in the baby on ECMO as fluid extravasates into the soft tissues during the early ECMO course. Therefore, meticulous recordings of the net fluid balance on ECMO should be maintained. Classically, the weight increases in the first 1–3 days as the patient becomes increasingly edematous. On the third day of ECMO, diuresis of the excess edema fluid begins, and can be facilitated with the use of furosemide. This diuretic phase is often the harbinger of recovery. In the event of renal failure on ECMO, hemofiltration or hemodialysis can be added to the ECMO circuit for removal of excess fluid and electrolyte correction. In a retrospective comparison of neonates on ECMO, use of hemofiltration was associated with shorter duration on ECMO and time on mechanical ventilation.[17]

Respiratory management on ECMO

Once the desired oxygen delivery is attained, the ventilator should be promptly weaned to avoid further oxygen toxicity and barotrauma. Such 'rest settings' have been studied and debated.[18] At the authors' institution, the FiO_2 is decreased to 0.21, PEEP to 5 cmH_2O, PIP to 20–25 cmH_2O, a rate of 12 breaths/minute and inspiratory time of 0.5 seconds if the infant's arterial and venous oxygenation are adequate.

If the baby remains hypoxic despite maximal pump flow, then higher ventilator settings may be temporarily required. Alternatively, hypoxic neonates on VV ECMO may need to be converted to VA ECMO for full cardiorespiratory support. On occasion, the chest x-ray will worsen in the first 24 hours independent of ventilator settings and improve after diuresis. As the patient improves on ECMO and the pump flow is weaned, ventilator settings are then modestly increased to support the baby off ECMO. In neonates, if the oxygen saturation is greater than 93%, the authors consider an FiO_2 of 0.4, PIP <28, PEEP of 5, and a rate <30 as adequate settings for a trial off ECMO.

In addition, during the course of ECMO, pulmonary toilet is essential to respiratory improvement and includes gentle chest percussion and postural drainage. Special attention should be made to the ECMO catheters and keeping the head and body aligned. Endotracheal suctioning is also recommended every 4 hours and as needed based on the amount of pulmonary secretions present.

Medical management

After the initiation of ECMO, vasoactive medications should be quickly weaned if the blood pressure remains stable. In the event of seizures, phenobarbital is usually given and maintained to prevent further seizures. In addition, gastrointestinal prophylaxis with an H_2-blocker, such as ranitidine, is instituted. Fentanyl and midazolam are usually administered for mild sedation, however the use of paralytics should be avoided. The baby's muscle activity is not only important for fluid mobilization of edema, but also for monitoring of neurologic activity.

At our center, infectious prophylaxis is provided by cefazolin, if no other antibiotics have been started. However, many neonates who are placed on ECMO are already on broad-spectrum antibiotics.

Due to the cannula and manipulation of the circuit at stopcocks, the risk of infection is a constant concern; therefore, strict observance to aseptic technique when handling the ECMO circuit should be maintained. Routine blood, urine, and tracheal cultures should be obtained to monitor for infection.

The caloric intake on ECMO should be maximized using standard hyperalimentation. For a newborn, total parenteral nutrition (TPN) should be started at 100 kcal/kg/day. Normally, this should be supplied as 60% carbohydrates (14.6 g/kg/day) and 40% fat (4.3 g/kg/day). Intralipid infusion may be used as a fat source, although there is some controversy with its use in the setting of severe lung disease. As a result, the percentage of fat in the hyperalimentation may be lowered. Amino acids may be added but must be considered in the setting of poor renal function and increasing blood urea nitrogen (BUN) levels. With normal renal function, approximately 2.5 g protein/kg/day should be provided in the TPN mixture.

Enteral nutrition is gaining acceptance in some centers. Initial concerns with feeding enterally on ECMO were that there was inadequate gut perfusion from the initial insult, which could lead to necrotizing enterocolitis when feeding was begun.[19] However, a retrospective study of 67 neonates supported with VA ECMO who were fed enterally, did not show any significant adverse effects.[20] While septic complications of enteral feeding appears to be low, many of these patients will have a gastrointestinal ileus. Of the previously mentioned 67 neonates, 21% had enteral feeding temporarily discontinued due to high gastric residuals.

Electrolytes should be closely monitored with potassium, calcium, and magnesium repleted as necessary. Sodium and phosphorus are usually not repleted as they are often provided in blood products and volume expanders.

Coagulation management

While on ECMO, the baby's hemoglobin is maintained at 15 g/dL to maximize the oxygen-carrying capacity of the blood. Platelet destruction during ECMO is anticipated and is secondary to the flow through the oxygenator and exposure to plastic surfaces. The platelet consumption should not exceed 0.5–3 units/day in neonates. In order to reduce the risk of bleeding during ECMO, the platelet count should be kept above 100 000/mm.[21] The authors recommend using 'hyperspun/concentrated' platelets to avoid the excess administration of fluid, and thus preventing further problems with volume overload and edema.

Heparin is initially administered as a bolus (100 units/kg) followed by a constant heparin infusion (30–60 units/kg/hour) to maintain a thrombus-free circuit. The level of anticoagulation is monitored by the activated clotting time (ACT). The heparin infusion is adjusted to maintain an ACT of 200–240 seconds. After decannulating, the heparin infusion is stopped and not reversed with protamine sulfate.

COMPLICATIONS ON ECMO

Mechanical complications

While hypovolemia is an important cause for poor venous return to the circuit and subsequent poor pump flow, other causes must be eliminated prior to volume infusion. These may include small venous catheter diameter, excessive catheter length, catheter kinks, improper catheter position, insufficient hydrostatic column length (i.e. patient height), and improper calibration or set up of the venous control module system. In addition, pneumothorax, cardiac tamponade, and abdominal compartment syndrome may need to be considered if there is no readily appreciated mechanical reason for poor venous return. After these causes have been excluded, small amounts of isotonic fluid (5–20 cc/kg) may then be introduced into the circuit to support higher pump flow rate. However, a large amount of volume infusion in conjunction with long-term muscle relaxants and venodilators can lead to anasarca, which in turn, can lead to poor chest wall compliance, compromised gas exchange and oxygen delivery. In some conditions, such as sepsis, there may be endothelial damage and capillary leakage, in which case anasarca may be unavoidable.

Neurologic complications

The most serious complications of the ECMO patient have been neurologic (e.g. learning disorders, motor dysfunction, cerebral palsy) and appear to be due to hypoxia and acidosis prior to ECMO. During the ECMO course, frequent neurological examinations should be performed, and paralytic agents should be avoided. The examination consists of evaluation of alertness and interaction, fullness of the fontanelles, reflexes, tone, spontaneous movements, eye findings, and presence of seizures. Intracranial hemorrhage is the most devastating complication on ECMO. Therefore, careful attention must be made to the rate of ECMO flow, rate of exchange of PCO_2, fluctuations in the ACT, and platelet count. Cranial ultrasounds should be performed every day to monitor ICH and after any major event, such as equipment malfunction, sudden worsening in oxygenation status, and pneumothorax. Electroencephalography (EEG) may also be helpful in the neurologic evaluation of the neonate.

Renal complications

Infants on ECMO may sustain acute tubular necrosis (ATN) marked by oliguria and increasing BUN and creatinine levels. ATN may extend into the first 24–48 hours of ECMO before improvement in urine output is seen. If the renal condition does not improve, poor tissue perfusion should be considered. A combination of inadequate ECMO flow rate, low cardiac output, and intravascular volume depletion from diuresis may lead to decreased renal function. If the infant remains in complete anuric renal failure and requires dialysis, a hemofiltration module can be added in series to the ECMO circuit to remove excess fluid and stabilize electrolyte abnormalities.

WEANING FROM ECMO

As the patient improves during the ECMO course, the flow of the circuit is weaned, based on improving postductal arterial and venous oxygenation. Neonates supported with VV ECMO should be weaned using the patient's SaO_2 as the SvO_2 will be artificially high from recirculation. Neonates supported with VA ECMO should be weaned using the patient's SvO_2. From starting flows as high as 150 cc/kg/minute, the flow is decreased to 30–50 cc/kg/minute while maintaining adequate perfusion. The ACT should be maintained at a higher level due to the lower flows to prevent thrombosis. If the baby tolerates the low flow, then the ECMO cannula (VV) or cannulas (VA) may be clamped while the ECMO circuit recirculates. The authors prefer to wean patients onto moderate conventional ventilator settings, i.e. IMV 20, FiO_2 0.4, PIP 25, and PEEP 5. Higher ventilator settings, though, may be tolerated if the risks of continuing ECMO outweigh those of discontinuing ECMO.

If the recirculation is tolerated, then decannulation is performed. As with the insertion, decannulation should be performed as a sterile surgical procedure. The patient should be placed in the Trendelenburg position and muscle relaxants should be administered to prevent air aspiration into the

vein. Prior to decannulation, vasoactive medication and hyperalimentation should be switched from the ECMO circuit to other vascular access. Once the catheter is removed, the vein is ligated and not repaired. This is also true for the artery in the case of VA ECMO.

ECMO IN INFANTS WITH CONGENITAL DIAPHRAGMATIC HERNIA

Neonates with CDH have abdominal viscera in the thoracic cavity, most commonly on the left side. This often leads to significant pulmonary hypoplasia and pulmonary hypertension. Pulmonary insufficiency can ensue, leading to hypoxemia, hypercarbia, and acidosis soon after birth; this can then lead to a vicious cycle of pulmonary vasospasm, pulmonary hypertension, right-to-left shunting of blood and worsening hypoxemia, hypercarbia, and acidosis. This cycle must be broken, if not medically, then with the assistance of ECMO. Medical management has improved greatly with the use of pulmonary vasodilators, such as tolazoline and inhaled nitric oxide.

If a fetus is antenatally diagnosed with a CDH, plans should be made for delivery in a medical center with ECMO capabilities in case of potential rescue therapy. There is no surgical indication or benefit to early delivery by Cesarean section. In the delivery room, intubation should be performed immediately after birth. The baby should then be transferred to a neonatal intensive care unit and started on mechanical ventilation to stabilize oxygenation and hemodynamics.

In the past, newborns with CDH have undergone repair as a surgical emergency. However, respiratory mechanics frequently worsen postoperatively, perhaps as a result of early repair.[22] In the 1980s, however, surgeons reported improved results with delayed surgery after postnatal medical stabilization.[23–28] A strategy of delayed repair in CDH patients after stabilization of respiratory and hemodynamic parameters with or without ECMO is the current standard of care.

Patient selection of newborns with CDH for ECMO support is particularly difficult. Neonates with CDH who present with overwhelming pulmonary hypoplasia that precludes gas exchange should not be offered ECMO. This group is characterized by the inability to attain a PaO_2 of 100 on an FiO_2 of 1.0 or a $PCO_2 < 50$. Their degree of pulmonary hypoplasia is incompatible with life and they would not be able to be weaned from ECMO. Appropriate candidates for ECMO will go through a 'honeymoon' period where they will maintain a $PaO_2 < 100$ on FiO_2 of 1.0 or a $PaCO_2 > 50$ for a period of time. Should they develop sustained hypoxemia ($PaO_2 > 40$), acidosis (pH > 7.2) or an alveolar arterial oxygen gradient < 600 for 10 hours, then ECMO should be instituted. This period of adequate gas exchange followed by deterioration suggests that these patients have a degree of reversibility of their pulmonary hypertension. Applying this criteria, 85% patients with a CDH supported on ECMO survived to discharge.[29]

OUTCOME AND FOLLOW UP OF NEONATES TREATED WITH ECMO

Mortality

Mortality statistics for neonates supported by ECMO are increasing according to the ELSO registry.[1] It is reasonable to extrapolate that improvements in ventilator strategies have increased the severity of illness of neonates placed onto ECMO. Severe respiratory failure from pulmonary hypertension has been a major cause for return hospitalization and late deaths, but mortality has remained specific to the primary diagnosis prior to ECMO.[1] For example, ECMO patients with the diagnosis of CDH have about a 50% mortality rate while the diagnosis of meconium aspiration syndrome has a mortality rate of about 5%.[1,30] For all diagnoses, the mortality rate for newborns placed on ECMO is about 20%.[1]

Of the infants who die on ECMO, about half die from severe bleeding complications. Another risk factor for mortality is a birth weight of < 2 kg. A retrospective study reviewed 300 newborns supported with ECMO, and the infants who weighed < 2.5 kg, although meeting the criterion of 2 kg, had a relative mortality risk of 3.45% compared to ECMO neonates with birth weights > 2.5 kg.[31]

Feeding and growth sequelae

After decannulation from ECMO, an important factor affecting neonatal intensive care unit (NICU) discharge is initiation of successful enteral feeding. Feeding problems have been reported in as many as one-third of ECMO-treated infants and varies in presentation.[32–34] These problems are due to a variety of possible causes which include interference from tachypnea, generalized central nervous system (CNS) depression, poor hunger drive, soreness in the neck from the surgical procedure, sore throat from intubation, poor oral–motor coordination, and manipulation or compression of the vagus nerve during the cannulation procedure.[34,35] Feeding problems also differ according to pre-ECMO diagnosis. For example, infants with CDH have a higher incidence of feeding difficulty than infants with MAS and RDS.[35–37] The CDH infants often have foregut dysmotility which leads to significant reflux, delayed gastric emptying, and feeding difficulties. Respiratory compromise and severe chronic lung disease also interfere with feeding. These babies may require prolonged nasogastric feeding or even a gastrostomy, fundoplication, and pyloroplasty to maintain adequate growth. However, ECMO infants generally do not have major long-term feeding complications.

Although normal somatic growth is most commonly reported, ECMO-supported children are more likely to experience problems with growth than normal controls. Head circumference below the 5th percentile occurs at a higher rate (10%) in post-ECMO children. Furthermore, poor head growth is associated with a major handicapping condition with a risk greater than 75% at five years of age.[38]

Although controversial, there have also been reports of macrocephaly, which follows a pattern of venous obstruction secondary to internal jugular vein ligation observed on neonatal neuroimaging.[38,39] Growth problems are most commonly associated with ECMO children who had CDH or residual lung disease.[36]

Respiratory sequelae

Significant respiratory problems are reported in ECMO survivors during the first two years of life, with a high rate of rehospitalizations for pulmonary conditions.[40,41]

Approximately 15% of infants supported with ECMO require oxygen at 28 days. By the age of five years, ECMO children were twice as likely to have a reported case of pneumonia as control children (25 versus 13%). Approximately half of the ECMO children with pneumonia were hospitalized compared to none of the control cases. Half of the cases of pneumonias in ECMO children occurred before one year of life compared to none in the control group. In addition, more than half of the ECMO rehospitalizations for pneumonia occurred within the first six months of life.

Of the ECMO-treated neonates, the primary diagnosis of CDH, in particular, has been found to be associated with chronic lung disease, defined by the need for bronchodilators, diuretics, or supplemental oxygen for the management of pulmonary symptoms. Specifically, the use of supplemental oxygen at discharge from the hospital has been reported in 22–80% of CDH patients.[37,42–44] Aggressive ventilator management and lung injury prior to initiating ECMO leads these children to develop bronchopulmonary dysplasia. Persistent oxygen requirements are due to pulmonary hypertension.

The age at the time of ECMO, correlating with the amount of time on mechanical ventilation prior to ECMO, is another factor associated with oxygen need past 28 days.[7] Neonates with severe respiratory failure had an 11.5-fold increased risk of bronchopulmonary dysplasia if ECMO was initiated at later than 96 hours of age. In addition, ECMO infants with birth weights of 2–2.5 kg have a greater risk for chronic lung disease than larger ECMO infants.[31]

Neurodevelopmental sequelae

Perhaps the most serious of post-ECMO morbidities is sensorineural handicap. Reports of neurodevelopmental outcome after one year of age have been published from multiple institutions. Among 540 ECMO survivors from 12 institutions, the total rate of sensorineural handicap (cerebral palsy, blindness, hearing impairment) is 6% on average, ranging from 2 to 18%.[38,45–57] Significant developmental delay among ECMO survivors is 9% on average, ranging from 0 to 21%. This is comparable to other critically ill neonates. For example, newborns with extremely low birth weights (<750 g) have a 15% rate of having major sensorineural handicap with 21% testing in the mentally retarded range.[58] Additionally, newborns with PPHN not supported with ECMO have an average sensorineural handicap rate of 23% (range 0–37%) among 162 survivors from eight institutions.[59–66]

At five years of age, 50% of children supported with ECMO as neonates had a normal neurologic outcome as defined by lack of a developmental delay, epilepsy, or cerebral palsy.[67] The remaining children had varying degrees of disability, most not being severe. The authors also found that low gestational age and low birth weight were significantly associated with a negative neurologic outcome. This further supports the notion that pre-existing factors contribute to negative neurologic outcomes rather than ECMO itself.

The underlying diagnosis prior to going onto ECMO may have a significant contribution to cognitive development. At an average age of 31 months at follow up, children with CDH supported by ECMO were more likely to have an abnormal cognitive status when compared to non-CDH ECMO survivors. Male gender and maternal education were also seen as risk factors.[55]

Auditory deficits are reported in more than 25% of ECMO neonates at the time of discharge.[68] The majority consists of mild–moderate deficit by brainstem auditory evoked response (BAER) testing which generally resolve over time. These auditory deficits may also be partly iatrogenic due to alkalosis secondary to furosemide administration or gentamicin ototoxicity. As a result, hearing screening is recommended at the time of NICU discharge. Examining data for 313 ECMO children from five centers shows an overall rate of 9% (range 4–21%).[38,50,52,54] This rate is not higher than that reported for non-ECMO PPHN children (23%, range 0–37%).[59–62]

Visual deficits in ECMO neonates are usually due to the immature retina in premature patients. This is uncommon in ECMO neonates weighing more than 2 kg. Concern about retinopathy of prematurity due to the hyperoxic condition of ECMO has not been borne out. Haney *et al.*[69] reported ocular findings in 16 of 85 ECMO neonates. These findings included vascular immaturity, vitreous and retinal hemorrhage, and optic nerve atrophy. However, not all infants were examined in this study and there may have been additional complications. Long-term sequelae were not reported, and non-ECMO controls were not tested.

Seizures, both clinical and electroencephalographic, are widely reported among ECMO neonates, ranging from 20 to 70%.[70–73] However, the timing and type of seizure activity is not consistent. In a group of five-year-old children previously supported with ECMO, only 2% had a diagnosis of epilepsy. Seizures in the neonate are associated with neurologic disease and poorer long-term outcome, including cerebral palsy and epilepsy.[74] According to one study, the handicap rate following neonatal seizures is 8%.[75] A predictive association between abnormal EEG and developmental status has been found, with only 18% of infants having normal EEGs with developmental delays; this is compared to 35% of infants with one abnormal EEG and 58% of ECMO infants with two or more abnormal EEGs.[71]

Neuromotor deficits range from a continuum of reports of mild hypotonia, gross motor delay, and asymmetry, to isolated cases of spastic quadraparesis. Although moderate hypotonia is not uncommon at discharge, it generally

improves over the next four to six months. However, these neuromotor findings are also seen in normal control children.[41] The incidence of severe non-ambulatory cerebral palsy is less than 5%.[38,45,50] These cases are generally accompanied by mental retardation, demonstrating a global insult to the brain. More commonly seen is a mild case of cerebral palsy in up to 20% of children supported with ECMO.

ECMO-supported neonates as a group most commonly function within the normal range.[38,45,47,50–57,76] The rate of major handicap appears to be stable across studies with an average of 11% (range 2–18%).

By the time of discharge, at approximately one month of life, ECMO infants still exhibit signs of general CNS depression, including lethargy, hypotonia, and weak primitive reflexes, an indication of moderate hypoxic–ischemic encephalopathy. By four months of age, ECMO infants typically function in the normal range defined by Bayley mental and motor scales. Residual hypotonia or mild asymmetry persists in about 25%. Mild motor delay usually accompanies the hypotonia. Significant neurological abnormalities and motor deficits (more than 2 s.d. below norm) are found in approximately 10–15% of affected individuals. By three years of age, the rate of handicap appears to be stable, but more subtle handicaps manifest at this age, such as learning disabilities, particularly with language and perceptual functioning.[34,77–79] By five years of age, a diagnosis of mental retardation (IQ <70, delay in social adaptive functioning) becomes more certain. In one five-year group, 11% of individuals studied were diagnosed as mentally retarded, most in the mild range with IQs of 50–70.

For ECMO children who had carotid artery cannulation and ligation, controversy remains over reconstruction of the artery. Baumgart *et al.* reported experience of 84 ECMO children who had carotid ligation and 41 who had right common carotid artery reconstruction.[80,81] Failure of the reanastomosis, defined by $>50\%$ occlusion or no flow, occurred in 25% of procedures. No significant differences were reported for occurrence of grade 3 and 4 hemorrhages, but 60% of the group reanastomosed had moderate to severe abnormalities on EEG, compared to 35% of the non-reconstructed group. Despite this, no differences were reported in the proportion of significant neurodevelopmental delays. An additional study of neonates with CDH supported by ECMO showed a 72% incidence of occluded or highly stenotic right common carotid artery, following reconstruction at two years of age. Similarly to previous studies, there was no significant difference in neurologic development when compared to controls.[82]

SUMMARY

Since the first use of ECMO in neonates in 1974, much has been learned about the treatment of infants with cardiac and respiratory disease. New, less invasive medication and techniques have been developed which have kept numerous babies from ECMO cannulation. Over the years, much has also been learned about ECMO; indications have been expanded and selection criteria honed. Currently, the successful treatment of a variety of neonatal respiratory diseases, such as meconium aspiration syndrome, persistent pulmonary hypertension of the neonate, and severe pneumonia can be achieved. ECMO may also be helpful in neonates with cardiac lesions and difficulty weaning from bypass. Difficult clinical scenarios, such as congenital diaphragmatic hernia and sepsis have also met with success through the use of ECMO. The criteria for ECMO candidates have been slowly fine-tuned to maximize survival rates and avoid unnecessary ECMO in infants with irreversible disease. Such criteria include early gestational age, low birth weight, coagulopathy, intracranial hemorrhage, lethal anomalies, and irreversible lung disease. In summary, any hypoxic infant who has a reversible pulmonary or cardiac condition, who is physically large enough for ECMO, and who has failed maximal medical therapy should be considered for ECMO. Meticulous attention and thorough documentation of each ECMO patient have improved knowledge about ECMO through the ELSO registry. With ECMO as a safety net, new therapies can be developed for this poor surviving group of newborns such that the ultimate success of ECMO will be its discontinuation.

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38

Bronchoscopy in the newborn

STEPHEN M KIERAN AND JOHN D RUSSELL

INTRODUCTION

Bronchoscopy in the newborn is an important diagnostic and therapeutic tool.[1] Diagnosis of congenital laryngotracheal malformations and management of airway complications secondary to prolonged intubation are the two most common indications for pediatric bronchoscopy.[2] Bronchoscopy in children was first performed by Killian in 1895.[3] It was, however, associated with a high rate of complications due to poor visibility through small-diameter bronchoscopes, lack of a satisfactory light source, and difficulty maintaining ventilation during the procedure. Modern Hopkins lens systems' intense yet 'cold' light sources together with modern anesthetic techniques have facilitated safer examination of the airway in the newborn.[4,5] Pediatric flexible bronchoscopy was initiated in the mid 1970s, after Ikeda introduced the flexible bronchofibersope in 1968. Since then newer and smaller instrumentation and the addition of suction channels have enabled the bronchoscopist to examine the airway without significantly distorting the anatomy or the normal physiology and has largely superseded rigid bronchoscopy for diagnostic purposes in the lower airway.[6] The development of the pediatric fiberoptic nasendoscope, while not permitting a view of the trachea or bronchi, has dramatically changed airway endoscopy in the newborn. Infants, with stridor who are otherwise well, can have their larynx and upper airways examined at the bedside or the outpatient clinic. If a diagnosis of laryngomalacia is made, laryngoscopy and bronchoscopy under general anesthesia may not be required. However, the airway control and therapeutic ability of rigid bronchoscopy have not been replaced and it remains an important and potentially life-saving procedure.

RIGID BRONCHOSCOPY

Indications for rigid bronchoscopy

Rigid bronchoscopy can be performed for both diagnostic and therapeutic reasons. (Box 38.1). The commonest causes of stridor and airway obstruction in a neonate are laryngomalacia, subglottic stenosis (both congenital and acquired), and vocal cord paralysis.[7] Less common causes include laryngeal clefts, hemangiomas, and papillomas. Rigid bronchoscopy is the diagnostic procedure of choice in the management of airway obstruction. Most neonates with stridor will have laryngomalacia and can be diagnosed with fiberoptic laryngscopy in an outpatient setting. However, there are three clinical situations where neonates with stridor warrant rigid bronchoscopy: (1) the neonate with severe stridor and significant airway obstruction, who will require urgent bronchoscopy and airway support; (2) the neonate with initially stable but deteriorating stridor; (3) the neonate with mild or moderate stridor but with poor weight gain or difficulty in feeding, apnea, or cyanotic episodes. Adjuvant investigations may suggest a particular diagnosis, e.g. a vascular ring on barium swallow; however, endoscopy is needed to confirm this diagnosis. In neonates with recurrent aspiration rigid bronchoscopy is necessary to rule out a laryngotracheal cleft. Even if pathology is found in the larynx, it is important to complete a systematic assessment as about 70% neonates undergoing rigid bronchoscopy have more than one airway pathology.[4]

Box 38.1 Indications of rigid bronchoscopy

- Foreign body removal
- Evaluation of subglottic and tracheal pathology
- Management of severe upper airway obstruction (to provide a temporary airway and facilitate intubation)
- Management of massive hemorrhage and blood clots
- To remove benign tumors (recurrent respiratory papillomatosis)
- Endoscopic management of strictures, webs, granulation tissue
- Open airway surgery
- Re-expansion of consolidated/atelectatic pulmonary lobes

Instrumentation

A systematic assessment of the neonatal airway should be performed and includes laryngoscopy, tracheoscopy, and bronchoscopy. A wide range of equipment of varying sizes is required including laryngoscopes, bronchoscopes, telescopes, and telescopic forceps. The senior author's preference is for Karl Storz telescopes and the Lindholm–Benjamin laryngoscope. Suspension of the laryngoscope on a Mayo stand is essential for therapeutic procedures, freeing the surgeon's second hand (Fig. 38.1). The components of a modern bronchoscope are (Fig. 38.2):

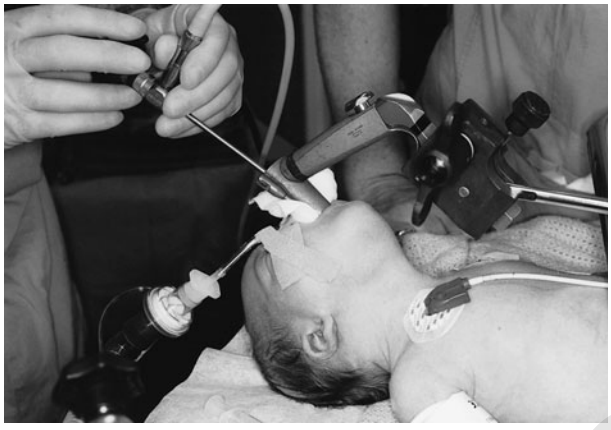

Figure 38.1 Benjamin–Lindholm laryngoscope attached to a Mayo infant is receiving sevoflurane/oxygen via a nasopharyngeal tube.

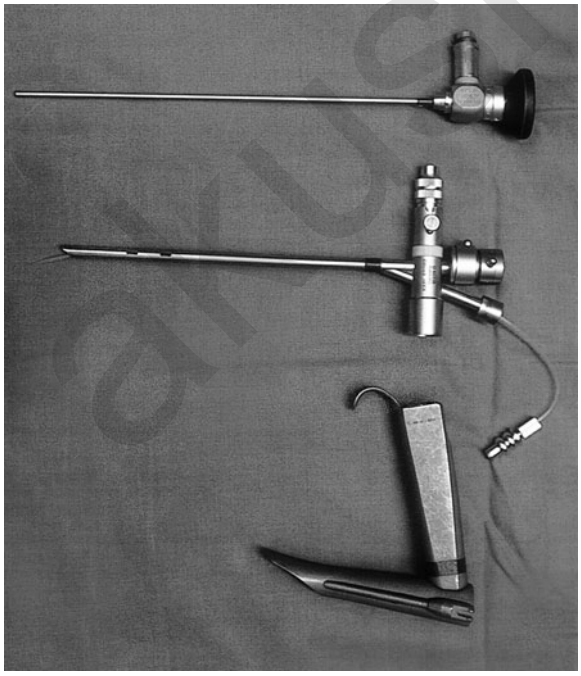

Figure 38.2 Equipment for rigid laryngobronchoscopy: 0° telescope (top); 2.5 mm ventilating bronchoscope (middle); Benjamin–Lindholm laryngoscope (bottom).

1. a closed gas system allowing connection to an anesthetic circuit
2. a rigid Hopkins rod telescope to allow distal illumination and vision
3. a side channel for the passage of suction catheters or flexible forceps.

The bronchoscopes range in size from 2.5 (outside diameter 4.0 mm) to 6.0 (outside diameter 8.2 mm). Sizes 2.5–3.0 are the most appropriate for neonates (Table 38.1).

Table 38.1 Diameter of rigid Storz bronchoscopes for newborns.

Length (cm)	Nominal size (mm)	Internal diameter (mm)	External diameter (mm)
20	2.5	3.2	4.0
20	3.0	4.2	5.0
26	3.0	4.2	5.0
20	3.5	4.9	5.7
26	3.5	4.2	5.0
30	3.4	4.9	5.7

Technique of rigid laryngobronchoscopy

Rigid laryngobronchoscopy requires general anesthesia. Modern techniques are versatile and controlled, allowing an unhurried and complete examination.[8] A full range of neonatal and pediatric laryngoscopes, bronchoscopes, and telescopes are essential. Modern 1 chip and 3 chip cameras allow magnification and excellent resolution of the image on screen of these tiny airways.

A spontaneous respiration technique is the anesthetic method of choice and has superseded transglottic jet ventilation. However, this technique is challenging to the anesthesiologist, requiring a balance as the patient must spontaneously breathe, while sedate enough to not develop laryngospasm or bronchospasm when instrumentation is introduced. Sevoflurane is, in most anesthesiologists' opinion, the anesthetic of choice. It allows a deep plane of anesthesia without causing respiratory arrest. The procedure should proceed in a systematic manner as outlined below.[9]

The neonate is anesthetized with a mixture of sevoflurane and oxygen via a face mask. The patient's chest is not covered with drapes so that respiration can be assessed. The surgeon sits at the head of the bed with the anesthetic machine positioned to the side in such a way that both the surgeon and the anesthesiologist should be able to read the patient's vital signs including oxygen saturation. The camera system's monitor should be positioned over the far end of the bed. The larynx is then briefly visualized using the laryngoscope and topical 4% lidocaine (0.5–2 mg/kg) applied (to prevent laryngospasm). An appropriately sized nasopharyngeal airway is inserted and the anesthetic agent is then provided via this route. Atropine may also be administered to prevent bradycardia and to dry up the secretions during the

assessment. A baby Lindholm laryngoscope is then inserted, by placing its tip in the vallecula, exposing the whole larynx. The scope is suspended on a Mayo table to avoid compression of the baby's chest or held with the non-dominant hand. The larynx is now examined using a 4 mm 0° Hopkins rod laryngeal telescope. Pathological conditions looked for in the larynx include: (1) laryngeal webs, (2) laryngeal cysts, (3) subglottic stenosis, and (4) hemangiomas. The mobility of the arytenoids is then assessed using a blunt laryngeal probe, which also allows palpation for small laryngeal clefts. Once the larynx has been thoroughly examined the telescope is passed into the subglottis and trachea. This allows a complete atraumatic inspection, easily passing to the carina. In order to examine the bronchi in detail one has to remove the laryngoscope and introduce an appropriately sized bronchoscope (Fig. 38.3). Turning the baby's head to the left allows entry through the right main bronchus and turning the head to the right allows entry into the left mainstem bronchus. On both the left and right sides, access to the upper lobe bronchus is the most challenging and may be aided by various dynamic maneuvers including flexing the infant's chin onto the shoulder and external pressure on the chest. The final part of the assessment is to examine the trachea and vocal cords as the baby is lightening up from the anesthetic. This is the only time when tracheobronchomalacia and vocal cord paralysis can be observed.

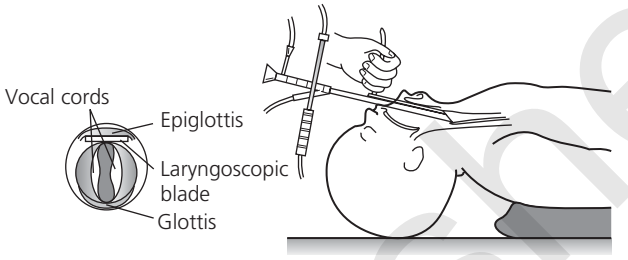

Figure 38.3 Under direct visualization of the larynx, the bronchoscope is introduced into the trachea.

Advantages of rigid bronchoscopy

The major advantage of rigid airway assessment is the excellent control of ventilation provided. This is of particular importance with the soft and collapsible neonatal airway. The rigid bronchoscope can also accommodate instruments, allowing therapeutic interventions to be performed endoscopically. Rigid bronchoscopy allows the lower airways to be inspected safely and in great detail while maintaining control over ventilation. Flexible bronchoscopy does not allow such control and in a small neonate or infant will cause significant, if not total airway obstruction. The image quality obtained by the rigid telescope is also superior to that obtained with the flexible fiberoptic bundles.

Complications of rigid laryngobronchoscopy

Despite the relative safety of modern rigid bronchoscopy, complications still occur with a complication rate of 2–4% reported. Safety is affected by the anesthetic technique (including intraoperative monitoring), the interventions performed during the endoscopy, availability of equipment, the expertise of the staff, and the condition of the patient.[5] Complications reported include laryngospasm, vocal cord trauma, subglottic edema, pneumothorax, pneumonia, hoarseness, hemorrhage, cardiac arrhythmia, and death. In Hoeve *et al.*'s series in 1993, a diagnosis of tetralogy of Fallot, undertaking biopsy or drainage, foreign body extraction, and tracheal stenosis were the main risk factors for complications. Interestingly, fewer complications occurred in the less than three months age group.[10]

FLEXIBLE BRONCHOSCOPY

Flexible bronchoscopy was first performed in the 1970s and since then newer and smaller scopes have enabled visualization of the airway of premature infants and neonates.[11] The advantages of flexible airway bronchoscopy are that examination of the distal lobar bronchi is less challenging than rigid bronchoscopy, that it can be performed as a day patient and requires little preparation except for no oral intake 4–6 hours preoperatively. Provided flexible bronchoscopy is performed by an experienced operator in a controlled setting, the procedure is very safe. Vauthy[6] reports over 10 000 flexible bronchoscopies with no mortality.

Indications for flexible bronchoscopy

Flexible bronchoscopy may be performed for diagnostic reasons in the neonate with mild stridor, unexplained wheezing, hemoptysis, chronic cough, persistent atelectasis, and persistent pulmonary infiltrates (Box 38.2). Flexible bronchoscopy is also increasingly performed in the neonatal intensive care unit (NICU).[12] Flexible bronchoscopy in the NICU can be performed via the existing endotracheal tube or tracheostomy (thus maintaining the airway) and negates the need to transfer the patient to the operating room. The bronchoscope can be used to check the position of the

Box 38.2 Indications for flexible bronchoscopy

Diagnostic
- Unexplained stridor
- Unexplained wheezing
- Hemoptysis
- Unexplained cough
- Persistent atelectasis
- Recurrent or persistent pulmonary infiltrates

Therapeutic
- To aid intubation
- Therapeutic bronchoalveolar lavage
- Brush biopsies
- Removal of airway secretions
- Diagnose and monitor after lung transplantation
- Transbronchial biopsy

endotracheal tube. Sudden respiratory deterioration in the NICU can be due to severe mucous plugging, atelectasis, granuloma formation, tracheitis, or tracheobronchomalacia. In these patients, flexible bronchoscopy may be both diagnostic and therapeutic, allowing careful direction of suction catheters to improve pulmonary toilet. Full-term infants tolerate flexible bronchoscopy with a 3.4 mm scope which has suction channels for insufflation of oxygen, suction and bronchial brushings, or bronchoalveolar lavage. Bronchoalveolar lavage aids the diagnosis of infection, gastro-esophageal reflux (detecting lipid laden alveolar macrophages) and the removal of mucous plugs.[13,14]

Technique of flexible bronchoscopy

Pediatric flexible bronchoscopy can be performed directly through the nose or mouth, via a face mask or laryngeal mask airway as well as through an endotracheal tube.[15] It is the authors' experience that the vast majority of patients require general anesthesia for flexible bronchoscopy. The neonate is placed on the table with the assistant providing oxygen via mask. The average diagnostic procedure lasts approximately 30 seconds and should be digitally recorded, so that the procedure can be reviewed. If performed as a day case post-procedure, the patient should be clinically observed for 1.5 hours and allowed to eat prior to discharge.

Common pitfalls for the unwary flexible bronchoscopist

CONCURRENT LESIONS

Children frequently have multiple airway abnormalities and these can often be missed due to the speed of the flexible assessment.

DIFFICULT NASAL PASSAGE

Nasal septal deviations or turbinate hypertrophy can lead to difficulty passing the flexible scopes. The use of a topical vasoconstrictor enables the nose to be entered in most cases. Wood,[16] in 1990, encountered only three patients in whom the transnasal passage of the flexible bronchoscope was not possible.

PHARYNGEAL HYPOTONIA

Patients with tracheostomies or who have reduced muscle tone because of neurologic disease often have pharyngeal hypotonia leading to an increase in the amount of secretions in the larynx, making visualization difficult.

Complications of flexible bronchoscopy

Complications of flexible bronchoscopy are generally minor and are reported to occur in 2–8% of cases.[17] Reported complications include laryngospasm, pneumothorax, epistaxis, bradycardia, and hemorrhage. Generally, high-risk patients are more likely to undergo rigid bronchoscopy as obstruction of a large proportion of the airway can lead to hypoxemia. It is also difficult to remove foreign bodies with a flexible scope. The relative contraindications to flexible bronchoscopy are: (1) hypoxemia, (2) respiratory distress, (3) hemorrhagic diathesis, (4) cardiac arrhythmia, and (5) a foreign body. All these problems increase the risk of complications with flexible bronchoscopy.

CONCLUSION

Modern rigid and flexible bronchoscopy in the newborn carried out by trained personnel is a safe, relatively atraumatic procedure with a low rate of serious complications. This is due to the advances in anesthesia, pharmacology, instrumentation, and camera technologies. Rigid and flexible bronchoscopy should be viewed as complementary and not competing mutually exclusive techniques. Both procedures should be in the armamentarium of the pediatric airway surgeon. There are advantages and disadvantages to each technique. It is to the neonate's advantage to have both types of endoscopes available so the procedure with the highest benefit-to-risk ratio can be employed.

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PART IV

ESOPHAGUS

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39

Esophageal atresia and tracheo-esophageal fistula

PAUL D LOSTY, WAJID B JAWAID, AND BASEM A KHALIL

> To anastomose the ends of an infant's esophagus, the surgeon must be as delicate and precise as a skilled watchmaker. No other operation offers a greater opportunity for pure technical artistry
>
> Willis Potts 1950[1]

INTRODUCTION

Surgery for esophageal atresia (EA) is widely regarded as one of the most notable success stories in newborn surgery. Advances in neonatal intensive care have now led to greater than 95% survival for many babies treated in the modern era with increasing attention now focusing on morbidity, long-term clinical outcomes, and quality of life (QoL) in adult survivors. Recent noteworthy developments in EA management include minimally invasive thoracoscopic surgery and the deployment of the axillary skin crease thoracotomy pioneered by Bianchi. Expert opinion controversially dominates best practice with regard to pure long-gap esophageal atresia without fistula, medical versus surgical treatment of gastro-esophageal reflux (GER) disease, therapies for anastomotic stricture, and tracheomalacia. Applied embryology and molecular genetic studies continue to yield fascinating background into the etiology of EA and tracheo-esophageal fistula (TEF), with insightful contributions emerging from animal models sharing striking similarity to the human phenotype.[2,3]

HISTORY

The history of EA and TEF is well described in the literature.[2,3] The first survivors were not recorded until 1939 with Leven and Ladd achieving success with staged esophageal repair. Cameron Haight (an American surgeon working at Ann Arbor, Michigan) is fully credited with the first successful primary repair and survival of a 12-day-old female neonate. Reports from the UK soon followed with Franklin (1947) at the Hammersmith Hospital, London, Sir Denis Browne (1948) at Great Ormond Street Hospital, London, and Peter Paul Rickham (1949) at Alder Hey Children's Hospital in Liverpool recording equally good outcomes. Thereafter, improvements in survival were truly spectacular. By the 1980s, pediatric surgery centers worldwide were achieving survival approaching 85–90% in many newborns with mortality falling to less than 10%, thus defining a modern era of care.[2]

CLASSIFICATION

In 1929, Vogt proposed the first anatomical classification of EA and TEF, based on radiological and post-mortem findings.[4] A variety of surgical classifications were suggested as operative treatment became successful, the most frequently employed being attributed to Gross.[5] The most detailed classification, however, is credited to Kluth, and incorporates all described anatomical variants of EA and TEF.[6] However, from a practical viewpoint a working classification based on the frequency of each anomaly is of greatest value to the neonatal surgeon (Fig. 39.1).

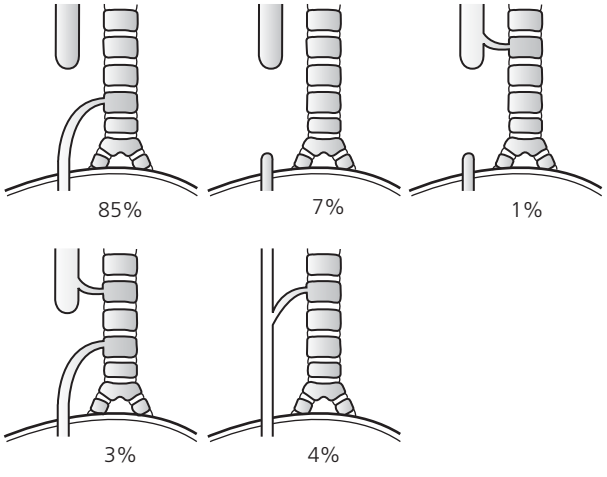

Figure 39.1 Classification and frequency of esophageal atresia (EA) and tracheo-esophageal fistula (TEF). EA and distal TEF, 85%; isolated EA, 7%; H-type TEF, 4%; EA with proximal and distal fistulas, 3%; EA and proximal fistula, 1%.

PROGNOSIS

Waterston's seminal paper describing the influence of pulmonary disease, birth weight, and associated congenital anomalies on outcome on newborns with EA-TEF provided an important historical basis for comparison of further refined better prognostic scoring systems.[7] It is now widely recognized that advances in neonatal intensive care have rendered the Waterston classification outdated. Spitz *et al.*,[8] in 1994, proposed a new risk categorization system based on birth weight and the presence or absence of congenital heart disease that is now widely accepted as applicable to the modern era [8] (Table 39.1). A Montreal classification system places greater emphasis on preoperative ventilator dependence and associated major anomalies as survival determinants.[9] Several studies report the negative influence of respiratory distress syndrome and pneumonia on outcome and the burden of aspiration events contributing to morbidity and late death following operative repair.[10,11] Variant anatomy also features as a risk factor(s) for favorable outcome with 'long gap' or 'pure' EA without fistula linked with significant morbidity including anastomotic leaks, stricture, increased requirement for fundoplication (and 'failure'/'redo' operations), and esophageal replacement procedures.[10,11,12]

Table 39.1 Spitz classification system

Group	Features	Survival
I	Birth weight >1500 g, no major cardiac	97%
II	Birth weight >1500 g, or major cardiac	59%
III	Birth weight >1500 g, and major cardiac	22%

EPIDEMIOLOGY

In the Liverpool region, the incidence of EA and TEF is 1 in 3300 live births.[13] The reported range varies from 1 in 2440 in Finland,[14] to 1 in 4500 both in Australia[15] and the US.[16] The sex ratio has been noted as equal by many authors, but others quote a slight male preponderance.[17] EA and TEF is more common in twin pregnancies. Exposure to teratogenic drugs during pregnancy has been implicated, and these include thalidomide, progesterone, and estrogen.[18]

GENETICS

The sporadic reports of vertical and transverse familial cases of EA and TEF suggest a polygenic hereditary etiology. The best estimate of risk of recurrence for parents of a single affected child is 0.5–2.0%, rising to 20% if another sibling is born with EA. The vertical transmission risk is 3–4%.[19]

A 10% incidence of non-specific chromosomal abnormalities (translocations, deletions, and duplications) has been noted. However, only trisomies 18 (Edwards syndrome) and 21 (Down syndrome) show any definite association with EA and TEF. Recognition of a syndrome suggestive of a major chromosomal abnormality in EA and TEF should prompt the urgent involvement of a clinical geneticist before corrective surgery is undertaken. EA and TEF have also been described in association with Feingold syndrome (autosommal dominant), Holt–Oram syndrome, DiGeorge sequence, polysplenia, and in babies with the Pierre Robin anomaly.[19]

ANIMAL MODELS

Significant contributions to our understanding of the embryology and genetic control of foregut development have evolved from basic laboratory research involving animal models of EA and TEF. The adriamycin rodent model was developed by Juan Tovar and colleagues in Madrid.[20] Timed pregnant rodents administered adriamycin (doxorubicin) in the prenatal period on gestational days 8 and 9 give rise to offspring with an EA-TEF variant phenotype.[20] These pups also demonstrate associated anomalies belonging to the VACTERL spectrum (denoting vertebral, anorectal, cardiac, tracheo-esophageal, radial/renal and limb anomalies).[21] A murine model of the VACTERL association has also been developed in mice with targeted deletions of the transcription factors Gli-2 and Gli-3 for the Sonic hedgehog (Shh) gene, which is pivotally linked with axial organogenesis. Gli-2–/–Gli-3–/– double mutants demonstrate the full phenotypic spectrum of the VACTERL syndrome confirming a crucial role for Shh in the genetic control of foregut development.[21,22]

EMBRYOLOGY

There is no unifying embryological theory which successfully explains all the anatomical variants of EA and TEF. The complete pathology has been demonstrated in the 5-week-old human embryo; therefore, causative factors must operate before this. In the developing embryo, the ventral aspect of the primitive foregut is destined to become the tracheobronchial tree. A median laryngotracheal groove develops in the ventral aspect of the foregut of the 23-day-old embryo. As the groove elongates with the growing esophagus, it is postulated that lateral epithelial ridges fuse to bring about foregut septation. While explaining the possible origins of tracheo-esophageal cleft and H-type variant EA fistula, caudocranial separation of the ventral trachea from the dorsal esophagus by a mesenchymal tracheo-esophageal septum clearly cannot adequately explain all variants of EA-TEF.

The finding of both an increased number of tracheal rings and a longer trachea in the adriamycin model of EA-TEF suggests localized abnormal proliferation and elongation of the ventral respiratory component of the common foregut tube. The preferential incorporation of tissue into the trachea may also result in esophageal discontinuity. The association of 13 pairs of ribs with long-gap TEF has also been used to strengthen the debate that abnormal forces, in this case hyper-somatization, result in a relative deficiency of tissue

which is preferentially absorbed into tracheal development at the expense of the esophagus.[23]

Further studies from the adriamycin model have shown that the notochord is also implicated in signaling activity to determine the fate(s) of neighboring cell populations. Shh protein, which is expressed in notochordal tissue, is thought to be pivotal in this dynamic signaling process.[24] Shh stimulates cell proliferation and inhibits apoptosis, via intermediary HOX gene expression. Shh binds to the cell surface protein 'Patched' (Ptc), which is upregulated by Shh, and thus limits the inductive capabilities of Shh. Ventral misplacement of the notochord may also result in an abnormal diffusion gradient for Shh and a localized imbalance of proliferation and apoptosis in the primitive foregut.

ASSOCIATED ANOMALIES

Associated anomalies are seen in over 50% of newborns presenting with EA and TEF.[2,25,26] Although some of these are relatively insignificant, a high proportion are life-threatening and significantly contribute directly to the morbidity and mortality of this condition. The early assessment of babies with EA-TEF should be prioritized with some urgency to address social, ethical, and surgical strategies relating to these coexistent anomalies. The incidence of these anomalies appears to be highest in newborns with pure EA without fistula and infants with orofacial clefts.[27] Babies born with EA-TEF have a higher incidence of prematurity than is seen in the normal population. Congenital heart disease (27%) is the commonest comorbid condition and probably has the greatest impact on survival. Aortic arch anomalies have been shown to occur frequently with 'long gap' EA-TEF variants. Other malformations include urogenital (18%), skeletal (12%), anorectal (12%), and gastrointestinal defects (9%) most notably duodenal atresia. The spectrum of associated anomalies encountered in 581 EA patients treated at Alder Hey Children's Hospital over four decades is shown in Table 39.2.

Several phenotypic variants have been described with EA-TEF babies. The VATER association,[27,28] now better referred to as the VACTERL sequence is defined by the presence of three or more anomalies. In a recent study from Alder Hey Liverpool, VACTERL associations were recorded in 19% of cases.[26] The CHARGE association refers to coloboma, heart disease, atresia choanae, retarded development, genital hypoplasia, and ear deformities with deafness. EA-TEF is also reported in the SCHISIS sequence, notably exomphalos, neural tube defects, cleft lip palate, and genital hypoplasia.[29–31]

Of interest, babies with EA and TEF have a higher than expected incidence of pyloric stenosis.[32] The almost universal association of gastro-esophageal reflux with EA may lead to delays in diagnosis if gastric outlet obstruction is not suspected. Tracheomalacia of variable severity is present in EA cases although the full spectrum of associated tracheobronchial and pulmonary abnormalities deserves further closer scrutiny. Significant anatomical tracheobronchial variant anomalies can be seen in 47% of infants undergoing bronchoscopy.[33] Pulmonary agenesis, foregut duplication cysts, congenital cystic adenomatoid malformations, and sequestered lobe have all been described in association with EA and TEF. Other rare foregut pathologies, such as laryngotracheo-esophageal cleft and congenital esophageal stenosis may coexist with EA and TEF.

Table 39.2 Abnormalities associated with esophageal atresia and TOF (Liverpool series 1953–97)[26,41]

Type	1953–97 (581 cases)
Cardiac	154 (27%)
Urogenital	105 (18%)
Skeletal	71 (12%)
Vertebral	64 (11%)
Anorectal	67 (12%)
Gastrointestinal	53 (9%)
Palate/laryngotracheal	44 (8%)
VASTERL[41]	25 (19%)

ANTENATAL PRESENTATION

Fetal diagnosis is now possible in cases of EA and TEF.[34] This may be clearly advantageous, as delivery can be planned at or near a specialist center with full neonatal surgical capability. Counseling is essential by a multidisciplinary team (obstetrician, pediatric surgeon, neonatologist) and a careful search for associated chromosomal or cardiac anomalies is important. The identification of a chromosomal abnormality may have implications for termination of pregnancy. Antenatal diagnosis of EA should theoretically reduce the likelihood of inadvertent feeding and aspiration pneumonitis. Despite the potential advantage of antenatal diagnosis, it is noteworthy that fetal ultrasonography selects an at-risk group of infants with a significantly worse prognosis.[35,36] The perinatal mortality (excluding termination of pregnancy) in a series from Newcastle, UK was reportedly 21%.[35] The classical sonographic features of EA and TEF in the fetus are absence of the stomach bubble and associated polyhydramnios.[37] Prenatal detection rates vary widely in fetal medicine centers (9–24%) and there appears to be a high rate of false-positive scans. Approximately 50% of all suspected cases on scanning are proven not to have EA after birth.[35]

CLINICAL PRESENTATION AND DIAGNOSIS

A newborn with EA is often noted to have difficulty clearing saliva. Episodes of coughing, choking, and even transient cyanosis may be observed shortly after birth. These signs are frequently overlooked and attempts to feed the infant result in immediate respiratory distress. The diagnosis is readily confirmed by the failure of passage of a firm nasogastric tube. A characteristic resistance is felt at the blind ending upper esophageal pouch, and the tube cannot be introduced into the stomach. A plain x-ray, which should include the chest and abdomen, demonstrates the nasogastric tube coiled in

the upper pouch. An associated TEF is confirmed by the presence of gas-filled intestinal loops below the diaphragm (Fig. 39.2). In isolated or pure EA, a featureless gasless abdominal x-ray is observed (Fig. 39.3). The presence of a double bubble on the abdominal film is highly suggestive of associated duodenal atresia (Fig. 39.4). A careful search for associated abnormalities is mandatory, specifically checking for patency of the anus. The cardiovascular system should be examined thoroughly to exclude a major congenital heart defect whose treatment may take priority over correction of the EA defect.

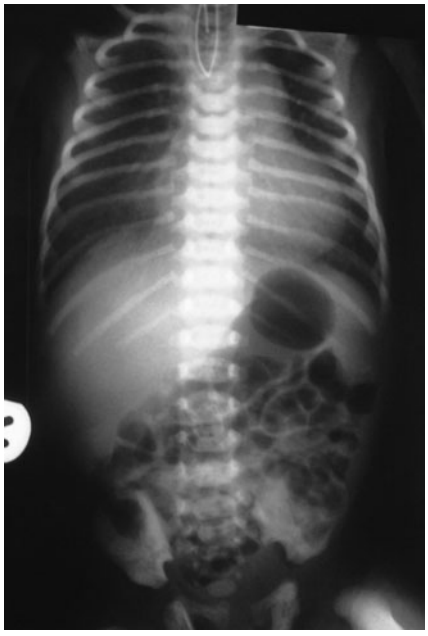

Figure 39.2 Chest x-ray film of a neonate with esophageal atresia and tracheo-esophageal fistula (TEF). Note the nasogastric tube coiled in the blind-ending upper esophagus. Air outlining intestinal loops below the diaphragm confirms the existence of a distal TEF.

Having established the diagnosis, i.v. fluids are commenced and a sump suction (Replogle) catheter introduced into the upper pouch to allow continuous aspiration of salivary secretions.[38] Alternatively, the upper pouch and oropharynx should be cleared of secretions by frequent intermittent suction. The infant is nursed in the supine or lateral position. Vitamin K should be administered intramuscularly after parental consent. Arrangements should be made for early transfer of the newborn to a neonatal surgical unit. Surgery is ideally performed within the first 24 hours following birth in an otherwise healthy baby, as pneumonitis is an ever-present risk from the aspiration of saliva and reflux of gastric acid through the lower pouch TEF.

Following admission to the neonatal surgical unit, the infant should be fully re-examined and radiology reviewed. The x-rays may be repeated with gentle downward pressure on the Replogle tube. On rare occasions, the authors have observed that a fine nasogastric tube may coil in an otherwise normal proximal esophagus, and the successful passage of the Replogle tube into the stomach prevents misdiagnosis and an unnecessary exploratory operation. In most instances, the diagnosis is fully established and an estimation of the length of the upper pouch on plain chest x-ray can give some idea as to the ease or difficulty of primary anastomosis. An echocardiogram should be performed prior to surgery as this will alert the surgeon and anesthetist to an underlying cardiac defect that may adversely influence prognosis, and may importantly, dictate the operative approach by identifying the side of the

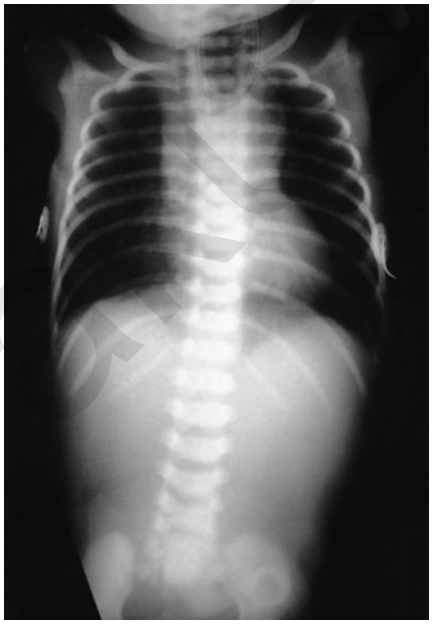

Figure 39.3 Case of 'pure' esophageal atresia without fistula. The nasogastric tube is lying coiled in the upper esophageal pouch. Absence of air-filled abdominal intestinal loops suggests that there is no distal esophageal fistula.

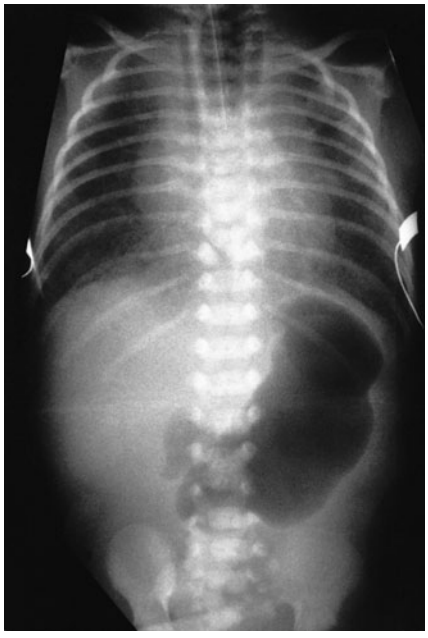

Figure 39.4 Esophageal atresia and tracheo-esophageal fistula with duodenal atresia. Nasogastric tube coiled in upper pouch. 'Double-bubble' appearance confirms duodenal atresia.

aortic arch. Blood should be taken for cross-match and a hematological and biochemical profile arranged preoperatively. Broad-spectrum antibiotics should be administered and i.v. fluids continued. Other investigations, notably whole-spine x-rays, renal and cranial ultrasonography can be deferred until after surgery. Contrast studies of the upper pouch to identify a rare upper pouch fistula have been superseded by preoperative bronchoscopy.

SURGICAL MANAGEMENT

Surgery for esophageal atresia is now usually performed as an elective procedure. Emergent operation rarely benefits the baby unless the surgeon is confronted with a 'high risk' ventilated neonate with severe respiratory distress and massive gastric distension with impending perforation where urgent transpleural fistula ligation is life saving (see below under Premature infant with RDS). It is common practice now for most surgical units to advocate preliminary rigid bronchoscopy after induction of general anesthesia when planning elective repair of EA and TEF. Depending on the infant's size, a 2.5–3.5 Fr neonatal bronchoscope (Storz) is used, as this permits the use of a suction catheter. Bronchoscopy allows confirmation of the diagnosis and in most cases will demonstrate the common variant fistula just proximal to the carina. Occasionally, a fistula may be seen arising at the level of the carina, or from one of the main bronchi. A careful search should be made to exclude an associated upper pouch fistula. The larynx should also be inspected to exclude a laryngotracheo-esophageal cleft.

Following bronchoscopy, an endotracheal tube is passed, taking care not to intubate the TEF. The infant is positioned for operation. In the classical operation, a right thoracotomy is planned with the baby in a lateral position, with the right arm raised across the head so that the scapula can be easily manipulated (Fig. 39.5). The neonatal surgeon may find the use of a headlamp and optical loupe magnification greatly facilitates the operation. A curved skin crease incision is made 1 cm below the angle of the scapula, extending from the anterior axillary line to the lateral margin of the erector spini muscles. Bianchi has also described a high axillary skin crease incision, which gives excellent cosmesis which we now increasingly deploy at Alder Hey.[39] The traditional Denis Brown vertical incision is least acceptable from an esthetic point of view. The anterior fibers of the latissimus dorsi are divided with electrocautery in the posterior aspect of the incision and the inferior digitations of the serratus anterior are separated from the ribs anteriorly. A retractor is used to lift the scapula off the chest wall, and the ribs are counted downwards from the second interspace. The chest is opened through the fourth interspace, dividing the intercostal muscle fibers using bipolar diathermy down to the level of the parietal pleura. The pleura is carefully separated from the ribs to commence an extrapleural dissection towards the fistula. The procedure is usually started with moist pledgets and, having developed the plane, may be continued by inserting a moistened gauze swab into the extrapleural space, sweeping the pleura away from the chest wall superiorly and inferiorly. Exposure is improved by introducing a Finochettio retractor for rib retraction. Great care is required with the dissection as it is particularly easy to create a pleural tear in the anterior aspect of the incision. If a significant pleural tear occurs during the dissection, it is probably wise to convert to a transpleural approach. The advantages of the extrapleural over the transpleural approach, include the possibility of avoiding a chest drain, and in the event of an anastomotic leak, the potential containment of contamination within the extrapleural space. The extrapleural exposure is completed by retracting the posterior mediastinal pleura forwards with a malleable retractor until the azygos vein is visualized as it enters the superior vena cava in the depths of the wound.

The azygos vein is mobilized and controlled with suture slings. The authors advocate temporary occlusion of the vein before ligation, as venous return to the heart may rarely be critically dependent on the azygos system. Provided this maneuver does not affect cardiac output, the azygos vein is ligated and divided as it enters the superior vena cava. Alternatively, some surgeons elect to preserve the azygos vein.[40] Once divided, the site of the fistulous communication between the trachea and the distal esophagus is usually readily apparent. Having confidently identified the distal esophagus, a vascular sloop is carefully passed around it. Traction on the sloop controls the fistula and enables its junction with the trachea to be located precisely. Although it is possible to suture ligate the fistula, the authors prefer to divide the fistula in stages and apply interrupted 5-0 or 6-0 monofilament prolene sutures to the tracheal component of the fistula. The distal esophagus is secured with a stay suture of the same material. The integrity of the TEF repair is evaluated by instilling saline into the thoracic cavity and requesting the anesthetist to exert positive airway pressure to ensure that no bubbles leak from the suture line. Occasionally, difficulty is encountered in identifying the distal esophagus, and it is quite possible to mobilize the descending aorta in the erroneous impression that this is the distal esophagus. The inexperienced operator may recognize the distal esophagus by following the vagus nerve as it courses distally, and by observing its rhythmic distension in time with ventilation.

Attention is then focused on the upper pouch, which is easily identified by requesting the anesthetist to push firmly on the Replogle tube. The upper pouch is usually a thick-walled bulbous structure, with a base readily identified by this maneuver. The upper pouch may be secured using a transfixion suture driven through the Replogle tube, which is used for traction during the mobilization of the upper pouch. Bipolar diathermy is ideal for this dissection, which should proceed to the thoracic inlet unless the gap is small. Mobilization is relatively easy except where the esophagus is closely applied to the trachea. Separation of this plane often requires sharp dissection, and should be performed with great care to avoid injury to the trachea. An upper pouch fistula may be identified at this stage, and should be repaired using 5-0 or 6-0 interrupted prolene sutures. The esophageal defect is closed with 5-0 or 6-0 interrupted polydioxanone sutures. Following full mobilization of the upper pouch it is usually possible to gauge whether a primary anastomosis is feasible. In most cases of EA with distal TEF, a primary

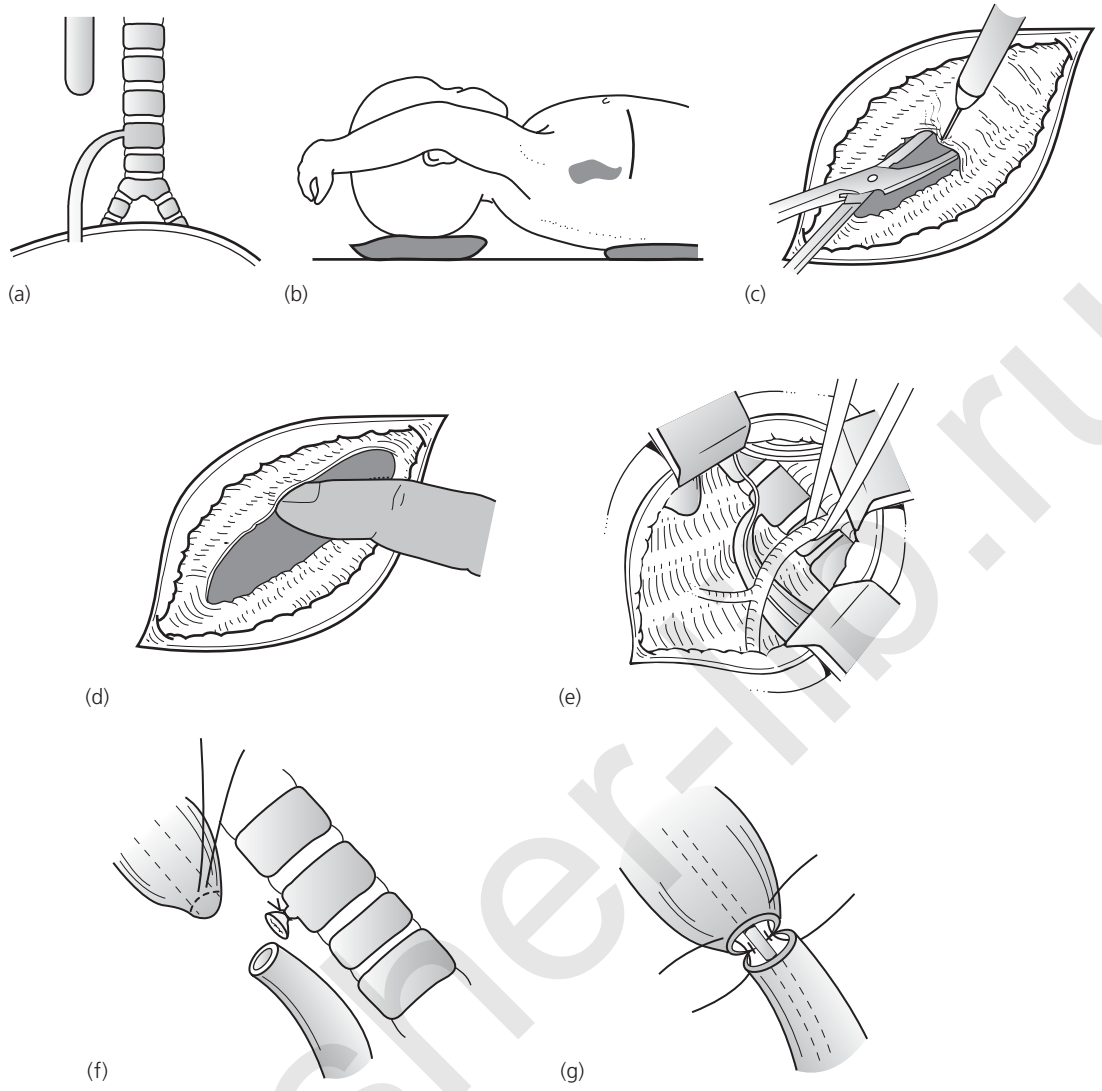

Figure 39.5 (a) The most frequent tracheo-esophageal anomaly. (b) Infant in lateral position prior to operation. Location of skin incision indicated. (c) Division of lateral thoracic and fourth space intercostal muscles. (d) Commencement of gentle stripping of parietal pleura from chest wall to develop extrapleural space. (e) Operative field when pleura and lung have been retracted medially. The azygos vein is easily seen. The other structures, i.e. the blind proximal esophageal pouch and the fistulous distal esophagus, with vagal fibers lying on its surface, will require some dissection, and are not as easily seen as is depicted in the diagram. (f) The fistula ligated and divided flush with trachea. (g) Lateral and posterior sutures and transanastomotic tube in place.

anastomosis is possible, although occasionally considerable tension is required to complete the repair.

The upper pouch is opened at its most distal extremity. The posterior wall of the anastomosis is commenced by placing two 5-0 or 6-0 polydioxanone sutures through all layers of the lateral margins of the distal esophagus, taking great care to avoid excessive tissue handling and trauma with tissue forceps. Sutures are completed by including all layers of the corresponding aspect of the upper pouch, so that the knot comes to lie on the inside. Before tying these sutures, two further posterior wall sutures are inserted. All are individually tied drawing the esophageal ends together. Having completed the posterior wall of the anastomosis, a 6–8 Fr fine bore nasogastric tube is passed by the anesthetist via the nose to the suture line, where it is grasped by the surgeon and carefully introduced into the lower esophagus and stomach. The anterior layer of the anastomosis is completed by laying the knots on the outside. Occasionally, generous mobilization of the lower pouch is also required to enable an anastomosis to be performed without excessive tension. Even when the gap seems too large to permit a primary anastomosis, this can sometimes be facilitated by creating either a Livaditis[41] myotomy of the upper pouch, or an upper pouch flap as described by Gough.[42] If the anastomosis is under tension, or has required one of these maneuvers, a chest drain is advisable. Under most circumstances where a satisfactory tension-free anastomosis has been completed without and where the extrapleural plane has been maintained, the authors, like others, consider a chest drain unnecessary.[43] The ribs are loosely approximated using absorbable pericostal sutures, and an anatomical closure of all muscle layers is performed. The chest drain, if present, should be attached to underwater drainage, and the patient transferred to intensive care for postoperative monitoring and ventilatory support.

Should additional surgical pathology be present, such as duodenal atresia or imperforate anus, these should be dealt with accordingly under the same anesthetic in the stable infant.

Long-gap EA with distal TEF

Rarely, the gap between the upper pouch and the distal esophagus is clearly too long to permit a primary anastomosis after division of the fistula, and full mobilization of both the proximal and distal esophagus. Under such circumstances, it is probably wise to proceed to cervical esophagostomy and feeding gastrostomy, accepting the need for esophageal replacement surgery at a later date.[2]

Right-sided aortic arch

Opinion is divided among pediatric surgeons regarding the optimal surgical strategy when a right-sided aortic arch is encountered. The incidence of right-sided arch in association with EA is 1.8–2.5%.[44,45] Chest x-ray may provide some clues. Preoperative echocardiography is at best 20% accurate in identifying this anomaly.[45] If the surgeon's suspicion remains high, magnetic resonance imaging should be arranged for definitive diagnosis. If a right-sided arch is identified from preoperative studies, experience from specialist centers advocate left thoracotomy. More commonly, the neonatal surgeon will encounter the anomaly unexpectedly in the course of the operation. The presence of a right-sided arch does not preclude a successful anastomosis in this situation, but the procedure is significantly more challenging as is evidenced by the 42% leak rate reported from Great Ormond Street Children's Hospital, London.[45] A trial dissection, including repair of the fistula, via right thoracotomy is appropriate, with completion of the esophageal anastomosis if this seems technically feasible.[46] Where significant difficulty is encountered with the dissection in preparation for the esophageal anastomosis, left thoracotomy is advisable following division of the fistula through the right or left chest as circumstances dictate. The second thoracotomy may be performed immediately or delayed, depending on the stability of the infant, and the experience of the surgeon.

PREMATURE INFANT WITH RDS

In premature babies with lung immaturity, emergency surgical intervention may become imperative if adequate ventilation is compromised by the TEF, resulting in abdominal distension and diaphragmatic splinting. The surgical priority is urgent division/ligation of the fistula via a transpleural approach to the anomaly. Should the infant's condition stabilize sufficiently after closure of the fistula, a primary repair of the esophagus is appropriate. Otherwise, a delayed repair is undertaken when the baby is stable. Sudden collapse due to gastric perforation is also a significant high risk event in these fragile babies. In such situations, emergent ligation of the fistula is a life-saving measure. Needle paracentesis with laparotomy, repair of the perforation, and feeding gastrostomy should follow.[47,48]

POSTOPERATIVE CARE

The infant should be nursed in the intensive care unit following repair of EA and TEF. Intravenous fluids and broad-spectrum antibiotics are continued. Weaning from ventilation need not be unduly prolonged in the stable infant with a satisfactory anastomosis. Where the anastomosis is under considerable tension, elective paralysis and ventilation for a period of 3–5 days is widely practiced.[49] It must be conceded, however, that there is no evidence base to support the claim that this technique favorably influences anastomotic healing.[50] There are some experimental data indicating that the level of tension in the anastomosis correlates with the severity of GER.[51] It is the authors' practice to commence all patients on H_2-antagonists (e.g. ranitidine) as prophylaxis against anastomotic stricturing potentiated by GER. A contrast esophagogram is optional after 5–7 days to evaluate the anastomosis, although major anastomotic leaks are clinically evident before this time. Minor (radiological) leaks are often seen on the postoperative contrast study. These are of no clinical significance and do not preclude the infant from being offered feeds.[52] In most cases, transanastomotic tube feeding can be commenced after 48 hours, and slowly increased as tolerated by the infant.

SURGICAL MANAGEMENT OF ISOLATED ('PURE') ESOPHAGEAL ATRESIA

The diagnosis of isolated EA without fistula is confirmed by the inability to pass a nasogastric tube, and a featureless 'gasless abdomen' on plain x-ray (Fig. 39.3). The absence of intestinal gas below the diaphragm, however, does not always completely exclude the presence of a distal fistula, as a small proportion of children may have a fibrotic connection between the lower pouch and the trachea, which does not readily permit the passage of air.[53]

Surgical management of these neonates is equally challenging and controversial. A majority of pediatric surgeons consider delayed primary anastomosis of the native esophagus the optimum approach. This strategy demands meticulous nursing care, physiotherapy, and careful attention to nutrition by supervised gastrostomy feeding. A prolonged period of hospitalization (6–12 weeks) is required to achieve this objective. Delayed primary esophageal anastomosis however, is associated with attendant morbidity, and further procedures to manage esophageal strictures and significant GER are commonly required.[54] The desire to preserve the infant's esophagus must be counterbalanced by the humility of knowing when to accept defeat, and to abandon the esophagus in favor of a replacement procedure. A feeding gastrostomy is created by minilaparotomy and special care should be taken to avoid injury to the small stomach in these babies with placement of the G-tube.[55] We do not advocate

an assessment of 'gap length' at the time of this operation and defer to a later session when the baby is more stable.

After a period of approximately 3 weeks, the extent of the gap can be assessed by fluoroscopy (Fig. 39.6). A radiopaque tube is pushed into the upper pouch and either contrast instilled via the gastrostomy, or a metal sound is introduced through the gastrostomy and directed via the esophageal hiatus into the distal esophageal stump. This procedure can be repeated at 2-week intervals, to assess whether the ends of the esophagus are sufficiently close to attempt delayed primary anastomosis.[56] A distance of less than two vertebral bodies separating upper and lower pouches is ideal. In practice, however, there is little to be gained by delaying restorative surgery beyond 12 weeks of age.

The operation of delayed primary anastomosis is essentially the same as has been described for EA and TEF. It is to be expected that the anastomosis may be created under considerable tension. The upper pouch should be fully mobilized to the thoracic inlet. The distal esophagus is frequently a primitive stump and not readily identified at thoracotomy without use of special aids. The surgeon can facilitate location of the distal esophageal stump by passing an illuminated neonatal gastroscope via the dilated G-tube tract site towards the esophageal hiatus. A brightly illuminated stump is easily identified in the depths of the thoracotomy wound. A stay suture (5-0 or 6-0 prolene) should be secured to the distal esophageal segment to aid mobilization and dissection. Some surgeons prefer passing metal sounds to identify the distal esophagus. The distal esophagus may be dissected to the diaphragmatic hiatus to help reduce tension on the anastomosis. A Livaditis myotomy or upper pouch flap may be helpful.[41,42,57–59] The authors prefer to perform a Livaditis myotomy over the inflated balloon of a Foley catheter passed by the anesthetist per-orally to the upper pouch. Extra length can be obtained by proceeding to laparotomy and creating a myotomy on the lesser curve as described by Scharli, or a Collis gastroplasty.[60,61] If a primary anastomosis is still not possible using these techniques, the options are a cervical esophagostomy and an esophageal replacement procedure at a later date. More often, a decision to convert to an immediate replacement of the esophagus is practiced provided the surgeon and team are sufficiently skilled. Options can include gastric transposition, a reverse gastric tube, colon replacement, or an operation regaining popularity, jejunal interposition.[2,62]

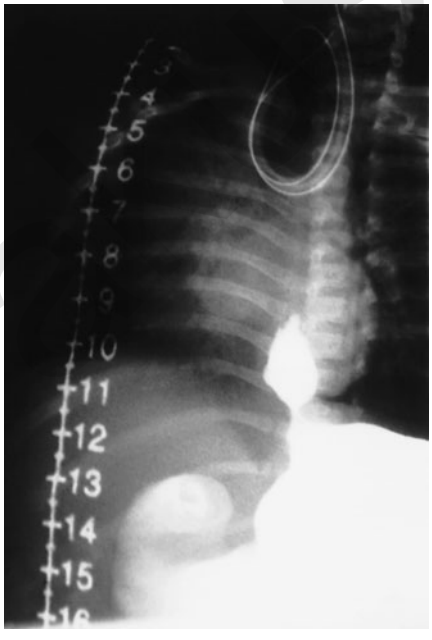

Figure 39.6 Gap assessment in a case of pure esophageal atresia. The scale bar represents gap length (cm).

Delays in restoring esophageal continuity have significant drawbacks. First, there is the ever-present risk of aspiration pneumonitis, and second, the inability to feed the infant via the normal oral route. Although the child's nutritional needs are met by gastrostomy feeding, the inability to establish oral feeds may lead to long-term feeding and speech problems. Spitz has recommended formally assessing the length of the gap when the gastrostomy is initially performed. A gap length less than six vertebral bodies (6 cm), would prompt him to abandon the esophagus and perform a cervical esophagostomy.[62] This approach of early cervical esophagostomy and delayed esophageal replacement permits early sham feeding, which theoretically promotes neuronal maturation and development of the learning skills needed for feeding and later speech acquisition.

A number of other innovative approaches to the operative treatment of long-gap EA have been described. True primary repair has been performed with reported gap lengths exceeding 5 cm. The hypothesis tested by Foker *et al.*[63] was that a well-constructed esophageal anastomosis can withstand considerable tension. The value-added technique for esophageal reconstruction (VATER) operation involves mobilizing the gastric fundus and performing a limited Thal fundoplication. At thoracotomy, the proximal stomach is drawn into the chest and a primary esophageal anastomosis is performed.[64] Staged neonatal colon esophagoplasty has also been described which involves the isolation of a short length of transverse colon based on the ascending branch of the left colic vessels at the time of open gastrostomy.[65] The conduit is positioned transhiatally in the posterior mediastinum to be retrieved at thoracotomy several days later, when continuity is restored.

Several well-established operations are available to restore gastrointestinal continuity in long-gap EA, where the infant's own esophagus has been abandoned.[62] Colonic or ileocolonic replacement was originally popularized by Waterston. The colonic conduit may be isoperistaltic (left colon based on the left colic vessels), or anteperistaltic (right colon based on the ileocolic vessels). The colon may be routed retrosternally, transmediastinally (via the hiatus), or through right or left chest cavities. Either pyloromyotomy or pyloroplasty is performed to promote gastric emptying. Cervical esophageal colonic anastomosis is prone to leakage. The colonic conduit tends to dilate, and kinking is common due to excessive tortuosity. Respiratory problems are seen due to recurrent aspiration.

The stomach may be utilized to create a neo-esophagus. A gastric tube esophagoplasty is fashioned from the greater curvature of the stomach, based on the left gastroepiploic (anteperistaltic) or right gastroepiploic arcades (isoperistaltic), and retrosternal, mediastinal, or thoracic routes may be used.[66]

The long suture lines of both the tube and new greater curve are prone to bleeding and leaking. Reflux is a problem and may predispose to anastomotic narrowing. However, dilatation and kinking are not encountered; reflux may be controlled by performing a posterior partial wrap fundoplication.

Gastric transposition has been advocated by Spitz and has the merit of simplicity.[62,67] The vascular supply is based on the right gastric and right gastroepiploic vessels, which allows full mobilization of the greater and lesser curvatures. After pyloroplasty, the stomach is passed through the mediastinum via the diaphragmatic hiatus and the esophagogastric anastomosis completed in the neck. Leakage from the anastomosis is reported in 12% of cases and strictures requiring periodic dilatation in a similar percentage of patients.[67]

Jejunal orthotopic interposition grafting has re-emerged as a useful technique for esophageal replacement following the encouraging reports from the Netherlands by Bax and colleagues.[68] Jejunal grafts do not dilate excessively and retain good peristalsis which may explain why GER does not appear to be problematic for these patients.[68,69]

H-TYPE TEF

H-type TEF is perhaps more accurately described as an N-type fistula as the track runs obliquely from trachea to esophagus. This is a rare anomaly comprising 4% of all EA-TEF variants.[2] Infants with H-type TEF usually present within the first month after birth, with a characteristic history of choking with feeds and cyanotic spells. Marked abdominal distension mimicking intestinal obstruction is an occasional presenting feature which the authors have encountered. Older children may have frequent chest infections with recurrent right upper lobe pneumonia due to aspiration.

Diagnosis may be established by a prone video esophagogram. In this study, contrast is injected through a nasogastric tube, which is slowly withdrawn from the esophagus. However, H-type fistulas may be missed in approximately half of all contrast studies. Where suspicion remains, bronchoscopy should be performed. At bronchoscopy, a size 4 Fr ureteric catheter is passed through the fistula into the esophagus to facilitate identification during subsequent neck dissection. A nasogastric tube is passed into the stomach, and broad-spectrum antibiotics commenced. A right transverse skin crease incision is marked a finger's breadth above the clavicle, before positioning the neck in extension with a sandbag placed under the shoulders. The sternomastoid is retracted laterally and, if necessary, its sternal head divided. The carotid sheath is mobilized after division of the middle thyroid vein. The ipsilateral recurrent laryngeal nerve should be identified and carefully preserved. Intraoperatively we have found that flexible bronchoscopy with a 2.2 mm instrument (Olympus) can aid precise identification by brightly illuminating the site of the fistula tract.[70] The esophagus is carefully dissected at this point and slung with vascular sloops both above and below the fistula. Caution should be taken with this maneuver, as the contralateral recurrent nerve is also vulnerable to injury at this point. Traction on the esophagus enables the fistula to be secured with stay sutures. After withdrawing the ureteric catheter (and 2.2 mm bronchoscope if deployed), the fistula is divided and the tracheal component repaired with 5-0 or 6-0 interrupted prolene sutures. The esophagus is closed with 5-0 or 6-0 polydioxanone sutures. Some authors recommend tissue interposition between esophageal and tracheal suture lines to prevent a recurrent fistula.

The infant should remain intubated and ventilated in the early postoperative period, as tracheal edema can result in progressive stridor.[71] The vocal cords should be checked on extubation, given the significant risk of recurrent nerve palsy. Nasogastric tube feeding may commence after 48 hours and oral feeds may be slowly introduced thereafter.

The Nd:YAG laser has also been successfully used to treat congenital H-type TEF. Repeated short duration pulses of laser light are used to coagulate the fistula.[72] Despite some success with this approach, the technique has not gained widespread acceptance, and open repair remains the gold standard. Complications following open surgery include recurrent laryngeal nerve palsy (both unilateral and bilateral), and rarely, recurrent fistula.

COMPLICATIONS AND SPECIAL CONSIDERATIONS

Anastomotic leak

The incidence of anastomotic leak following repair of EA and TEF ranges from 11 to 21%.[50,73] Major anastomotic disruption is uncommon and is usually manifested by early tension pneumothorax and gross salivary drainage from the chest drain. In these situations, it is rare for the anastomosis to be completely disrupted. Provided a transanastomotic tube is in place, it is usually possible to control the leak with an adequately sized chest drain. With good drainage, broad-spectrum antibiotics, and total parenteral nutrition, the esophagus will usually heal, although a prolonged period of chest drainage may be necessary. Some surgeons have used hyoscine patches in an attempt to 'dry up' the salivary leak. Others advocate early re-exploration (<48 hours), with direct repair of the esophagus if possible, and the establishment of satisfactory drainage.[13,74] This early re-operative approach may prove hazardous and further compromise a tenuous anastomosis. Where conservative management of a major leak proves unsatisfactory due to uncontrolled sepsis, the establishment of a cervical esophagostomy and a feeding gastrostomy are essential. This usually commits the child to some form of delayed esophageal replacement after recovery. It has been suggested that a clinical anastomotic leak predisposes to the development of an esophageal stricture.[75] While this association may seem logical, others have not been able to confirm such a correlation.[73]

GER

Significant GER occurs in 40–50% of children following repair of EA and TEF. GER may cause failure to thrive, can predispose to recurrent aspiration episodes, and may lead

to esophagitis and stricture formation.[2] Management of symptomatic GER initially entails aggressive medical therapy. Postural therapy and close attention to feeding regimes, with calorie supplementation of formula feeds, combined with the selective use of overnight continuous pump feeding by nasogastric tube and frequent small daytime bolus feeds may prove effective management strategies. Feed thickeners (e.g. Carobel) antacid preparations (e.g. Gaviscon), H_2-antagonists (e.g. ranitidine), proton pump inhibitors (e.g. omeprazole), and prokinetic agents (e.g. domperidone), may be used in various combinations if vomiting is significant. However, should such measures fail to control GER, surgical treatment may be the only option.

GER may contribute to recurrent aspiration episodes, with frequent symptoms of respiratory distress including tachypnea, apneic episodes, cyanosis, and x-ray evidence of patchy pneumonic changes. The differential diagnosis in this clinical setting also includes swallowing incoordination and respiratory distress due to significant tracheomalacia. It is not uncommon to see infants in whom all of these factors are operating to a variable degree. It is important not to overlook the possibility of a recurrent TEF as a cause of repeated episodes of respiratory distress, although the history of choking and cyanotic episodes during feeding is usually much more evident in infants with a recurrent fistula. The selective use of esophageal pH monitoring, contrast meal, bronchoscopy, and assessment of swallowing by video fluoroscopy, may assist in evaluating the contribution of GER and other pathologies to respiratory symptoms. Failure to control GER-related symptoms despite full medical therapy is an indication for fundoplication.

Fundoplication rates following surgery for EA vary widely between centers (6–45%), reflecting the differing enthusiasm for anti-reflux operations in this clinical setting.[2,76] There are several reasons for caution when considering fundoplication in EA patients. Dysphagia may be aggravated as a consequence of underlying esophageal dysmotility. Furthermore, fundoplication following EA has a higher failure rate (15–38%) than is generally seen in otherwise normal patients with isolated GER.[77] Some authors recommend a partial wrap (Thal) fundoplication, because of the lower incidence of postoperative dysphagia.[76] Despite these concerns, many pediatric surgeons prefer a short (1.5–2.0 cm) 360° floppy Nissen wrap for its proven effectiveness in reducing GER.[78] The high failure rate of fundoplication and the significant complications associated with surgical treatment of GER, demand vigilant follow up in this group of patients.

Anastomotic stricture

Reported definitions of esophageal stricture following repair of EA lack consistency. The incidence of symptomatic strictures requiring dilatation varies from 37 to 55%.[50,75] Some degree of anastomotic narrowing is seen in all postoperative contrast studies, but this is rarely of a sufficient degree to cause symptoms in the early postoperative period. Parents should be counseled to report symptoms of prolonged feeding, incomplete feeding, or associated respiratory difficulty. Contrast studies may be arranged. More often such symptoms reported by well-trained parents prompt us to arrange surveillance endoscopy to assess the caliber of the esophageal anastomosis. Balloon dilatation is our preferred method of treating symptomatic strictures. The radial dilating forces generated during balloon dilatation are considered to be less traumatic than the longitudinal shearing forces caused by conventional bougienage.[79] Balloon dilatation is performed under fluoroscopic control, by passing a guide wire through the stricture, over which a balloon dilator of appropriate size is introduced. Its position is confirmed by partially filling the balloon with contrast medium, so that 'waisting' due to the stricture is centrally located (Fig. 39.7). The balloon is then maximally inflated using contrast medium to dilate the stricture. A contrast esophagogram is performed after removing the balloon to ensure there has been no perforation. If a stricture requires repeated dilatations, GER should be fully investigated by a combination of an upper gastrointestinal contrast study, pH study, and endoscopy. Recalcitrant strictures may require repeated dilatations, fundoplication, and rarely formal resection at thoracotomy.

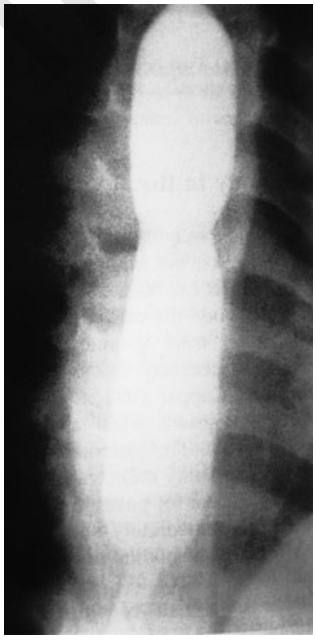

Figure 39.7 'Waisting' due to anastomotic stricture at balloon dilatation.

Tracheomalacia

Tracheomalacia is present to a variable degree in all patients with EA. It is thought to be responsible for the characteristic barking TEF cough.[2] Infants with tracheomalacia demonstrate expiratory stridor, which may result in episodes of desaturation, apnea, cyanosis, and bradycardia (often associated with feeding), and life-threatening so-called 'dying episodes'. Severe tracheomalacia may be evident in the early postoperative period, when it proves difficult to wean the infant from the ventilator.

Indications of the severity of tracheomalacia include ventilator dependency, respiratory distress characterized by stridor, and chronic carbon dioxide retention, and dying episodes. Full investigation for severe GER and recurrent TEF (see below) is advisable alongside evaluation of tracheomalacia, as aspiration secondary to GER and a recurrent fistula can mimic these symptoms. The extent of tracheomalacia is assessed by bronchoscopy under conditions of spontaneous respiration. The lumen of the trachea is significantly compressed anteroposteriorly and assumes a scabbard-like appearance during expiration due to tracheal cartilage deficiency. A further contribution is often made by the upper esophagus, which may bulge posteriorly into the airway. Tracheobronchomalacia can extend beyond the carina into the main bronchi.

As tracheomalacia can be self-limiting, surgical intervention is reserved for patients with life-threatening symptoms.[2] Treatment options include continuous positive airway pressure (CPAP), aortopexy, tracheostomy, and, more recently, tracheal stenting.[77,80] CPAP is a useful temporizing measure, but may be required for several weeks. Aortopexy is traditionally performed by anterior left thoracotomy through the third interspace. The left lobe of the thymus is excised to gain access to the root of the aorta taking care not to damage the phrenic nerve. Plegetted sutures incorporating reinforcing dacron squares are placed through the adventitia of the aortic root and the ascending aorta. The sutures are passed through the periostium of the manubrium and tied, hitching the aorta forwards, thereby relieving compressive forces on the trachea. Although this operation cannot resolve distal tracheobronchomalacia, it often provides immediate dramatic symptomatic relief. Failure of aortopexy may be an indication for tracheostomy, although some authors advocate tracheal stenting in this situation.[2,77,80]

Recurrent TEF

This complication is thought to occur in 5–15% of cases.[81] A recurrent TEF may result from an anastomotic leak, but the possibility of a missed upper pouch fistula should always be considered. Symptoms include recurrent chest infections and choking attacks during feeding. A high index of suspicion is required if the diagnosis is not to be overlooked. Chest x-ray may sometimes reveal an air esophogram. The initial investigation is prone video esophagography. If this study fails to demonstrate a fistula and the diagnosis remains strongly suspected, combined esophagoscopy and bronchoscopy should be performed. Rigid bronchoscopy is performed initially, and the site of the original fistula carefully examined. The fistula is gently probed with a ureteric catheter and methylene blue is carefully instilled into the fistula pit. Synchronous flexible esophagoscopy is performed to see if the dye can be seen entering the esophagus. Should this fail to demonstrate the fistula, an air/water test is a useful supplementary investigation. The esophagus is filled with water and positive pressure ventilation applied to the bronchoscope. Occasionally, bubbles of air can be seen emanating from the fistulous opening into the esophagus (Rintala, personal communication).

Several strategies have been described to deal with the recurrent TEF. The traditional approach is formal repair via right thoracotomy. At bronchoscopy, an attempt should be made to pass a fine ureteric catheter through the fistula into the distal esophagus. A flexible miniature bronchoscope (2.2 mm, Olympus) may be useful to navigate, cannulate, and brightly illuminate the fistula tract. The fistula is repaired using a similar strategy to that deployed for the H-type variant, i.e. isolation/slooping the esophagus repairing the fistula as described above under H-type TEF. Tissue interposition between suture lines is sometimes advisable in an attempt to reduce the chances of further fistula formation. A 10–22% risk of refistulation has been reported.[82] Other approaches have been described to treat recurrent TEF including diathermy fulguration of the fistula tract.[82] This technique has been refined using the Nd:YAG laser to obliterate the epithelial communication. Sclerosing agents, histoacryl, and fibrin glues have all been injected subepithelially to occlude fistulae. A recent review of endoscopic therapies reported an overall closure rate of 55% with several sessions required to effect cure. A study from Oxford concluded that formal surgical re-exploration remained the treatment of choice, except in high-risk patients.[81]

RECENT ADVANCES

Developments in minimally invasive surgery have now extended to the EA and TEF newborn population. In 2002, Rothenberg reported the technical feasibility of endoscopic repair in a personal series of eight newborns with EA-TEF ranging in weight from 2.1 to 3.4 kg.[83] This study followed the first pioneering operation of EA in a two-month-old infant in 1998. Collaboration from members of the International Pediatric Endoscopic Surgery Group (IPEG) promoted a 2005 multi-institutional analysis of thoracoscopic repair from centers in the US, Europe, and Hong Kong.[84] One hundred and four babies with common variant EA and TEF (excluding H-type and long-gap without fistula) were included. Of these, there were five (4.8%) conversions to open thoracotomy and a staged repair in one baby due to unforeseen long-gap EA-TEF. Twelve infants (11.5%) developed early leaks and strictures and 32% required esophageal dilatation(s). Survival in this selected population was 97% with three deaths recorded of which one was directly related to the EA-TEF repair on the 20th postoperative day. Additional operations were required for associated anomalies. These included duodenal atresia repair, imperforate anus surgery, aortopexy, and cardiac procedures. Twenty-five babies (24%) also underwent laparoscopic fundoplication for GER. In 2009, MacKinlay reported equally good outcomes in a study of 26 infants – 88% survival, 27% leak rate – all minor not requiring operation and 35% acquired strictures needing dilatation(s).[85] Long-term benefits from minimally invasive surgery include a reduction in musculoskeletal morbidity, notably winged scapula, and unsightly skin scarring. For pediatric surgery centers currently not offering advanced endosurgical repair, the axillary skin crease incision popularized by Bianchi provides an excellent alternative with good esthetic outcome and comparable reductions in skeletal morbidity.[39]

QUALITY OF LIFE AND LONG-TERM OUTCOME

The improved survival of babies born with EA and TEF has prompted a more detailed analysis of morbidity, with emphasis on long-term outcome data.[86] Several studies have examined respiratory function in EA children.[87–90] Symptoms of asthma and bronchitis are frequent, especially in the young child, and may persist into adolescence. Almost half of all children require future hospitalization due to ongoing respiratory morbidity. In a large, Melbourne series comprising 334 EA children, episodes of pneumonia were seen in 31% of children under the age of five, compared with 5% of those over 15.[89] The prevalence of annual attacks of bronchitis in these two age groups was 74 and 41%, respectively, with asthmatic symptoms reported in 40% of patients from each age range.[87] Spirometry studies have demonstrated both obstructive and restrictive abnormalities in over half the patients, and a similar proportion had a maximal working capacity below the normal range.[88] Tracheobronchial inflammation and airway narrowing have been demonstrated by bronchoscopy in one-third of patients, with histological evidence of inflammation in a further third.[89] It is plausible that abnormalities of bronchial anatomy, which are common in EA and TEF, may contribute to respiratory morbidity. Regular clinical assessment by a respiratory physician, with chest physiotherapy and aggressive antibiotic treatment for infective exacerbations is recommended. The contribution of aspiration episodes, whether due to esophageal dysmotility or GER, to respiratory symptoms, should be actively investigated. Recognition of the long-term respiratory morbidity associated with EA patients, prompted the establishment of a specialist TEF clinic at Alder Hey, which is staffed by pediatric surgeons, respiratory physicians, physiotherapists, and dieticians. This multidisciplinary team approach ensures that attention is focused on all aspects of the child's ongoing welfare. Other centers equally report the benefits to the child and family of this coordinated follow-up plan.

Esophageal dysmotility is a significant factor in long-term morbidity.[91] It is clearly implicated in many cases of food bolus impaction when endoscopy reveals no significant anastomotic narrowing. Less severe symptoms of dysphagia have been reported in 20% of adolescents[91] and in 48% of adults on long-term follow up. Esophageal manometry and fluoroscopy studies will demonstrate degrees of dysmotility in nearly all patients.[88] The dysmotility associated with EA may reflect intrinsic innervation abnormalities of the esophagus.[92] This may further contribute to respiratory morbidity through repeated 'silent' aspiration episodes.

GER may persist into adult life. Reported symptoms of heartburn and acid brash range from 18%[89] to 50%[88] in long-term follow-up studies. Clinical symptoms may underestimate the true incidence of GER as demonstrated by esophageal pH monitoring. An 8% incidence of Barrett's esophagus has been reported.[93] The relative risks of esophageal adenocarcinoma are uncertain although five cases have been recorded in the literature.[94,95] These observations highlight the importance of comprehensive long-term follow up with the pediatric surgeon's duty to ensure robust transitional care pathways for children as they become adolescents with transfer to adult medical and surgical services where indicated.

Various quality of life measures have been used to evaluate adults treated for EA and TEF. Using a Spitzer index and a gastrointestinal QoL index, it has been shown that adults who underwent primary anastomosis as newborns enjoyed an unimpaired quality of life. Quality of life measures were more favorable in patients who had native esophageal repair compared to colonic interposition.[86] Psychosocial assessment scores have further demonstrated more learning, emotional, and behavioral difficulties in EA adults than the general population.[96] Cognitive performance was also significantly impaired in a high risk group characterized by associated major congenital anomalies and/or the requirement for prolonged ventilation in the neonatal period.[90]

An energetic support group (TOFS), a UK-based charity was founded in 1982 for the benefit of children and parents. The organization with over 1000 members (www.tofs.org.uk) provides a useful resource of excellent information together with a handbook 'The TOF Child'.[97] With regular conferences attended by health care professionals and families, opportunities exist for exchange of knowledge and advice. The TOFS organization also raises valuable funds for research.[2] Similar valuable support networks exist in other European countries, e.g. KEKS in Germany.

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Congenital esophageal stenosis

SHINTARO AMAE AND MASAKI NIO

INTRODUCTION

Difficulties in obtaining a differential diagnosis of congenital esophageal stenosis (CES) from achalasia and secondary esophageal stenosis, especially stricture due to reflux esophagitis,[1] have resulted in various clinical problems in its treatment. CES is defined as an intrinsic stenosis of the esophagus caused by congenital malformation of the esophageal wall architecture. This malformation may result from:

- tracheobronchial remnants in the esophageal wall;[2–16]
- fibromuscular thickening of the esophageal wall;[1,11,17–21]
- membranous mucosal diaphragm or web.[8,11,22–30]

Achalasia, inflammatory esophagitis, and stenosis caused by tumor or extrinsic compression of the esophagus should be excluded from this category. The localization of the stenosis varies with the type of pathology. Stenosis due to tracheobronchial remnants is the most common type of pathological anomaly, and is localized to the distal esophagus,[12] whereas fibromuscular thickening is generally found in the middle or lower portions of the esophagus.[11,21] Membranous webs are normally observed in the upper or middle levels of the esophagus.[11,26–30] In general, the stenotic area in cases with tracheobronchial remnants is usually localized, and that of fibromuscular stenosis varies from one to several centimeters in length with circular thickening of the esophageal wall. In almost all cases of membranous web, a single web is found in children;[26,28,30] however plural webs, termed multiple trachea-like rings, are observed in young adults.[31–33]

PATHOLOGICAL FEATURES

In the stenotic segment caused by tracheobronchial remnants, mature or immature cartilage, the seromucous tracheobronchial glands and ciliated epithelium are generally found microscopically. Tracheobronchial remnants are believed to be the result of failure in the normal separation of the embryonic respiratory tract from the foregut. In fibromuscular cases, circumferential proliferation of smooth muscle fibers with moderate fibrosis was revealed.[11,21,34] Singaram *et al.*[35] reported a significant reduction of myenteric nitrinergic neurons and fibers in the muscle layer of two young adults diagnosed with CES. Lack of submucosa[27] and loose, vascular connective tissue, and diffuse lymphocytes[26] were observed microscopically in specimens of membranous web.

CLINICAL FEATURES

CES is a rare condition that occurs in 1 in 25 000–50 000 live births.[1,11] Although the reason is unknown, the incidence of CES is higher in Japan than elsewhere.[8,36] There is no sex predisposition. The incidence of other anomalies in association with CES has been reported to be 17–33%.[11,36] For instance, the association of CES with congenital esophageal atresia,[9–11,18,19,24,37–42] cardiac anomalies,[11,24] intestinal atresia,[11,23] anorectal malformation,[10,36] chromosomal anomalies,[7,11,21,23] etc. has been reported in the literature. Surgeons should keep in mind the association of congenital esophageal atresia with distal CES due to tracheobronchial remnants.

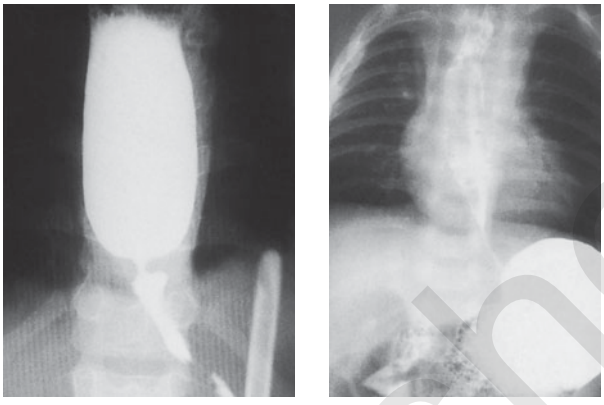
Symptoms of CES include vomiting or regurgitation, dysphagia, recurrent respiratory tract infections, and growth retardation. The onset of regurgitation coincides characteristically with the introduction of semi-solid and solid foods around the age of six months in patients with tracheobronchial remnants.[34] However, the development of symptoms rarely occurs in newborns.[25] In some patients, a foreign body in the esophagus may be the first symptom noted.[1]

DIAGNOSIS

Patients who develop the symptoms described earlier should undergo a barium swallow. Esophagograms show a tapered or abrupt narrowing of the esophagus in association with

various degrees of dilatation of the suprastenotic portion of the esophagus (Fig. 40.1). Most of the stenoses due to tracheobronchial remnants are present as an abrupt narrowing on the esophagogram, while fibromuscular stenosis usually shows a tapered narrowing.[40,42] Following surgery for the treatment of congenital esophageal atresia with or without tracheo-esophageal fistula (TEF), an esophagogram should be evaluated with great care to avoid failing to find a narrowing at the mid-distal esophagus. It was reported that 4.9–14% of TEF cases were associated with CES.[40,43,44] Esophagoscopy, manometric study, and pH monitoring are helpful tools for the differential diagnosis of CES from achalasia and secondary esophageal stricture due to gastro-esophageal reflux. Esophageal endoscopy can directly evaluate not only the stenotic area (Fig. 40.2) and the site of the gastro-esophageal junction but also the presence of esophagitis. The mucosa distal to the stenosis is normal in CES. In addition to esophagoscopy, endoscopic ultrasonography has been recently employed to evaluate the etiology of CES and is useful in deciding the strategy, either balloon dilatation or surgical treatment.[41,45,46]

In cases of CES, preoperative esophageal manometry demonstrates a normal pattern of the lower esophageal sphincter and a small high-pressure zone in the resting pressure profile (Fig. 40.3), which corresponds to the stenotic area of the esophagus (this small high-pressure zone disappears after corrective surgery). Moreover, an esophageal motility study reveals aperistalsis corresponding to the stenosis. pH monitoring revealed that significant positive reflux is not a feature in patients with CES in contrast to that seen in patients with gastro-esophageal reflux.



(a) (b)

Figure 40.1 Abrupt (a) and tapered (b) narrowing on esophagograms.

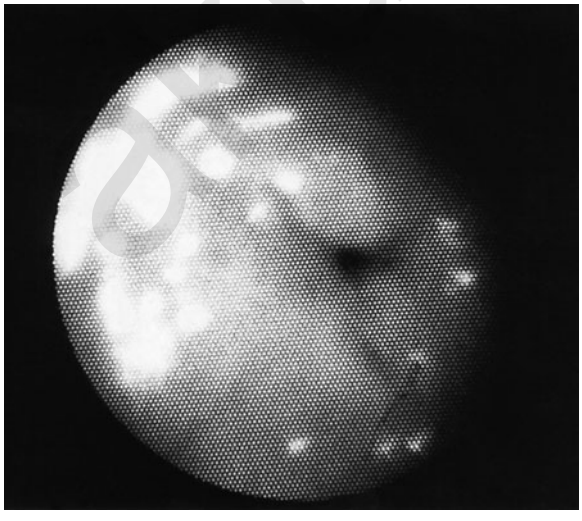


Figure 40.2 Endoscopic view of the stenotic portion of the esophagus.

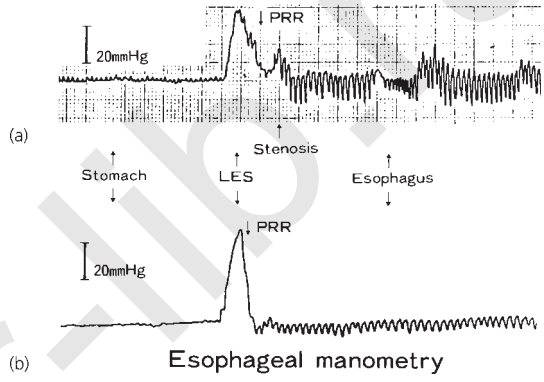


Figure 40.3 (a) Preoperative and (b) postoperative resting pressure profile of the gastro-esophageal junction and the esophagus in a case of CES with tracheobronchial remnants. A small high-pressure zone in the lower esophagus is noted and this disappeared after the corrective operation.

TREATMENT

The principles in the treatment of CES patients are the relief of the symptoms caused by esophageal stenosis and maintenance of the anti-reflux mechanism of the gastro-esophageal junction. This condition can be treated conservatively or by surgical intervention.

Balloon dilatation, as a conservative treatment, is the first choice of treatment for CES patients. Balloon dilatation should be tried not only for patients with tapered narrowing but also in patients with abrupt narrowing, when a balloon catheter can be passed safely through the stenotic area. We usually use the low-compliance (Rigiflex®) balloon catheter.[42] The effect of balloon dilatation varies with the type of pathology. Cases with membranous web of the esophagus and some cases of fibromuscular stenosis can be treated successfully by suitable dilatation.[11,26,28,29] Recently, successful treatment of membranous web using endoscopic instruments (electrocauterization, high-frequency-wave snare/cutter) have been reported.[47,48]

As a rule, when patients fail to respond to repeated (four to six times) attempts of bougienage, surgical intervention should be considered. Surgical resection of the stenosis followed by end-to-end esophageal anastomosis is a general surgical treatment for many cases with tracheobronchial remnants[6,8,10–16,36,39–42] and several cases with fibromuscular

thickening.[21,34] Circular myectomy was recently developed as the new surgical option to release the stenotic segment due to tracheobronchial remnant.[49,50]

Complications of treatment, as reported in the literature, are iatrogenic esophageal perforation by bougienage,[10,41] anastomotic stenosis, and leakage after surgical resection. In particular, iatrogenic esophageal perforation often requires an emergency operation. Circular myectomy is expected to prevent postoperative leakage and re-stenosis of esophageal anastomosis.[49,50]

PREOPERATIVE PREPARATION

Those patients who are undernourished should have their nutritional status corrected prior to surgery. Such patients may require total parenteral nutrition and/or enteral nutrition via a nasogastric tube or gastrostomy. Prior to the surgical procedure, it is essential that the surgeon knows the exact site and extent of the stenosis, and the distance from the gastro-esophageal junction. When the stenosis is situated in the distal portion of the esophagus, the authors always perform cineradiography and another special fluorographic procedure. In this procedure, first, a balloon catheter is inserted through the esophagus across the stenosis, and then barium is orally administered. Immediately following this, the balloon is inflated and pulled up. Adequate traction should position the balloon just below the stenosis allowing a clear image of the stenotic area (Fig. 40.4).

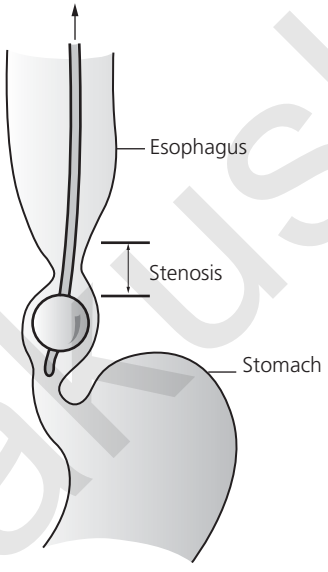


Figure 40.4 A special fluorographic examination for the evaluation of the exact site and extension of the stenosis. Stenosis is located between the dilated pouch of the esophagus and the balloon.

OPERATIVE PROCEDURE

Most cases of CES can be operated upon via the thoracic approach. However, when the stenosis is localized in the abdominal esophagus, the abdominal approach may be utilized. In a few cases of CES, complete resection of the stenotic segment using the thoracoscopic[51] or laparoscopic approach[52] has been reported. In the thoracic approach, right thoracotomy is employed for a stenosis in the middle portion of the esophagus, and left thoracotomy for a stenosis in the lower part of the esophagus. After exposing the esophagus, the authors insert a balloon catheter beyond the stenotic segment from the mouth to locate the stenotic segment. The balloon catheter is inflated and pulled up to confirm the lower margin of the stenosis. Following resection of the distal end of the stenosis, a sterile balloon catheter is passed through the stenotic area from the oral stump of the esophagus. The upper margin of the stenosis is decided by pulling down the catheter (Fig. 40.5).[42]

Complete removal of the stenotic area should be performed. Anastomosis should be made without tension. The use of single- or double-layer interrupted sutures using absorbable material is justified. The surgeons should, of course, pay attention to preservation of the phrenic and vagal nerves during surgery.

The possibility of simple excision of cartilaginous remnants and subsequent repair of the esophageal wall is limited.[5,11,42] Therefore, segmental resection with end-to-end anastomosis of the esophagus should be a standard procedure for patients with a stenosis in the mid or lower esophagus that is not close to the gastro-esophageal junction.

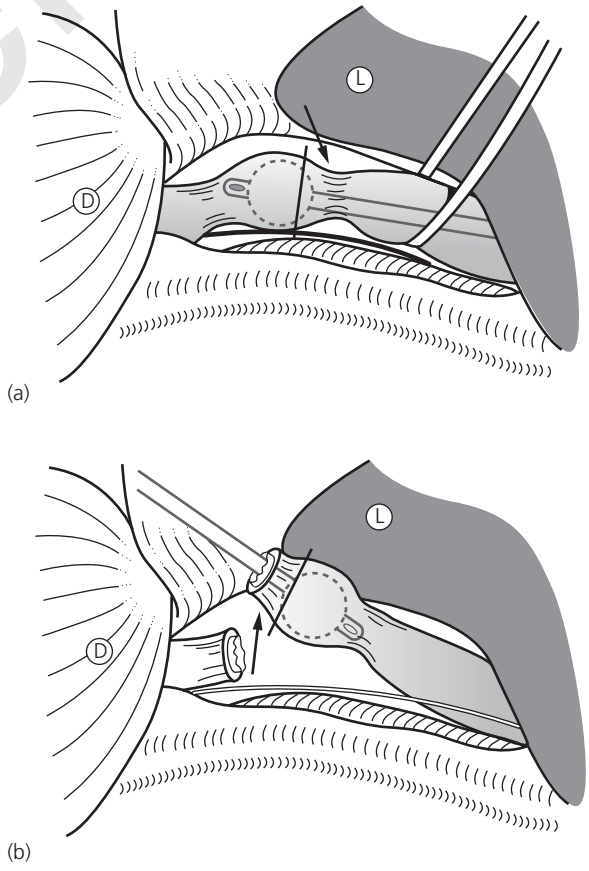


Figure 40.5 An intraoperative procedure by use of a Foley catheter to determine the (a) distal and (b) proximal sites of stenosis (arrows). (Solid line, resection line; D, diaphragm; L, lung.)

However, to prevent postoperative reflux, an anti-reflux procedure, for example a Nissen's fundoplication (Fig. 40.6) may be necessary, in addition to segmental resection, when the stenosis is situated close to the gastro-esophageal junction.[42] If the vagal nerve is severed by accident, a pyloroplasty should be performed. Patients with extensive fibromuscular stenosis necessitating resection of the esophagus of more than 3 cm may require esophageal replacement with a colon, jejunum, or gastric tube.

In circular myectomy, the stenotic segment is determined by pulling up and pushing down a balloon catheter inserted through the mouse. The muscular layer is incised to the mucosal layer at the lower and upper margins. Subsequently, the muscular layer is dissected circumferentially using sharp scissors or cautery (Fig. 40.7). The muscular layer is closed horizontally by interrupted absorbable sutures.[49,50]

Complications, such as an iatrogenic esophageal perforation following bougienage[10,53] and a leakage after segmental resection and reconstruction of the esophagus,[11] have been reported. Perforations and major leakages require surgical drainage, but minor leakages can be treated successfully by maintaining the patient on total parenteral nutrition. When gastro-esophageal reflux develops following simple resection and anastomosis, the anti-reflux procedure should be carried out.

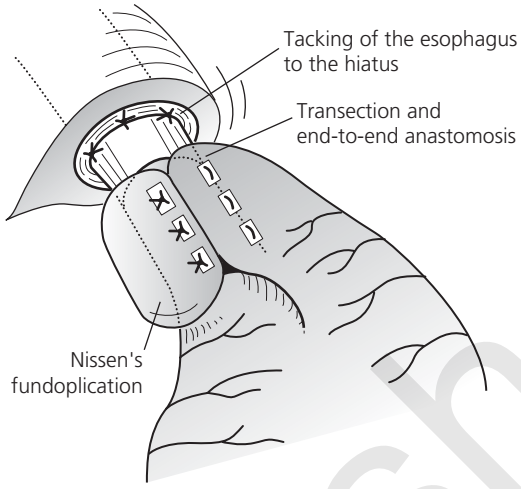


Figure 40.6 Transection of the distal esophagus with end-to-end anastomosis combined with an anti-reflux procedure (Nissen's fundoplication).

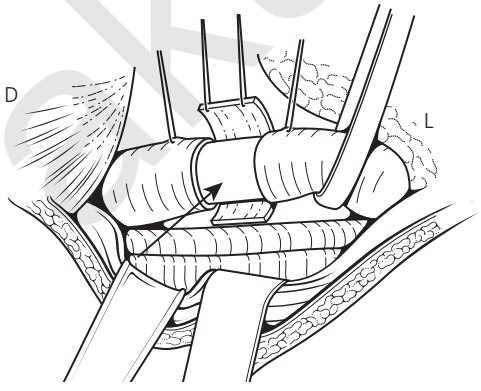


Figure 40.7 Procedure of circular myectomy of stenotic segment. (Arrow, dissected muscular layer; D, diaphragm; L, lung.)

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41

Esophageal duplication cysts

DAKSHESH PARIKH AND MICHAEL SINGH

INTRODUCTION

Esophageal duplications and bronchogenic cysts are part of the spectrum of foregut malformations as both seem to have their origin in the primitive foregut.[1] Foregut duplication cysts in children account for up to one-third of mediastinal cysts and are one of the main differential diagnoses for posterior mediastinal tumors. In the literature, approximately 21% of gastrointestinal duplications are reported to be of esophageal origin.[2,3]

Esophageal duplication cysts are seen in close proximity to the esophagus. There may be associated duplications elsewhere in the gastrointestinal tract. Some of the esophageal duplications can be thoraco-abdominal in nature.[4,5] In contrast, bronchogenic cysts are more frequent and are closely associated with the tracheobronchial tree or within the lung parenchyma. Unlike bronchogenic cysts esophageal duplication cysts are commonly associated with vertebral anomalies. In the presence of a vertebral anomaly, rarely an intraspinal communication can be identified. This variant is called a neuroenteric cyst.[6]

ETIOLOGY

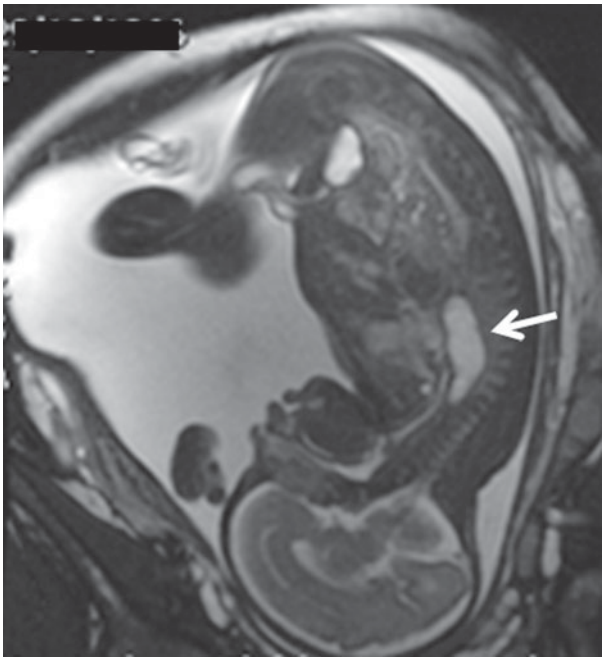
Esophageal duplications are thought to be a result of an aberrant dorsal foregut development during weeks 4–8 of gestation. One of the embryological theories implicates inappropriate canalization or failure of connection of the vacuoles as canalization of the gastrointestinal tract occurs to form a lumen. The other theory proposes a diverticulum occurring during the development of the gastrointestinal tract that may result in duplication with or without connection with the intestinal lumen. Both these theories fail to explain the various types of duplications occurring in the gastrointestinal tract. The split notochord theory in contrast can explain the association of vertebral anomalies with mediastinal duplications. The notochord is formed by the ingrowth of the mesodermal cells and separates from the endoderm. In the event of adhesion with the endodermal lining, it is drawn inside the spinal canal not allowing the spinal canal to close ventrally. It is possible that both ends of this connecting tract may remain open or closed on either side. The cephalic end may represent a fibrous cord, or connect to the cysts on either side, or disappear altogether as seen in most instances.[1]

PATHOLOGY

Esophageal duplications are described as cystic, tubular, or neuroenteric in nature. Over 60% of the esophageal duplication cysts are associated with the lower esophagus and the rest are identified within the upper and middle third of the esophagus. They generally have a thin wall of muscle coat and are in close proximity to the native esophagus or can be within the esophageal wall. Rarely some of the esophageal duplications can be simple epithelial lined cysts. The cysts can contain either a clear mucoid, brown, or blood-stained serous fluid. The majority do not communicate with the spinal canal or have an associated vertebral anomaly. Duplication cysts can have a wide variety of mucosal linings: squamous, gastric, pseudostratified, cuboidal, columnar, ciliated respiratory tract lining, or pancreatic cells.[4,5] A mixed epithelial lining within the cyst is commonly reported.[3,7,8] The symptomatic duplication may therefore bleed within the cyst or cause pressure symptoms onto the surrounding structures, such as trachea, esophagus, or fistulate.

PRESENTATION

The majority of esophageal duplication cysts present in early childhood and some are detected antenatally (Fig. 41.1a). In our experience of the antenatally detected, cystic thoracic lesions, approximately 5% of cases are subsequently diagnosed as foregut duplications. The majority of antenatally detected cases are asymptomatic at birth. Patients can present in infancy with: acute respiratory distress, stridor, dysphagia,



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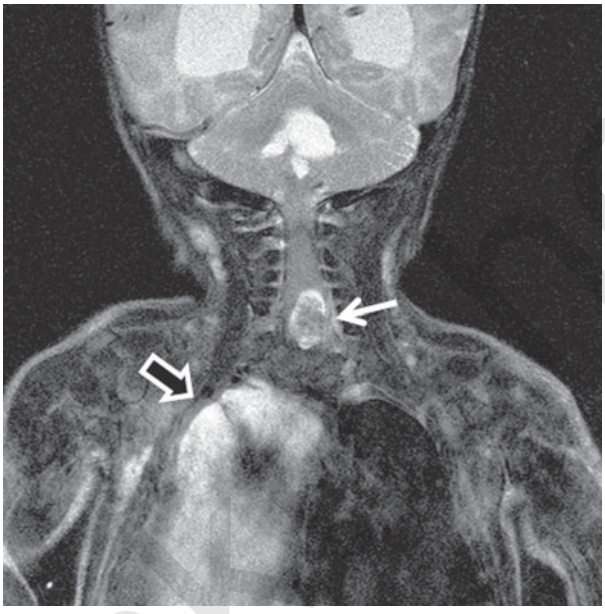
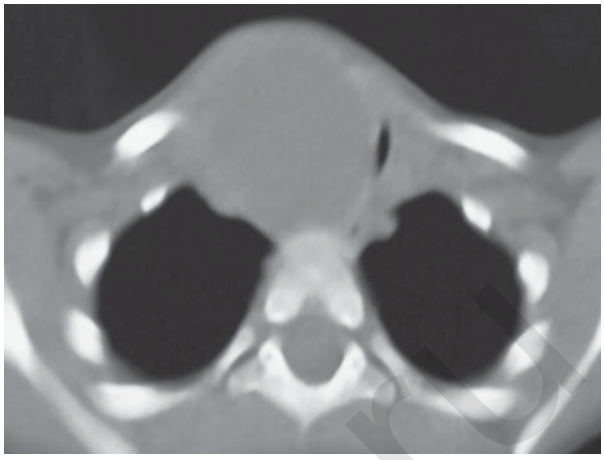


(b)

Figure 41.1 (a) Fetal magnetic resonance imaging (MRI) confirming antenatal ultrasound findings of foregut duplication cyst with intraspinal extension. (b) Postnatal MRI showing a large tubular esophageal duplication cyst (hollow arrow) with a cervical intraspinal component (white arrow).

meningitis, and the sudden appearance of a cervical mass (Fig. 41.2a,b). Sudden death has been reported in some untreated cases where the most plausible explanation would be the rupture of the cyst into the tracheobronchial tree.[8,9]

Occasionally, duplications may be an incidental finding on chest x-ray (Fig. 41.3). The symptoms in older children are generally related to pressure on the surrounding structures. Esophageal compression causes dysphagia (Fig. 41.4b).



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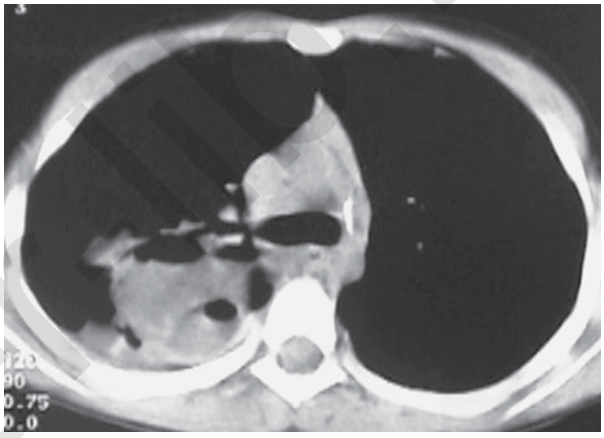


(b)

Figure 41.2 (a) Computed tomography (CT) scan demonstrating a large cervical esophageal duplication with tracheal compression and deviation, in a patient with acute stridor and sudden appearance of a cervical mass. (b) CT scan showing an infected duplication cyst with a fistula into the right upper lobe bronchus. This patient had recurrent pneumonia and developed a right upper lobe lung abscess seen on chest x-ray.

Tracheal compression results in stridor or respiratory compromise (Fig. 41.2a). These cysts may ulcerate, bleed, and rupture into the esophagus or tracheobronchial tree causing recurrent pneumonia, pain, hemoptysis. and lung abscess (Fig. 41.2b).[3,7,8] Both squamous cell carcinoma and adenocarcinoma in esophageal duplication cysts have been reported in adults.[10,11]

A high preoperative mortality (10%) has been reported in a large retrospective study.[8] The reported deaths are a consequence of exsanguinating bleeding into the esophagus, respiratory compromise, or septic complications.[8]

DIAGNOSIS

All antenatally diagnosed thoracic, cystic lesions must be investigated postnatally with contrast-enhanced computed tomography (CT) scan. A foregut duplication on CT scan is located in the posterior mediastinum in contact with the

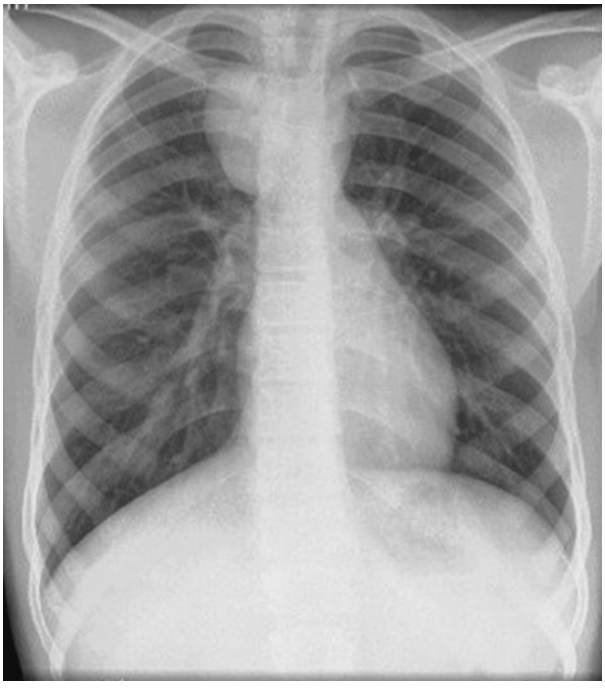


Figure 41.3 Incidental chest x-ray finding of a duplication cyst in a previously asymptomatic patient. This x-ray was done for blunt chest trauma. Subsequent investigation confirmed this to be an esophageal duplication.

esophagus or trachea. Typically, they are described as a low attenuation, homogenous cystic mass with a smooth border (Figs 41.4c and 41.5d).[12]

Plain x-ray may reveal a paravertebral, smooth round shadow. In symptomatic cases there may be a deviated or compressed trachea (Figs 41.2a and 41.4c). The plain x-ray is also useful in demonstrating associated vertebral anomalies (Fig. 41.5a).

In children presenting with dysphagia, a contrast swallow will demonstrate a smooth shadow compressing the esophagus (Fig. 41.4b). In the acute onset of stridor, a CT scan will show a cystic mass causing tracheal compression (Fig. 41.2a). The lower esophageal duplication cysts are likely to remain asymptomatic and can present in adulthood either on an incidental x-ray or with symptoms such as chest pain, dysphagia, or hematemesis (Fig. 41.5b). Magnetic resonance imaging (MRI) should be considered in the presence of vertebral anomalies for the diagnosis of an intraspinal component (Figs 41.1b and 41.5c). Upper gastrointestinal endoscopy and esophageal ultrasonography add little to the diagnosis of the esophageal cyst.

MANAGEMENT

Esophageal duplications warrant complete excision as incomplete excision inevitably results in a recurrence.[8] Antenatally diagnosed cases after investigation should be electively excised preferably with the thoracoscopic approach. In most instances, symptomatic cases are suitable for thoracoscopic resection with the exception of infected cases with fistulation (Fig. 41.2b). Thoracoscopic excision is being increasingly used for the management of esophageal duplication cysts.[13–15] The thoracoscopic approach has been shown to have lower opioid requirements, shorter duration of chest tube drainage and hospital stay.[14,15] Previous inadequate resection with recurrence may require an open approach for a complete resection.

Thoracoscopic resection

Central endotracheal intubation is used in most cases with the exception of older children where single lung anesthesia is possible. The patient is placed in the lateral position, with the affected side uppermost. The optical port is generally inserted just anterior to the angle of the scapula in the mid-axillary line. Two or three additional ports are inserted under thoracoscopic vision for the best possible manipulation. The lung is collapsed and retracted with creation of a pneumothorax with minimal pressures (5–7 mmHg of CO_2, flow rates of 1.5–2 L/min) to expose the posterior mediastinal cyst.

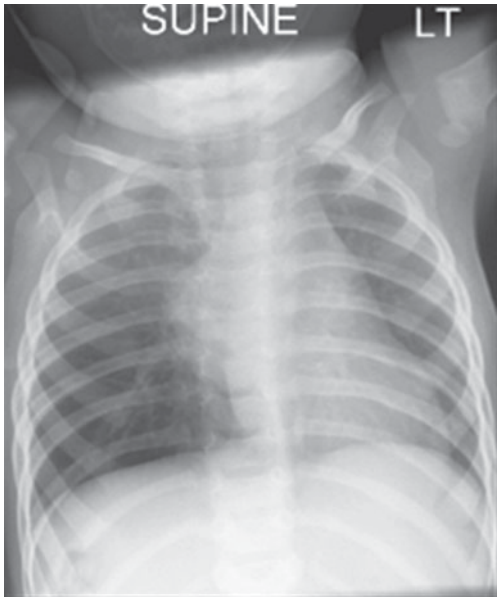
The pleura at the base of the cyst is incised either with scissors or diathermy hook. Two types of duplications are encountered, requiring slightly different techniques during their resection. The commonly encountered duplication has a separate muscle wall and is attached to the native esophagus by connective tissue adhesions. The dissection can be completed using either diathermy scissiors, harmonic scalpel, or LigaSure™ (ValleyLab, Boulder, CO, USA). The vagus, phrenic nerve, and thoracic duct are at risk of injury during the resection of the thoracic inlet duplication. Esophageal duplications sharing a common muscle wall with the native esophagus are relatively rare and a technical challenge to resect thoracoscopically. A nasogastric tube or an endoscope placed *in situ* during resection can help avoid resection of a major portion of wall and mucosa of the native esophagus. The cyst should be completely excised with the esophageal mucosa left intact if possible. Marsupialization should be avoided as leaving residual cyst wall tends to result in recurrence.[8] Once the cyst is removed, the defect in the esophageal musculature and mucosa can be sutured with absorbable sutures. The specimen is decompressed by aspiration and delivered by expanding one of the anterior ports.

In the presence of a thoraco-abdominal duplication cyst, complete resection is achieved by an additional laparoscopic approach. A separate intra-abdominal cyst can be successfully resected either at the same time or at a subsequent laparoscopic resection.[5]

Most esophageal duplications following resection do not require postoperative chest drains. We recommend a chest drain only if the esophageal mucosa is breached during the resection.[16] Postoperative pain is managed by i.v. paracetamol and oral anti-inflammatory drugs. The majority of thoracoscopically resected cases can be discharged the following day.

Thoracotomy and resection

A lateral thoracotomy through the bed of the fifth rib is recommended for an open resection. Adhesions, either



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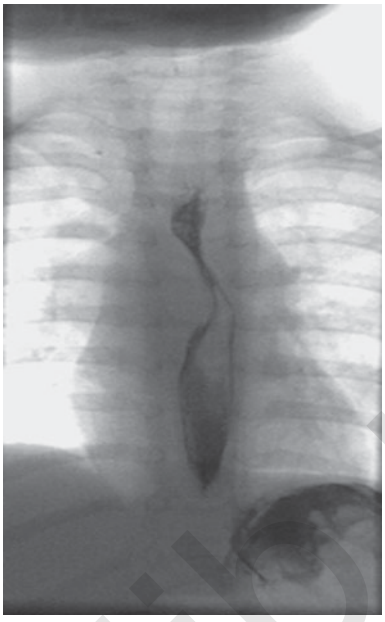

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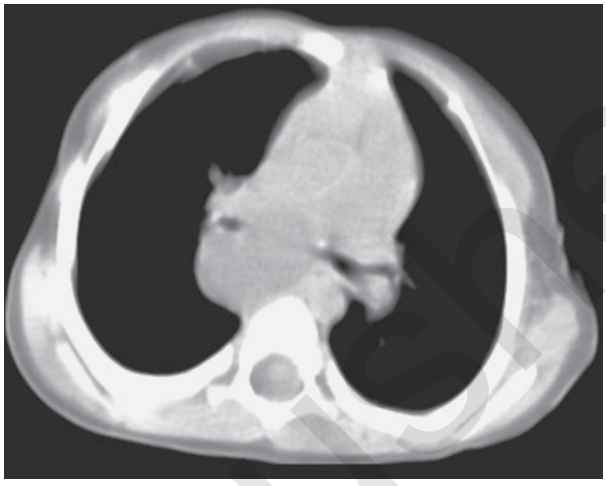

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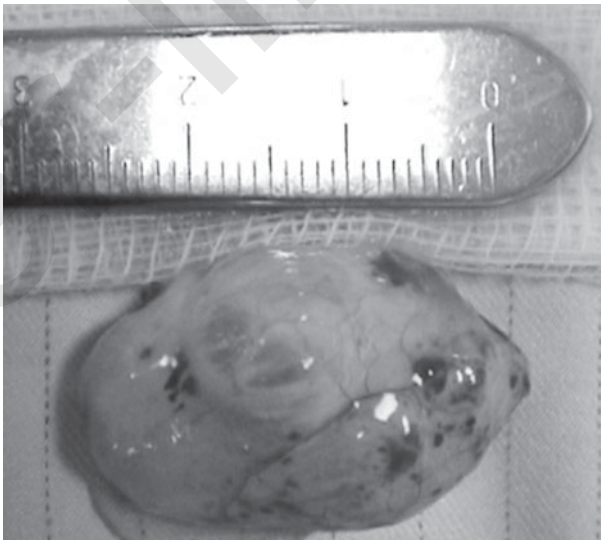

(d)

Figure 41.4 (a) This patient presented with recurrent chest infections. Chest x-ray shows mild emphysema of the right lung with a smooth round mediastinal mass. (b) A contrast swallow shows the classical smooth shadow compressing the esophagus. (c) Computed tomography scan revealed a typical low attenuation, homogenous cystic mass with a smooth border compressing the right main bronchus. (d) Duplication cyst specimen following thoracoscopic excision.

inflammatory or as a result of a previous operation, are the cause of complications in open operations. Bleeding and air leaks, either from the lung parenchyma or from fistulation, should be managed intraoperatively in order to avoid postoperative complications. The above-mentioned nerves and thoracic duct are also at risk of injury as bleeding or adhesions may obscure their presence near the duplication.

Cervical and suprasternal cysts

Cervical excision can be achieved by placing the patient supine with a roll under the shoulders. Once the cyst wall is identified, the dissection is continued staying close to its surface. The recurrent laryngeal nerve is particularly at risk of injury as it can travel on the surface of the esophageal duplication.

SURGICAL COMPLICATIONS

Surgical complications are related to the site and mode of surgery. Incomplete excision is associated with recurrence and the need for further surgery.[8] Esophageal leak is a possibility with both the open and thoracoscopic approach. A minor leak can be managed conservatively with a period of

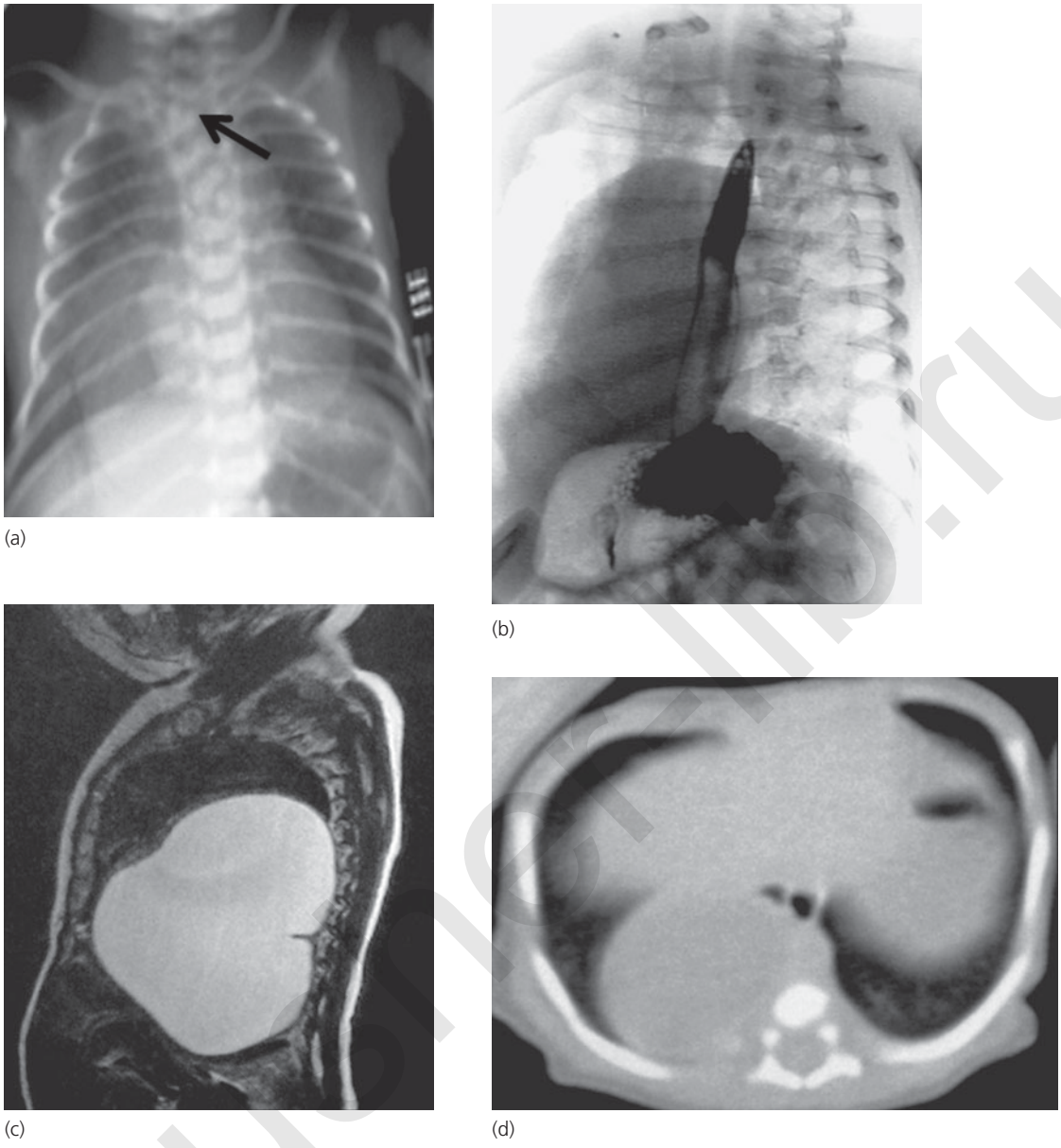

Figure 41.5 (a) Chest x-ray showing vertebral anomalies in an antenatally detected foregut duplication cyst. (b) Contrast study demonstrating a large posterior mediastinal duplication cyst. (c) Magnetic resonance imaging was done to rule out neuroenteric component in the presence of vertebral anomalies. (d) Computed tomography confirmed a smooth low attenuation posterior mediastinal duplication cyst.

nil by mouth with parenteral nutrition, antibiotics, and chest drainage. However, major leaks may require thoracotomy, esophageal repair, and chest drainage.[7,13] This group of patients are at risk of esophageal stricture long term, that may respond to dilation. Esophageal pseudodiverticulum is a long-term risk if the esophageal musculature is not approximated.[15] A persistent air leak will require thoracotomy and formal repair of the bronchus or trachea.[13] In a retrospective series, two postoperative deaths have been reported secondary to septic complications – one from an esophageal leak and the other from cyst-related sepsis.[8]

Injury to the vagus, recurrent laryngeal nerve, and phrenic nerve in the cervical and the superior mediastinial duplication can be avoided by careful dissection and staying close to the cyst wall. Judicious use of the monopolar diathermy in dissecting close to the nerves is recommended. There is a higher risk of nerve or thoracic duct injury during surgery for an infected cyst because of adhesions and bleeding.

LONG-TERM OUTCOME

All esophageal duplications should be excised because of the potential for life-threatening complications: peptic ulceration and bleeding or perforation, acute airway obstruction, recurrent infection, mediastinitis, meningitis, and the long-term risk of cancer. Thoracoscopic excision in the asymptomatic patient has a lower complication rate than surgery for a cyst-related complication. Patients who are known to have

incomplete excision should be monitored for recurrence. The patients with vertebral anomalies should be monitored for scoliosis. Rarely, a motility disorder of the esophagus is noted in some cases after resection as a result of damage to the pharyngeal plexus. After resection of the cervical duplication, a pharyngeal pouch can be a long-term consequence.

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42

Esophageal perforation in the newborn

DAVID S FOLEY AND HIRIKATI S NAGARAJ

INTRODUCTION

Iatrogenic esophageal perforation occurs rarely in neonates given the repeated orotracheal and oro-esophageal instrumentation of these patients, and was first reported in the literature by Eklof and colleagues.[1] In the past two decades, perforation of the esophagus in extremely premature neonates has become increasingly recognized and reported. Spontaneous perforation of the esophagus (neonatal Boerhaave syndrome) is extremely rare, and Fryfogle[2] performed the first successful repair. Despite the favorable results of non-operative management in cases of neonatal esophageal perforation, this condition may be fatal without early diagnosis and treatment, and aggressive surgical therapy is occasionally warranted.[3–5] Surgeons must continue to play a central role in the individualization of care in these patients.

CLASSIFICATION AND ETIOLOGY

Esophageal perforation in newborns can be classified as iatrogenic or non-iatrogenic. Non-iatrogenic perforations are extremely rare, and are usually seen in full-term infants when they occur. The most common site of perforation is the lower third of the esophagus. Etiological hypotheses for spontaneous perforation include increased intra-abdominal pressure at delivery, perinatal hypoxemia, and reflux-associated peptic esophagitis.[6]

Iatrogenic perforation of the esophagus is most commonly seen in premature, small for gestational age (SGA) infants,[7] and usually occurs in the cervical esophagus or hypopharynx. Pharyngeal suctioning with a stiff catheter, traumatic laryngoscopy, esophageal intubation, and digital manipulation of the neonatal head during breech delivery have all been described as causative.[8–11]

During instrumentation, when the neck is hyperextended, perforation of the esophagus may occur at the level of the cricopharyngeus muscle, where the posterior esophageal wall is compressed by the sixth or seventh cervical vertebra. Submucosal injury by a laryngoscope blade or endotracheal tube may be the initial injury to the hypopharynx, resulting in cricopharyngeal spasm.[12] Endotracheal intubation, especially in premature, SGA neonates, may further compromise the esophageal introitus. Subsequent oropharyngeal suctioning or insertion of a nasogastric tube may extend the submucosal injury into a full-thickness perforation.

Perforation of the middle esophagus is usually associated with dilatation of a stricture, or a postoperative anastamotic leak following esophageal atresia repair.[13,14] An improperly placed chest tube may cause disruption of a fresh esophageal anastamosis, or may penetrate a proximal myotomy site.[15] Direct pressure necrosis of an otherwise normal esophagus has been reported in a premature neonate.[16]

Distal esophageal perforation may be associated with dilatation of an esophageal stricture secondary to esophagitis, a technical error during antireflux surgery, or a misplaced gastrostomy balloon.[17]

DIAGNOSIS AND CLINICAL MANIFESTATIONS

Newborns with iatrogenic esophageal injury may demonstrate excessive salivation and mucoid secretions due to difficulty swallowing, and many will have overt respiratory distress. The examiner will have difficulty passing a nasogastric tube, either as the inciting event, or as a result of swelling or a false tract created by prior instrumentation. In neonates, an abnormal position of the nasogastric tube on post-placement chest x-ray is commonly the first indication of esophageal perforation.[7]

In premature infants, the presence of blood-tinged oral secretions after endotracheal intubation warrants serial x-ray examinations of the chest. The proper diagnosis often will be missed in the absence of such an examination. The symptoms of perforation may not be recognized until the child develops esophageal obstruction, and may be mistaken for esophageal atresia.[7,11] Esophageal perforation may be differentiated from atresia of the esophagus by an asymptomatic interval after birth, a premorbid history of repeated attempts at intubation or vigorous suctioning, absence of prenatal polyhydramnios,

and the position and course of the nasogastric tube on chest x-ray.[7] Some perforations of the esophagus create respiratory distress secondary to the development of hydropneumothorax. In these cases, the right pleural space is most commonly affected.[3,5,9,11] Thoracentesis or tube thoracostomy should yield serosanguinous fluid or the contents of the previous feeding. Chylopneumothorax has also been reported in association with neonatal esophageal perforation.[18]

Anteroposterior and lateral x-rays of the chest and neck should be obtained in any suspected case of perforation. The abnormalities seen in these cases depend on the site of injury. Hypopharyngeal and cervical perforations frequently demonstrate extraluminal air in the neck, without pneumomediastinum initially. Mid-esophageal perforations may demonstrate pneumomediastinum, pneumothorax, or hydrothorax. An unusual course of the nasogastric tube (right pleural cavity, pericardial cavity (Fig. 42.1) or right side of the mediastinum) supports the diagnosis, and may be confirmatory. Widening of the mediastinum and blurring of the mediastinal margin may occur secondary to the development of mediastinitis, but are later and more subtle findings. These changes should prompt esophagography. Mollit *et al.*[19] described three types of injuries that are seen in premature neonates: (1) a pharyngeal diverticulum created by a local cervical leak; (2) a mucosal perforation extending posteriorly in parallel to the esophagus; and (3) a free intrapleural perforation where there is obvious leakage of air and esophageal contents into the pleural cavity.

In cases where chest x-ray demonstrates the nasogastric tube to be located in the pleural cavity or pericardium, the diagnosis of esophageal perforation can be confirmed (Fig. 42.2). In this situation, precise localization of the site of perforation may be unnecessary, unless the patient's clinical condition deteriorates after removal of the nasogastric tube and tube thoracostomy drainage. If symptoms suggest esophageal obstruction, esophagography should be performed by administering a small quantity of diatrizoate meglumine (Hypaque™), diatrizoate sodium (Renografin) or metrizamide into the proximal esophagus; gastografin and barium should be avoided due to the risk of worsening mediastinitis or inducing significant pulmonary inflammation with aspiration. In cases of pharyngeal–esophageal perforation, cricopharyngeal spasm may be so severe that no contrast material will enter the native esophagus. In these cases, several clues may help to differentiate submucosal perforation or peudodiverticular formation from congenital esophageal atresia.[20] These include:

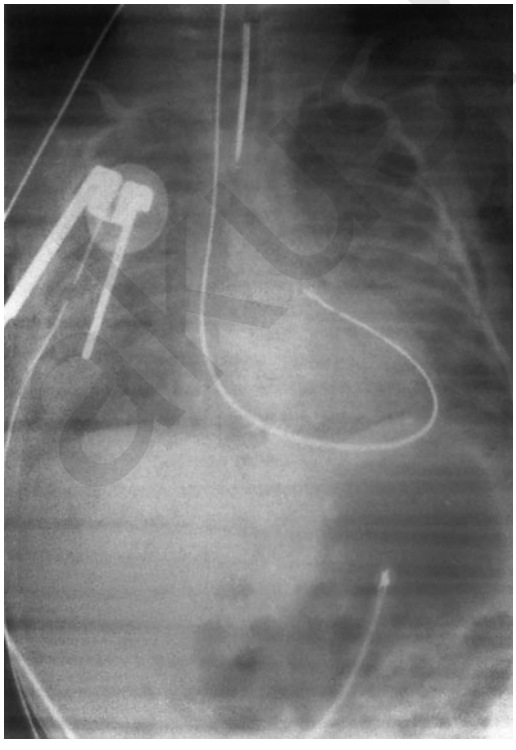


Figure 42.1 Chest x-ray shows displacement of the nasogastric tube to the pericardial sac.

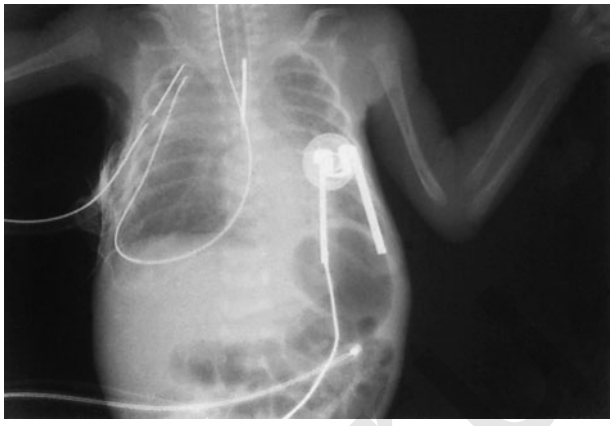


Figure 42.2 Anteroposterior view demonstrates coiled nasogastric tube in right pleural cavity and chest tube placed for tension pneumothorax.

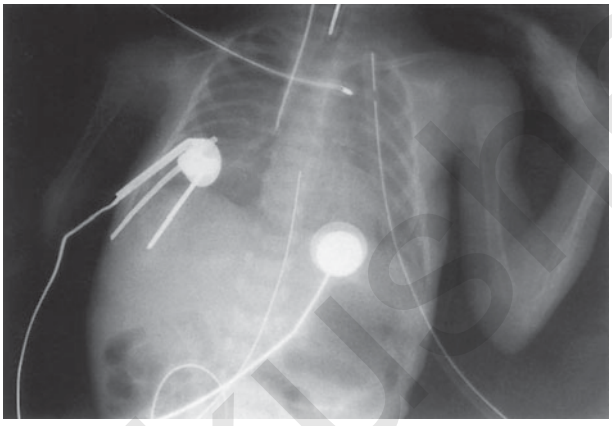
- the distance between the trachea and opacified tract on lateral x-ray is greater than that of the pouch in a congenital esophageal atresia, which is closely associated with the trachea;
- the opacified tract in perforation cases is longer, narrower, and more irregular than in esophageal atresia;
- the trachea is slightly compressed on lateral x-ray by the upper pouch in esophageal atresia, but this is not so in esophageal perforation.

Esophagoscopy is usually not indicated at the time of diagnosis, and may actually enlarge the perforation.

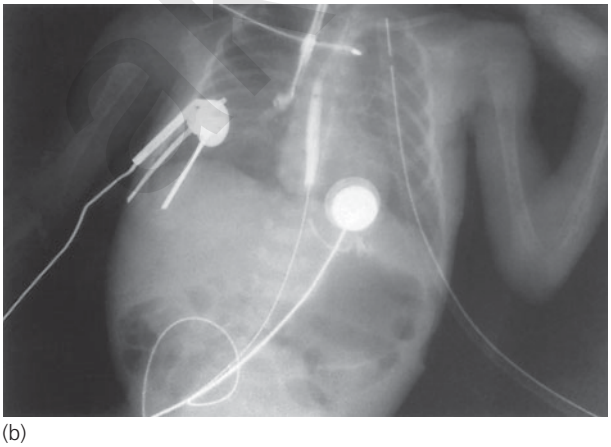
Spontaneous perforation of the neonatal esophagus usually presents with respiratory distress, which may be immediate or delayed for several hours after the event. There is a greater predilection for right-sided pneumothorax in neonatal Boerhaave syndrome, in contrast to the left-sided pneumothorax typically seen in adults.[6,16] This may be explained by the close adherence of the aorta to the left side of the esophagus in neonates, which provides an additional mediastinal barrier on the left side. If the perforation remains undiagnosed, respiratory distress will worsen with subsequent feedings. Esophagography must be performed in all suspected cases of free perforation, to evaluate the extent of the damage and to localize it.

MANAGEMENT

The management of neonatal esophageal perforations has favored a selective approach in recent years.[5,19,21,22] Esophageal perforation can be a rapidly fatal condition that requires immediate recognition and aggressive management for a successful outcome. However, the treatment of esophageal perforation must be individualized according to the site and size of injury, the systemic response of the neonate, and the time interval between the injury and initiation of treatment. Small submucosal perforations of the hypopharynx and esophagus, limited to the mediastinum and without systemic symptoms, may be managed by non-operative methods (Fig. 42.3). Actual localization of the peforation is not essential in these infants. If the nasogastric tube is noted in the mediastinum or pericardial cavity, the tube can be withdrawn and a new tube placed under fluoroscopic control. A broad-spectrum antibiotic must be given for 7–14 days. Intravenous fluids and hyperalimentation should be administered, as oral feedings must be withheld. Esophagography should be performed 7–10 days after the injury. If the perforation is completely healed, oral feeding may be resumed. If the perforation has not healed during this interval, conservative treatment for another week will usually allow complete healing.



(a)



(b)

Figure 42.3 Contrast study demonstrating contained, submucosal perforation of the proximal esophagus.

In general, routine surgical intervention does not appear to improve the rate of survival in these newborns. Tube thoracostomy should be placed when the chest x-ray indicates pneumomediastimun, pneumothorax, or hydrothorax (Fig. 42.4). All newborn infants with esophageal perforation must be carefully monitored during treatment, including the use of white blood cell counts or C-reactive protein levels, platelet counts, blood gas analyses, and chest x-ray evaluation. If there is clinical deterioration or respiratory compromise, and closed chest drainage does not handle the leak, direct repair of the perforation is indicated.

In cases where direct repair of the perforation is not technically feasible because of scarring, inflammation and tissue friability, diverting cervical esophagostomy with closure of the perforated area and concomitant gastrostomy is indicated. If at all possible, efforts should be made to avoid future esophageal replacement. Long, linear perforations to the lower end of the esophagus require an immediate thoracotomy, debridement of the necrotic edges and primary repair of the defect with pleural flap coverage. A gastrostomy tube may be inserted in these situations to minimize the risk of gastroesophageal reflux during healing.

If there is a delay of more than 24 hours in the diagnosis of a spontaneous perforation of the esophagus, unprotected primary repair cannot be safely accomplished. After adequate debridement, the treatment should be local esophagectomy with closure of the proximal and distal esophagus, proximal esophagostomy, and gastrostomy tube placement. Critically ill newborns should be managed with chest tube drainage, cervical esophagostomy (with or without ligation of the cardio-esophageal junction), and gastrostomy.[23] Broad-spectrum antibiotics, i.v. fluids, and hyperalimaentation should be continued until clinical signs of sepsis improve. Gastrostomy feedings may be attempted after 48 hours. In cases where extensive debridement or resection is necessary, esophageal substitution is indicated after an interval of at least six months, when the mediastinal inflammation has resolved.

Perforations that occur following dilation of esophageal anastamotic strictures are usually managed non-operatively, as long as the leak is contained or can be adequately drained by tube thoracostomy. These perforations may take some

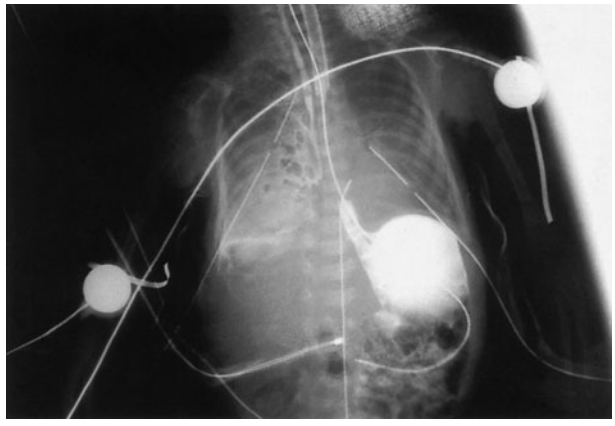


Figure 42.4 Free spillage of contrast material into right pleural cavity, indicating a free perforation in this infant. Clinical deterioration warranted direct repair.

time to heal due to obstruction at the stricture site. Recently, endoscopic stenting has been reported as a means of containing leakage and promoting healing in these cases.[24]

CONCLUSION

Iatrogenic perforation of the esophagus is more common than reported in the literature, and may be fatal without early diagnosis. The incidence of recognized pharyngeal and esophageal perforations is low, however, considering the large number of pharyngeal instrumentations that are performed on premature infants in modern neonatal intensive care units.[19] Gentle laryngoscopy with proper visualization of the vocal cords during intubation, avoidance of protruding stylets, careful suctioning of the pharynx, and avoidance of forceful nasogastric tube placement are all essential factors in the prevention of these injuries.

It is generally accepted that most iatrogenic perforations of the esophagus in newborns are cervical, and made when inexperienced personnel attempt to intubate the trachea. With early diagnosis, most of these perforations can be managed non-operatively with successful outcomes.[25] However, these infants should be monitored closely. If they develop systemic illness, appropriate operative intervention is often required. Early diagnosis of this condition allows for more treatment options, which include non-operative therapy, closed chest drainage, and primary repair. The mortality rate in neonates with esophageal perforation (4%) is significantly less than that in older children and adults (25–50%).[5,26] Delayed diagnosis may result in the inability to repair the injury primarily, a significant increase in mortality, and the eventual need for esophageal replacement among survivors. Surgical consultation is warranted in all cases of esophageal perforation to allow timely and selective management, thereby limiting both mortality and long-term morbidity.

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43

Gastro-esophageal reflux in the neonate and small infant

MICHAEL E HÖLLWARTH

INTRODUCTION

Gastro-esophageal reflux (GER) is the term that describes the back flow of gastric content into the esophagus, sometimes reaching even the mouth. It is a common phenomenon and occurs in otherwise normal individuals several times during day and night, especially after ingestion of fluids, e.g. soup, tea, coffee, or milk. Therefore, reflux episodes are more common in neonates and infants as long as they are nourished mainly with milk. The typical reflux symptoms in this age group are regurgitation, spitting up and flaccid leak out of milk after meals and when asleep. Pathological reflux defines a situation when the reflux causes symptoms in the neonate, such as failure to thrive, sleep disturbance, and obviously pain. The aim of this chapter is to discuss the normal esophagus in newborns and its function, the typical symptoms of reflux in this age group, the investigating procedures, and the conservative and operative therapy.

ANATOMY

The esophagus is a muscular tubular organ responsible for the transport of food from the mouth to the stomach. The upper half is composed of striated muscles and its lower half consists of smooth muscle. The lumen is covered by a non-keratinizing, stratified squamous epithelium. At the esophageal–gastric junction the epithelial layer changes to a monolayer columnar epithelium, the so-called cardia epithelium.

The diaphragmatic hiatus of the esophagus is fixed by the phrenico-esophageal membrane, which is incompetent in the case of a hiatal hernia. The medial wall of the esophagus directly continues into the lesser curvature of the stomach while the lateral wall forms a kind of incisure – the so-called His angle. Within the lumen at the His angle is a mucosal fold (flutter valve), which is passively pressed against the lower esophageal sphincter (LES) when the gastric fundus is filled, thus preventing reflux (Fig. 43.1).[1] The flatter the angle of His, the less developed is the flutter valve, and the more readily a reflux occurs by anatomical reasons.

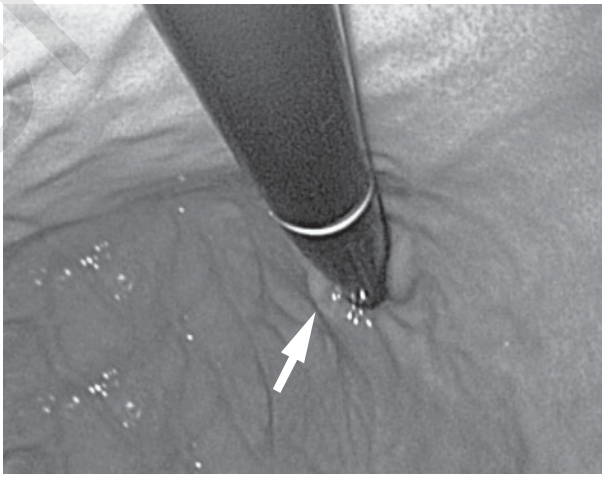

Figure 43.1 Typical mucosal 'flutter valve' at the site of the His angle within the stomach.

INNERVATION

The esophagus has a parasympathetic innervation through the vagus nerve which runs along the esophagus. Sympathetic innervation arises from post-ganglionic neurons of the sympathetic chain. The myenteric plexus and the submucosal plexus contain also non-adrenergic and non-cholinergic nerves, and execute the complex activity of the esophagus through a number of neurotransmitters. Most important is a central regulation by consecutively activated nuclei in the brainstem responsible for the peristalsis and relaxations of the esophageal sphincters.

THE SPHINCTERS

There are two sphincter systems at the upper and lower end of the esophagus. In adults, the tone in the upper esophageal sphincter (UES) is markedly higher (between 40 and 80 mmHg) than in the LES (between 15 and 25 mmHg). The UES relaxes during propulsion of food from the oral cavity, but also when refluxed volume reaches the upper esophagus from below; then, refluxed material can reach the hypopharynx and eventually the oral cavity.

Reflux of the contents of the stomach into the esophagus is prevented by the LES. The pressure ranges between 15 and 25 mmHg in adults. On manometry, the pressure zone permits easy identification of the exact position of the sphincter. The pressure transition of the LES lies exactly within the diaphragm. The upper half of the sphincter can be assigned to the chest cavity while the lower portion of the pressure zone is assigned to the abdominal cavity (Fig. 43.2).

PERISTALSIS

Once food enters the esophagus, it is transported by a propulsive peristaltic wave into the stomach (primary peristalsis). In any local distension of the esophagus, as in cases of reflux, a propulsive peristaltic wave arises locally and transports the contents of the esophagus back into the stomach (secondary peristalsis). Isolated and disorderly contractions are defined as tertiary peristalsis or pathological contractions.

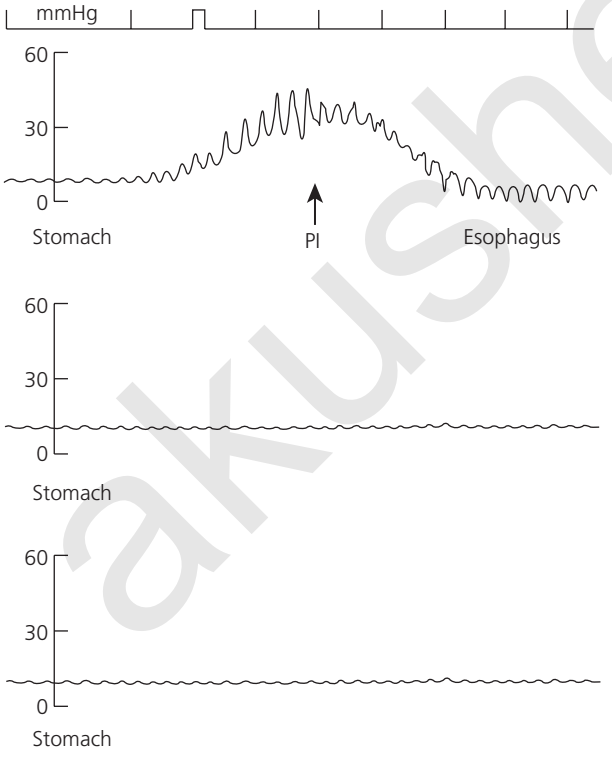

Figure 43.2 Slow pull-through manometry through the lower esophageal sphincter (LES) in a newborn child. PI indicates the pressure inversion from a typical stomach tracing to a typical esophageal tracing. Thus, the PI is located within the diaphragmatic hiatus and one part of the LES belongs to the abdomen and the other part to the thorax. Except for the sphincter, there is no intra-abdominal esophagus.

CAUSES OF REFLUX

One of the specific characteristics of the LES is that its tonus not only relaxes when food enters the esophagus through a propulsive peristaltic wave, but regular spontaneous relaxations of 5–10 seconds' duration (spontaneous transient LES relaxation (STLESR)) occur even in the absence of any other esophageal activity in healthy individuals. Thereby, a common space is opened between the stomach and the esophagus and can be demonstrated on manometry as a sudden change of the typical esophageal tracing into an abdominal pressure curve, the 'common cavity phenomenon' (CCP) (Fig. 43.3). Usually, these relaxations remain unrecognized because in

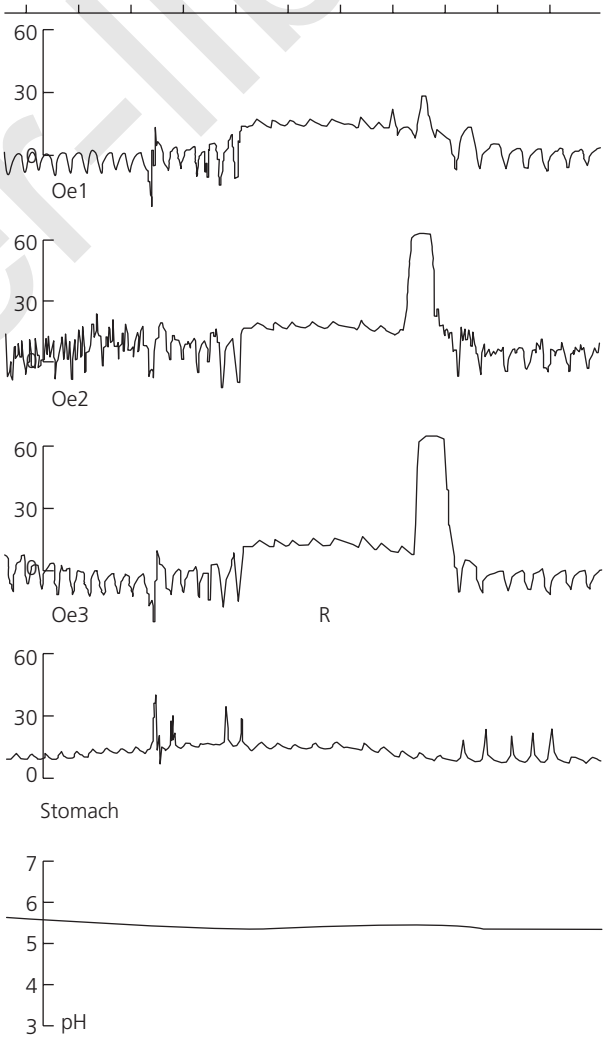

Figure 43.3 Spontaneous pressure inversion of the esophageal tracing to an abdominal tracing indicates the opening of the lower esophageal sphincter due to a transient relaxation. This is the manometric sign of reflux – the common cavity phenomenon. It is always terminated by a secondary propulsive peristalsis.

most events the reflux reaches only the lower esophagus. The volume is immediately returned to the stomach by a secondary peristalsis (volume clearance). Any drop of the pH, however, is neutralized in a stepwise manner by saliva during subsequent acts of deglutition (acid clearance). In patients with pathological reflux or reflux disease, STLESRs occur significantly more often and for longer.

THE DEVELOPMENT OF THE ESOPHAGUS IN THE NEONATE AND SMALL INFANT

The best way to investigate the esophageal function in this age group is manometry combined with pH monitoring. Studies in premature and newborn babies have shown that the length of the LES is 10.7 mm. The tone of the LES in these groups of babies was in the range 18.0–23.0 mmHg. Thus, the tone in the LES is identical to the tone in older age groups and in adults (Table 43.1).[2]

Manometric studies have shown that there is a physiological delay in the development of propulsive esophageal peristalsis. Induced swallows in the youngest group of patients have been followed in only 59% by a propulsive peristalsis and in 41% by simultaneous contractions of the esophagus. However, already at the age of 4 weeks nearly all investigated babies had a normal peristaltic response in eight of ten induced swallows.

Table 43.1 Results of esophageal manometry: the LES pressure values in newborn babies and infants are already normal.

	n	Age (days)	LES tone (mmHg) x ± s.d.	LES length (mm) x ± s.d.	PS ($n = 10$)
Premature (GA 30–36)	7	7–28	23.0 ± 3.6	1.0 ± 1.1	–
Newborns	24	1–10	20.4 ± 8.0	10.7 ± 0.8	5.2[a]
Newborns	19	11–28	21.8 ± 10.0	11.0 ± 0.5	7.3
Infants	20	>28	18.0 ± 7.0	11.3 ± 1.1	7.9

[a] $p < 0.05$.
LES, lower esophageal sphincter.
PS is the response of propulsive peristaltic waves in the esophagus after ten induced swallows. The results show that the response is significantly lower within the first 10 days of life, but thereafter it is normal with nearly eight propulsive responses out of ten induced swallows.

REFLUX IN THE NEWBORN

Mild spitting, a flaccid leak out, or vomiting of milk as a sign of a pronounced GER is observed in approximately half of all newborns and young infants. The subsequent development shows that these symptoms become less frequent after the first four to six months of the infant's life and are no longer observed at 12 months in most cases. Previously, it was believed that frequent reflux in these young age groups was caused by a physiologic absence of tone in the LES. However, our former studies using adequate manometric techniques have clearly shown that the incidence of GER in newborns and infants is not caused by a low or even absent pressure of an immature LES nor by a deficient esophageal peristalsis, but it is the consequence of other factors (Table 43.1).

What is immature in this age group and what might cause the higher incidence of reflux? Three factors have to be considered:

1. **Spontaneous LES relaxation**: we were able to show that GER in newborn and infants is caused by STLESRs. Babies with pathological reflux have significantly more frequent and more prolonged STLESRs, but a normal LES tone (Table 43.2).[2,3] These findings were later confirmed by Omari *et al.*[4] Further investigations showed that pathological STLESRs are associated with immaturity of the normal propulsive peristalsis of the esophagus. Thus, we can conclude that reflux in this age group is not caused by an absent LES tone, but must be regarded as delay in the central motor coordination in the esophagus and its sphincters. The particularly high prevalence of reflux in infants with sleep apnea is an additional indicator in the conclusion that immature central regulatory structures are responsible for the frequent STLESRs.[5] In most cases, a spontaneous maturation of this functional instability occurs within the first year of life and thereafter the reflux pattern is identical to that of adults. However, it has been shown that the disappearance of the clinical signs of reflux around the age of 12 months does not necessarily mean that the esophageal function is normalized.[6] Despite persistent reflux, the clinical signs may be mild or even absent but years later sequelae of a chronic pathological reflux may become evident. Recent investigations in adults have shown that approximately half of young adults with reflux disease had marked symptoms in their childhood.[7]
2. **The His angle** may have a significant impact on the function of the LES and the incidence of spontaneous relaxations in this age group. In contrast to older children, the His angle in newborns and infants is not sharp but flat and no mucosal valve can be seen during endoscopy (Fig. 43.4). Any increased intragastric pressure after meals is then exerted directly towards the sphincter due to the lack of the mucosal valve mechanism.

Table 43.2 CCP occur significantly more often and longer in babies with GER when compared to normal controls. However, the LES tone is not different between groups.

	Seconds	With reflux (*n*)	Controls (*n*)
CCP episodes	<7	12.4 ± 2.6[a]	3.3 ± 0.5
	7–15	9.6 ± 1.1[a]	3.4 ± 0.4
	>15	3.0 ± 0.8[a]	0.7 ± 0.2
Total CCP time (%)		2.0 ± 0.3[a]	0.5 ± 0.05
LES tone (mmHg)		25.3 ± 2.6	30.2 ± 1.4

[a] $p < 0.05$.
CCP, common cavity phenomenon; GER, gastro-esophageal reflux; LES, lower esophageal sphincter.

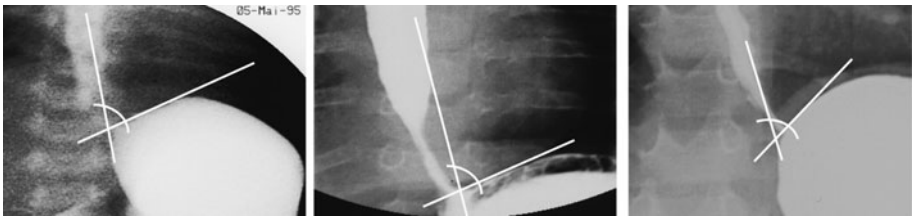

Figure 43.4 Development of the His angle: the diaphragm moves upward with age and the His angle becomes markedly sharp angled in this child with a primary gastro-esophageal problem.

3. Finally, it is well known that any **ingested fluid causes reflux** episodes. The largely liquid nutrition (milk) given in infancy causes frequent refluxes. The number of reflux events is significantly reduced towards the end of the first year as soon as nutrition is more solid.

SYMPTOMS OF PATHOLOGICAL REFLUX IN NEWBORNS AND INFANTS

Pathological reflux in this age group may be characterized by different symptoms. The most typical reported signs are regurgitation, effortless leak out of milk or food after meals, between meals, and when asleep. A moist pillow is another sign of reflux. Further symptoms of pathological reflux are restless sleep with sudden wake up and crying periods. If recurrent vomiting of food is significant, the child may develop malnutrition and failure to thrive.[8–10] Rarely one may observe even rickets despite seemingly adequate vitamin D supplementation as a consequence of the recurrent vomiting. Further suspicious symptoms are developmental disorders, recurrent respiratory tract infections due to microaspirations, greater irritability and agitation. Quite often the reflux-related problems in feeding the baby may significantly disturb the interaction between mother and child. However, the clinical symptoms are not reliable indicators of a GER disease and often demonstrate poor correlation with the results of 24-hour pH monitoring or histology.[11]

The most significant complication of GER is esophagitis, which is caused by too frequent and prolonged relaxations of the LES and chronic acid exposure of the esophagus. The resulting inflammation of the mucosa may cause microbleeding and result in chronic anemia. If the inflammation spreads to deeper layers of the esophageal wall, it may eventually cause stenosis due to simultaneous formation of scars. However, in newborns and infants, as long as the babies are largely fed with milk, the acidic gastric juice is largely buffered during the first 2 hours after feeding (Fig. 43.5). Thus, esophagitis is a very rare occurrence in this age group.

DIAGNOSIS OF REFLUX

There are several diagnostic tests to determine a pathological reflux. However, in most cases only a few of them are needed in the newborn age group. It depends on the underlying problem whether or not an extensive diagnosis is needed.

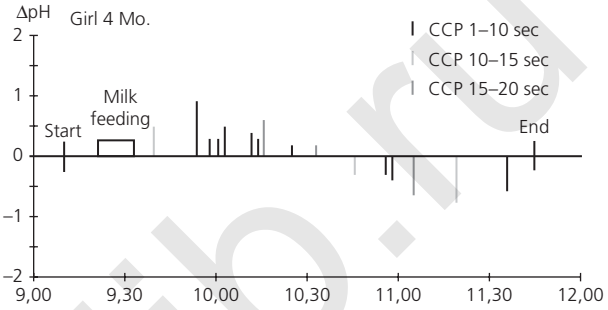

Figure 43.5 Combined manometric study and pH monitoring after a typical milk meal in a four-month-old child. The lines indicate reflux episodes with a common cavity phenomenon of different duration. The results show that refluxes are accompanied by a slight pH decrease only 1 hour after feeding.

In this section, the principal diagnostic tests to determine a pathological gastro-esophageal reflux are described.

Radiological investigation of esophageal passage

The primary purpose of x-ray diagnosis is to investigate the morphology and peristaltic function of the esophagus. Visualization of the gastro-esophageal junction, demonstration of a gliding or fixed hiatus hernia, assessment of the angle of His, the finding of smooth or pathological pharyngo-esophageal deglutition, the course of esophageal peristalsis, and any remarkable features in the epithelium as signs of inflammation constitute the most important information that needs to be obtained from a radiological investigation. A further finding is evidence of aspiration of contrast medium during the investigation. In contrast, the actual evidence of reflux is of less importance because radiological exposure time is short and the true extent of reflux may be overestimated or underestimated. Indirect signs of a pathological reflux include air reflux during the investigation, a positive water siphon test (reflux after taking a large sip of water as a reflux provocation), and the height of the reflux events must be documented.[12] This may yield an evaluation scheme which however, should be used only if it concurs with a 24-hour pH-metry.

Twenty-four-hour pH monitoring

This investigation is the gold standard to evaluate the function of the esophagus. The thinnest possible glass or

antimony electrodes are introduced by the nasal route and the ongoing pH values are recorded on a battery-driven recorder. Ideally, multichannel probes are used and pH values in the stomach, the lower esophagus, and the upper esophagus are registered. Thus, a pH drop in the esophagus can be correlated with the pH in the stomach, and the number of acidic refluxes that reach the upper esophagus can also be determined.

All pH drops below 4 of at least 15 seconds' duration (number of refluxes), the time required for normalization of pH and/or the increase of pH to 4 (reflux clearance), the number of refluxes with a clearance time of more than 5 minutes and the longest reflux are evaluated. Intake of food and the time in lying or upright position are also registered. Different institutions use different cut-off values which are partly influenced by values in adults. We use the threshold values shown in Table 43.3. The low threshold value of 3% used in infants fed largely on milk takes into account the fewer number of acidic refluxes during which the pH drops below 4 (Fig. 43.5).

The weakness of the method is the fact that it does not demonstrate refluxes with a neutral pH or mildly alkaline refluxes with an increase in pH.

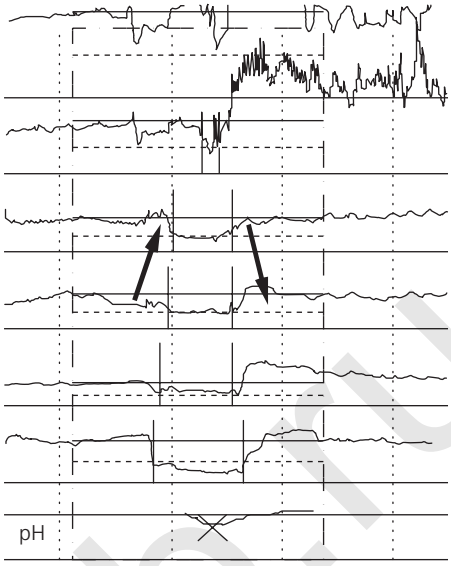

Figure 43.6 Combined impedance and pH monitoring: it shows a short reflux episode with a not significant decrease of the pH in the esophagus which would not be detected by pH monitoring alone.

Table 43.3 Cut-off values in our GI laboratory: the lower pH-% value in children under one year of age is the result of the fact the gastric acidity is neutralized in infants who are mainly fed with milk products (see also Figure 43.5).

Age (year)	pH < 4 in%	No. of refluxes	Refluxes >5 min	Reflux number	Clearance
<1	<3	<30	<5	<50	<1
>1	<5	<35	<5	<50	<1

Combined impedance/pH monitoring

Combining the impedance technique with pH monitoring allows determination of all refluxes and the direction of bolus movements. Thus, even all neutral and alkaline refluxes can be recorded over 24 hours (Fig. 43.6). This provides a much more informative and valuable assessment of a true reflux compared to simple pH-metry.[13–15] As microaspirations of non-acid refluxes may play an important role in recurrent respiratory tract infection, combined impedance/pH monitoring may well replace simple pH monitoring in the near future as the new gold standard of investigation.

Manometry

Manometric investigations of esophageal function were introduced as a diagnostic procedure in the late 1960s, primarily to measure pressure in the LES. It was presumed at the time that low pressures are responsible for the reflux. Initial manometric investigations in newborns and infants appeared to confirm this fact.[16] However, only with the use of low-perfusion, low-compliance pumps has it been possible to obtain relevant pressure data.

As mentioned earlier under Reflux in the newborn (p. 418), our investigations performed in the 1970s showed that even at this age, normal pressure values are registered in the LES.[2] Furthermore, manometry is an excellent method to demonstrate the motor function and peristalsis of the esophagus. It shows that reflux of the contents of the stomach occurs during spontaneous transient relaxations of the LES. The manometric sign of these relaxations is the CCP, which is characterized by an increase of the esophageal pressure tracings up to abdominal pressure values and the typical reversal to abdominal pressure fluctuations with the respiration (Fig. 43.3). Secondary peristalsis causes the refluxed volume to be conveyed back to the stomach. Normalization of the drop in pH is achieved in a stepwise manner by swallowing saliva. In combination with pH-metry, the CCP also allows the investigator to analyze non-acid, neutral, or alkaline refluxes and thus draw conclusions such as those derived from impedance measurement. However, the disadvantage of manometry is that it is a motion-dependent investigation and requires a quiet child; therefore, it is not suitable as a routine method, but is indispensable for scientific questions.

Endoscopy and histology

Investigations with flexible fiberoptic endoscopes and biopsies are invasive investigations but the only way to diagnose esophagitis. As such, they are a part of the standard procedure in older patients with GER but are rarely needed as a routine procedure for reflux in newborn infants.

Briefly, the endoscope is introduced into the esophagus under visual control and is usually extended down to the duodenum. Biopsies from the duodenum and antrum of the stomach are taken routinely. The tip of the device is inverted in the stomach in order to inspect the gastro-esophageal junction from below. Under normal circumstances, the esophagus encloses the device tightly and the above-mentioned flutter valve (see Anatomy, p. 416) can be seen at the lateral circumference. In contrast, in a hiatus hernia the cardia is slightly opened and the investigator is able to see into the herniated stomach, whereas the LES encircles the device higher up.

By withdrawing the endoscope further, the gastro-esophageal junction and the Z-line are inspected precisely. In normal cases, the esophageal epithelium is smooth and milky-red in color (grade 0). In the presence of esophagitis, one may find reddening, swelling (grades 1 and 2), striated erosion (grade 3), deep ulceration (grade 4), or stenosis (grade 5). Mild reddening of the mucosa at the distal esophagus is a normal condition. Grades 0–2 are largely prone to subjective assessment and often do not concur with the histological outcome. Therefore, it is essential to take several biopsy specimens, starting 1–2 cm proximal to the Z-line, upward into the upper esophagus. The quality of the biopsied material is of decisive importance for an accurate histological diagnosis. Therefore, an endoscope with the largest possible external diameter should be used to obtain the best possible material with the largest biopsy forceps. The biopsy specimens should be placed on a piece of cork, correctly oriented immediately after the specimen is taken, and then inserted in formalin. An optimal biopsy specimen should include the entire epithelium, as well as the basal-cell layer. Thickening of the basal-cell layer and relative elongation of the papilla (due to a thinner epithelial zone) are signs of increased cell turnover and pathological reflux. Evidence of intraepithelial eosinophils then confirms the presence of obvious esophagitis even in the absence of corresponding symptoms. Erosions and ulcerations are, by nature, signs of severe chronic esophagitis. However, in children, this condition is not always associated with unequivocal symptoms. On the other hand, the presence of more than 20 eosinophils per 'high-power' field is a sign of non-reflux-related allergic/atopic disease, which is also known as eosinophilic esophagitis.

Nuclear medicine investigations

Scintigraphic investigations permit the investigator to observe migration of the bolus through the esophagus, any reflux-related aspiration of nuclear medicine tracer material in the lungs, and the measurement of the time taken to empty the stomach after standardized meals. This consists of a solid and a liquid portion, e.g. an egg dish and water. ^{99m}Tc-labeled sulfur colloid is used as tracer. The act of swallowing is visualized in dynamic sequences. After setting the regions of interest (ROI), on the one hand refluxes are registered and on the other hand the mean time taken to empty the stomach is measured as a time/activity curve. Investigations after 24 hours permit the investigator to establish the presence of tracer in the lung, provided aspiration has occurred.

CONSERVATIVE THERAPY OF THE REFLUX DISEASE

A pathological reflux may be considered to exist when the infant has a history of significant regurgitation and flaccid vomiting, suffers from recurrent respiratory tract infections and/or pain, is restless at night, or has other typical symptoms. As the risk of esophagitis is very low at this age, an endoscopic investigation does not need to be performed if no other indications are present. In addition to a 24-hour pH monitoring or impedance pH monitoring, a contrast swallow of the esophagus and an ultrasound investigation of the pylorus are usually needed to exclude any pathologies that would hinder spontaneous healing of the reflux disease, such as hiatal hernia, chronic organo-axial gastric volvulus, gastric stenosis, pylorus hypertrophy, or other anatomic problems.

Since esophageal dysfunction with pathological reflux matures spontaneously in 90% of the otherwise normal infants, conservative measurements are the therapy of choice. Former investigations have shown that the prone position with the trunk raised most effectively prevents reflux, because the hiatus is in the highest position.[17] However, the risk of sudden infant death is markedly increased in this position because vomiting during sleep may result in an obstruction of the nose and mouth and cause prolonged apneic spells and sudden infant death syndrome (SIDS). Today, the supine position with an elevated trunk or left side positioning during sleep and elevation of the head of the bed is recommended.[18,19]

Frequent small volume meals and thickening of food with rice gruel are recommended. There is no clear evidence from the literature that any of these measurements and/or special manufactured milk formulas are effective in reducing the reflux index scores but they do reduce the vomiting episodes.[8,19–21] In most cases, the symptoms abate within the next few months. Prokinetic therapy has not proved to be effective and is no longer used in children.[10]

As mentioned above, the disappearance of the symptoms does not necessarily mean that there is no more reflux, it might just not reach the mouth. Therefore, at the end of the first year a control 24-hour impedance/pH monitoring should be performed to exclude definitively persistent reflux.[22,23]

About 10% of these children still have pathological results and need further treatment and controls. In these patients, addition of acid suppressive therapy is usually indicated, e.g. proton pump inhibitors (PPI). However, more studies are needed to determine which symptoms in infants and children should be treated with PPI.[24] When administering any form of medication for the treatment of reflux, one should be aware of the fact that the production of gastric acid is largely reduced, but the number of non-acidic refluxes will not necessarily be reduced. They may cause recurrent aspiration especially during sleep and chronic respiratory tract infections.

Our experience has shown that spontaneous normalization of the esophageal function may still occur until the age of three to four years and conservative treatment can be continued if the symptoms are minimal and the parents want

to avoid surgery. However, after this time, a spontaneous maturation of the function cannot be expected and surgical therapy is indicated. It has been shown that in these patients pathological reflux pattern continues until adulthood.[7]

SURGICAL THERAPY

As mentioned above, surgery of reflux is not indicated in most of the newborns and infants due to the spontaneous maturation of the esophageal function within the first year of life. However, there is a small group of patients in which any trials of conservative therapy are ineffective, even when treated under in-hospital supervision. Additionally, the process of spontaneous normalization of a pathological reflux cannot be expected in babies after correction of an esophageal atresia, diaphragmatic hernia, congenital hiatal hernia or even upside down stomach, organo-axial gastric volvulus and some other congenital anomalies. In these children, surgical procedures are indicated because the long-term sequelae of unphysiologic neutralization of gastric acid with PPI are problematic.

The strategic principles of reflux surgery consist of creating an intra-abdominal portion of the esophagus and a complete (Nissen) or partial plication (dorsal Toupet, ventral Thal) of the gastric fundus around the esophagus.[25] The standard approach today is by laparoscopy. The choice of the method depends on the surgeon and good results are achieved with all three methods. However, long-term follow-up controls after fundoplication show a relatively high failure rate, especially in cerebrally handicapped patients, in prematures, and when the procedure has been performed in early childhood.[26] The most common complication is recurrent reflux, which has been observed with all three surgical methods (Table 43.2).[27–29] It is related to the natural agitation in this region due to the movement of the diaphragm during respiration and to the significant shortening of the esophagus that occurs during swallowing.[30] Further risk factors for recurrence are severe rumination and regurgitation which occur in some cerebrally handicapped children.[31] Rare complications after a Nissen procedure may occur in patients with a rather tight fundoplication and the inability to vomit, a gas bloat syndrome, or dumping.

A rarely used method which might be useful in a patient with a very small stomach is the Collis gastroplasty, for which the His angle is deepened parallel to the esophagus with a stapler. The lengthened fundus is then used for a Nissen, Toupet, or Thal plication around the elongated esophagus.

The gastro-esophageal dissection is another method which is useful in rare cases of severely cerebrally handicapped infants with massive rumination and recurrent GER.[32] The esophagus is detached from the stomach and anastomosed to a Roux-en Y jejunal loop. Orally ingested food is thus diverted directly into the jejunum and recurrent reflux or rumination is rendered impossible.[33]

In the last few years, a number of new technical methods have been introduced for the treatment of reflux in adults, such as creation of a mucosal fold by an intraluminal stapler, radiowave damage of the cardia (Stretta procedure), or endoscopic submucosal injection of foreign material (Enteryx®). Experiences in children are rare and long-term results are lacking.[34–37]

SPECIAL PROBLEMS OF REFLUX IN THE NEWBORN AND INFANT

Laryngopharyngeal reflux

Chronic microaspiration of acidic reflux during the day and/or night may causes laryngeal symptoms, such as hoarseness, the urge to cough, and dysphagia. Each endoscopic investigation is incomplete if the larynx is not inspected. Reddening, ulcerations, or pseudopolyps on the vocal cords are typical signs of laryngeal reflux. However, these findings are very rare in this age group as long the babies are mainly fed with milk. As regards therapy, medication with PPI is recommended.

Reflux-associated infections of the respiratory tract

Aspiration of acidic or even non-acidic reflux is the cause of recurrent respiratory tract infections and pneumonia. Other causes, such as cystic fibrosis, aspirated foreign bodies, H-type fistulas, or other malformations of the respiratory tract must be excluded. In cerebrally handicapped children, disruption of the pharyngo-esophageal transport – disturbed swallowing – is also a well-known cause of recurrent aspiration.

Diagnosis is not simple, except when the radiological investigation shows aspiration of the contrast material during reflux phases. Neither bronchioalveolar lavage nor nuclear medicine investigations are unequivocal. pH monitoring with one recording point in the upper and one in the lower esophagus provides only indirect signs, when a large number of refluxes extend into the upper esophagus. If evidence of recurrent reflux-associated aspiration is obtained, surgery is indicated.

Reflux and apnea syndrome

Apnea and SIDS are the most common causes of death between the ages of two and six months. The association of reflux and apneic spells has been investigated with unequivocal results.[38] Some studies have not proved a temporal relationship between GER and apnea.[8,39,40] Although an increased rate of GER was observed after feeding in preterm infants, a corresponding increase of apneic spells was not found. Our investigations with manometry and pH-metry in infants with pathological sleep apnea have not shown that acidic refluxes are directly causing apneic spells. However, we did register a markedly delayed maturation of motor function of the esophagus in babies with sleep apnea or apparent life-threatening events (ALTE).[5] Further studies have shown that infants investigated due to a pathologic sleep apneic pattern frequently have also pathological reflux, whereas infants with a primary history of pathological reflux have no remarkable

apneic spells.[41] These investigations support the hypothesis that infants with sleep apnea syndrome or ALTE suffer from a deeper localized underlying immaturity of regulation centers in the brainstem, while the causes for a delay in the maturation of the esophageal motor function are localized in higher brainstem regions and therefore not necessarily associated with disorders of the respiratory regulation.[2]

Hiatal hernia

Any upward gliding of portions of the stomach into or above the esophageal hiatus are called hiatal hernia (HH). A gliding HH is rare in newborns and infants, but one cannot expect a spontaneous normalization of this anatomic malformation. The previously used term 'forme mineure' for minimal HH in infants is no longer considered a pathology, but is known as a normal finding of the special anatomy of the gastro-esophageal junction in this age group.

Para-esophageal hernias are not so rare findings after fundoplication. A part of the stomach slips through the hiatus into the chest, lateral to the gastro-esophageal junction. If a small postoperative para-esophageal hernia is combined with reflux or any other symptoms, surgical correction is indicated. A congenital form of para-esophageal hernia is the upside-down stomach in the newborn, which is a more or less complete displacement of the stomach into the chest while the gastro-esophageal junction remains in the normal position.

Esophageal atresia and diaphragmatic hernia

The lower segment of the esophagus in patients with esophageal atresia is characterized by an abnormal or absent propulsive peristalsis, even after uneventful surgery. Due to the absent peristalsis refluxed material remains for a prolonged time in the esophagus and volume as well as acid clearance are significantly prolonged. In this age group, the long acid clearance time may already cause a chronic esophagitis. A spontaneous normalization of the pathology cannot be expected; therefore, surgical correction is usually necessary.

Children with congenital diaphragmatic hernia frequently suffer from a pathological reflux due to the abnormal anatomy of the gastro-esophageal-diaphragmatic anatomy.[42] Early fundoplication is indicated because a spontaneous normalization of the disturbed function cannot be expected.

REFLUX IN NEUROLOGICALLY IMPAIRED CHILDREN

In patients with severe neurological impairment gastro-esophageal reflux disease is a common disorder that may lead to a number of complications, such as esophagitis, esophageal stenosis, anemia, and/or Barrett esophagus. Although these symptoms usually become clinically evident only in later childhood, vomiting, recurrent respiratory tract infections as well as failure to thrive are, in small babies, strong indicators that the underlying pathology is accompanied by a significant reflux problem.[43] Manometric studies show that these children suffer not from a sphincter insufficiency but from too many spontaneous LES relaxations. These findings again support the hypothesis that pathological reflux is strongly connected to a dysfunction of the regulation centers in the brain. Whether a conservative therapy including PPI, a fundoplication (with or without a button gastrostomy), or an esophagogastric dissection is needed has to be decided on an individual basis considering the quality of life and circumstances of the child.

CONCLUSION

Gastro-esophageal reflux is common in neonates and small infants. It is caused in most cases not by an insufficient LES but by a delay in the development of the esophageal function characterized by many spontaneous relaxations of the LES. In more than 90% of the babies, a spontaneous maturation of the esophageal function can be expected until the end of the first year of life and, therefore, unspecific conservative measurements are usually sufficient. In contrast, babies with severe and recurrent complications of reflux, e.g. recurrent respiratory tract infections and/or congenital malformations, usually need a surgical therapy by a semi-circular or complete fundoplication.

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PART V

GASTROINTESTINAL

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44

Pyloric atresia and prepyloric antral diaphragm

VINCENZO JASONNI, ALESSIO PINI PRATO, GIOVANNI RAPUZZI, AND GIROLAMO MATTIOLI

PYLORIC ATRESIA

Introduction

Gastric outlet obstruction in the newborn may be due to pyloric atresia, antral web, or hypertrophic pyloric stenosis. The most common cause of gastric outlet obstruction is hypertrophic pyloric stenosis.

Pyloric atresia is a rare congenital malformation representing less than 1% of all atresias and diaphragms of the gastrointestinal tract.[1–3] Up to 50% of these patients have associated abnormalities, of which epidermolysis bullosa is the most common.[1,4–6] Familial occurrence of pyloric atresia has been reported.[5,7] Puri *et al.*[8] described pyloric atresia in three consecutive siblings in a family.

Etiology

Although certain etiology is still unknown, mucosal desquamation has been suggested to play a role, mainly in patients with associated epidermolysis bullosa.[9] Junctional epidermolysis bullosa associated with pyloric atresia (EB-PA (congenital disorders and malformations) OMIN 226730) is a rare autosomal recessive inherited disease in which mucocutaneous fragility is associated with this type of gastrointestinal atresia.[9] This association is usually fatal during the first few weeks or months of life, even following surgical correction of intestinal obstruction. Recently, mutations in the genes encoding the subunit polypeptides integrin alpha 6 beta 4 (ITGA6 and ITGB4) have been identified in several patients with epidermolysis bullosa and pyloric atresia.[9–11] Regardless of association or not with epidermolysis, Bar-Maor *et al.*[12] and El Shafie *et al.*[13] concluded that there is strong evidence to support a genetic determination of pyloric atresia with an autosomal recessive mode of inheritance.

Pathology

There are three main different types of pyloric obstruction: type A, membranous pyloric obstruction; type B, longitudinal segmental atresia; and type C, pyloric aplasia (Fig. 44.1). Table 44.1 shows the incidence of different types of pyloric obstruction.[2,3]

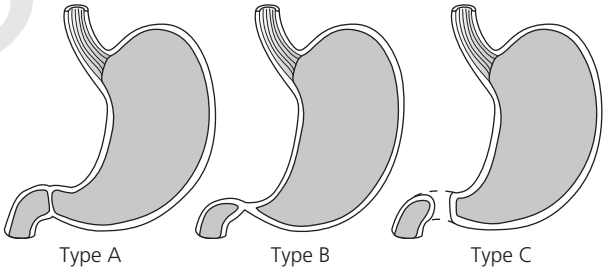

Figure 44.1 Anatomical varieties of congenital pyloric obstruction: type A, membranous pyloric obstruction; type B, longitudinal segmental atresia; type C, pyloric aplasia.

Table 44.1 Incidence of the different pyloric atresia types ($n = 140$).

Type of atresia	No. of cases	%
Membranous (type A)	77	57
Atresia (type B)	46	34
Aplasia (type C)	12	9
No data	5	3.5

Data from Muller *et al.*[2] and Lorenzet and Morger.[3]

History and physical examination

Prenatal diagnosis of pyloric atresia can be suspected when polyhydramnios is present and associated with a dilated stomach. Prenatal diagnosis of pyloric atresia and epidermolysis bullosa can be performed in pregnancies at risk for recurrence of this syndrome. However, some sonographic signs suggest the possibility of significant cutaneous desquamation and blister formation in a fetus, especially when there is positive amniotic acetylcholinesterase coupled with elevated alphafetoprotein.[14] Recently, prenatal magnetic resonance imaging has been used to confirm the diagnosis but its utility remains unclear.[15]

Presentation

The newborn with complete pyloric obstruction presents shortly after birth with persistent non-bilious vomiting and epigastric distension.[16] There is no significant gender predominance and there are a high proportion of infants with low birth weight.[17,18] Respiratory problems are common, and dyspnea, tachypnea, cyanosis, and/or excessive salivation may suggest esophageal atresia.[19] Very rarely, congenital gastric outlet obstruction can be associated with esophageal atresia.[20]

Delayed diagnosis of pyloric atresia can determine gastric perforation, although this complication has also been reported as early as 12 hours post-delivery.[21] See Table 44.2 for clinical features.[2,3]

Table 44.2 Clinical features of pyloric atresia ($n = 140$ patients).

Symptoms and signs	Occurrence (%)
Bile-free vomiting	100
Single stomach bubble (one bubble) on x-ray	98
Distended epigastrium	68
Polyhydramnios	63
Birth weight <2500 g	53
Prematurity	45
Jaundice	21
Peristaltic movements in the epigastrium	18
Hemorrhagic vomiting	12

Data from Muller *et al.*[2] and Lorenzet and Morger.[3]

Diagnosis

A plain x-ray of the abdomen will usually confirm the clinical diagnosis. X-ray (Fig. 44.2) will show severely dilated stomach without air below. Contrast study, although unnecessary, can confirm complete obstruction at the pyloric region. The radiological diagnosis is based on the identification of three radiological signs: the single gas bubble sign, the absence of beak sign (typical of hypertrophic pyloric stenosis), and the presence of the pyloric dimple sign on a contrast study.[22] The single gas bubble sign is not specific for the diagnosis of pyloric atresia, but it is an indicator of a gastric outlet obstruction. The ultrasonographic examination can be helpful and demonstrates the absence of normal pyloric muscle and canal, which is specific for the diagnosis of this entity.[22]

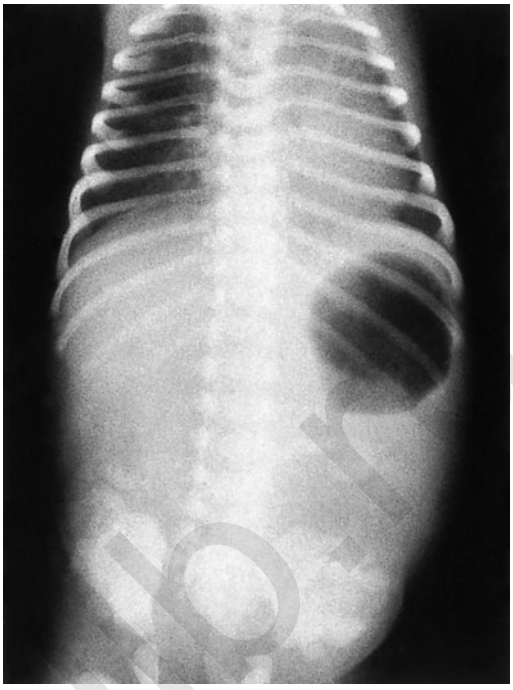

Figure 44.2 Abdominal x-ray showing absence of air beyond the stomach.

Management

Depending on the type of pyloric obstruction, different operative procedures are used. The best results from operative treatment of membranous obstruction are obtained by excision of the membrane associated with pyloroplasty according to Heineke-Mikulicz or Finney.[1–4] Transgastric excision of the pyloric membrane without pyloroplasty has also been reported.[23] In the case of longitudinal segmental atresia, the operative method depends on the length of the atresia. When the atresia is short, a Finney pyloroplasty can be carried out. For longer atresias, the procedure of choice is excision and end-to-end gastroduodenostomy.[4] Gastrojejunostomy is not recommended, due to the high mortality rate[4] and because of the risk of marginal ulcer and blind loop syndrome.

Preoperative management

Usually newborns are referred to the hospital and admitted within the first 2 days of life. They are generally in good physical condition, except those with epidermolysis bullosa. Preoperative preparation should consist of gastric decompression by nasogastric tube insertion. An i.v. infusion should be started to correct dehydration, electrolyte imbalance, and metabolic alkalosis in most cases. A central line should be

inserted to administer parenteral nutrition and long-term medical treatment specifically in those newborns with associated epidermolysis bullosa.

Operative technique

LAPAROTOMY

A transverse abdominal incision is made 2 cm above the umbilicus, starting 2 cm to the left of the midline and running laterally in a skin crease for about 5 cm (Fig. 44.3a). The abdominal cavity is opened in the line of the incision. Careful exploration and search for other intestinal atresias are performed at this site.[13]

IDENTIFICATION OF THE SITE OF OBSTRUCTION

During the procedure, it may prove difficult to identify the exact disease, therefore a gastrotomy can be helpful in this regard.[16] Another way to find the exact location of the web and prevent the gastrotomy can be achieved by placing a firm 12–14 Ch nasogastric tube, to be advanced up to the region of the obstruction.[24]

PYLOROPLASTY

This procedure is indicated for membranous pyloric obstruction (type A) and short atresia (type B).[4,8,12]

After identification of the pylorus, a longitudinal incision is made with cutting diathermy or scissors, starting on the gastric side of the pylorus to the duodenum (Fig. 44.3b). A blunt dissecting forceps, which is inserted into the lumen, is useful at this stage. Care must be taken that no inadvertent damage is done to the posterior wall of the stomach or duodenum. The total length of the incision should be 1.5–2 cm, extending approximately 1 cm on the gastric side and 1.5–1 cm on the duodenal side of the pylorus; it should be performed on the midline between the greater and lesser curvatures of the stomach and superior and inferior borders of the duodenum. The greater length on the gastric side is necessary because of the thicker gastric wall and in order to properly align both margins of the incision in the transverse direction. The membrane is excised circumferentially and the mucosa approximately with 5-0 readsorbable sutures (Fig. 44.3c). The duodenal lumen is inspected and a catheter is pushed down to exclude further distal atresias. The longitudinal incision is then closed transversely in two layers after meticulous hemostasis (Fig. 44.3d).

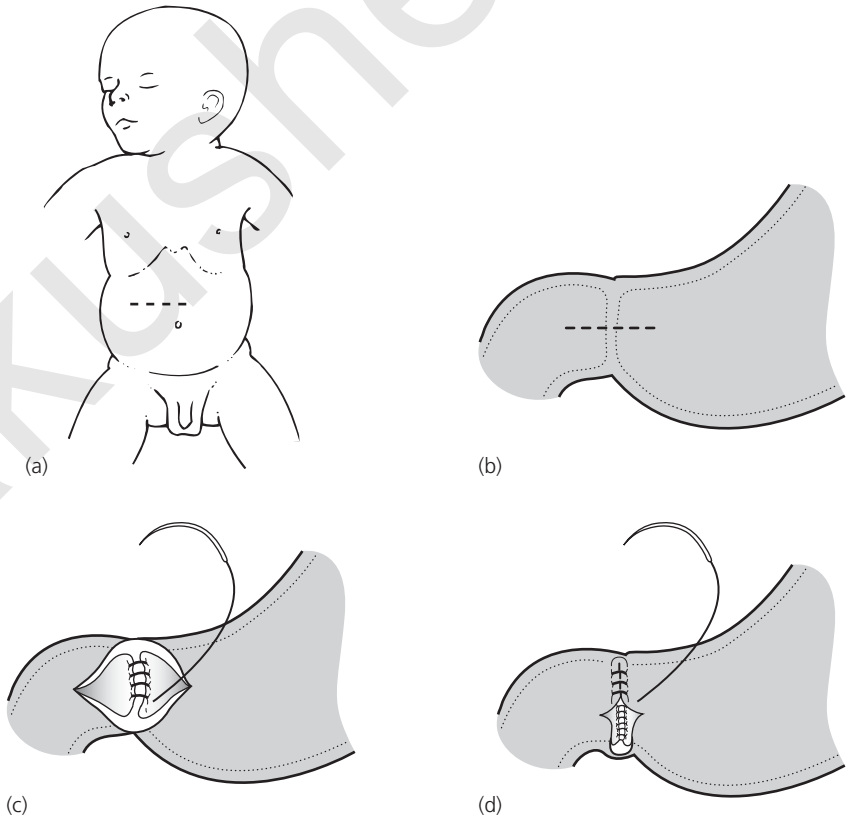

Figure 44.3 Operative technique of pyloroplasty: (a) skin incision; (b) pyloric longitudinal incision; (c) incision of the membrane and suture; (d) longitudinal incision closed transversely.

CLOSURE OF ABDOMEN

Gastrostomy is generally not necessary. The abdomen is closed in two layers and the nasogastric tube is left in the stomach for decompression.

LAPAROSCOPY

Although literature reports are still lacking, laparoscopic approach to pyloric atresia is an alternative option to the conventional open procedure. Although newborns have high sensitivity to insufflation, pneumoperitoneum is usually well tolerated if CO_2 pressure is maintained below 8 mmHg.[25] If achieved laparoscopically, the procedure should not significantly differ from that performed with the conventional laparotomic approach.

Postoperative management

Parenteral nutrition should be discontinued when the patient can be fed predominantly by mouth. The nasogastric tube should be kept *in situ* for 2–3 days to maintain gastric decompression or even longer if there are signs of delayed gastric emptying. Intravenous broad-spectrum antibiotics are administered intraoperatively and should be discontinued after 3–5 days, according to the patient's condition.

Complications

Complications are uncommon but include strictures, leakage, adhesions, infections, and bleeding as for any other abdominal surgery. Wound dehiscence and/or infection can occur, particularly in patients with epidermolysis bullosa.

Long-term results

Early diagnosis and surgical intervention with adequate neonatal supportive care has significantly improved the survival of pure pyloric atresia. Mortality has been associated with delayed diagnosis,[12,13] but it is mainly due to the associated malformation. Survival and long-term results are excellent in isolated forms of pyloric atresia. The overall mortality rate is about 45% and the majority of these fatal cases are those with epidermolysis bullosa and other multiple intestinal atresias.[6,26] On the basis of these considerations, Rosenbloom and Ranter[27] suggested the non-operative management of pyloric atresia, unless the skin disease is responsive to treatment. On the other hand, Hayashi *et al.*[7] reported long-term survival in four of five patients with pyloric atresia and epidermolysis bullosa. A comprehensive review from Dank and coworkers,[28] in 1999, reported that 51 of 70 patients with pyloric atresia associated with epidermolysis bullosa had been operated upon worldwide, with a long-term survival of roughly 31%. It was not surprising that survival was mainly observed in patients with mild forms of epidermolysis.

PREPYLORIC ANTRAL DIAPHRAGM

Introduction and etiology

Prepyloric antral diaphragm is a rare anomaly involving a submucosal web of gastric tissue covered by gastric mucosa and found in the distal gastric antrum. A total of about 150 cases has been reported, divided between pediatric and adult age ranges.[29] Reports have suggested both acquired and congenital forms, citing epidemiological and histological evidence.[30]

Pathology

There are three groups of patients: a neonatal group with complete or partial obstruction; a group presenting later in childhood; and a group not diagnosed until later in life.[31] Significant associated abnormalities are noted in about 30% of children with antral web, including mainly the gastrointestinal tract and cardiovascular system.[30]

History, presentation, and diagnosis

In the neonatal group, non-bilious vomiting is the predominant presenting symptom. Other symptoms include apnea, cyanosis, and no weight gain.[30] The older children complain of abdominal pain, vomiting, fullness after eating, and bloating. In the adult group, the clinical history consists of episodic cramping, epigastric pain or fullness following meals, and intermittent vomiting. There is one report describing a case in the eighth decade of life.[32]

The diagnosis of antral web with a central aperture is with a barium meal in 90% of cases.[30] The typical appearance of a web in an infant is a thin, membranous septum, projecting into the antral lumen, perpendicular to its longitudinal axis 1–2 cm proximal to the pylorus (Fig. 44.4a).

Gastroscopy has recently been noted to be of use in confirming clinical and radiological evidence of the web in older infants and in children.[33] Features of the web include:

- a small fixed central aperture surrounded by gastric mucosa that is smooth and devoid of folds;

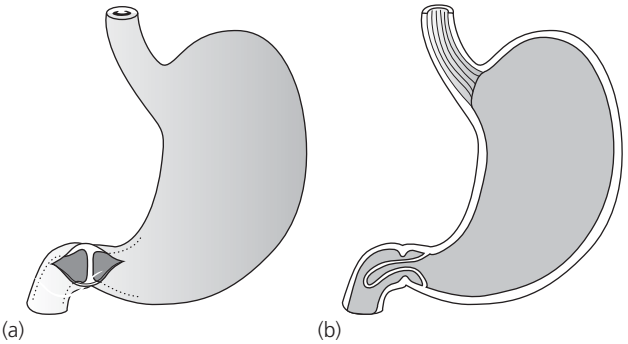

Figure 44.4 (a) Prepyloric antral web; (b) windsock antral membrane protruding into the duodenum.

- no change in the opening size of the web with peristalsis;
- that the gastric wall proximal and distal to the web is seen to contract normally.[34]

Management

Preoperative and postoperative management does not significantly differ from that of pyloric atresia. Surgery for partially obstructing antral web consists of excision of the web, combined with pyloroplasty if the web is very close to the pylorus (same as pyloric atresia). Furthermore, at operation, it is important to pass a Foley catheter distally to the stomach, and then to inflate the balloon and withdraw the catheter.[24] Windsock pyloric and antral membranes protruding into the duodenum have been reported (Fig. 44.4b) and would be missed at laparotomy by simple inspection of the gastric lumen.[35] Other methods have been reported. Most noticeably, some reports described successful endoscopic transection using a standard papillotome[36] and forceful dilatation of antral membrane without pyloroplasty.[37]

Medical treatment has been reported with success in infants without pronounced obstruction.[38] While this concept of conservative management is supported by some surgeons, the majority of the reports preferred the surgical correction of this entity, which reduces and prevents morbidity and unnecessary counseling in this group of babies and children.[4,29]

Complications and long-term results

Complications do not significantly differ from those of pyloric atresia.

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Hypertrophic pyloric stenosis

PREM PURI, BALAZS KUTASY, AND GANAPATHY LAKSHMANADASS

INTRODUCTION

Hypertrophic pyloric stenosis (HPS) is the most common condition requiring surgery in the first few months of life. It is characterized by hypertrophy of the circular muscle of the pylorus, causing pyloric channel narrowing and elongation. The incidence of pyloric stenosis varies widely with geographic location, season, and ethnic origin.[1] The incidence has been reported to be approximately three per 1000 live births.[2] There is some evidence that in recent years the incidence of pyloric stenosis has increased significantly in some parts of the UK.[3–5] Boys are affected four times more often than girls.[6] Recently, a dramatic rise in incidence among male infants but not for females was reported, so that rates for the two sexes were 6.2 and 0.9 per 1000 infants per year.[7,8]

ETIOLOGY

Although earlier diagnosis, advances in fluid and electrolyte therapy, and pediatric anesthesia have reduced the mortality to practically zero, the exact etiology of pyloric stenosis is unknown.[9] This condition is usually classified as a congenital disorder. It is almost unknown in stillbirths, associated anomalies are very uncommon, and the patient usually presents with vomiting after the second week of life. For these reasons, it has been suggested that it may be an acquired condition. Rollins *et al.*[10] measured pyloric muscle dimensions on ultrasonography in 1400 consecutive newborn infants. Nine of these infants subsequently developed pyloric stenosis and were operated upon. Their pyloric muscle measurements at birth were all within the normal range. This study clearly showed that congenital pyloric muscular hypertrophy is not present in babies who later develop pyloric stenosis.

The occurrence of infantile hypertrophic pyloric stenosis (IHPS) has been associated with several variables such as genetic, environmental, and mechanical factors. The pyloric sphincter, a zone of intermittently increased pressure, is able to contract tonically and phasically and produce an effect on gastric emptying. Pyloric sphincter function and motility is under a complex control system which involves the enteric nervous system, gastrointestinal hormones, and interstitial cells of Cajal (ICC); these pathways have been investigated in IHPS and abnormalities in hormonal control, extracellular matrix, smooth muscle fibers, growth factors, and ICC have been implicated in the pathogenesis of the disease.

EXTRINSIC FACTORS

Various environmental and mechanical factors have been proposed as potential causes of IHPS. Maternal smoking has been shown to double the risk for IHPS.[11] Recently, the significantly higher prevalence of breast milk feeding in early pyloric stenosis (in the first 2 weeks of life) has been found.[12] Another risk factor, maternal age, has been related to IHPS: significantly increased risk for IHPS with young maternal age (<20 years) and significantly decreased risk with maternal age 30 years and older.[8]

Neonates treated with erythromycin for different types of infection in the first 2 weeks of life have been found to carry an up to ten-fold risk of IHPS.[13] Erythromycin has been associated with an increased risk of IHPS as it acts as a motilin agonist and induces strong gastric and pyloric contractions that may lead to pyloric hypertrophy. Infants of mothers exposed to erythromycin during lactation have been reported to be at higher risk of IHPS while prenatal exposure has not been found to be associated with increased risk.[14]

In a small number of cases, IHPS has been believed to develop as secondary effect to a primary gastric outlet obstruction by mechanical factors. A transpyloric feeding tube, an antral polyp, and a pyloric cyst have been associated with IHPS.[15]

GENETICS

As IHPS tends to run in families, genetic factors have been implicated in its etiology. IHPS is relatively rare in babies of

African, Indian, and Chinese extraction.[16,17] Boys are affected four times more often than girls,[10] and IHPS has been reported in multiple siblings and multiple births.[18–20] Siblings of patients with IHPS are 15 times more likely to suffer the condition than children who have no family history of IHPS.[21] In a follow-up study extending over 45 years, Carter and Evans found that 5–20% of the sons and 2.5–7% of the daughters of affected patients developed IHPS.[22] Sons and daughters of affected female patients had three to four times the incidence of IHPS than sons and daughters of affected male patients.[21]

IHPS has been associated with a number of inherited genetic syndromes, such as Smith-Lemli-Opitz and Cornelia de Lange, as well as chromosomal abnormalities including partial trisomy of chromosome 9, partial trisomy of chromosome 13, and partial monosomy of chromosome 8 and 17.[23]

Although a specific gene responsible for IHPS has not yet been discovered, several susceptible loci have been identified, such as 16p12-q13, 16q14, 11q14-q22, and Xq23.[24,25] In view of the implication of the enzyme neuronal nitric oxide synthase (nNOS) in the pathogenesis of IHPS, NOS1, the gene encoding nNOS on chromosome 12q has been investigated by linkage analysis and evaluation of nNOS mRNA expression[26] and suggested as a susceptibility locus.

ABNORMALITIES OF HORMONAL CONTROL

The human pylorus is characterized by a zone of elevated pressure that relaxes with antral peristalsis, contracts in response to intraduodenal stimulation, and prevents the retrograde movement of duodenal contents into the stomach.[27] The hormonal control of the pyloric sphincter function by mediators such as gastrin, cholecystokinin, and secretin, has been reported to be the same as in other gastrointestinal (GI) sphincters.[4] Since Dodge successfully induced pyloric stenosis by prolonged perinatal maternal stimulation with pentagastrin in approximately one-half of a litter,[28] together with the finding of elevated serum gastrin levels in infants with IHPS,[29] much attention has been paid to the role of gastrin in the pathogenesis of IHPS. It has been suggested that repeated hyperacid stimulation of the duodenum induced by gastrin evokes repeated pyloric sphincter contractions with work hypertrophy of the pylorus.[30] However, Janik *et al.*[31] failed to induce pyloric stenosis in other species by prenatal administration of pentagastrin. Some investigators found significantly high plasma gastrin levels in affected infants compared to healthy controls,[29,32] whereas others failed to confirm this finding.[33,34] Since raised serum gastrin levels return to normal following pyloromyotomy, it is believed that they are secondary to antral stasis.[33]

Prostaglandins are produced in response to acid secretion and have a role in gastrointestinal motility, as well as cytoprotective and trophic effects. Prostaglandins PGE2 and PGE2a in the gastric juice have been found to be elevated in IHPS as compared with controls and based on the belief that they influence pyloric contraction, it has been suggested that these substances may be responsible for pylorospasm and pyloric hypertrophy.[35] Although the finding of elevated PGE2 in IHPS has been confirmed, evidence on prostaglandins causing relaxation of circular smooth muscle has challenged the hypothesis that prostaglandins cause pyloric hypertrophy.[36] However, prostaglandin treatment for cyanotic congenital heart disease has been shown to induce antral hyperplasia and gastric outlet obstruction that mimics IHPS.[37]

ABNORMALITIES OF PYLORIC INNERVATION

Although the smooth-muscle sphincter tone is myogenic, contraction and relaxation are under neural control via activation of excitatory and inhibitory pathways, respectively. Sympathetic stimulation is believed to exert an excitatory effect on the pyloric sphincter, while parasympathetic stimulation has either an excitatory effect via cholinergic neurons or an inhibitory effect via non-adrenergic non-cholinergic neurons.[38]

The innervations of the musculature regulating motility is particularly dense at the level of the smooth-muscle sphincters of the GI tract.[39] Relaxation of the sphincter is accomplished by activation of inhibitory motor neurons.[40] As a defect in pyloric relaxation has been thought to be responsible for the gastric-outlet obstruction and development of pyloric muscle hypertrophy, many investigators have sought evidence for a neural abnormality in specimens of IHPS, that may explain the failure of pyloric muscle relaxation.[9] Earlier studies concentrated on abnormalities in the myenteric plexus,[41–48] and more recent studies with advances in laboratory techniques and equipment have focused on the glial cells, the synaptic function, and the neurotransmitter status in both the myenteric plexus and pyloric muscle layers.[26,48–59]

Ganglion cells

Many investigators have reported conflicting morphologic findings as regards ganglion cells in the myenteric plexus in IHPS. A number of early authors found decreased numbers of ganglion cells, which were attributed either to degenerative changes related to vagal overstimulation[41,42,45] or to immaturity.[43,44] On the other hand, Rintoul and Kirkman[46] suggested that Dogiel type I ganglion cells (primarily motor) were selectively absent in IHPS. Belding and Kernohan[42] and Spitz and Kaufmann[47] found that the majority of myenteric ganglion cells in the hypertrophic pylorus showed degenerative changes. However, Tam,[48] using immunohistochemical stains for neuron-specific enolase, stated that neurons were neither immature nor severely degenerated. Langer *et al.*[60] demonstrated using electron microscopy that there were fewer nerve cell bodies in the myenteric plexus in IHPS and the total number of ganglia was lower than that in control samples.

Cholinergic and adrenergic innervations

Cholinergic nerve distribution has been studied using acetylcholinesterase (AChE) histochemical staining. Strong AChE staining was observed in the myenteric plexus and the

muscle layers in controls, whereas in IHPS specimens AChE staining was markedly decreased in the muscular layers but strong in the myenteric plexus.[52]

The studies from our laboratory have reported that adrenergic immunoreactivity is absent in the muscular layers and markedly decreased in the myenteric plexus in IHPS in comparison to controls.[9]

Nitrergic innervation

Nitric oxide (NO) is a gaseous free radical, synthesized from L-arginine in a reaction catalyzed by nNOS. NO has a well-described role as a major NANC inhibitory neurotransmitter that mediates pyloric relaxation in the enteric nervous system.[61] Vanderwinden *et al.*[57] and Kobayashi *et al.*[51] have reported that enzyme NADPH diaphorase, which is identical to NO synthase (NOS), is absent or markedly reduced in hypertrophic pyloric muscle while it is preserved in the myenteric plexus in IHPS. Furthermore, a NOS gene-deleted knockout mouse model is described in which the only abnormality is gastric-outlet obstruction due to pyloric hypertrophy.[62] Barbosa *et al.*[63] administered nitro-L-arginine methyl ester hydrochloride (L-NAME), a known NOS inhibitor, to pregnant rats and their newborns then noted that the L-NAME rats had larger stomaches and pyloric hypertrophy. Kusafuka and Puri,[26] using RT-PCR technique, demonstrated low levels of nNOS mRNA in pyloric muscle of IHPS patients compared to normal controls. Since a low level of nNOS mRNA may lead to impaired local production of NO, it is suggested that the excessively contracted hypertrophied circular muscle in IHPS is a result of reduced expression of the nNOS gene at the mRNA level.[26]

Synapse formation

Synapses provide the final neuronal control of the GI tract by regulating neurotransmission at the neuromuscular terminals. The reduction of synaptic vesicles and presynaptic terminals in hypertrophied pyloric muscle layers have been demonstrated.[49,55] Furthermore, a study from our laboratory reported markedly reduced neural-cell adhesion molecule (NCAM) expression on nerve fibers within circular and longitudinal muscles in patients with IHPS compared with normal pylorus.[51] NCAM plays an important role in the formation of initial contacts between nerve and muscle cells and affects tissue formation during embryogenesis.[64,65] These reports suggest that there is impairment of neurotransmission between nerves and muscle in IHPS.

Nerve-supporting cells

The nerve-supporting cells permit cell bodies and processes of neurons to be ordered and maintained in a proper spatial arrangement, and are essential in the maintenance of basic physiological functions of neurons.[66] The nerve-supporting cells of the intrinsic enteric nervous system are often referred to as enteric glia.[9] Enteric glia have been reported to express various markers for both astrocytes and Schwann cells, such as: (1) glial fibrillary acidic protein (GFAP), a specific marker for astrocytes within the central nervous system; and (2) S-100, a marker for astrocytes and Schwann cells. A study from our laboratory demonstrated that in IHPS cases S-100 and GFAP-immunoreactive fibers were either absent or markedly reduced within the hypertrophied circular and longitudinal muscles.[50] The absence or marked reduction of nerve-supporting cells in IHPS corresponds to the absence or reduction of peptidergic, nitrergic, cholinergic, and adrenergic nerve fibers, and is additional evidence that a defect of intramuscular innervation exists in IHPS.

ABNORMALITIES OF THE INTESTINAL PACEMAKER SYSTEM (ICC)

Interstitial cells of Cajal are small fusiform or stellate cells with prominent nuclei and varicose processes that form networks in the GI tissues. They express C-KIT, a transmembrane protein kinase receptor, essential for their development and maintenance. Morphologic studies have suggested three major functions of ICC: (1) they are pacemaker cells in GI smooth muscle; (2) they facilitate active propagation of electrical events; and (3) they mediate neurotransmission.[67,68] A number of investigators have reported a lack of ICC in hypertrophic pyloric muscle from patients with IHPS using C-KIT antibody and electron microscopy.[69,70] The lack of ICC in IHPS suggests the disruption of their network and the interruption of the generation of slow waves may contribute to the motility disturbances of the pyloric sphincter.[69]

Carbon monoxide (CO) acts as a neurotransmitter in the gastrointestinal tract and has been shown to cause smooth muscle relaxation. The main source of endogenous CO is through degradation of heme, catalyzed by heme oxygenase (HO). Heme-oxygenase-2 (HO-2), an isoform of HO, is present in the enteric neurons and in intramuscular ICC, suggesting that CO may serve as an intercellular messenger between enteric neurons, ICC, and smooth muscle cells.[71] Our laboratory has investigated immunocolocalization of HO-2 and ICC in IHPS and reported that although intramuscular ICC were HO-2 positive in controls, HO-2 and ICC were not detected in IHPS. It is suggested that impaired intercellular communication between ICC and smooth muscle cells may contribute to motility dysfunction in infants with IHPS.[72]

ABNORMALITIES OF EXTRACELLULAR MATRIX PROTEINS

Previous studies have reported an increase in connective tissue in IHPS, particularly in the septa that run between the circular muscle bundles.[41,42] Extracellular matrix (ECM) proteins, particularly collagen, are important microenvironmental factors of the neuronal processing pathway in the early embryonal stage and an important matrix for cell adhesion and movement.[9] Cass and Zhang[73] reported an increase in ECM proteins such as chondroitin sulfate,

fibronectin, and laminin in specimens of pyloric muscle in IHPS. Another study reported abnormal amounts of elastin fibers and elastin in the pyloric muscle in IHPS.[74] Using M-57 antibody, which can distinguish newly synthesized type I procollagen from fully processed mature collagen, it was reported that type I procollagen was markedly increased in not only the connective tissue septa between circular muscle bundles, but also among the circular muscle fibers in patients with IHPS, suggesting that the hypertrophied circular muscle in IHPS is actively synthesizing collagen.[74,75] These studies suggested that increased ECM proteins may be responsible for the characteristic 'firm' nature of the pyloric tumor.

Desmin is the main protein of intermediate filaments and is important for the organization and function of muscle fibers. A strong expression of desmin was observed in pyloric muscle biopsies from infants with IHPS, in contrast to absent or weak expression in controls. A similar pattern of strong desmin expression has been demonstrated in the fetal pylorus, suggesting that the organization of intermediate filaments in IHPS is in a fetal state of development.[76]

ABNORMALITIES OF SMOOTH-MUSCLE CELLS

The ongoing contractile tone in the smooth-muscle sphincters is generated by myogenic mechanisms. Langer *et al.*[60] found smooth-muscle cells (SMC) in IHPS to be morphologically normal, containing contractile filaments, intermediate filaments, dense bodies, and caveolae. They found, however, that SMC in IHPS were frequently in a proliferative phase, with large amounts of dilated rough endoplasmic reticulum with a lower proportion of contractile filaments, and very few gap junctions exhibited between SMC compared with control specimens. In contrast, they demonstrated significant ultrastructural abnormalities of the inhibitory enteric nervous system in IHPS. We performed quantitative evaluation of proliferative activity in pyloric muscle in IHPS and showed that proliferative activity is markedly increased in SMC in IHPS.[77]

Gentile *et al.*[78] studied cytoskeletal elements of pyloric SMC in IHPS using immunohistochemical staining and confocal laser microscopy. Talin, a protein responsible for SMC–ECM interaction, and dystrophin, a protein with adhesion properties, were present in controls but absent in IHPS patients, suggesting that the membrane–cytoskeleton interactions and the cell–matrix communications are altered.

Romeo *et al.*[79] investigated dystroglycans and sacroglycans, two proteins that, along with dystrophin, form the dystrophin–glycoprotein complex which is important for maintaining the structural integrity and function of muscle fibers. They reported that although dystroglycans showed similar expressions in IHPS and controls, sacroglycans were present in controls but absent in IHPS. It is suggested that lack of sacroglycans can alter the physiology of SMC and predispose to IHPS.

ABNORMALITIES OF GROWTH FACTORS

Growth factors are peptides that control cell proliferation and modulate cellular functions by binding to specific high-affinity cell membrane receptors. Although the mechanisms responsible for smooth-muscle hypertrophy are unknown, with progress in molecular biology, there is increasing evidence to suggest that the growth of SMC is regulated by several growth factors.[80–82] IGF-I and PDGF-BB are potent SMC mitogens *in vitro* and act synergistically to stimulate SMC proliferation. IGF-I mediates the growth-promoting effects of PDGF in mesenchymal cells.[83] IGF-I and PDGF have been shown to be produced by SMC, and their effects are mediated via their receptors.[84,85] Transforming growth factor alpha (TGF-α) is a growth regulatory peptide found in a wide range of embryonic and adult tissues. It has been recognized that TGF-α has a growth-promoting effect on vascular and visceral SMC.[86] EGF is best known as a potent growth stimulator. It appears to play a critical role early in growth of cultured smooth muscle, in which its production is highest and its growth-promoting effects are greatest.[86] The studies from our laboratory have reported increased expression of IGF-I, PDGF-BB, TGF, and EGF, in hypertrophic pyloric muscle in IHPS,[87–90] suggesting that the increased local synthesis of peptide growth factors in SMC may play a critical role in the development of pyloric muscle hypertrophy in IHPS.

PATHOLOGY

In IHPS, the mean appearance of the pylorus is that of an enlarged muscle mass usually measuring 2–2.5 cm in length and 1–1.5 cm in diameter. On histological examination, marked muscle hypertrophy and hypoplasia[77] primarily involving the circular layer and hypertrophy of the underlying mucosa is described.[91] Increased fibroblast, fibronectin, proteoglycan chondroitin sulfate, desmin, elastin, and collagen have been found on the immunohistochemical analysis of the hypertrophic muscle.[73,74] Abnormally contorted and thickened nerve fibers have been shown with confocal microscopy.[92] These changes are causing either partial or complete obstruction of the pyloric canal.

CLINICAL FEATURES

The usual onset of symptoms occurs between 3 and 6 weeks of age. It may present earlier and has been rarely reported in premature infants.[93] Demian *et al.*[12] investigated 278 patients with IHPS and only 16 (5.8%) presented during the first 14 days of life. Presentation of HPS in infants older than 12 weeks of age is considered rare and reports in the literature are few and far between.[94,95]

Vomiting is the most common presenting symptom. Initially there is only regurgitation of feeds, but soon it is characteristically projectile and free of bile. In 17–18% of cases, the vomitus may contain fresh or altered blood, usually attributed to irritative gastritis or esophagitis.[96]

Owing to inadequate fluid and calorie intake, dehydration and weight loss soon become apparent. In patients who present late, there is disappearance of subcutaneous fat and wrinkled skin. Stools become infrequent, dry, firm, and scanty. However, some infants have diarrhea (starvation diarrhea).

Jaundice occurs in about 2% of cases and has been shown to be related to decrease in glucoronyl transferase, which occurs as a consequence of starvation.[97]

Pylorospasm and gastro-esophageal reflux give similar clinical findings and it may be difficult to differentiate them from IHPS without further evaluation. Other surgical causes of non-bilious vomiting include gastric volvolus, antral web, preampullar duodenal stenosis, duplication cyst of the antropyloric lesion, and ectopic pancreatic tissue within an antropyloric muscle, which are all far less common than IHPS. Common medical causes of non-bilious vomiting are gastroenteritis, increased intracranial pressure, and metabolic disorders (Box 45.1).[23]

Associated anomalies are found in 6–20% of patients.[6,18] These include esophageal atresia, malrotation of bowel, Hirschsprung's disease, anorectal anomalies, cleft lip and palate, and urological anomalies.

Box 45.1 Differential diagnosis of IHPS

Surgical conditions
- Gastric volvolus
- Antral web
- Preampullar duodenal stenosis
- Duplication cyst
- Ectopic pancreas within the pyloric muscle

Medical conditions
- Pylorospasm
- Gastro-esophageal reflux
- Gastroenteritis
- Increased intracranial pressure
- Metabolic disease

DIAGNOSIS

It should be possible to diagnose HPS on clinical features alone in 80–90% of infants.[98–100] The important diagnostic features of pyloric stenosis are visible gastric peristalsis and a palpable pyloric tumor. Physical examination of the infant is best carried out during a test feed which relaxes the abdominal wall and makes the detection of pyloric tumor easier. The abdomen is completely exposed and observation made for gastric peristalsis, which is often visible in this condition as a bulge appearing in the left upper quadrant and moving slowly to the right across the epigastrium. On palpation of the abdomen, an olive-shaped pyloric tumor is palpable in most cases just above the umbilicus at the lateral border of the rectus muscle below the liver edge.

In general, the diagnosis of pyloric stenosis can be made with confidence on the basis of the history and clinical examination alone. When the clinical findings are equivocal, the diagnosis can be confirmed by sonography or barium meal.

The diagnosis by ultrasonography relies on the measurement of the pyloric diameter, pyloric length, and muscle thickness. Of the three parameters, muscular wall thickness is considered to be the most precise on sonography. Blumhagen and Coombs[101] were the first to point out that pyloric muscle thickness of the hypoechoic ring is the most important sonographic parameter in the diagnosis of pyloric stenosis (Fig. 45.1). They considered a thickness of 4 mm or more to be pathological. Other investigators believe that muscle thickness of 5 mm or more is most reliable for the diagnosis of pyloric stenosis.[102] False-positive results are rare, but false-negative rates range from 0 to 19% and largely depend upon the skill of the ultrasonographer.[6,102] In recent years, ultrasound has been used by surgeons to diagnose pyloric stenosis and leaving only problematic or equivocal cases for the radiologist. With this method, IHPS is diagnosed immediately from the emergency room decreasing hospital stay.[103]

Barium meal study is still a highly sensitive examination for the diagnosis of IHPS. In patients in whom the pyloric tumor cannot be palpated and ultrasound is not definitive, usually it confirms the diagnosis and it may also detect gastro-esophageal reflux or intestinal malrotation. Before barium study, the stomach should be emptied with a nasogastric tube, then 30–60 mL of barium is instilled under fluoroscopic control. The characteristic radiological feature of pyloric stenosis is a narrowed elongated pyloric canal giving a 'string' or 'double track' sign caused by compressed invaginated folds of mucosa in the pyloric canal (Fig. 45.2). However, barium meal study provides indirect information about the antropyloric canal status. Failure of the relaxation of the antropyloric lesion, known as pylorospasm, demonstrates the same findings as those of IHPS. The emptying speed of the barium meal to the distal bowel will be important to differentiate these two conditions.[104]

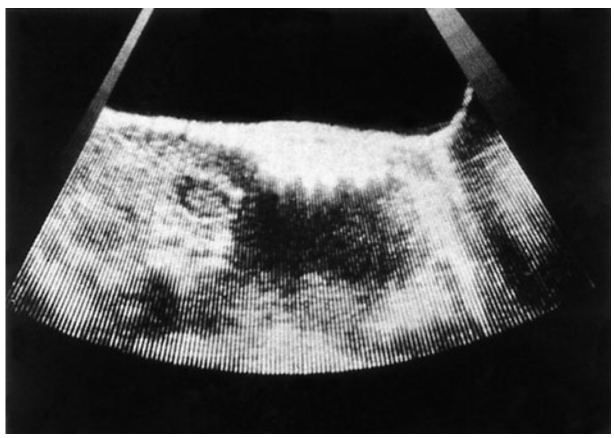

Figure 45.1 Longitudinal real-time sonogram section reveals hypoechoic ring with echogenic center typical of pyloric tumor.

MANAGEMENT

Preoperative management

Persistent vomiting in these patients results in chloride depletion and metabolic alkalosis. Estimation of serum electrolyte level, urea nitrogen level, hematocrit, and blood gases

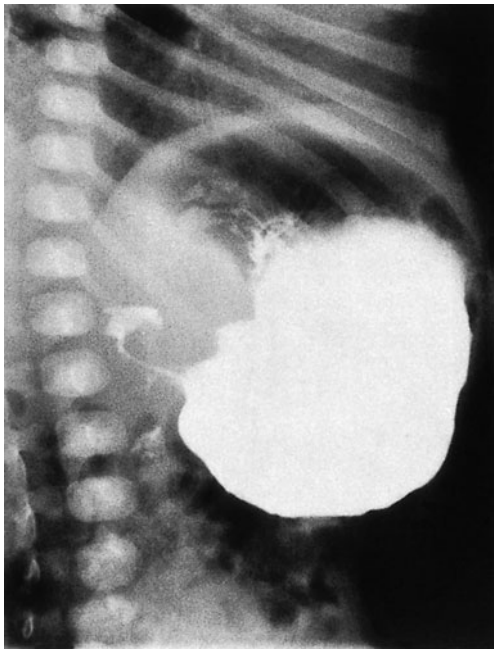

Figure 45.2 Pyloric stenosis. Severe narrowing of pyloric region giving the 'string sign' in this 3-week-old infant who presented with projectile vomiting.

should be done to determine the state of dehydration and acid–base abnormalities. A nasogastric tube is passed to keep the stomach empty. Saline irrigation through the nasogastric tube may help in removing mucus and milk curd. If the barium meal study has been carried out prior to surgery, it may be necessary to remove the residual barium meal by gastric aspiration.

Nowadays, many babies with pyloric stenosis do not show any clinical evidence of dehydration on admission and their serum electrolyte levels are usually normal. They are given their maintenance requirements of fluid as half-straight saline, and are operated on as soon as feasible.

If the infant is mildly dehydrated and has hypochloremic alkalosis, maintenance fluids can be given as 0.45% saline with 5% dextrose containing 10 mmol of potassium chloride per 500 mL, together with adequate volumes of isotonic saline to correct for continuing nasogastric losses. If the infant is more severely dehydrated (>5%), sodium and chloride ions must be replaced with isotonic saline to enable the kidney to excrete bicarbonate, thereby correcting the acid–base status.[6,17] The operation for pyloric stenosis is not an emergency and should never be undertaken until serum electrolyte levels have returned to normal.

Operation

The Ramstedt's pyloromyotomy is the universally accepted operation for pyloric stenosis.

INCISION

A 3 cm transverse right upper quadrant incision provides excellent exposure and direct access to the pylorus with minimal retraction (Fig. 45.3). Another incision which is commonly used is an umbilical fold incision.[105–108]

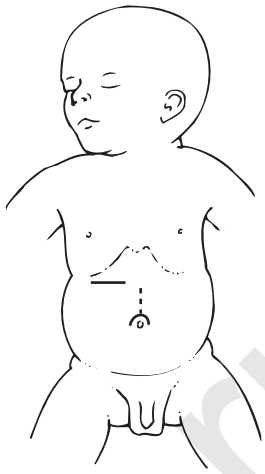

Figure 45.3 Skin incision for pyloromyotomy.

PROCEDURE

The transverse incision lateral to the rectus muscle is cut through all layers of muscle and peritoneum. The pyloric tumor is delivered by gentle traction on the stomach (Fig. 45.4). The surgeon applies an index finger to the duodenal end of the pylorus and stabilizes the pyloric tumor. An incision is then made over the anterosuperior part of the pylorus, beginning at the clearly demarcated pyloroduodenal junction about 2 mm proximal to the pyloric vein and extending onto the gastric antrum, where muscle is thin (Fig. 45.5). The pyloric muscle is then widely split down to the mucosa using mosquito forceps (Fig. 45.6). Some surgeons prefer a Denis Browne pyloric spreader. When the pyloric muscle has been adequately split, the mucosa can be seen to be bulging (Fig. 45.7). To test the mucosal injury, the stomach is inflated through the nasogastric tube and passage of air through the pylorus to duodenum is confirmed. Then the pylorus is dropped back into the abdomen. The peritoneum is closed with 4-0 polyglactin (Vicryl) and muscles approximated using 3-0 polyglactin (Vicryl). 5-0 Vicryl is used for subcuticular stitches.

Tan and Bianchi described the supraumbilical fold approach for pyloromyotomy. Circumumbilical incision is made through about two-thirds of the circumference of the umbilicus. The skin is undermined in a cephalad direction above the umbilical ring and linea alba is exposed. The linea alba is divided longitudinally in the midline from the umbilical ring to as far cephaled as necessary to allow easy delivery of the pyloric tumor.[105–108]

Although supraumbilical skin fold incision for pyloromyotomy certainly gives a superior cosmetic result, this incision does not offer any advantage as regards postoperative feeding tolerance or duration of hospital stay. The problem with the supraumbilical incision is that it does not always allow easy access to the hypertrophic pyloric muscle. Delivery of a large pyloric tumor can be fairly difficult and

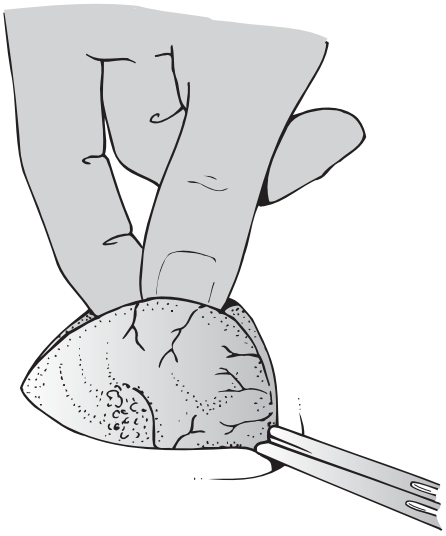

Figure 45.4 Delivery of pyloric tumor.

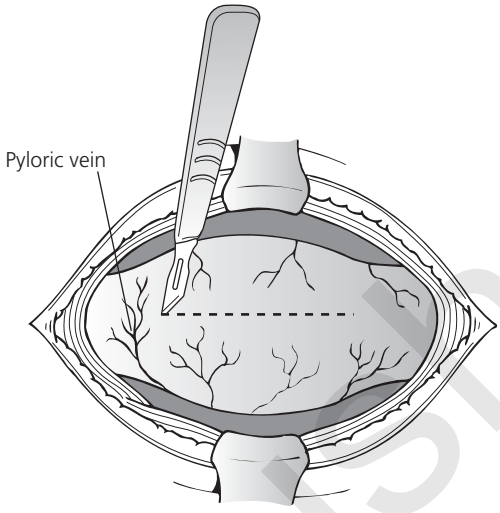

Figure 45.5 Incision through the serosa of the pyloric tumor.

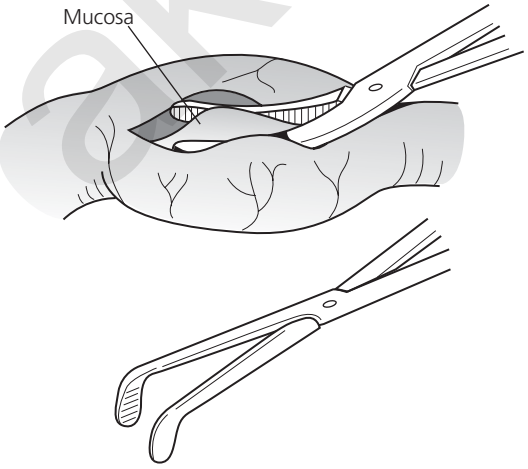

Figure 45.6 Splitting of pyloric muscle.

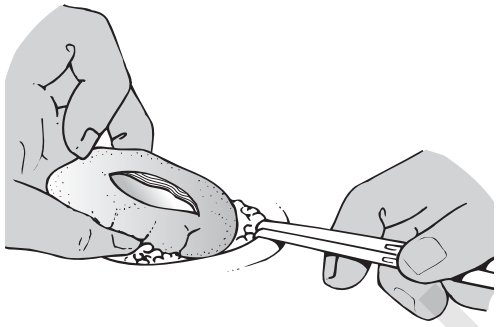

Figure 45.7 Bulging mucosa seen after complete splitting of pyloric muscle.

time consuming and may damage the serosa of the stomach or duodenum by tearing.[105] Moreover, in comparison with the transverse incision approach, some studies observed that the supraumbilical approach led to an increase in the rate of wound infection.[109]

LAPAROSCOPIC PYLOROMYOTOMY

Since 1991,[110] when the first laparoscopic pyloromyotomy was reported, there have been numerous publications supporting this approach,[104,111] and recently, single incision laparoscopic pyloromyotomy has also been reported.[112] For the laparoscopic procedure, the patient is placed in the supine position at the end of the table. A 5 mm port is placed in the umbilical fold after an open technique under direct vision. Pneumoperitoneum is established with CO_2 at maximum pressure of 6–8 mmHg. Two additional access sites are placed in the left and right mid-clavicular line just below the costal margin under direct vision with the camera. The duodenum is grasped with atraumatic forceps just distal to the pylorus olive to stabilize it. An endotome or diathermy hook is placed through the right incision and the pylorus is incised in its avascular plane from the prepyloric vein well into the gastric antrum (Fig. 45.8). The muscular layer is then separated with an endoscopic spreader (Fig. 45.9). A satisfactory pyloromyotomy is evidenced by ballooning of the intact mucosa. The absence of mucosal perforation is checked by insufflations of air in the nasogastric tube; if none is seen, the instruments and ports are removed. The umbilical fascia is closed with 4-0 absorbable suture and the skin of all the wound is reapproximated with 5-0 subcuticular absorbable sutures.[23]

Compared to open pyloromyotomy, laparoscopic pyloromyotomy is associated with significantly shorter postoperative recovery, decreased analgesia requirements, and superior cosmetic results in prospective, randomized controlled trials.[113–115] However, there is not much cosmetic advantage when compared with the umbilical approach. Moreover, laparoscopy is associated with higher frequency of incomplete pyloromyotomy: the reported incidence of incomplete myotomy is 2–8%, whereas this complication is extremely uncommon with open surgery.[113]

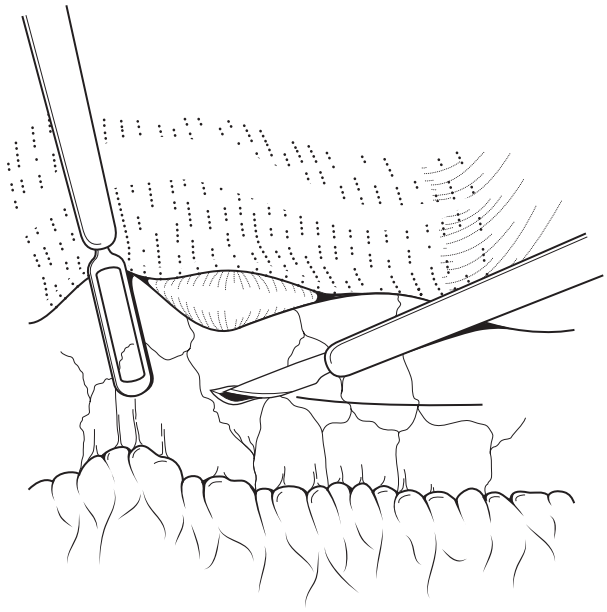

Figure 45.8 Laparoscopic incision.

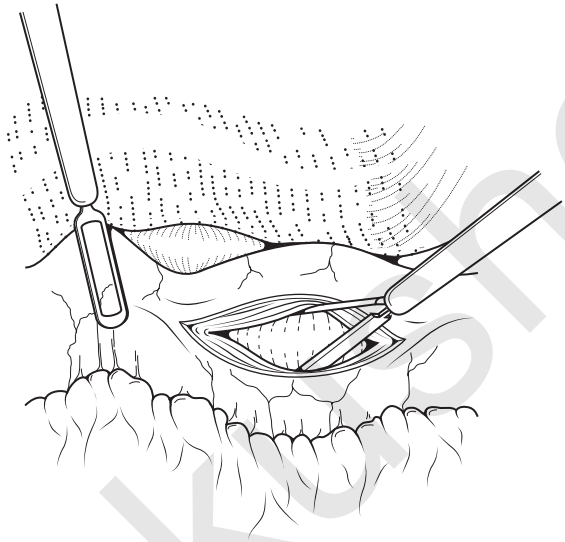

Figure 45.9 The muscular layer is separated with an endoscopic spreader.

Postoperative care

Maintenance i.v. fluids are continued postoperatively until the infant is feeding satisfactorily. The timing of reintroduction of feeds continues to be controversial.[116–119] Several studies have investigated postoperative feeding regimens for IHPS patients with respect to time of reintroduction of feeding and speed of advancement in an attempt to discover the safest and most cost-effective method. Some surgeons recommend starting oral feeds 4–6 hours after operation and gradually increasing the volume and concentration so as to resume normal feeds by the third or fourth day. Others have shown that postoperative vomiting is reduced if feeds are not started until 24 hours postoperatively. The vomiting following pyloromyotomy is usually self-limiting and independent of the timetable or composition of the postoperative dietary regimen.[119] A previous study showed that a postoperative standardized feeding regimen for patients with IHPS, where feeding was begun in the immediate postoperative period or 2–6 hours postoperatively decreased the length of hospitalization and hospital costs without adverse effects.[118]

COMPLICATIONS

Duodenal perforation is usually the result of excessive separation of fibers at the distal end of the pylorus. It is not serious provided that it is recognized and closed with one or two sutures. A patch of omentum should be brought up and tied over the wound. The need for reoperation after pyloromyotomy because of recurrent vomiting is reported with an incidence of up to 8%. Other complications included hemorrhage, wound infection, and wound dehiscence. With improvements in techniques, the incidence of complications after pyloromytomy is very low.

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46

Gastric volvulus

ALAN E MORTELL

INTRODUCTION

Gastric volvulus is a rare, potentially life-threatening condition first described by Berti in 1866.[1] A review of the world literature in 1980 identified only 51 cases in children under 12 years of age.[2] Of these, 26 (52%) were infants and half of these were younger than one month of age. In a recent series, neonates have accounted for only 21% of cases of gastric volvulus.[3,4] In older children, gastric volvulus may be associated with neurodevelopmental handicap and splenic abnormalities but in neonates there is a strong link with diaphragmatic defects. In the last two decades, numerous descriptions of acute and chronic gastric volvulus in children have been published, bringing the total number of reported cases to more than 580.[3–8]

ETIOLOGY

Gastric volvulus may be defined as an abnormal rotation of one part of the stomach around another;[9] the degree of twist varies from 180 to 360° and is associated with closed loop obstruction and the risk of strangulation. Lesser degrees of gastric torsion are probably common, frequently asymptomatic, and are not diagnostic of volvulus. Such cases may be associated with transient vomiting in infants but spontaneous resolution is the rule.[7,10] Gastric volvulus may be either organoaxial, occurring around an axis joining the esophageal hiatus and the pyloroduodenal junction, or mesenteroaxial, around an axis joining the midpoint of the greater and lesser curves of the stomach (Fig. 46.1). The majority of patients present with organoaxial volvulus (54%) compared to mesenteroaxial volvulus in 41% and combined volvulus in only approximately 2% of cases.[3] A mixed or combined picture occurs if the stomach rotates around both axes simultaneously. The usual direction of rotation is anterior, i.e. in organoaxial volvulus the greater curve moves upwards and forwards above the lesser curve, causing the posterior gastric wall to face anteriorly. The gastro-esophageal junction and the pylorus may both become obstructed. In anterior mesenteroaxial rotation, the antrum comes to lie anterosuperior to the fundus and obstruction is usually in the antropyloric region.

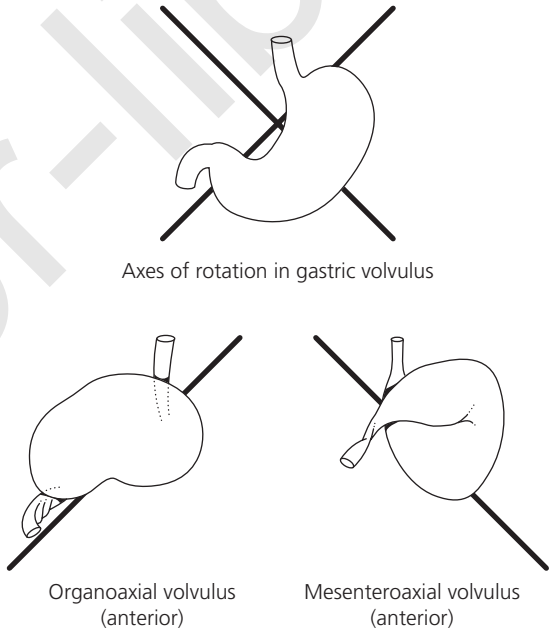


Figure 46.1 Diagrammatic representation of the main types of gastric volvulus.

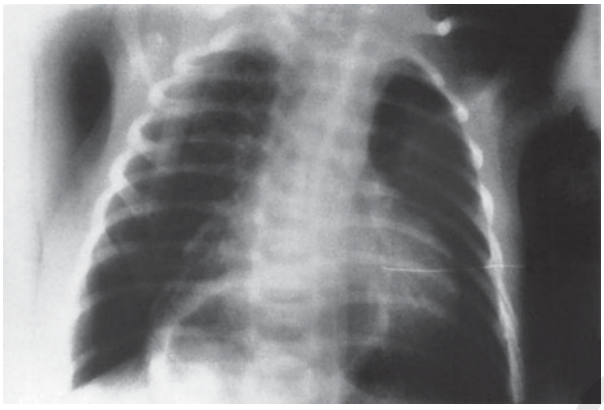
Acute, complete volvulus is most often seen in infancy in contrast to chronic and partial varieties, which more often occur in older children and adults. More complex patterns of gastric volvulus have been described in neonates and infants with abnormal gastric bands or adhesions (see below under Pathogenesis), and in older children after gastrostomy[11,12] or Nissen fundoplication, performed either open[13–15] or laparoscopically.[16]

CLINICAL CASES

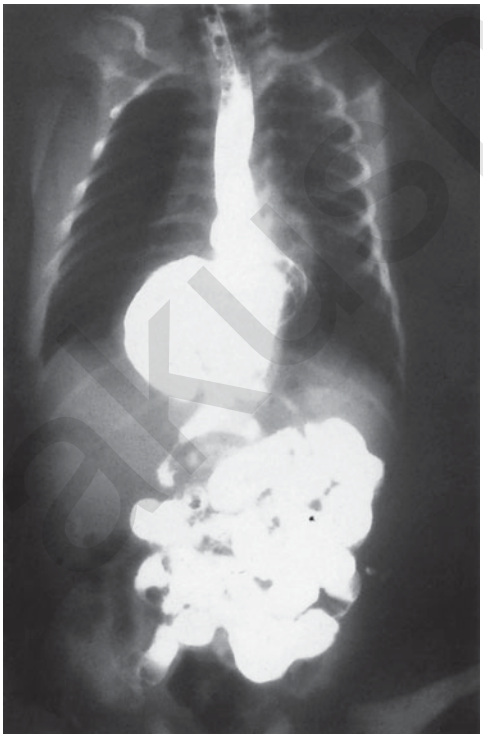
The following three cases illustrate different aspects of the presentation and management of gastric volvulus in infancy.

Case 1

A full-term male infant presented soon after birth with cyanotic attacks during feeding. A tracheo-esophageal fistula was initially suspected, but a plain chest x-ray (Fig. 46.2a) showed a gastric shadow lying in front of the heart and a barium swallow (Fig. 46.2b) demonstrated an organoaxial gastric volvulus within the chest. Via a left thoracotomy, the stomach was derotated and reduced into the abdomen with repair of the esophageal hiatus. A gastropexy was not performed and subsequent progress was uneventful.



(a)



(b)

Figure 46.2 (a) Plain chest radiograph showing an air-filled viscus in the chest (case 1). (b) Barium study showing the stomach lying above the diaphragm with the greater curvature uppermost (case 1).

Case 2

A full-term male infant presented at 4 days of age with intermittent vomiting. This was initially attributed to a urinary infection, but the vomiting continued and a barium meal showed that there was delayed passage of contrast into the stomach from the esophagus. When the barium was injected via a nasogastric tube, the stomach was seen to lie horizontally and to empty very slowly. At laparotomy, the pylorus was hypertrophied and the stomach was distended. The gastrocolic omentum was deficient along most of the greater curve, allowing free organoaxial rotation of the stomach. A pyloromyotomy and anterior gastropexy were performed, after which the child became symptom-free.

Case 3

A female infant presented at the age of three months with a history of loud borborygmi, inability to bring up wind after feeding, and occasional vomiting. On examination, bowel sounds were heard in the chest. Barium meal showed an organoaxially rotated intrathoracic stomach. Via an abdominal approach, a large paraesophageal hernia was reduced, followed by a crural repair and Nissen fundoplication. The child remained asymptomatic four years later.

PATHOGENESIS

The stomach is relatively fixed at the esophageal hiatus and at the pyloroduodenal junction and is also stabilized by four 'ligamentous' attachments – the gastrohepatic, gastrosplenic, gastrocolic. and gastrophrenic ligaments (Fig. 46.3). Despite these attachments, considerable changes in shape and position of the normal stomach are possible. This is highlighted by the gastric rotation that can sometimes be observed during air insufflation of the stomach at the time of laparoscopically assisted percutaneous endoscopic gastrostomy insertion.[17] Absence or attenuation of the normal anatomical anchors results in abnormal gastric mobility, which may be encouraged still further by a coexistent diaphragmatic defect. Most

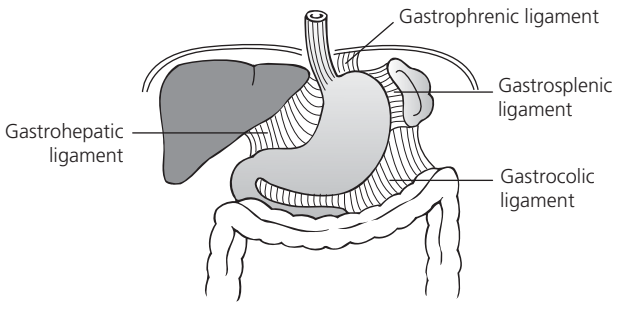


Figure 46.3 Diagrammatic view of the stabilizing gastric ligaments.

cases of gastric volvulus in the newborn are secondary to diaphragmatic defects with or without deficient ligamentous attachments.[18–24] The contribution of the gastrocolic and gastrosplenic ligaments to fixation of the stomach is demonstrated by the observation in the cadaver that their division allows 180° rotation of the normal stomach.[2,5,25]

Eventration or herniation of the diaphragm is present in about two-thirds of all children presenting with gastric volvulus.[3] However, this proportion is as high as 80% in some series of infants.[2,19] Diaphragmatic hernias are typically paraesophageal or posterolateral defects but gastric volvulus within a Morgagni hernia is also possible.[3,26] The presumed mechanism of gastric volvulus in this situation is upward displacement of the transverse colon, which pulls up the greater curve of the stomach into the expanded left upper quadrant. Acute gastric volvulus may therefore present as an early complication of diaphragmatic defects.

Gastric distension may encourage the development of gastric volvulus.[25] Infantile hypertrophic pyloric stenosis may rarely be a predisposing factor, as described in case 2 above. Two similar cases have been reported but those infants also had diaphragmatic defects.[27,28] Air swallowing can also cause gastric distension, and intermittent gastric volvulus has been reported in an aerophagic neurologically impaired child.[23]

Other rare causes of gastric volvulus in the neonate and infant include: abnormal bands or adhesions producing an axis of rotation for the stomach;[6,19,29] rectal atresia with consequent overdistension of the transverse colon;[30] congenital absence or resection of the left lobe of the liver which may promote abnormal gastric mobility;[31,32] and congenital deficiency of the gastrocolic omentum.[5,33] The asplenic syndrome (asplenia, congenital heart disease, with or without intestinal malrotation and deficiency of the gastric ligaments) is increasingly recognized as a predisposing condition.[34,35] Nakada *et al.*[36] reported gastric volvulus as a complication in three of 25 patients with asplenia, the youngest of whom was one month of age. Anchoring gastric ligaments were deficient in all cases. Because of the potentially fatal outcome of acute gastric volvulus in this situation, Okoye *et al.*[37] have recommended prophylactic gastropexy. Defective fixation and ligamentous laxity also account for the association between gastric volvulus and a wandering spleen.[38–40] Intestinal malrotation is associated with gastric volvulus, even in the absence of asplenia.[6,29,36,41]

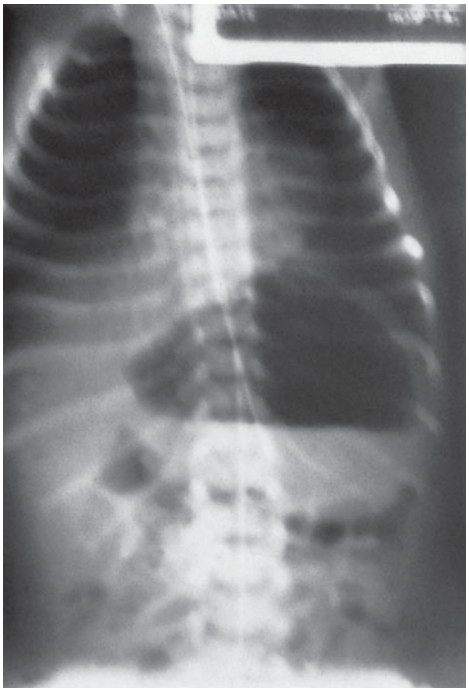
Gastric volvulus in children may rarely arise as a postoperative complication. It has been described after Nissen fundoplication, presumably because the stomach has been extensively mobilized by division of gastrosplenic and gastrocolic attachments.[13–15,42] There is one recorded case of gastric volvulus developing after repair of a diaphragmatic hernia[19] and another as an iatrogenic complication of gastric transposition in infancy.[43]

CLINICAL FEATURES

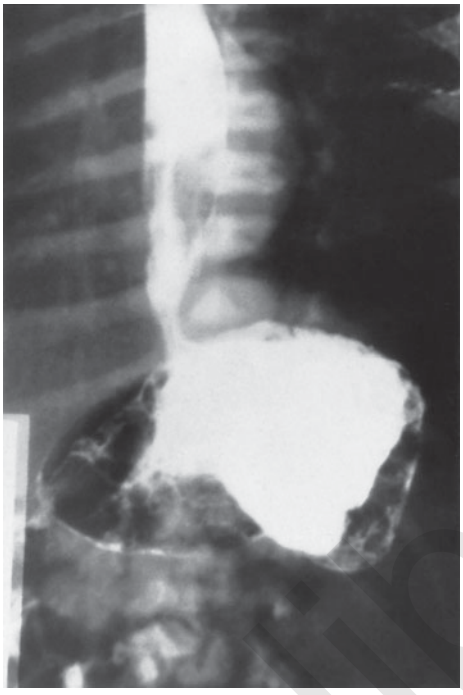
The clinical features depend on the degree of rotation and obstruction. In adults, the triad of Borchardt is diagnostic of acute volvulus: (1) unproductive retching; (2) acute localized epigastric distension; and (3) inability to pass a nasogastric tube.[44] These features are difficult to assess in the infant and may be absent. Persistent regurgitation and vomiting (sometimes unproductive) are common, although nonspecific, presenting symptoms in the newborn. The vomitus may or may not contain bile, depending on the degree of pyloric obstruction. Hematemesis and anemia are well described and occasionally the vomiting is described as projectile. Failure to thrive and chest infections are sometimes evident.[41] Upper abdominal pain and distension may be noted in older infants and children. However, abdominal signs may be minimal if the stomach is intrathoracic, when respiratory distress and tachypnea are the dominant features.[2,20,22,45,46] Failure to pass a nasogastric tube may have several causes in the newborn and the successful passage of a tube does not exclude the diagnosis.[15,19] In neonates, confusion with esophageal atresia is possible but arrest of the nasogastric tube in the distal esophagus and radiographic abnormalities on routine films should raise suspicion and prompt investigation by contrast studies.[47] In older children, presenting symptoms may be intermittent, chronic and also non-specific.[15]

DIAGNOSIS

Plain abdominal and chest x-rays are essential. A distended stomach in an abnormal position should suggest the possibility of gastric volvulus. In mesenteroaxial volvulus, the stomach is spherical on the plain film taken with the patient in the supine position, and two fluid levels are often visible on the erect film – one in the fundus (the lower) and the other in the antrum (upper) (Fig. 46.4a); these findings may be absent if the stomach has been decompressed by a nasogastric tube. A paucity of distal bowel gas in acute volvulus can indicate gastric outlet obstruction.[48] Contrast studies clarify the anatomy (Fig. 46.4b) and the site(s) of obstruction, which is usually at the pylorus, giving a so-called 'beak' deformity.[18] Organoaxial volvulus is more difficult to diagnose on plain films (especially if there is no associated diaphragmatic defect) and may indeed be missed during a contrast study. The distended stomach lies rather horizontally on the plain film, with a single fluid level. On contrast examination, the esophagogastric junction is lower than normal, the greater and lesser curves are inverted, and the antrum and duodenum are distorted (Fig. 46.5). In the presence of a diaphragmatic defect, such as a paraesophageal hernia, the antrum may herniate into the retrocardiac position, producing a fluid level in the chest above the gastric fundus, and thus organoaxial volvulus can also rarely give rise to two fluid levels.[49] Computed tomography (CT) has been used in cases where gastric volvulus was not diagnosed on plain films; however, it should not be necessary if an upper gastrointestinal contrast study is performed and may only serve to delay treatment.[48] A CT scan can yield further information about structural abnormalities, such as splenic position or absence.



(a)



(b)

Figure 46.4 (a) Plain abdominal x-ray showing a distended stomach but only a single fluid level in this neonate with mesenteroaxial gastric volvulus. (b) Barium study confirming mesenteroaxial gastric volvulus.

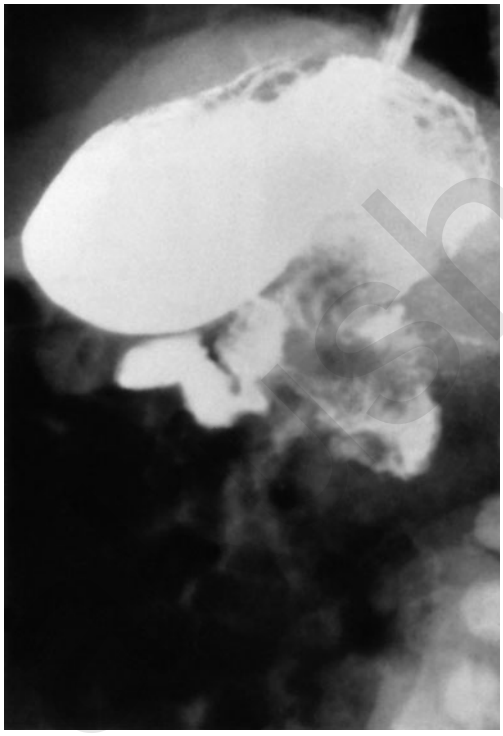


Figure 46.5 Oblique view of barium meal demonstrating an organoaxial gastric volvulus in a neonate who presented with intermittent vomiting (case 2).

TREATMENT

Acute gastric volvulus requires appropriate resuscitation and urgent surgery if ischemic necrosis and gastric perforation are to be avoided. If possible, the stomach should be decompressed preoperatively by nasogastric suction but vigorous attempts to pass a tube must be avoided because of a risk of gastric perforation.[19] An abdominal approach is recommended, even when the stomach lies in the chest, since this allows identification of any associated gastrointestinal anomalies and accurate diaphragmatic repair if required. Occasionally, preliminary needle aspiration of the stomach may be warranted before manipulating a tensely dilated stomach and reducing the volvulus.[50] Any associated diaphragmatic defect should be repaired and the stomach fixed to the anterior abdominal wall (Box 46.1).

Gastrostomy alone may be used for gastric fixation in neonates, since it provides adequate fixation, postoperative decompression, and a route for postoperative feeding. A Stamm gastrostomy using a 10 or 12 French gauge Malecot catheter secured by a double purse-string absorbable suture is appropriate (Fig. 46.6a). In infants with no predisposing diaphragmatic defect, an anterior gastropexy should be added (Fig. 46.6b). This involves suturing the greater curve of the stomach to the parietal peritoneum of the anterior abdominal wall and the under surface of the diaphragm by a series of non-absorbable sutures. There are three recorded cases of recurrence following this approach.[51,52] Fundoplication may be necessary if there is evidence of gross gastro-esophageal reflux, but several authors have achieved good results in such cases

Box 46.1 Surgical options for gastric volvulus in the neonate/infant

- Repair of diaphragmatic defect, division of congenital bands, etc., and anterior gastrostomy
- Crural repair (if necessary) and anterior gastropexy
- Crural repair and fundoplication for cases with severe gastro-esophageal reflux

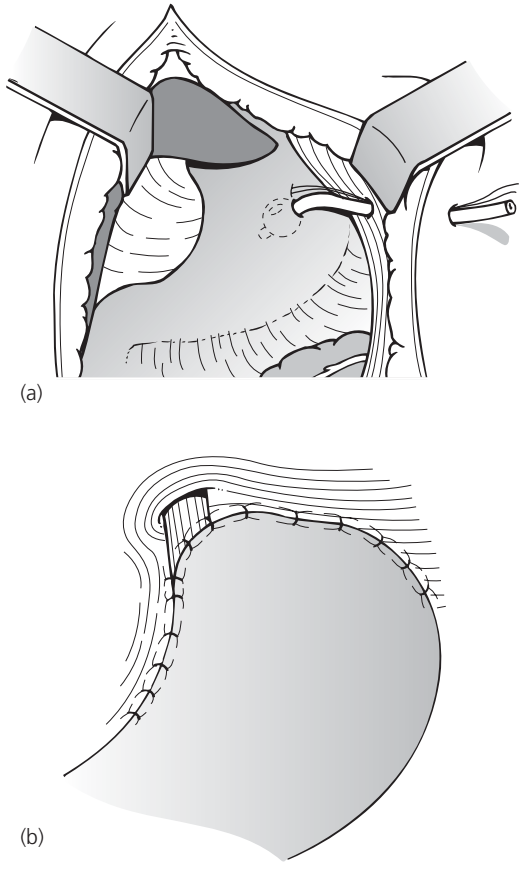


Figure 46.6 Operative techniques in neonatal gastric volvulus. (a) Anterior Stamm gastrostomy using a Malecot catheter. (b) Anterior gastropexy.

with a crural repair alone and a more conservative approach is warranted provided the tendency to volvulus is prevented.[41,42] Diaphragmatic crural repair must be performed meticulously, as there is often a common hiatus for the esophagus and aorta in these patients.[42] There is no justification for gastrectomy, gastroenterostomy, or the colonic displacement operation described by Tanner[9] in this age group.

In older children with isolated gastric volvulus preliminary nasogastric decompression followed by a laparoscopic anterior gastropexy is an option[33] and this technique has also been reported in a neonate.[53] In gastric volvulus due to a wandering spleen, splenopexy alone may be sufficient.[54]

COMPLICATIONS

A number of complications can result from gastric volvulus including prolonged gastric ileus, pyloric ischemia, gastric outlet obstruction, gastric necrosis, and perforation.[6]

The mortality from gastric volvulus is difficult to assess with recent series reporting mortality rates of 7.1% in acute gastric volvulus compared to 2.7% in chronic cases.[6] Untreated, gastric volvulus has a mortality rate of up to 80%, highlighting the importance of prompt recognition and treatment. Deaths have been reported due to missed or delayed diagnosis, with subsequent gastric necrosis and perforation, or inadequate gastric fixation.[4,8,19,21,24]

Most recent series report uncomplicated early outcomes after surgery. One long-term follow-up study of nine infants demonstrated no recurrences or late complications.[4]

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47

Gastric perforation

ROBERT K MINKES

INTRODUCTION

Gastric perforation in the neonatal period is rare, however it continues to be associated with significant morbidity and mortality. Spontaneous neonatal gastric perforation is estimated to occur in one in 2900 live births[1] and accounts for approximately 10–15% of all gastrointestinal perforations in neonates and children (Table 47.1). Gastrointestinal perforations occur more commonly in males, however there appears to be no sex predilection for those occurring in the stomach.[2–4] Recent series may suggest a male predominance, but this remains inconclusive.[5–7] The terminology used to describe neonatal gastric perforation has been inconsistent and its etiology remains a topic of debate. Spontaneous or idiopathic gastric perforations refer to those with no identifiable underlying cause and account for the majority of gastric perforations in most reported series.[1,3,5–13] Nevertheless, many pediatric surgeons believe that an underlying cause can be found in most cases of neonatal gastric perforation.[14]

Siebold, in 1926, is credited with the first description of a gastrointestinal perforation with no demonstrable cause, the so-named spontaneous perforation.[15] In 1929, Stern *et al.*[16] reported attempts at surgical repair. Agerty *et al.*[17] reported the first successful repair of a neonatal intestinal (ileum) perforation in 1943 and Leger *et al.*,[18] in 1950, described the first successful repair of a neonatal gastric perforation. Survival following a neonatal gastric perforation was rare prior to the 1960s. While mortality has improved since that time it remains significant and ranges from 25 to over 50% in most series.[1,2,4–7,14,19,20]

ETIOLOGY

Gastric perforations in neonates can be broadly categorized as spontaneous (idiopathic), ischemic, or traumatic; however, in many instances, the etiology may be multifactorial. Ischemia, necrosis, and perforation may occur with no obvious inciting factors.[21] Box 47.1 lists several possible causes and associations with gastric perforations. Spontaneous gastric perforations most often occur on the greater curvature.[1,21,22] Neonatal gastric perforation can occur in full-term, premature, and small for gestational age neonates. Some infants appear to have been healthy and medically stable prior to the development of the perforation, whereas others have underlying medical conditions or congenital anomalies. There are reports of intrauterine gastric perforation with no known underlying cause.[23] Unrecognized overdistension or ischemic insult may result in a perforation that is thought to be spontaneous. Ischemic perforations occur in the setting of physiologic stress such as prematurity, asphyxia, sepsis, and necrotizinig enterocolitis. The perforations are often associated with ulcerations and ischemic tissue. Traumatic perforation results from pneumatic distention during mask ventilation, positive pressure ventilation, or iatrogenic injury during gastric intubation. Several specific causes of neonatal gastric perforation have been reported including intestinal atresias, prenatal stress, trauma, exposure to corticosteroids and non-steroidal anti-inflammatory agents (Box 47.1). Several theories on the etiology of spontaneous (idiopathic) gastric perforations have been suggested but no single theory is universally accepted. Theories include congenital absence of the gastric muscle,[8,10] forces exerted during vaginal delivery,[24] and pneumatic distention.[25,26] Studies in dogs and human neonatal cadavers suggest that rupture is caused by overdistention and is in keeping with the law of Laplace.[11] With gastric distention the greatest wall tension is exerted on the fundus, the site of most spontaneous perforations. In addition, overdistension can cause ischemic changes, a finding present in many cases of perforation.[4] Recent studies suggest a deficiency of the tyrosine kinase receptor C-KIT$^+$ mast cells and a lack of C-KIT$^+$ intersitial cells of Cajal may contribute to idiopathic gastric perforation.[27,28] Mice lacking C-KIT$^+$ mast cells develop spontaneous gastric ulceration or perforation. In addition, postmortem examination of stomachs of neonates who died of idiopathic gastric perforation, revealed a deficiency in both C-KIT$^+$ mast cells and interstitial cells of Cajal when

Table 47.1 Incidence of gastrointestinal perforation.

Author	Year	Total	Stomach	Duodenum	Small bowel	Colon/rectum	Non-designated
Grosfeld *et al.*[19]	1996	179	16	9	105	37	12
Tan *et al.*[12]	1989	56	?5	2	26	23	
Bell[2]	1985	60	10	6	30	10	4 (multiple)
Borzitta and Groff[45]	1988	29	?5	1	12	11	6 (multiple)
St-Vil *et al.*[46]	1992	81	7 stomach–duodenum		38	32	?4
Total		405	43 (10%)	18 (5%)	211 (52%)	113 (28%)	(5%)

Box 47.1 Causes and associations of neonatal gastric perforation

- Idiopathic
- Perinatal stress
  - hypoxia
  - asphyxia
- Prematurity[3,12]
- Anatomic defect
  - distal obstruction
    - pyloric atresia[47]
    - duodenal atresia[3]
    - midgut volvulus[34]
  - tracheo-esophageal fistula[25,48–51]
  - congenital deficiency of gastric muscle
- Iatrogenic
  - nasogastric tube[29]
  - aggressive bag ventilation with or without tracheo-esophageal fistula[25,26]
  - cardiopulmonary resuscitation[36,52]
  - positive pressure ventilation
  - inadvertent perforation during surgery (ventriculoperitoneal shunt)[35,53]
  - vaginal delivery[24]
- Medication
  - indomethacin[38,54]
  - corticosteroids[39]

compared to controls. The authors suggest that these abnormalities could result in impaired immunity and abnormal motility predisposing to gastric perforation.

CLINICAL PRESENTATION

The clinical presentation of gastric perforation is variable. The majority of cases present within the first 7 days of life, however later presentations are reported.[2,6,7,12,21,22,29] The neonates are often premature or have a history of asphyxia or hypoxia.[3,4,12,20–22] Neonates may present with feeding intolerance or emesis that may contain blood. Many develop abrupt onset of rapidly progressive abdominal distension from pneumo- or hydroperitoneum.[30] These infants progress to respiratory distress, hemodynamic instability, and signs of shock, such as hypothermia, cyanosis, poor peripheral perfusion, and low urine output. The abdomen may rapidly become tense and tender with signs of peritoneal irritation. Ventilation may be impaired or ineffective until the abdomen is decompressed. Subcutaneous emphysema in the abdominal wall or pneumoscrotum may be perceived.[31,32] Infants with posterior perforations into the lesser sac may present with a more insidious course, making the diagnosis difficult.

Infants with perforation secondary to an underlying process often have evidence of the predisposing condition, such as findings of tracheo-esophageal fistula, duodenal atresia, malrotation, or diaphragmatic hernia.[3,25,33,34] In some instances, a secondary cause is found at the time of operation. In cases of iatrogenic perforation, a history of traumatic naso- or orogastric intubation, prior surgery, corticosteroid or nonsteroidal administration, and aggressive ventilation or cardiopulmonary resuscitation may be obtained.[29,35–39]

DIAGNOSIS

The diagnosis of gastric perforation is made from the clinical history, physical examination, and radiographic studies. In infants with massive pneumoperitoneum, a plain abdominal x-ray will demonstrate air under the diaphragm that extends laterally, trapping the abdominal viscera medially and producing a saddlebag appearance.[40] The stomach is not visualized by plain x-ray in 90% of cases.[41] Other plain x-ray findings include subcutaneous emphysema, pneumoscrotum, ascites, or an oro- or nasogastric tube outside the confines of the stomach. Pneumatosis intestinalis and portal venous air are signs of necrotizing enterocolitis, which may coexist with gastric perforation. Calcification and dilated loops of bowel are common findings of more distal perforation and a gasless abdomen is seen in cases of neonatal volvulus. A definitive diagnosis may not be made prior to laparotomy. A water-soluble contrast study will reveal extravasation from the stomach into the peritoneal cavity (Fig. 47.1). Ultrasound may show ascites or fluid collections. In premature infants with known lung disease, pneumoperitoneum can result from air tracking from the mediastinum. A chest film demonstrating pneumomediastinum, an air–fluid level in the stomach, a negative peritoneal aspirate, and an intra-peritoneal drain that bubbles with the ventilator cycle can help to exclude an intra-abdominal process.

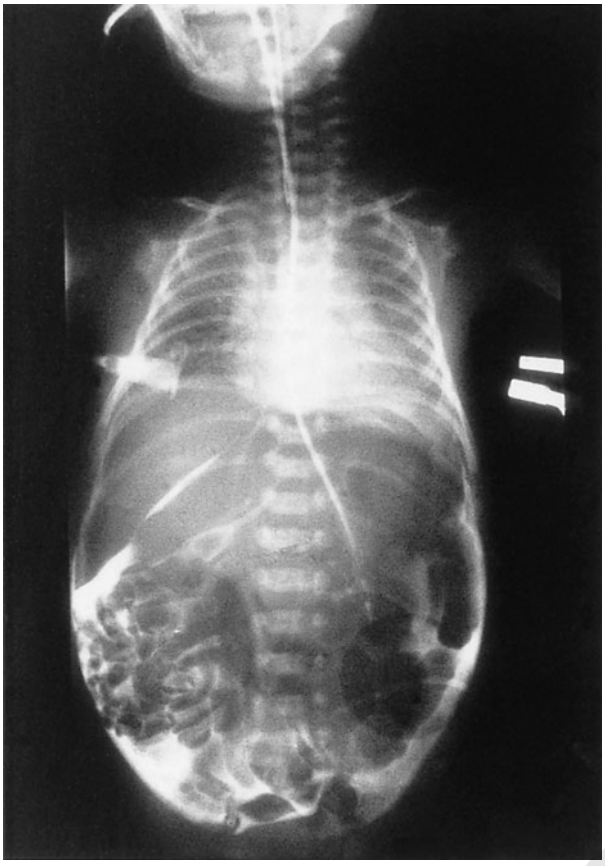

Figure 47.1 Diagnosis. Contrast study demonstrating gastric perforation. Abdominal distention, pneumoperitoneum, and contrast extravasation into the peritoneal cavity are seen. There is no evidence of lung disease and no findings suggestive of enterocolitis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is broad and includes conditions that cause sudden deterioration in the newborn and conditions that produce vomiting and abdominal distention. Conditions causing cardiovascular collapse include sepsis, pneumothorax, cardiac dysfunction, intraventricular hemorrhage, electrolyte abnormalities, hypoglycemia, necrotizing enterocolitis, perforated viscus, and malrotation with midgut volvulus. Conditions associated with vomiting and abdominal distention include Hirschsprung's disease, intestinal atresia, meconium ileus, meconium plug syndrome, imperforate anus, perforated viscus, necrotizing enterocolitis, and midgut volvulus.

PERIOPERATIVE CARE

Infants with gastric perforation develop septic parameters and need to be resuscitated accordingly. Neonates may become unstable prior to the development of free intra-abdominal air. Infants who develop respiratory distress require intubation and increased ventilator support is needed as the abdomen becomes more distended. Appropriate laboratory investigations include blood cultures, white blood cell count, hemoglobin, hematocrit, platelet count, electrolyte profile, and blood gas analysis. Broad-spectrum antibiotics should be initiated. Fluid boluses and blood transfusions are given to achieve hemodynamic stability and adequate urine output. An oro- or nasogastric tube should be carefully passed and placed on low intermittent suction. Once free intra-abdominal air is identified, the patient is stabilized and a laparotomy should be performed. Aspiration of the peritoneum with an i.v. cannula when an overly distended abdomen is impeding ventilation can be a life-saving measure.[4]

SURGICAL TECHNIQUE

Traditionally, open exploration and repair is required. Recently, successful laparoscopic repair of neonatal gastric perforation has been reported.[42] For an open repair an upper abdominal transverse skin incision (Fig. 47.2) is made and dissection carried through the rectus muscle until the peritoneum is entered. The umbilical vein is divided. The incision can be extended as needed. Peritoneal fluid and debris are evacuated. The abdomen is explored for the site of perforation. When a perforation of the stomach is not found, careful exploration of the gastro-esophageal junction, duodenum, small bowel, and colon should be performed. The lesser sac should be opened and inspected for contamination and integrity of the posterior surface of the stomach.

The most common site of a spontaneous perforation is near the greater curvature. The perforation can be small or extensive and extend high on the stomach. For isolated perforations, the devitalized edges of the perforation are debrided back to viable tissue (Fig. 47.3). The defect is closed in one or two layers and may be reinforced with an omental patch (Fig. 47.4). Stapled closure of a perforation, as well as repair around a gastromy tube have also been successful. A variety of techniques have been used to manage extensive perforations or necrosis that requires subtotal or total gastrectomy. In a stable infant, subtotal gastrectomy can be performed with reconstruction with an esophagogastric

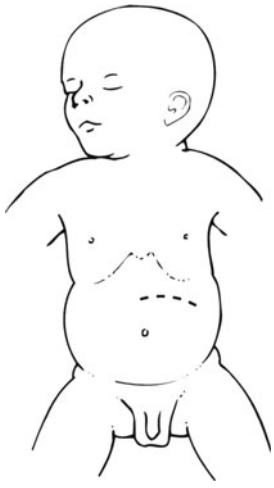

Figure 47.2 Incision. Upper abdominal transverse skin incision. The incision can be enlarged to gain access to the entire abdomen.

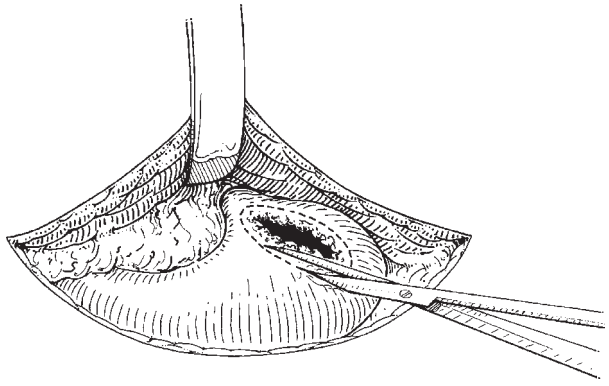

Figure 47.3 Exposure and resection. The entire perforation is exposed. A variable area of the stomach is found to be devitalized or necrotic. The edges of the perforation are resected back to bleeding viable tissue. On rare occasions, extensive resection, subtotal, or total gastrectomy are required.

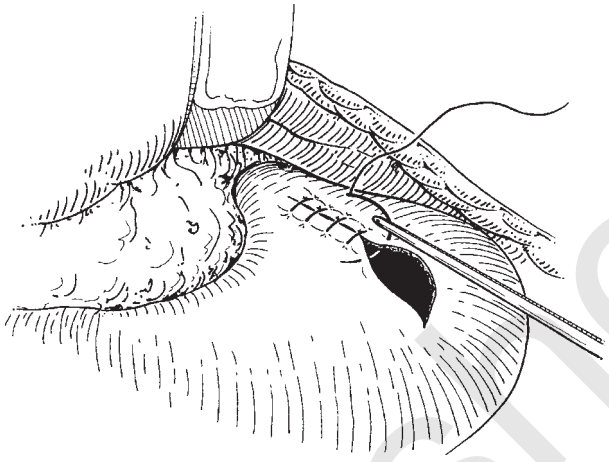

Figure 47.4 Closure. The free edges of healthy tissue are closed in one (depicted) or two layers. An omental patch may be used. Careful inspection of the posterior wall of the stomach and the entire small and large bowel should be performed to exclude additional areas of necrosis.

anastamosis.[43] Several techniques for reconstruction after total gastrectomy have been reported including transverse colon interposition, Roux-en-Y esophago-jejunal anastomosis and Hunt–Lawrence pouch reconstruction.[5,29,44] Reconstruction following total gastrectomy in an unstable neonate can be delayed and performed in stages. In the initial surgery, the esophagus is closed and a feeding tube placed distally through the distal gastric remnant or separate jejunostomy. The esophagus is decompressed and the child supported with parenteral nutrition until tube feedings can be initiated through the feeding tube. Reconstruction can be considered several weeks later when the clinical condition and nutritional status have improved.

Following repair of the perforation, the abdomen is lavaged with warm saline. Peritoneal drainage is not needed for most primary repairs but is used routinely by some surgeons. The fascia and skin are closed in standard fashion. Postoperatively, supportive and resuscitative care is continued. The child is maintained on broad-spectrum antibiotics, gastric acid suppression therapy, and total parenteral nutrition. The stomach should be decompressed. Feedings are held until the infant has stabilized. Many surgeons obtain a contrast study prior to initiating enteral feeds.

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48

Gastrostomy

MICHAEL WL GAUDERER

INTRODUCTION

Gastrostomy, one of the oldest abdominal operations in continuous use,[1] has played an important role in the management of various surgical conditions of the neonate.[1–7] The procedure was frequently employed for feeding as well as intestinal decompression. Additionally, a combination of gastric drainage with post-pyloric feeding via a jejunal tube was most helpful in the pre-parenteral nutrition era. In the past four decades, however, improvement in surgical techniques and postoperative care has led to a more selective use of gastrostomies in patients with major congenital anomalies of the gastrointestinal tract and abdominal wall. On the other hand, there has been an increased utilization of gastrostomies in infants and children without surgical pathology. In most of these, the indication is an inability to swallow, usually secondary to central nervous system impairment. Ironically, these are often patients who have survived because of aggressive neonatal resuscitation and technological advances.

INDICATIONS

In infants, the three main indications are long-term feeding, decompression, or a combination of both modalities. Additional indications include gastric access for esophageal bougienage and administration of medications.

Nasogastric feeding tube versus gastrostomy

Because the newer 5F and 8F infant feeding tubes are highly biocompatible and remain smooth and soft for prolonged periods of time, they are usually well tolerated, even by the smallest premature infants. In general, feeding tubes should be preferred if the expected length of enteral access is up to one to two months. Beyond this arbitrary time frame, complications such as naso-otopharyngeal infections and gastro-esophageal reflux tend to increase. Gastrostomies should be considered when direct gastric access for feeding or the administration of medication is expected to last more than several months.

Nasogastric decompression tube versus gastrostomy

With careful attention to appropriate intragastric position and regular flushing, naso- or orogastric tubes generally decompress more effectively than do gastrostomy tubes. The newer 8 or 10F tubes are well tolerated for up to several weeks. The author's preference when performing gastric decompression lasting up to 3–4 weeks in newborns is a 10–20 inch (38–51 cm) long, 8F single-lumen tube. Longer tubes are prone to plugging, thus becoming ineffective. It should be remembered that most commercially available 8F tubes are designed for feeding and have only two holes. Additional holes of appropriate size should therefore be added. However, care must be taken not to make the holes too big in order to avoid kinking. These 8F tubes should be attached directly or via a short connecting tube to a spill-resistant open container and irrigated regularly. No suction should be applied to single-lumen tubes. Double-lumen (vented) catheters, such as the 10F Replogle tube, originally designed for the aspiration of saliva in patients with esophageal atresia, tend to be much stiffer and are therefore more likely to cause problems. Additionally, if the venting lumen is obstructed and suction is applied, mucosa is sucked into the holes, leading to trauma and rendering the tube ineffective.

GASTROSTOMY IN SELECT NEONATAL SURGICAL PATHOLOGY

Esophageal abnormalities

Once considered essential in the management of patients with esophageal atresia, gastrostomies are no longer employed routinely. Analysis of large series demonstrates that esophago-esophagostomy without the use of a gastrostomy is

safe[8] and may in fact be beneficial for decreasing the incidence of gastro-esophageal reflux.[9] A gastrostomy is indicated in esophageal atresia without fistula, when a difficult repair or a stormy course is anticipated, in staging procedures, and when the child has associated anomalies that may interfere with feeding. The stoma, employed for the decompression or feeding, can also be used to provide access for the management of anastomotic complications such as leakage or strictures.

Duodenal obstruction

Congenital duodenal obstruction is usually associated with proximal duodenal dilatation and atony, as well as gastric dilatation. Total parenteral nutrition and nasogastric decompression are generally effective in postoperative management. However, if the need for prolonged gastric decompression is anticipated, a valuable alternative in this setting is the placement of a fine silicone rubber catheter alongside a gastrostomy catheter, across the anastomosis and into the proximal jejunum[1,10] (Fig. 48.1). Although these tubes are at times difficult to place and maintain, this simple and time-honored technique can decrease or eliminate the need for parenteral nutrition.

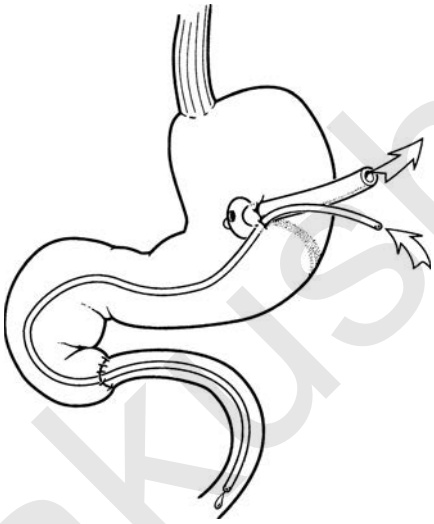

Figure 48.1 Combination gastric decompression and intrajejunal feeding, demonstrated diagrammatically in a newborn with repaired duodenal atresia.

Major abdominal wall defects

Prolonged ileus typically follows the repair of gastroschisis and occasionally other major wall defects. Although decompressive gastrostomies are not routinely employed, they can be helpful in patients with gastroschisis and associated atresia, particularly those requiring long-term continuous feeding.

Short-gut syndrome

Infants who have lost over 50% of their small bowel have profound alteration of gastrointestinal physiology. Initial gastric hypersecretion may require prolonged drainage. As the remaining intestine undergoes adaptive changes, continuous enteral feedings become necessary. As this latter process can be fairly lengthy, direct gastric access via gastrostomy is desirable.

Other surgical pathology

In any neonatal or infant condition in which a prolonged ileus or partial luminal occlusion (e.g. recurrent adhesive bowel obstruction, complicated meconium ileus, small bowel Hirschsprung's disease) is anticipated or in whom a complex feeding regimen is likely (e.g. those with intestinal lymphangiectasia), a gastrostomy can facilitate management. Gastrostomies are also helpful in some children with extra-abdominal surgical pathologies (Fig. 48.2).

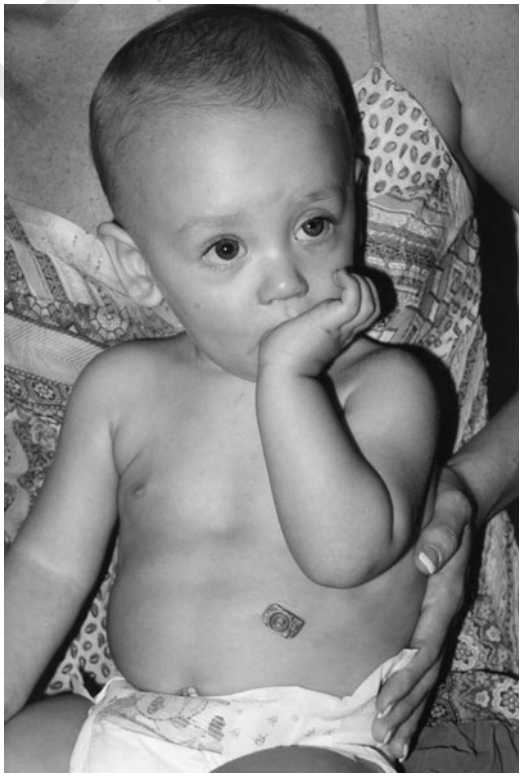

Figure 48.2 Ten-month-old child who presented with respiratory distress shortly after birth because of a large left cervical neuroblastoma. The lesion was fully resected on the 2nd day of life. However, the extensive dissection resulted in difficulty swallowing. A percutaneous endoscopic gastrostomy was placed at age 4 weeks and swallowing therapy initiated. Normal feeding gradually returned, and a few weeks after this picture was taken the gastrostomy could be removed. The only residual side effect is a left-sided Horner's syndrome.

'Non-surgical' pathology

The number of pediatric patients with an inability to swallow referred to the surgeon for the placement of a gastrostomy continues to increase. The main indications in infants are swallowing difficulty secondary to central nervous system lesions as well as other abnormalities of deglutition, feeding supplementation, large volume medications, and chronic malabsorption syndromes. Because the neurologically impaired children frequently have foregut dysmotility and gastro-esophageal reflux in addition to swallowing difficulties, anti-reflux procedures are at times added to gastrostomies. The question of whether to use gastrostomy only or gastrostomy plus an anti-reflux procedure continues to be a subject of considerable debate.[11,12]

ADVANTAGES AND DISADVANTAGES OF GASTROSTOMIES

Direct access to the stomach provides the surgeon with valuable perioperative access for drainage of air or fluids, a reliable long-term source of intermittent or continuous administration of nutrients, or a combination of both. As stated, nasogastric tubes tend to drain better than gastrostomies in the immediate postoperative period. However, a gastrostomy can eliminate the need for long-term naso- or orogastric intubation and the complications associated with placement and maintenance of these tubes. Gastrostomies interfere less with oral feedings than do nasogastric tubes, although the newer, smaller catheters are better tolerated. Gastrostomies are preferred over jejunostomies because the latter are less physiological and more prone to mechanical complications.[1]

The disadvantages of gastrostomies in the neonatal period include: the need for an operative intervention with or without laparotomy; the observation that the procedure is not always simple, particularly if the child has associated anomalies; and the observation that gastrostomy placement may interfere with gastric emptying and increase the incidence of gastro-esophageal reflux.[1,9] It has also been recognized that both nasogastric tubes and gastrostomies may promote gastric colonization with bacteria. Gastrostomies, as well as any other enteral tubes placed in infants, are associated with a long list of potential early and late complications.[1,13–18]

TECHNIQUE

There are multiple approaches to construct a gastrostomy. These techniques and their many variations are based on three fundamental principles:

1. Formation of a serosa-lined channel from the anterior gastric wall around a catheter. This catheter is placed in the stomach and exits either parallel to the serosa as in the Witzel technique, or vertically as in the Stamm or Kader approaches.[1,19]
2. Construction of a tube or conduit from a full-thickness gastric wall flap, leading to the skin surface. A catheter is then introduced intermittently for feeding. Several different configurations of the gastric wall flap have been described.[1,19]
3. Percutaneous techniques, i.e. without laparotomy, in which the introduced catheter holds the gastric and abdominal walls in apposition, with or without the aid of special fasteners.[1,19]

The Stamm technique, illustrated here, is the most widely employed gastrostomy with laparotomy in the neonatal setting, either as an isolated intervention, or when employed in conjunction with another intra-abdominal procedure. It can be used in children of any size and even on the smallest stomach (e.g. in newborns with esophageal atresia without fistula). A standard gastrostomy tube or a skin-level device can be placed under local anesthesia, although general anesthesia is preferred because abdominal wall relaxation is required. The procedure is usually short. After the tract is well healed, this stoma is suitable for the passage of dilators or guide wires.

The construction of a gastric wall tube is difficult in very young children. For a variety of reasons, this approach is not appropriate for newborns.

The first of the gastrostomies without laparotomy was the percutaneous endoscopic gastrostomy (PEG), initially developed for high-risk pediatric patients. The diagrams represented follow the initial description of the 'pull' PEG.[20] It has been employed in neonates weighing as little as 2.5 kg, usually for the purpose of long-term enteral feeding.[13–21] Although there is no need for abdominal wall relaxation, general endotracheal anesthesia is employed in this age group so that the airway is protected from compression during endoscopy. The procedure is very short and there is no postoperative ileus, no potential for bleeding or wound disruption and only minimal interference with subsequent interventions on the stomach, such as a fundoplication. The main disadvantage of this and other pure endoscopic techniques is that the virtual space between the stomach and the abdominal wall cannot be visualized. This shortcoming can be overcome by the addition of laparoscopic control.[22,23] Although in the typical PEG a long tube is initially employed, a primary insertion of a skin-level device is also possible.[24,25]

Several other methods of gastrostomy without laparotomy have been introduced and most are suitable for newborns. One of these is the percutaneous endoscopic 'push' technique which is performed with the aid of needle-deployed gastric anchors or 'T' fasteners, and the Seldinger method of guidewire introduction followed by progressive tract dilatations. A long tube or skin-level gastrostomy device is then inserted.[26] A similar approach is used by interventional radiologists and found to be suitable for even very small stomachs.[27–30]

In the last couple of decades, minimally invasive, laparoscopically aided approaches have been introduced. These are essentially expansions of the above methods, significantly increasing the choices of gastric access techniques available to surgeons managing infants.[31–36] Studies

comparing various techniques have been recently published.[37] One of the most widely employed laparoscopically aided gastrostomies is illustrated below. For infants with an abnormal epigastric anatomy, in whom the above techniques are difficult or impossible to perform, a hybrid procedure employing a mini-laparotomy and the PEG principle was developed.[38]

Stamm gastrostomy

The child is placed on the table with a small roll behind the back. When possible, a nasogastric tube is inserted for decompression and to help identify the stomach, if necessary. A small transverse incision is made over the left upper rectus abdominis muscle (Fig. 48.3). This incision should be neither too high, because it would bring the catheter too close to the costal margin, nor too low, avoiding the colon and the small bowel. A short vertical incision is an alternative. However, this approach is less desirable because the linea alba is the thinnest area of the abdominal wall. Bleeders are simply clamped. Fascial layers are incised transversely and the rectus muscle retracted or transected. When identification of the stomach is not immediate, downward traction of the flimsy greater omentum readily allows visualization of the transverse colon and stomach.

The site of gastrotomy placement on the anterior gastric wall is critical in infants. A position midway between the pylorus and the esophagus is chosen (Fig. 48.4). The site should be neither too high, because this would interfere with a fundoplication should one be needed in the future, nor too low, because stomas at the level of the antrum are prone to leakage and pyloric obstruction by the catheter. The surgeon must not place the catheter too close to the greater curvature, to avoid the so-called gastric pacemaker and to minimize the potential for gastrocolic fistula.[1]

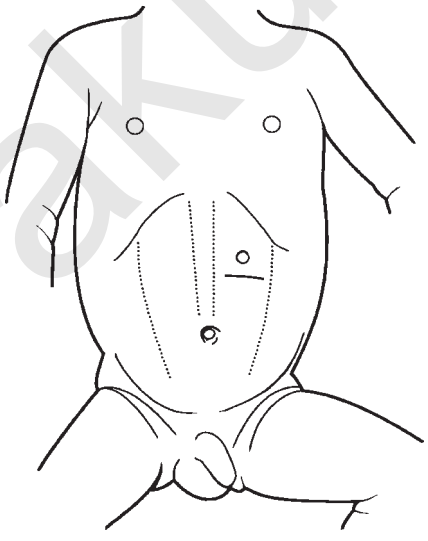

Figure 48.3 Gastrostomy incision and catheter exit site. An alternative is a short vertical midline incision.

The anterior gastric wall is lifted with two guy sutures (4-0 silk) at the site of the stoma, ensuring that the posterior wall is not included (Figs 48.4–48.7). A concentric purse-string suture (4-0 synthetic, absorbable material) is placed (Figs 48.4–48.6). The gastrotomy, at the center of the purse string, is made sharply through the serosa and muscular wall of the stomach.

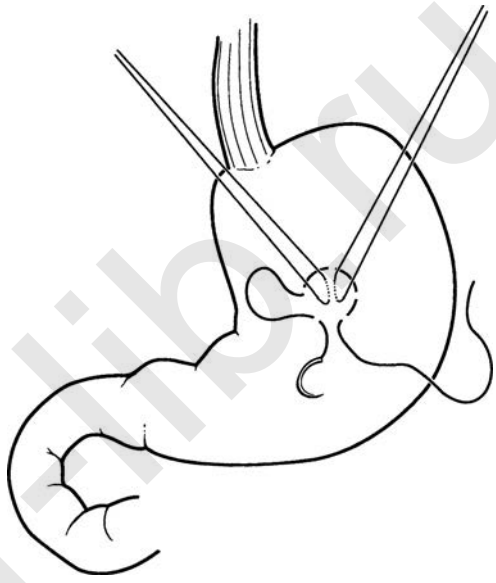

Figure 48.4 Gastrotomy site on the anterior gastric wall. The traction guy sutures and the purse-string suture are shown.

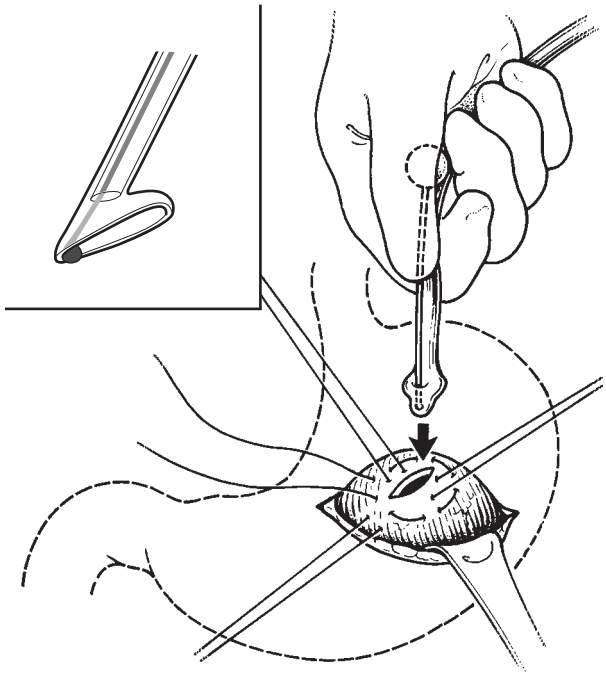

Figure 48.5 Introduction of a de Pezzer catheter using a simple stylet. The inset shows insertion of a percutaneous endoscopic gastrostomy-type catheter. Reproduced with permission from Ref. 19.

A small hemostat is introduced to confirm access into the gastric lumen. We prefer a mushroom-type catheter (de Pezzer), sizes 12–14 Fr gauge, for neonates. The mushroom head of the catheter is stretched with a short stylet to allow atraumatic introduction into the stomach (Fig. 48.5). The purse string is tied to invert the seromuscular gastric wall around the tube (Fig. 48.6). Other suitable catheters are the Malecot or the 'T' tube, but both have the disadvantage of becoming more easily dislodged. However, a short 'T' tube is useful if the stomach is very small. It is also our preferred tube for infant jejunostomies. We avoid the Foley or balloon-type catheters because the main lumen is proportionately smaller and the balloon occupies more intragastric space. Long balloon-type catheters, which may rupture, also have a greater propensity for distal migration into the small bowel. Skin-level devices (buttons or balloon-type) may be inserted during the operation, instead of the traditional long tubes.[19] The exit site for the catheter should be through the mid-portion of the rectus muscle about 1–2 cm above or below the laparotomy incision (Figs 48.3, 48.7, and 48.8). Although some surgeons bring the catheter out by way of the primary abdominal incision, wound complications that may occur in this setting tend to be more complex.[1] Once the exit site is chosen, the anterior gastric wall is secured to the posterior aspect of the anterior abdominal wall with four equidistant sutures or, as illustrated, with a continuous suture of double-ended 4-0 synthetic monofilament thread (Figs 48.6 and 48.7).[21] The catheter position is tested by injecting and aspirating saline. Gentle traction on the catheter ensures that its intragastric position is maintained.

The posterior rectus sheath is closed with a running suture of 4-0 absorbable, synthetic material. The anterior rectus sheath is approximated with interrupted sutures of the same material. The subcutaneous layer is closed with a couple of 5-0 or 6-0 synthetic, absorbable sutures. The skin can be approximated with either interrupted or continuous 5-0 or 6-0 subcuticular sutures. Adhesive strips cover the incision (Fig. 48.8). The catheter is firmly secured with two sutures of 3-0 or 4-0 synthetic, monofilament thread. These sutures are removed after 1 week and a small cross-bar is placed loosely to prevent distal catheter migration. Occlusive dressings are not used after the first couple of postoperative days. Conversion of a long tube to a 'button' can be performed after a firm adherence between gastric and abdominal wall is established.

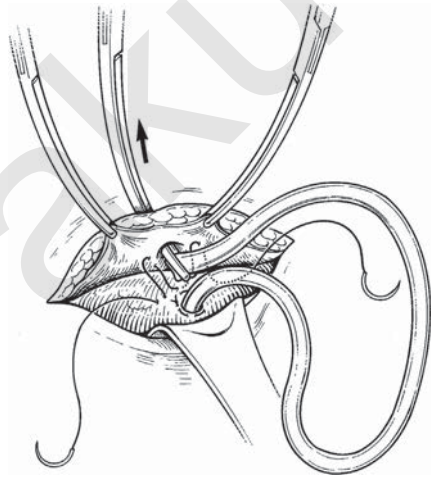

Figure 48.6 The purse-string suture is tied. The continuous monofilament suture, used to anchor the stomach to the anterior abdominal wall, has been partially placed. The catheter is brought out through the counter-incision. Reproduced with permission from Ref. 19.

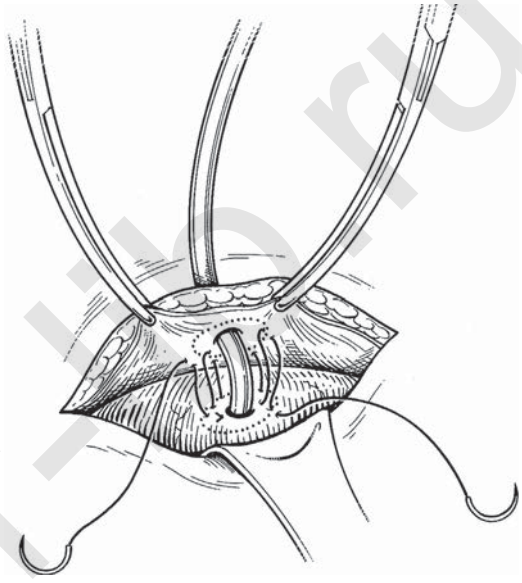

Figure 48.7 The continuous monofilament suture placement is continued anteriorly and then tied. This provides a 360° fixation of the stomach to the anterior abdominal wall with a watertight seal. Reproduced with permission from Ref. 19.

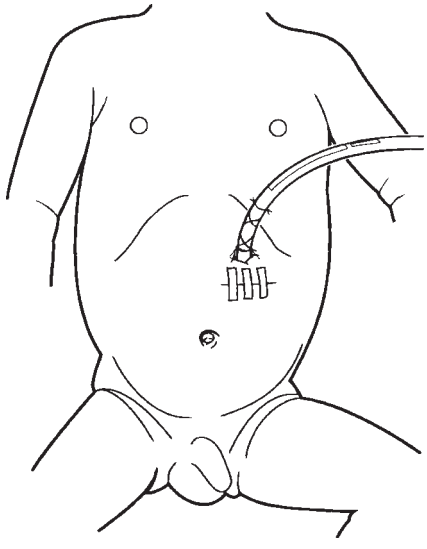

Figure 48.8 Completed procedure. The subcuticular closure, adhesive strips, and secured gastrostomy catheter are shown. The immobilizing sutures are removed after several days and a small cross-bar is placed to prevent distal catheter migration. An alternative is the placement of a 'button' or a balloon-type skin-level device, instead of a long tube, at the initial procedure.[19]

Percutaneous endoscopic gastrostomy

The PEG technique, as initially described,[20] is applicable to neonates and small infants.[21] The procedure must, however, be done with great precision and endoscopic skill. PEG incorporates four basic elements:

1. Gastroscopic insufflation brings the stomach into apposition to the anterior abdominal wall (Fig. 48.9).
2. With the stomach apposed to the abdominal wall, a cannula is introduced percutaneously into the gastric lumen under direct endoscopic guidance (Fig. 48.10).
3. This cannula serves as access to introduce a guide-wire, which is then withdrawn out of the patient's mouth with the gastroscope (Fig. 48.11). A tract is thus established.
4. A PEG catheter with a tapered end is attached to the oral end of the guide-wire and pulled in a retrograde fashion until it assumes its final position, keeping the stomach firmly apposed to the abdominal wall (Fig. 48.12).

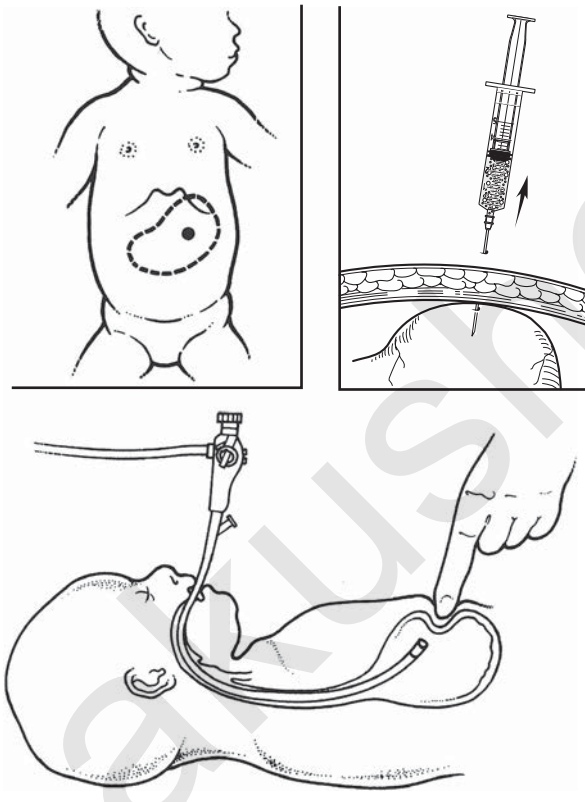

Figure 48.9 Percutaneous endoscopic gastrostomy (PEG). The air insufflated through the endoscope approximates the stomach to the abdominal wall and displaces the colon caudally. Digital pressure is applied to the proposed gastrostomy site, which usually corresponds to the area where transillumination is brightest. Transillumination and clear visualization of an anterior gastric wall indentation are key points. Without these, an open or laparoscopic technique should be employed. Long-lasting local anesthetic is drawn into a syringe and the proposed PEG site injected. The needle is advanced further and continuous aspirating pressure is applied to the plunger. Air aspiration should only occur when the tip of the needle enters the gastric lumen. Reproduced with permission from Ref. 19.

Although there are multiple variations of the original PEG technique[1,20,22–26] and several types of catheters, one must be cautious, because most of these are not suitable for use in infants. We employ a 16 Fr gauge (or smaller) commercially available silicone rubber pediatric PEG catheter. Larger, stiffer catheters, or those with a stiff, non-collapsible inner retainer, can easily tear the infant's esophagus.

A single dose of an i.v. broad-spectrum antibiotic is administered at the outset. The child remains in the supine position throughout the procedure. The abdomen is cleansed and sterilely draped. Gastroscopy is performed with the smallest pediatric gastroscope available. The scope is inserted and advanced slowly into the stomach, at which point the light is seen through the left upper quadrant abdominal wall. With the gastroscope in place, insufflation distends the stomach, apposes it against the anterior abdominal wall, and displaces the colon downward. When the room lights are dimmed, the gastric contour is clearly visible, particularly in small children.

The preferred gastrostomy site is over the mid-portion of the left rectus muscle, as depicted in the inset of Figure 48.9. Digital pressure is exerted at this site, and this is seen by the endoscopist as a 'polypoid lesion' or 'mound' on the anterior gastric wall. (Gastric transillumination and endoscopically visualized digital indentation of the stomach are the most important factors in safe PEG placement.) The endoscopist

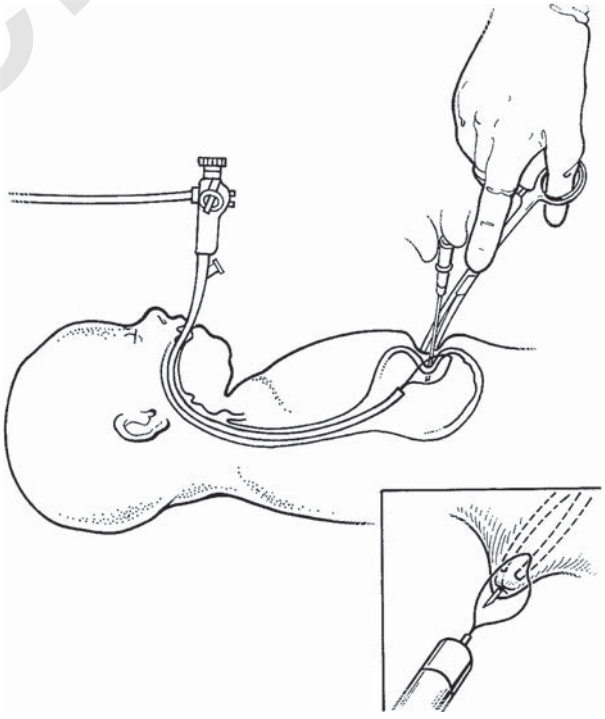

Figure 48.10 A small skin incision is made and a Kelly-type hemostat applied to maintain the intragastric indentation. The endoscopist places the polypectomy snare around the 'mound', the cannula is introduced between the slightly spread prongs of the hemostat and then thrust through the abdominal and gastric walls into the open snare. The snare is partially closed, but not tightened around the cannula. Reproduced with permission from Ref. 19.

then places an endoscopic polypectomy snare around this invagination of the anterior gastric wall. Digital pressure is released and a 0.5–0.7 cm skin incision is made. A hemostat with slightly opened prongs is placed in the incision, recreating and maintaining the intragastric 'mound' (Fig. 48.10). Through this incision and through the prongs of the hemostat, a 16-gauge, smoothly tapered, i.v. cannula and needle are thrust through abdominal and gastric walls under endoscopic visualization. This should be performed quickly to avoid displacing the stomach from the abdominal wall. The snare, if properly positioned initially, will be around the advancing cannula. If not, it can be maneuvered to encircle the cannula. A long, monofilament synthetic suture or a plastic-covered steel guide-wire is then advanced through the cannula and grasped by the snare (Fig. 48.11). If there is difficulty with the snare, a biopsy or alligator-type forceps may be used. As the gastroscope and snare are withdrawn, the suture is brought out of the patient's mouth (Fig. 48.11, inset). The previously selected PEG catheter is then connected to the suture outside the patient's mouth and both suture and catheter are coated with a water-soluble lubricant. Traction on the abdominal portion of the suture or guide-wire pulls the catheter in a retrograde fashion, through the mouth, esophagus, and stomach, and across the abdominal wall (Fig. 48.12). The gastroscope is reintroduced to verify the catheter position under direct vision. While re-endoscopy might theoretically be unnecessary, we believe it adds safety to the procedure.

Traction on the catheter is continued until the inner catheter retainer or 'dome' loosely touches the gastric mucosa (Fig. 48.12). Markings on the commercially available catheters, or markings added to tubes without marks, are helpful in indicating the final position of the tube. The external cross-bar is then placed (Fig. 48.12). Excessive pressure by the external cross-bar on the abdominal wall will produce pressure necrosis and eventual catheter extrusion, and should be avoided. The tapered catheter end is cut off and a connector attached. Tape is used for temporary catheter immobilization. Although the tube can be used immediately, we have arbitrarily placed it to gravity drainage for the first 24 hours and instituted tube feedings the day after the procedure. The catheter may be converted to a skin-level device by using the external port valve at any time. To replace the PEG catheter with a 'button' or balloon-type skin-level device, we find it is prudent to wait until firm adhesions between the stomach and abdominal wall are established. This may take one to two months or longer.

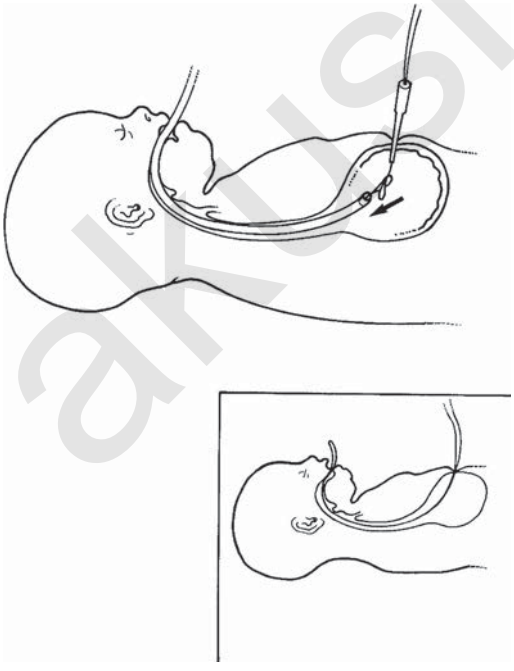

Figure 48.11 The needle is removed and the guide-wire inserted. The polypectomy snare grasps the guide and exits it through the mouth. An alternative to the polypectomy snare is an alligator or biopsy forceps. Reproduced with permission from Ref. 19.

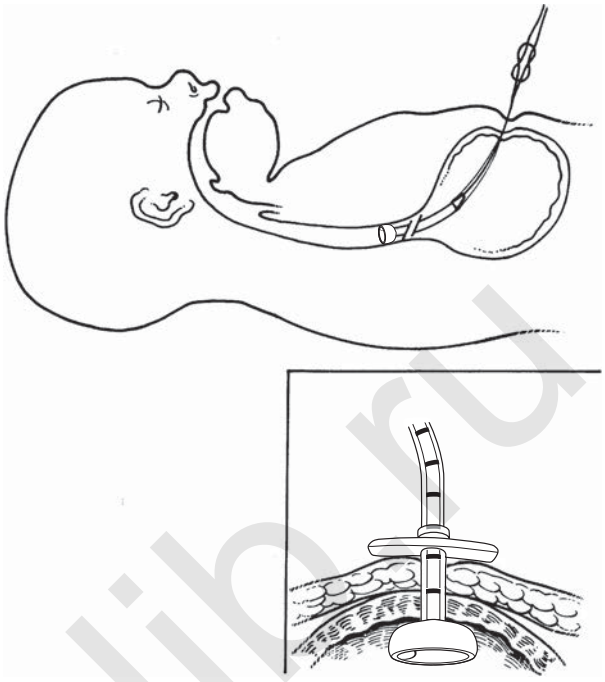

Figure 48.12 The appropriate size percutaneous endoscopic gastrostomy catheter is attached to the oral end of the guide-wire and pulled in a retrograde manner through the infant's esophagus and stomach, then across gastric and abdominal walls. The inset shows the position of the catheter at the end of the procedure. Reproduced with permission from Ref. 19.

Laparoscopically assisted gastrostomies

Direct visualization by a laparoscope expands the options for constructing a gastrostomy.[31–36] Several approaches have been described. In addition to the videoscopically controlled PEG, the two most common methods are adaptations of the Stamm technique and modifications of the 'push' PEG. Our preference is for the latter because, in order to place a purse-string suture through the exposed segment of the anterior gastric wall, the trocar site must be sufficiently enlarged. This may predispose the site to leakage. In order to

temporarily anchor the stomach to the abdominal wall, different approaches may be employed, notably T-fasteners and U-stitches. The most suitable site for the gastrostomy is selected in the left upper quadrant and marked. A nasogastric tube is inserted. Pneumoperitoneum is established in the child's size-appropriate manner, a trocar is placed at the umbilicus and the laparoscope is introduced. A needle is pushed through the previously marked abdominal wall site and the appropriate relation between the anterior gastric wall and the stoma site established. A small skin incision is made and a 5 mm trocar inserted. A grasper is introduced and the gastrotomy site on the anterior gastric wall is lifted toward the parietal peritoneum (Fig. 48.13). A U-stitch is passed through the abdominal wall, through the anterior gastric wall, and back out through the abdominal wall. A second U-stitch is passed parallel to the first one, 1–2 cm apart (Fig. 48.13). The sutures are lifted, maintaining the stomach in contact with the abdominal wall. The grasper and the trocar are removed. The stomach is insufflated with air through the nasogastric tube and a needle is inserted through the trocar site into the gastric lumen, between the two U-stitches. A Seldinger-type guide-wire is passed through the needle into the stomach (Fig. 48.14). The tract is dilated over the guide-wire to the size required to insert either a Foley-type catheter or a balloon-type skin-level device. These are placed over the same guide-wire. Stiffening of the catheter shaft with a thin metallic dilator is helpful. The previously placed U-stitches are tied over the wings of the 'button' (Fig. 48.15). If a long tube is placed, a pair of bolsters is employed. Care must be taken to avoid excessive tension. In a recently described technique, the U-stitches are replaced by a continuous suture.[39]

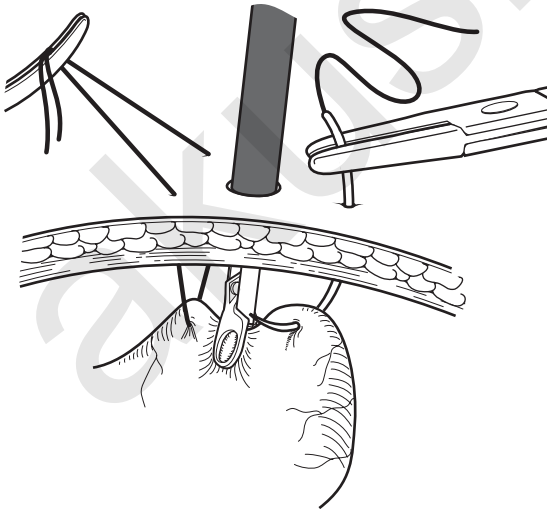

Figure 48.13 Laparoscopically assisted gastrostomy. Following the establishment of pneumoperitoneum and insertion of a trocar at the gastrostomy site, a grasper is introduced and the appropriate portion of the anterior gastric wall is lifted. Two sutures are placed in the manner shown. Reproduced with permission from Ref. 19.

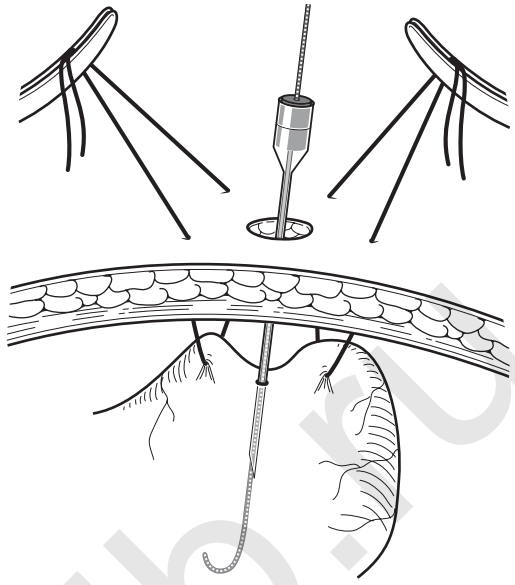

Figure 48.14 The stomach is insufflated with air through the nasogastric tube and a needle is inserted through the trocar site into the gastric lumen, between the two U-stitches. A Seldinger-type guide-wire is passed through the needle into the stomach. The tract is dilated over the guide-wire to the size required to insert either a Foley-type catheter, a balloon-type skin-level device, or other low-profile access device. These are placed over the same guide-wire. Reproduced with permission from Ref. 19.

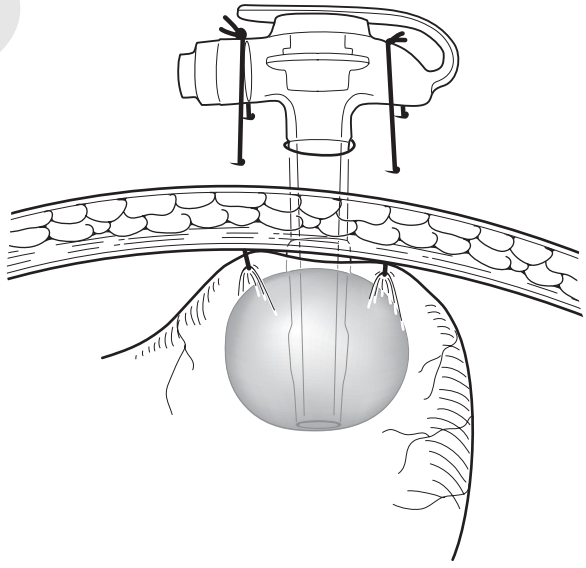

Figure 48.15 A balloon-type 'button' has been placed. The previously placed U-stitches are tied over the 'wings' of the skin-level device. Reproduced with permission from Ref. 19.

SELECT COMPLICATIONS OF GASTROSTOMIES

Although frequently considered a simple procedure and often delegated to a junior member of the surgical team, a

gastrostomy has a considerable potential for early and late morbidity, particularly among neonates.

Complications related to operative technique

SEPARATION OF STOMACH FROM ABDOMINAL WALL

This serious mishap most commonly occurs after early gastrostomy tube reinsertion, before a firm adhesion between gastric and abdominal walls has occurred. However, it can also occur at any time thereafter. During the attempt to replace a dislodged catheter, the stomach is pushed away from the abdominal wall; that displacement leads to a partial or complete separation of the stoma. If recognition of the problem is delayed, severe peritonitis and death may result.[1,2,5,6,13–16] To avoid this and other mechanical problems, the stomach must be firmly anchored to the anterior abdominal wall and the catheter well secured to the skin, particularly with the open, Stamm-type techniques. In the event of early removal or dislodgement of the tube, the tract can be gently probed and a thin Foley catheter inserted. This must be followed by injection of a radio-opaque contrast material under fluoroscopy to ensure an intragastric position of the tube and absence of intraperitoneal leakage. If there is any question about the position of the catheter, prompt exploration is necessary.

WOUND SEPARATION, DEHISCENCE, AND VENTRAL HERNIA

These are usually the result of technical problems and carry high morbidity and mortality rates.[1,3,5,6] Leakage from an enlarged incision can be life threatening.[3] Such mishaps can be minimized by the use of appropriate, small incisions and by bringing the tube out through a counter-incision. These complications will not occur after a PEG, or a laparoscopic gastrostomy, because there is no laparotomy.

HEMORRHAGE

Major bleeding is described in pediatric series[4,6] and is usually related to inadequate hemostasis at the time of catheter insertion. Gentle traction on the catheter can control the bleeding, but reoperation may become necessary.

INFECTION

This complication can occur with any type of gastrostomy.[1,3–5,13–18] Although usually limited to the skin and subcutaneous tissue, it can lead to full-thickness abdominal wall loss. Infections are less common following PEG placement[8] or laparoscopic gastrostomy and can usually be avoided through the use of prophylactic antibiotic administration and a skin incision only slightly larger than the diameter of the tube.

INJURY TO THE POSTERIOR WALL OF STOMACH

The posterior gastric wall can be damaged or perforated not only during the initial procedure,[33] but also later during catheter change.[1] Once the tube is introduced, air or saline should be injected to test the tube's position and function.

INJURY TO OTHER ORGANS

During open procedures, damage to the liver and spleen can occur through the improper use of retractors or other instruments. The distended colon may be mistaken for the stomach, particularly in patients with intra-abdominal adhesions in whom mobility of intestinal loops is limited.

GASTROCOLIC FISTULA

Although it can occur with any gastrostomy, this complication is more likely with the percutaneous endoscopic techniques.[1,13] With proper technique however, this problem should be rare. During the PEG procedure, the importance of appropriate gastric insufflation with downward colonic displacement, transillumination, and the indentation on the anterior abdominal wall cannot be overemphasized. On the other hand, overinflation must be avoided because it can distort the local anatomy, including the position of the colon. Additionally, air-filled small bowel loops will displace the colon cranially and move it between the stomach and the abdominal wall.

Complications related to care of stoma

SKIN IRRITATION AND MONILIASIS

Next to granulation tissue, these are the most frequent problems encountered. Usually related to leakage, and compounded by occlusive dressings, irritation is best prevented by avoiding any occlusive devices, including nipples, tape, or gauze pads.[1] The site should be kept open and dry at all times. Ointments and other solutions, except for the treatment of moniliasis, should be avoided. Catheters, if kept long, can be immobilized with a small external cross-bar.

TUBE PLUGGING

Catheters must be flushed with water after each feeding to prevent blockage. In neonates, the amount should be small and added to the fluid intake.

ADMINISTRATION OF IMPROPER FEEDINGS

Careful and slow administration of the appropriate nutrient prevents metabolic abnormalities, as well as diarrhea and excessive reflux.

DELAY IN THE REINTRODUCTION OF A DISLODGED CATHETER

Accidental dislodgement of long gastrostomy catheter is fairly common. The catheter must be replaced before the tract closes, which can be in a few hours unless it is well matured and epithelium lined. Careful dilation of the tract is usually successful.

TRAUMA DURING REINSERTION OF CATHETER

Improper catheter reintroduction can lead to damage to the pancreas, liver, or spleen, particularly if long stylets or other traumatic instruments are used to elongate a mushroom-type tip. Small children are more prone to this complication, given the short distance of these organs from the abdominal wall. Gentle insertion and aiming toward the gastric cardia or fundus is the method least likely to project injury.

Complications related to catheters

GRANULATION TISSUE

This is by far the most frequent problem associated with gastrostomies. Usually, granulation tissue formation is mild, and a few applications of silver nitrate are curative. If this condition is neglected, however, granulation tissue will predispose to leakage, bleeding, and chronic discharge. With excessive growth, excision and cauterization become necessary. Granulation tissue formation will cease once epithelialization of the tract has occurred. We have found that a cream combining an antifungal and a steroid preparation helps to minimize the formation of this abnormal tissue.

LEAKAGE

Severe continuous leakage is uncommon in properly constructed gastrostomies.[1,3] However, severe widening of the stoma can lead to skin excoriation, dislodgment of the tube, metabolic imbalance, and even death.[1,3] The main cause of leakage in most children is enlargement of the stoma by the pivoting motion of the gastrostomy tube, which is often too large or too stiff.[1] Catheters brought through the incision or the thinner midline are more prone to this problem. Management of leakage begins with control of granulation tissue and placement of a smaller, softer catheter to avoid pivoting motion. A variety of other methods have been tried with varying degrees of success.[1] In extreme cases, reoperation or stoma relocation becomes necessary.

INTERNAL MIGRATION

Distal migration of a long catheter producing high intestinal obstruction is a well-known problem.[1,3,5] It can occur with any gastric tube, but is particularly common with long, balloon-type catheters.

EXTERNAL MIGRATION

Overzealous approximation of external immobilizing devices, such as the bumper, can lead to embedding of the inner cross-bar of a PEG catheter, mushroom tip, or balloon in the gastric and abdominal wall.[1] The usual presentations are malfunction with limited flow, leakage, lack of to-and-fro motion of the catheter, or the formation of an abscess. The catheter should be removed and replaced. This problem can be avoided by giving the catheter enough 'play', i.e. a little to-and-fro motion.

PERFORATION OF ESOPHAGUS AND SMALL BOWEL

The balloon of a Foley-type catheter can be accidentally inflated in the esophagus[40] or small bowel,[41] leading to wall disruption.

PERSISTENT GASTROCUTANEOUS FISTULA

In the longstanding gastrostomy, an epithelium-lined channel will form. Although most stomas close spontaneously after a few days, excision of the tract with simple closure is indicated if drainage persists after several weeks.[1]

Prevention

A long list of additional complications is recorded, and these can be particularly dangerous in the newborn age group.[1,3–7,13–18] Most of the common gastrostomy care-related problems can be prevented with meticulous attention to detail during placement and subsequent follow up.[15] The use of skin-level devices such as the original gastrostomy button,[1,42] the balloon-type versions, or the externally placed port-valve[43] has dramatically decreased the most common problems associated with older, long tubes. Many techniques, whether open, endoscopic, or laparoscopically aided, now permit the initial placement of one of these well-tolerated skin-level devices (Figs 48.16 and 48.17).

CONCLUSION

Although gastrostomy is a basic and fairly simple procedure, the surgeon must carefully consider the advantages versus disadvantages when using it in conjunction with another major intervention in the newborn. If the gastrostomy is used for long-term enteral feeding, careful consideration must be given not only to the often difficult ethical problems encountered in some neonatal patients, but also to the duration of these enteral feedings, potential complications, and the problem of gastro-esophageal reflux. These children benefit from a team approach, including the neonatologist, pediatric surgeon, pediatric gastroenterologist, primary nurse, and nutritionist. It is also paramount that the parents or caregivers be an integral part of the decision-making process at the different stages of management. Long-term

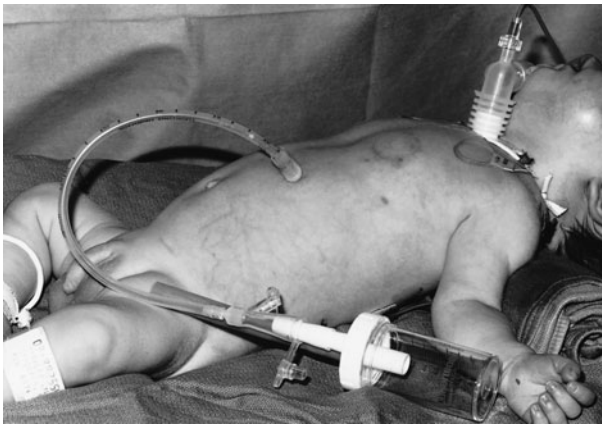

Figure 48.16 Completed percutaneous endoscopic gastrostomy and tracheostomy in a four-month-old child, weighing 3.5 kg, with poor swallowing and severe bronchopulmonary dysplasia. The child was born prematurely at 29 weeks' gestation and was hospitalized following an eventful neonatal course. Sutures are not used after the percutaneous endoscopic gastrostomy and the catheter is connected to a small clear plastic trap. After 24 hours, the external cross-bar is checked and loosened, if necessary, to accommodate for wound edema. Feedings are then started.[30] Notice the tracheal traction sutures used as safety measures with the child's tracheostomy and the scar of a previously repaired inguinal hernia.

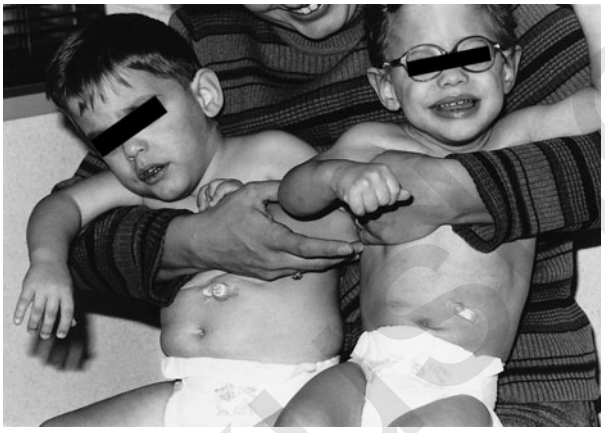

Figure 48.17 Two former premature infants with complex neonatal courses. Both receive supplemental feedings and medication via the gastrostomy. The child on the left has a balloon-type skin-level device and the one on the right has an original, low-profile gastrostomy button.

follow up is essential, and its importance cannot be overemphasized. Whether the gastrostomy is placed as an adjunct, or for the prime purpose of feeding, every effort should be directed towards resuming oral feeding whenever possible.

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49

Duodenal obstruction

YECHIEL SWEED

INTRODUCTION

Congenital duodenal obstruction is the most common cause of intestinal obstruction in the newborn period, occurring in 1 in 5000–10 000 live births.[1–3]

Duodenal obstruction is the result of intrinsic lesion, extrinsic lesion, or a combination of both. Intrinsic duodenal obstruction may be caused by duodenal atresia, stenosis, diaphragm, a perforated diaphragm, or a 'windsock' web. The windsock web is a duodenal membrane which is ballooned distally as a result of peristalsis from above.[4,5] Extrinsic duodenal obstruction may be caused by annular pancreas, malrotation, or preduodenal portal vein. Although the annular pancreas forms a constricting ring around the second part of the duodenum (Fig. 49.1), it is not believed to be the cause of duodenal obstruction[6,7] and there is usually an associated atresia or stenosis in patients with an annular pancreas.[8–10] Similarly, preduodenal portal vein has also seldom been reported to be the cause of duodenal obstruction and it is often associated with other causes of intestinal obstruction, such as malrotation or duodenal atresia.[11,12]

Duodenal atresias have been traditionally classified by Gray and Skandalakis[13] into three types (Fig. 49.2). Type I defect, the most common (Fig. 49.2a), is represented by a mucosal and submucosal diaphragmatic membrane with an intact muscle wall. The opening of the bile duct at the ampulla of Vater is almost always located proximal to the duodenal web. Type II defect has a short fibrous cord that connects the two atretic ends of the duodenum (Fig. 49.2b). In type III defect, there is a complete separation of the atretic ends with a mesenteric defect (Fig. 49.2c). The reported prevalence of type I is about 92%, type 2 is 2%, and type 3 is 7%.[7] Duodenal stenosis is approximately half as prevalent as atresia.[14]

Figure 49.3 shows the wide spectrum of various types of duodenal obstruction. The proximal and distal segments of the duodenum may be separated by a gap (Fig. 49.3a), be in apposition (Fig. 49.3b), or be joined by a fibrous cord (Fig. 49.3c). Other types include duodenal stenosis (Fig. 49.3d), complete diaphragm (Fig. 49.3e), a perforated diaphragm (Fig. 49.3f), a windsock web (Fig. 49.3g), and an annular pancreas (Fig. 49.3h).

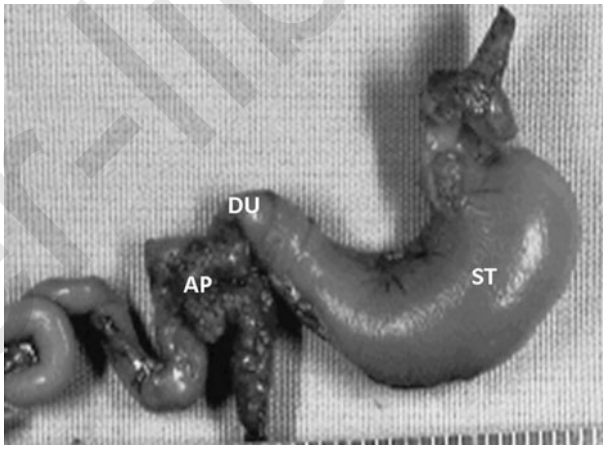


Figure 49.1 Duodenal obstruction caused by an annular pancreas associated with duodenal stenosis in post-mortem of a 14-week-old fetus with a diagnosis of Down syndrome. AP, annular pancreas; DU, duodenum; ST, stomach.

ETIOLOGY

The underlying cause of duodenal atresia remains unknown although its pathophysiology has been well described. Frequent association of duodenal atresia or stenosis with other neonatal malformations suggests that both anomalies are due to a developmental error in the early period of gestation. Duodenal atresia differs from other atresias of the small and large bowel, which are isolated anomalies caused by mesenteric vascular accidents during later stages of development. This theory of vascular disturbance was presented by the classic study of Lauw and Barnard.[15]

No predisposing maternal risk factors are known. Although up to one-third of patients with duodenal atresia have Down

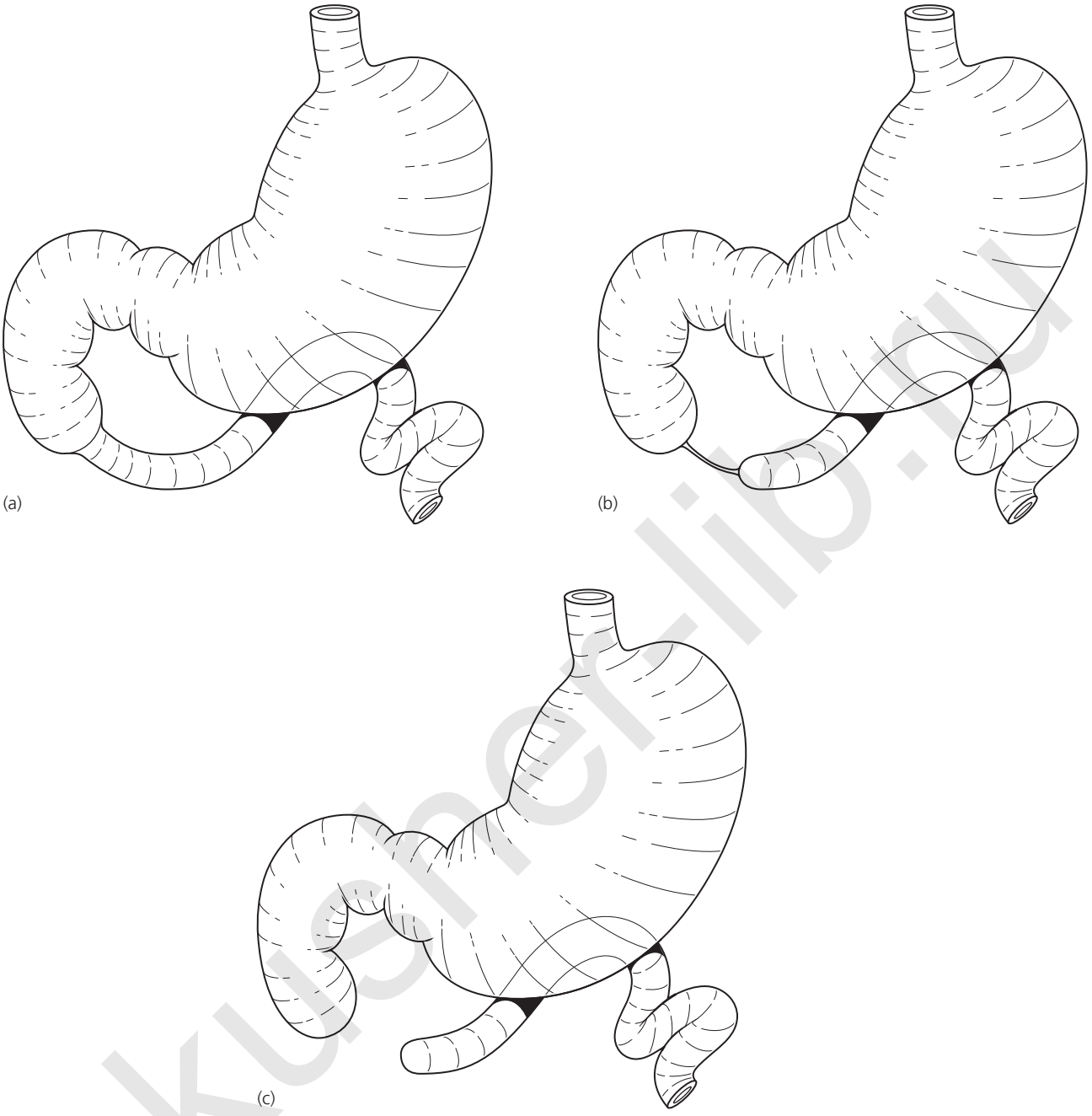


Figure 49.2 Types of duodenal atresia (by Gray and Skandalakis[13]). (a) Type I, mucosal membrane with intact muscle wall. (b) Type II, fibrous cord connecting the two atretic ends of duodenum. (c) Type III, a complete separation of the atretic ends with a mesenteric defect.

syndrome (trisomy 21) it is not an independent risk factor for developing duodenal atresia.[16] In the large California population-based registry of 2.5 million infants, the risk of duodenal atresia was found to be 265 times higher in infants with Down syndrome compared to those without it and the corresponding frequencies were 46 and 0.12 per 1000 births.[17]

Although duodenal obstruction is usually not regarded as a familial condition there have been several reports of familial cases,[18–21] and a very rare group of hereditary multiple intestinal atresias with fatal outcome.[22]

PATHOPHYSIOLOGY

Duodenal atresia, web, and stenosis usually occur in the second part of the duodenum, close to the area of intense embryological activity involved with the development of the biliary and pancreatic structures. These anomalies are believed to result from a developmental error during early fetal life.[23–25]

Duodenal maldevelopment occurs secondary to either inadequate endodermal proliferation (gut elongation outpaces

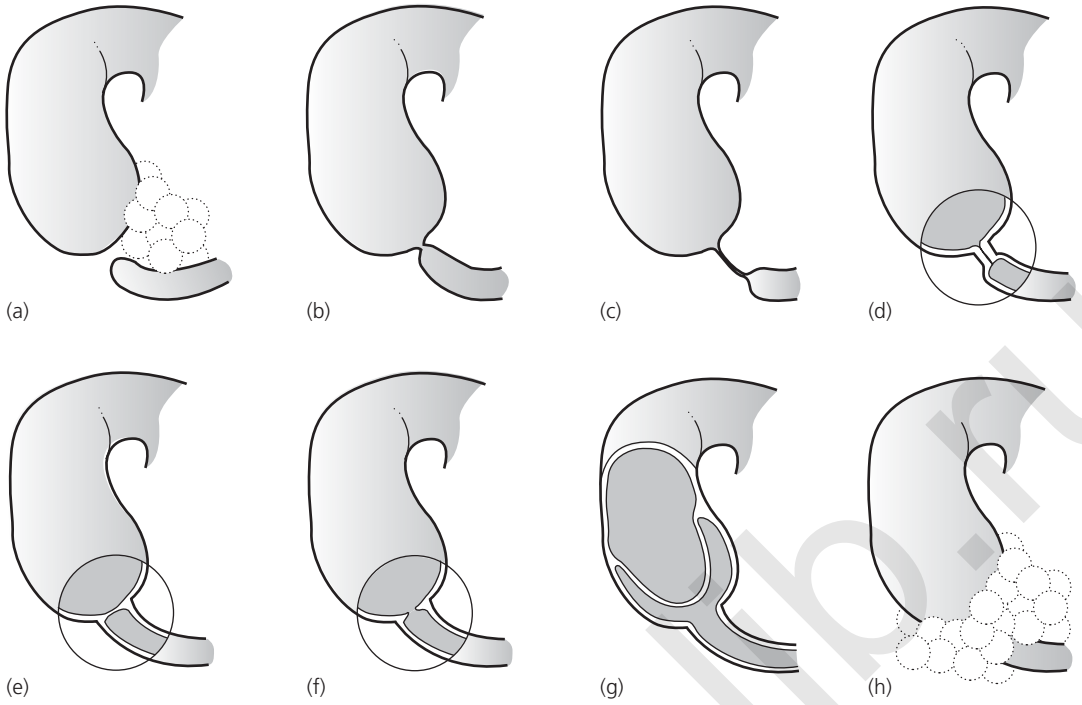


Figure 49.3 Various types of duodenal obstruction. (a) Blind ends separated by a gap. (b) Two ends in apposition. (c) Ends joined by a fibrous cord. (d) Duodenal stenosis. (e) Complete duodenal membrane. (f) Perforated diaphragm. (g) Windsock web. (h) Annular pancreas.

proliferation) which occurs at 5 weeks of embryonic life or failure of the epithelial solid cord to recanalize (failure of vacuolization) which appears at 11 weeks of gestation.

Many investigators have demonstrated that the epithelium of the duodenum proliferates during 30–60 days of gestation, completely plugging the duodenal lumen. A subsequent process termed vacuolation occurs whereby the solid duodenum is recanalized. Vacuolation is believed to occur by way of apoptosis, or programmed cell death, which happens during normal development within the lumen of the duodenum. Occasionally, duodenal atresias are associated with annular pancreas. This is likely due to failure of duodenal development rather than robust and/or abnormal growth of the pancreatic buds.[26]

At the cellular level, the gastrointestinal tract develops from the embryonic gut, which is composed of an epithelium derived from endoderm, surrounded by cells of mesodermal origin. Cell signaling between these two embryonic layers appears to play a critical role in coordinating patterning and organogenesis of the duodenum. Sonic hedgehog genes encode members of the hedgehog family of cell signals. Both are expressed in gut endoderm, whereas target genes are expressed in discrete layers in the mesoderm. Mice with genetically altered sonic hedgehog signaling display duodenal stenosis, suggesting that genetic defects in the sonic hedgehog family of genes may influence the development of duodenal abnormalities.[27]

Recently, fibroblast growth factor-10 was found to be active in the duodenum at a late stage of development, and serves as a regulator in normal duodenal development. Fibroblast growth factor-10(–/–) mutant mice demonstrated duodenal atresia with variable phenotype similar to clinical findings in humans. The phenotype occurred in an autosomal–recessive pattern with incomplete penetrance (38%).[28] This finding suggest a genetic cause of duodenal obstruction although few reports of familial association have been published.[18]

The obstruction of the duodenum usually occurs distal to the ampulla of Vater. Pre-ampullary obstruction is much less common, occurring in about 20% of cases.[29] Occasionally, there may be a bifid termination of the bile duct with one limb of the duct system opening into the duodenum above the atresia and one below.[24,25,30]

ASSOCIATED MALFORMATIONS

There is a high incidence (approximately 50%) of associated anomalies in patients with intrinsic duodenal obstruction, especially Down syndrome which occurs in about 30% of these patients.[3,7,8,31–34]

Table 49.1 presents the overall prevalence and distribution of associated anomalies of duodenal atresia. The data are the collected statistics of 1759 patients with duodenal obstruction from a dozen large series.[32] The associated anomalies in order of frequency are: Down syndrome (28%), annular pancreas (23%), congenital heart disease (22.6%), malrotation (20%), esophageal atresia (8.5%), genitourinary malformations (8%), anorectal anomalies (4.4%), and other bowel atresias (3.5%).

Vertebral anomalies were reported to range between 2%[35] and 37%[36] in these patients. Reports of duodenal atresia have also shown a low incidence of musculoskeletal anomalies.[34]

Other rare anomalies include De Lange syndrome,[35] chromosomal abnormalities,[36–38] multiple intestinal

Table 49.1 The incidence of associated congenital anomalies (%) (collected statistics) ($n = 1759$ patients).

Associated anomaly	%
Down syndrome	28.2
Annular pancreas	23.1
Congenital heart disease	22.6
Malrotation	19.7
Esophageal atresia tracheo-esophageal fistula	8.5
Genitourinary	8.0
Anorectal	4.4
Other bowel atresia	3.5
Others	10.9

Data from Sweed Y. Duodenal obstruction. In Puri P (ed.). *Newborn surgery*, 2nd edn, London: Arnold, 2003: 423.

abnormalities,[39] choledochal cyst,[40,41] immunodeficiency,[42] tracheomalacia,[34] and situs inversus.[43]

The complex cardiac anomalies among all other associated malformations are the major cause of morbidity and mortality in patients with duodenal atresia.[3,7,14,44,45] Dalla Vecchia *et al.*[14] attributed all the operative mortality (4%) to associated complex congenital heart anomalies in a group of 138 patients with duodenal obstruction in a 25-year survey. Two other important factors affecting higher morbidity and mortality of these patients are prematurity and low birth weight.[7,44,46] The mortality rate is even higher in neonates born with three or more anomalies of the VACTERL association with an overall survival rate of 40–77%.[47–49] Spitz and colleagues reported the combination of esophageal and duodenal atresias as particularly lethal, with mortality rates ranging from 67 to 94% in various series.[50] Jackson *et al.*[51] inferred that the majority of these deaths are caused by failure to recognize the second abnormality preoperatively.

PRENATAL DIAGNOSIS/HISTORY

Maternal polyhydramnios has been reported to be present in 17–75% of cases of duodenal atresia[1,8,14,46,52,53] and is the most common ultrasonographic finding in fetuses with intrinsic duodenal obstruction.[54] Ultrasound is usually performed for suspected fetal or maternal abnormalities when polyhydramnios or a large-for-date pregnancy is established. Although the majority of cases are diagnosed during the seventh or eight month of gestation,[46,55] sonographic detection of duodenal atresia was reported as early as 12 gestational weeks by Tsukerman *et al.*[56] and 19 weeks by Romero.[57]

There has been an increase in prenatal ultrasonographic diagnosis of duodenal atresia during the last three decades, from 14% between the years 1972 and 1991,[58] and 18%[59] to the high rate of 57% for the period 1991–95.[52]

The prenatal sonographic diagnosis relies on the demonstration of the 'double bubble' sign, which is due to simultaneous distension of the stomach and the first part of the duodenum (Fig. 49.4). In many cases, this sonographic sign is observed in the second half of pregnancy, probably due to hydrostatic pressure needed to dilate the duodenum and also to the degree of the duodenal obstruction.[55] Visualization of a fluid-filled double bubble (Fig. 49.4) on prenatal ultrasound scan is associated with duodenal obstruction secondary to intrinsic or extrinsic lesion. This sonographic finding is known to have a low false-positive rate. Zimmer and Bronstein[60] have reported recently that in a few cases it may represent a transient finding in an otherwise healthy fetus. It is possible that intestinal peristalsis in a fetus may show transient dilatation suggesting duodenal obstruction.[55] On the ultrasound examination, it is also important to demonstrate the continuity between the gastric and duodenal bubbles (Fig. 49.4) to exclude other causes, such as choledochal cyst which lacks such communication[61,62] or duodenal duplication.[63]

Often other anomalies can also be diagnosed by ultrasound. Kawana *et al.*[64] and Pameijer *et al.*[65] reported the ultrasonic prenatal diagnosis of a fetus with combined duodenal and esophageal atresias associated with VACTERAL anomalies. Prenatal ultrasonographic diagnosis of annular pancreas has also been reported showing the co-incidence of the double bubble sign together with hyperechogenic bands around the duodenum (corresponding with the tissue of annular pancreas).[66]

Cohen-Overbeek *et al.*[53] investigated the impact of antenatal diagnosis in cases diagnosed with isolated or non-isolated duodenal obstruction. They found that the outcome of prenatally and postnatally diagnosed duodenal obstruction is not essentially different despite the fact that more prematurity and a lower birth weight were observed in the former.

The rapid advancement in imaging technology, including magnetic resonance imaging (MRI) should allow for

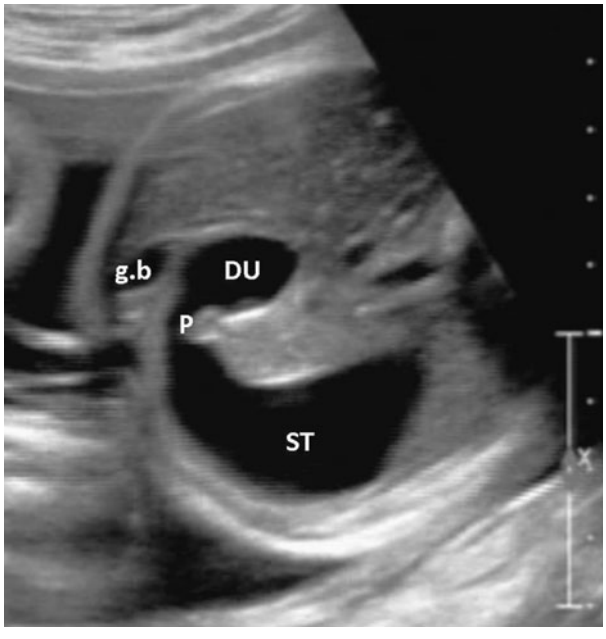


Figure 49.4 Ultrasonography (transverse view) of 24 week gestational age fetus showing the 'double bubble' sign. DU, duodenum; g.b gallbladder; P, pylorus; ST, stomach.

diagnosis during the first and early second trimester, enabling termination.[56] Alternatively, early prenatal diagnosis of duodenal obstruction should lead to karyotype analysis for prenatal screening for trisomy 21 and other associated anomalies.[58,65,67,68]

CLINICAL PRESENTATION AND DIAGNOSIS

About half of these patients are premature and have low birth weight.[7,8,14,44,46,69] Vomiting is the most common symptom and is usually present on the first day of life. Since 80% of the obstructions are located in the post-ampullary region of the duodenum, vomitus in the majority of cases is bile stained. In supra-ampullary atresia it is non-bilous. Orogastric aspiration also yields significant volumes of bile-stained gastric fluid. There is minimal or no abdominal distension because of the high level of obstruction. The infant may pass some meconium in the first 24 hours of life and thereafter constipation may develop. Dehydration with weight loss and electrolyte imbalance (hypokalemic/hypochloremic metabolic alkalosis) soon follows if the diagnosis is done late and if fluid and electrolyte losses have not been adequately replaced.[53,70] Incomplete duodenal obstruction usually leads to the delayed onset of symptoms.[7,44,58]

The diagnosis of duodenal obstruction is confirmed on x-ray examination. An abdominal x-ray will show a dilated stomach and duodenum, giving the characteristic appearance of a double bubble sign (the stomach and the proximal duodenum are air-filled) with no gas beyond the duodenum (Fig. 49.5). In partial duodenal obstruction, a plain film of the duodenum will show a double bubble appearance but there is usually some air in the distal intestine (Fig. 49.6). Occasionally in cases of duodenal atresia, air may be seen distal to the site of obstruction due to associated bile duct bifurcation.[71] X-ray findings in patients with annular pancreas are usually indistinguishable from duodenal atresia or stenosis.

In some cases of partial duodenal obstruction, plain films may be normal. Upper gastrointestinal tract contrast x-ray is indicated in these patients to establish the cause of incomplete duodenal obstruction. This may show a stenotic segment of duodenum with dilatation of the proximal segment, or a sharp termination of the dilated segment, indicating a perforated diaphragm (Fig. 49.7).

Incomplete duodenal obstruction usually leads to delayed onset of symptoms, and the diagnosis of duodenal diaphragm with a central aperture is sometimes delayed for months or even years.[72–74] Mikaelsson *et al.*[75] reported the late diagnosis and treatment of eight out of 16 patients with membranous duodenal stenosis. Their patients were diagnosed and operated at between the ages of one month and four years. Occasionally, a duodenal diaphragm may be stretched and ballooned distally, giving the windsock appearance on contrast study (Fig. 49.8).[72]

The most important differential diagnosis of duodenal obstruction is duodenal obstruction caused by malrotation resulting in extrinsic compression related to Ladd's bands across the duodenum, or volvulus of the midgut loop, although this is rare. Midgut volvulus may result in gangrene of the entire midgut within hours and thus diagnostic investigation is urgently required, though the symptoms may relent because the obstruction may be incomplete or intermittent in malrotation. Part of these extrinsic obstructions exhibit the double bubble sign with distal air on plain film, while the majority can be identified from the coil spring appearance of small bowel volvulus following barium injection.[76] However, Samuel *et al.*[77] observed that volvulus neonatorum was not encountered in neonates with duodenal atresia and stenosis who had associated malrotation. They suggested that duodenal obstruction could perhaps be a flood-gate that prevents volvulus in these children.

Preduodenal portal vein is a rare anomaly and generally asymptomatic. It is a rare cause of duodenal obstruction and often coexists with other anomalies resulting in bowel obstruction.[78–80] In most of these patients, it is impossible to diagnose preduodenal portal vein prior to surgery.

The wide variety of additional congenital anomalies with special emphasis on cardiac malformation, often severe,[7,14,32,44,81] makes preoperative diagnosis imperative. Anterior-posterior and lateral chest and abdominal x-rays ascertaining visualization of the entire spine, should also be performed.

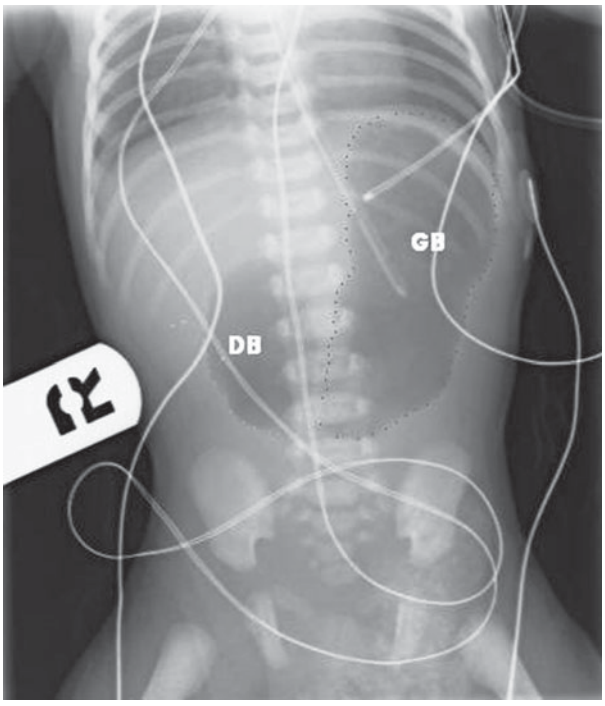
Soon after the x-ray, cardiac and renal ultrasound should be carried out routinely in all these babies. A micturating cystourethrogram should be performed in those babies with abnormal urogenital ultrasound or an associated anorectal anomaly. Rectal biopsy should be taken in babies with constipation and the combination of Down syndrome and duodenal atresia, to exclude Hirschsprung's disease.[34,44]

PREOPERATIVE MANAGEMENT

Although duodenal atresia is a relative emergency, the patient should not be rushed to the operating room until the infant's hemodynamic and fluid and electrolyte status is stable. If the clinical history and findings on physical examination indicate that the baby is in no distress, and the x-rays are consistent with the usual presentation of duodenal atresia with no air beyond the second bubble (excluding malrotation), operation should be performed on an elective basis.

A nasogastric tube decompresses the stomach, and i.v. fluid resuscitation can be initiated. Blood samples for electrolyte determination should be obtained and any derangements should be corrected. Prolonged vomiting can result in a hypokalemic hypochloremic metabolic alkalosis. Passage of the orogastric tube rules out esophageal atresia and careful inspection of anal defect variants of imperforated anus should be obtained.

Care is taken to preserve body heat and avoid hypoglycemia, since many of these newborn patients are premature and small-for-date.[7,14,52] Very low birth weight infants or those with respiratory distress syndrome and associated severe anomalies, e.g. congenital heart disease, may occasionally need special preparation, such as resuscitation and ventilation.



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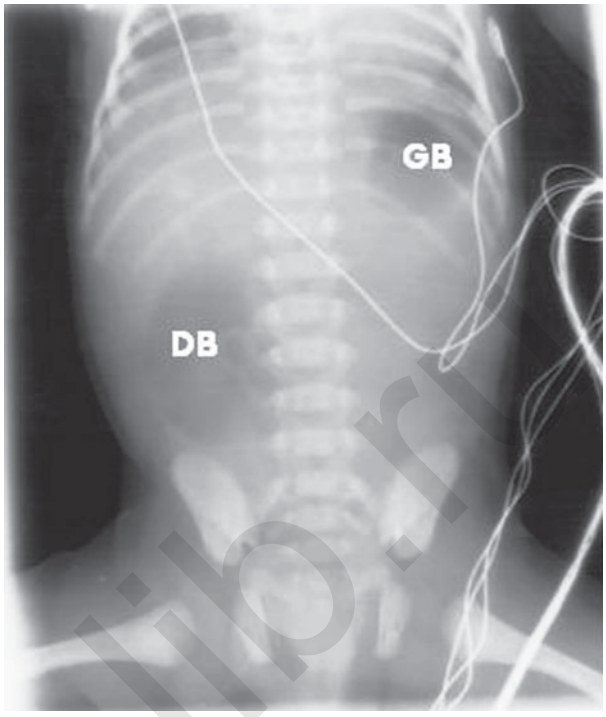

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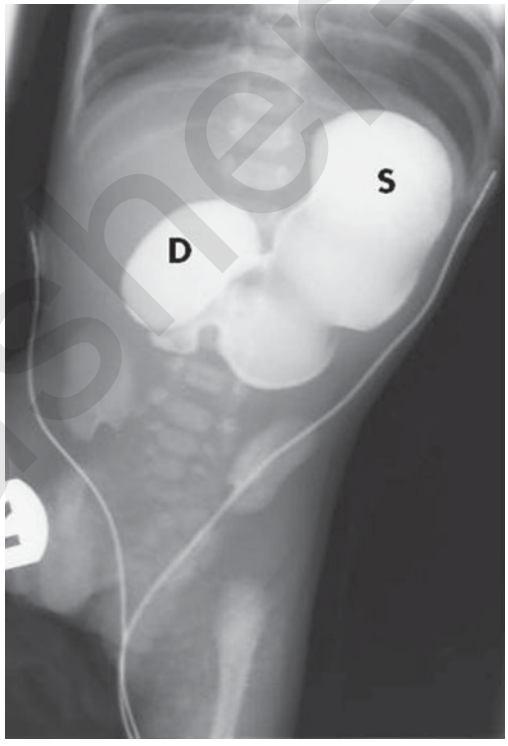

(c)

Figure 49.5 (a) Abdominal erect x-ray showing grossly distended stomach and duodenum with double bubble sign with no air beyond the duodenum. DB, duodenal bubble; GB gastric bubble. (b) Abdominal x-ray showing the double bubble sign. In this case duodenal bulb is more prominent than the gastric bulb. At operation duodenal membrane was found and excised. DB, duodenal bubble; GB gastric bubble. (c) Duodenal atresia evident on upper gastrointestinal x-ray contrast study. D, duodenum; S, stomach.

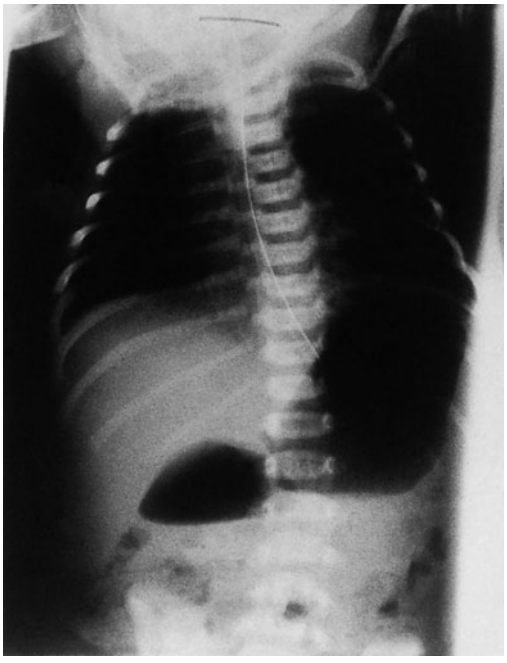

Figure 49.6 Duodenal stenosis erect abdominal x-ray demonstrating a double bubble sign with air beyond the duodenum.

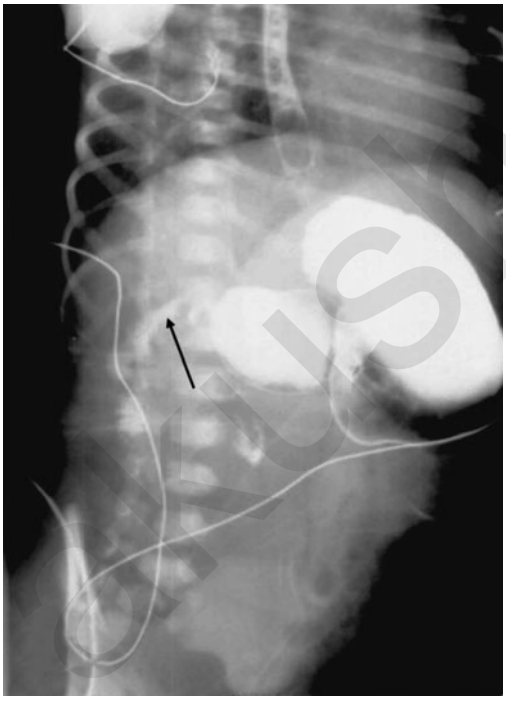

Figure 49.7 An oblique abdominal x-ray contrast study showing marked distention of duodenum terminating abruptly with narrow caliber distally (arrow). A perforated diaphragm was found at operation. Annular pancreas and malrotation were also found in this patient.

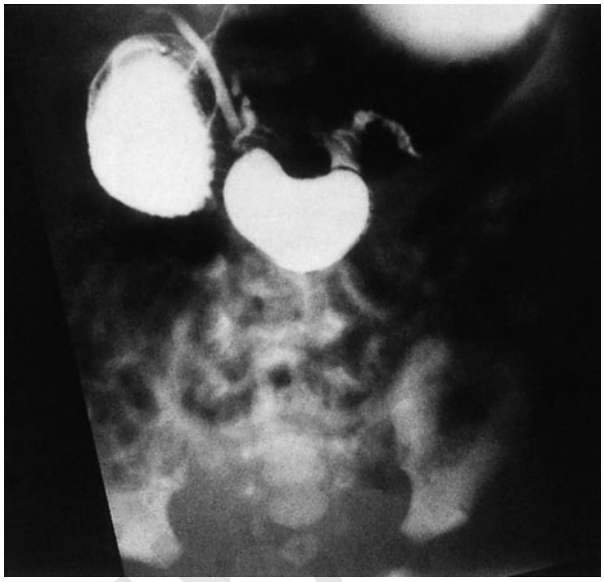

Figure 49.8 Windsock web. Dilated duodenum demonstrated with duodenal membrane ballooned distally, giving characteristic windsock appearance. Reflux of contrast medium into pancreatic and common blie duct is seen.

OPERATION

Duodenoduodenostomy is the procedure of choice for patients with duodenal atresia, stenosis, and annular pancreas.[8,14,45,82,83]

Duodenoduodenostomy can be performed in either 'diamond shape' (proximal transverse to distal longitudinal) anastomosis as described by Kimura *et al.*[84,85] (Fig. 49.9), or side-to-side fashion (Fig. 49.10). The 'diamond shape' duodenoduodenostomy has been reported to allow earlier feeding, earlier discharge, and good long-term results.[85,86]

Recently, Bax *et al.*[87] and Rothenberg[88] reported the first case and the first series, respectively, on the laparoscopic management of duodenal obstruction. They indicated that the laparoscopic approach has proven to be safe and effective and represents an alternative to the open procedure. They also emphasized that this minimal invasive surgical technique should be used only if the surgeon has appropriate instruments and suturing and laparoscopic skills (Fig. 49.11).[87–89]

Incision

The baby is placed supine on the table with a small roll under the upper abdomen on a warming blanket. Endotracheal anesthesia is used. The abdominal skin is prepared by cleaning with prewarmed povidone iodine.

A transverse supra-umbilical abdominal incision is made 2 cm above the umbilicus starting in the midline and extending laterally into the right upper quadrant for

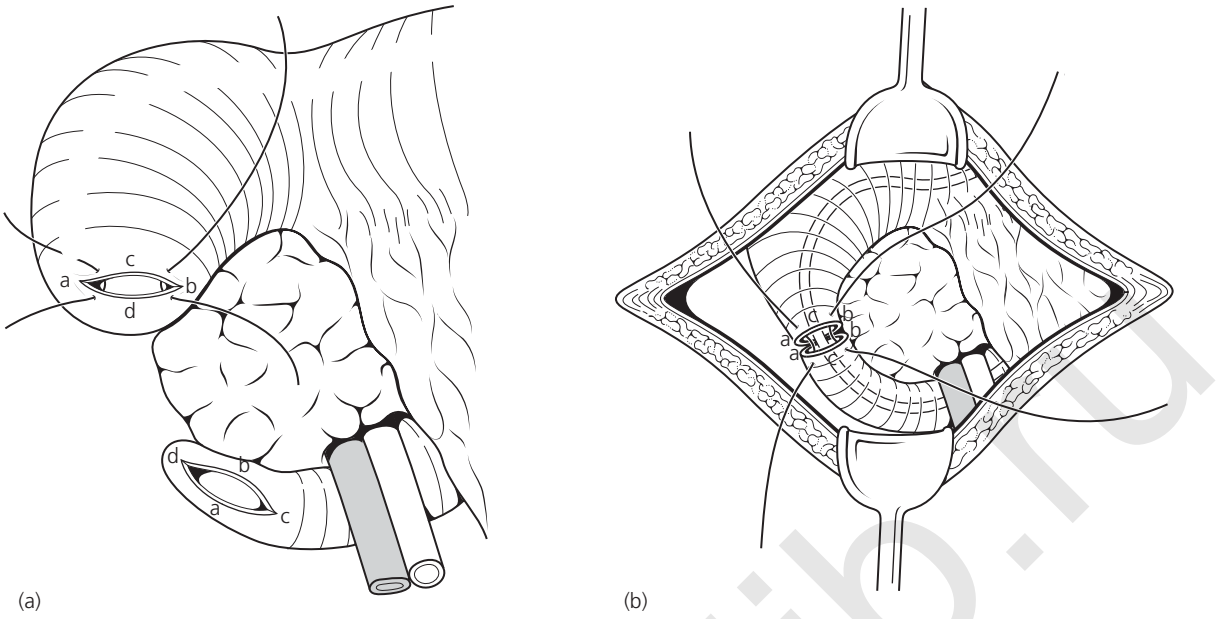

Figure 49.9 Diamond-shaped duodenoduodenostomy. (a) A transverse incision is made in the distal end of the proximal dilated duodenum and a longitudinal incision is made in the smaller limb of the duodenum distal to the occlusion. (b) A single layer anastomosis using interrupted 5/0 Vicryl sutures with posterior knots tied inside the posterior wall of the anastomosis and anterior knots tied outside the anterior wall is performed.

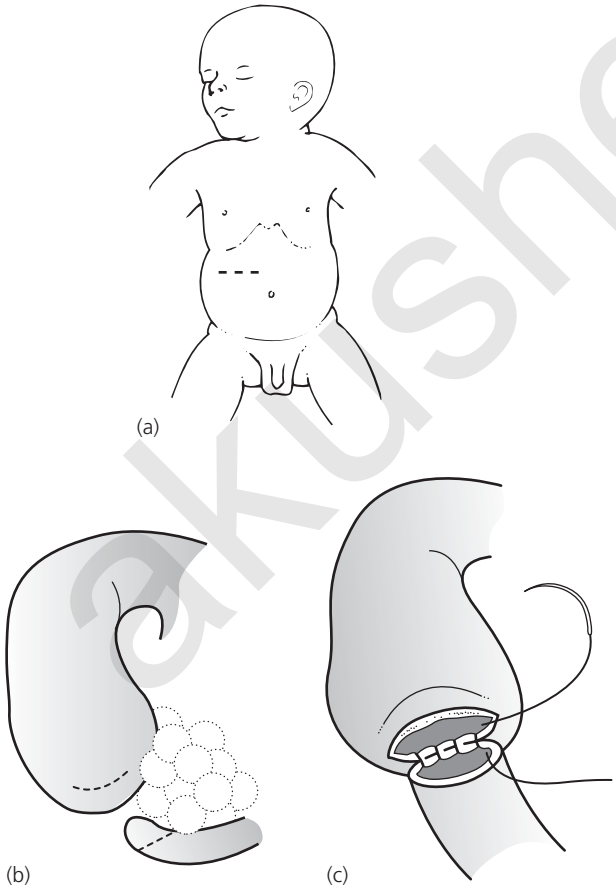

Figure 49.10 (a) Side-to-side duodenoduodenostomy. (b) Parallel incisions of about 1 cm are made in the proximal and distal duodenum. (c) The anastomosis is performed using single-layer interrupted 5/0 Vicryl sutures.

about 5 cm. The abdominal muscles are divided transversely with cutting diathermy and the peritoneal cavity is opened in the line of incision.

Exploration and identification of pathology

After exposing the peritoneal cavity, the surgeon inspects the entire bowel for the presence of other bowel anomalies. There may be an associated annular pancreas, malrotation (in about one-third of the patients), or in rare cases preduodenal portal vein. If the colon is in the normal position, malrotation is probably not a coexisting factor.

The stomach and first portion of the duodenum are usually thickened and dilated. The liver is carefully retracted superiorly. The ascending colon and the hepatic flexure of the colon are mobilized medially and downwards to expose the dilated duodenum.[90]

The duodenum is then adequately mobilized and freed from its retroperitoneal attachments – the Kocher maneuver. Great care must be exercised not to dissect or manipulate either segment of the duodenum medially, to avoid injury to the ampulla of Vater or the common bile duct. The tube in the stomach is then passed distally into the dilated duodenum and helps to locate the point of obstruction and determine if a windsock deformity is present (Fig. 49.3g).

The types of atresia as well as any pancreatic abnormality (e.g. annular pancreas) are noted. In patients with an annular pancreas, the pancreatic tissue should never be divided and should always be bypassed. The duodenum distal to the site of obstruction is small and decompressed. The requirements for distal mobilization vary according to the location of the atresia and to the gap between the two segments (Fig. 49.2). If necessary, the ligament of Treitz is divided and mobilization

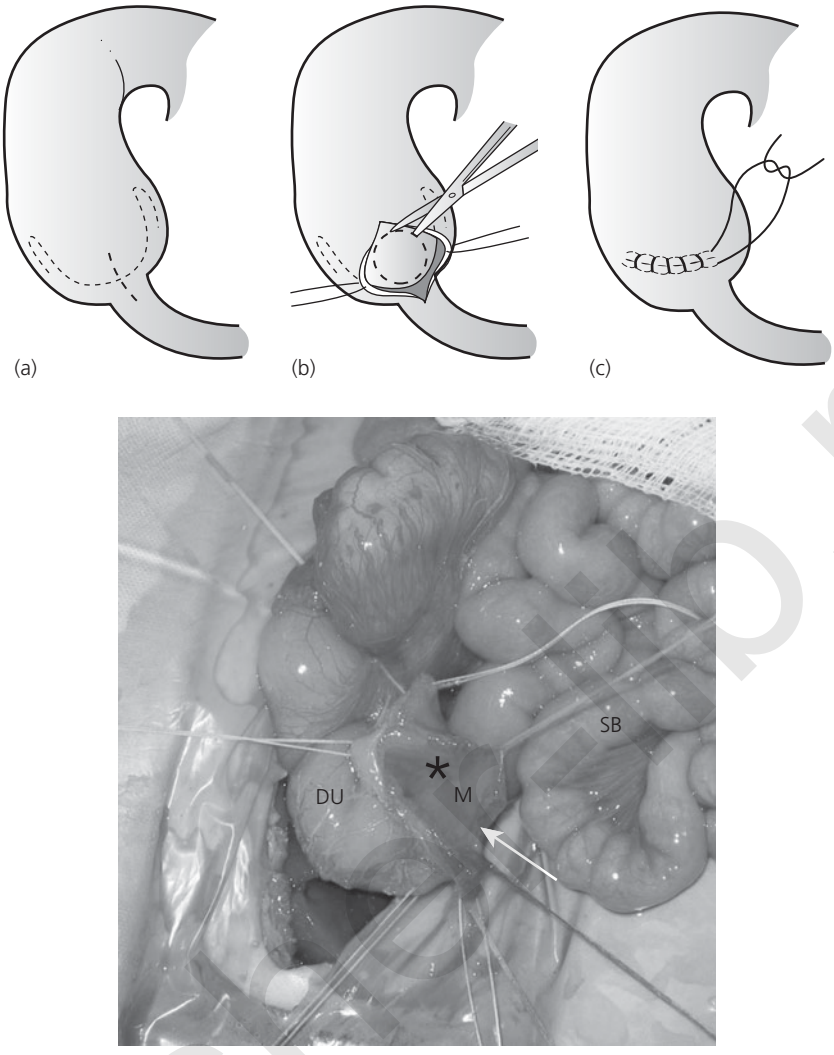

Figure 49.11 Operative technique for duodenal web. (a) Longitudinal incision above the 'tranzitional zone' of the duodenum. (b) Excision of the web leaving the medial third of the membrane intact. (c) The Duodenum is closed transversely. (d) Intraoperative photograph of a 2-week-old infant born with duodenal web with an aperture. DU, opened duodenum; M, membrane, *, papilla of Vater; SB, small bowel. The white arrow points to the excisional line of the membrane.

and displacement of the distal duodenum is performed behind the superior mesenteric vessels, thus allowing a satisfactory anastomosis to be performed without any tension.

'DIAMOND-SHAPED' DUODENODUODENOSTOMY

After abdominal exploration, the duodenum is adequately mobilized. With two traction sutures, the redundant wall of the proximal duodenum is pulled downward to overlie the proximal portion of the distal duodenal segment. A transverse incision is made in the distal end of the proximal duodenum and a longitudinal incision is made in the smaller limb of the duodenum distal to the occlusion.

These are made in such a position as to allow good approximation of the openings without tension.

The papilla of Vater is located by observing bile flow. This is performed by gentle compression of the gallbladder.

The orientation of the sutures in the 'diamond shape' anastomosis and the overlapping between the proximal transverse incision and the distal longitudinal incision are shown in Fig. 49.9.

Additionally, a 10 French Foley catheter should be passed proximally into the stomach and distally into the jejunum and pulled back with the balloon inflated, to ensure that no additional web or a windsock deformity is overlooked. The distal duodenum can be distended to a larger size during this maneuver facilitating the anastomosis. Before pulling back the catheter from the distal duodenum, the surgeon should inject 30–40 mL of warm saline through the catheter to rule out distal atresias of the distal small bowel. The catheter is then removed.

A single layer anastomosis is performed using 5/0 or 6/0 vicryl sutures with posterior knots tied inside the posterior wall of the anastomosis and interrupted sutures with anterior knots tied outside the anterior wall. Before completion of the anterior part of the anastomosis, a 5F silicon nasojejunal transanastomotic feeding tube may be passed down into the upper jejunum for an early postoperative enteral feeding[91] using the same insertion technique as was reported for

patients who underwent surgical repair for esophageal atresia and tracheo-esophageal fistula.[92] Others, however, do not use the nasojejunal tube because they suggest that it may delay the commencement of oral feeding.[14,85]

Then, the right colon is returned to its former position so that the mesocolon covers the anastomosis. The Ladd procedure with inversion appendectomy is performed in patients with malrotation.[58] In these patients, the cecum should be placed in the left lower quadrant to reduce the risk of midgut volvulus.

The wound is closed in layers: the peritoneum and posterior fascia, and the anterior fascia by two layers using continuous 4-0 Vicryl. The skin is closed with running intracuticular suture using 5-0 Vicryl.

SIDE-TO-SIDE DUODENODUODENOSTOMY

The dilated proximal duodenum and the distal collapsed duodenum are approximated using two stay sutures (5-0 Vicryl). Then, parallel incisions with a length of about 1 cm are made in the proximal and distal duodenum (Fig. 49.10). An 8 Fr Foley catheter should be inserted both to the proximal dilated duodenum and to the distal collapsed duodenum in order to rule out windsock membrane and distal atresias, as similarly described in the diamond shape duodenoduodenostomy.

The posterior layer of anastomosis is completed using interrupted 5/0 Vicryl sutures.

At this stage, a transanastomotic 5 Fr gauge silastic nasojejunal tube may be inserted for an early enteral feeding.

The anastomosis is then completed using interrupted 5-0 Vicryl sutures for the anterior layer. The abdomen is closed in the same manner as described in the diamond shape duodenoduodenostomy.

In patients with malrotation, Ladd's procedure and inversion appendectomy should be performed before closure of the abdomen.

In premature infants, some surgeons prefer to perform a gastrostomy and insert the transanastomotic silicon tube via the gastrostomy. The tip of the tube should be well down in the jejunum as to decrease the chance of it becoming displaced.

OPERATIVE TECHNIQUE FOR DUODENAL WEB

A longitudinal incision is performed above the transitional zone between the wide and narrow segments of the duodenum (Fig. 49.11) and the duodenum is opened. The membrane is usually located in the second part and occasionally in the third portion of the duodenum. It can be complete or have a hole. Anatomically, the ampulla of Vater may open directly into the medial part of the membrane, or posteriorly close to it, thus the close relationship of the membrane to the ampulla of Vater makes its identification mandatory, before excision of the web (Fig. 49.11d). Excision of the web should proceed from the lateral duodenal wall, leaving the medial third of the wall intact to avoid damaging the sphincter of Oddi or the ampulla of Vater and continue leaving a circumferential rim of tissue of 1–2 mm (Fig. 49.11b). The resection line is then oversewn using continuous sutures of Vicryl 5/0 and the duodenum is closed transversely in two layers using Vicryl 5/0 (Fig. 49.11c). Because of the pitfalls in cases of the lax membrane that may bulge downwards distally into the distended duodenum (the so-called windsock phenomenon), and in order to avoid missing the anomaly, before closure of the duodenum, the distal patency of the distal duodenum must be verified by inserting a 8 Fr Foley catheter through a duodenotomy.

The experience with fiberoptic duodenoscopy indicates the usefulness of the technique for both the diagnosis and non-operative management of duodenal membrane.[93–95] However, based on reports describing anomalous entry of the pancreatobiliary channels,[96] the delineation of the ducts at endoscopic retrograde cholangiopancreatography may be necessary prior to endoscopic intervention. Most surgeons believe that a duodenotomy is preferable to the potential risk of inadvertent pancreatic or bile duct injury.[96]

LAPAROSCOPIC MANAGEMENT OF DUODENAL OBSTRUCTION

The application of minimally invasive surgical techniques for the correction of congenital anomalies has increased significantly over the last ten years. The ability to perform delicate dissection and intracorporeal anastomosis has broadened the scope of entities that can be approached including neonatal duodenal obstruction. Although most neonatal conditions presenting with bowel obstruction present a difficult problem for laparoscopy because of the dilated bowel and limited abdominal cavity, this is not the case in duodenal atresia. The entire small and large bowel is decompressed, and there is excellent exposure of the proximal duodenum.[87]

For the laparoscopic approach (Fig. 49.12), neonatal laparoscopic instruments (3 mm) and trocars are used. The patient is positioned supine at the end of the operating table. The operating surgeon stands at the patient's feet. The abdomen is insufflated through a 5 mm umbilical port, for a 30° laparoscope. A 3 mm and a 5 mm port are placed in the

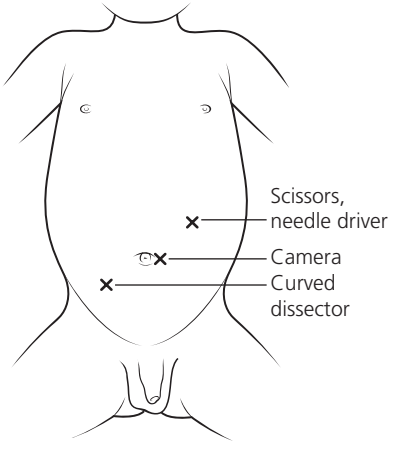

Figure 49.12 Trocar placement and instrumentation for laparoscopic repair of duodenal atresia.

right lower quadrant and left upper quadrant, respectively. The left upper quadrant port is placed for the introduction of suture.

The duodenum is then kocherized, the type of obstruction becomes easily visible, and the dilated proximal and decompressed distal segments are identified.[88,89] A proximal transverse and distal longitudinal duodenotomy is then made. As with the open repair, stay sutures are placed at each corner to facilitate the anastomosis. A diamond-shaped anastomosis is performed with either a separate running suture for the posterior and then anterior wall, or single interrupted stitches of Vicryl. Intracorporeal knot tying is used. An extra port can be placed in the right upper quadrant to help retract the liver and set up the anastomosis. Alternatively, the apical stitch can be tied and brought out through the abdominal wall to assist with retraction and align the enterotomies for the anastomosis. The distal bowel is examined in all cases to ensure that there are no obvious secondary atresias. Once the anastomosis is completed, the ports are removed and the sites are closed with absorbable sutures.

Recently, Spilde *et al.*[97] reported their experience with laparoscopic repair of duodenal obstruction using U-clips for the anastomosis because of the ability of these clips to approximate tissue tightly with little tissue damage.[98] In their report they compared 14 patients who were treated by an open approach and 15 patients who underwent laparoscopic repair of duodenal obstruction. They demonstrated significantly shorter time to initiation of feeds, time to full feeds, and postoperative hospitalization in the laparoscopic group.[97]

The experience with laparoscopic duodenoduodenostomy demonstrates that it can be performed safely and successfully in the neonate with excellent short-term outcomes.[86,87,97] Surgeons with experience in advanced laparoscopic techniques can learn the laparoscopic duoenoduodenostomy and have excellent results.

POSTOPERATIVE CARE

The baby is returned to an incubator (or radiant heat cot) at the thermoneutral temperature for its size and maturity. An i.v. infusion of dextrose/saline is continued in the postoperative period and further fluid and electrolyte management depends on clinical progress, loss by gastroduodenal aspiration, and serum electrolyte levels. Postoperatively, patients may have a prolonged period of bile-stained aspirate through the nasogastric tube, which is mainly due to the inability of the markedly dilated duodenum to produce effective peristalsis, and to a lesser extent, partial mechanical obstruction by the feeding tube (if it was used). Enteral feeding through the transanastomotic feeding tube is generally started within 24–48 hours postoperatively.

The commencement of oral feeding depends on the decrease of the gastric aspirate and may be delayed for several days and occasionally for 1–2 weeks or longer. Once the volume of the gastric aspirate decreases, the feeding tube is withdrawn and the infant can be started on oral feeding.

Spigland and Yazbeck[99] in their follow up of 33 neonates found that bowel transit was established after an average of 13.1 days, 7.5 days after partial web excision, 12.4 days following duodenoduodenostomy, and 15 days after duodenojujenostomy (which is rarely performed today). Spilde *et al.*[97] recently reported that the time to initial feeding was 11.3 days for patients with an open repair of duodenal obstruction compared to 5.4 days for those who were treated by laparoscopic approach. They also found that the average time to full oral intake was 16.9 days for the open group compared to 9 days for the laparoscopic group.

MANAGEMENT OF PERSISTENT MEGADUODENUM BY DUODENOPLASTY

The deformity and dysfunction of the first part of the duodenum – the megaduodenum – are the causes of well-known morbidity[99,100] and occasionally these patients require duodenoplasty.[101] The malfunction of the greatly dilated gut and the absence of effective peristalsis were demonstrated by Nixon in the small bowel,[100,102] but the same phenomenon is thought to occur in the dilated duodenum proximal to the duodenal atresia. Several techniques of duodenoplasty have been described, and it is of the utmost importance to visualize and identify the ampulla of Vater within the duodenal lumen prior to resection and tapering of the duodenum. Hutton and Thomas have reported success by extensive tapering duodenoplasty.[103] Adzick *et al.*[104] and Grosfeld and Rescorla[58] emphasized the merit of tapering duodenoplasty at the primary operation of neonates with dilated duodenum, to improve the immediate postoperative gastrointestinal function and the prevention of further development of megaduodenum. Other techniques include resection and suturing,[105] resection and stapling,[104] and elliptical seromuscular resection.[106]

However, refashioning the anastomosis or bypass techniques usually fail.[100,107,108] Another technique of subtotal duodenal resection with reconstruction of the duodenum by the proximal jejunum as an onlay patch was demonstrated in two children. In this technique, the diseased duodenal wall is completely removed, except for the area of the ampulla of Vater and the duodenum is reconstructed by the jejunum.[109]

OUTCOME AND LONG-TERM RESULTS

The survival of babies with duodenal obstruction has gradually improved over the last 40 years since the first report of surgical correction of intrinsic duodenal obstruction by Ladd in 1931[110] (Table 49.2).[1,3,8,14,46,53,58,59,69,70,82,89,111–113] All agree that the three main factors contributing to the mortality rate in this group of patients are high incidence of associated anomalies, especially severe cardiac malformations, prematurity, and low birth weight.[1,3,7,14,53,58,112] In a recent review covering 45 years (1951–95) of management of duodenal obstruction, Murshed *et al.*[52] found that in the first 15 years, survival reached 51%, in the next 15 years it was 80%, and in

Table 49.2 Survival rates of patients with duodenal atresia and stenosis. Table shows gradual improvement in survival reported over the past 40 years. Most deaths are related to the associated complex cardiac malformations.

Reference	No. patients	% Survival
Fonkalsrud *et al.*[1]	503	68
Nixon and Tawes[69]	62	57
Girvan and Stephens[8]	158	67
Wesley and Mahour[82]	72	74
Davey[111]	68	67
Danismend *et al.*[112]	98	74
Hancock and Wiseman[46]	34	94
Bailey *et al.*[113]	138	93
Grosfeld and Rescorla[58]	103	95
Akhtar and Guiney[59]	49	94
Dalla Vecchia *et al.*[14]	138	86
Cohen-Overbeek *et al.*[53]	91	91
Choudhry *et al.*[3]	65	96
Kilbride *et al.*[70]	51	98
Kay *et al.*[89 a]	17	100

[a]Laparoscopic duodenoduodenostomy (years 2004–2008).

the last 15 years 95%. During the latest period, mortality was almost entirely the consequence of associated anomalies.

Dalla Vechia *et al.*[14] reported a relatively low rate of postoperative complications in a series of 138 infants. The early complication rate included anastomotic obstruction in 3%, congestive heart failure in 9%, prolonged adynamic ileus in 4%, pneumonia in 5%, and wound infection in 3%.

Late complications included adhesive bowel obstruction in 9%, megaduodenum and duodenal dysmotility that required tapering duodenoplasty in 4%, and gastro-esophageal reflux requiring surgery in 5%.

Weber *et al.*[83] reported the complication rate and morbidity of three methods of technical repair in a group of 41 newborns with duodenal atresia. The three techniques were: (1) side-to-side duodenoduodenostomy, (2) side-to-side duodenojejunostomy (which is rarely performed today), and (3) diamond-shaped duodenoduodenostomy. There was no difference in the complication rate, but the diamond shape technique was found to be superior for repair, resulting in earlier feeding and discharge. Recently, Kimura *et al.*[85] reported on their experience with 44 patients with the diamond-shaped technique, without the use of gastrostomy or transanastomotic tube, and found a very low rate of complications and good long-term results.

Long-term results of congenital duodenal obstruction were reported by Kokkonen *et al.*,[114] who studied 41 patients aged 15–35 years. They found that growth and development, including body weight, were satisfactory. Although the great majority was symptom-free, on barium meal examination all but two had abnormal findings, including megaduodenum in nine cases. They concluded that some gastrointestinal disturbances are common, even in asymptomatic patients, and careful follow up is important. Salonen and Makinen[115] reported previously on their experience in a small group of nine patients aged 3–21 years and found, in contrast, a normal barium meal in all groups except one. Their result was similar to the ducomentation by Kimura *et al.*[85] with the diamond-shaped technique.

Ein *et al.*[100,108] encountered five patients with late complications of duodenal atresia repair that appeared suddenly between the ages of six months and 24 years. The duodenal repair was functionally obstructed – caused by proximal, dilated duodenal atony. Plication of the dilated atonic proximal duodenum was curative.

The main benefits of laparoscopic approach for the treatment of duodenal atresia are the excellent visualization of the obstruction and the ease of the anastomosis. However, the possible disadvantage of this approach may be that evaluation of the distal bowel for other atretic segments is more difficult to accomplish.[88] The bowel can be inspected visually for distal obstructed segments, but internal webs may be more difficult to see. It is important to emphasize that last-report results of laparoscopic approach for duodenal obstruction are related to short-term follow up. As for the long term, there are no results yet.[88,89,97,116]

Over the last few decades, advances in neonatal intensive care, parenteral nutrition, management of associated anomalies, and improvements in operative technique and postoperative care have improved the outlook for patients born with duodenal atresia and stenosis.[3,7,14,53,58] Mortality today has been reduced to 5–10% and is now related mostly to associated cardiac anomalies.

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Malrotation

AGOSTINO PIERRO AND SHIREEN ANNE NAH

INTRODUCTION

Malrotation is the term used to denote an interference with the normal process of orderly return of the fetal intestine from the physiological hernia to the abdominal cavity during which it undergoes systematic rotation and fixation.

EMBRYOLOGY

The intestine initially develops as a tube extending down the midline for the embryo. As the intestine lengthens it protrudes through the umbilical ring into the physiological umbilical hernia where it undergoes further lengthening before returning back into the abdominal cavity. Three stages of development of the midgut are recognized:

Stage I: 4–10 weeks: midgut protrudes and develops in the physiological umbilical hernia.

Stage II: 10–12 weeks: midgut migrates back into the abdomen in an orderly manner, small bowel first and cecocolic loop last. The cecum initially lies on the left but it rotates through 270° to attain its final position in the right iliac fossa. Simultaneously, the duodenum undergoes a 270° anticlockwise rotation.

Stage III: Final phase consisting of fusion of various parts of the mesentery with fixation of cecum and ascending colon and the descending colon.

INCIDENCE

Although it is recognized that malrotation may exist undetected throughout life (0.2%), it is generally accepted that once the diagnosis has been established, surgical correction should be carried out to avoid the occurrence of a volvulus. Fifty-five percent of malrotations present within the first week of life and 80% in the first month. Thereafter, sporadic cases occur throughout life. Malrotations may coexist in association with a number of life-threatening congenital anomalies, e.g. exomphalos and diaphragmatic hernia.

CLINICAL PRESENTATION

Neonatal period

- Recurrent episodes of subacute obstruction with intermittent bilious vomiting.
- Strangulating intestinal obstruction as a consequence of midgut volvulus. The infant presents with bile-stained vomiting which may contain altered blood, abdominal distension and tenderness, the passage of dark blood per rectum, and shock. As the strangulation progresses to gangrene, perforation, and peritonitis, edema and erythema of the anterior abdominal wall becomes evident.

Older infant and child

- Intermittent or cyclical vomiting which often contains bile.
- Failure to thrive.
- Intermittent severe abdominal colicky pain.
- Anorexia as a result of pain associated with eating.
- Malabsorption and/or diarrhea.

RADIOLOGICAL DIAGNOSIS

The plain abdominal x-ray in the infant with midgut volvulus typically shows a 'gasless' appearance with air in the stomach

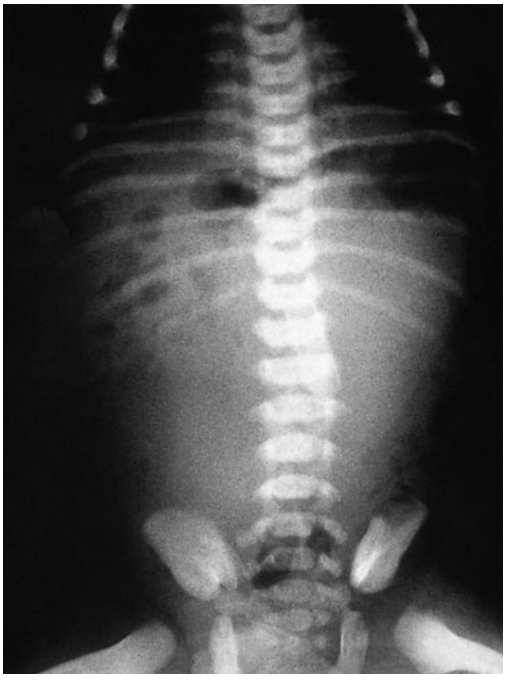

Figure 50.1 Plain abdominal radiograph showing gas in the stomach and first part of the duodenum with a paucity of gas in the rest of the intestinal tract.

and duodenum and little or no gas in the rest of the intestines (Fig. 50.1).

Contrast studies are diagnostic. The procedure of choice is the upper gastrointestinal contrast study which shows the abnormal configuration of the duodenum, the duodenojejunal junction to the right of the midline, and the small bowel located on the right side of the abdomen. Where volvulus has occurred, the duodenum and upper jejunum show a 'twisted ribbon' or 'corkscrew' appearance (Figs 50.2 and 50.3). The barium enema will show the cecum and appendix in an abnormal position, usually in the right hypochondrium or midabdomen.

Ultrasonography to determine the relationship between the superior mesenteric vein (SMV) and superior mesenteric artery (SMA) has been advocated as a non-invasive method of diagnosing malrotation but this investigation is operator dependent and not reliable in approximately 20% of affected children. Normally, the SMV lies to the right of the SMA whereas in malrotation the position is reversed with the SMV to the left of the SMA. Colour Doppler ultrasound may reveal the ominous 'whirlpool' appearance, which is created when the SMV and mesentery wrap around the SMA in midgut volvulus.

TREATMENT

The operative correction of a malrotation should be regarded as a surgical emergency. Patients presenting with acute strangulating obstruction as a result of midgut volvulus require a brief period (not more than 2–3 hours) of intensive resuscitation in preparation for surgery. An i.v. infusion of crystalloids or 5% human albumin is given at 20 mL/kg administered as rapidly as possible, repeated as required, followed by 0.45% saline in 5–10% dextrose at 10 mL/kg per hour until induction of anesthesia. A nasogastric tube of suitable size is passed and gastric content aspirated and a prophylactic dose of broad-spectrum antibiotics given parenterally. A specimen of blood is taken for crossmatch, hematology and serum electrolyte estimation. Blood for transfusion must be available at the commencement of the laparotomy.

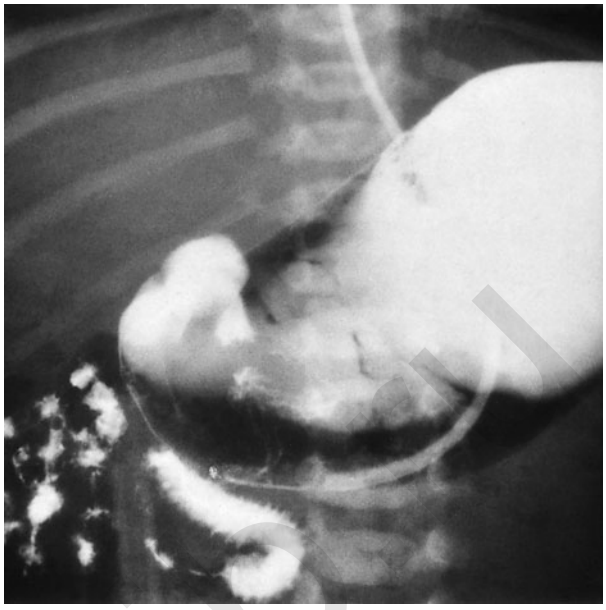

Figure 50.2 Upper gastrointestinal contrast study showing the duodenojejunal flexure to the right of the vertebral column and small intestinal loops in the right upper quadrant of the abdomen.

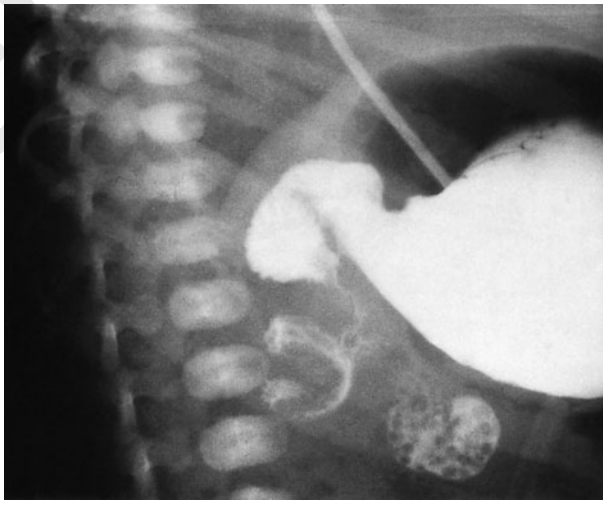

Figure 50.3 Lateral view of an upper gastrointestinal contrast study showing a dilated proximal duodenum with a 'twisted ribbon' appearance of the upper small intestine indicating volvulus of the midgut.

THE OPERATION

Open procedure

INCISION

A laparotomy is performed via a right upper abdominal transverse muscle-cutting incision extending across the rectus abdominis muscle (Fig. 50.4). The obliterated umbilical vein in the free edge of the falciform ligament is ligated and divided. The bowel is delivered into the wound. A small volume of yellowish, free-peritoneal fluid is present in any early intestinal obstruction, but blood-stained fluid is indicative of intestinal necrosis.

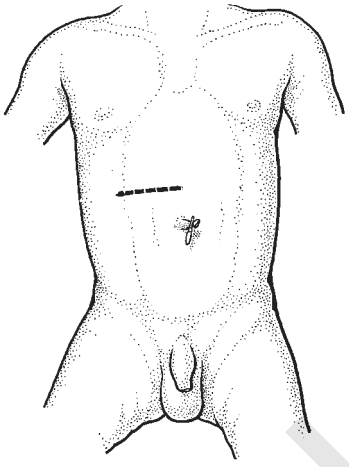

Figure 50.4 Incision to right of midline in the upper abdomen but should be extended across to the left if additional exposure is required.

MANAGEMENT OF MIDGUT VOLVULUS

The volvulus occurs around the base of the narrowed midgut mesentery (Fig. 50.5). The twist usually occurs in a clockwise direction and is untwisted by counter-clockwise rotation of as many 180° rotations as required (Fig. 50.6). Moderately ischemic bowel, which appears congested or dusky, rapidly resumes a normal pinkish color on reduction of the volvulus. Frankly necrotic bowel may be extremely friable and may disintegrate on handling. Bowel of questionable viability should be covered, after untwisting, with moist swabs and left undisturbed for approximately 10 minutes before assessing the extent of ischemic damage. A Ladd's procedure for the malrotation is carried out (see below).

In patients with extensive intestinal gangrene, frankly necrotic bowel should be resected and the bowel ends either tied off or stomas fashioned with a view to a second-look laparotomy in 24–48 hours when a clearer line of demarcation will have established. At this stage, an end-to-end anastomosis may be feasible. In the intervening period, the patient is electively ventilated and resuscitative measures continued.

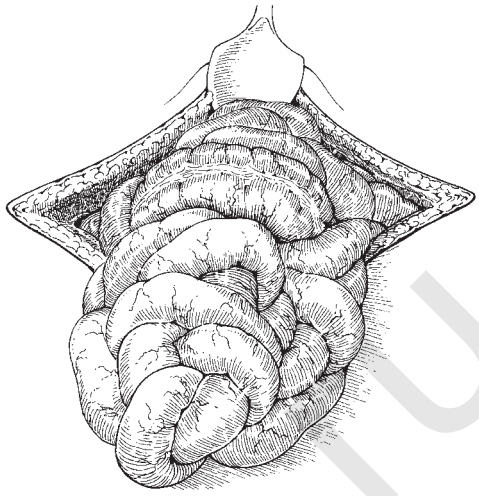

Figure 50.5 Appearance of midgut volvulus which occurs in a clockwise direction.

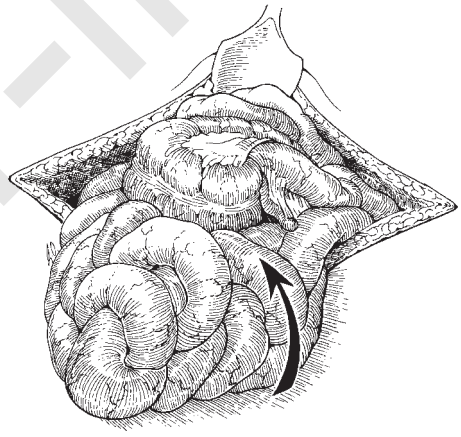

Figure 50.6 Untwisting of a midgut volvulus in a counter-clockwise direction.

MANAGEMENT OF THE UNCOMPLICATED MALROTATION (LADD'S PROCEDURE)

Having untwisted a volvulus, attention is now directed at the narrow-based mesentery of the midgut and the orientation of the duodenum and colon.

The peritoneal folds which extend from the cecum and ascending colon laterally across the second part of the duodenum and cranially towards the liver and gallbladder are carefully divided (Fig. 50.7). This procedure leaves the right colon freely mobile to allow its displacement to the left side of the peritoneal cavity.

Attention is now directed to the duodenojejunal junction. The ligament of Treitz at the apex of the duodenojejunal flexure is divided and the duodenal loop straightened by mobilizing the third and fourth parts of the duodenum from the head of the pancreas (Fig. 50.8).

The superior mesenteric vessels coursing in the root of the mesentery between the duodenojejunal junction and the

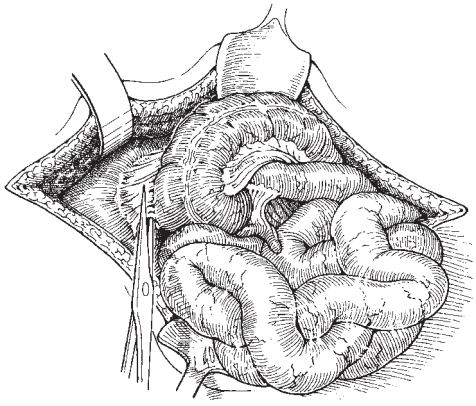

Figure 50.7 Division of peritoneal folds extending from the cecum and ascending colon across the duodenum towards gall bladder and liver (Ladd's bands).

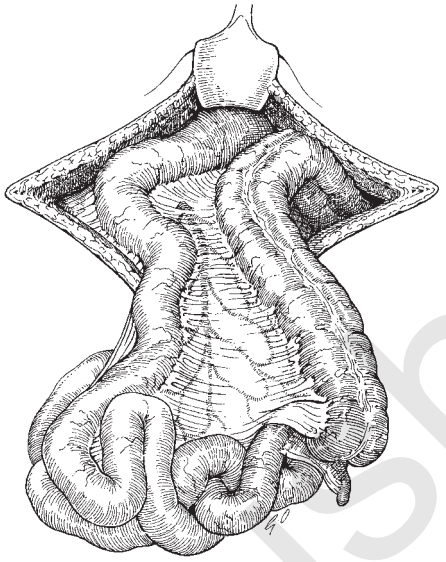

Figure 50.8 The duodenojejunal flexure has been mobilized and the narrow-based mesentery is clearly obvious.

ascending colon are exposed by dividing the anterior layer of the mesentery (Fig. 50.9). The mesentery is often thickened and edematous and care should be taken to avoid trauma to the main vessels. Numerous small lymphatic vessels require electrocoagulation or ligation before division to avoid a chylous leak. There is often quite dense fibrous tissue in the root of the mesentery and this requires careful division in order to achieve adequate widening at the base of the mesentery.

An appendicectomy is usually performed if the viability of the bowel permits, as the cecum will be placed in the left upper quadrant of the abdomen and appendicitis could pose considerable diagnostic difficulty in the future. In infants, the appendix may contribute to the maturation of the intestinal immune system and there may be advantages in preserving it. The parents need to be informed that the appendix is retained and may be in an atypical position.

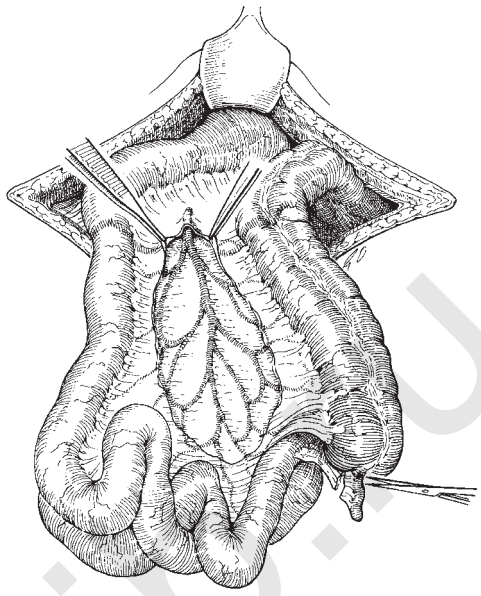

Figure 50.9 Splaying of the root of the mesentery by dividing the anterior layer of the mesentery and dividing fibrous bands crossing over the superior mesenteric vessels.

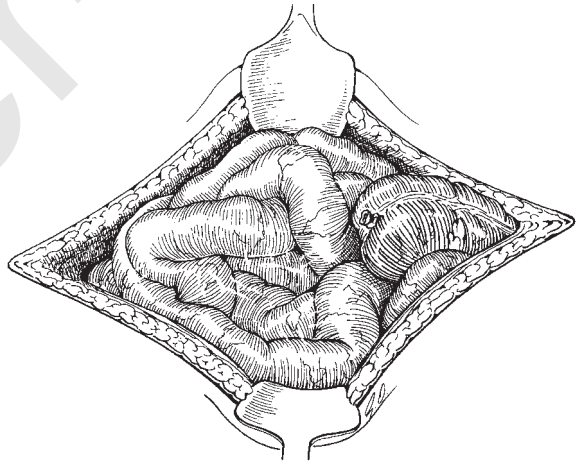

Figure 50.10 Intestine has been replaced into the peritoneal cavity with the small bowel on the right side and the cecum and ascending colon in the left upper quadrant. An appendicectomy has been performed (an alternative is an inversion appendicectomy).

The intestines are now replaced into the peritoneal cavity, commencing with the proximal jejunum which is placed on the right side and ending with the terminal ileum and cecum which are placed in the left upper quadrant (Fig. 50.10). No attempt is made to fix the bowel in this position, although some authors advocate stabilization of the mesentery to prevent recurrent volvulus.

LAPAROSCOPIC CORRECTION OF MALROTATION

A cannula is inserted peri-umbilically using an open technique. Pneumoperitoneum is created (maximum pressure 10 mmHg) and a 5 mm 30° telescope is introduced (Fig. 50.11).

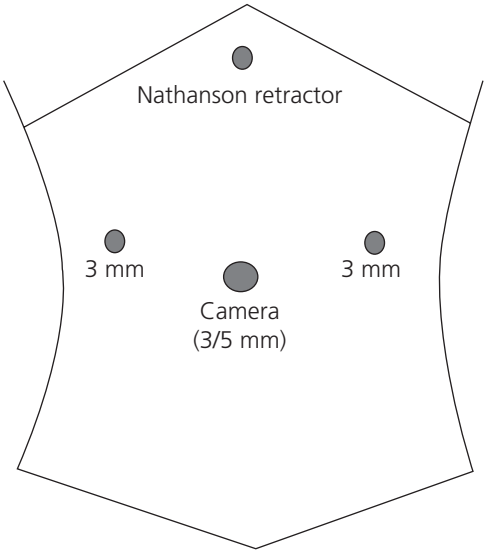

Figure 50.11 Position of ports in laparoscopic Ladd's procedure.

Two 3 or 5 mm instrument ports are inserted in the right and left flanks. A Nathanson retractor may be inserted in the epigastrium for retraction of the liver if needed. The head of the patient is elevated and the right flank may be elevated by rotating the table to help the dissection of the duodenum.

Explorative laparotomy is carried out. Volvulus is not a contraindication to laparoscopy, but presence of strangulation or necrosis may indicate the need for conversion. The ligament of Treitz is identified and the duodenum is straightened using 3 mm hook diathermy and sharp dissection. The thickened fibrous tissue in the root of the mesentery is divided to widen its base, carefully avoiding the superior mesenteric vessels lying in the root of the mesentery. The operation is not different from the description given above in the open procedure.

Volvulus (if present) is untwisted in an anticlockwise direction. The small bowel is placed on the right of the abdomen and the colon on the left.

An appendicectomy may be performed extracorporeally, by delivering the appendix via the instrument port site which usually requires an extension of the incision. Alternatively, with the use of a 5 mm instrument port, the appendix base may be ligated intracorporeally with an endoloop, and the appendix removed.

This operation can be done laparoscopically in children with corrected major exomphalos or congenital diaphragmatic hernia.

POSTOPERATIVE MANAGEMENT

Return of bowel function may be delayed for prolonged periods during which parenteral nutrition may be required but, in general, oral nutrition can be resumed in 5–7 days. Infants who have undergone massive small bowel resection will require parenteral nutrition for many months pending adaptation of the residual intestine.

OUTCOME

Adhesional intestinal obstruction is common after open surgery where up to 50% of patients needs admission to hospital and approximately half may require laparotomy. This risk of adhesional intestinal obstruction is theoretically reduced by the usage of laparoscopy. Published rates of recurrent volvulus range widely from $<0.5\%$ after open surgery to as high as 19% after laparoscopic correction. It is possible that either inadequate widening of the mesenteric base and/or lack of adhesions post-laparoscopy may be associated with an increased risk of recurrent volvulus. Laparoscopy may be difficult in newborn infants due to the small size of the abdominal cavity. More long-term studies are needed to evaluate the effect and suitability of laparoscopic operations for malrotation and volvulus.

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51

Persistent hyperinsulinemic hyperglycemia of infancy

PAUL RV JOHNSON

INTRODUCTION

Persistent hyperinsulinemic hyperglycemia of infancy (PHHI), or congenital hyperinsulinism (CHI) as it is now more broadly termed, is a spectrum of conditions characterized by profound hypoglycemia in the presence of inappropriately high insulin secretion.[1,2] Although rare overall, CHI is a significant cause of hypoglycemic brain injury and mental retardation[3] and therefore, all those involved in the medical and surgical management of neonates need to be familiar with this condition so that the diagnosis can be made promptly, and early treatment implemented. This chapter provides an overview of the etiology, diagnosis, and management of CHI to facilitate this.

ETIOLOGY

Over the past decade, our understanding of the etiology of CHI has increased enormously.[4,5] This has not only led to more focused treatment for certain subforms of the condition, but has also meant that genetic counseling can be offered to some families. CHI can either occur sporadically with an incidence of 1 in 40 000–50 000 or can be familial with an incidence as high as 1 in 2500. Genetically, CHI is a heterogeneous condition, and mutations of seven different genes related to insulin secretion have been reported. Mutations can be sporadic, autosomal recessive, or autosomal dominant.[5] The most common abnormality underlying CHI, is a dysfunction of the ATP-sensitive potassium channel within the pancreatic beta cell (channelopathies).[6] This ion channel is composed of two subunits, each of which is encoded for by a different gene, namely the sulfonylurea receptor gene *SUR1,* and the inward-rectifying potassium channel gene *KIR6.2.* Mutations of the SUR1 gene account for 50–60% of CHI, whereas mutations of the KIR6.2 gene are less common and only responsible for 10–15% of cases.[7] The abnormal potassium channel results in the beta cell being in a constant state of depolarization, and therefore it is constantly secreting insulin despite the cell environment being one of hypoglycemia (Fig. 51.1). A less common group of underlying causes of CHI are the 'metabolopathies', which result from enzyme deficiencies (e.g. glutamate dehydrogenase (GDH), glucokinase (GK), or short-chain L-3-hydroxyacyl-CoA dehydrogenase (SCHAD)), or dysfunction of the insulin receptor. Finally, CHI can be associated with certain specific syndromes such as Beckwith-Wiedemann, Perlman syndrome, and Sotos syndrome, each of which has associated chromosomal abnormalities.

PATHOLOGY

The original term for CHI was nesidioblastosis. This term was created by Laidlaw in 1938, and described the histological finding of islet cells proliferating by budding off the pancreatic ductal tissue within pancreases of infants with severe symptoms of hypoglycemia.[8] However, this term has since been abandoned as it was realized that not only does CHI represent a spectrum of different disorders, but more specifically, that many normal neonatal pancreases also exhibit nesidioblastosis.[9]

However, the most important advance in our understanding of CHI over recent years has been the discovery that there are two distinct histopathological forms, namely a focal form and a diffuse form. Focal CHI is characterized by a focal hyperplasia of the pancreatic beta cells and is to be distinguished from the more discrete adenoma or insulinoma seen in older children or adults. Normal islets are seen outside the focal abnormality (see Fig. 51.2). In the diffuse form of CHI, the islets are abnormal throughout the whole pancreas and exhibit large, pleomorphic, hyperchromatic nuclei (see Fig. 51.3). Distinguishing focal from diffuse CHI is important to ensure that the correct surgical treatment is undertaken.

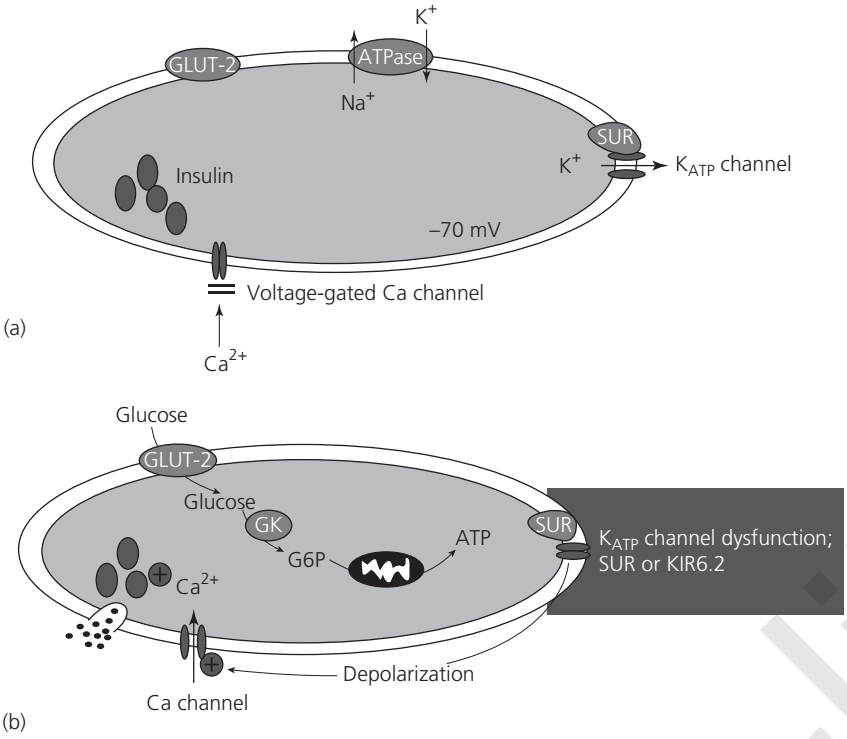

Figure 51.1 (a) Normal resting beta cell. At rest the normal K_{ATP} channel is closed which maintains the membrane potential at −70 mV. This results in the calcium channels remaining closed, preventing any calcium influx or consequent insulin release. (b) Congenital hyperinsulism (CHI) beta cell. The abnormal K_{ATP} channel in the non-stimulated CHI beta cell results in the channel remaining closed even at rest. This causes depolarization of the membrane and opening of the calcium channel. The consequent calcium influx results in insulin degranulation and release.

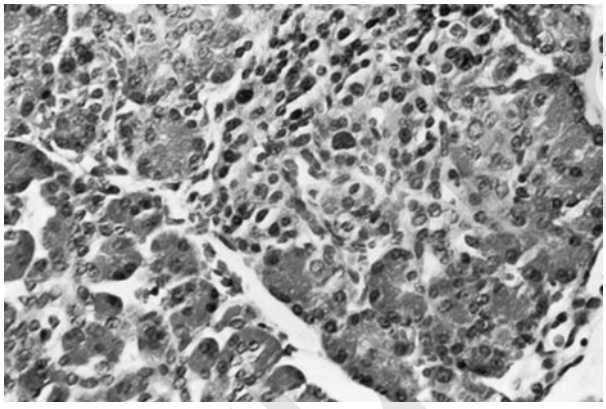

Figure 51.2 Diffuse congenital hyperinsulism: islets have large, pleomorphic, hyperchromatic nuclei present throughout pancreas.

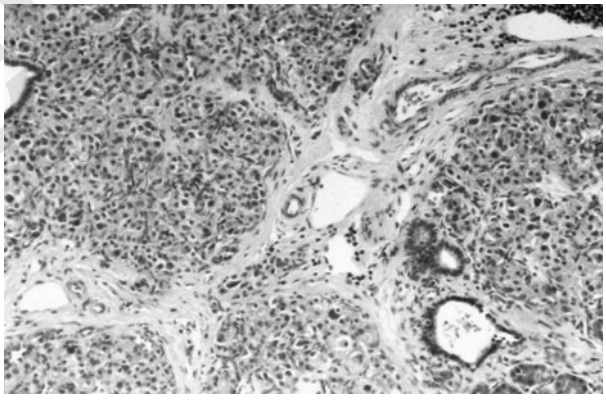

Figure 51.3 Focal congenital hyperinsulism: nodules of adenomatous islet cell hyperplasia with normal islets outside the lesion.

PRESENTATION

Congenital hyperinsulism usually presents within the first few hours or days of life in both premature and term babies, but can occasionally present later in infancy.[7] Babies can present with non-specific symptoms of hypoglycemia such as poor feeding, irritability, or lethargy, or more severe symptoms such as seizures or coma. This explains why ideally all neonates should undergo BM testing shortly after birth. A proportion of babies with CHI are macrosomic, and some have mild facial abnormalities, such as a high forehead, a small nasal tip, and a short columella.[10] CHI is most commonly an isolated condition, but can be associated with certain specific syndromes as described above under Etiology. CHI can sometimes be transient rather than persistent, but it is the persistent forms that are of most relevance to surgeons.

DIAGNOSIS

Congenital hyperinsulism is characterized by hyperinsulinemic, hypoketotic, hypofattyacidemic hypoglycemia.[1] The following diagnostic criteria are used: (1) laboratory blood glucose readings of <2.5–3 mmol/L; (2) a glucose infusion rate of >8 mg/kg/min; (3) unsuppressed insulin

concentrations of >1 mU/L; (4) a positive response to the subcutaneous or intramuscular administration of glucagon (plasma glucose concentrations increasing by 2–3 mmol/L following a 0.5 mg subcutaneous glucagon injection); (5) negative ketone bodies in the plasma and urine.

Until recently, the definitive investigation used to distinguish diffuse and focal forms of the disease was serial venous sampling of insulin. This procedure was invasive, time-consuming, and often resulted in inaccurate localization of focal disease. Over the last few years, the gold standard investigation has become [^{18}F]DOPA positron emission tomography (PET) combined with computed tomography (CT) angiography with 3D reconstruction.[11,12] This test is non-invasive and is both sensitive and specific and gives excellent localization of focal lesions. However, the [^{18}F]fluoro-L-DOPA isotope is only currently available in a few centers.

MANAGEMENT

The main aim of management is to prevent hypoglycemic brain damage and to allow normal psychomotor development. In mild cases, it may be possible to maintain acceptable levels of blood glucose by dietary measures alone. In the majority of cases however, i.v. administration of high concentrations of glucose are required to maintain blood glucose levels above 2.6 mmol/L. Glucose infusion rates in excess of 20 mg/kg/minute, i.e. 15–20% glucose, may be required. In these cases, it is essential to insert a central venous catheter to provide a central route for administration of high concentrations of glucose and to allow frequent monitoring of blood glucose levels.

Medical management

Diazoxide is the first-line medical treatment and is an agonist of the K_{ATP} channel. It is commenced at a dose of 5–20 mg/kg/day in three divided doses. It can be highly effective in the treatment of the transient and syndromic forms of CHI, but in the more severe neonatal forms in which a mutation of the K_{ATP} channel is present, the beta cells may be unresponsive.[7,13] Diazoxide is usually used in conjunction with chlorothiazide at a dose of 7–10 mg/kg/day in two divided doses. These two agents exert a synergistic effect on the K_{ATP} channel with diazoxide. Octreotide is a long-acting analog of the pancreatic hormone somatostatin, and is used in CHI both as a short-term measure to stabilize the baby pending definitive treatment, or sometimes as a long-term treatment combined with frequent feeding, for diffuse disease. Subcutaneous or i.v. glucagon is used in the acute management of hypoglycemia, often in combination with octreotide. Nifedipine has been used successfully in a small number of patients,[14] and is a calcium channel blocker which is aimed at reducing the calcium flux resulting from the constant depolarization of beta cells in CHI. The systemic effect of calcium blockade can be restrictive.

Surgical management

Surgical treatment is indicated when an infant remains dependent on i.v. glucose administration despite maximum medical treatment. Whereas 95% pancreatectomy was until recently the treatment of choice for all cases of CHI that were unresponsive to medical treatment,[15] improvements in our understanding of the histopathology of CHI has enabled more limited and targeted surgical resection treatment to be used for the focal form of the disease.[16,17] Pancreatectomy can be performed using traditional open operative techniques, or can be undertaken using laparoscopic techniques.[18,19] The surgical principles are the same for both techniques.

INCISION

For the open technique, a laparotomy is performed via a generous supra-umbilical transverse muscle-cutting incision, extending through both rectus abdominus muscles (Fig. 51.4). For the laparoscopic approach, a three trocar technique is used with triangulation centered around the umbilicus. Within the peritoneum, a thorough search is made for sites of ectopic pancreatic tissue.

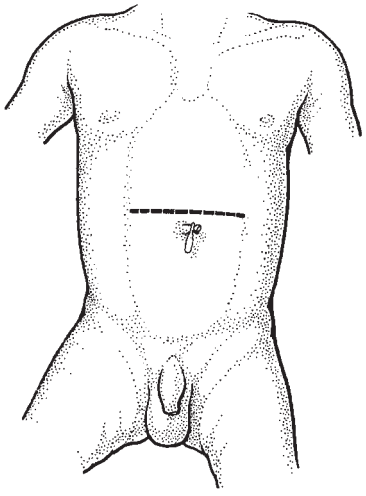

Figure 51.4 Transverse upper abdominal incision extending across both rectus abdominus muscles.

EXPOSURE

The anterior surface of the pancreas is exposed by entering the lesser peritoneal sac via the gastrocolic omentum, ligating and dividing vessels in the greater omentum along the greater curvature of the stomach (Fig. 51.5). The tail of the pancreas lies in the hilum of the spleen. The hepatic flexure is reflected medially and the duodenum kocherized to expose the head of the pancreas. The entire pancreas is carefully examined or inspected.

95% PANCREATECTOMY

In the diffuse form, the dissection of the pancreas proceeds medially from the tail towards the neck of the pancreas that lies just to the right of the superior mesenteric vessels. It is essential for future immunologic competence to preserve the spleen whenever possible. This is accomplished by carefully exposing the short pancreatic vessels passing from the splenic vessels to the pancreas. These vessels, especially the veins, are extremely friable, but meticulous dissection will allow individual ligation, application of metal clips, or electrocoagulation, and division of the vessels without traumatizing the main vessels (Fig. 51.6). Should hemorrhage occur from damage to the splenic vein, direct repair should be attempted. In the event of failure to achieve hemostasis, ligation of the splenic vein with preservation of the splenic function can be expected due to collateral supply from the short gastric vessels. When the dissection has progressed to the right of the superior mesenteric vessels, attention is directed to the head of the pancreas and in particular the uncinate process (Fig. 51.7).

The uncinate process is carefully dissected from behind the superior mesenteric vessels and, after positively defining the course of the common bile duct, the head of the pancreas to the left of the common duct and in the concavity of the duodenal loop is excised, leaving a sliver of pancreatic tissue on the surface of the duodenum and on the left wall of the common duct. The pancreatic duct is identified and ligated with a non-absorbable ligature. Hemostasis is carefully and meticulously achieved. The remaining pancreatic tissue consists of that part of the gland between the duodenum and the common bile duct and the sliver of tissue on the medial wall of the second part of the duodenum (Fig. 51.8). This represents approximately 5% of the total volume of the pancreas, but can vary considerably from patient to

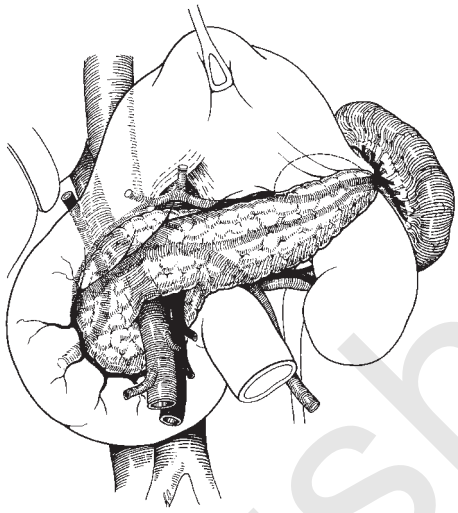

Figure 51.5 Exposure of the head, body, and tail of the pancreas by entering the lesser sac dividing the vessels in the greater omentum along the greater curvature of the stomach.

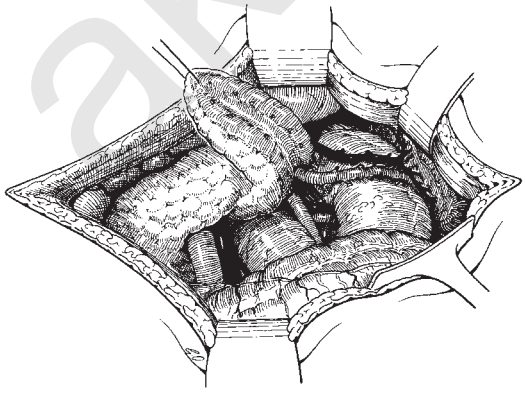

Figure 51.6 The short pancreatic vessels arising from the splenic vessels are divided and the body and tail of the pancreas are gradually dissected towards the head.

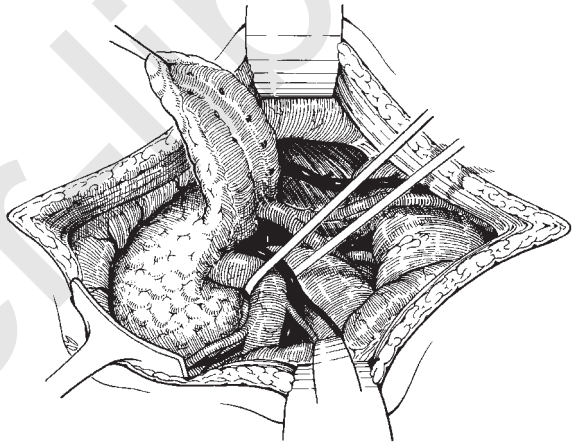

Figure 51.7 The superior mesenteric vessels are displayed and retracted towards the left, exposing the uncinate process of the pancreas.

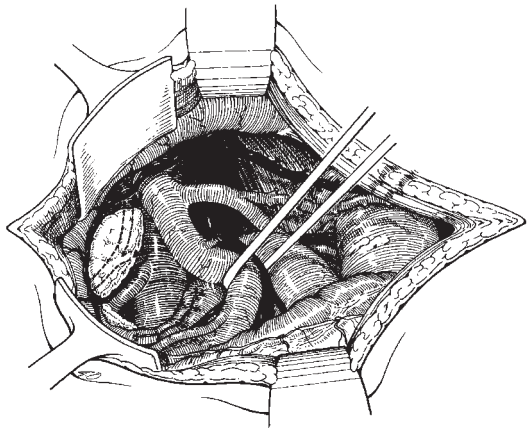

Figure 51.8 Final appearance following 95% pancreatectomy. The only remaining pancreatic tissue lies to the left of the common bile duct and a sliver in the C-curvature of the duodenum. Note splenic vessels and the completer excision of the ucinate process.

patient. A suction drain via a separate stab incision is left in the pancreatic bed.

Laparoscopic resection is performed in a similar manner, but it is easiest to perform the resection using a hook diathermy in a piecemeal manner, using a stay suture at different intervals along the pancreas as dissection proceeds from the pancreatic tail towards the head. For the transection of the pancreas itself, the harmonic scalpel ensures good hemostasis and occlusion of the pancreatic duct and cut parenchyma.

RESECTION OF FOCAL DISEASE

Exactly the same principles as described above apply for resection of focal disease. Based on the preoperative PET scan, the focal lesion is resected leaving the normal pancreas behind.[17] If the focal disease is within the head of the pancreas, occasionally a major Whipple-type resection is required.

POSTOPERATIVE CARE

Postoperatively, glucose infusions and CHI medications are directed by constant monitoring of blood glucose. The infant is kept nil by mouth with a nasogastric tube *in situ* until the postoperative ileus has resolved.

COMPLICATIONS

Each of the medical treatments of CHI can have its side effects.[7] Long-term use of diazoxide is associated with hypertrichosis (excessive growth of hair in areas where hair does not normally grow) and this can limit its long-term use. Octreotide is associated with a wide range of side effects including gastrointestinal upset (abdominal pain, nausea, bloating, and diarrhea), and suppression of growth hormone (GH), thyroid stimulating hormone (TSH), and adrenocorticotropic hormone (ACTH). Recurrent hypoglycemia can occur as a result of insufficient surgical resection of the diffuse form of the disease, or due to failed localization in the focal form, and should be evident within the first 72 hours after the operation. Persistent hypoglycemia may require further surgical resection. Other surgical complications include postoperative infection, bleeding, and operative trauma to the bile duct.[20] If the latter is diagnosed preoperatively, then primary repair and drainage is performed. Delayed diagnosis of bile duct injury can be treated operatively or conservatively depending on the degree of damage and the timing of presentation.

LONG-TERM RESULTS

The neurological outcome of patients with CHI depends on the age of presentation.[3] Neonates with CHI that is unresponsive to medical treatment are at increased risk of brain injury, as are those with a delayed diagnosis and delayed implementation of treatment.[3] The form of CHI per se does not seem to influence outcome. In patients undergoing 95% pancreatectomy, the majority will develop insulin-dependent diabetes by the second decade of life.[21,22] These patients require close monitoring of their glucose homeostasis and a yearly glucose-tolerance test is indicated. For those who do develop diabetes, novel, minimally invasive treatments, such as pancreatic islet transplantation are now achieving excellent results for reversing diabetes in adults.[23] The majority of these patients will require oral pancreatic exocrine replacement. The recent emphasis on limited pancreatic resection for focal CHI means that both exocrine and endocrine insufficiency can be reduced in this group of patients.

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52

Jejuno-ileal atresia and stenosis

ALASTAIR JW MILLAR, ALP NUMANOGLU, AND HEINZ RODE

INTRODUCTION

Jejuno-ileal atresia, defined as a congenital defect in continuity of the bowel, is a common cause of intestinal obstruction in the newborn.[1–3] The incidence of jejuno-ileal atresia varies from 1 in 330 and 1 in 400 live births,[4] to between 1 in 1500 and 1 in 3000 live births.[5] Jejuno-ileal occlusions occur more frequently than duodenal or colonic.[1,6] With improved neonatal and perioperative care, safe anesthesia, refined surgical techniques and management of short bowel syndrome, a survival rate of greater than 90% can be expected in well-resourced centers. At the Red Cross War Memorial Children's Hospital in Cape Town during the 51 years 1959–2009, 333 jejuno-ileal atresias, 251 (75%) jejunum, and 82 (25%) ileum were seen (Table 52.1). Down syndrome is most uncommon in babies with jejuno-ileal atresia (only one baby in the Red Cross Hospital series) compared with duodenal atresias. The first successful surgical repair of an intestinal atresia was in 1911.[7] The mortality rate remained high over the next four decades and it was only in the mid 1950s that an improved understanding of the pathogenesis and pathology of the condition led to innovative surgical techniques which resulted in greatly improved surgical outcome.[5,6]

Table 52.1 Jejunal atresia and stenosis: Red Cross Children's Hospital experience 1959–2009.

Type	Jejunum	Ileum	Total (%)
Stenosis	21	13	10.2
I	61	18	23.7
II	19	13	9.6
IIIa	27	24	15.3
IIIb	60	60	18
IV	63	14	23
Total	251	82	333

ETIOLOGY

In 1889, Bland Sutton postulated that atresia occurred at the site of 'obliterative embryological events' and he quoted atrophy of the vitelline duct.[8] In 1900, Tandler,[9] supported by embryonal studies, suggested that intestinal atresia was related to a lack of recanalization of the solid stage of the intestine, while others have questioned these theories.[10–12] In 1952, Louw published the results of an investigation of 79 patients treated at Great Ormond Street, London, and suggested that jejuno-ileal atresia was probably due to a vascular accident rather than the result of inadequate recanalization.[5] At his instigation, Barnard perfected the experimental model in pregnant mongrel bitches. Mesenteric vascular insults, such as volvulus, intussusception, and interference with the blood supply to a segment of bowel were created in the dog fetus.[13] This not only confirmed the hypothesis but led to a change in the surgical procedure for correcting atresias and stenosis of the jejunum and ileum with a marked improvement in outcome.[14–16] Subsequently, these experimental findings were confirmed by others in several different animal models and in clinical practice.[17–21] Evidence of bowel infarction was present in 42% of 449 cases of jejuno-ileal atresia in a collected series which further supported the vascular hypothesis.[22] Furthermore, the localized nature of the vascular accident occurring late in fetal life would explain the low incidence (less than 10%) of coexisting abnormalities of extra-abdominal organs.

The anomaly is usually not genetically determined although affected monozygotic twins and siblings have been described. A genetic basis however has been established for type IIIb and IV multiple atresias.[23–26]

PATHOLOGY

The classification of jejuno-ileal atresia into three types by Bland Sutton in 1889 has stood the test of time, except for the

subdivision of type III into two categories (a and b) and the addition of type IV (Fig. 52.1).[8,27,28] This subdivision has allowed a better long-term prognostication. In stenosis, the proximal dilated and narrower distal bowel are in continuity with an intact mesentery, but at the point of junction there is a short, narrow, somewhat rigid segment with a narrow but patent lumen. The small intestine is of normal length (Fig. 52.2).

In atresia type I (membrane or web) the dilated proximal and collapsed bowel are in continuity and the mesentery is intact. The intraluminal pressure in the proximal bowel produces bulging of the web into the distal intestine so that the transition from the distended to collapsed bowel is conical in appearance – the 'windsock' effect. The distal bowel is completely collapsed and the small intestine is of normal length (Fig. 52.3).

In atresia type II (blind ends joined by a fibrous band), the proximal bowel terminates in a bulbous blind end which is grossly distended and hypertrophied for several centimeters and is often hypoperistaltic. The bowel proximal to this is usually also considerably distended and hypertrophied for a further 5–10 cm. More proximally, the bowel distension is less marked and the bowel assumes a normal appearance. The distal collapsed bowel commences as a blind end which is sometimes bulbous due to remains of a fetal intussusception. The two blind ends are joined by a thin fibrous band. The corresponding intestinal mesentery is normal but may occasionally be deficient, leaving a V-shaped gap. The small intestine is usually of normal length (Fig. 52.4).

In atresia type IIIa (disconnected blind ends) the appearance is similar to that in type II but the blind ends are completely separate. There is always a V-shaped gap in the mesentery and the total bowel length is reduced (Fig. 52.5).

In atresia type IIIb (apple peel,[17] Christmas tree,[29] or maypole[6] deformity), as in IIIa, the blind ends are disconnected and the mesenteric defect is substantial. This type is the consequence of an extensive infarction of the midgut secondary to a superior mesenteric artery occlusion just distal to the middle colic origin, producing a proximal jejunal atresia with loss of a varying segment of jejunum. The distal ileum remains viable, receiving its blood supply via a precarious collateral from the arterial supply to the right colon, around which the ileum is coiled. Occasionally, additional type I or type II atresias are found along the coiled length of bowel towards the distal blind end. There is always a significant reduction in intestinal length (Fig. 52.6). These babies are usually premature and of low birth weight. In addition, they may have associated anomalies such as malrotation and may develop short bowel syndrome with increased morbidity and mortality.[22] A familial incidence has been reported by Blyth and Dickson[30] and Mishalany and Najjar.[25]

In atresia type IV, multiple atresias are present, which could be a combination of types I–III and often have the appearance of a string of sausages. The bowel length is usually reduced (Fig. 52.7). The site of the most proximal atresia determines whether it is classified as jejunal or ileal.

The intestine proximal to the obstruction becomes dilated and hypertrophied. This dilated bowel frequently has a cyanosed appearance and may have some necrotic areas either from sustained intraluminal pressure or secondary volvulus. Perforation may develop antenatally, leading to

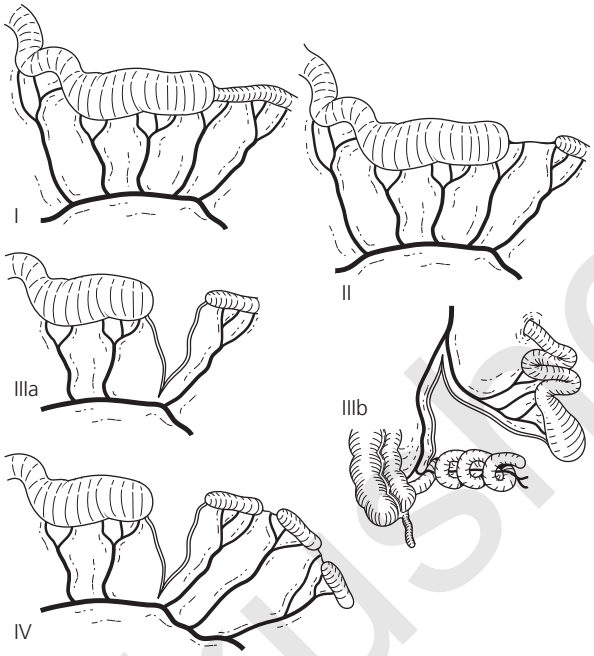


Figure 52.1 The different types of small bowel atresia according to the modified classification by Grosfeld *et al.*[1]

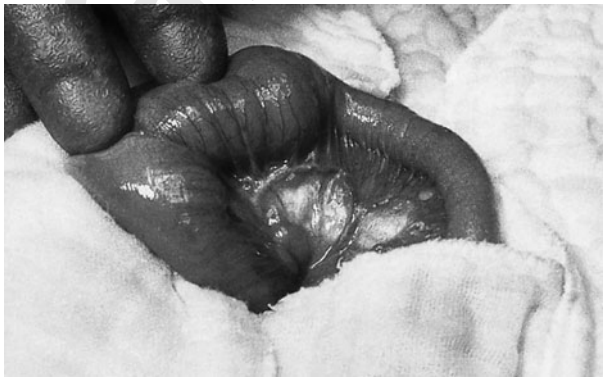


Figure 52.2 The clinical appearance of stenosis.

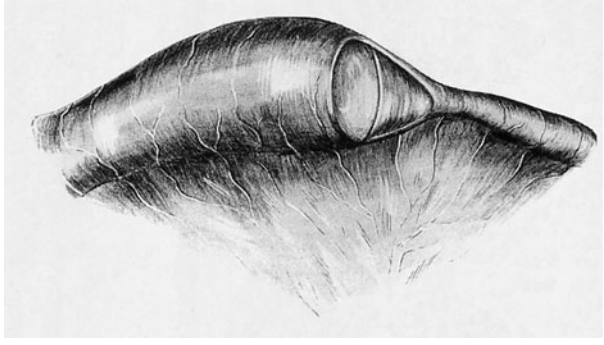
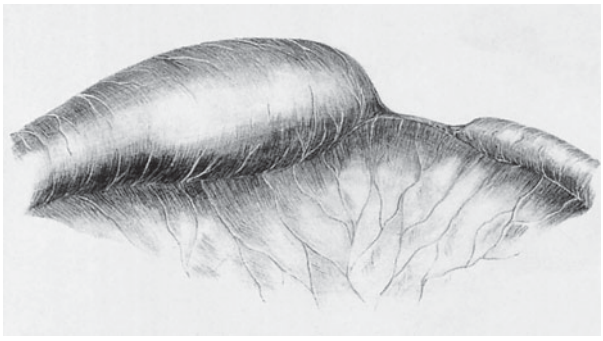


Figure 52.3 Atresia type I. Obstruction caused by an intrinsic membrane. The proximal bowel is dilated and the distal collapsed, with intact mesentery.



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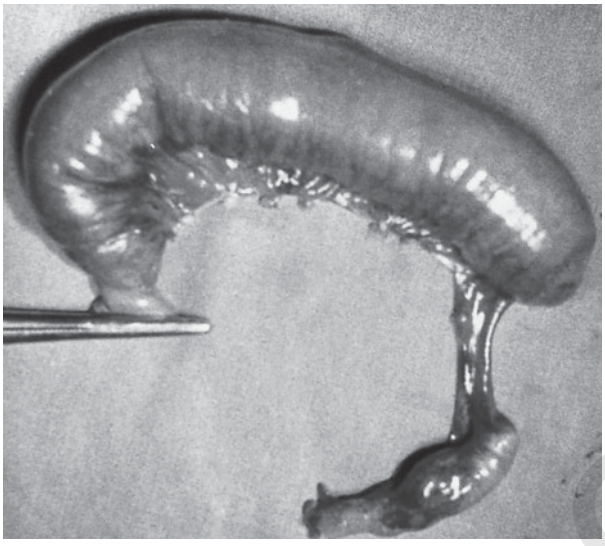
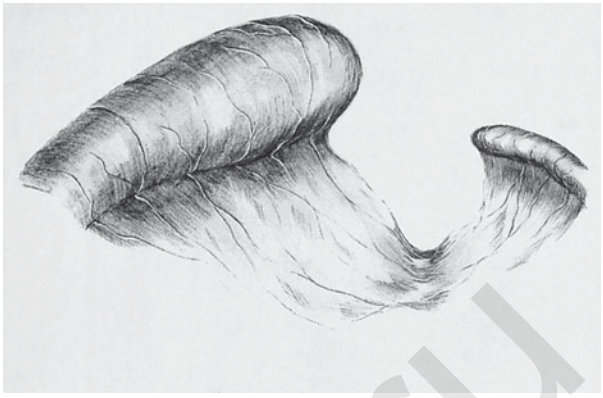


(b)

Figure 52.4 Atresia type II. Blind ends joined by a band with an intact mesentery and normal length of bowel.



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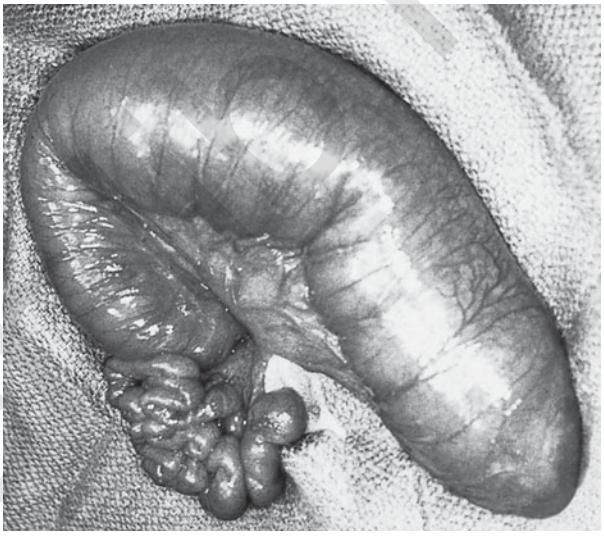


(b)

Figure 52.5 Atresia type IIIa. Blind ends disconnected with a V-shaped defect in the mesentery. The bowel length is reduced. The grossly dilated obstructed bowel tapers proximally into intestine of normal caliber. The distal collapsed bowel illustrates how difficult it may be to assess the length of this segment.

meconium peritonitis or may occur as a postnatal event, especially if diagnosis is delayed. The peristaltic movements in this segment are subnormal and ineffective, and histologic and histochemical abnormalities can be observed up to 20 cm cephalad to the atretic segment (Fig. 52.5).[31,32] In contrast, the distal bowel is unused and worm-like in appearance, but potentially normal in length and function.

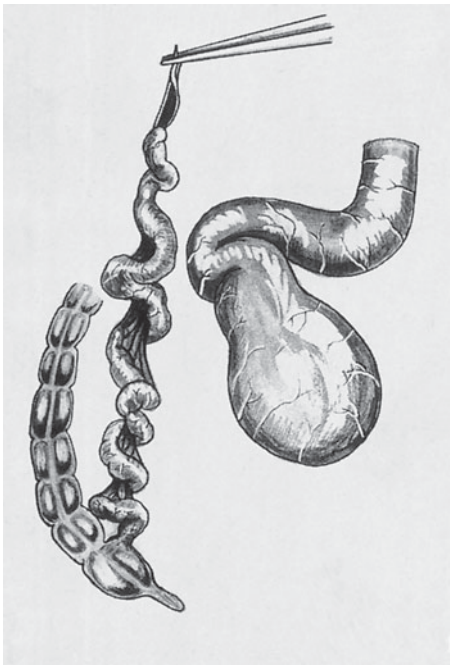
Of the 333 patients in our series, there were 34 (10.2%) with stenosis, 79 (24%) with type I, 32 (9.6%) with type II, 51 (15%) with type IIIa, 60 (18%) with type IIIb, and 77 (23%) with type IV atresias (Table 52.1).

CLINICAL FEATURES

A prenatal history of polyhydramnios is frequent and many babies with intestinal atresia are diagnosed by ultrasonographic investigation of the fetus, showing dilated and obstructive fetal intestine.[33] The family history may help to identify hereditary forms and conditions that may predispose to atresia, i.e. cystic fibrosis and anomalies of intestinal rotation.

Atresia or severe stenosis of the small intestine presents clinically as neonatal intestinal obstruction with persistent bile-stained vomiting dated from the first or second day of life. In general, the higher the level of obstruction the earlier and more forceful the vomiting, whereas in low intestinal obstruction the vomiting may be delayed. Abdominal distension is frequently present, more so with the distal ileal intestinal atresias where the distension is generalized compared with the more proximal jejunal atresias where it is confined to the upper abdomen and is relieved by nasogastric tube aspiration. In delayed diagnosis or where perforation has occurred, the distension may be severe and associated with respiratory distress. Constipation is usually not absolute and the meconium passed varies from normal in colour to the more common gray plugs of mucus. Occasionally, if ischemic bowel is present, as in type IIIb atresia, blood may be passed rectally.

Diseases that can mimic jejuno-ileal atresia include midgut volvulus, meconium ileus, duplication cysts, internal hernia, ileus due to sepsis, birth trauma, prematurity, and transplacental crossing of maternal medication.



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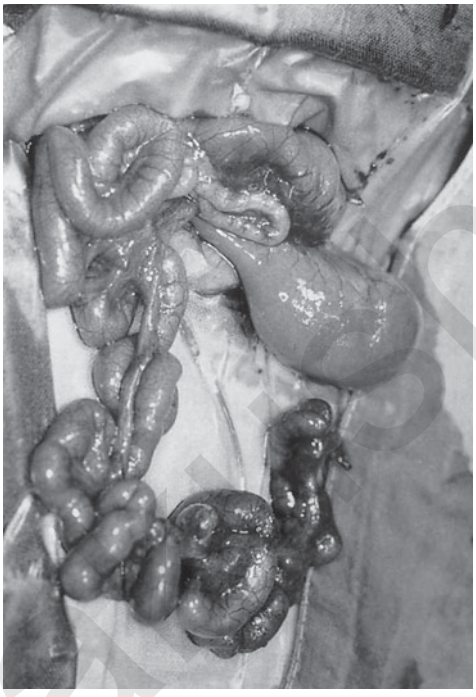
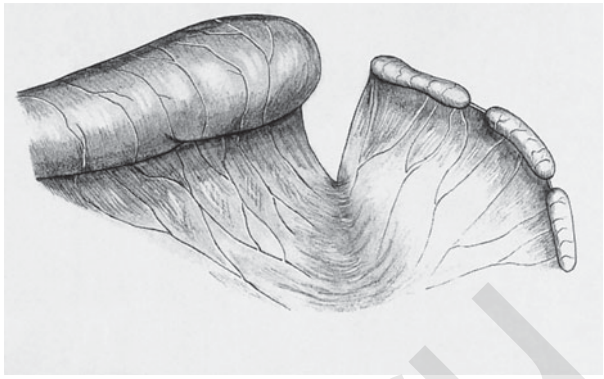


(b)

Figure 52.6 (a) Atresia type IIIb with a gross mesenteric defect and the coiled distal ileum with precarious collateral blood supply, producing the typical 'apple-peel' appearance. (b) Note the classical clinical appearance of the apple-peel atresia. Note the precarious blood supply of the terminal portion of the distal bowel and the grossly dilated proximal jejunum. There is always significant reduction in intestinal length.



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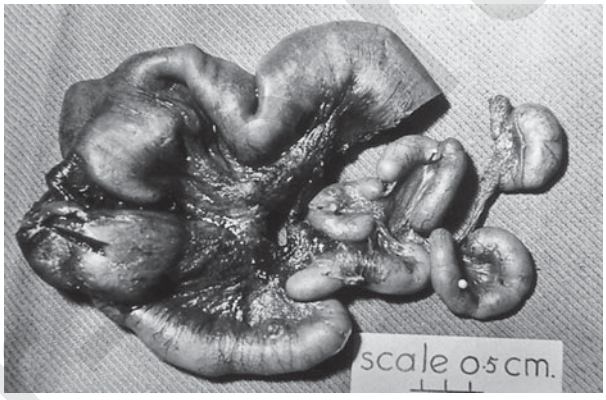
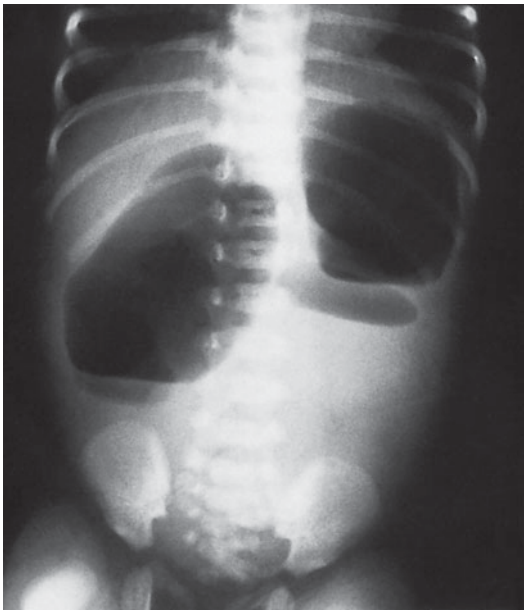


(b)

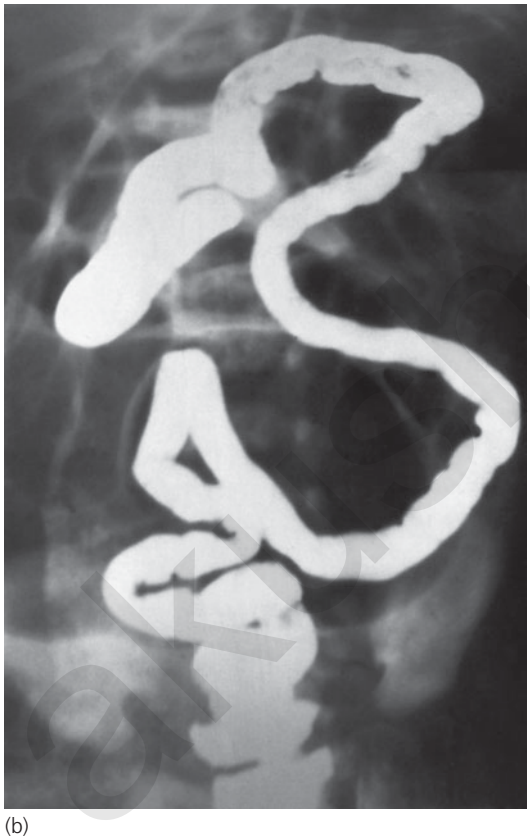
Figure 52.7 Multiple atresias with a typical 'string of sausages' seen clinically. The bowel length is usually reduced.

Erect and supine abdominal x-rays will reveal distended small bowel loops and air–fluid levels (Fig. 52.8a). The lower the obstruction, the greater the distended loops of bowel and the more fluid levels will be observed. A single large loop of bowel and air–fluid level would indicate atresia rather than other causes of neonatal intestinal obstruction. A prone lateral view is useful to distinguish between low small bowel and colonic obstruction. In some instances, the first abdominal x-ray may reveal a completely opaque abdomen due to a fluid-filled obstructed bowel. Emptying of the stomach by means of a nasogastric tube and injection of air will demonstrate the level of the obstruction. With intestinal stenosis, the caliber of the proximal obstructed intestine is greater than the distal gut but because the obstruction is incomplete the diagnosis is often delayed. When the abdominal x-ray suggests a complete obstruction, a contrast enema may be performed to exclude colonic atresia, distinguish between small and large bowel distension, determine whether the colon has the typical microcolon appearance, and locate the position of the cecum as an indication of malrotation. It also makes saline injection of the colon at surgery unnecessary, a sometimes tedious maneuver.

The classical appearance of the colon distal to jejuno-ileal atresia is an unused or microcolon (Fig. 52.8). When an incomplete small bowel obstruction is diagnosed, an upper gastrointestinal contrast study is indicated to demonstrate the site and nature of the obstruction. Malrotation may also be observed in 10–30% of babies with jejuno-ileal atresia. Occasionally, dystrophic intraperitoneal calcification of



(a)



(b)

Figure 52.8 (a) Erect abdominal x-ray of a newborn infant showing obstructed upper small bowel loops with fluid levels. No air is visible in the distal bowel. (b) Contrast enema showing the unused or microcolon distal to a jejuno-ileal atresia. In addition, evidence of malrotation is present.

meconium peritonitis may be seen on plain x-ray, signifying intrauterine bowel perforation. If the atresia has formed late in intrauterine life, the bowel distal to the atresia may assume the caliber of a used colon.

GUIDELINES FOR MANAGEMENT

The guidelines for management of jejuno-ileal atresia are as follows:

- Prenatal
  - polyhydramnios, affected family, ultrasonography
- Preoperative preparation
  - gastric decompression
  - fluid management
    - maintenance
    - replacement of deficiency/ongoing losses
  - plain abdominal radiograph (air contrast)
  - contrast enema
  - correction of hematological and biochemical abnormalities
  - prophylactic antibiotics
- Operative
  - identify type of atresia and possible cause
  - establish patency of distal small bowel
  - resection of the proximal bulbous component, ischemic bowel
  - derotation for high jejunal atresia
  - limited distal bowel resection
  - establish patency of distal bowel with saline injection
  - careful measurement of residual bowel length
  - end-to-end, single-layer interrupted suture anastomosis
  - bowel length conservation method – tapering, plication
- Postoperative
  - gastrointestinal decompression
  - antibiotics
  - parenteral nutrition
  - early and graduated enteral feeding with breast milk, special, or polymeric feeds
  - surveillance for gastrointestinal dysfunction
- Special problems
  - anastomotic dysfunction
  - short bowel syndrome
  - associated congenital anomalies.

Adapted from Haller *et al.*[34]

TREATMENT

The newborn baby tolerates operative intervention all the better after a few hours of preoperative preparation, especially if the diagnosis has been delayed. In general, this preparation should pay particular attention to hypothermia, hypoxia, hypovolemia, hypoglycemia, and hypoprothrombinemia. The operation should not be delayed unduly as there is always a danger of further infarction of the bowel, fluid and electrolyte disturbances, and increased risk of infection. In neglected cases with dehydration, more energetic therapy is required.

Operation

STERILIZATION OF SKIN AND DRAPING

The umbilical cord is cleansed with 70% alcohol and is ligated and transected at the level of the abdominal wall. The operative field is sterilized with pre-warmed povidone–iodine 2% in 70% alcohol. Sterile warm Gamgee rolls are placed alongside the baby, who is then draped with towels, and a sterile transparent adhesive drape is applied over the operative field to ensure that they remain dry during the operative procedure, thus preventing heat loss.

INCISION

An adequate incision is required. Exposure is obtained through a supra-umbilical transverse incision transecting the recti muscles 2–3 cm above the umbilicus. The ligamentum teres is subsequently divided and ligated. Alternatively, a small circumumbilical incision may be adequate.[35]

EXPLORATION

If free gas escapes on opening the peritoneum, or if there is contamination of the peritoneal cavity, a pus swab is obtained for Gram stain and culture and the site of the perforation is sought and closed before further exploration is carried out. In the presence of peritoneal contamination, the cavity is irrigated with warm saline or antibiotic-containing fluid – cefoxitin sodium 1 g/L. The entire bowel is exteriorized to determine the site and type of obstruction and to exclude other areas of atresia or stenosis and associated lesions, such as incomplete intestinal rotation or meconium ileus. The appearance of the atretic segment depends upon the type of occlusion, but in all cases the maximal dilatation of the proximal bowel occurs at the point of obstruction; this segment is often aperistaltic and of questionable viability, while the bowel distal to the obstruction is collapsed, tiny and worm-like (Figs 52.5, 52.6, and 52.9).

After the location and type of lesion has been identified, the distal bowel is carefully examined to exclude other atretic segments, which are present in 10–20% of cases. Saline is instilled into the lumen of the distal bowel to confirm patency. Malrotation is corrected if present. The total length of small bowel is measured as this has prognostic significance and may determine the method of reconstruction. The normal length at full-term birth is approximately 250 cm.

After complete patency of the distal small bowel and colon has been established, the next task is to suture the disproportionate proximal and distal blind ends. This is facilitated by applying an atraumatic bowel clamp about 6–8 cm from the distal blind end and distending the intervening segment by injection with half-normal saline, taking care not to split the serosa (Fig. 52.9).

RESECTION

The atretic area and adjacent distended and collapsed bowel are isolated by walling off the rest of the abdominal cavity with moist packs. To ensure adequate postoperative function, the proximal distended and hypertrophied bowel should be liberally resected, even if it appears viable. If the bowel length is adequate (more than 75 cm plus ileocecal valve) the bulbous hypertrophied bowel proximal to the atresia is resected to approximately normal bowel diameter; usually a 10–15 cm section is removed. After milking the intestinal contents into the proximal bulbous end, an atraumatic bowel clamp is applied across the bowel a few centimeters proximal to the site selected for transection. The mesentery adjoining the portion to be resected is divided using bipolar diathermy or ligated up to the proposed lines of section of proximal and distal bowel (Fig. 52.10). The blood supply at this point should be excellent and therefore the bowel is divided at right angles, leaving an opening of about 1.5 cm in width; 2–3 cm of the distal bowel is also removed. This bowel may be transected slightly obliquely and an incision may be continued along the antimesenteric border to create a 'fish-mouth', which renders the opening about equal to that of the proximal bowel (Fig. 52.11). Alternatively, the bowel can be transacted at right angles if an end-to-end anastomosis is planned. In patients with a relatively short segment of severely dilated proximal intestine, de-rotation of the proximal segment, resection to the distal second part of duodenum and establishment of continuity by end-to-end anastomosis with tapering of the duodenum is a good option. However, in patients with long segments of proximal intestine that are significantly dilated, resection of the whole involved segment may result in inadequate remaining intestinal length to allow absorption of enteric nutrients (i.e. short-bowel syndrome). Therefore, these patients frequently are treated by either imbrication or tapering enteroplasty of the proximal dilated segment. In a few cases with extensive congenital short bowel primary serial transverse enteroplasty has been attempted.[36]

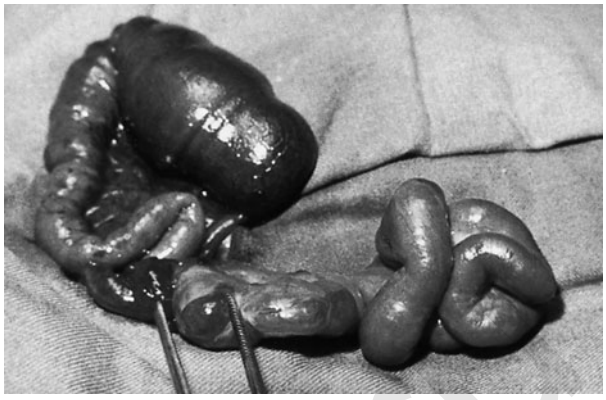
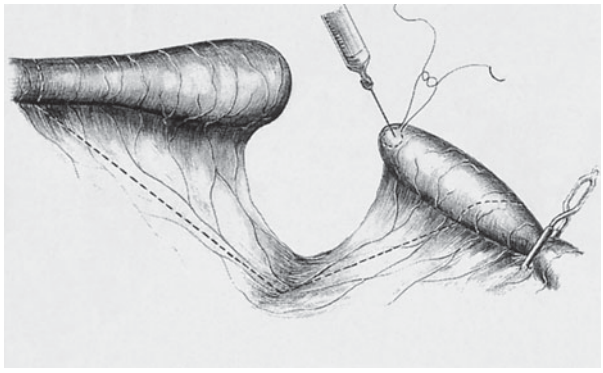


Figure 52.9 The proximal atretic bowel is grossly dilated, aperistaltic, and of questionable viability.

ANASTOMOSIS

An inverting mattress of 5-0 or 6-0 polydioxanone sutures unites the mesenteric borders of the divided ends, and temporary stay sutures are inserted at the antimesenteric angles to facilitate accurate approximation. The 'posterior'



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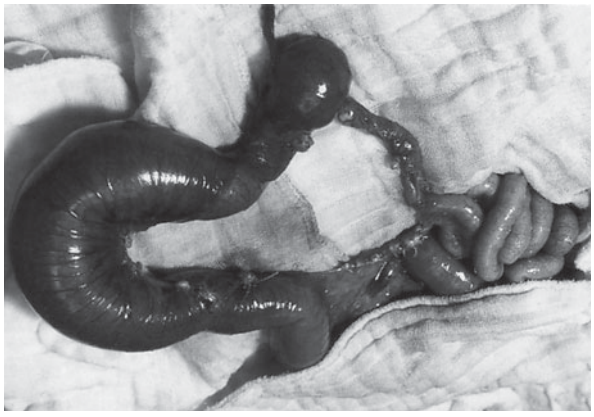


(b)

Figure 52.10 (a) The distal bowel distended with saline proximal to the bowel clamp. The extent of the resection is indicated by the dotted line. (b) The extent of resection in the clinical situation is depicted. Note that all grossly dilated bowel is resected.

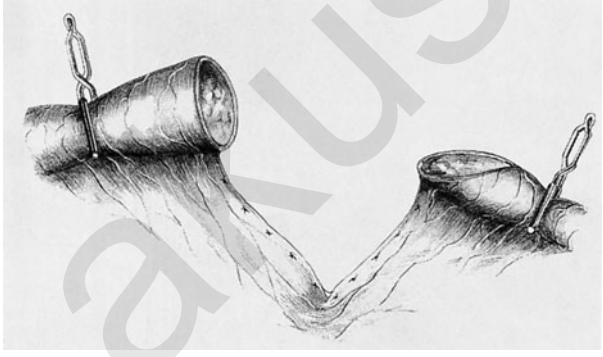
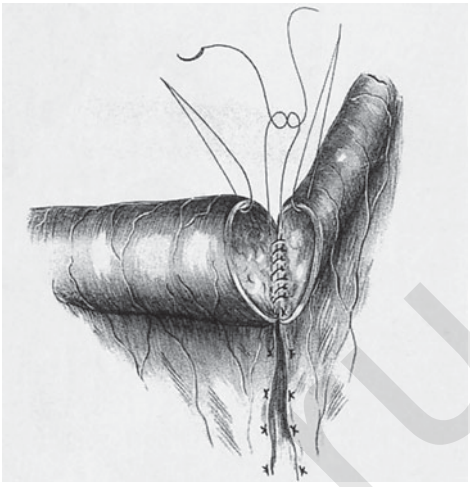


Figure 52.11 The proximal bowel has been transected at right angles and the distal obliquely with continuation of the incision along the antimesenteric border to create a 'fish-mouth'.

edges of the bowel are united with interrupted through-and-through 5-0 or 6-0 polydioxanone sutures tied on the mucosal aspect (Fig. 52.12a). The 'anterior' edges are joined by similar through-and-through sutures tied on the serosal surface (Fig. 52.12b). The completed anastomosis is not strictly end-to-end but a modification of Denis Browne's



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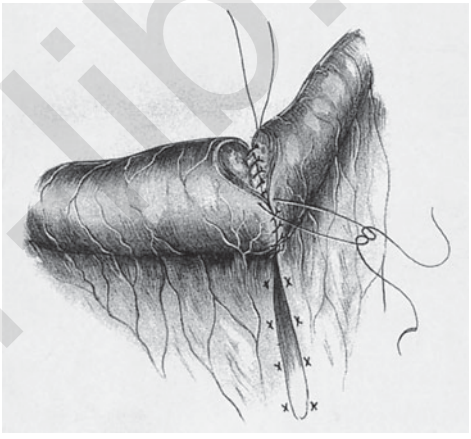
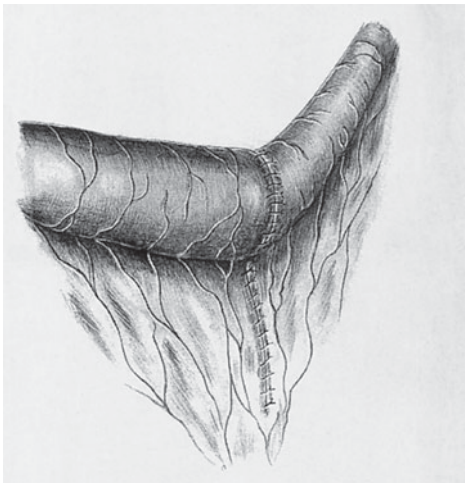


(b)

Figure 52.12 (a) Anastomosis of the posterior wall with interrupted sutures. (b) The anterior anastomosis.

'end-to-back' method. An alternative suture technique includes extramucosal anastomosis and the use of 5-0 or 6-0 monofilament absorbable sutures and end-to-end sutures taking larger bites on the proximal bowel. Where there is a discrepancy of less than 4:1 between the proximal and distal bowel lumens, an end-to-end extramucosal anastomosis is advised as there is thought to be an earlier return of normal peristalsis. The suture line is tested for leakage and reinforcing sutures are inserted as required. The defect in the mesentery is repaired by approximating (and overlapping if necessary) the divided edges with interrupted sutures (Fig. 52.13). The intestines are returned to the peritoneal cavity. During this procedure, if the mesentery is kept in the configuration of an open fan, kinking or volvulus of the bowel will be avoided.

A similar technique is used for stenosis and intraluminal membranes. Procedures such as enteroplasties, excision of membranes, and bypassing techniques are not recommended because they fail to remove the abnormal segment of bowel; side-to-side anastomosis is avoided due to the risk of creating blind loops.



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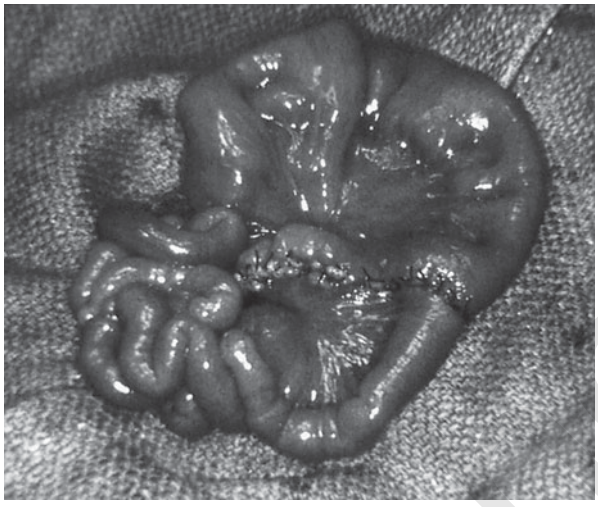

(b)

Figure 52.13 (a) Completed anastomosis and repair of mesenteric defect. (b) The clinical appearance of completed anastomosis.

GASTROSTOMY/ENTERAL DECOMPRESSION AND EARLY ENTERAL FEEDING

It was customary in babies with high jejunal atresias just beyond the duodenojejunal flexure to place a transanastomotic feeding tube for early enteral feeding when parenteral feeding techniques were less sophisticated. The tube was passed into the small bowel distal to the anastomosis before completing the anterior layer of sutures and stabilized at the anastomotic site by a single tethering mucosal stitch, in order to prevent its retrograde displacement into the stomach. The transanastomotic tube was either passed via the nasogastric route or via a Stamm gastrostomy performed on the anterior wall of the stomach. More recently, the value of such transanastomotic tubes has been questioned and the authors have abandoned routine use of these for high jejunal and duodenal atresias.[37] Nutrition is provided by the parenteral route until full enteral feeds are established.

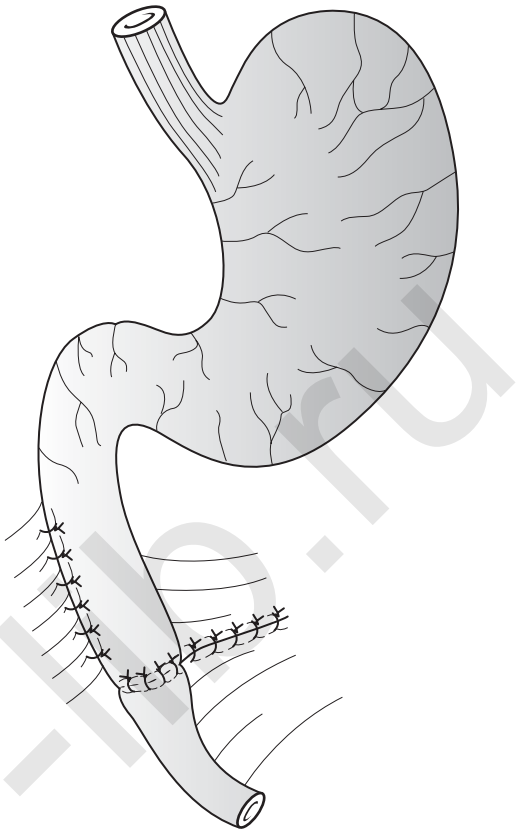

Figure 52.14 The surgical procedure for high jejunal atresia includes derotation of the bowel, back resection into the second part of the duodenum, tapering duodenoplasty or linear seromuscular stripping and inversion plication followed by bowel anastomosis.

CLOSURE OF ABDOMINAL WOUND

Where there has been soiling of the peritoneal cavity from a perforation, the abdominal cavity is again irrigated with saline and all macroscopic debris removed.

The abdominal wound is closed with a single continuous layer of polydioxanone 3-0 or 4-0 sutures to include all layers of the abdominal wall, excluding skin. In fat babies, the adipose layer is approximated with interrupted or continuous 4-0 absorbable sutures. The skin is approximated with continuous subcuticular 5-0 monofilament sutures.

Other surgical maneuvers

In babies in whom the initial insult has resulted in atresias with a markedly reduced length of small intestine or when large resections of multiple atretic segments are required, certain surgical techniques have been advocated in an attempt to preserve maximal intestinal length for survival and growth.[38,39] In addition, disparity in anastamotic size is reduced and prograde duodenal function is facilitated. In high jejunal atresias, the duodenum is fully derotated and the proximal resection extended into the second part of the duodenum with antimesenteric tapering duodenoplasty or inversion plication of the proximal mega duodenum (Figs 52.14 and 52.15).[40,41]

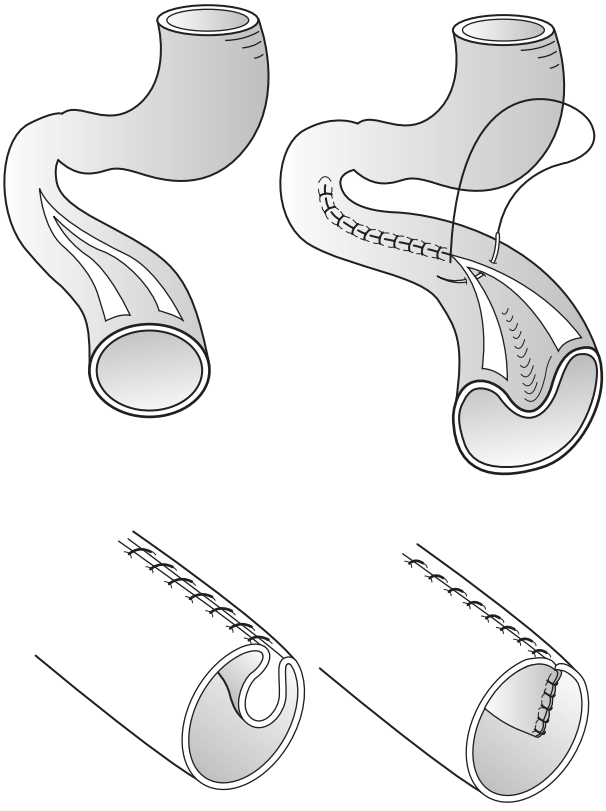

Figure 52.15 The technique of seromuscular stripping and inversion plication. This technique preserves mucosal surface for absorption and prevents unraveling of the placation.

The dilated bowel is trimmed to a lumen size of a 22 Fr gauge catheter. An intestinal autostapling instrument may be used. Inversion plication without excision and tapering has the advantage of preserving valuable mucosa if the bowel length is short. Tapering may have an advantage over plication, as the latter has the tendency to unravel within a few months with subsequent peristaltic dysfunction, especially if the mucosal strip/excision technique has not been utilized. Following this tailoring, the anastomosis is performed as described above and the bowel is returned to the abdomen in the position of nonrotation. In type IIIb, any restricting bands along the free edge of the distal narrow mesentery are released to avoid kinking and interference with the blood supply. The mesentery from any resected bowel is retained and may assist in closure of mesenteric defects. This technique is very helpful and prevents kinking or distortion of the anastomosis. Furthermore, the potential for kinking the single marginal artery and vein requires careful placement of the bowel into the peritoneal cavity at the completion of the anastomosis.

Although isolated type I atresias are best dealt with by primary resection and anastomosis, multiple diaphragms have successfully been perforated and dilated with bougies passed along the length of the bowel. In multiple atresias, multiple resections and anastomosis may be advisable to save as much bowel length as possible. They are, however, often localized, requiring resection and a single anastomosis. A silastic tube passed through the lumen of the entire bowel facilitates these anastomotic procedures.[42]

The fashioning of stomas, e.g. Bishop–Koop,[43] Santulli and Blanc,[17] Rehbein and Halsband,[44] or double barrel,[45] as practiced by some, is not routinely advocated unless there is gross intraperitoneal contamination, making a primary anastomosis unsafe. Jejuno-ileal atresia associated with a gastroschisis is treated by resection and primary anastomosis only if there is no evidence of edema and matting due to amniotic peritonitis. Initial reduction of the eviscerated bowel with the atresia intact and primary closure of the abdominal wall defect, if possible, is preferred. After allowing for disappearance of the edema (10–14 days), a re-laparotomy is performed with resection of the atretic segment and primary anastomosis. Stomas with the potential for fluid and electrolyte loss, wound infection, and other stoma-related complications are thus avoided. There is little place for bowel lengthening procedures at the initial operation. It is advisable to delay such procedures until the neonatal bowel length has grown to its maximum potential length and maximum bowel adaptation has occurred.

POSTOPERATIVE CARE

Postoperative care is conducted according to current standards and guidelines. Nasogastric decompression is usually required for approximately 4 days postoperatively. High jejunal atresias may require a longer period of decompression. Feeding is delayed until the gastric aspirate is no longer bile stained, the abdomen is not distended, and the baby has passed meconium. In babies with a transanastomotic tube, continuous feeding is commenced 24 hours postoperatively. Graduated polymeric feeds are then commenced and increased as tolerated. Oral or gavage feeds are started with return of prograde proximal bowel function.

If at any time there is a suspicion of a leak at the anastomosis as suggested by clinical deterioration, abdominal distension, and vomiting, a plain x-ray of the abdomen may reveal free air in the abdomen. When more than 24 hours have elapsed since surgery, this would indicate a leak or perforation and immediate laparotomy should be performed. Other postoperative complications observed have been ischemia leading to frank necrosis, late onset stenosis, adhesive obstruction, and perforation of the bowel by the transanastomotic tube. Infants with human immunodeficiency virus (HIV) exposure or infection have poor healing with an increased incidence of anastomotic breakdown and wound sepsis with dehiscence.[46]

In babies in whom less than 75 cm of small bowel remains, especially if the ileocecal valve is absent, loose frequent stools and excessive water loss may become problematic. In these patients, and in every instance where normal enteral alimentation cannot be established within 5 postoperative days, parenteral feeding is indicated. Carbohydrate, amino acid, and fat-containing solutions are introduced in a graduated manner over a period of 3 days. Peripheral venous push-in lines are used for short-term total parenteral nutrition (TPN) but for long-term TPN (longer than 10 days), a central line is preferred. Once intestinal function has been re-established, the baby is gradually weaned from a

parenteral to an enteral feeding program. Careful dietary tailoring is required, as each patient may have different tolerance thresholds.

Predictions of the degree of intestinal dysfunction are based upon the known residual length of small intestine. The short bowel syndrome can be contemplated if more than 70% of the bowel length was lost or if the minimal bowel length left after surgery is less than 70 cm. These babies can be divided into four main functional groups: (1) uncorrectable intestinal insufficiency; (2) adequate bowel function for survival after adaptation and/or lengthening and tailoring procedures; (3) adequate alimentary function for growth and development; and (4) normal alimentary function with a degree of intestinal reserve.

When gross intestinal insufficiency is expected the infant is managed as short-bowel syndrome.[47–49] The patient's oral intake is gradually increased in volume and energy content, while the small intestine is allowed to adapt until maximum intake tolerance is reached, which can take months to years.[50] Pharmacological control of intestinal peristaltic activity has been achieved more effectively since the introduction of loperamide hydrochloride. Vitamin B_{12} and folic acid should be administered to patients without the terminal ileum to prevent megaloblastic anemia. The long-term outcome for most of the babies is optimistic, although TPN-associated complications are frequent and sometimes fatal, unless liver and intestinal transplantation is undertaken.[51]

In predicting the ultimate functional outcome, the following factors must be taken into consideration: the ileum adapts to a greater degree than the jejunum; the neonatal small intestine still has a period of maturation and growth ahead of it; and the actual residual small intestinal length is difficult to determine accurately after birth. The proximal obstructed bowel segment is dilated and its functional potential may be overestimated, while that of the distal unused collapsed bowel may be underestimated. Of critical importance is an intact ileocecal valve, which allows for accelerated intestinal adaptation with shorter residual jejuno-ileal length. The absence of the ileocecal valve also leads to an increased transit time, malabsorption, diarrhea, and increased bacterial contamination of the small bowel.

RESULTS

Before 1952, the mortality rate for congenital atresias of the small intestine in Cape Town was 90%. Between 1952 and 1955, 28% of the babies with this condition could be saved. At that stage, most were treated by primary anastomosis without resection. With liberal resection of the blind ends and primary end-to-end anastomosis, the survival rate increased to 78% during 1955–58.[52,53]

During the 20-year period from 1990 to 2010, 130 patients with jejuno-ileal atresias and stenoses were admitted to the pediatric surgical service at the Red Cross War Memorial Children's Hospital. There were nine deaths (93% survival). Factors contributing to the mortality rate were: type of atresia (type III, 32%), proximal bowel infarction with peritonitis, anastomotic leaks, a missed distal atresia, the short-bowel syndrome with parenteral nutrition-associated liver disease, sepsis, and more recently HIV infections. Overall experience is recorded in Table 52.2.

Table 52.2 Mortality related to type of atresia.

Type	Patients	Mortality	%
Stenosis	34	0	0
I	79	4	5.1
II	32	4	12.5
IIIa	51	8	15.7
IIIb	60	10	16.7
IV	77	9	11.7
Total	333	35	10.3

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53

Colonic and rectal atresias

TOMAS WESTER

COLONIC ATRESIA

Introduction

According to Evans,[1] Binninger was the first to describe colonic atresia in 1673. The first survivor was reported in 1922, when Gaub[2] opened a diverting colostomy in a child with an atresia of the sigmoid colon. Potts[3] successfully performed a primary anastomosis in a neonate with an atresia of the transverse colon in 1947.

Atresia of the colon is a rare cause of bowel obstruction in the neonate. The incidence of colonic atresia related to live births has been difficult to ascertain, but an incidence of approximately 1 in 20 000 live births has been considered to be realistic based on the experience in major pediatric surgical centers.[4] In the northwest of England, isolated colonic atresia has been reported to occur in 1 in 66 000 live births.[5] Other investigators have reported that colonic atresias account for 1.8–10.5% of total bowel atresias,[6,7] the incidence of which has been estimated to be 1 in 1500 to 1 in 20 000 live births.[1,8]

Except for stenosis or incomplete occlusion of the colon, three different types of intrinsic occlusion have been distinguished:[9,10]

1. Type I atresia or a membrane (Fig. 53.1a)
2. Type II atresia with blind ends of bowel joined together by a cord-like remnant of bowel, with or without a gap in the mesentery (Fig. 53.1b)
3. Type III atresia with separated blind ends of bowel and a gap in the mesentery (Fig. 53.1c).

Furthermore, a hereditary form with multiple atresias of the gastrointestinal tract has been described, suggested to be of non-vascular origin.[11,12] Type III atresia appears to be most common in atresias proximal to the splenic flexure, whereas types I and II are more common in atresias distal to the splenic flexure.[13,14] In a literature survey it was reported that type III occurred in 60.4% of the cases.[15] Most series

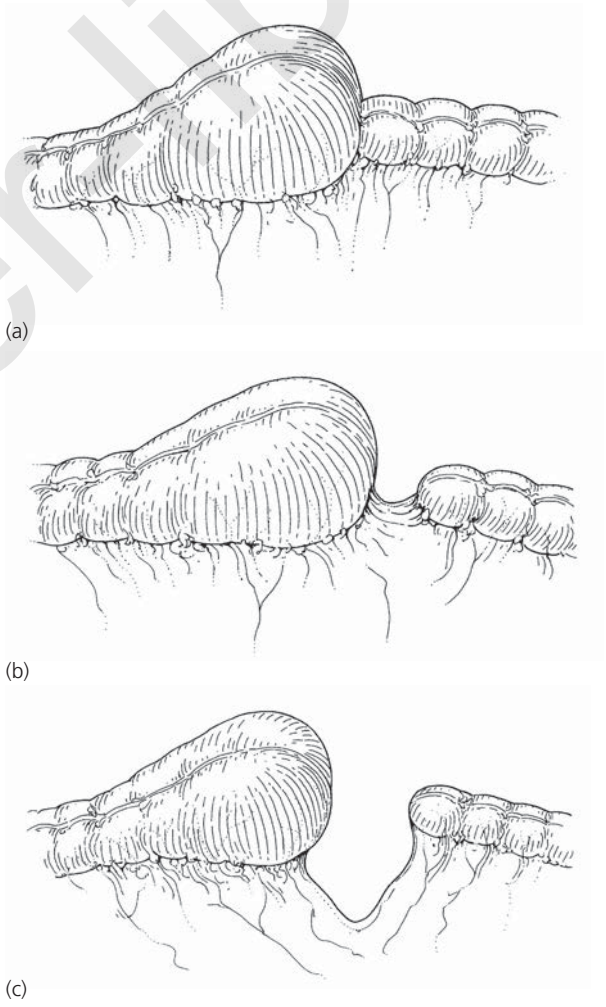


Figure 53.1 (a) Type 1: there is continuity of the outer layers of the bowel wall; the lumen is obstructed by a membrane covered with two layers of mucosa. (b) Type II: the bowel ends are connected by a fibrous band and the mesentery is intact. (c) Type III: a defect in the mesentery is accompanied by a gap between the bowel ends.

show an even distribution between atresias proximal and distal to the splenic flexure.[6,7,16,17]

Etiology

Colonic atresia is probably the result of intrauterine vascular insufficiency. The finding of bile, squamous epithelium, and hair in the bowel distal to the atresia supports the hypothesis that the vascular accident occurs late in development.[9] Several pathological conditions may result in compromised blood supply to the bowel, such as intussusception, volvulus, herniation, tight gastroschisis, and embolic or thrombotic events. It appears likely that focal resorption of the sterile gut occurs after ischemic necrosis. Animal experiments have been performed in which the blood supply was interrupted to different parts of the small intestine or colon, thus inducing various types of atresias. These experiments confirm the etiologic role of *in utero* vascular occlusion.[9,18,19]

Colonic atresia has been reported in monozygotic twins and genetic causes of colonic atresia have been discussed, although their role is not clear.[20]

Presentation

Neonates with colonic atresia present with symptoms indicating distal bowel obstruction. Abdominal distension is usually present at birth, but otherwise develops over the first 24–48 hours of life. Vomiting of bile is very common, but this is not always an early symptom. Failure to pass meconium is the rule and neonates that do not pass meconium within the first 24 hours of life should be considered for further investigations. On examination, the abdomen is distended and often slightly tender, sometimes with visible bowel loops. In those who have an abdominal wall defect, associated atresias should always be suspected.

Colonic atresia is associated with abdominal wall defects, such as omphalocele, gastroschisis, and vesicointestinal fissure, which complicate the management of the patient.[4,14] Boles *et al.*[14] found that four of their 11 patients had gastroschisis. In the series reported by Philippart,[4] 22 of 36 patients with colonic atresia had no associated anomalies, whereas six had vesicointestinal fissures, and three had other abdominal wall defects. Five of the 36 patients had jejunal atresia associated with the colonic atresia. Rarely, colonic atresia has been reported to occur concomitantly with imperforate anus.[7] Malrotation has also been reported to be a common associated anomaly.[15] One important associated anomaly is Hirschsprung's disease, which has been reported in a few cases. Although the colonic atresia was diagnosed at birth in these patients, there was a considerable delay in diagnosing the associated aganglionosis. It is therefore recommended that resected bowel is examined for Hirschsprung's disease.[21] Rectal suction biopsies are suggested in patients who do not gain normal bowel function postoperatively.[22] Some authors recommend that rectal suction biopsies are routinely taken in all patients with colonic atresia.[20,23] Isolated colonic atresia is sometimes associated with skeletal anomalies such as syndactyly, polydactyly, absent radius, and clubfoot.[4] Furthermore, colonic atresia has been reported in association with eye anomalies, such as exophthalmos and optic nerve hypoplasia.[13] In the series reported by Davenport *et al.*,[5] one patient had trisomy 18 and esophageal atresia. The fact that chromosomal abnormalities do occur in patients with colonic atresia makes it reasonable to recommend chromosomal analysis, at least in those patients who have other associated anomalies.

Diagnosis

Prenatal diagnosis of colonic atresia has been reported. However, prenatally detected colonic dilatation may also be the result of Hirschsprung's disease or anorectal malformations.[24]

Plain x-rays show a distal bowel obstruction with multiple dilated loops with air–fluid levels (Fig. 53.2a). A large right-sided loop, corresponding to the proximal dilated colon, has been considered characteristic in patients with colonic atresia.[5] The level of obstruction is confirmed by a contrast enema, which reveals the distal microcolon and incomplete colonic filling (Fig. 53.2b). Pneumoperitoneum, indicating colonic perforation, is not rare and has been reported in about 10% of the cases.[4]

Management

PREOPERATIVE

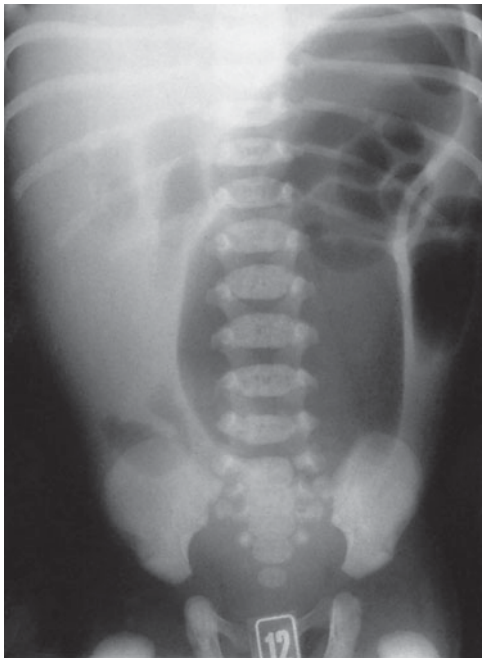
Correction of fluid and electrolyte abnormalities is started as soon as bowel obstruction is suspected. The gastrointestinal tract is decompressed with a nasogastric tube. Prophylactic antibiotics are administered. The neonate should be in a stable condition before general anesthesia and operation are started.

OPERATIVE

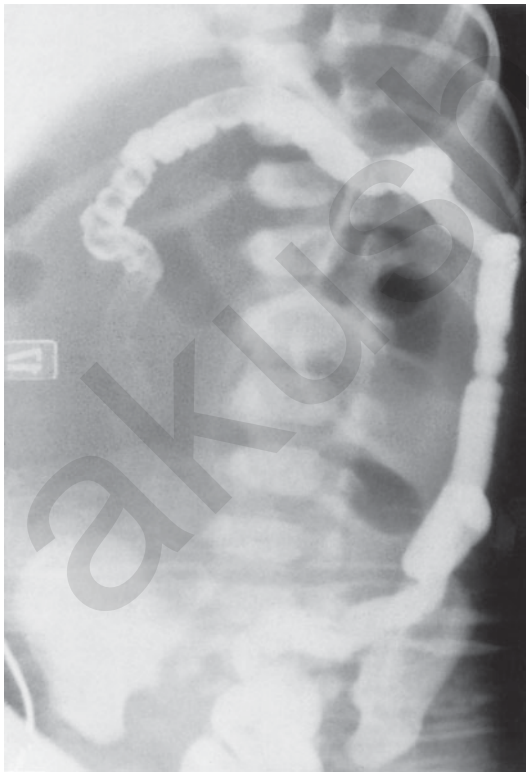
The two therapeutic options available are primary resection with anastomosis and colostomy with anastomosis at a later stage. Traditionally, many authors distinguished between the management of colonis atresias distal and proximal to the splenic flexure. Atresias proximal to the splenic flexure were treated with primary resection and anastomosis, whereas the distal atresias were treated with primary colostomy and delayed establishment of the gastrointestinal continuity.[4,7,13,17,25] More recently, it has been suggested that staged repair should be undertaken in complex cases with, for instance, questionable bowel viability, colonic perforation, and peritonitis, and in patients with concomitant abdominal wall defects. On the other hand, in uncomplicated cases, resection and primary anastomosis was proposed to be the method of choice for atresias at all levels of the colon.[25] There is no evidence that this later approach increases the mortality or complication rate.[5]

The abdomen is opened through a transverse incision a finger diameter above the umbilicus and to the right. The

incision may be extended as required. Cautery is used to divide the muscle layers of the abdominal wall and the umbilical vein is ligated and divided. The site and type of atresia are assessed. It is extremely important that additional atresias are excluded. The patency of the distal colon must always be tested by, for instance, injection of saline. In cases with colonic stenosis, a longitudinal incision, closed transversely is an alternative option for treatment. Some authors have considered the experience with this approach to be limited and therefore recommended resection and primary anastomosis as a more reliable method.[26] In those with type I atresias the bowel adjacent to the atresia is resected and a primary anastomosis is performed. In patients with type II and III atresias, with adequate bowel length, the excessively dilated proximal bowel should also be resected (Fig. 53.3a). A few centimeters of the distal narrow bowel are resected. The mesenteric vessels are divided close to the bowel wall to preserve the blood supply to the adjacent bowel. The distal bowel is incised along the antimesenteric border to achieve lumina of a similar size (Fig. 53.3b). A single-layer anastomosis is performed using interrupted 5-0 absorbable sutures (Fig. 53.4). The wound is closed in layers with absorbable sutures.



(a)

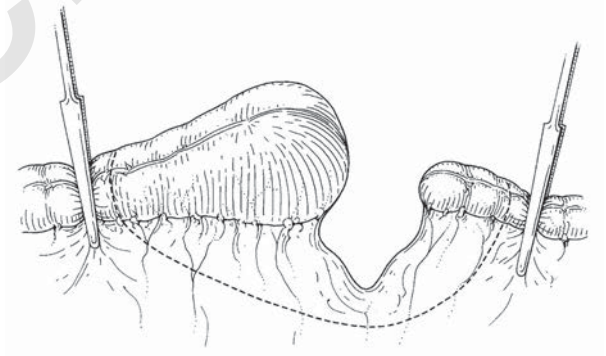


(b)

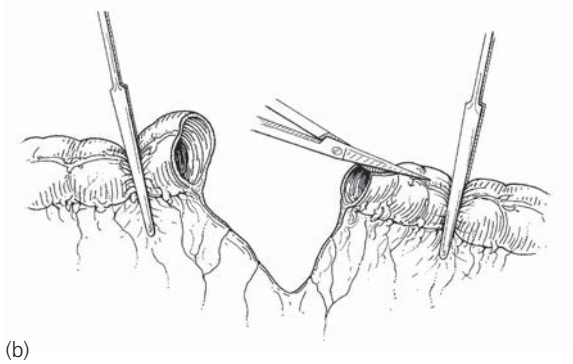
Figure 53.2 (a) Plain abdominal x-rays often show the hugely dilated bowel segment proximal to the atresia. (b) A contrast enema is diagnostic of a colonic atresia, as demonstrated in this infant with an isolated hepatic flexure defect.

POSTOPERATIVE

During the first postoperative days, parenteral nutrition is administered. Feeding can be started when the baby is well and the gastric aspirates have decreased. In cases with a primary anastomosis, it usually takes a few days before the neonate starts to pass stools. If a colostomy has been



(a)



(b)

Figure 53.3 (a) The dilated proximal and the relatively ischemic portion of colon just distal to the atresia are resected. (b) The distal colon is incised along its antimesenteric border to match the luminal diameters of the two portions of bowel to be joined.

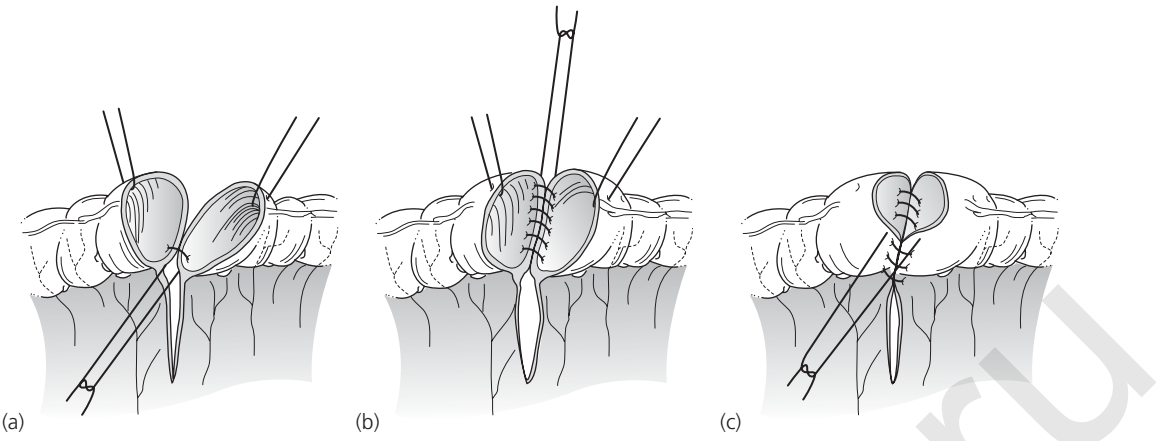


Figure 53.4 (a–c) The anastomosis is performed with a single layer of interrupted sutures.

fashioned the parents are instructed to take care of the stoma. Usually the colostomy is closed at two to three months of age.

Complications and long-term results

Many factors have led to an improvement in the results of patients with colonic atresia, including early postnatal diagnosis, improved neonatal intensive care and anesthesia, and more efficient transport facilities. Today, mortality related to the colonic atresia or its treatment is rare. In the series reported by Davenport *et al.*[5] no deaths occurred in the patients who underwent surgery, although one patient, who was never operated on, died of concomitant abnormalities. The mortality rate in earlier series varied from 9 to 33%, in many cases as a result of associated anomalies, but also attributable to late diagnosis, nutritional deficiencies, infectious complications, and technical errors.[6,7,13,14,17] Etensel *et al.*[15] recently reported a lethal outcome in 27% of the cases collected for a literature review.

Powell and Raffensperger[13] reported 15 postoperative complications in 19 patients. Problems related to the colostomy were encountered in three of 11 patients treated with colostomy and delayed anastomosis, whereas anastomotic strictures were seen in six of the 19 patients. Boles *et al.*[14] reported significant complications in four of 11 cases. The use of contemporary principles of neonatal surgery has, however, reduced the morbidity rate and Davenport *et al.*[5] reported recovery without complications.

RECTAL ATRESIA

Introduction

Rectal atresia is a very rare lesion, which has been reported to account for 0.3–1.2% of all anorectal anomalies.[27–29] Interestingly, a much higher incidence of 14% has been reported from Tamilnadu in the southern part of India.[30] The reason for this high incidence has been poorly understood. However, in recent years the incidence in Tamilnadu has been reduced and is now similar to that in other parts of the world.

Although it has been proposed that rectal atresia should be classified as a colonic atresia,[6] it is usually considered to be part of the spectrum of anorectal malformations. Rectal atresia was classified as a type IV anomaly in the Ladd and Gross classification of anorectal anomalies.[31] In the International classification and the Wingspread classification, it was also classified as a separate type of high anomaly.[32,33] Peña's classification describes rectal atresia as a separate entity.[34,35] The more recent Krickenbeck classification describes rectal atresia/stenosis among rare or regional variants of anorectal malformations.[36] Five types of rectal atresia have been distinguished, namely: type 1 with a membrane and intact bowel wall; type 2 with blind ends separated by less than 2 cm, which is the most commonly encountered type; type 3 with a long distance between the blind ends; type 4, which is rectal stenosis; and type 5 with a urinary fistula accompanying the rectal atresia.[37]

Etiology

Magnus[38] described the autopsy findings in a female neonate with multiple atresias of the small and large bowel, including a rectal atresia. It was found that there were intact remnants of the internal sphincter, that the epithelium of the anal canal was normally developed, and that the external sphincters were normal (Fig. 53.5). There was a fibromuscular band between the blind rectal pouch and the anal canal. Based on the findings in the autopsy specimen, the author suggested that rectal atresia is the result of vascular insufficiency, rather than a developmental defect. It is speculated that this could be the result of an intrauterine infection. It was also estimated that the lesion occurred between the 65 mm and 112 mm stages of development. Dorairajan[30] has suggested that the middle rectal artery is involved, rather than the superior rectal artery, which has been proposed by other investigators.

Presentation

Neonates with rectal atresia present with abdominal distension and failure to pass meconium, indicating distal bowel obstruction. The perineum and anal canal are normal and the

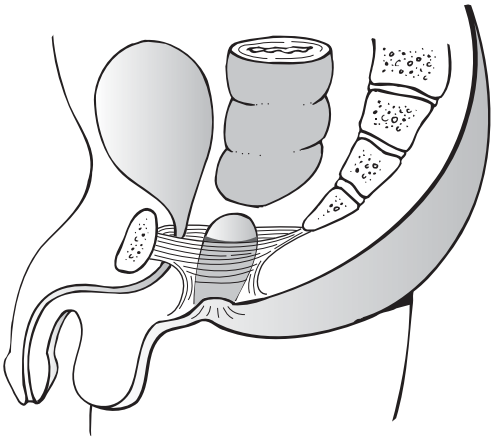


Figure 53.5 Diagrammatic representation of the anatomy in rectal atresia. Except for the high atresia, the anorectum is virtually normally developed.

diagnosis may therefore easily be delayed. The atresia is usually located 1–3 cm above the anal verge.

The incidence of associated anomalies in patients with rectal atresia has been considered to be extremely low.[39] In the series reported by Dorairajan,[30] associated anomalies were found in 2% of the 147 cases. No significant abnormalities were found in the urinary tract. Patients with rectal atresia usually have a normal perineum and a normal sacrum. However, associated malformations do occur; for instance, the author was recently involved in the management of a boy with rectal atresia, who had a concomitant cardiac malformation and vertebral anomalies, similar to that usually seen in patients with vertebral anorectal cardiac tracheoesophageal renal/radial limb (VACTERL) association. Rectal atresia occurs in patients with multiple atresias of the bowel.[38] Two of Dorairajan's[30] patients had ileal atresia and one had multiple small bowel atresias.

Diagnosis

The condition is diagnosed when an attempt is made to pass a thermometer or a tube to decompress the colon. After a colostomy has been opened, a contrast study with simultaneous injection of contrast material through the colostomy into the rectal pouch and the anal canal clearly outlines the anatomy of the anomaly (Fig. 53.6).

Management

In the past, several different techniques, such as abdominoperineal and sacroperineal pull-through procedures, referred to by Stephens and Smith[40] and de Vries *et al.*[41] were used to treat this condition. More recently, other methods have been described. Gauderer and Izant[42] placed a string across the membrane using fluoroscopy and progressively dilated the rectal canal in one patient. Zia-ul-Miraj Ahmad *et al.*[43] used a Duhamel procedure in seven cases with rectal atresia and rectal stenosis. Dorairajan[30] fashioned a transverse colostomy

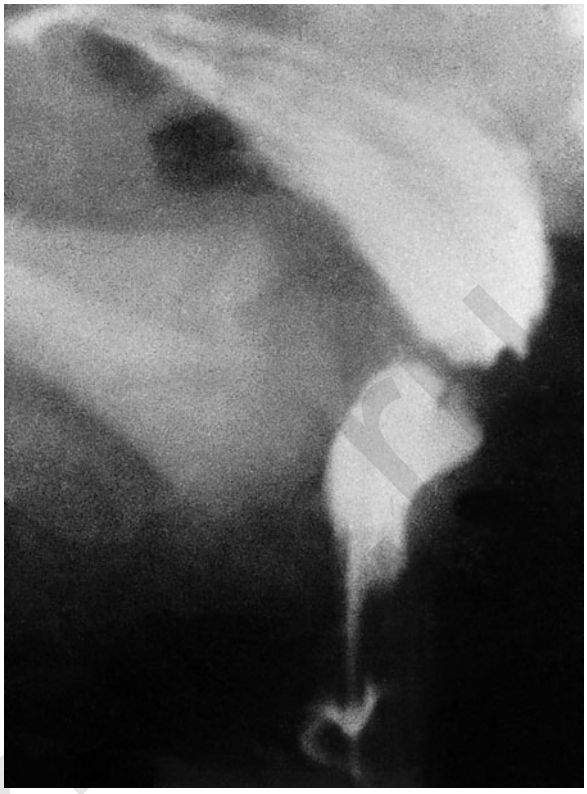


Figure 53.6 Simultaneous injection of contrast material into the upper pouch (via the sigmoid colostomy) and the anorectum clearly outlines the distance between the two pouches.

in the newborn and did a definitive sacroperineal pull-through operation at approximately one year of age. If the blind rectal pouch ended above the pubococcygeal line, a sacro-abdominoperineal or an abdominoperineal approach was preferred. The third stage comprised closure of the colostomy. In the first edition of this book, Upadhyaya[37] recommended his previously described approach, transanal end-to-end rectorectal anastomosis.[44] One advantage of this technique is that luminal continuity is restored without injuring the functional anatomy of the region. A sigmoid colostomy is opened in the neonate and the definitive procedure is performed at approximately three months of age. A Hegar dilator is advanced distally from the colostomy until it pushes the rectal pouch into the anal canal. The end of the anal canal is opened and the margins retracted with stay sutures. Then the rectal pouch is opened and the edges of the anal canal and the rectal pouch are approximated to form an end-to-end anastomosis.

Peña *et al.*[45] suggested that posterior sagittal anorectoplasty (PSARP) is a very useful method for the repair of rectal atresia and stenosis. It is recommended that a diverting colostomy is opened in the newborn and the definitive procedure is performed at a later stage.[34] A midline skin incision is performed and the levator muscle and muscle complex are separated exactly at the midline to expose the bowel. The blind end of the rectum is usually separated from the anal canal with a few millimeters of fibrous tissue. The rectum has to be mobilized to allow an end-to-end anastomosis to be performed without tension. Then the

wound is closed by reconstruction of the muscle structures. Daily dilatations are performed starting 2 weeks postoperatively. The colostomy is closed approximately three months after the operation, provided the diameter of the anastomosis is appropriate.[45] Very few pediatric surgeons gain more than limited experience with the management of rectal atresias. However, many pediatric surgeons are familiar with the posterior sagittal approach to treat other types of anorectal malformations. For this reason, an end-to-end anastomosis performed through the posterior sagittal approach seems to be an attractive option for these patients.

In utero repair of rectal atresia was recently reported in a fetus that also had a sacrococcygeal teratoma.[46]

Complications and long-term results

In patients with rectal atresia, the anal canal, sacrum, and sphincteric mechanisms are virtually normal. Therefore, the prognosis with respect to functional outcome is favorable. Although the number of cases reported is very limited, the outcome in patients with rectal atresia or stenosis treated through a posterior sagittal approach is excellent. Peña[34] reported voluntary bowel movements with total continence and without soiling in all of his five cases. However, two of the five patients had constipation. Constipation has also been reported to occur frequently after other procedures used to treat rectal atresia or stenosis.[43] Upadhyaya[44] reported an uneventful recovery and normal continence in two patients treated with his method. Dorairajan[30] was able to follow up 37 of 60 patients that were treated with sacroperineal pull-through operations and who had their colostomy closed. The outcome was excellent in 20% of the patients, whereas 65% had occasional soiling at night, and 15% had soiling also in daytime. The mortality rate in this series was 35%.

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Meconium ileus

GUIDO CIPRANDI AND MASSIMO RIVOSECCHI

INTRODUCTION

Meconium ileus is an early manifestation of cystic fibrosis (CF), due to abnormal, inspissated and viscid mucus of intestinal origin. In children affected by this condition, the impacted meconium produces an intraluminal obstruction occurring in the midileum, leading to a progressive distension. As an ultimate evolution, different mechanical complications can be associated, including intestinal volvolus, atresia, gangrene and necrosis, perforation, peritonitis with abdominal calcifications, and finally, meconial pseudocyst. In this view, meconium diseases in infancy cannot be firmly separated into three categories such as meconium plug syndrome, meconium ileus, and meconium peritonitis, nor can therapy of each condition.

HISTORY

Intestinal occlusion, both associated with inspissated meconium and gross pathologic pancreatic changes, was firstly reported by Landsteiner[1] in 1905 and subsequently confirmed by Kornblith and Otani[2] and Fanconi *et al.*,[3] who correlated a chronic lung disease and a pancreatic insufficiency. In 1936, Fanconi and Uehlinger described this complex and lethal newborn condition as a cystic fibrosis of the pancreas.

In the mid-twentieth century, Bodian's[4] perception of an abnormal sticky intestinal mucus, with a lower content of water, advanced the basis for a modern treatment with intraoperative saline irrigations, thus avoiding undue small bowel resections. Mikulicz, Gross, Bishop and Koop, Santulli and others were responsible, in those years, for different surgical techniques including distal or proximal enterostomies.[5] More recently, Noblett[6] and Shaw[7] reported relief of the intestinal obstruction, irrigating with various solutions, such as normal saline, 1% *N*-acetylcysteine, hyperosmolar gastrografin enema, surfactant, DNase. With respect to different types of surgical and medical efforts, the survival rate at one year increased from 10 to 90% and the operative mortality drastically decreased to 15–23% of treated newborns.[8]

INCIDENCE

Meconium ileus accounts for 9–33% of all neonatal intestinal obstructions (300 new cases in Italy each year), and could be defined as the third most common cause of neonatal small bowel obstruction after ileal and duodenojejunal atresia and malrotation.[9]

It is more frequently observed in Caucasian countries, where the presence of CF is higher, ranging from 1 in 1200 to 1 in 2700 live births. In contrast, the disease is almost absent in some Asian and African populations. Although meconium ileus can rarely occur in otherwise normal patients, the majority of children affected by this condition have CF. The mean incidence of meconium ileus in CF is at least 18%, with no difference in the gender; when this association coexists, meconium ileus is the presenting symptom in 12% of these children.[10] Different to this pathology, meconium plug syndrome is more commonly seen in premature infants, is characterized by colonic obstruction, and is infrequently associated with CF.[11] Approximately half of neonates with meconium ileus present with complicated intestinal obstruction and they always require a surgical procedure. In contrast, only 6–10% of uncomplicated forms fail a non-operative management using a water-soluble contrast enema; these patients are candidates for a temporary diversion or a major procedure.[12,13]

PATHOGENESIS

Meconium ileus is an essential expression of CF, which is the most common lethal autosomal recessive disorder in white populations, and is characterized by dysfunctional chloride ion transport across epithelial surfaces. Parents are not affected, but both are heterozygotes carrying the abnormal gene(s).

Intestine, pancreas, lungs, sweat glands, liver, and salivary glands are all involved as a result of an abnormal exocrine gland activity. However, these organs will be differently affected during life, the pancreas being the first, because the progressive retention of secretions and the atrophy of the acinar cells starts during fetal life; in contrast, the lungs are normal at birth and the mucous plugging of the distal airways will be responsible for a progressive pulmonary insufficiency during adolescence. Meconium ileus is a rare expression of CF in premature infants, suggesting that the intestinal abnormalities take place during the last period of fetal life.

Although recurrent lung infections and pulmonary insufficiency are the principal causes of morbidity and death, gastrointestinal signs and symptoms commonly precede the pulmonary findings and may suggest the diagnosis in infants and young children. The gastrointestinal manifestations of CF result primarily from abnormally viscous luminal secretions within hollow viscera and the ducts of solid organs. As a result bowel obstruction may be present at birth due to meconium plug syndrome or meconium ileus. The first biochemical studies of the altered meconium showed a lower content of carbohydrate, more proteins, and the so-called 'mucoproteins' and albumin, which had been previously used as a screening. Meconium ileus more recently appeared as a result of abnormal intestinal secretions, but not so closely related to the sweat electrolyte defect (high levels of sodium and chloride). In fact, the impermeability of CF epithelia to chloride ions is not correlated to the severity of intestinal involvement and the pancreatic lesions play a secondary role. The sweat test is the main laboratory test used for diagnosis, but after the 1990s genetic analysis has been commonly used for diagnostic as well as prognostic purposes.

From a genetic point of view, the CFTR, or cystic fibrosis transmembrane conductance regulator, is the gene product defective in CF, and was first identified in 1989.

This gene is normally located in the apical membrane of the epithelial cells from the stomach to the colon: a mutation of CFTR on chromosome 7 is responsible for CF evidence. The most common mutation is ΔF-508 and can be identified using DNA testing in affected neonates as well as in family members, possible carriers of the specific gene.

The CFTR gene codes for a 1480 amino acid protein that act as a chloride channel, regulated by cyclic AMP. In the small intestinal wall, the clinical expression of CF depends largely on the decreased secretion of fluid and chloride ions, the increased permeability of the paracellular space between adjacent enterocytes, and the sticky mucous cover over the enterocytes. As a rule, the brush border enzyme activities are normal and there is some enhanced active transport as shown for glucose and alanine. As a result, the gastrointestinal content in children affected by meconium ileus differs mainly from the normal condition by the lower acidity in the foregut and the accretion of mucins and proteins resulting in intestinal obstruction in the ileum but also in the colon. During growth, the small intestinal mucosa will not be functioning at maximal capacity. Better understanding of the CF gastrointestinal phenotype may contribute to improvement of the overall well-being of these first-seen newborn patients. In recent years, the Na^+-dependent amino acid transporter called ATB(0), which has been previously localized in the 19q13.3 region, did not appear to be associated with CF-MI disease; however, fine chromosomal mapping of other genetic factors and loci, in human as well as in animal models, such as in mouse, could be useful in determining the association with the intestinal phenotype of CF. We assume that this work will be very difficult because more than 1000 mutations have been identified in the CFTR gene and the final impact of these mutations on the genotype–phenotype correlation is unknown. In addition, the discordant phenotype observed in CF siblings suggested that genes other than CFTR modulate the CF phenotype.[14–16]

HISTOPATHOLOGY

In the meconium ileus, the intestine shows different aspects if the proximal, the middle, and the distal ileum are considered. In the first portion, a nearly normal evidence is present, with a progressive dilatation at the mid-portion borderline. In the proximal ileum, the content has a semiliquid consistency and is not yet viscous. A marked and severe dilatation of the middle ileum is always seen; the intestine contains thick, dark green and putty-like meconium, firmly adherent to the walls. The intestinal obstruction causing an hyperperistalsis is responsible for the congestion and hypertrophy of the walls. The distal ileum is full of concretions called 'rabbit pellets', gray stained and with a beaded typical appearance. This small bowel condition is responsible for a narrow, empty, and small colon, which is never used, and is called a microcolon.[17]

When the meconium ileus is complicated, more severe aspects can be seen: the dilatation is responsible for wall perforation and secondary meconium peritonitis, with calcifications. The spontaneous healing of the ileal perforation can lead to resorption of the involved portion of bowel and finally to an intestinal atresia. When the peristalsis is vigorous, the twisting of the ileal tract full of dense meconium may result in a massive volvolus, with a high risk of perforation. Sometimes, when the bowel perforation is massive, an intense reaction to the meconial spillage may produce a giant meconial pseudocyst. Obviously, postnatal perforative evolution of meconium ileus is complicated by bacterial peritonitis.

CLINICAL PICTURE

Polhydramnios is the most frequent feature observed in prenatal diagnosis of complicated forms of meconium ileus. The presence of fetal hyperechogenic bowel on the ultrasound, associated with dilated bowel and/or ascites could be indicative of an intestinal obstruction. A family history of CF is clearly evident in almost 25% of these patients. Meconium ileus is uncommon in premature infants (5–12%), and associated congenital anomalies are rare.[18]

Main symptoms include abdominal distension (96%), bilious vomiting (50%), and delayed passage of meconium (36%). From a clinical point of view, it is possible to recognize two different conditions: a simple, uncomplicated type not requiring surgery, and a complicated, severe type, with a mortality of at least 25% of all cases. In the first type (58%),

signs and symptoms of a distal ileal obstruction are seen not later than 48 hours after birth. These are generalized abdominal distension with dilated and visible as well as palpable loops of bowel, bilious vomiting, no stools, and narrowing of the anus and rectum, with only a dense and rubber-like gray meconium sticking to the anal wall. In the second type (42%), the neonate represents a surgical emergency which must be treated within 24 hours before birth, when the signs of a hypovolemic shock or sepsis are not well established. Fetuses with complex meconium ileus are at increased risk for postnatal bowel obstruction and perforation.[19]

In this serious illness, the progressive abdominal distension may culminate in respiratory distress. If a perforation occurs, a pneumoperitoneum and sepsis are the unfavorable consequences. Infrequently, meconium in the vagina or scrotum are evidence of a fetal perforation. Sometimes, the onset is directly with meconium peritonitis, which could involute in a giant meconial pseudocyst. When this happens, the abdominal skin edema and translucency are evident and associated with a palpable right lower mass.

At present, whatever the clinical presentation picture, the overall survival rate is at least 95%.[20]

PRENATAL ULTRASOUND AND RADIOLOGIC PATTERN

Meconium usually fills the small bowel during the 20th week of gestational age, so that identification of meconium ileus before this period is rare. Prenatal ultrasound has led to confidence in the antenatal diagnosis of intestinal obstruction allowing counseling and birth planning. In this regard, the presence of fetal hyperechogenic bowel on the ultrasound, associated with dilated bowel and/or ascites could be indicative of an intestinal obstruction. The increased echogenicity of the intestinal loops is due to a higher density of the intraluminal content (hyperdense and dry meconium). However, it is not easy to determine exactly whether this feature arises from intra- or from extraluminal structures and other different conditions may present with a similar ultrasound pattern, such as prenatal infections, neoplasm, or chromosomal trisomy. In addition, these findings may also represent transient normal variants.[18,21,22]

When the meconium ileus evolutes in a volvulus, the ultrasound shows enlarged hyperechogenic loops without peristalsis. Polhydramnios is the most frequent feature observed in prenatal diagnosis of complicated forms of meconium ileus. Obviously, if the parents are found to be carriers for a CF mutation, the correlation between ultasound findings and meconium ileus is achieved.

Plain x-ray shows distendend and gas-filled intestinal loops (Fig. 54.1). Sometimes, air–fluid levels are seen (one-third of cases), thus mimicking an ileal atresia. Where a sharp stop image is evident, this is the exact point of the obstruction. A usual image of fine, granular soap-bubble (Singleton's sign) or ground-glass appearance (Neuhauser's sign) is due to a dense meconium mixed with air, typical of the distal ileum; this picture is usually located in the midabdomen or in the right iliac fossa. Nevertheless, this image has also been observed in

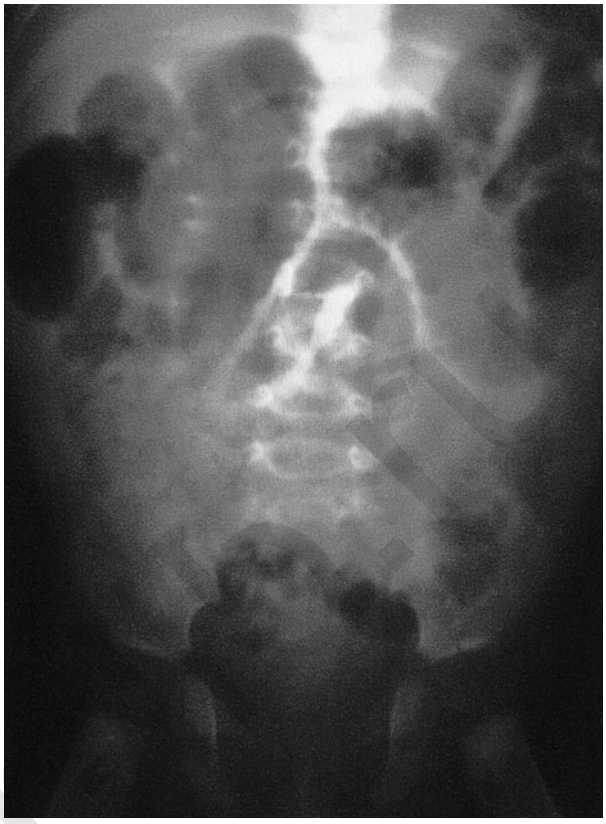

Figure 54.1 Plain x-ray showing distended loops of intestine and Neuhauser's sign.

neonates with meconium plug syndrome, Hirschsprung's disease, or small bowel atresia. The meconium hyperdensity may produce various images, depending on the length or localization of the obstructed bowel, but also on the filling (complete or partial) of the intestinal loops affected. When the meconium ileus is complicated, the abdominal x-ray may show calcification as a result of meconium peritonitis due to a fetal perforation of the intestine. A double-bubble image or air–fluid levels can be seen when a secondary ileal atresia (single or double) is the final bowel remodeling after a complete volvulus associated with severe ischemic damage. If the intestinal perforation occurs early in the antenatal period, the x-ray appearance of a round rim of calcification underlines a meconium pseudocyst. The colon is always a microcolon (unused colon), because the meconium never fills the large bowel during fetal life. Thus the length is normal but the caliber is small because of the small amount of feces (thick and dry meconium) passing through.

A water-soluble contrast enema is useful both for diagnostic and therapeutic purposes: the iso-osmolar agents facilitate evacuation of meconium without loss of large amounts of fluids and solutes (Fig. 54.2).

DIAGNOSTIC CRITERIA AND DIFFERENTIAL DIAGNOSIS

The sweat test provides a quantitative estimate of sodium and chloride on a sample of sweat usually collected from the

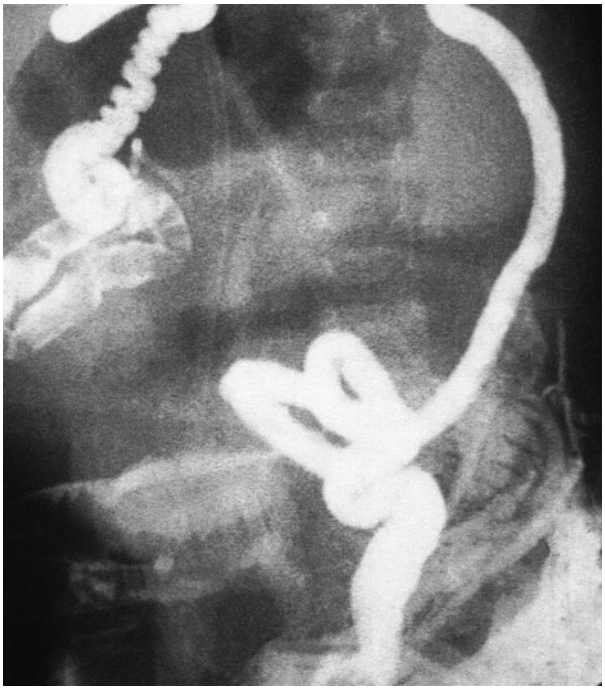

Figure 54.2 Contrast enema showing microcolon and pellets in terminal ileum.

forearm. A cholinergic drug acts to stimulate the sweat production with the help of a mild electrical current applied for 3–6 minutes (pilocarpine iontophoresis technique). Concentrations of these two cations above 60 mEq/L are diagnostic if at least 100 mg of sweat is collected. However, in the early neonatal stage, it is difficult to obtain a sufficient quantity of sweat to provide an accurate analysis and the collection must be done two or three times before a satisfactory quantity is achieved. In borderline cases, results are not significant for CF and further analysis is needed. Another problem is the high levels of sodium and chloride in neonates otherwise normal. In this situation, it is necessary to wait and provide another series of results after an interval of at least a month after the first test. More recently, the DNA probe analysis test for the ΔF508 mutation and other common alleles allows for a precise diagnosis, and misses only a small percentage of patients affected by CF. This method detects both affected children as well as heterozygote carriers.

Other causes of distal intestinal obstruction of the newborn may present with similar clinical patterns, including jejuno-ileal atresia, Hirschsprung's disease, meconium plug syndrome, and neonatal small left colon syndrome. In particular, a congenital megacolon is suspected when the bowel contents are liquid and air–fluid levels are constantly seen in the dilated bowel.

Other conditions may mimic surgical obstruction, such as delayed peristalsis associated with prematurity (the so-called functional immaturity) and adynamic ileus from sepsis. If a volvulus without malrotation or neonatal invagination are seen, these patients may undergo a sweat test to exclude CF. Although unusual, meconium ileus can exist as an isolated entity, not associated with CF. These patients account for 6–12% of the total, and the course of the illness is more often benign and without complications.[23]

MEDICAL AND SURGICAL TREATMENT

The first step of treatment includes nasogastric tube decompression, antibiotic prophylaxis with cephalosporin and aminoglycosides, and correction of dehydration, electrolytes, and hypothermia.

A contrast enema with water-soluble and hyper- or iso-osmolar contrast is the medical treatment of choice and mucosal safe, for uncomplicated meconium ileus. A recent study which used various enema solutions administered in a mouse model showed that surfactant and Gastrographin were the most efficacious for the *in vivo* relief of constipation, in comparison with perflubron, Tween-80, Golytely, DNase, *N*-Acetylcysteine, and Viokase. Intestinal mucosal damage was absent and viscosity had been significantly reduced *in vitro*.[24]

Enema evacuation should be obtained under fluoroscopic control, with a gentle and progressive increasing of intraluminal pressure, thus avoiding unexpected fractures of the colon. A correct procedure prevents leakage of the contrast medium by taping the buttocks, as well as catheter dislocation. If the contrast medium fails to progress into the dilated small bowel loops, the presence of an acquired atresia is definite and the radiologist must stop the examination because of the high risk of perforation. Fifty percent of neonates given this procedure benefit from enema alone over the next 48 hours, without any additional treatment. Iin some cases, a second enema may be used with a complete evacuation of the meconium filling the ileal loops. Acetylcysteine administered by mouth is useful and helps to relieve the obstruction. X-rays are done at 3, 6, 12, 24, and 48 hour intervals, with the aim of evaluating progression and possible complications. At this time feeding is begun. Hypovolemic shock and early perforation are possible problems, but an appropriate and meticulous procedure can avoid these complications.

When medical treatment is unsuccessful in spite of an uncomplicated meconium ileus, surgery is mandatory and an open evacuation, resection, and ileostomy are the possible options. In a simple meconium ileus, the surgeon should carry out the minimal procedure to free the lumen of all materials, such as pellets, sticky meconium, and sometimes, small calcifications. In this case, limited enterotomy and repeated warm saline irrigations through a smooth catheter provide the best result. In this event, meconium discharge may be manually supported, using the enterotomy placed in the dilated hypertrophic ileum. The catheter is two-way directed with care, clearing the small as well as the large bowel. At the same time as irrigation, the surgeon controls the enema progression, and the bowel may be inspected for distension degree, mesenteric orientation, covered perforation, gangrenous tract, and atretic single or multiple segments. The colon is inspected too, searching for possible perforation or microperforation. The T-tube ileostomy can be an additional, effective, and safe treatment, without any

additional surgery in 90% of treated patients; the T-tube should be removed within the first 8 weeks after surgery.[25,26]

At the end of this treatment, discussion is about whether to resect or not, because some authors stress the risk of a leakage at the anastomotic site. It must be borne in mind that resection and termino-terminal anastomosis are possible only if any signs of infection or sepsis is absent.

Usually a resection is done with the aim to promptly restore normal peristalsis; in these patients, the intestinal resection is limited to a huge dilation, at risk for foci of regional infection. In fact, bowel resection with primary anastomosis has proven to be as effective and safe as stoma formation, but is associated with a reduced length of initial hospital stay.[20] However, in complicated forms of meconium ileus, primary resection and anastomosis should have some advantages, such as shorter hospital stay and no later surgical procedure for stoma closure.[27]

Ileostomy can be performed in different fashions. The simplest method is a double-barreled ileostomy (Mikulicz), with the two loops brought out side-to-side; this solution is quick and avoids an intra-abdominal anastomosis. However, neonates may lose a large amount of fluids and solute from this method; in selected cases, as an alternative to a peripheral line a central venous catheter is scheduled, both for nutritional and medical purposes. Several alternatives have been described: distal ileostomy with end-to-side ileal anastomosis (Bishop–Koop), which is termed 'distal chimney enterostomy'; proximal chimney enterostomy is the Santulli procedure, with a proximal ileostomy with end-to-side ileal anastomosis.

The enterostomy is closed between 7 and 12 days after surgery by an end-to-end anastomosis.

In a few selected cases, gastrostomy may be needed, but only when recovery of intestinal functions is expected to be delayed.

In general, the shorter the length of the intervention and the less extended the resection, the earlier the recovery of peristalsis and the less complicated and uneventful will be the postoperative care.

Complications include pulmonary infections, which is the most important one, with an incidence of at least 8–10%. Anastomotic leakage occurs for different reasons: a technical mistake, an insufficient blood supply, a distal unrecognized obstruction. Delayed recovery of peristalsis is another frequently observed complication and is due to abnormal stretching of the intestinal walls during fetal life. Total parenteral nutrition is the support of choice and a central venous catheter is mandatory in these situations.

PROGNOSIS

Meconium ileus may be an early indication of a more severe phenotype of CF. This was suggested by the significantly lower pulmonary function found in children with a history of meconium ileus compared to age- and sex-matched children who did not have meconium ileus.[28] The complicated form is susceptible to a greater number of long-term surgical complications, including especially small bowel obstructions and blind loop syndromes. Long-term complications in neonates affected by uncomplicated meconium ileus who were non-operatively treated are never seen, and only mild and transient complications have been observed in newborns treated with minor surgical procedures, such as enterotomies and irrigations.

Survival of neonates with meconium ileus has improved over the last two decades because of neonatal intensive care, improved surgical techniques, and medical treatment. In general, an overall immediate survival of 90% is achieved using modern protocols, and nearly all deaths are pertinent to adolescents. Only few children die due to liver and/or septic complications. Deaths are mainly due to staphylococcal or Pseudomonas sepsis, primary or secondary to a pulmonary interstitial emphysema or to an aspiration pneumonia. In a large series reported and analyzed by Fuchs, only one child died because of the meconium ileus itself. More recently, different studies suggest that adequate initial nutritional and medical management of meconium ileus allows further quite similar nutritional and lung well-being compared with children affected by an early discovered and symptomatic CF.[29] In conclusion, even if meconium ileus is often associated with longer hospitalization, surgical procedures, high-risk infections, and sepsis, an early diagnosis of CF did not impair the long-term pulmonary outcome in these patients.[30]

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Meconium peritonitis

JOSE BOIX-OCHOA AND JOSE L PEIRÓ

INTRODUCTION

Meconium peritonitis is an aseptic peritonitis caused by spill of meconium in the abdominal cavity through one or several intestinal perforations which have taken place during intrauterine life. Extravasation of sterile meconium into the fetal peritoneal cavity causes an intense chemical and foreign body reaction with characteristic calcification. Often, the perforations seal before the infant is born. Gastrointestinal perforations that occur following birth, even though the gut still contains meconium, constitute an entirely different group of clinical problems and should not be included in the syndrome of meconium peritonitis.[1,2]

Meconium peritonitis was first reported by Morgagni in 1761 in *De sedibus et causis morborum*. Simpson[3] managed to find 25 cases in 1838 and it was Agerty[4] in 1943 who reported the first successful operation.

The estimated incidence of meconium peritonitis is currently 1:30 000.[5,6]

A review of the world literature up to 2004 revealed 1681 cases of meconium peritonitis with 946 survivors (Table 55.1). Previous collected series have made this task easier.[7–13]

In the last 15 years, continuing progress in prenatal diagnostic procedures and postnatal intensive care has decreased mortality rates to less than 10% in some series,[14,15] and in our last experience the mortality rate fell to 7.2%.

Table 55.1 Mortality rate in meconium peritonitis among 1681 cases reported in the world literature.

Years	Total	Survivors	Mortality (%)
Before 1952	100	8	92
1952–1962	102	19	81.4
1963–1968	145	51	64.8
1969–1988	752	375	50.1
1989–1995	210	150	28.6
1996–2004	374	343	8.3
	1681	946	56.3

The current authors' experience is based on 67 cases of pure meconium peritonitis that underwent surgical treatment. All of these patients presented with the classical picture of meconium peritonitis at laparotomy and had histological evidence of (1) meconium inclusions (Fig. 55.1) or reaction to foreign bodies, and (2) visible perforation or microscopic evidence of intestinal cicatrization.

ETIOLOGY

Intrauterine intestinal perforation may result from various causes. Patients with meconium peritonitis are divided into those with and without associated intestinal obstruction. In the case of meconium peritonitis without obstruction, there is no clear-cut explanation for the perforation. Various hypotheses, such as segmental absence of the muscular coats,[13] absence of the muscularis mucosa,[16] vascular occlusion,[17] and general hypoxia of the fetus in the perinatal period[18] have been put forward. None of these hypotheses has been substantiated. In the current authors' research with rats, it has been clearly demonstrated that all these findings

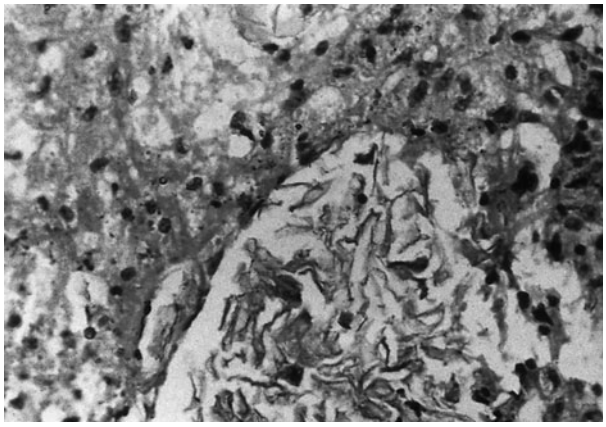

Figure 55.1 Granulomatous tissue with giant cells of foreign bodies related to meconial corpuscles.

are a consequence of meconium peritonitis and not primary etiology.[19] In the current authors' experience, intestinal atresia, intestinal volvulus, and meconium ileus constitute 94% of etiological factors (Table 55.2). Other causes include Hirschsprung's disease, meconium plug syndrome, congenital bands, internal hernias, Meckel's diverticulum, and rectal perforation.

The incidence of cystic fibrosis in infants with meconium peritonitis was previously reported to vary between 8 and 40%.[20]

However, in some cases it is impossible to find its etiology, in spite of pathological changes. The tabulation of the medical and perinatal reports demonstrated that 80% of these patients had neonatal anoxia and respiratory distress.

Labor research demonstrates the consequences of the hypoxia on the splanchnic area and blood distribution in the studied animals.[21,22]

If these findings are correlated with the current authors' studies, it can be postulated that there is diminished blood flow to the intestine of the hypoxic infant. The mucosa, which is very sensitive to ischemia, undergoes diminished mucin production and degenerative alterations. The proteolytic enzymes can now attack the bowel wall, which is normally protected by mucin. The consequence of this is a break in the mucosal integrity followed by perforation. Sometimes, the 'jamming' of this reflex mechanism prevents the return to normality and can cause such severe ischemia that it leads directly to a covered perforation. The less vascularized zones, and therefore the more exposed to ischemia and perforation, are situated in the ileocecal region and splenic flexure, where the current authors have found 60% of all idiopathic lesions.

PATHOLOGY

In the current authors' experimental work with rats, it has been shown that meconium gives rise to a peritoneal reaction with rapid fibroblastic proliferation enveloping the lesion. Later, foreign body granulomas and calcifications are seen. This reaction may be local or generalized, the parietal peritoneum having lost its sheen. The intestinal loops are intimately adherent structures with a fibrous tissue which is difficult to dissect, calcifications or meconial inclusions are disseminated, and the perforation is hard to identify. When the intestinal perforation does not cicatrize and there is a fibrinous reaction instead, the consequence is the formation of a cyst, the walls of which are formed of fibrin, meconium, and intestinal loops, intimately united. Such a cyst may occupy two-thirds of the abdomen (Fig. 55.2). The possibility of meconium spreading out by a hematologic or lymphatic route (via the brain or lungs) has been described.[23]

Lorimer and Ellis[24] described three major types of meconium peritonitis: fibro-adhesive, generalized, and cystic. Two other types which have been described are the healed form of meconium peritonitis and microscopic meconium peritonitis.

The fibro-adhesive type is the result of an intense fibroblastic reaction in response to the severe chemical peritonitis caused by the digestive enzymes in the meconium. This type produces obstruction by adhesive bands and the site of perforation is usually sealed off.

The cystic type occurs when the site of perforation is not effectively sealed and a thick-walled cyst is formed by the fixed intestinal loops.[25–28] This condition prevents communication of the perforation with the remainder of the viscera. Calcium deposits line the cyst wall. The formation of a pseudocyst represents an attempted intra-abdominal healing process to confine the perforation.

The generalized type usually occurs perinatally.[29–35] Calcified meconium is scattered throughout the peritoneal cavity and the bowel loops are adherent by thin fibrinous adhesions. In the current authors' experience, this is the most frequent type (74% of all cases).

The healed form of meconium peritonitis, presenting as an inguinal or scrotal mass, is clinically and pathologically of special interest. These patients usually present with no relevant recent clinical history, although the majority show a unilateral hydrocele at birth. Radiological studies of the scrotum and abdomen are usually helpful in making the diagnosis by demonstrating scrotal as well as peritoneal calcifications.[36–45] This combination is pathognomonic of meconium peritonitis.[37,45,46] In some cases, the peritoneal calcifications are the only symptomatology. In cases in which the diagnosis can be established clinically, no surgical intervention is necessary and, in the majority of these cases, the nodules regress spontaneously.[46–49] Microscopic examination of the resected specimen shows a fibrosis of the serous membrane, dissociation of the muscular layer, foci of

Table 55.2 Associated congenital malformations and operative findings.

Malformation	Total	Survivors	Mortality (%)
Intestinal atresia	38	34	10.5
Volvulus	12	7	41.6
Meconium ileus	11	7	36.3
Other	8	8	0

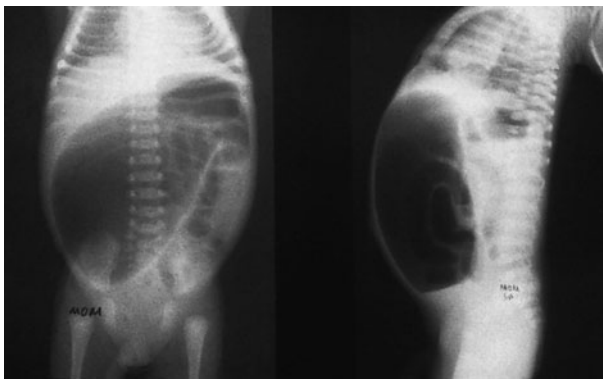

Figure 55.2 Typical roentgenogram of a giant meconium cyst. Prenatal ileal perforation was secondary to atresia of ileum.

calcification, and granulomatous lesions with foreign body giant cells.

There is another type of microscopic meconium peritonitis described by Tibboel *et al.*[50] without clinical or therapeutic significance. In the majority of cases it is a casual finding during laparotomy for other causes (Fig. 55.3). Many patients with this 'microscopic' type of meconium peritonitis present with atresia and the current authors feel that such an atresia should be regarded as scarring of the site of a perforation which must have occurred at a relatively early stage of fetal development. A careful microscopic examination of the visceral and parietal peritoneum will, however, reveal bile pigment and/or squamous cell remnants. The presence of these meconium components proves that a perforation must have occurred. The presence of collagen, calcium deposits, and giant cells surrounding meconium particles indicates that the peritoneal cavity must have contained meconium for a considerable length of time. Its etiology should be examined for intestinal perforations at an early stage of development, resulting in intestinal atresia induced by a vascular lesion. At other times, the perforation can achieve complete recovery and not lead to any significant tissue deterioration; the only remnant of this pathology is the microscopic meconium peritonitis as a casual finding and without clinical significance.

SYMPTOMATOLOGY AND DIAGNOSIS

The diagnosis of meconium peritonitis in the postnatal period is based on clinical and radiological, and ultrasonographic findings of intestinal obstruction, and occasionally one or more of the following: calcification, pneumoperitoneum, cyst formation, or ascites. The clinical symptomatology is that of any intestinal obstruction. A typical baby with meconium peritonitis is born with abdominal distension, or develops it soon after birth, and this is accompanied by bile-stained vomiting and failure to pass meconium. Occasionally, severe abdominal distension may result in dystocia or respiratory distress. Sometimes, cryptorchidism is the indication that the fetal abdominal pathology has prevented the physiological descent of the testicles. Pathognomonic of this is the appearance of a scrotal edema or hydrocele with retention of the testes and intrascrotal calcification.[51] X-ray and ultrasound[52] examination show the intestinal ileus, the ascites when it exists, the ground-glass appearance of the abdomen due to the meconium, and rarely the presence of a pneumoperitoneum, since the quick formation of adhesions prevents the intestinal gas from escaping.

Intra-abdominal calcifications are characteristic[53–55] and can easily be seen on plain abdominal films (Fig. 55.4). It is the current authors' belief that the origin of these calcifications may be the catalytic effect of the fatty meconial compounds on the precipitation of calcium salts. Proof of this is that in their investigations in laboratory animals with low serum levels of calcium, it has not been possible to reproduce calcifications. Faripor[56] is of the opinion that the pathogenesis of calcifications, after the analysis of seven cases with light microscopic observation, is undoubtedly in response to keratin debris. Keratin, however, cannot be the only source because of the presence of granulomas devoid of keratin. Due to the fact that some of these granulomas resemble gouty tophi, it may be as a result of inflammation caused by uric acid present in meconium. So early do the calcifications appear, that the prenatal diagnosis of meconium peritonitis is easily made on sonographic examination.[57–70] Diagnosis of associated pathology is of vital importance because of its repercussions in the immediate postoperative period.[71,72] Finkel and Slovis[73] indicate that the presence of intraperitoneal calcifications does not exclude but favors a diagnosis of cystic fibrosis in spite of the fact that they are scarcer than in the other types of meconium peritonitis. Detection of cystic fibrosis[74] is done by screening for the most common gene mutations and sweat chloride test, and also is recommended screening for congenital infections, including herpes simplex virus, cytomegalovirus, parvovirus B19, and toxoplasmosis.

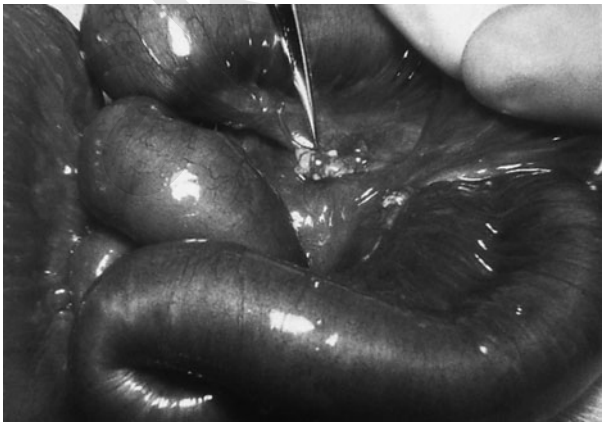

Figure 55.3 Causal finding of calcifications on an intestinal atresia without the clinical evidence and operative findings of meconium peritonitis. This case is not included in our material.

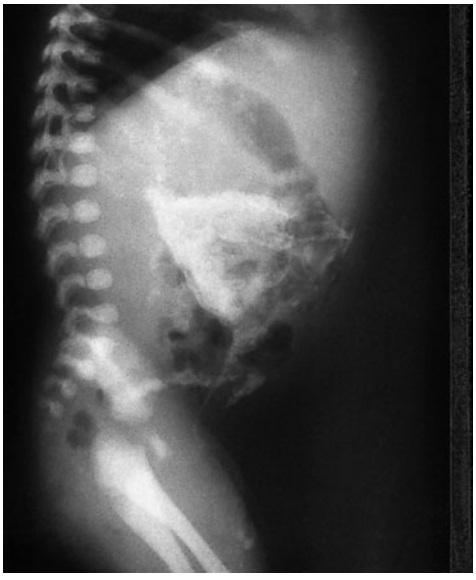

Figure 55.4 Pathognomonic abdominal calcification in a case of meconium peritonitis.

Newborns presenting with scrotal swelling with or without discoloration resulting from calcified meconium within the patent processus vaginalis have been described with increased frequency.[40,45,46]

Meconium peritonitis may result in a number of genital manifestations, including inguinal and scrotal or labial hydrocele containing meconium or calcifications and hard tumor-like scrotal masses.[75]

Early diagnosis is a decisive factor for the prognosis of these newborns, because the commencement of bacterial colonization of the meconium starts after birth. In a study carried out by the current authors in 134 normal newborns, meconium cultures were positive in 24% at 12 hours of life and in 86% at 72 hours.[19] On the other hand, the laboratory studies carried out by the current authors already demonstrated the existence of a 'meconium spreading factor' which accelerates and worsens the sepsis. Owing to this, it is not then surprising that early diagnosis is of paramount importance. In the current authors' series of 67 cases, the patients who were operated on after 36 hours of life had a mortality rate three times higher than those who were operated on during the first 24 hours of life (Table 55.3). Tibboel and Molenaar[12] reported a 91% mortality rate for patients operated on after 48 hours of life.

The natural history of meconium peritonitis diagnosed *in utero* is markedly different from that diagnosed in the newborn because some cases diagnosed prenatally normalize spontaneously during the gestational follow up. The normal ultrasound features are polyhydramnios, fetal ascites, intra-abdominal calcifications, and dilated intestinal loops.[76]

Recently, it was reported[14] that magnetic resonance imaging afforded higher prenatal diagnostic accuracy of meconium peritonitis than ultrasonography (57.1 versus 42%). Ultrasonography, however, is most widely used as a primary tool.

Zangheri *et al.*[15] proposed a prenatal classification that was divided into four grades of progressive severity, based on the number of pertinent ultrasonographic findings: grade 0, isolated intra-abdominal calcifications; grade 1, intra-abdominal calcifications and ascites, pseudocyst, or bowel dilatation; grade 2, two associated findings; and grade 3, all sonographic features.

Patients with a score greater than grade 1 have a high probability for urgent neonatal surgery and therefore should be transferred *in utero* to a tertiary center with available neonatal surgery.

The cases in grades 0 where initial prenatal ultrasound findings subsequently disappeared during gestation can deliver at term without any complication at 40 weeks of gestation.

For fetuses with suspected intrauterine meconium peritonitis, pathological sonographic findings detectable throughout the pregnancy, such as intra-abdominal calcifications, ascites, meconium pseudocyst, bowel dilatation, hydrops fetalis, and polyhydramnios, an elective preterm delivery by Cesarean section is recommended at a median gestational age of 35 weeks[77] in order to stop evolution of the disease and to operate on the patient earlier. In recent years, with improvement in antenatal diagnosis, parents can decide upon termination of the pregnancy in some cases of meconium peritonitis with other severe associated anomalies. Early detection is not associated with poor neonatal outcome, and selective termination is unnecessary.[78]

Dirkes *et al.*[20] reported that only 22% of fetuses with prenatal diagnosis of meconium peritonitis developed complications that required surgery, and the overall mortality rate in their series was 11%.

Table 55.3 Time of operation related to prognosis.

Time (hours)	Total	Survivors	Mortality (%)
<24 postnatally	25	23	8
24–36	31	26	16.1
36–48	6	4	33.3
>48	5	1	80
	67	54	19.4

TREATMENT

The indication for operation in newborns with meconium peritonitis is a clear sign of intestinal obstruction or perforation. The diagnosis of meconium peritonitis without intestinal obstruction or pneumoperitoneum does not constitute an indication for operation. Infants with neonatal meconium calcifications, meconium ascites with hydrocele, or calcified meconium found in the hernial sac do not require operation, but they have to be observed and feeding withheld for 48 hours. With an absence of clinical symptoms, enteral feeding can be started with caution, gradually progressing to formula. Antibiotic coverage is desirable. After a prenatal diagnosis, fetal paracentesis could sometimes be beneficial to reduce intra-abdominal pressure, to improve mesenteric vascular supply, and to remove inflammatory debris.[79]

Surgical treatment

All the conditions for the preparation of the newborn for surgery, such as monitoring for vital signs, control of temperature and measures for impeding its loss and ambient temperature in the operating theater, should be adhered to. An i.v. cannula should be placed for i.v. fluids. Blood should be cross-matched and prophylactic antibiotics started.

Operative treatment

Based on our experience of 67 cases with a survival rate of 92.8% in the past 15 years, the current authors act according to the following protocol:

1. If the perforation is visible, do not try to suture it. Intestinal resection and end-to-end anastomosis is performed.

2. In cases of localized or generalized peritonitis, attempt the lysis of the adhesions only to discover the perforation or to relieve obvious obstructions. Only when necessary should an attempt be made to dissect the adhesions, since fibro-adhesive peritonitis disappears after 8–14 days; this has been confirmed in the current authors' patients who had the two-stage operation and in investigation with laboratory animals.
3. Once the etiology has been determined (atresia, stenosis, or meconium ileus), an attempt must be made to perform an end-to-end anastomosis according to Louw's technique[80] if the condition of the patient and the difference in the intestinal calibers allow it.

Rehbein's two-stage operation[9] (exteriorization followed by laparotomy and anastomosis) is used only if the patient's condition is very serious, or if the existing peritonitis can endanger the suture line, or when there are great differences in caliber of the two loops of bowel. The anastomosis is performed 2 weeks later, if the newborn's general status allows the second stage of the operation. During the interval between the two operations, enteral and total parenteral nutrition are indispensable for maintaining the newborn in the best condition as well as the stimulation of the distal portion with the contents of the proximal end. The two-stage operation offers a series of advantages that should always be considered by the surgeon:

- Rapid solution of the surgical problem.
- It allows the surgeon to deal with the peritonitis which would endanger the suture in a one-stage operation.
- It allows recovery of the general state of the patient with the increase of energy reserves by means of parenteral nutrition and antibiotic therapy.
- It allows time for the disappearance of bowel adhesions and the normalization in caliber and absorptive function of the intestinal mucosa by means of the growth stimulation offered by perfusion of the enteral diet through a soft silicone feeding tube in the distal portion.
- It allows the maturation of the neuroendocrine system.

The two-stage operation has been associated with a lower mortality rate in the current authors' series when compared with the one-stage operation (7.2 versus 22%).

When faced with a meconial cyst, in view of the small number of successful cases published,[24,81–83] the current authors always perform decortication with great care and a two-stage operation.[84]

Another option is cyst drainage by ultrasound-guided punction and later laparotomy. A drainage procedure was always accompanied by supportive treatment of decompression, broad-spectrum antibiotics, and parenteral nutrition. Tanaka *et al.*[85] reported two cases of cystic meconium peritonitis which initially underwent emergency percutaneous drainage with ultrasonic guidance under local anesthesia. They found that such procedure is safe and effective in decompression of gastrointestinal tract and prevention of bacterial infection. They recommended cyst drainage just after birth and elective surgery later based on the general condition of the baby. During the second operation, the general condition is more stable, the adhesions will be less, the identification of the bowel loops easier, and the bleeding minimal.[86]

To summarize, the current authors are convinced that the low morbidity rate achieved by them is due to the planning of the operation in two stages, whenever faced with the slightest doubt as to the probable success of a primary anastomosis.

With early diagnosis, the advances in surgical techniques, and postoperative treatment, current survival of the patients with meconium peritonitis is near to 100%.[87]

COMPLICATIONS

Among the postoperative complications, adhesion ileus is the most frequent. In the current authors' series of 67 patients, seven developed adhesion ileus, five had anastomotic leakage, two had necrosis of the ileostomy stump, and one had an enterocutaneous fistula. There were 13 deaths in the series, seven directly attributable to lung complications in patients with cystic fibrosis. The other six patients died of sepsis. Gentle and delicate operative manipulation is required to reduce the morbidity.

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56

Duplications of the alimentary tract

ALAN MORTELL AND PREM PURI

INTRODUCTION

Duplications of the alimentary tract are rare spherical or tubular structures which can occur anywhere in the tract from mouth to anus.[1–3] Ladd,[4] in 1937, introduced the term 'alimentary tract duplication' in the hope of clarifying the nomenclature which had previously included descriptive terms such as enteric or enterogenous cysts; giant diverticula; ileal, jejunal, or colonic duplex, an unusual Meckel's diverticulum. Ladd proposed that the unifying term 'alimentary tract duplications' be applied to congenital anomalies that involved the mesenteric side of the associated alimentary tract and shared a common blood supply with native bowel.[4] Most duplications might indeed be called simply 'enterogenous cysts', since in only very few cases is there an actual doubling of the alimentary tract and these are therefore deserving of the name 'duplication'.

EMBRYOLOGY

Numerous theories have been developed to account for the multitude of gastrointestinal (GI) tract duplications. In a comprehensive review of gastrointestinal duplications, Stern and Warner[1] outlined the most widely held theories regarding GI duplication.

Embryologically, duplications have been categorized into foregut, midgut, and hindgut types.[1] Foregut duplications include the pharynx, respiratory tract, esophagus, stomach, and the first portion and proximal half of the second portion of the duodenum. Midgut duplications include the distal half of the second part of the duodenum, the jejunum, ileum, cecum, appendix, ascending colon, and proximal two-thirds of the transverse colon. The hindgut is composed of duplications of the distal third of the transverse colon, the descending and sigmoid colon, the rectum, anus, and components of the urological system. In one series, 39% of duplications involved the foregut, whereas 61% represented duplications of both mid- and hindgut.[5]

Partial twinning

Certain duplications appear to represent partial twinning, particularly the tubular duplications of the terminal ileum and colon.[6–10] There is a wide spectrum of abnormalities, from complete twinning of the lower trunk and extremities to mere doubling of the lumen of hindgut structures. These lesions are often associated with duplication of the lower urinary tracts.[11–13] Many rare examples of abortive cephalic twinning have also been described.[14] When there is complete doubling of the colon, one or both lumens may open as a fistula into the perineum or into the genitourinary (GU) tract, and may be associated with an imperforate anus. Doubling of the anus, vagina, and bladder have all been detailed and often can be associated with other severe deformities, such as double spines or two heads.

Split notochord

The most satisfactory of several theories of the origin of GI duplications is that relating to the development of the neurenteric canal. Saunders,[15] in 1943, noted that thoracic duplications are frequently associated with abnormalities of the cervical and thoracic vertebrae. These duplications may be attached to the vertebral bodies or connected to the spinal canal. These findings gave rise to the Bentley and Smith 'split notochord theory'.[16–18] The embryo initially has two layers: ectoderm and endoderm. Mesoderm forms between the two but for a short time these two layers remain adherent. A transient opening (the notochordal plate) appears, connecting the neural ectoderm with the intestinal endoderm. This notochordal plate normally migrates dorsally and becomes 'pinched' off from the endoderm by the ingrowth of mesodermal cells from each side. If the notochordal plate fails to migrate as a result of adhesions to the endodermal lining, the spinal canal cannot close ventrally and a tract resembling a diverticulum is established with the primitive gut. This tract may remain open, leaving a fistula between the gut and the spinal canal, or close leaving only a fibrous tract.

However, in the majority of cases it disappears completely, leaving only the duplication of the GI tract. This theory explains the formation of thoracic and caudal duplications, which may be associated with vertebral anomalies. However, the absence of spinal defects in many alimentary tract duplications makes this theory less tenable as a unifying model of their origin.

Embryonic diverticula and recanalization defects

In a study on human (4–23 mm) and animal embryos, Lewis and Thyng[19] found tiny bands of intestinal epithelium protruding into the subepithelial connective tissue. The identification of numerous diverticula in the intestines of embryos, led to the proposal of an extension of the diverticula into duplications. The frequent ileal position of these diverticula is congruous with the frequent ileal location of human GI duplications. Although this theory could explain duplications in the absence of spinal anomalies, it fails to account for the variability of the mucosal lining and specifically for the frequency of heterotopic gastric mucosa. Furthermore, the diverticula identified in this pathological series were located throughout the bowel circumference as opposed to the general locations of duplications on the mesenteric side of the intestine.

The occurrence of tubular duplications would also not be explained by this theory (Fig. 56.1). Bremer[20] believed that abnormal recanalization of the intestinal lumen after the solid stage of development of the primitive gut in the sixth to seventh week of gestation resulted in duplications.[21] Such duplications, however, would not be confined to the mesenteric side of the bowel. Also opposing this theory is the finding that the solid stage of development in the human does not usually extend beyond the duodenum.[21]

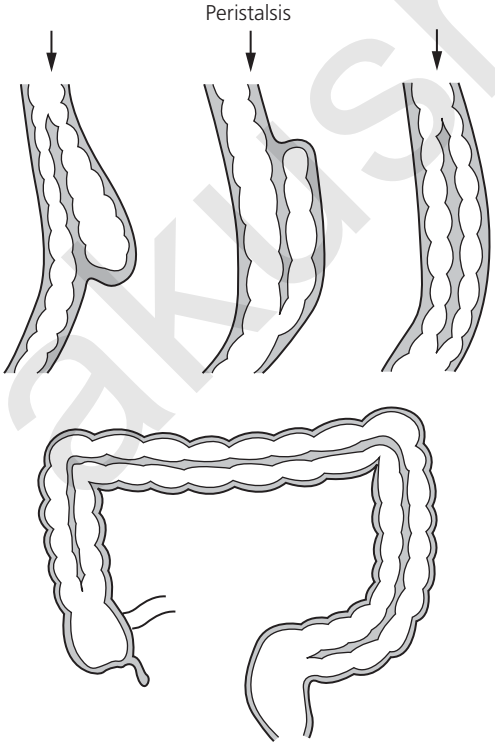


Figure 56.1 Various types of tubular duplications of the intestine.

In 1961, Mellish and Koop[22] proposed an environmental theory, which held that trauma or hypoxia could induce duplications and twinning in lower orders. Based on the work of Louw, they concluded that vascular insufficiency could lead to the recognized GI duplications seen in humans.[23] In addition, intrauterine vascular accidents are known precipitators of other congenital anomalies, such as gastrointestinal atresias.

PATHOLOGY

Duplications are hollow structures that involve the mesenteric side of the associated GI tract.[24] They tend to share a common muscular wall and blood supply with its mature bowel, although each has its own separate lining.[25] They are usually isolated lesions and are more often cystic than tubular with a variable size. The lesions have a muscular coat in two layers and are usually lined with epithelium similar to that found in the associated portion of the alimentary tract. The duplications, however, are occasionally lined with heterotopic epithelium; the presence of colonic mucosa has been described at the base of the tongue and sinuses lined with gastric mucosa have been found near the anus.[26] Duplications containing gastric mucosa are at risk of peptic ulceration, perforation, and hemorrhage.[27] Patches of ectopic gastric mucosa along the GI tract may represent the mildest manifestation of duplication abnormalities. Ectopic pancreatic tissue has been reported in duplications of the stomach, ileum, and colon.[28] The contents of a duplication vary with the type of epithelial lining of the structure, the presence or absence of a communication with the proximate part of the GI tract, and the absence or necrosis of the duplication wall. If an opening is present, the duplication contents will be similar to that of the adjacent intestinal tract. Communication between the two structures is rare and the cysts usually contain chyle or mucus. Multiple duplications can occur in the same patient.[26,29,30] There is an increased incidence of other associated anomalies such as vertebral anomalies,[31] myelomeningocele,[32] imperforate anus,[33] malrotation of the bowel,[34] genital anomalies,[30] polysplenic syndrome,[35] and duodenal atresia.[36] No genetic tendency has been demonstrated.

Malignant carcinomatous changes are rare complications of intestinal duplications. Adenocarcinomas arising from small bowel as well as large bowel duplication cysts have been reported in adult life.[37–40]

INCIDENCE

Duplications of the alimentary tract are rare. Table 56.1 summarizes the larger published series of duplications.

Table 56.1 Incidence and locations of duplications.

Author	Total No.	No. neonates	Cervical	Mediastinal	Thoraco-abdominal	Gastric	Duodenal	Jejunal-ileal	Colonic	Rectal
Gross[41]	68	20	1	13	3	2	4	32	9	4
Sieber[29]	25[a]	–	–	5	–	4	2	16	5	–
Grosfeld *et al.*[42]	20	–	–	4	–	1	–	9	4	–
Favara *et al.*[30]	37[b]	–	3	4	2	3	4	20	4	–
Wrenn[26]	22[c]	–	–	3	2	1	2	12	3	3
Lister and Zachaary[33]	32	24	–	3	–	1	–	20	5	3
Holcomb *et al.*[28]	96[d]	36	1	20	3	8	2	47	20	–

[a]One patient had two, one had three, and one had five duplications.
[b]One patient had three duplications.
[c]Two patients each had two duplications.
[d]Ninety-six patients had 106 atresias.

In many cases the numbers of patients reported represent up to 40 years' work in these centers. Only a small percentage of the total cases reported actually present in the neonatal period.[40–44]

ESOPHAGEAL DUPLICATION

The esophagus is a relatively common site for foregut duplications (19%) with the majority being intramural, non-communicating cystic structures related to the right side of the esophagus. Patients often present late in childhood as they cause relatively few symptoms; however, cervical esophageal duplications can cause significant respiratory distress requiring urgent surgery. Some lesions do not share a common wall with the esophagus and can be easily removed through open or minimally invasive techniques.[45] Plain x-rays may show an air or fluid-filled structure adjacent to the esophagus, although this is not usually enough to confirm the diagnosis. Contrast studies can provide useful information regarding the mass effect of the lesion and whether or not their lumens communicate. Ultrasound and computed tomography (CT) are useful for establishing a diagnosis and also for ruling out multiple lesions, which can be present in 10–20% of cases. Technetium scans (^{99m}Tc) may reveal the presence of heterotopic gastric mucosa in the case of gastrointestinal bleeding.

Treatment

The surgical approach depends largely on the location of the cyst. Cervical esophageal duplications can be removed through a supraclavicular incision, with particular attention being paid to the vagus and phrenic nerves as well as the thoracic duct to avoid unnecessary damage. Intrathoracic duplications are resected through a standard posterolateral thoracotomy or a thoracoscopic approach.[46] A chest drain may be left *in situ* but is not always required.

THORACO-ABDOMINAL DUPLICATION

Thoraco-abdominal duplications are rare representing only 4% of all gastrointestinal duplications. They often lie separate from the esophagus, more often on the right than the left side, but may be attached to other important structures, such as the aorta, azygous vein, and tracheobronchial tree. They frequently lie in the posterior mediastinum and pass through the diaphragm to communicate with the stomach, duodenum, or small bowel. The imaging studies employed are similar to those for esophageal duplications, with special attention being paid to imaging of the vertebral column/spinal cord for a possible intraspinal component. CT and/or magnetic resonance imaging (MRI) are particularly useful in this regard, especially if neurological symptoms of spinal cord compression or bony spinal abnormalities are present.

Treatment

These challenging duplications require resection of the thoracic and abdominal components through two different open procedures or alternatively they may be dealt with by a combined thoracolaparoscopic approach.[47] Although the abdominal portions are often asymptomatic, the thoracic components can cause symptoms as a result of mass effect on the lungs and airway. The presence of gastric mucosa within the thoracic duplication cyst can lead to peptic ulceration and possible erosion into the lung parenchyma, presenting with hemoptysis. This complication may require a lobectomy. Once the lesion is mobilized in the thorax, it is freed from the posterior aspect of the diaphragm prior to mobilization and removal of the abdominal component.

GASTRIC DUPLICATION

The stomach is one of the less common sites of duplications, accounting for only 9% of all GI duplications. Over 60% of

cases are diagnosed during the first year of life, with a significant number (40%) appearing in the neonatal period by the finding of a palpable cystic mass in the upper abdomen accompanied by vomiting and weight loss.[48,49] Rarely, they undergo peptic ulceration and if the cyst communicates with the stomach, hematemesis and/or melena may be the presenting feature. Rarely, a carcinoma may arise within a gastric duplication cyst.[50] Gastric outlet obstruction, mimicking hypertrophic pyloric stenosis, is also a common presenting feature of this duplication.[51] Gastric duplications occur twice as often in females as in males.[24] Gastric triplication, although rare, has been described in the literature.[52]

It is often difficult to make a preoperative diagnosis of gastric duplication. Plain x-rays are usually negative and therefore unhelpful. A contrast meal may show compression of the stomach, usually along the greater curvature. Contrast may delineate a connection between the stomach and duplication, but only in a small minority of cases. In these cases, contrast may be retained in the duplication long after the remainder has passed from the GI tract. Ultrasonography has been shown to be useful in the diagnosis of gastric duplications. The vast majority of gastric duplications are located in the greater curvature (Table 56.2). Occasionally these are pedunculated,[32,53] but most are closed spherical cysts or tubular structures.

Associated anomalies occur in 3% of gastric duplications.[54] The most common is another cyst, usually of the esophagus.[55] Dual duplications of the stomach and pancreas have been reported.[56,57] These are thought to arise from an error in rotation of the ventral pancreatic anlage.

Table 56.2 Location of duplications of stomach in 87 reported cases.

Location	No. cases
Greater curvature	55
Lesser curvature	7
Anterior wall	9
Posterior wall	9
Others	7

Treatment

The management of gastric duplications is surgical because of the high incidence of complications due to obstruction, bleeding, or peritonitis. As most duplications occur in the greater curvature, a wedge of stomach is excised together with the cyst and the gap closed with a single layer of horizontal inverting mattress sutures (Fig. 56.2). Partial gastrectomy should be avoided in children if possible, and if necessary only 25–30% of the stomach should be resected because of the associated long-term complications.

When extensive resection of the adjoining stomach is impractical, as with the long tubular duplications of the greater curvature (Fig. 56.3a), the main part of the duplication is excised and the mucosa stripped off (Fig. 56.3b). The remaining seromuscular cuff can be sutured over the denuded area (Fig. 56.3c) after checking that the common wall between the stomach and duplication has not been perforated, by insufflating the stomach with air. The use of a stapling gun to divide the common wall along the length of the greater curvature has also been described.[58]

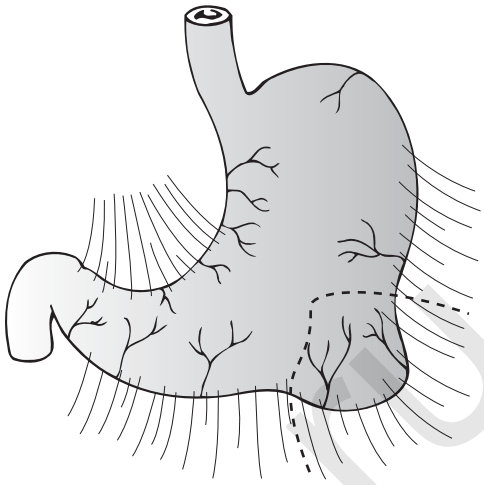


Figure 56.2 Gastric duplication located at the greater curvature. A wedge of stomach is excised together with the cyst and the gap closed with a single layer of horizontal inverted mattress sutures.

PYLORIC DUPLICATIONS

True pyloric duplications are extremely rare, with very few being reported in the English literature and most of these presenting within the first week of life.[48,59–62] They simulate the symptoms and signs of hypertrophic pyloric stenosis.[63] Vomiting, weight loss, and a palpable abdominal mass are the main findings. There are certain physical features which are consistent with duplication: the mass is usually large and smooth, in contrast to the smaller and often more mobile 'olive' mass in hypertrophic pyloric stenosis.[63]

Because of the non-specific physical examination, radiographic procedures are essential for diagnosis. Plain film x-rays may show signs of gastric outlet or duodenal obstruction with a lack of distal bowel gas,[64] or rarely calcification within a cyst wall.[65] Ultrasonography may demonstrate an inner echogenic mucosal layer and outer hypoechoic muscular layer differentiating the duplication from a mesenteric cyst. Contrast studies may help differentiate the duplication from pyloric stenosis. If there is a clinical concern, then preoperative endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), or magnetic resonance cholangiography/pancreatography (MRCP) should be performed to evaluate the involvement of the biliary/pancreatic ducts.

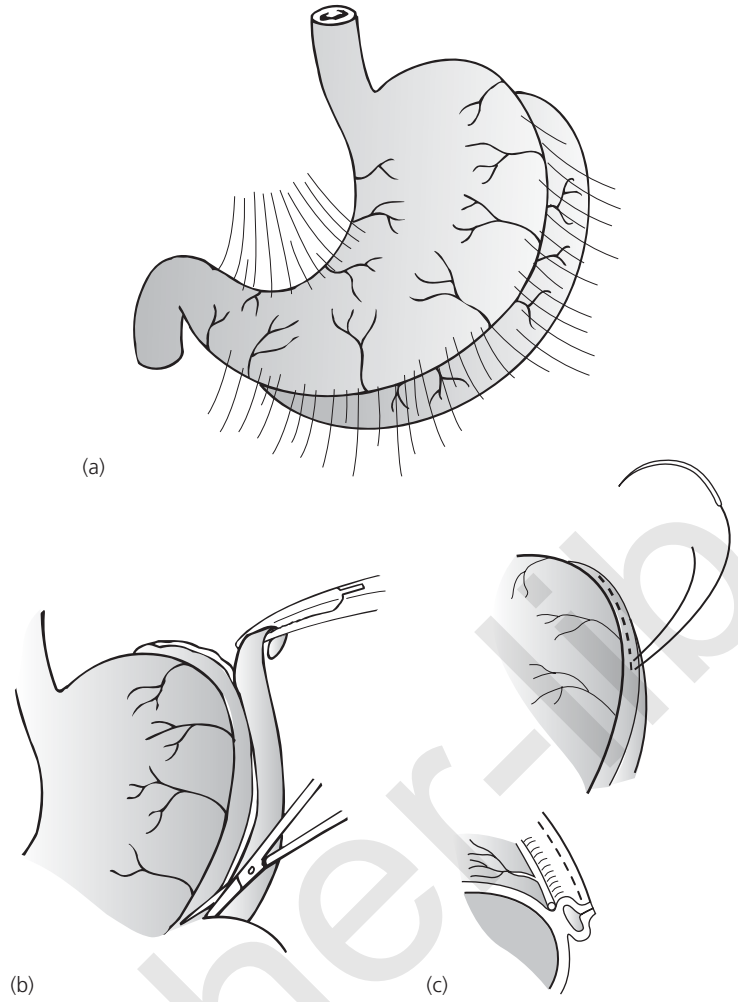


Figure 56.3 (a) Tubular duplication of the greater curvature of the stomach. (b) The mucosa is stripped from the entire length of the duplication. (c) The seromuscular cuff is closed over the denuded area.

Treatment

Of the cases of pyloric duplication reported, the majority underwent simple surgical excision after opening the pyloric canal longitudinally. The pylorus was then closed transversely with no complications.[48,58,61] However, if there is a risk of damage to pancreatic or bile ducts an acceptable alternative is to drain the cyst into the duodenum or into a Roux limb of upper small bowel.

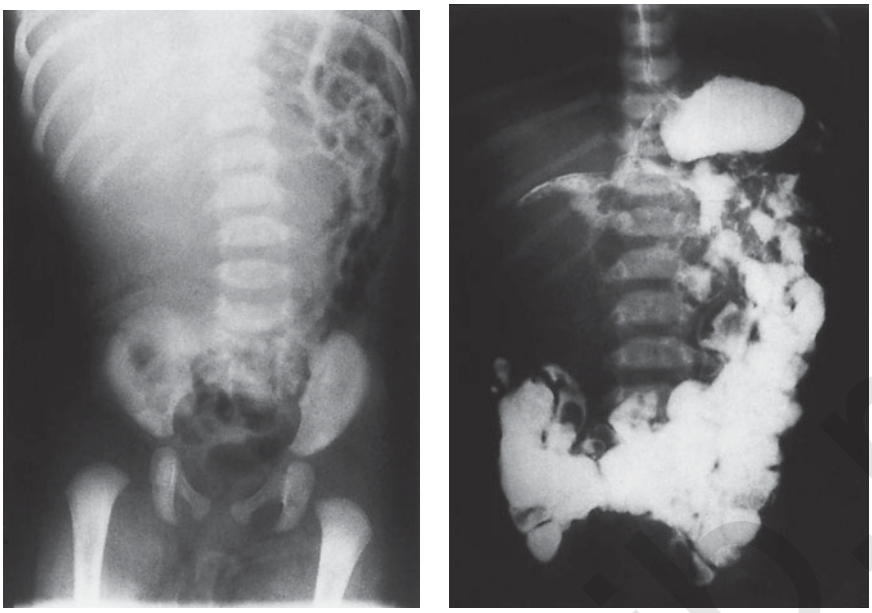
DUODENAL DUPLICATIONS

The duodenum is involved in only 4% of all duplications. They are often behind the duodenum and do not communicate with the bowel lumen.[66] Vomiting secondary to partial or complete duodenal obstruction and an upper abdominal mass are present in the majority of cases.[67] They may present with hematemesis or perforation, as gastric mucosa is present in 10–15% of cases.[68] Alternatively, because of their location, they may present with biliary obstruction or pancreatitis. If the duplication is of sufficient size, it may appear on plain x-rays as a large opacity in the right side of the abdomen displacing the intestine (Fig. 56.4a). Contrast studies will show the duodenum to be displaced upwards and a 'beak-like' projection due to compression of the duodenal lumen by the duplication (Fig. 56.4b).[69] Contrast entering into the cyst confirms the presence of a luminal communication. Ultrasonography may show a cystic lesion below the liver and a classical double-layered appearance or 'muscular rim' sign (Fig. 56.5a).

Treatment

In view of the occasional occurrence of gastric mucosa in the duplication cyst, these lesions should, if possible, be dissected from the duodenum and excised, closing the resulting defect in the duodenum in two layers. Intraoperative cholangiography will help determine the relationship of the cyst to the biliary and pancreatic ducts.[70]

If the lesion is extensive (Fig. 56.5b), or if eversion of the cyst may compromise the biliary system, then cystoduodenostomy may be performed.[71] The cyst may also be only partially excised, stripping off all the lining mucosa and leaving the part of the cyst which is adherent to the duodenum or pancreas.[70]



(a) (b)

Figure 56.4 (a) Supine view in this 1-day-old baby showing a large soft tissue mass in the right upper and central abdomen displacing bowel loops to the left. (b) Barium study demonstrates beak-like projection of proximal duodenum superiolaterally characteristic of duodenal duplication cyst.

DUPLICATIONS OF THE SMALL INTESTINE

Small bowel duplications constitute 45% of all alimentary tract duplications.[72] The vast majority of small bowel duplications are spherical cysts in the terminal ileum. Jejunal and ileal cysts are found on the mesenteric side of the bowel, sharing a common muscularis with the adjacent bowel. They may cause obstruction by external pressure on the lumen,[73] by acting as a lead point for intussusception[74,75] or occasionally by causing a volvulus.[76]

Tubular duplications have the same features as the cystic variety, but they communicate with the normal lumen of the intestine and are more likely to contain gastric mucosa.[77] Pancreatic mucosa has also been described in these duplications. Tubular duplications can range in length from a few millimeters to the whole length of the small bowel.[78,79] The communication may be at the cephalad end, which will cause the duplication to become grossly distended with intestinal contents, or if at the caudal end, will allow the duplication to drain freely. Communication at several different points may be present.

Hemorrhage occurs most often in tubular duplications, but perforation has been reported as well.[80,81] Plain abdominal x-rays may show non-specific displacement of bowel gas shadows by the cyst, or signs of intestinal obstruction or perforation. Ultrasonography can help to differentiate between a mesenteric and a duplication cyst. A contrast meal may demonstrate displacement of the bowel (Fig. 56.6).

Treatment

Cystic duplications are relatively straightforward to deal with. Resection of the cyst with adjacent bowel (Fig. 56.7a) is performed; the two ends of the bowel are anastomosed with one layer of horizontal inverting mattress sutures and the mesenteric defects are closed (Fig. 56.7b).

Tubular duplications, if very short, can be resected as in a cystic lesion, but the majority involve a considerable length of small bowel and much ingenuity and patience may be required to meet the needs of any one particular case.

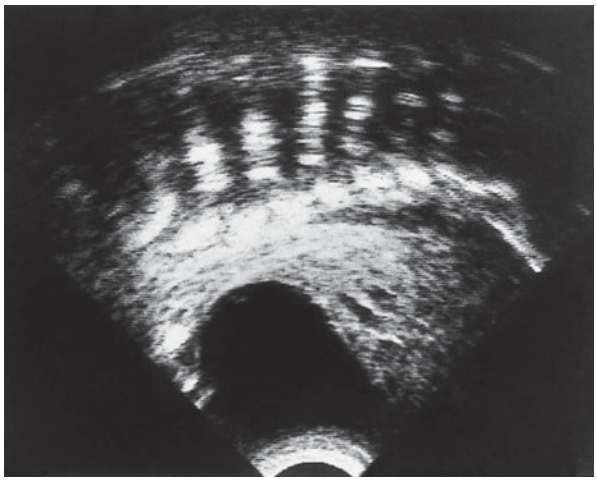
Wrenn[82] suggested coring out the mucosal lining of a long tubular duplication through multiple seromuscular incisions in the wall of the duplication.

Norris *et al.*[83] employed a technique first described by Bianchi[84] for bowel lengthening, to separate two leashes of blood vessels passing to each side of the small intestine (Fig. 56.8). Using this method, the entire mucosa and almost the entire muscle wall can be excised. The remaining cuff of muscle wall can be oversewn, preserving the blood supply to the normal bowel.

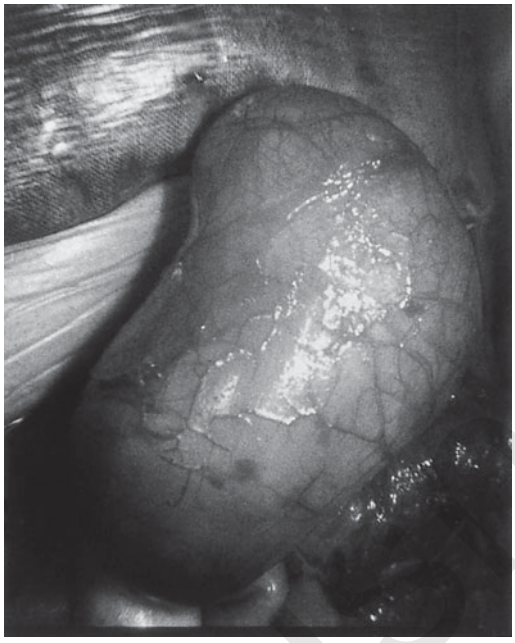
Bishop and Koop[85] described the techniques of anastomosing the distal end of the duplication to adjacent normal intestine, allowing free drainage of the contents. Malignant change in the mucosa has, however, been described as a late complication of this procedure.[86] Whichever technique is utilized, it is essential that the junction of normal and duplicated bowel is resected since heterotopic gastric mucosa is frequently present in tubular intestinal duplications.

COLONIC DUPLICATIONS

Colonic duplications are among the rarest reported. They are frequently diagnosed in infancy and some reports suggest a female predilection. McPherson *et al.*[87] proposed a simple classification of colonic duplications: type I mesenteric cysts, type II diverticula, and the more common type III tubular



(a)



(b)

Figure 56.5 Duodenal duplication. (a) Ultrasound shows the cystic lesion below the liver. (b) Large duodenal duplication cyst.

colonic duplication. A number of etiological factors may be involved in the development of the 'double colon'. The most valid theory suggests division of the hindgut into two parts at a stage during which the anlage possessed a multi-organ developmental potential.[87,88] The hindgut anlage normally forms the distal ileum, colon, rectum, bladder, and urethra. Division of the anlage at the same initial stage could therefore be responsible for duplication of the lower urinary tract as well.[87]

Simple cysts (type I) and diverticula (type II) occasionally result. They can be identified on plain x-rays or on contrast studies. A contrast enema may demonstrate a communication between the colon and duplications in types II and III. Associated genitourinary and lumbosacral spinal abnormalities can also be demonstrated on the appropriate radiographic studies, particularly when dealing with type III

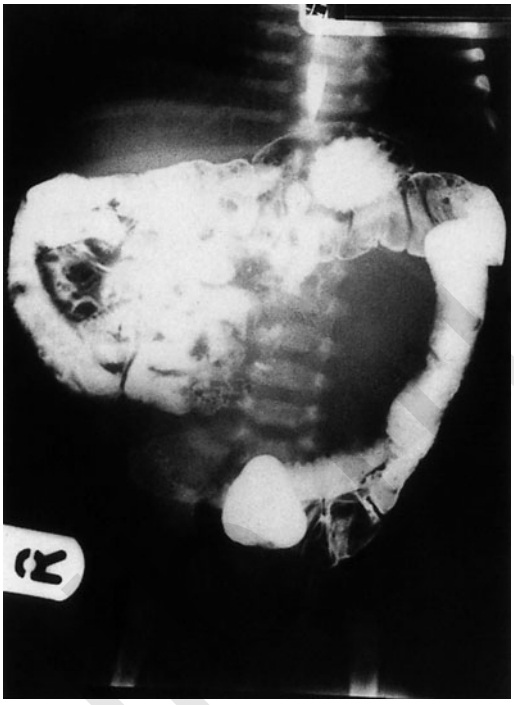
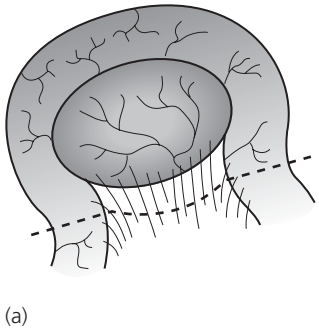


Figure 56.6 Barium study demonstrates a space-occupying lesion displacing bowel. At laparotomy a large ileal duplication cyst was found.



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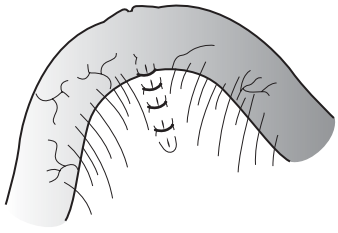

(b)

Figure 56.7 Cystic ileal duplication. (a) Resection of the cyst with adjacent bowel is performed. (b) The two ends of the bowel are anastomosed.

duplications. Isotope scans are rarely of benefit with colonic duplications, as they contain only colonic mucosa.

Complete duplication of the colon is usually asymptomatic in the neonatal period unless duplication of the anus or an abnormal orifice, in addition to the normal orifice in the perineum, is present. One or both orifices at the distal end of the colon may end as rectovaginal or recto-urethral fistulas.[88]

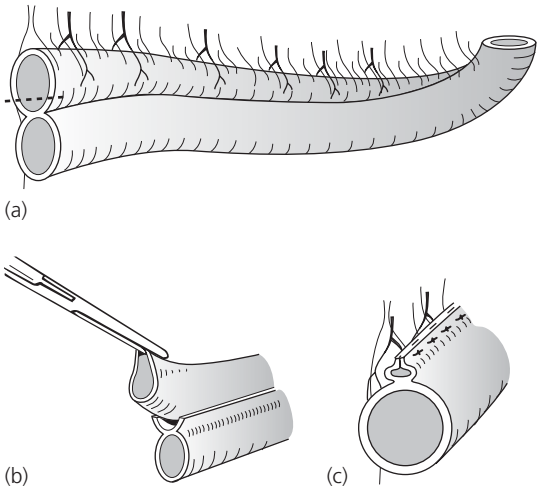

Figure 56.8 Tubular duplication of small bowel. (a) The main part of the tubular duplication is excised. (b) The mucosa is stripped from the entire length of the duplication. (c) The sermuscular cuff is closed over the denuded area.

Treatment

Surgery for colonic duplication is rarely indicated in the neonatal period unless there are complications, e.g. obstruction or an associated imperforate anus. All cystic and most tubular colonic duplications can be dealt with by simple resection and anastomosis utilizing a single-layer extramucosal technique. With rare total colonic duplication, the principal aim of management is to end up with two colons draining through one anal orifice. If one part of the colon has already reached the perineum, then the other colon is divided and anatomosed to its partner. This can be achieved by using a linear stapling device. If neither colon reaches the perineum, then a formal pull-through procedure will be required. Neonatal management in any of these situations is confined to fashioning a defunctioning colostomy to drain both colons.

RECTAL DUPLICATIONS

Approximately 70 cases of rectal duplications have now been reported in the literature, comprising only 5% of all gastrointestinal duplications. More than 50% of these have been examples of hindgut twinning.[89]

The embryogenesis of rectal duplication cysts is attributed to a 'pinching off' of a diverticulum in the 20–30 mm embryo,[90] in contrast to the 'caudal twinning' which occurs in the 10 mm embryo and is associated with complex hindgut anomalies.[91,92]

Rectal duplications often present in the neonatal period with a fistula or perineal mucosal swelling extending to the perianal area. Presentation of the cysts depends on: (1) size and their mass effect, (2) fistulas, (3) infection, (4) ulceration if they contain gastric mucosa, and (5) malignancy.[93] The duplication cyst usually forms in the retrorectal space and contains colorless mucus, which can become infected. They frequently present in 20–45% of cases.[89,90] No cases of a fistula between the rectum and urinary tract have been described. Malignant degeneration has been reported in the rectal duplication from the fourth decade onwards.[94,95]

Treatment

Treatment of the rectal duplication cyst is surgical excision or fenestration of the common wall. Depending on the anatomical variations, a transanal or transcoccygeal (Kraske) approach can be employed. For longer or more complicated cysts, a longer posterior sagittal incision will provide better exposure. As with other duplications, it is of prime importance to remove all mucosa in the duplication. The muscularis can be left *in situ*.

Associated anomalies such as presacral tumours (16%) and anorectal malformations (21%) are frequently described in the literature.[96] Management of these lesions may be difficult and often requires preoperative evaluation of both the gastrointestinal and genitourinary tract. Continence of both systems is imperative, and therefore, treatment strategies must be individualized based on the findings of each patient.

It is clear that duplications of the GI tract represent a diverse and complex group of anomalies. Small duplications in readily accessible areas (i.e. the small intestine) may be excised with adjacent bowel. In other locations, where resection would endanger adjacent structures, simple anastomosis between the cyst and normal intestine can be performed, provided that there is no gastric mucosa in the cyst. If bleeding has been a persisting complaint, the presence of gastric mucosa can be assumed. If resection is contraindicated, the lining mucosa may be stripped from the cyst, leaving the muscle wall *in situ*.

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57

Mesenteric and omental cysts

BENNO URE

INTRODUCTION

The first report on a mesenteric cyst was published by an Italian anatomist in 1507.[1] Since then, the origin and classification of mesenteric and omental cysts has been a matter of debate. Moynihan attempted in 1897 a differentiation of abdominal cysts on the basis of fluid content.[2] Serous cysts are characterized by a translucent, straw-colored fluid of low specific gravity. Their chemical composition is similar to plasma. In contrast, chylous cysts contain an opaque fluid of high specific gravity, with lipids and fat globules contributing to the fluid content. Subsequent attempts at a more appropriate classification of intra-abdominal cysts have been based on suspected etiology initially proposed by Beahrs *et al.* in 1950.[3] However, the etiology of many intra-abdominal cysts is questionable, rendering classifications of this type of limited clinical usefulness. A more appropriate classification, based on histologic findings, was proposed in 1987 by Ros *et al.*[4] This differentiation is applicable to all operative cases and can provide the basis for a more uniform evaluation of the clinical and pathologic characteristics of these cysts (Box 57.1).

Up to the present day, the terminology is still descriptive of anatomic location without information as to the specific histology or pathology of mesenteric, mesothelial, or omental cysts. Several authors suggested differentiating cystic lymphangiomas from mesenteric and omental cysts.[5,6] A lymphangioma wall shows endothelial cells, small lymphatic spaces, lymphoid tissue, and smooth muscle cells. Mesenteric cysts do not have lymphatic spaces and smooth muscles and the cells of their wall are cuboidal or columnar (Box 57.2).[7] All these cystic lesions are generally of isolated pathology with few reports of associated developmental anomalies.

The incidence of mesenteric and omental cysts is rare and has not been systematically determined in the general population. Large reviews have indicated a male predominance.[8]

Box 57.1 Classification of abdominal cysts[1,6,13]

- Embryonic/developmental
  - enteric
  - urogenital
  - dermoid
  - embryonic defects of lymphatics (retroperitoneal, mesenteric, and omental cysts)
- Traumatic/acquired
  - Hemorrhagic (sanguinous)
  - Ruptured lacteal
  - Chylous extravasation
- Neoplastic
  - benign (lymphangioma)
  - malignant (lymphangioendothelioma)
- Infectious
  - mycotic
  - parasitic
  - tuberculous
  - hydatid
  - cystic degeneration

SPECTRUM AND MORPHOLOGY

Lymphangiomas represent approximately 90% of the cysts encountered in the mesenterium and omentum of the neonate. They are characterized by multiple thin-walled cystic spaces with a distinct endothelial lining similar to that seen in the subcutaneous location. These lesions are presumed to be congenital, with an etiology secondary to proliferating lymphatic tissue without access to adequate drainage. Lymphangiomas appear most frequently in the mesentery of the small bowel and may be encountered in the mesocolon and

Box 57.2 Histologic classification of mesenteric/omental cysts[14]

- Enteric cyst
  - enteric lining
  - no muscle layer
- Enteric duplication
  - enteric lining
  - double muscle layer with neural elements
- Lymphangioma
  - endothelial lining
- Mesothelial cyst
  - mesothelial lining
- Pseudocyst (non-pancreatic)
  - no lining
  - fibrous wall

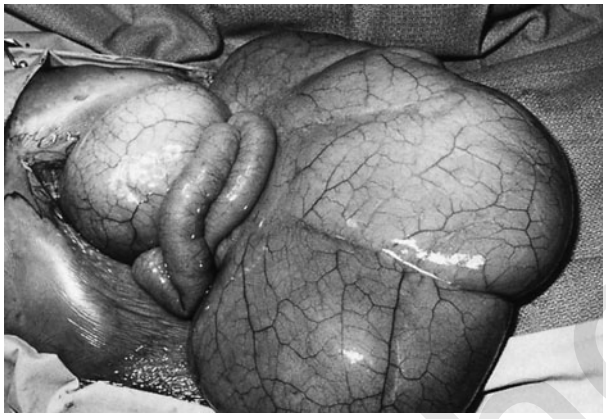


Figure 57.1 Chylous mesenteric lymphangioma.

omentum. Extension to the retroperitoneum has been frequently described.[8,9] Gross, solitary multiloculated, fluid-containing cysts are encountered, which can reach an enormous size (Fig. 57.1). The fluid may be serous or chylous with chyle being characteristic of a small bowel location and the associated high lymphatic fat content. Hemorrhagic fluid is not uncommon.

Mesothelial cysts are less common, but represent the majority of non-lymphangiomatous congenital cysts encountered in the omentum (Fig. 57.2). They may also occur within the mesentery. Mesothelial cysts are generally unilocular, serous-containing, and lined by mesothelium. They are thought to arise from incomplete fusion of the mesothelial leaves of omentum or mesentery.

Enteric duplication cysts are not included under the heading of mesenteric cysts, but should be mentioned due to their frequent neonatal presentation, mesenteric location, and occasional similarity in appearance (Fig. 57.3). Therefore, they should be included in the differential diagnosis of intra-abdominal cystic lesions in the neonate. These cysts may occur anywhere along the gastrointestinal tract as saccular or tubular unilocular lesions, usually within the mesentery adjacent to a normal intestine. Histologically, they are composed of all the layers seen in normal intestine and they share a common blood supply with the adjacent

Figure 57.2 Typical omental mesothelial cyst containing serosanguinous fluid.

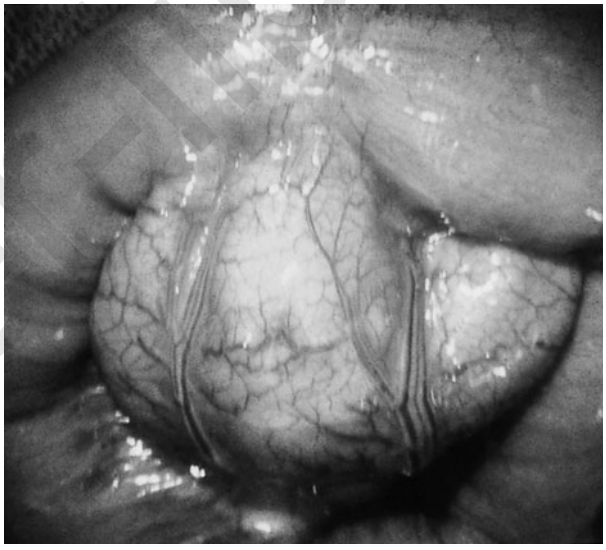


Figure 57.3 Saccular intestinal duplication simulating the appearance of a mesenteric cyst. Lesion distinguished grossly by common wall and blood supply shared with adjacent intestine.

intestine. Duplication cysts may contain mucous-producing cells.

CLINICAL CHARACTERISTICS

The cysts may be diagnosed *in utero* with the use of routine prenatal ultrasonography.[10] However, most series report mean ages of three to five years at presentation,.[11–13] and the age at diagnosis has gradually decreased over the years. Omental and mesenteric cysts may be an incidental finding, but more than half of these children present with acute clinical problems.

The symptoms of mesenteric or omental cysts are related to mechanical forces due to cyst location and size. The majority of children present with abdominal complaints, such as pain, vomiting, and distension (Table 57.1). Several

Table 57.1 Clinical presentation (281 children).[1–6,8,11–14,18]

Symptom	%
Pain	41
Mass	35
Obstruction	32
Distension	25
Miscellaneous[a]	23

[a]Failure to thrive, nausea, gastrointestinal bleeding, diarrhea, etc.

authors have suggested that the high incidence of symptoms in children versus adults may be related to the higher incidence of lymphangiomas in young individuals.[8,9] A palpable mass is the most common physical finding, but this may be apparent in only 60% of affected children due to the flaccidity and mobility of the cyst. The mass, if present, is generally smooth, not tender and mobile in character. Of the affected children, 50% or more will present with complications. Intestinal obstruction, either partial or complete, is frequent and usually due to compression of the adjacent intestine. Volvulus can occur around the cyst and result in infarction of the bowel with perforation, peritonitis, and shock.[14] Hemorrhage within the cyst secondary to expansion or erosion may lead to rapid enlargement and pain.[15] Torsion of the cyst itself, rupture, and urinary obstruction have been reported.[15,16]

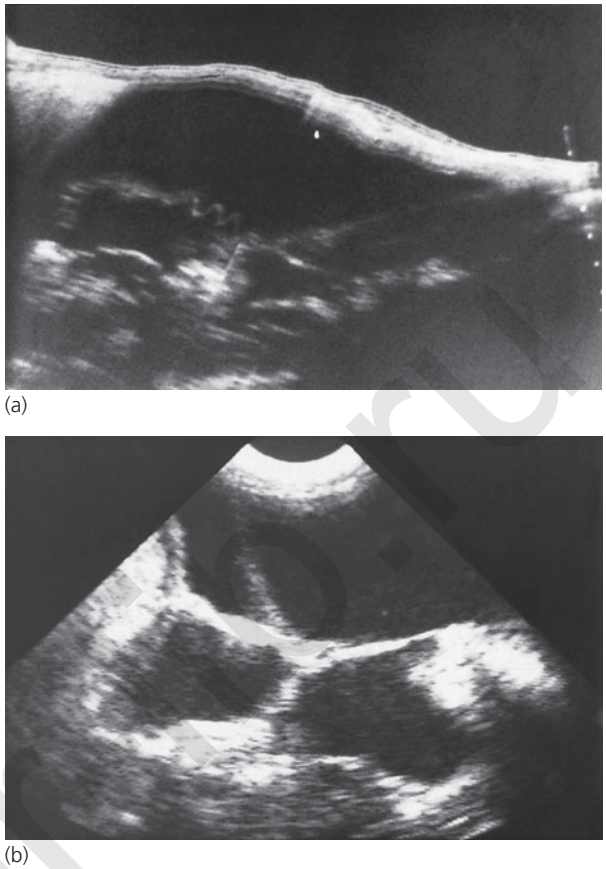
DIAGNOSIS

In most cases, a definitive preoperative diagnosis is not possible. Laboratory evaluation is pertinent only to complications which may be associated with the cyst. Sonography is the most useful diagnostic modality and represents the imaging technique of choice. The lesions appear as a well-defined, hypoechoic to anechoic smooth-walled mass, with echogenicity related to the cyst contents. In lymphangiomas, multiple thin septae may be apparent (Fig. 57.4).

Computer tomography (CT) or magnetic resonance imaging (MRI) may be used in the differential diagnosis of these lesions. They frequently demonstrate a fluid-filled mass, but the thin septae, diagnostic of lymphangioma, may not be apparent. Ros *et al.*[4] suggested that a lymphangioma is usually a multiloculated cyst that shows no discernible wall on CT and that may have characteristics of fat. A basic x-ray of the abdomen is not routinely indicated and may demonstrate a mass, ascites, or evidence of intestinal obstruction. Contrast radiography is rarely useful and may evidence a mass effect with varying degrees of compression of normal bowel in mesenteric cysts.

DIFFERENTIAL DIAGNOSIS

Other intra-abdominal lesions sometimes difficult to distinguish from a mesenteric or omental cyst mostly include ovarian cysts, choledochal cysts, pancreatic cysts, splenic cysts, and enteric duplication. The majority of these can be differentiated preoperatively by sonography and/or CT. Enteric duplication cysts have a thick wall, and a common muscular wall with the adjacent bowel. A mucosal line may be visible on sonography.



(a)

(b)

Figure 57.4 (a,b) Longitudinal and transverse abdominal ultrasound of a child with a large omental lymphangioma demonstrating a hypoechoic, septated mass immediately beneath the anterior abdominal wall.

Large cysts may mimic ascites in the neonate. Unless the ascites is loculated, shifting will occur with movement and the bowel will flow centrally as opposed to in the lateral dislocation associated with mesenteric or omental cysts.

Remaining lesions commonly referred to as mesenteric and/or omental cysts are non-pancreatic pseudocysts with no distinct cellular lining. They are seldom encountered in the neonate and are secondary to inflammation or trauma. Because of this etiology, the contained fluid may be hemorrhagic or purulent. A non-pancreatic pseudocyst is usually a unilocular or multilocular cyst with abundant debris sonographically and an enhancing wall on CT. An enteric duplication cyst is a unilocular cyst, but also with an enhancing wall.

TREATMENT

Preoperatively, the diagnosis may be in doubt and parents have to be informed that management may require intestinal

resection. Routine mechanical bowel preparation and intraoperative bladder catheterization are not required. Routine broad-spectrum antibiotics are only administered in cases with bacterial contamination, i.e. bowel resection.

In recent years, minimally invasive techniques have been suggested for the management of cystic abdominal masses and alimentary duplications.[17,18] The initial aim of laparoscopy is to locate the cyst and to determine its nature. The patient is placed in a supine position and the surgeon, pathology, and the monitor are placed in line. The optimal position of the ports is determined after exploration of the abdominal cavity via the first umbilical trocar. Mesenteric and omental cysts can be resected laparoscopically, but the location and fragility of the cyst wall may interfere with the feasibility of laparoscopy. Intraoperative aspiration of the cyst and subsequent analysis prior to removal is not indicated unless there is a question of biliary or pancreatic origin. Large cysts may be punctured to reduce the size and improve exposition, but this may make dissection more difficult. Management options include enucleation or resection. If any obvious plane exists between the cyst and adjacent bowel wall, enucleation should be undertaken. In cases requiring a limited resection of bowel, the cyst and affected loop are exteriorized via the umbilical approach and the resection and anastomosis are performed outside the abdominal cavity. Alternatively, a transverse mini-laparotomy may be used after the optimal location has been determined by laparoscopy.

The conventional operation is performed via a supra-umbilical transverse approach. Omental cysts are generally immediately apparent upon entering the peritoneal cavity. They present as large, translucent, solitary fluid-filled sacs overlying the bowel. The omentum and associated cyst is gently withdrawn from the abdomen and placed on the abdominal wall. The cyst may then be easily removed by transection at the junction with normal omentum or transverse colon (Fig. 57.5). Care should be taken to ligate the numerous omental vessels at the level of the transection. Larger mesenteric cysts may also be apparent upon opening the peritoneal cavity or, if they are smaller, require exploration. Once localized, the area of involvement is mobilized, eviscerated and the remaining bowel secured with sponges to facilitate exposure and resection (Fig. 57.6).

If any obvious plane exists between the cyst and adjacent bowel wall, enucleation should be undertaken. In larger cysts, enucleation may require incision on both sides of the mesentery. Generally, a plane of loose areolar tissue is present, enabling mobilization. This may be facilitated with gentle downward traction on the cyst wall (Fig. 57.7). Dissection is continued circumferentially until the cyst can be totally enucleated (Fig. 57.8). Following enucleation, the mesenteric defect is closed, approximating both leaves of the mesentery (Fig. 57.9).

In instances where a definite plane between the cyst and adjacent bowel cannot be identified, resection of the intestine in continuity with the cyst is required. Dissection should be

Figure 57.6 A mesenteric cyst amenable to removal without intestinal resection.

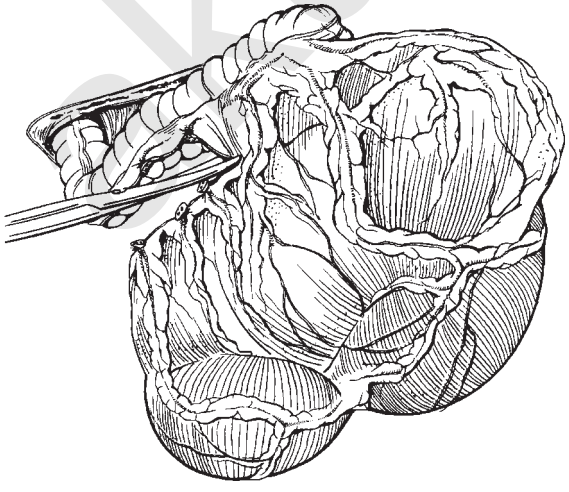


Figure 57.5 Removal of omental cyst by transection of the omentum at the transverse colon.

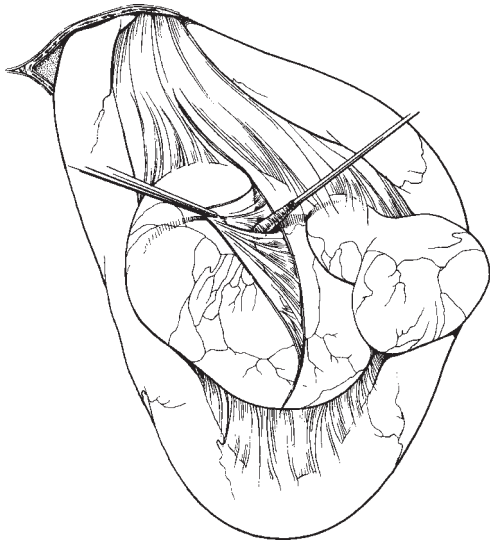


Figure 57.7 Gentle dissection of the mesenteric leaf overlying the cyst.

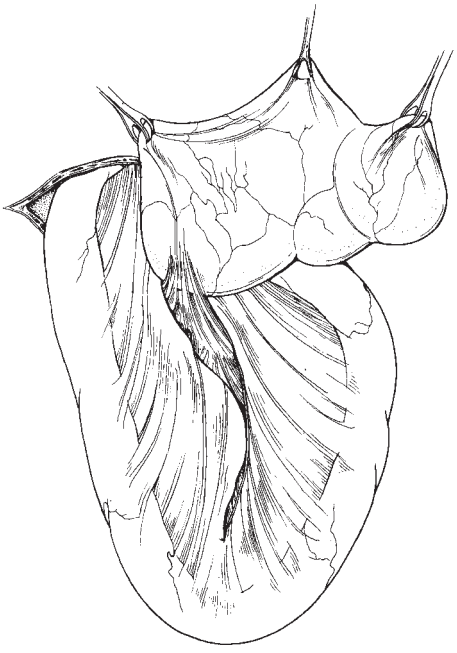


Figure 57.8 Removal of the mesenteric cyst from between the leaves of the mesentery.

Figure 57.10 Mesenteric cyst removed en bloc with adjacent bowel.

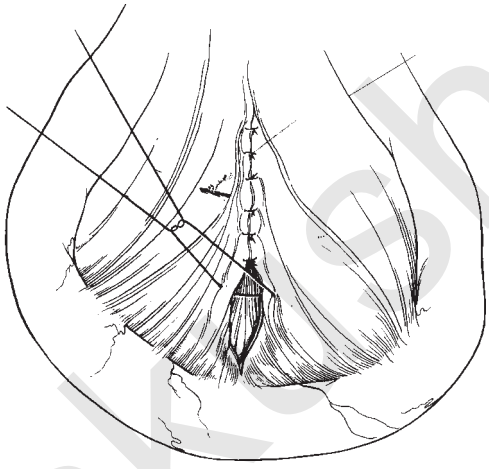


Figure 57.9 Closure of the mesenteric dissection with fine interrupted absorbable sutures.

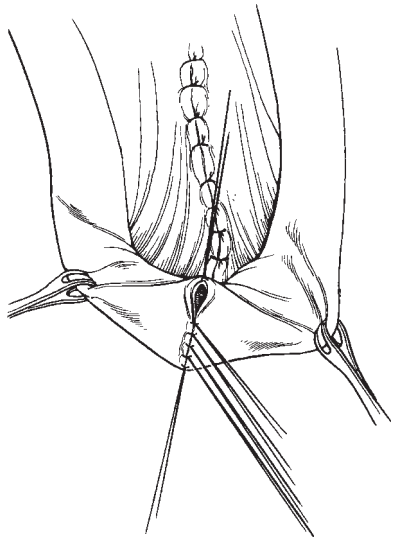


Figure 57.11 Reapproximation of the intestine with a single layer of interrupted absorbable sutures.

planned so as to remove as little bowel as possible (Figs 57.10 and 57.11).

OUTCOME

The outcome of resection or enucleation of mesenteric and omental cysts is very favorable. However, recurrence has been reported in up to 14% of patients, mostly with retroperitoneal cysts, which requires re-resection.

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58

Neonatal ascites

PREM PURI AND ELKE RUTTENSTOCK

INTRODUCTION

Ascites is defined as an abnormal accumulation of intraperitoneal fluid in the peritoneal cavity, that consists of transudate (low protein count and low specific gravity) or exudate (high protein count and high specific gravity. The relatively rare condition of ascites in the newborn may occur due to a wide range of medical and surgical causes. The surgical conditions that most likely result in neonatal ascites are obstructive uropathy, spontaneous perforation of the extrahepatic biliary tree, and chylous ascites.

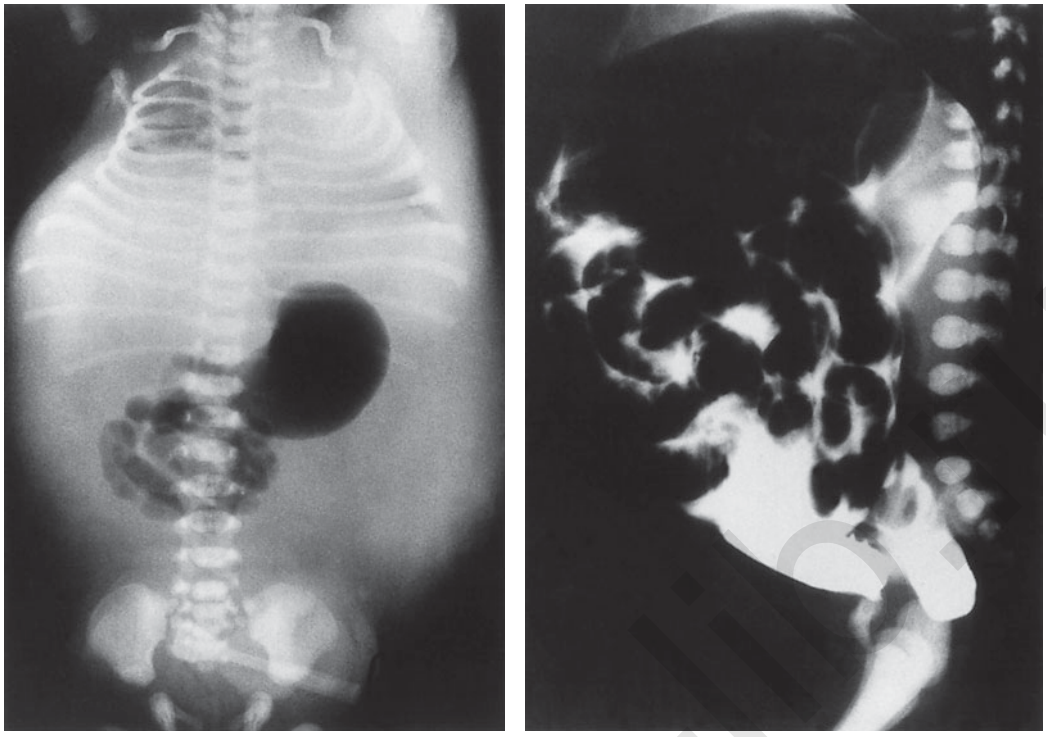
URINARY ASCITES

Urinary ascites which occurs almost exclusively in boys is an uncommon, life-threatening condition which accounts for up to 30% of all cases of neonatal ascites.[1] Abdominal distension sufficient to cause respiratory embarrassment, ascites, and signs of renal insufficiency are known as the most common presenting symptoms. Urinary tract obstruction from posterior urethral valves is the most reported cause of urinary ascites.[1,2] Other causes include ureteropelvic junction obstruction, ureterocele, lower ureteral atresia, bladder neck obstruction, and neuropathic bladder.[3] Ascites due to bladder rupture is also recognized, most commonly secondary to umbilical arterial catheterization.[4,5] Rarely, urinary ascites may occur in the absence of a demonstratable urinary tract obstruction.[6,7] The ascites usually results from extravasation of urine into the peritoneal cavity due to urinary tract perforation above a point of obstruction. The perforation may occur in the bladder, but most often occurs in the upper tracts.[3] In obstructive causes of extravasation, prolonged high pressure in the kidney leads to atrophy and dysplasia, which predispose to rupture of the collecting system. Urine may collect as a perinephric urinoma within Gerota's fascia encapsulating the kidney, or as urinary ascites in the peritoneal cavity.[8]

The presence of urine in the peritoneal cavity leads to an autodialysis effect, in which solutes and water follow their concentration gradients. This effect explains why ascites fluid with sodium and potassium results are not dissimilar from plasma, as well as hyponatremia and hyperkalemia. Furthermore, in all cases one would expect higher levels of urea and creatinine with lower levels of bicarbonate in the ascites fluid than found in blood. This unique biochemical profile, in the presence of renal impairment, is peculiar to a diagnosis of urinary ascites.[4,9]

The diagnosis of urinary ascites is based on clinical assessment, together with ultrasonography and abdominal x-rays.[1,10] The typical patient with neonatal urinary ascites is a male infant who presents with gross abdominal distension and ascites at birth. The abdominal distension may be severe enough to cause respiratory distress. Plain abdominal films will show diffuse opacity (Fig. 58.1a). If the amount of intraperitoneal fluid is large, splaying of the lower rib cage and centrally located floating intestines will be demonstrated. Micturating cystourethrogram is necessary to diagnose posterior urethral valves and ipsilateral vesico-ureteral reflux may further elucidate the diagnosis (Fig. 58.1b). Computed tomography (CT) has been recommended to reveal the underlying pathology.[11] Intravenous pyelography may show a characteristic 'halo' sign produced by extravasation of contrast material into the perirenal area. Abdominal paracentesis confirms the diagnosis via elevated creatinine levels and urine in the fluid.[4,12]

Treatment of neonatal urinary ascites must be individualized, depending upon the general condition of the baby at diagnosis and also on the site of perforation. Fluid and electrolyte imbalance are first corrected. Immediate drainage of the ascites is not necessary unless respiratory compromise or an abscess is present.[13] Prophylactic antibiotics are given in the face of urinary obstruction until definitive correction is undertaken. Prompt decompression of the urinary tract by nephrostomy or bladder catheter drainage upon the site of perforation has been recommended, but if the respiratory status is stable and an adequate urinary output has been established, conservative management with serial ultrasound may be elected.[14,15] Correction of the underlying pathology may then be carried out electively.



(a) (b)

Figure 58.1 Urinary ascites. This infant had severe respiratory distress at birth due to gross abdominal distension requiring abdominal paracentesis. (a) Supine film immediately after removal of 650 mL of fluid shows stomach and small bowel loops floating centrally in the peritoneal fluid. Note splaying of ribs. (b) A micturating cystourethrogram shows leakage of contrast into the peritoneal cavity. Spontaneous perforation of the bladder was found at operation. There was no demonstrable anatomical obstruction in the urinary tract.

Long-term outcome of bladder and kidney function is reported to be surprisingly good in cases of neonatal urinary ascites secondary to severe obstructive uropathy.[3] Intrauterine pressure relief in the collecting system through urinary extravasation ('pop-off' mechanism) protects renal function and this decompression of the urinary tract prevents severe secondary changes to bladder function.[16,17]

CHYLOUS ASCITES

Chylous ascites is a rare condition seen during the newborn period and infancy; however, it is a challenging disorder with regard to its successful treatment.[18,19] Generally, it presents with abdominal distension with or without respiratory embarrassment and occasional signs of peritoneal irritation and malabsorption.[20] About 10% of all infants with chylous ascites have lymphedema of the limbs.[21] The most common cause of chylous ascites (45–60% of cases) is congenital malformation of the lymphatic channels, such as atresia or stenosis of the major lacteals, mesenteric cysts, and generalized lymphangiomatosis.[19,22] The other causes are external compression with obstruction of the lymphatics, namely intestinal malrotation,[23] trauma, child abuse,[24] incarcerated hernia, and inflammatory lesions (25–30% of cases).[25]

Infants with chylous ascites present with abdominal distension at birth or it may develop in the first few days of life. Plain abdominal x-ray shows opaque distended abdomen, indicating ascites.

Abdominal paracentesis is not only a diagnostic but also a therapeutic method in the management of chylous ascites.[26] The chyle is usually color free; however, its appearance and composition are not constant and depend on multiple factors, such as the size of fat particles, cellular content, and diet.[27] After oral feedings have been started, the chylous fluid is milky white with a high fat content. Diagnosis is confirmed by determining high lipid content in the ascitic fluid. Although lymphangiography is the gold standard in defining the cause of the lymphatic obstruction, lymphoscintigraphy is also useful to evaluate the patency of the lymphatic vessels.

Treatment of chylous ascites is usually conservative. The majority of patients respond to abdominal paracentesis and an enteral diet containing medium-chain triglycerides (MCT) and high protein. Dietary management is an important treatment modality in chylous ascites. An MCT-based diet is accepted as the first measure to implement for reducing the chyle production in the peritoneal fluid.[28] MCTs are not re-esterified within the intestinal cell and thus bypass the enteric lymphatics and directly enter the portal system. It is believed that the reduction in dietary long-chain fats reduces lymphatic flow and pressure within the lymphatic system and decreases the amount of lymph leakage. For severe or complicated chylous ascites or chylous ascites that persists after a maximum of 10 weeks of diet, total parenteral nutrition (TPN) has been successfully used in treating these infants by resting the gastrointestinal tract.[29] Somatostatin analogs have been demonstrated to be effective in reducing

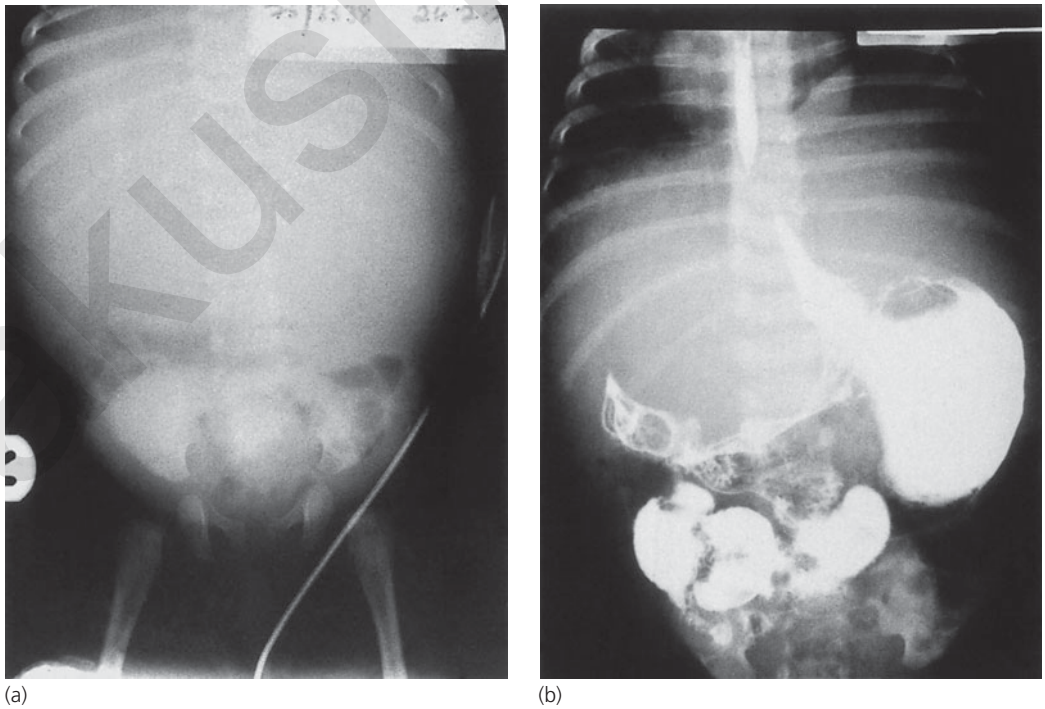
lymphorrhea and may be proposed prior to considering the surgical approach. The exact mechanisms of somatostatin on drying lymphatic flow are not completely understood. It has been previously shown to decrease the intestinal absorption of fats, lower triglyceride concentration in the thoracic duct, and attenuate lymph flow in the major lymphatic channels.[30] Satisfactory results were achieved by the administration of the somatostatin combined with TPN.[31,32] Surgical intervention is recommended if one to two months of conservative approach has failed.[33] Successful surgical treatment of congenital chylous ascites by resecting the macroscopically localized anomaly or by ligation of an identifiable lymphatic leak has been described.[31] A peritoneovenous shunt, of either Leveen or Denver type, has been also reported to be successful, at least temporarily, in children in whom repeated attempts at medical or surgical approach have failed.[19,34]

BILE ASCITES

Bile ascites in infancy is a rare condition usually resulting from spontaneous bile duct perforation (SBP).[35–37] Most often, SBP is seen in infants aged 2–20 weeks, but it has been reported in neonates as young as 3 days.[36,38] The site of perforation is most often the junction of the cystic duct with the common bile duct. The exact cause of SBP is unknown. Numerous etiologies have been proposed, such as congenital mural weakness of the common bile duct, ischemia, stones, infection, distal bile duct stenosis, inspissated bile, and pancreatic reflux from anomalous pancreaticobiliary ductal union (APBDU).[36,37,39,40] In the majority of cases, there is no apparent cause for the perforation. Some authors suggest that spontaneous bile duct perforation is not merely spontaneous but may be related to APBDU and choledochal cyst, i.e. the perforation of the bile duct and congenital choledochal cyst may be interrelated problems with a common pathogenesis.[41] Occasionally, the perforation is secondary to bile duct obstruction.[42]

Affected patients are typically previously healthy infants with unremarkable birth and perinatal histories. Signs and symptoms generally appear gradually and subacutely, but they can also present acutely with peritonitis, septic shock, or even pulmonary collapse.[38,43] The classic subacute presentation occurs in 80% of infants with fluctuating mild jaundice, normal to acholic stools, slowly progressive ascites, and abdominal distension.[44] Associated symptoms may include irritability, anorexia, failure to thrive, nonbilious emesis, mild fever, and dark urine.[45] In some cases, bile staining of hydroceles or inguinal hernias is present from distension of the tunica vaginalis by the bilious ascites.[45]

The diagnosis may not be made before surgery, but should be suspected in the presence of abdominal distension, intermittent jaundice, and ascites. Abdominal x-rays will show ascites and barium meal may demonstrate collection of fluid between the liver and stomach (Fig. 58.2). If paracentesis is performed, the concentration of bilirubin in the ascetic fluid is higher than in the serum. However, paracentesis is not necessary to establish the diagnosis if a hepatobiliary scan confirms the presence of biliary leakage.[36] Ultrasound is the imaging modality of choice in children, especially for



(a) (b)

Figure 58.2 Biliary ascites. (a) Marked abdominal distention with opacity in upper and central abdomen and downward displacement of bowel loops. (b) Barium study shows compression with downward displacement of stomach and duodenum. At operation, perforation of common hepatic duct was found.

evaluating jaundice. Free or loculated intraperitoneal fluid with normal intrahepatic and extrahepatic ducts will confirm the presence of SBP.[46] Hepatobiliary scintigraphy is highly sensitive and specific for SBP and it is the preoperative test of choice when SBP is suspected.[47,48] It can provide useful information about liver function, biliary patency, site of perforation based on localized accumulation of radiotracer, and any biliary leakage into the peritoneum. Magnetic resonance cholangiopancreatography (MRCP) is also useful in children, including infants.[49,50] Loculated fluid collection or pseudocyst formation can be more easily visualized on MRCP than ultrasound.

Surgical management is mandatory as soon as the diagnosis of SBP is confirmed.[51] A preoperative cholangiogram should be performed to delineate the location of the perforation and exclude distal obstruction. If the perforation is in the gallbladder or cystic duct, simple cholecystectomy is curative.[36,45] Several surgical approaches have been described, including simple drainage with or without cholecystectomy, primary repair with or without external drainage, and hepaticojejunostomy if pancreaticobiliary malformation or distal obstruction is present.[47,52,53] Most authors recommend a conservative approach of draining the abdomen to decompress the biliary tree, unless there is distal biliary tract obstruction requiring biliary-intestinal anastomosis.[39,54] Spontaneous closure is typical even with distal obstruction, once the biliary tree is decompressed.[43] The drains should not be removed too early, since this can lead to reaccumulation of bile in the peritoneal cavity. In situations where the surgeon encounters biliary perforation without a preoperative diagnosis, the safest policy is to drain the area and place a T-tube through the perforation. Suture repair of the bile duct or biliary reconstruction remains controversial because of the potential for stricture formation resulting from inflammation.[55] Reported complications have included portal vein thrombosis, bile leak, and cholangitis.[56] In a few cases, further surgery, including biliary revision and portosystemic shunting, was reported.[56] Overall, the prognosis is good with early recognition and surgical management.

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Necrotizing enterocolitis

SHANNON CASTLE, TRACY GRIKSCHEIT, AND HENRI R FORD

INTRODUCTION

Necrotizing enterocolitis (NEC) is the most common medical and surgical emergency affecting the gastrointestinal tract of infants in the neonatal intensive care unit. NEC affects 1–5% of all preterm infants.[1,2] Up to 50% of neonates who develop NEC eventually require surgical intervention,[3,4] with the mortality rate for these patients varying from 20 to 50%,[5,6] and approaching 100% for infants with pan-intestinal NEC.[6] The majority of infants who develop NEC have extremely low birth weight. As advances in neonatal medicine have resulted in increased survival of these infants, the incidence of NEC continues to rise.

Multiple risk factors have been implicated in the pathogenesis of NEC; these include prematurity, hypoxia, initiation of enteral feeding, congenital heart disease, and bacterial infection. The majority of cases develop in infants less than 36 weeks of gestational age, though NEC has also been described in term infants, particularly those with cyanotic heart disease.[7] NEC is characterized by intestinal inflammation and mucosal destruction, leading to gut barrier failure. In its most severe form, NEC is characterized by full-thickness destruction of the intestinal wall leading to intestinal perforation, peritonitis, sepsis, and death. Infants who recover from NEC may encounter significant morbidity, including intestinal obstruction from stricture formation, short bowel syndrome as a result of extensive intestinal resection, intestinal dysmotility, as well as complications related to parenteral nutrition.[5,8,9]

ETIOLOGY

Immature intestinal barrier

The intestinal epithelium consists of a single layer of polarized epithelial cells (enterocytes) whose primary functions include absorption of micronutrients and digestion of macronutrients from the intestinal lumen, as well as formation of a selective barrier to protect the host from luminal pathogens.[10,11] Both extrinsic and intrinsic barriers prevent translocation of various antigens and microbes across the epithelial barrier. Extrinsic barriers include epithelial tight junctions, gastric acidity, intestinal peristalsis, and mucin production, all of which serve to limit adhesion of bacteria to the cell surface, the first step in the process of translocation.[12–14] Gastric acidity serves as a first line of defense against bacterial passage into the proximal intestine. Intrinsic barriers include the plasma membrane of the epithelial cells and intercellular tight junctions.[15]

Intestinal bacteria

Bacterial colonization is believed to be a prerequisite for the development of NEC.[16,17] Although no single bacterial or viral species has been consistently isolated in cases of NEC, a variety of pathogens have been implicated in the disease, including *Enterobacteriaceae*, *Clostridia*, and *Staphylococcus*.[18,19] NEC occurs in both sporadic and clustered distributions, which support the role of pathogenic bacteria in the development of the disease.[19] Although at birth the intestine is sterile, it is rapidly colonized by bacteria from the environment. While there is considerable variability among infants, *Escherichia coli* and streptococci rapidly colonize most infants, along with *Enterobacter* sp. Colonization with other bacteria, including *Enterococci*, *Lactobacilli*, *Clostridia*, and *Bacteroides* sp. follows.[20,21] Factors influencing the type of bacterial colonization include the birth method (vaginal or Cesarean section), the environment at birth, hygienic measures employed, and the type of feeding administered. Initial colonization in preterm infants is heavily influenced by the hospital environment.[17] Abnormal bacterial colonization patterns of neonates admitted to the neonatal intensive care unit may further increase susceptibility to NEC.[22]

Role of enteral feeding

Aggressive advancement of enteral feedings has been associated with the development of NEC. By contrast, early

trophic feeds have not been associated with increased risk of developing NEC. Optimal strategy for advancing feeds in low birth weight infants remains controversial.[23,24] The practice in the 1970s and 1980s was generally to withhold enteral feeds in preterm infants because of the known increased risk of NEC after starting feeds.[25] Multiple trials subsequently failed to show an increased risk of NEC in infants given low-volume (2–24 mL/kg/day) feeds.[26,27] Advancing feeds beyond these minimal volumes in the first 10 days of life in preterm infants, however, has been shown to significantly increase the rate of NEC.[28] Compared to formula, breast milk has been shown to protect against the development of NEC in both human as well as animal studies.[23,29,30] The mechanism by which breast milk protects against NEC is unknown and remains an active field of study.

Probiotics

Probiotics are non-pathogenic microbial organisms that colonize the intestinal tract and modulate the gut immune response.[31] The most commonly studied bacteria for prevention of NEC are *Lactobacillus* and *Bifidobacteria* species,[32] but the healthy adult and child intestine contains a wide variety of commensal bacteria, including abundant anerobes and moderate numbers of facultative anerobes.[20] Such non-pathogenic bacteria have been studied as a potential therapy for neonatal NEC, given the hypothesis that abnormal bacterial colonization of the preterm infant intestine increases the risk of NEC. Studies have been limited by the fact that there are diverse species of commensal bacteria with possibly diverse effects. There are also safety concerns because, even though administration of probiotics has not been shown to cause bacteremia or sepsis in infants with NEC, they have been implicated in bacteremia in adults, children, and infants when used for treatment of other conditions. Some recent studies have shown a decrease in NEC in groups treated with probiotics.[33,34] While the use of probiotics for prevention and treatment of NEC shows promise, further studies are needed prior to adopting this approach as a standard treatment modality.

Inflammatory mediators and NEC

The current hypothesis regarding the pathogenesis of NEC is that a hypoxic or infectious insult allows bacteria to invade the intestinal wall, inciting an inflammatory cascade that ultimately leads to gut barrier failure.[19,35] Various inflammatory mediators have been implicated in the development of NEC, including TNF-alpha, platelet activating factor, IL-1, IL-6, IL-18, endothelin-1, thomboxanes, and oxygen free radicals.[36–39]

Nitric oxide (NO) has been implicated as a key inflammatory mediator in the pathogenesis of intestinal barrier failure in NEC. NO is the product of nitric oxide synthase (NOS), which exists in three isoforms. Two of these, endothelial NOS and neuronal NOS, are expressed constitutively at low levels. The third, inducible NOS, is expressed at high levels during inflammation. The resultant NO then damages the intestinal barrier via its toxic intermediate, peroxynitrite ($ONOO^-$).[38,40]

Prostanoids are inflammatory mediators formed by conversion of membrane lipid arachadonic acid to prostaglandin G2 by cyclooxygenase (COX). Prostaglandin G2 is then converted to multiple biologically active prostanoids by specific synthases.[41] The COX enzymes are critical in the maintenance of intestinal barrier function, and have also been implicated in the pathogenesis of NEC. Induction of high levels of COX-2 seen during inflammation may damage the gut barrier and exacerbate the disease process, while low levels present under normal conditions are protective.[42]

DIAGNOSIS

Clinical features

Neonates with NEC may present with gastrointestinal and systemic signs, including feeding intolerance, abdominal distension, blood in the stool, hypoxia, apnea, respiratory distress, and hypoperfusion. Age at presentation is variable; NEC tends to occur later in infants born at an earlier gestational age.[43] Full-term infants may present in the first few days of life.[44]

In 1978, Bell introduced a grading system for NEC, in order to standardize diagnoses based on clinical and radiographic criteria.[45] It has been widely used since, with one modification to distinguish between perforated and non-perforated NEC (Box 59.1).[46] The Bell criteria allow for categorization of the severity of NEC for purposes of research as well as for treatment guidelines. Since its introduction, however, increased viability of infants at lower gestational ages, due to surfactant therapy and other advances in neonatal medicine, has resulted in an arguably more heterogeneous group of preterm infants. Some authors have argued that the Bell criteria need re-evaluation and modification as cases that are better classified as having focal intestinal perforation have been grouped with NEC under the old system for purposes of research and treatment.[47]

Laboratory findings

Laboratory abnormalities in NEC include thrombocytopenia, leukocytosis or leukopenia, metabolic acidosis, hypercapnea, and hypoxia.[48] While the white blood cell count may initially be elevated, neutropenia is common, with roughly 37% of severe cases having a WBC less than 1.5×10^9.[49,50] Thrombocytopenia is also common and severe thrombocytopenia (<100) is associated with worse outcomes.[50] An elevated C-reactive protein, while not specific for NEC, is useful in differentiating NEC from more benign abdominal conditions, such as ileus. Persistently elevated C-reactive protein has been shown to predict complications, such as abscess or stricture formation, or the need for surgical management.[51] Bacteremia is present in up to 50% of patients.[17]

Box 59.1 Modified Bell's stages of necrotizing enterocolitis

I Suspected disease
- IA:
  - Mild systemic signs (apnea, bradycardia, temperature instability)
  - Mild intestinal signs (abdominal distension, gastric residuals, occult blood in stool)
- IB:
  - Mild systemic signs (apnea, bradycardia, temperature instability)
  - Mild intestinal signs (abdominal distension, gastric residuals, occult blood in stool)
  - Non-specific or normal radiological findings

II Definite disease
- IIA:
  - Mild systemic signs (apnea, bradycardia, temperature instability)
  - Additional intestinal signs (absent bowel sounds, abdominal tenderness)
  - Specific radiologic signs (pneumatosis intestinalis or portal venous air)
  - Laboratory changes (metabolic acidosis, thrombocytopenia)
- IIB:
  - Moderate systemic signs (apnea, bradycardia, temperature instability, mild metabolic acidosis, mild thrombocytopenia)
  - Additional intestinal signs (absent bowel sounds, abdominal tenderness, abdominal mass)

III Advanced disease
- IIIA:
  - Severe systemic illness (same as IIB with additional hypotension and shock)
  - Intestinal signs (large abdominal distension, abdominal wall discoloration, peritonitis, intestine intact)
  - Severe radiologic signs (definite ascites)
  - Progressive laboratory derangements (metabolic acidosis, disseminated intravascular coagulopathy)
- IIIB:
  - Severe systemic illness (same as IIIA)
  - Intestinal signs (large abdominal abscess, abdominal wall discoloration, peritonitis, intestinal perforation)
  - Severe radiologic signs (definite ascites and pneumoperitoneum)
  - Worsening laboratory derangements (metabolic acidosis, disseminated intravascular coagulopathy)

Differential diagnosis

The differential diagnosis of NEC includes infectious enterocolitis (both bacterial and viral), cow's milk allergy, sepsis, and ileus.[47,52] In addition, obstruction due to Hirschsprung's disease, intussusception, volvulus, meconium ileus, or intestinal atresia may mimic NEC.

Focal intestinal perforation (FIP), which is more commonly seen in very low birth weight infants, is generally recognized as a distinct disease from NEC, with different pathologic characteristics.[53,54] In particular, FIP seems to be related to inhibition of mucosal blood flow regulation in the distal ileum due to combined presence of COX inhibitors and steroids. As a result, FIP tends to be truly focal and is associated with less risk of significant stricture. It also tends to be more common in very premature babies with chronic lung disease and symptomatic patent ductus arteriosus.

RADIOGRAPHIC STUDIES

Abdominal x-rays

Plain abdominal x-rays (anteroposterior and a left lateral decubitus) should be obtained at the first suspicion of NEC. X-ray findings pathognomonic for NEC include intramural gas (pneumatosis intestinalis), portal venous gas, and, when perforation is present, free intraperitoneal air.[55] Pneumatosis intestinalis is a hallmark of NEC, and is seen as the presence of air in the intestinal wall (Fig. 59.1).

Dilation of the bowel with gas is an early, non-specific sign, but the presence of a persistent loop of bowel on x-ray that remains unchanged in position over serial films is referred to as a 'fixed loop', and is associated with transmural necrosis. Portal venous gas is present in up to 30% of preterm patients with NEC, and is the result of intramural gas being absorbed by the venous system (Fig. 59.2). With increasing gestational age, the presence of portal venous gas is more common.[56] While the presence of portal venous gas has previously been thought to be associated with worse outcomes and the need for surgical intervention, recent studies have challenged this notion.[57–59] In a single-center study of

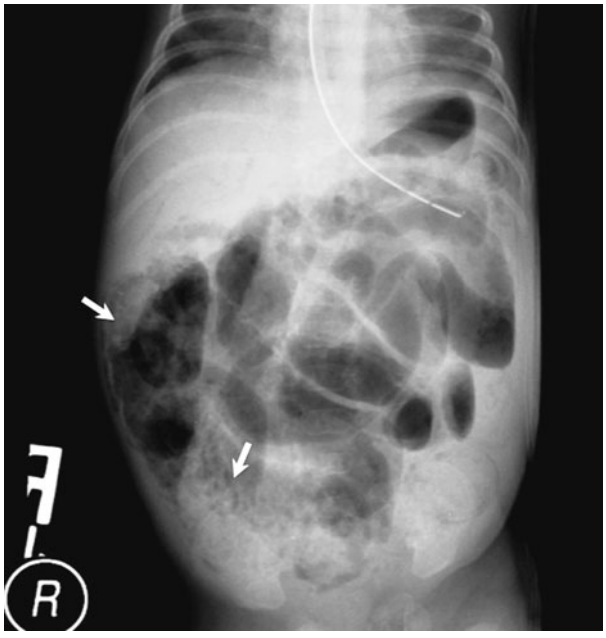

Figure 59.1 Abdominal x-ray of an infant with necrotizing enterocolitis. Arrows indicate area of pneumatosis intestinalis.

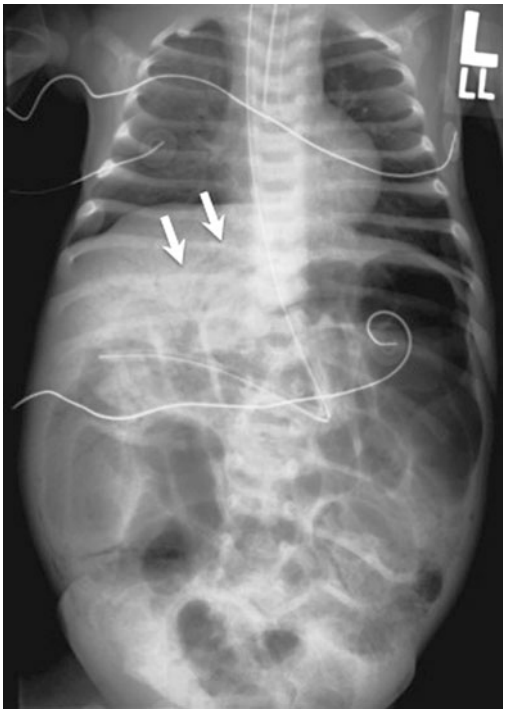

Figure 59.2 Abdominal x-ray of an infant with necrotizing enterocolitis demonstrating portal venous gas, indicated by arrows.

194 infants, there was no difference in survival with and without portal venous gas (17 versus 20%).[59]

Contrast studies

There is no indication for contrast studies in the initial evaluation and diagnosis of NEC. However, patients with a history of NEC who subsequently develop intestinal obstruction should be evaluated with contrast studies to look for intestinal strictures.[60]

Ultrasound

The use of abdominal ultrasound in the evaluation of infants with suspected or confirmed NEC is advantageous in that it can show bowel wall thickness and fluid collections with greater sensitivity than plain films. It can also evaluate bowel gas patterns, the presence of intramural air, and the presence of free air or portal venous gas.[61,62] It remains dependent on operator experience for its sensitivity and thus has not replaced plain abdominal x-rays as the standard of care.

PATHOLOGY

Histologic examination of the diseased bowel in infants with NEC may reveal epithelial sloughing, edema, and submucosal gas (Fig. 59.3).[63] More severe cases show transmural necrosis, with or without perforation. The terminal ileum is the most commonly affected site, but NEC can occur anywhere in the small or large intestine, with pan-necrosis of the bowel developing in the most severe cases. However, NEC is ultimately a clinical, rather than a pathologic diagnosis.

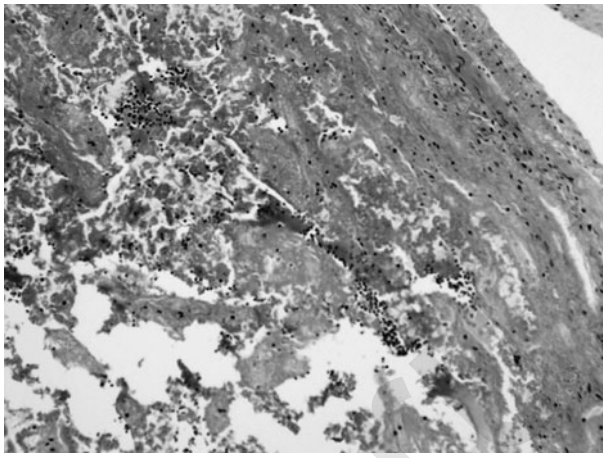

Figure 59.3 Hematoxylin-eosin staining of intestinal tissue from an infant with necrotizing enterocolitis showing edema and cellular infiltrate.

MANAGEMENT

Medical management

When NEC is suspected or confirmed, initial management should include bowel rest (cessation of oral feeds and placement of an orogastric tube) and broad-spectrum antibiotics. Fluid resuscitation is vital as most patients are hypovolemic because of accompanying sepsis. Patients may require ventilatory support and/or hemodynamic support with pressors, depending on the severity of illness. Acidosis should be corrected by implementing proper resuscitation measures, and coagulopathy or thrombocytopenia corrected with the infusion of blood products.

The infant should be monitored for progression of disease with serial abdominal x-rays and close monitoring of laboratory values.[64] For infants who do not require surgical intervention, medical therapy should continue for 7 days before bowel rest and antibiotics are stopped. While there is insufficient evidence to support a particular antibiotic regimen or duration, the use of broad-spectrum antibiotics is based on the high rate of bacteremia. There is evidence from animal models that antibiotics improve survival.[45,64,65] Commonly used antibiotic regimens include ampicillin with either gentamicin or a third-generation cephalosporin (i.e. cefotaxime), plus metronidazole or clindamycin, or piperacillin-tazobactam. Vancomycin may be added for staphylococcal coverage.

Surgical management

Surgical intervention is indicated when necrosis extends through the bowel wall and causes intestinal perforation. However, extensive necrosis can occur in the absence of perforation or free air on abdominal x-ray. Surgery may also

be indicated in the presence of diffuse peritonitis with hemodynamic instability.

Surgical management of NEC remains a subject of ongoing controversy. Ein *et al.*[66] first introduced the concept of peritoneal drainage (PD) as a temporizing measure in the management of hemodynamically unstable infants with perforated NEC, prior to definitive treatment with laparotomy. Subsequent reports have advocated PD as definitive treatment for some infants, and this approach has gained popularity over the last three decades. Some authors have advocated primary PD in all patients with stage III NEC,[67,68] but others report that the majority of these infants eventually require laparotomy and that in patients with birth weight >1000 g, the overall outcome is unchanged.[69] A meta-analysis of ten studies from 1978 to 1999 failed to show any superiority of PD over laparotomy.[70] A subsequent prospective, non-randomized multi-institutional study by Demestre *et al.*[71] of 44 neonates showed improvement in 86% of infants after PD; 54% required surgery after PD. Overall survival was 95% for infants over 1000 g. Blakely *et al.* prospectively studied long-term outcome in extremely low birth weight infants (<1000 g) undergoing primary PD versus laparotomy for perforated NEC. They did not find a significant survival difference between infants treated with primary laparotomy versus PD.[5,72] Twenty-three percent of patients required subsequent laparotomy after initial PD. This study included patients with a preoperative diagnosis of NEC and FIP. It showed that while PD was more likely to be used with FIP, and laparotomy with NEC, survival after PD without laparotomy was only 32% in NEC compared to a survival of 57% in the cohort treated with initial laparotomy.[72]

Moss *et al.*[73] conducted a multi-institutional randomized controlled trial of PD versus laparotomy in 177 patients under 34 weeks' gestational age and weighing <1500 g, with perforated NEC. The primary outcome measure was 90-day mortality, and the secondary outcomes examined were the need for long-term total parenteral nutrition (TPN) and length of stay (LOS). They reported that the PD and laparotomy groups had similar mortality rate (34.5 versus 35.5%) and there was no difference in TPN need or LOS in survivors. Roughly 38% of those randomized to PD needed subsequent laparotomy for deteriorating status. Interestingly, in non-enrolled infants, those who underwent PD had a 41% mortality rate compared to a mortality rate of 15% for those undergoing initial laparotomy. These data suggest the possibility that better outcomes can be achieved with careful patient selection for laparotomy. Rees *et al.*[74] also published a randomized multicenter study, involving 31 countries. A total of 69 infants with birth weight <1000 g and a diagnosis of NEC or FIP were enrolled. They found a trend towards increased survival in those treated with primary laparotomy. They noted that rescue laparotomy was required in 26/35 (74%) of those randomized to PD. Only 11% of the infants received PD as definitive treatment. The authors argue that there was no benefit to PD in this population.

Infants weighing >1500 g and requiring surgical intervention for perforated NEC are probably best managed with laparotomy and resection of the necrotic intestine. Disease may be limited to a short segment or to several segments of intestine, or it may be more diffuse, with necrosis of a large percentage of the gut. The goal is to limit the extent of intestinal resection to preserve the maximum amount of viable intestine and avoid the complication of short bowel syndrome.[45]

For infants with segmental NEC and a focal or isolated perforation, controversy exists regarding whether resection and primary anastomosis is indicated in this setting or whether resection with ostomy creation should be performed. Proponents of primary repair cite the high morbidity associated with ostomy creation and subsequent takedown in very low birth weight infants.[75] Multiple authors have reported 'safe' use of primary anastomosis,[76–78] even in infants weighing <1000 g.[79] A study from Great Ormond Street Hospital published in 1996, examined the outcome of 18 infants with NEC in whom a primary anastomosis was performed after resecting the diseased segment.[76] There were no anastomotic leaks, and the mortality ($n=2$, 18%) was comparable to published rates in infants managed with enterostomies. Although the mean birth weight in this group was 1494 g, a subsequent paper from the same institution reported ten infants under 1000 g managed with primary anastomosis.[79] Six of these had a final diagnosis of NEC (versus focal intestinal perforation). In both papers, the authors concluded that primary anastomosis, in selected patients, has comparable morbidity and mortality to stoma formation.

Proponents of intestinal diversion argue that ostomies are very well tolerated in infants and that there is a higher rate of survival with enterostomy versus primary anastomosis. Cooper *et al.*[80] reviewed 173 patients over a 14-year span; 27 underwent primary repair, based on surgeon's preference, while the remainder was treated with resection and stoma creation. They reported a 48% survival rate in the primary repair group versus 72% in the enterostomy group.

With pan-necrosis of the bowel, different authors have proposed different surgical techniques. The various options include resection of necrotic bowel with creation of multiple ostomies, proximal diversion with or without a 'second-look' procedure, and the 'clip and drop-back' technique introduced by Vaughan et al. in 1996.[81] The creation of multiple ostomies, an approach that was widely used in the past for patients with multiple segments of necrotic intestine, leads to loss of viable bowel. Initial aggressive resection of all non-viable appearing bowel leads to sacrifice of segments with borderline viability. Therefore, some authors have advocated proximal diversion and a 'second-look' procedure when there are multiple areas with questionable viability.[82] Proximal diversion alone has been shown to limit the extent of resection without increasing morbidity or mortality.[83] A variation of this approach is the 'clip and drop-back' technique in which the proponents resect all non-viable bowel without anastomosis at the time of initial laparotomy.[81,84] A second-look operation is then performed after 48–72 hours. Due to small numbers of reported patients and the lack of randomized, prospective studies, the ideal management remains controversial.

At our institution, we favor management of segmental necrosis with resection and enterostomy. Infants with pan-involvement are treated with initial laparotomy and proximal diversion alone. Those too unstable for laparotomy may be

treated with PD as part of their initial resuscitation followed by delayed laparotomy. If the infant does not improve clinically in 24–48 hours, a second-look laparotomy may be indicated.

COMPLICATIONS

Acute

Infectious complications associated with NEC include sepsis, meningitis, peritonitis, and on occasion, intra-abdominal abscess formation. The resultant inflammation may lead to coagulopathy and disseminated intravascular coagulation, respiratory and cardiovascular compromise, and metabolic complications, such as hypoglycemia and acidosis. Thus, any infant with suspected or confirmed NEC should be carefully monitored and aggressively resuscitated.

Chronic

Long-term complications include strictures, which occur in over 30% of patients with medically or surgically treated NEC,[8,85,86] and short bowel syndrome, which occurs in 10% of patients after surgical intervention.[8] Strictures may occur anywhere in affected bowel, but the most common location is in the colon.[87] If a stricture is suspected based on clinical symptoms of obstruction, the preferred radiographic evaluation is with water-soluble contrast enema or upper gastrointestinal study. Any stricture requires surgical resection. Short bowel syndrome occurs when the amount of functional intestine remaining after resection of diseased segments is insufficient for absorption of fluids and nutrients.[88] A patient with short bowel syndrome (or intestinal failure) is thus dependent on parenteral nutrition, which carries a risk of i.v. line infection and sepsis, cholestatic liver disease and liver failure.[89,90] Surgical treatment of short bowel syndrome with intestinal lengthening procedures is indicated in some, and some success has been reported with small bowel transplant.[91]

Survivors of NEC, in particular very low birth weight infants, have an increased risk of neurodevelopmental impairment.[92] The incidence appears to be higher in patients requiring surgical intervention, presumably due to more severe disease.[93] Strategies for optimal management to avoid these complications in survivors of NEC are a subject of ongoing research.

In summary, the etiology of NEC is multifactorial, primarily affecting premature infants with immature intestinal barrier function in the face of other risk factors such as hypoxia, aggressive enteral feeding, or abnormal bacterial colonization of the gut. Diagnosis is based on classic radiographic findings and laboratory abnormalities. While less severe NEC may be managed with bowel rest and antibiotics, surgical intervention is absolutely indicated for bowel perforation. Preferred management of segments of necrotic bowel is with resection and enterostomy, followed by a second operation for re-anastamosis. Survivors of NEC may have long-term complications including strictures, short bowel syndrome, and neurodevelopmental impairment.

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60

Hirschsprung's disease

PREM PURI

INTRODUCTION

Hirschsprung's disease (HD) is a relatively common cause of intestinal obstruction in the newborn. It is characterized by absence of ganglionic cells in the distal bowel beginning at the internal sphincter and extending proximally for varying distances. The aganglionosis is confined to rectosigmoid in over 80% of patients. In the remaining patients, the aganglionosis extends beyond the rectosigmoid involving the descending colon and transverse colon or it may involve the entire colon along with a short segment of terminal ileum. Total intestinal aganglionosis with an absence of ganglion cells from the duodenum to the rectum is the most rare form of HD and is associated with high morbidity and mortality.[1–4]

The incidence of HD is estimated to be 1 in 5000 live births (Table 60.1).[5–7] Spouge and Baird[6] studied the incidence of HD in 689 118 consecutive live births in British Columbia and reported an incidence rate for this disease to be 1 in 4417 live births. Significant interracial differences in the incidence of HD have been reported: 1 in 10 000 births in Hispanic subjects, 1 in 6667 white subjects, 1 in 4761 in black subjects, and 1 in 3571 Asian subjects.[8] The disease is more common in boys, with a male-to-female ratio of 4:1.[7,9] The male preponderance is less evident in long-segment HD, where the male-to-female ratio is 1.5–2:1.[5–7]

Table 60.1 Incidence of Hirschsprung's disease.

Author	Incidence	Area
Passarge[5]	1 in 5000	Cincinnati
Orr and Scobie[7]	1 in 4500	Scotland
Goldberg[20]	1 in 5682	Baltimore
Spouge and Baird[6]	1 in 4417	British Columbia

ETIOLOGY

Neural crest cell migration

The enteric nervous system (ENS) is the largest and the most complex division of the peripheral nervous system. It provides the gastrointestinal tract with its unique network of innervation within its walls and functions largely independently of the central nervous system. The ENS contains more neurons than the spinal cord and is responsible for the coordination of normal bowel motility and secretory activities. Most of the neurons are located in either myenteric ganglia or submucosal ganglia and a few scattered within the mucosa. It is generally accepted that the enteric ganglion cells are derived primarily from the vagal neural crest cells.[10–13] During normal development, neuroblasts migrate from the vagal neural crest along the bowel wall in a cranio-caudal direction from esophagus to anus. The embryonic neural crest arises in the neural tube, originating with the central nervous system, but neural crest cells detach from this tissue via reduction of cell–cell and cell–matrix adhesion. The epithelio-mesenchymal transformation allows crest cells to migrate along pathways. Pathway selection is most likely achieved by balanced combinations of molecules that promote and reduce adhesion.

In the human fetus, neural crest-derived neuroblasts first appear in the developing esophagus at 5 weeks, and then migrate down to the anal canal in a cranio-caudal direction during the 5th to 12th weeks of gestation. The neural crest cells first form the myenteric plexus just outside the circular muscle layer. The mesenchymally derived longitudinal muscle layer then forms, sandwiching the myenteric plexus after it has been formed in the 12th week of gestation. In addition, after the cranio-caudal mitration has ended, the submucous plexus is formed by the neuroblasts, which migrate from the myenteric plexus across the circular muscle layer and into the submucosa; this progresses in a cranio-caudal direction during the 12th to 16th weeks of gestation.[13] The absence of ganglion cells in HD has been attributed to a failure of migration of neural crest cells. The earlier the arrest of migration, the longer the aganglionic segment is.

Several investigators have suggested that the enteric neurons follow a dual gradient of development from each end of the gut toward the middle, with vagal neural crest cells providing the main source of enteric neurons and sacral–neural crest cells innervating the hindgut.[14–16] Whether the sacral neural crest contributes to the ENS in the human is less clear. Failure of the vagal-derived neural crest cells to colonize the hindgut results in failure of ENS development in this region, suggesting an interaction between sacral and vagal enteric neural crest cells may be necessary for sacral neural crest cell contribution to the ENS.[16]

Genetic factors

Genetic factors have been implicated in the etiology of HD. HD is known to occur in families. The reported incidence of familial cases varied from 3.6 to 7.8% in different series.[17] A familial incidence of 15–21% has been reported in total colonic aganglionosis and 50% in the rare total intestinal aganglionosis.[3,18]

Recurrence risk to siblings is dependent upon the sex of the person affected and the extent of aganglionosis. Badner *et al.*[19] calculated the risk of HD transmission to relatives and found that the recurrence risk to siblings increases as the aganglionosis becomes more extensive (Table 60.2). The brothers of patients with rectosigmoid HD have a higher risk (4%) than sisters (1%). Much higher risks are observed in cases of long-segment HD. The brothers and sons of affected females have a 24% and 29% risk of being affected, respectively. The relationship with Down syndrome also tends to suggest a probable genetic component in the etiology of HD. Down syndrome is the most common chromosomal abnormality associated with aganglionosis and had been reported to occur in 4.5–16% of all cases of HD.[20–22] Other chromosomal abnormalities that have been described in association with HD include interstitial deletion of distal 13q, partial deletion of 2p, and reciprocal translocation, and trisomy 18 mosiac.[17] A number of unusual hereditary syndromes have been reported in patients with HD. These include Waardenburg syndrome, Von Recklinghausen's syndrome, type D brachydactyly, and Smith-Lemli-Optiz syndrome.[17]

During the past 15 years, several genes have been identified that control morphogenesis and differentiation of the enteric nervous system. These genes, when mutated or deleted, interfere with enteric nervous system development. So far, 14 genes are known to be involved in the development of Hirschsprung's disease (Table 60.3). One of these genes, the RET gene, encoding a tyrosine-kinase receptor, is the major gene causing HD.[23,24] Mutations in the coding region of RET are responsible for 50% of familial HD cases and 15% of sporadic ones.[25,26] All the genes that have been implicated in the development of HD together only account for 20% of all cases of HD.[27–30]

This implies that other genes are also involved in the development of Hirschsprung's disease.

Table 60.2 Recurrence risk to siblings.

Relative	Recurrence risk (%)
Brothers of patients with rectosigmoid HD	?4
Sisters of patients with rectosigmoid HD	?1
Brothers of females with long-segment HD	24
Sons of females with long-segment HD	29

HD, Hirschsprung's disease.

Table 60.3 Genes involved in the morphogenesis and differentiation of the ENS.

Gene	
RET	10q11.2
GDNF	5p12-13.1
EDNRB	13q22
EDN3	20q13.2
NTN	19p13
SOX10	22q13.1
ECE-1	1p36.1
ZFHX1B	2q22
PHOX2B	4p12
NRG1	8p21
GFRα	10q26
SIP1	2q22
PAX3	2q35
KIAA1279	10q21.3

PATHOPHYSIOLOGY

The pathophysiology of HD is not fully understood. It has long been recognized that obstructive symptoms in HD are secondary to the abnormal motility of the distal narrow segment, but there is still no clear explanation for the occurrence of the spastic or tonically contracted segment of bowel.[31] Several abnormalities have been described to explain the basis for motility dysfunction in the contracted bowel.

Cholinergic hyperinnervation

In association with aganglionosis, there is a marked increase in cholinergic nerve fibers in the intermuscular zone and submucosa of the aganglionic segment. These fibers appear as thick nerve trunks and correspond to extrinsic preganglionic parasympathetic nerves.[32–36] The continuous acetylcholine release from the axons of these parasympathetic nerves results in an excessive accumulation of the enzyme acetylcholinesterase that is typically found in the lamina propria mucosae, muscularis mucosae, and circular muscle with histochemical staining techniques.[30] Both the thick nerve trunks and the increased acetylcholinesterase activity are most pronounced in the most distal aganglionic rectum and progressively diminish proximally as normal bowel is approached.[37] The proximal extent of increased cholinergic activity does not necessarily correspond to the extent of the aganglionosis,

which usually extends more proximally to a variable degree. Pharmacologic investigations of the colon in HD have demonstrated higher acetylcholine release in the aganglionic segment at rest and after stimulation compared with the proximal ganglionic bowel.[38,39] Acetylcholinesterase concentration has also found to be higher in the serum and erythrocytes of children suffering from HD.[40] Cholinergic nerve hyperplasia has been proposed as the cause of spasticity of the aganglionic segment since acetylcholine is the main excitatory neurotransmitter. However, in the chemical animal model of aganglionosis, after application of benzalkonium chloride or corrosive sublimate, the aganglionic bowel does not show hypertrophic nerve bundles and the bowel still appears narrow and animals exhibit typical obstructive symptoms.[41,42] Therefore, the cholinergic hyperinnervation does not seem to be a prerequisite to the appearance of a narrow spactic segment.

Adrenergic innervation

Fluorescent-histochemical studies for localization of adrenergic nerves have demonstrated that they are increased in number in the aganglionic colon of HD and have a chaotic distribution. They are also present in the circular and longitudinal muscle layers as well as in the mucosa whereas they are almost never found in normal ganglionic colon.[43–45] However, the sensitivity of the aganglionic bowel to epinephrine is apparently not increased, despite the elevated number of adrenergic fibers.[46,47] The tissue concentration of norepinephrine is two to three times higher in the aganglionic bowel than in the normal colon; and also there is a corresponding increase in tyrosine hydroxylase, an enzyme that regulates norepinephrine biosynthesis.[44] Because adrenergic nerves normally act to relax the bowel, it is unlikely that adrenergic hyperactivity is responsible for increased tone in the aganglionic colon.[48]

Nitrergic innervation

Nitric oxide (NO) is considered to be one of the most important neurotransmitters involved in relaxation of the smooth muscle of the gut.[49] It is synthesized in a reaction catalyzed by nitric oxide synthase (NOS) and depends on L-arginine and molecular oxygen as co-substrates to form L-citrulline and NO. Nitric oxide binds to cytosolic guanylate cyclase and increases the production of 3′5′-cyclic guanosine monophosphate (cGMP) with subsequent relaxation of smooth muscle.[50] NOS has been shown to colocalize with reduced nicotine adenine dinucleotide phosphate (NADPH) diaphorase, which has been demonstrated to have identical functions.[51,52] Several investigators have studied NOS distribution in the ganglionic and aganglionic bowel in patients with HD using nitric oxide synthase immunohistochemistry or NADPH diaphorase histochemistry.[53–58] In normal and ganglionic colon from patients with HD, there is a strong NADPH diaphorase staining of the submucous and myenteric plexuses and a large number of positive nerve fibers in the circular and longitudinal muscle as well as in the muscularis mucosae.[50] In the aganglionic segment of HD patients, there are no ganglia and there is an absence or marked reduction of NADPH diaphorase positive nerve fibers in both muscle layers and in the muscularis mucosae. The typical hypertrophied nerve trunks appear weakly stained.[50] Kusafuka and Puri[59] examined the expression of neural NOS mRNA in the aganglionic segment from seven patients who had HD and demonstrated that NOS mRNA expression was decreased at least 1/50 to 1/100 of the level expressed in ganglionic bowel. These findings indicate that there is impaired NO synthesis in the aganglionic bowel in HD and this deficiency could prevent smooth muscle relaxation, thereby causing the lack of peristalsis in HD. In an interesting experiment, Bealer *et al.*[60] compared the effect of an exogenous source of NO, *S*-nitroso-*N*-acetylpenicillamine (SNAP) on the isometric tension of smooth muscle strips from aganglionic bowel and demonstrated a 70% reduction of resting tension. These results suggest that the defective distribution of nerves containing NOS may be involved in the pathogenesis of HD.

Interstitial cells of Cajal

Abnormalities of interstitial cells of Cajal (ICC) have been described in several disorders of human intestinal motility including HD. Vanderwinden *et al.*[53] using c-kit immunohistochemistry first described that ICC were scarce and its network appeared disrupted in aganglionic segments of HD whereas the distribution of ICC in the ganglionic bowel of HD was similar to that observed in controls. Yamataka *et al.*[61,62] found few c-kit positive cells in the muscle layers in HD and a moderate number around the thick nerve bundles in the space between the two muscle layers in the aganglionic bowel. Horisawa *et al.*[63] reported no differences in c-kit immunopositive cells in aganglionic segments compared with the corresponding area of ganglionic bowel. Rolle *et al.*[64] using whole-mount and frozen sections stained with c-kit immunohistochemistry preparations showed an altered distribution of ICC in the entire resected bowel of HD patients and not only in the aganglionic segment. Moreover, gap junctions connecting ICC were immunolocalized by anti-Connexin 43 antibody and found to be absent from the aganglionic part of HD bowel and highly reduced from the transitional zone.[65] Rolle *et al.*[64] proposed that persistent dismotility problems after pull-through operation in HD may be due to altered distribution and impaired function of ICC.

Enteroendocrine cells

Using the generic enteroendocrine cell immunohistochemical markers chromogranin A and synaptophysin, Soeda *et al.*[66] demonstrated that the number of enteroendocrine cells in the aganglionic colon in patients with HD were significantly increased compared with the number in the normal ganglionic segment. The increase of enteroendocrine cells in the mucosa of aganglionic colon may well influence sustained contraction of the bowel wall mainly mediated by the release of 5-hydroxytryptamine.

Smooth muscle

Since smooth muscle is the final effector for bowel motility, it is likely that it could also be abnormal in HD. The smooth muscle cell's cytoskeleton consists of proteins whose primary function is to serve as a structural framework that surround and support the contractile apparatus of actin and myosin filaments in the body of the smooth muscle cell. Nemeth *et al.*[67] studied the distribution of cytoskeleton in the smooth muscle of HD bowel by means of immunohistochemistry and found that dystrophin, vinculin, and desmin immunoreactivity was either absent or weak in the smooth muscle of aganglionic bowel, whereas it was moderate to strong in the smooth muscle of normal bowel and ganglionic bowel from patients with HD. Neural cell adhesion molecule (NCAM) is a cell surface glycoprotein involved in cell–cell adhesion during development that has been suggested to play an important role in development and maintenance of the neuromuscular system.[68–70] NCAM is present in the innervation of normal infant bowel and, less densely, in some components of the enteric smooth muscle. Contradictory results have been published regarding the NCAM expression in the smooth muscle of aganglionic bowel. Kobayashi *et al.*[54] have described a lack of expression of NCAM in the muscularis propria of the aganglionic bowel compared with the ganglionic segment, whereas Romanska *et al.*[71] have found an increased NCAM expression in muscle, particularly in the muscularis mucosae. In any case, both authors agree that there is a strong expression of NCAM in the hypertrophic nerve trunks from the aganglionic segment.

Extracellular matrix

Although extracellular matrix (EM) abnormalities have been described mainly related to the pathogenesis of HD, they could also have an influence on its pathophysiology. The lethal spotted mouse, an animal model which develops aganglionosis in its distal bowel, displays an abnormal distribution of EM components including laminin, collagen type IV, glycosaminoglycans and proteoglycans in the smooth muscle layer.[72,73] Parikh *et al.*[74] have demonstrated that the laminin concentration in aganglionic bowel was twice as high as in the normoganglionic bowel of HD and three times higher than in age-matched controls. Moreover, by means of immunohistochemistry, they found an uneven distribution of laminin and collagen type IV in the muscularis propria of aganglionic bowel, being more intensely expressed in the circular layer than in the longitudinal layer.[75] The same authors have described that EM components tenascin and fibronectin are more intensely expressed in aganglionic bowel from HD.[76]

PATHOLOGY

The characteristic gross pathological feature in HD is dilation and hypertrophy of the proximal colon with abrupt or gradual transition to narrow distal bowel (Fig. 60.1).

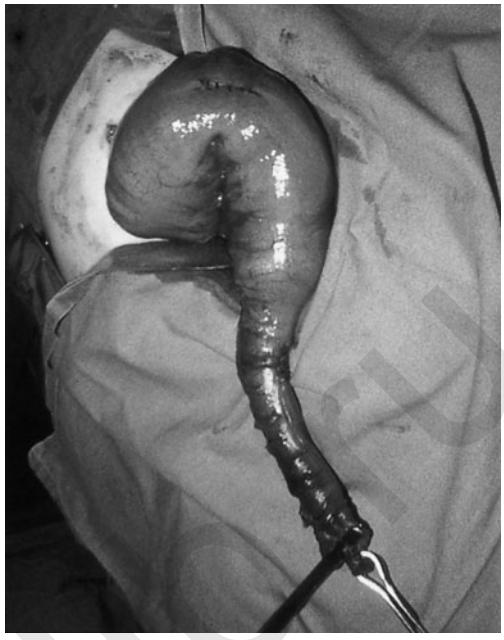


Figure 60.1 Typical gross pathology in Hirschsprung's disease, with transitional zone at rectosigmoid level.

Although the degree of dilation and hypertrophy increases with age, the cone-shaped transitional zone from dilated to narrow bowel is usually evident in the newborn.

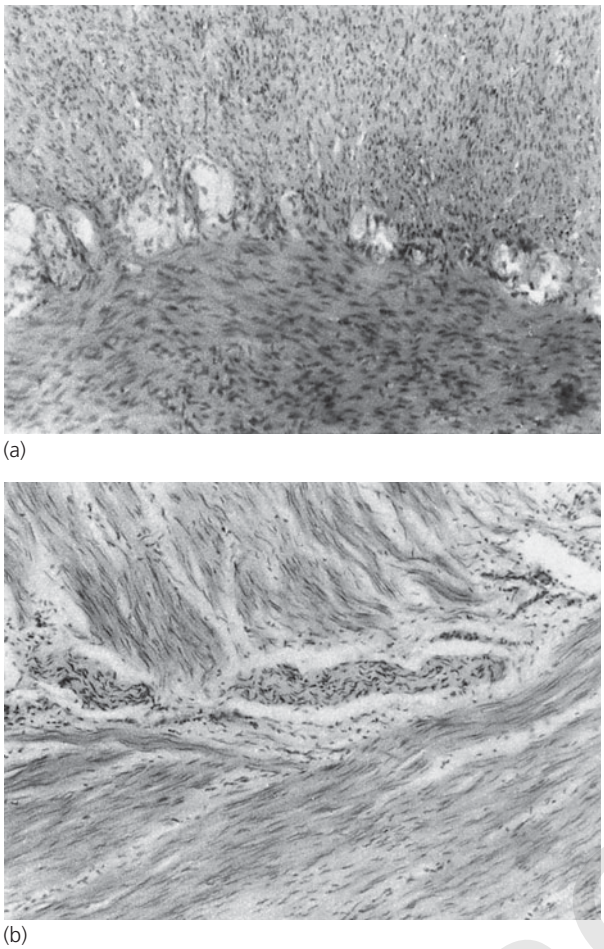
Histologically, HD is characterized by the absence of ganglionic cells in the myenteric and submucous plexuses and the presence of hypertrophied non-myelinated nerve trunks in the space normally occupied by the ganglionic cells (Fig. 60.2). The aganglionic segment of bowel is followed proximally by a hypoganglionic segment of varying length. This hypoganglionic zone is characterized by a reduced number of ganglion cells and nerve fibers in myenteric and submucous plexuses.

DIAGNOSIS

The diagnosis of HD is usually based on clinical history, radiological studies, anorectal manometry, and in particular on histological examination of the rectal wall biopsy specimens.

Clinical features

Of all cases of HD, 80–90% produce clinical symptoms and are diagnosed during the neonatal period. Delayed passage of meconium is the cardinal symptom in neonates with HD. Over 90% of affected patients fail to pass meconium in the first 24 hours of life. The usual presentation of HD in the neonatal period is with constipation, abdominal distension, and vomiting during the first few days of life (Fig. 60.3). About one-third of the babies with HD present with diarrhea. Diarrhea in HD is always a symptom of enterocolitis, which remains the most common cause of death. Enterocolitis may



(a)

(b)

Figure 60.2 (a) Auerbach's plexus, containing ganglion cells. (b) Hypertrophied nerve trunks in rectal biopsy from a patient with Hirschsprung's disease.

resolve with adequate therapy or it may develop into a life-threatening condition, the toxic megacolon, characterized by the sudden onset of marked abdominal distension, bile stained vomiting, fever and signs of dehydration, sepsis, and shock. Rectal examination or introduction of a rectal tube results in the explosive evacuation of gas and foul-smelling stools. In older children, the main symptom is persistent constipation and chronic abdominal distension.

Radiological diagnosis

Plain abdominal films in a neonate with HD will show dilated loops of bowel with fluid levels and airless pelvis. Occasionally, one may be able to see a small amount of air in the undistended rectum and dilated colon above it raising the suspicion of HD (Fig. 60.4a). Plain abdominal x-rays obtained from patients with total colonic aganglionosis (TCA) may show characteristic signs of ileal obstruction with air–fluid levels or simple gaseous distension of small intestinal loops.

In patients with enterocolitis complicating HD, plain abdominal x-ray may show thickening of the bowel wall with

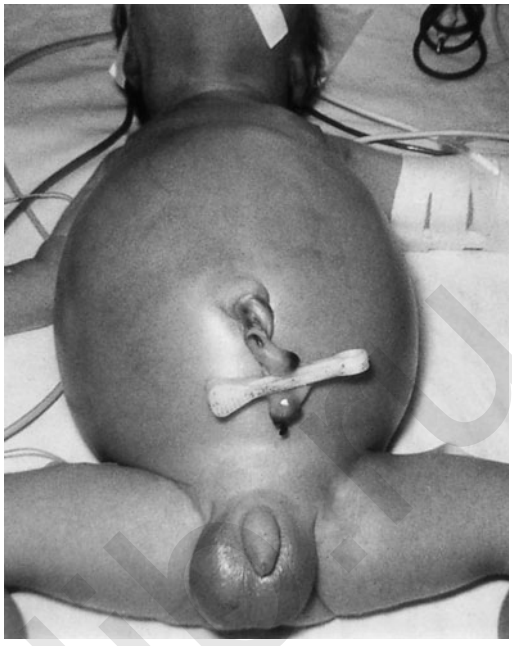


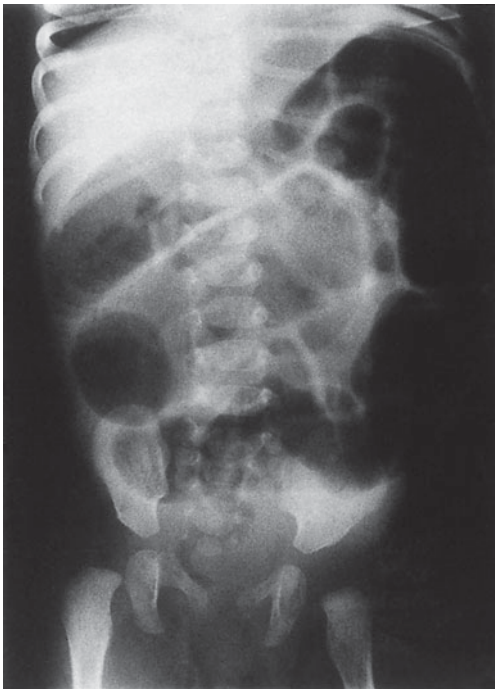
Figure 60.3 A 2-day-old infant with marked abdominal distention and failure to pass meconium. Suction rectal biopsy confirmed Hirschsprung's disease.

mucosal irregularity or a grossly dilated colon loop, indicating toxic megacolon. Pneumoperitoneum may be found in those with perforation. Spontaneous perforation of the intestinal tract has been reported in 3% of patients with HD.[77]

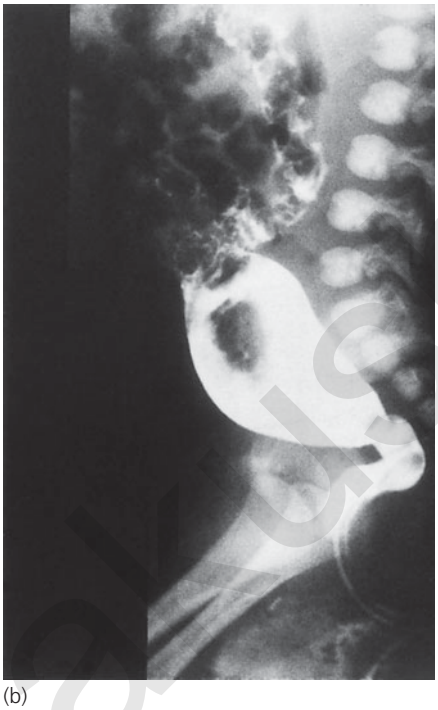
Barium enema performed by an experienced radiologist, using careful technique should achieve a high degree of reliability in diagnosing HD in the newborn. It is important that the infant should not have rectal washouts or even digital examinations prior to barium enema, as such interference may distort the transitional zone appearance and give a false-negative diagnosis. A soft rubber catheter is inserted into the lower rectum and held in position with firm strapping across the buttocks. A balloon catheter should not be used due to the risk of perforation and the possibility of distorting a transitional zone by distension. The barium should be injected slowly in small amounts under fluoroscopic control with the baby in the lateral position. A typical case of HD will demonstrate flow of barium from the undilated rectum through a cone-shaped transitional zone into dilated colon (Fig. 60.4b). Some cases may show an abrupt transition between the dilated proximal colon and the distal aganglionic segment, leaving the diagnosis in little doubt.

In some cases, the findings on the barium enema are uncertain and a delayed film at 24 hours may confirm the diagnosis by demonstrating the retained barium and often accentuating the appearance of the transitional zone (Fig. 60.5). In the presence of enterocolitis complicating HD, a barium enema can demonstrate spasm, mucosal edema, and ulceration (Fig. 60.6).

In TCA, the contrast enema is not pathognomonic and may not provide a definitive diagnosis. The colon in TCA is of normal caliber in 25–77% of cases.[78]



(a)



(b)

Figure 60.4 Hirschsprung's disease. (a) Abdominal radiograph in a 4-day-old infant showing marked dilation of large and small bowel loops. Note gas in undilated rectum. (b) Barium enema in this patient reveals transitional zone at sigmoid level.

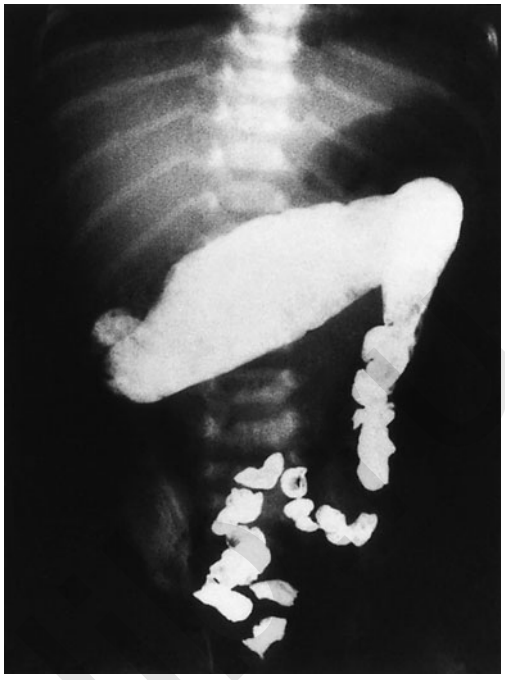


Figure 60.5 Delayed 24-hour film in lateral position showing barium retention with accentuated transition at splenic fixture in a 10-day-old baby.

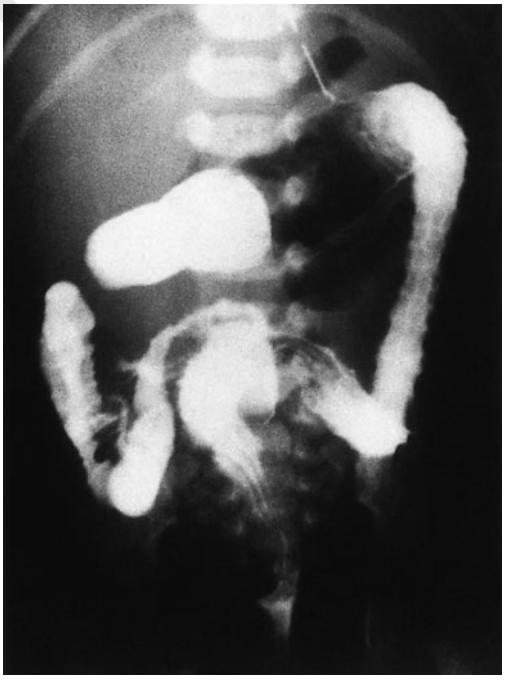


Figure 60.6 Enterocolitis complicating Hirschsprung's disease. Spasm in rectosigmoid shown in barium enema, with fine mucosal ulceration and mucosal edema giving cobblestone appearance.

Anorectal manometry

In the normally innervated bowel, distension of the rectum produces relaxation of the internal sphincter rectosphincteric reflex. In normal individuals, upon distending the rectal balloon with air, the rectum immediately responds with a transient rise in pressure lasting 15–20 seconds; at the same time, the internal sphincter rhythmic activity is depressed or abolished and its pressure falls by 15–20 cm, the duration of relaxation coinciding with the rectal wave.

In patients with HD, the rectum often shows spontaneous waves of varying amplitude and frequency in the resting

phase. The internal sphincter rhythmic activity is more pronounced. On rectal distension, with an increment of air, there is complete absence of internal sphincter relaxation. Failure to detect the rectosphincteric reflex in premature and term infants is believed to be due to technical difficulties and not to immaturity of ganglion cells. Light sedation, particularly in infants and small children, may overcome technical difficulties encountered in this age group.

Rectal biopsy

The diagnosis of HD is confirmed on examination of rectal biopsy specimens. The introduction of histochemical staining technique for the detection of acetylcholinesterase (AChE) activity in suction rectal biopsy has resulted in a reliable and simple method for the diagnosis of HD.[79–81] Full-thickness rectal biopsy is rarely indicated for the diagnosis of HD except in total colonic aganglionosis. In normal individuals, barely detectable acetylcholinesterase activity is observed within the lamina propria and muscularis mucosa, and submucosal ganglion cells stain strongly for acetylcholinesterase. In HD, there is a marked increase in acetylcholinesterase activity in lamina propria and muscularis which is evident as coarse, discrete cholinergic nerve fibers stained brown to black (Fig. 60.7).

In TCA, AChE activity in suction rectal biopsies presents an atypical pattern, different from the classic one. Positive AChE fibers can be found in the lamina propria as well as the muscularis mucosae. However, cholinergic fibers present a lower density than in classical HD.

DIFFERENTIAL DIAGNOSIS

Several conditions must be considered where an infant is being evaluated for HD. Box 60.1 provides a list of common differential diagnoses. Colonic atresia gives similar plain film findings to HD but is readily excluded with barium enema showing complete mechanical obstruction. Distal small bowel atresia shows gross distension of the bowel loop immediately proximal to the obstruction with the widest fluid level in it.

In meconium ileus the typical mottled thick meconium may be seen. Also clear, sharp fluid levels are not a feature in erect or lateral decubitus views. However, HD can sometimes simulate meconium ileus in plain films and may give equivocal findings on Gastrografin or barium enema.

Meconium plugs obstructing the colon can present as HD with strongly suggestive history and plain films. Small left colon syndrome with marked distension proximal to narrowed descending colon also simulates HD at the left colonic flexure. These two conditions usually resolve with Gastrografin enema, but a minority of these cases will actually have HD which should be excluded clinically.

MANAGEMENT

Once the diagnosis of HD has been confirmed by rectal biopsy examination, the infant should be prepared for surgery. If the newborn has enterocolitis complicating HD, correction of dehydration and electrolyte imbalance by infusion of appropriate fluids will be required. It is essential to decompress the bowel as early as possible in these babies. Deflation of the intestine may be carried out by rectal irrigations, but some babies may require colostomy.

In recent years, the vast majority of cases of HD are diagnosed in the neonatal period. Many centers are now performing one-stage pull-through operations in the newborn with minimal morbidity rates and encouraging results. The advantages of operating on the newborn are that the colonic dilation can be quickly controlled by washouts and at

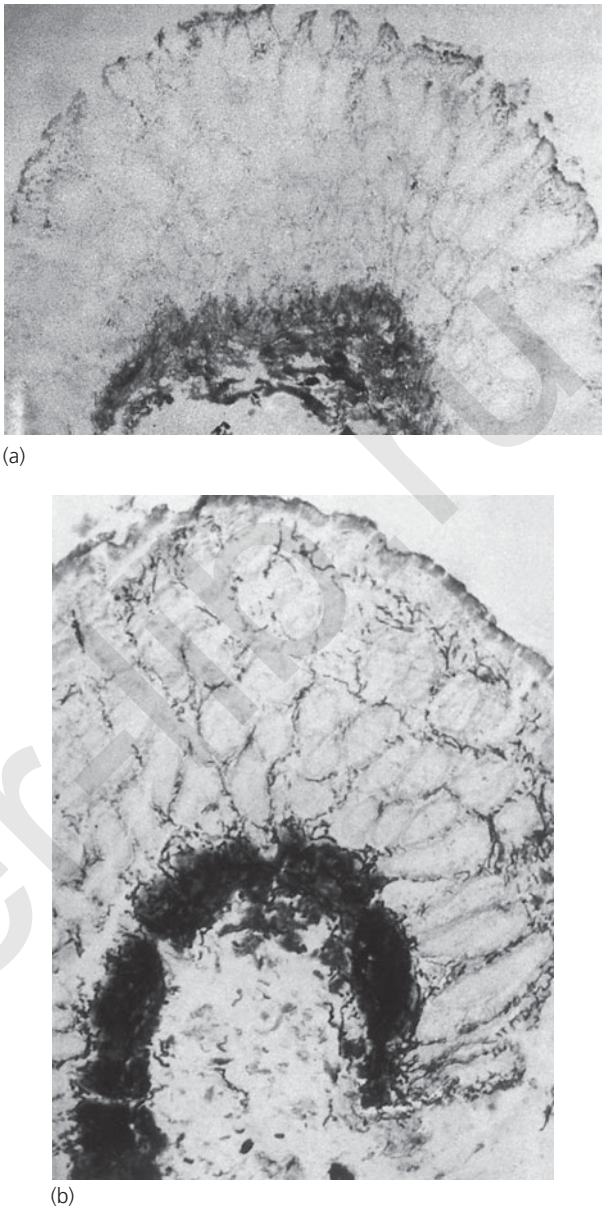


Figure 60.7 Acetyl-cholinesterase staining of suction rectal biopsy. (a) Normal rectum showing minimal acetyl-cholinesterase staining in mucosa, lamina propria, and muscularis mucosae (× 4). (b) Hirschsprung's disease characterized by marked staining of cholinesterase-positive nerves in the lamina propria and muscularis mucosae (× 40).

Box 60.1 Differential diagnosis of Hirsch-Sprung's disease

- Neonatal bowel obstruction
- Colonic atresia
- Meconium ileus
- Meconium plug syndrome
- Small left colon syndrome
- Malrotation
- Low anorectal malformation
- Intestinal motility disorders/pseudo-obstruction
- Necrotizing enterocolitis
- Medical causes: sepsis, electrolyte abnormalities, drugs, hypothyroidism, etc.

operation the caliber of the pull-through bowel is near normal, allowing for an accurate anastomosis that minimizes leakage and cuff infection. A number of different operations have been described for the treatment of HD. The four most commonly used operations are the rectosigmoidectomy developed by Swenson and Bill, the retrorectal approach developed by Duhamel, the endorectal procedure developed by Soave, and deep anterior colorectal anastomosis developed by Rehbein.[82] The basic principle in all these procedures is to bring the ganglionic bowel down to the anus. The long-term results of any of these operations are satisfactory if they are performed correctly. Recently, a number of investigators have described and advocated a variety of one-stage pull-through procedures in the newborn using minimally invasive laparoscopic techniques. More recently, a transanal endorectal pull-through operation performed without opening the abdomen has been used with excellent results in rectosigmoid HD.

Transanal one-stage endorectal pull-through operation

Over 80% of patients with HD have rectosigmoid aganglionosis. A one-stage pull-through operation can be successfully performed in these patients using a transanal endorectal approach without opening the abdomen. This procedure is associated with excellent clinical results and permits early postoperative feeding, early hospital discharge, no visible scars, and low incidence of enterocolitis.[83–85] The author prefers transanal endorectal pull-through operation in patients with classical segment rectosigmoid HD.

PREOPERATIVE MANAGEMENT

A good barium enema study is essential for this technique. A typical case of rectosigmoid HD will demonstrate flow of barium from undilated rectum through a cone-shaped transition zone into dilated sigmoid colon (Fig. 60.4b). Once the diagnosis of HD is confirmed by suction rectal biopsy, the newborn is prepared for surgery. Rectal irrigations are carried out twice a day for 2–3 days prior to surgery. Intravenous gentamicin and metronidazole are started on the morning of operation.

OPERATIVE TECHNIQUE

The patient is positioned on the operating table in the lithotomy position. The legs are strapped over sandbags. A Foley catheter is inserted into the bladder. A Denis-Browne retractor or anal retractor is placed to retract perianal skin. The rectal mucosa is circumferentially incised using the cautery with a fine-tipped needle, approximately 5 mm from the dentate line, and the submucosal plane is developed. The proximal cut edge of the mucosal cuff is held with multiple fine silk sutures, which are used for traction (Fig. 60.8). The endorectal dissection is then carried proximally, staying in the submucosal plane.

When the submucosal dissection has extended for about 3 cm, the rectal muscle is divided circumferentially, and the full thickness of the rectum and sigmoid colon is mobilized out through the anus. This requires division of rectal and sigmoid vessels, which can be done under direct vision using cautery.

When the transition zone is encountered, full-thickness biopsy sections are taken, and frozen section confirmation of ganglion cells is obtained. The rectal muscular cuff is split longitudinally either anteriorly or posteriorly. The colon is then divided several centimeters above the most proximal normal biopsy site (Fig. 60.8), and a standard Soave-Boley anastomosis is performed (Fig. 60.8). No drains are placed. The patient is started on oral feeds after 24 hours and discharged home on the third postoperative day. Digital rectal examination is performed 2 weeks after the operation. Routine rectal dilatation is not performed unless there is evidence of a stricture.

COMPLICATIONS

Early postoperative complications which can occur after any type of pull-through operation include wound infections, anastomotic leak, anastomotic stricture, retraction or necrosis of the neorectum, intestinal adhesions, and ileus. Late complications include constipation, enterocolitis, incontinence, anastomotic problems, adhesive bowel obstruction, and urogenital complications.

Anastomotic leak

The most dangerous early postoperative complication following the definitive abdominoperineal pull-through procedure is leakage at the anastomotic suture line. Factors responsible for anastomotic leak include ischemia of the distal end of the colonic pull-through segment, tension on the anastomosis, incomplete anastomotic suture lines, and inadvertent rectal manipulation. If a leak is recognized in a patient without a colostomy, it is imperative to perform a diverting colostomy promptly, to administer i.v. antibiotics and to irrigate the rectum with antibiotic solution a few times daily. Delay in establishing fecal diversion is likely to result in an extensive pelvic abscess which may require laparotomy and transabdominal drainage.

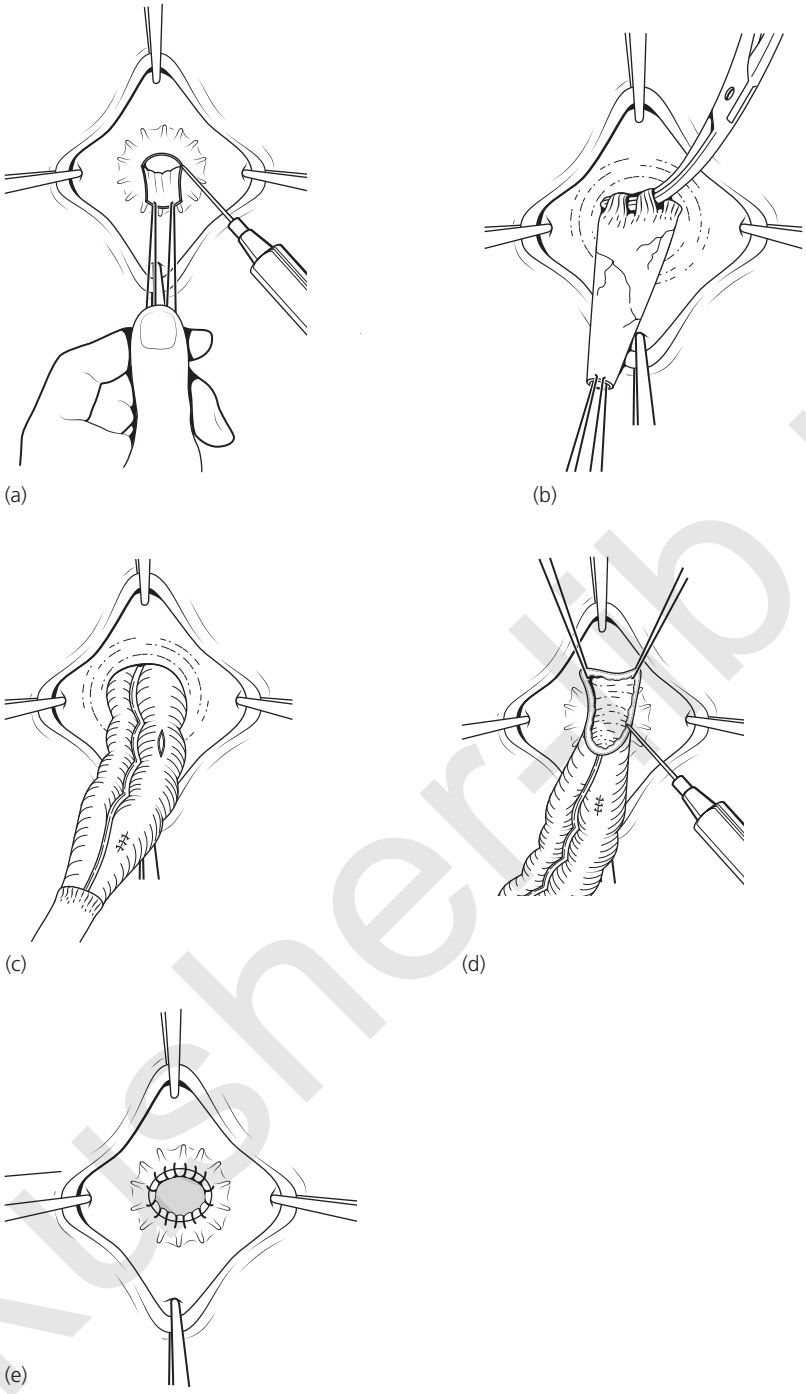


Figure 60.8 Transanal endorectal pull-through (a) Rectal mucosa is circumferentially incised using the needle-tip cautery approximately 5 mm above the dentate line and the submucosa plane is developed. (b) When the submucosal dissection is extended proximally for about 3 cm, the muscle is divided circumferentially, and the full-thickness of the rectum and sigmoid colon is mobilized out through the anus. (c) On reaching the transition zone, full-thickness rectal biopsies are taken for frozen section to confirm ganglion cells. (d) Colon is divided several centimeters above the most proximal biopsy site. (e) A standard Soave-Boley anastomosis is performed.

Retraction of pull-through

Retraction of a portion or all of the colonic segment from the anastomosis can occur and is usually seen within 3 weeks of the operation. Evaluation under general anesthesia is generally necessary. In occasional patients, resuturing the anastomosis may be feasible transanally. For those with separation of less than 50% of the anastomosis, but with adequate vascularity of the colon, a diverting colostomy for approximately three months is necessary. For patients with wide separation at the anastomosis, early transabdominal reconstruction of the pull-through is recommended.

Perianal excoriation

Perianal excoriation occurs in nearly half of the patients undergoing pull-through procedure, but generally resolves within three months with local therapy and resolution of diarrhea. It is helpful to begin placing a barrier cream on the perianal skin promptly after the operation and to continue after each movement for the first few weeks. Resolution of diarrhea will often hasten the clearance of perianal skin irritation.

Enterocolitis

Hirschsprung's associated enterocolitis (HAEC) is a significant complication of HD both in the pre-and postoperative periods.[77] HAEC can occur at any time from the neonatal period onwards to adulthood and can be independent of the medical management and surgical procedure performed. The incidence of enterocolitis ranges from 20 to 58%.[77] Fortunately, the mortality rate has declined over the last 30 years from 30 to 1%. This decrease in mortality is related to earlier diagnosis of HD and enterocolitis, rectal decompression, appropriate vigorous resuscitation, and antibiotic therapy. It has been reported that routine postoperative rectal washouts decrease both the incidence and the severity of the episodes of enterocolitis following definitive surgery. In episodes of recurrent enterocolitis, which can develop in up to 56% of patients, anal dilatations have been recommended. However, prior to commencing a treatment regime, a contrast enema should be performed to rule out a mechanical obstruction. Patients with a normal rectal biopsy may require a sphincterotomy.

Constipation

Constipation is common after definitive repair of HD and can be due to residual aganglionosis and high anal tone. Repeated and forceful anal dilations of botulinum toxin injection into the sphincter under general anesthesia may resolve the problem. In some patients, internal sphincter myectomy may be needed. In patients with scarring, stricture, or intestinal neuronal dysplasia proximal to aganglionic segment, treatment consists of treating the underlying cause.

Soiling

Soiling is fairly common after all types of pull-through operation, its precise incidence primarily dependent on how assiduously the investigator looks for it. The reported incidence of soiling ranges from 10 to 30%.[85] The attainment of normal postoperative defecation is clearly dependent on intensity of bowel training, social background, and respective intelligence of the patients. Mental handicap, including Down syndrome, is invariably associated with long-term incontinence. Those patients with preoperative enterocolitis would also seem to have a marginally higher long-term risk of incontinence. In some patients in whom soiling is intractable and a social problem, a Malone procedure may be needed to stay clean.

LONG-TERM OUTCOME

The vast majority of patients treated with any one of the standard pull-through procedures achieve satisfactory continence and function with time.[78,84–87] The attainment of normal continence is dependent on the intensity of bowel training, social background, and respective intelligence of patients. Mental handicap, including Down syndrome, is invariably associated with long-term incontinence.[88]

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61

Anorectal anomalies

MARC A LEVITT AND ALBERTO PEÑA

INTRODUCTION

Anorectal anomalies present with a spectrum of defects. This spectrum extends from patients with minor malformations that require minimal treatment who usually achieve excellent surgical results, to patients who are very sick with a complex defect. These more critical patients pose a serious technical challenge, and typically do not achieve perfect bowel, urinary, and sexual function despite accurate anatomic reconstruction. A newborn with an anorectal malformation may represent a surgical emergency related to intestinal obstruction or associated urologic or gastrointestinal defects requiring aggressive and efficient management. Other patients with these defects do not represent an emergency because they have a fistula that allows intestinal decompression. In these cases, the repair of the defect can become an elective procedure or, if the baby is in good condition, can be definitively managed in the newborn period.

Frequency

Anorectal malformations occur with a frequency of approximately 1 to 4000 or 5000 newborns.[1–3]

Classification

Box 61.1 gives a practical classification that is anatomically based.[4,5]

Box 61.1 Classification of anorectal malformations

Male defects
- Rectoperineal fistula
- Recto-urethral bulbar fistula
- Recto-urethral prostatic fistula
- Rectovesical (bladder neck) fistula
- Imperforate anus without fistula
- Rectal atresia and anal stenosis

Female defects
- Rectoperineal fistula
- Rectovestibular fistula
- Imperforate anus without fistula
- Rectal atresia and anal stenosis
- Cloacal malformation

CLINICAL FEATURES AND DIAGNOSIS

Male defects

RECTOPERINEAL FISTULA

This is the lowest defect seen in males and often presents with a 'bucket-handle' malformation (Fig. 61.1). The common anatomic feature is the fact that the rectal opening is located anterior to the center of the sphincter mechanism, as demonstrated by electrical stimulation during the repair (Fig. 61.2). We prefer to avoid terms such as 'anterior ectopic anus', since this opening is not really an anus as it has no pectinate line and is not surrounded by a sphincter. A rectoperineal fistula is a more accurate description. The fistula can occur anywhere along the median raphe; the closer to the scrotum the longer the common wall between the rectum and urethra. These defects can be treated primarily without a protective colostomy. Most of the time, the patient is able to pass small amounts of meconium through the fistula. Sometimes it takes a few hours before the baby passes meconium. Often a midline raphe subepithelial fistula is seen which looks like a black or white ribbon; also evidence of this type of defect (Fig. 61.3). Otherwise, the patients have a normal-looking perineum. The diagnosis is made by clinical inspection and usually no radiologic studies are necessary. The chance of having an associated genitourinary defect is extremely low. The patient's spine should be screened for an associated, albeit rare, tethered cord.

Figure 61.1 'Bucket handle' malformation.

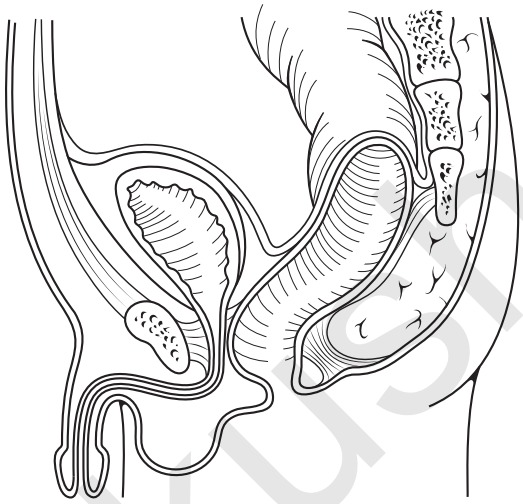

Figure 61.2 Rectoperineal fistula – sagittal view.

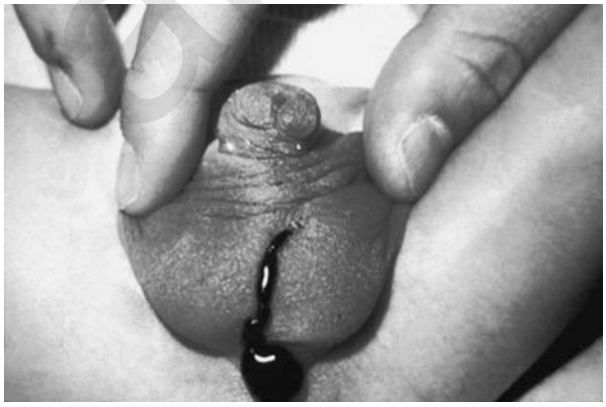

Figure 61.3 Cutaneous (subepithelial) fistula.

RECTO-URETHRAL BULBAR AND RECTO-URETHRAL PROSTATIC FISTULAS

The rectum can open into the bulbar urethra (Fig. 61.4) or into the prostatic urethra (Fig. 61.5). Both rectum and urethra have a common wall located above the fistula site which is longer in the case of bulbar fistula and shorter in the prostatic type.

These two types of defects are similar from a clinical point of view. However, the patient has more chance of having a 'good-looking' perineum connoting good sphincters in a case of recto-urethral bulbar fistula (Fig. 61.6); this means having a prominent midline groove and anal dimple. In cases of recto-urethral prostatic fistula, the chances of having a short sacrum and a flat perineum (Fig. 61.7) increase.

The neonatal nurse may notice that the baby is passing meconium through the urethra. A cross-table lateral film, with the patient in the prone position and the pelvis elevated, is a reliable study but depends on dilated distal rectum overcoming compression by the sphincteric funnel.[6] Fig. 61.8 shows a rectum very close to the perineal skin and Fig. 61.9 shows a higher rectum. The chances of recto-urethral fistula cases being associated with urological problems vary from 25% in cases of urethral bulbar fistula, to 66% in cases of urethral prostatic fistula. These newborns need a diverting colostomy.

RECTOVESICAL (BLADDER NECK) FISTULA

This defect accounts for approximately 10% of all anorectal defects in males. The rectum opens into the bladder neck in a 'T' fashion (Fig. 61.10). The entire pelvis of these babies seems to be hypodeveloped. It is frequently associated with poor muscle development and the perineum looks rather flat in most patients (Fig. 61.7); although some patients with this defect may have a 'good-looking' perineum (Fig. 61.6) with a midline groove and a prominent anal dimple. The frequency of associated urological anomalies in this specific defect is very high (up to 90%),[7] and therefore a urologic work up is mandatory. A cross-table lateral film, with the patient in the prone position and with the pelvis elevated, shows an image consistent with air much higher than the pubococcygeus

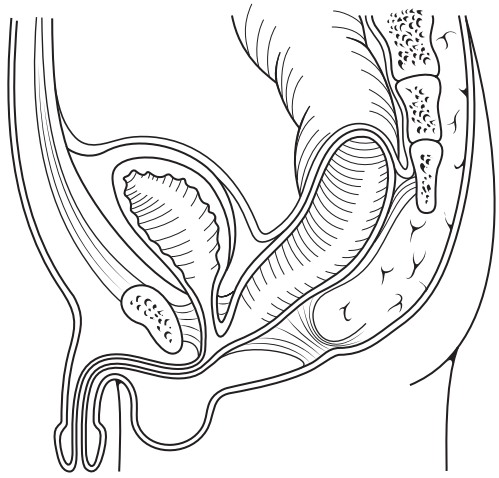

Figure 61.4 Recto-urethral bulbar fistula – sagittal view.

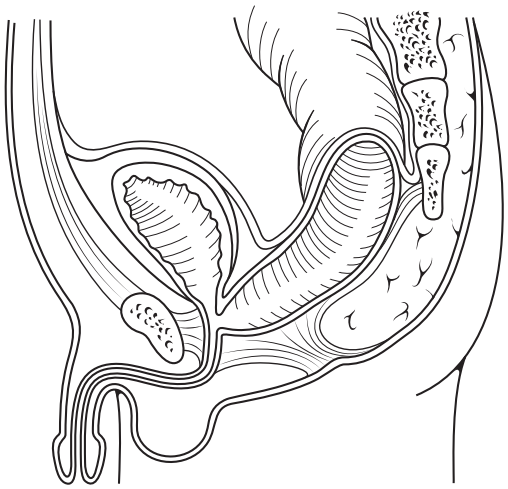

Figure 61.5 Recto-urethral prostatic fistula – sagittal view.

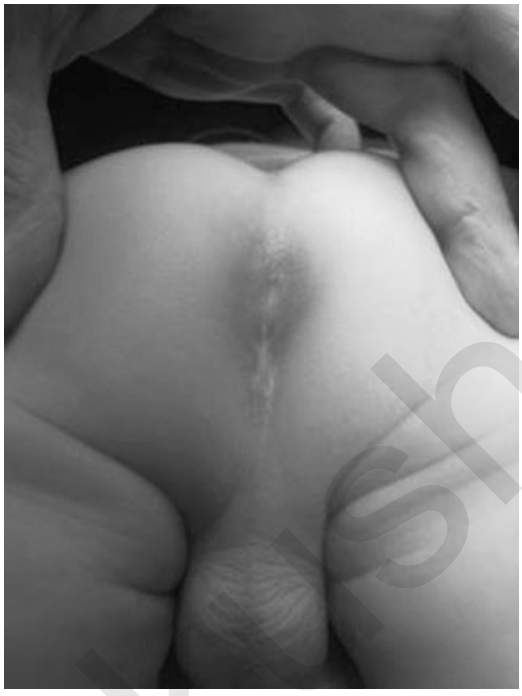

Figure 61.6 'Good-looking' perineum.

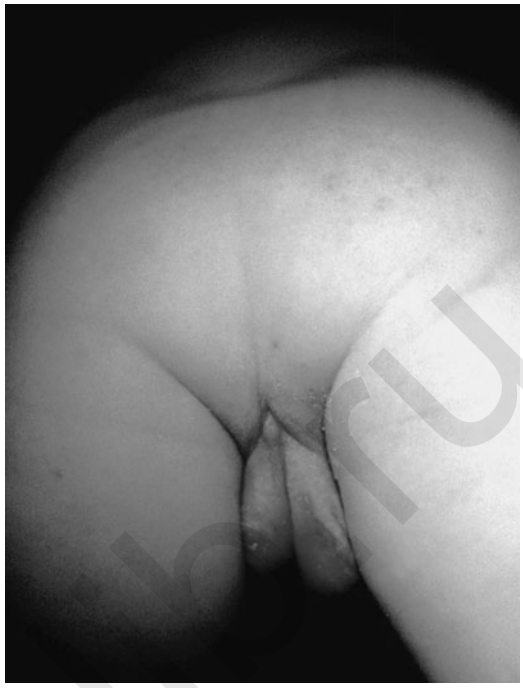

Figure 61.7 Flat bottom.

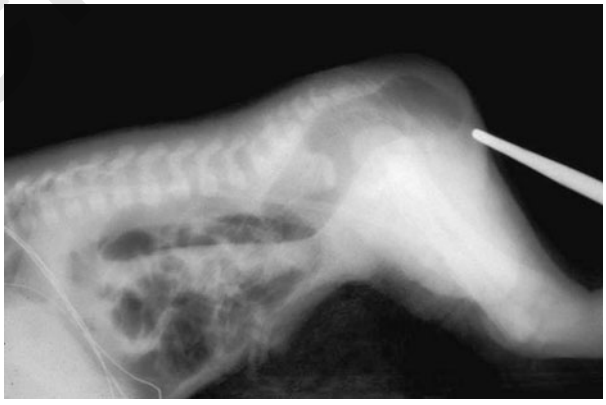

Figure 61.8 Cross-table lateral film of rectoperineal fistula, within 1–2 cm of perineal skin.

line (Fig. 61.9). The neonatal nurse may note that the baby is urinating meconium. Manifestations of intestinal obstruction will become evident during the first 12–24 hours. In addition to these symptoms, the baby may show symptoms consistent with acidosis and sepsis secondary to an obstructive uropathy. These patients require a colostomy. They will also require an abdominal approach (laparoscopic or laparotomy) during the definitive repair, in addition to the posterior sagittal approach.

IMPERFORATE ANUS WITHOUT FISTUAL

In this type of defect, the blind rectum is usually located at the level of the bulbar urethra. Even when there is no communication between rectum and urethra, the wall that separates both of them is very thin and has no surgical plane of separation. This defect is uncommon, but it has good muscle development, and therefore most of the time the perineum is a 'good-looking' one. The frequency of this defect is approximately 5% of male defects.[8] However, a distal colostogram that is not done properly with the aim of demonstrating a recto-urethral fistula will give an incorrect assessment of 'no fistula'. A successful colostogram requires the injection of contrast into the blind rectal pouch under enough hydrostatic pressure as to demonstrate the passage of contrast material into the urethra.[9] The rectum in all types of malformations is surrounded by voluntary muscle (Figs 61.2, 61.4, 61.5, and 61.10) and the hydrostatic

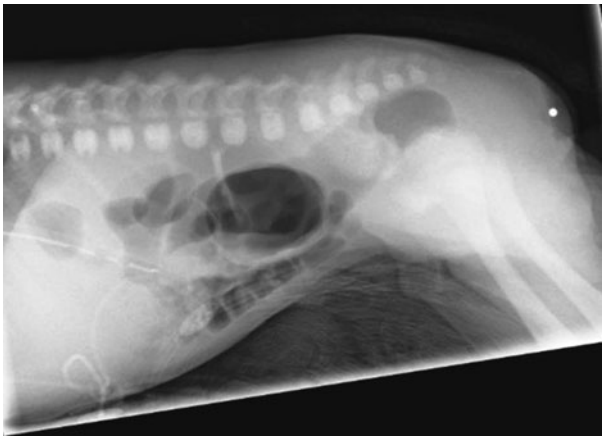

Figure 61.9 Cross-table lateral film of a rectum that is greater than 2 cm from the perineal skin representing probably a recto-urethral or rectobladder neck fistula.

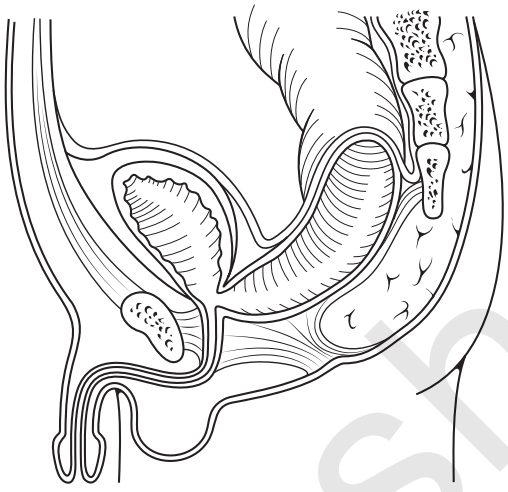

Figure 61.10 Rectovesical (bladder neck) fistula sagittal view.

pressure must be high enough to overcome the muscle action which is compressing the distal rectum. The lack of pressure represents a frequent error that may explain the reporting of higher numbers of imperforate anus without fistula when actually this is a rather unusual defect. It is interesting to note that out of all our cases of imperforate anus with no fistula, approximately half of the cases have Down syndrome. The other half is predominantly made up of patients with other syndromes. Also, in all of our Down syndrome patients with imperforate anus, 95% have no fistula, clearly pointing to a genetic impact on anorectal malformations.[10,11] These patients also require a newborn diverting colostomy. The chances for these patients to have an associated defect are low.

RECTAL ATRESIA AND ANAL STENOSIS

This is a rare type of defect classically described as the one that is diagnosed by the nurse while passing the thermometer during the initial newborn physical examination. The reason for this is that these babies are born with a normal anal canal and have an atresia located appoximately 1–2 cm above the anal verge. Superior to that, there is a dilated rectal pouch. In some cases, the patient actually has a stenosis. The separation between the blind pouch and the anal canal may be a very thin membrane, but more frequently there is a thick fibrous septum of 3–7 mm in length. These patients need a colostomy. The perineum looks normal, the sacrum is usually normal, and the chances of associated defects are extremely low. A presacral mass must be looked for by ultrasound and/or magnetic resonance imaging. These patients have all the necessary anatomical elements to become totally continent; the muscles are intact and the anal canal has normal sensation.

Female defects

RECTOPERINEAL FISTULA

This is the lowest defect seen in females and it is equivalent to the same defect already described in males. The fistula site is located anywhere between the vestibule and the center of the anal dimple (Fig. 61.11). The entire fistula site is surrounded by skin and therefore it is also given the name 'cutaneous fistula'. The orifice is variable in size and may be sufficient for a full-bowel evacuation. If not, anal dilations can be utilized to provide good bowel movements if the repair will not be done in the neonatal period. Our routine is to do the repair in the newborn period and then to keep the patient NPO (nothing by mouth) on i.v. nutrition for 7 days after the repair.

These patients do not require a protective colostomy as part of their treatment. The most prominent anatomical feature in this type of defect is that the rectum and vagina do not share a common wall (Fig. 61.11). Thus, the technical implication is that the rectum can be mobilized without risking injury to the vagina. Patients have otherwise normal muscle structures and a normal sacrum. The incidence of associated defects of the urinary tract or spine is very low.

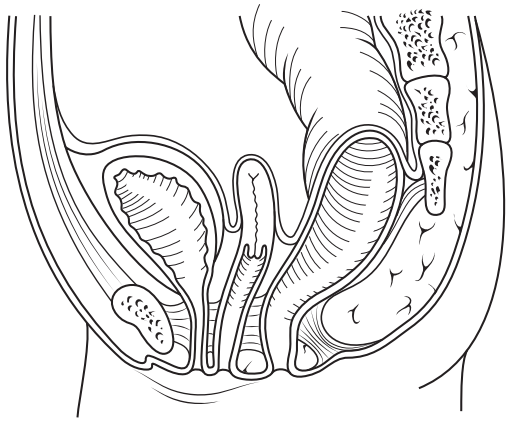

Figure 61.11 Rectoperineal fistula in a female patient.

RECTOVESTIBULAR FISTULA

This is the most frequent defect seen in females. The distal rectum opens into the vestibule, which is the space located immediately outside the hymen (Fig. 61.12). The most notable anatomic feature in this defect is the presence of a very long common wall between rectum and vagina located above the fistula site (Fig. 61.12). The vagina must be completely separated from the rectum in order to achieve good mobilization and a tension-free repair. There is no surgical plane of separation between these two structures and one must be carefully created. The fistula is usually represented by a short (5–15 mm), narrow rectal opening, which sometimes is not wide enough to decompress the bowel and requires dilatations if the surgeon is not proceeding with a newborn repair. Above that, there is a completely normal rectum. Sometimes the orifice is wide enough to allow a satisfactory decompression. The opening of a colostomy is the safest way to manage these babies but an experienced surgeon can operate on this defect primarily without a colostomy if the baby is otherwise healthy. In such a case, we would operate in the newborn period and would keep the patient NPO and on i.v. nutrition for 7 days after surgery. The incidence of associated urogenital malformations is 30%,[7] and the sacrum is usually normal. The perineum of these babies shows a prominent mid-line groove and a very obvious anal dimple. Occasionally in this type of defect we see a 'poor-looking' perineum as well as a short or abnormal sacrum.

RECTOVAGINAL FISTULA

A true rectovaginal fistula is a very unusual defect. Less than 1% of females have this malformation. On the other hand, rectovaginal fistula is presented in the traditional literature as a relatively common defect. A recent review of the authors' own experience with reoperations in female patients showed 80 female patients operated on at other institutions with a diagnosis of rectovaginal fistula. During our reoperations, objective evidence indicated that none of these patients actually had rectovaginal fistulas. In fact, two-thirds of them had cloacas. The original surgeons were unaware of the correct diagnosis; they repaired the rectal component of the malformation and left the patient with a persistent urogenital sinus. The remaining one-third of the patients actually had rectovestibular fistulas and that diagnosis was also missed by the surgeon.[12] The importance of this observation is not only semantic; the group of patients who were born with cloacas were mislabeled as having rectovaginal fistulas and these patients missed a good opportunity to have their entire malformation repaired during the first operation. The results of a second procedure are never as good as the first one. Furthermore, the patients with a rectovestibular fistula were erroneously subjected to an unnecessary abdominal perineal procedure and, as a result, suffer from fecal incontinence from resection of the rectosigmoid. Therefore, it is very important to increase the index of suspicion for malformations such as cloaca and rectovestibular fistula, and to recognize that rectovaginal fistulas are almost non-existent defects.

To make the diagnosis of a real rectovaginal fistula (Fig. 61.13), it is necessary to perform a meticulous inspection of the genitalia which is sometimes not easy to perform in the newborn period due to swelling. Patients with rectovaginal fistulas would show meconium coming from inside the vagina through the hymen. These babies may have a significant incidence of associated urological defects (around 70%).[7] If the rectum is high in the pelvis and the

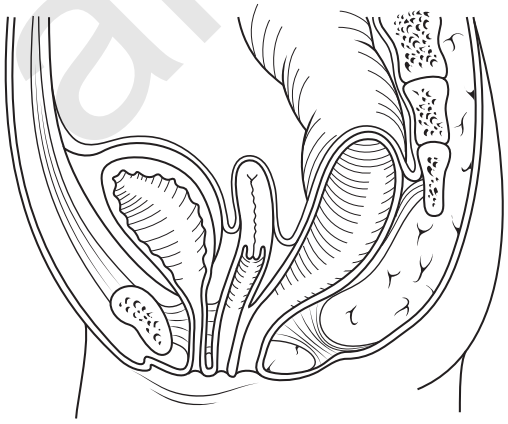

Figure 61.12 Rectovestibular fistula.

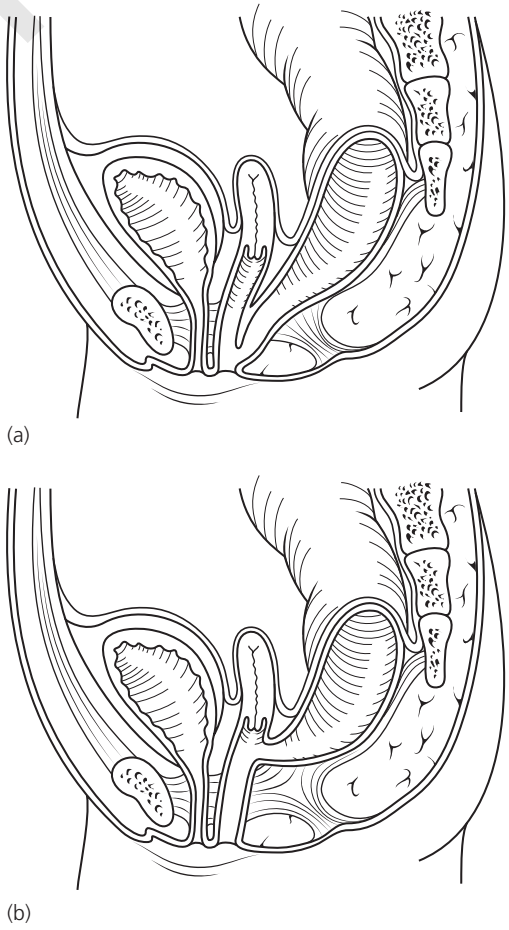

Figure 61.13 Rectovaginal fistula: (a) low; (b) high.

urethra and vagina are normal, this is a rare but useful indication for a laparoscopy in a female with anorectal malformation.

IMPERFORATE ANUS WITHOUT FISTULA

All that was written regarding this defect in males is valid regarding females, the only difference obviously being that the anterior rectal wall is separated from the posterior vaginal wall, not the urethra.

RECTAL ATRESIA AND ANAL STENOSIS

This type of defect is identical to the one described in males, except that its frequency in females seems to be higher. The clinicians must always remember to screen for a presacral mass.

PERSISTENT CLOACA

This is the most complex anorectal malformation seen in females. It represents approximately 10% of the total number of anorectal defects. A cloaca is defined as the junction of rectum, vagina, and urethra into a single common channel (Fig. 61.14). Cloacas represent another spectrum by themselves. At one end of the spectrum a rather benign, short common channel (<3 cm) type of cloaca with good prognosis and no associated defects may be found. At the other end of the spectrum, there exists a more complex defect with a common channel geater than 3 cm in length, a very short vagina, severe associated obstructive uropathy as well as a very poor sacrum and poor muscles (Fig. 61.15). Therefore, the prognosis for this last type of case will be very poor for bowel and urinary control. The spectrum of cloacas include many different types, among them patients with a very dilated vagina which becomes evident as a palpable abdominal mass called 'hydrocolpos'. The dilated vagina usually causes urinary obstruction from compression of the ureters at the trigone (Fig. 61.16). A frequent finding is a double vagina and double uterus; and the rectum may open at different levels in the mid-vaginal septum (Fig. 61.17). The majority of these long channel cloacas require an abdominal approach during the definitive repair, in addition to the perineal operation.[13]

The most important fact to remember in this type of defect is the high incidence of associated urinary tract

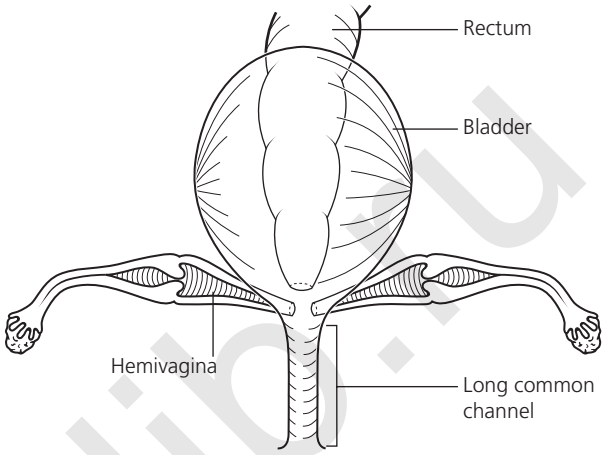

Figure 61.15 High cloaca with common channel of 5 cm.

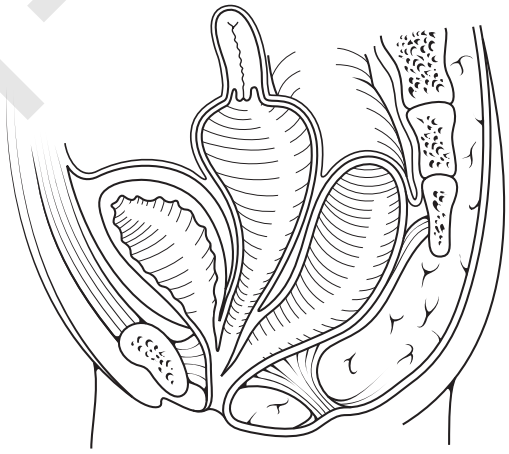

Figure 61.16 Cloaca with hydrocolpos.

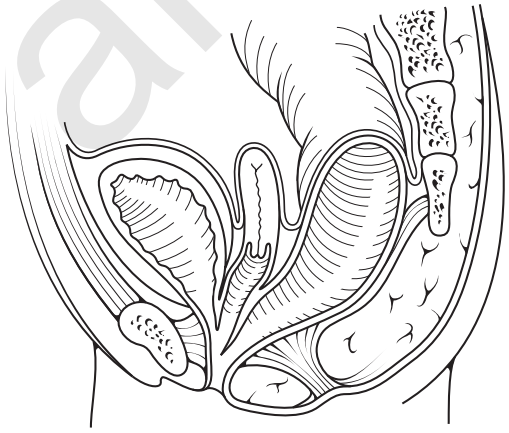

Figure 61.14 Persistent cloaca.

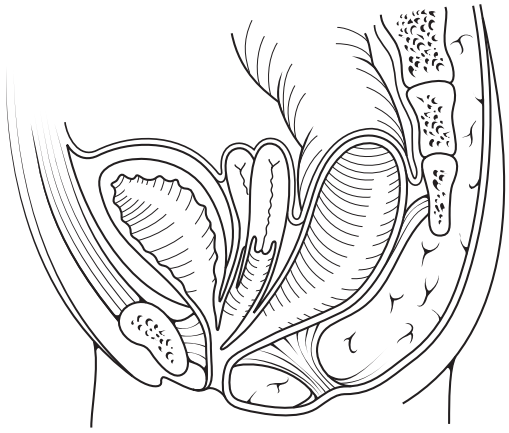

Figure 61.17 Duplicate Müllerian system.

obstruction (70–90%).[7] Obstructive uropathy is the main cause of morbidity and even mortality in these patients. The diagnosis of a cloaca is a clinical one. General practitioners, pediatricians, and neonatologists, as well as pediatric surgeons, must suspect this defect if they want to detect it and make an early diagnosis. A baby girl with absent anus and small-looking genitalia must arouse the suspicion for the presence of a persistent cloaca (Fig. 61.18). If the labia minora is separated, a single orifice becomes evident. These findings are pathognomonic for a cloaca. At that point, the priority in a newborn is the evaluation and treatment of the associated defects of the urinary tract. The external appearance of the perineum in these babies may vary. Sometimes a 'poor-looking' perineum is found, which means a flat bottom, a very poor midline groove, and almost absent anal dimple. However, a cloaca with good muscles and a good sacrum may be found. A cloaca always needs a completely diverting colostomy. If a hydrocolpos is present the patient also needs a vaginostomy. Very rarely a vesicostomy is indicated. In addition to the urologic evaluation (mandatory in cases of cloacas), x-ray films done during the newborn period in females with anorectal malformations are seldom useful, since most of these patients have a visible fistula opening or pass stool through the perineum.

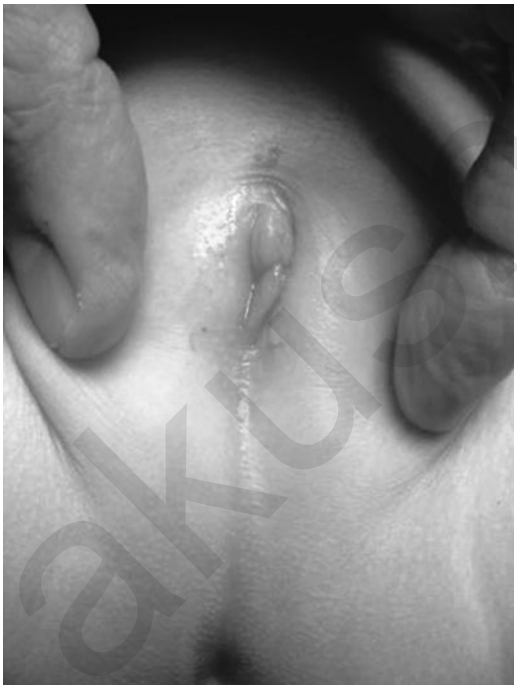

Figure 61.18 Cloaca, perineal appearance.

PREOPERATIVE CARE

Figs 61.19 and 61.20 show decision-making algorithms for the initial management of newborns with anorectal malformations.

In approximately 90% of the males, physical examination (perineal inspection) produces enough information to determine whether or not the patient needs a colostomy. The presence of a rectoperineal subepithelial midline raphe fistula or a 'bucket-handle' defect are all in the group of defects traditionally known as 'low'. These can be treated during the newborn period with a simple anoplasty and without a protective colostomy. In cases of very ill babies, a series of anal dilatations may be enough to allow bowel decompression, leaving the anoplasty to be done later as an elective procedure. On the other hand, a flat bottom, evidence of meconium in the urine, a very abnormal sacrum or spine, or other severe associated defects are enough information to proceed with a colostomy. These babies receive an emergency colostomy, and 4–8 weeks after the colostomy, provided that the patient is growing well, and after radiologic evaluation of the distal colon, a posterior sagittal anorectoplasty (PSARP) is performed.

The remaining 10% of males have questionable clinical evidence. In these cases, we recommend the cross-table lateral film with the patient in prone position.[6] An intraluminal bubble located more than 1 cm from the skin is considered an indication for a colostomy (Fig. 61.9). If the patient does not have signs of a recto-urinary fistula, the case most likely is one of imperforate anus with no fistula. If the patient has Down syndrome,[11] it is even more likely that there will be no fistula. On the other hand, if the rectum is located closer than 1 cm from the skin (Fig. 61.8), the patient was probably born with a rectoperineal fistula and stool has not yet passed out of the fistula. The surgeon should inspect the perineum again and may find a tiny orifice, so narrow that it does not allow the passage of meconium in the first hours of life. The baby can then be treated with a minimal PSARP without a colostomy.

Fig. 61.20 shows the decision-making algorithm used for the initial management of newborn females with anorectal defects. The process of decision-making in females is easier than in males, mainly because the vast majority of females have some form of fistula either to the perineum, vestibule, or genitalia which indicates the type of defect that they have.

The presence of a cloaca (single perineal) orifice, as previously discussed, represents an indication for an urgent urological evaluation. In addition, the patient will require a colostomy and sometimes a vaginostomy. Provided the baby is growing well, the patient may undergo the definitive repair of her defect at the age of three to six months.

For cases in which the meconium comes from the vestibule, an experienced surgeon can perform a primary repair or else a protective colostomy is needed. Often the fistula opening is large enough to decompress the bowel, and therefore there is no need for an emergency colostomy and the definitive repair can be delayed for several months.

The presence of a cutaneous (rectoperineal) fistula indicates that the baby has the most benign type of anorectal defect. This can be treated with a 'minimal' posterior sagittal anoplasty without a protective colostomy. If the rectoperineal fistula is large enough to decompress the intestine, the anoplasty can be postponed and done on an elective basis. The remaining 5% of female patients who have no fistula need a colostomy followed by a PSARP 4–8 weeks later.

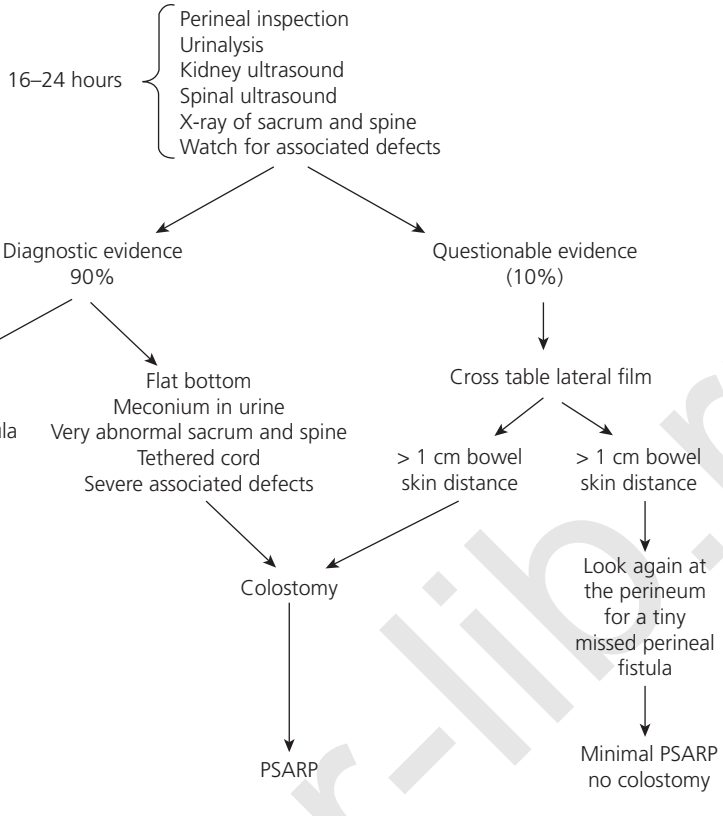

Figure 61.19 Male newborn algorithm for anorectal malformations. PSARP, posterior sagittal anorectoplasty.

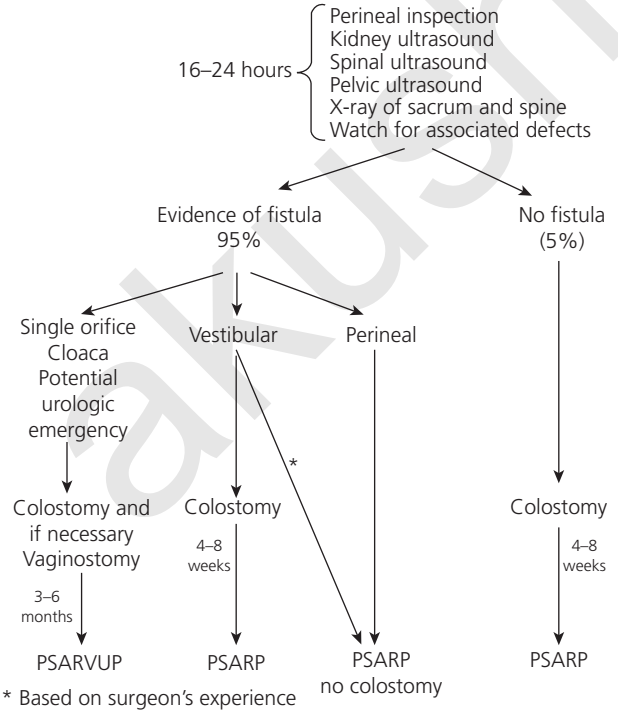

Figure 61.20 Female newborn algorithm for anorectal malformations. PSARP, posterior sagittal anorectoplasty; PSARVUP, posterior sagittal anorectovaginourethroplasty.

Every surgeon must develop their own learning curve for the surgical management of these defects. We prefer to do the repair in the newborn period if appropriate, and otherwise within the first one to three months of life. As one gains confidence with this technique, the main repair can be done earlier and earlier. There are both theoretical and practical advantages to doing these repairs early in life. From the theoretical point of view, placing the rectum in its normal position early may allow the creation of new nerve synapses which may be advantageous in terms of future bowel control.[14] From a practical point of view, it is much easier to dilate the anus of a small baby than trying to do it in an older patient. The healing of the perineal repair is also quicker in a baby who does not yet crawl.

We promote the trend to operate on newborns with anorectal malformations primarily, without a protective colostomy when feasible.[15] When compared to the alternative of three operations (colostomy, main repair, and colostomy closure), a single procedure is highly attractive. However, what remains to be seen is whether or not such treatment will result in better functional results. Those who embrace the new treatment modality are morally obligated to report their results, including complications. Concerning the laparoscopic approach of these malformations,[16] it must be kept in mind that as we have described, 90% of the male cases can be repaired via the posterior sagittal route without opening the abdomen. These patients experience minimal pain, eat the same day of surgery, and could even go home the same

day of the operation. Laparoscopy was created and conceived as minimally invasive surgery but it is not clear whether it is better to repair malformations through the peritoneal cavity that are able to be repaired in an extra-abdominal and extraperitoneal way. There is one particular defect (recto-bladder neck fistula), that represents 10% of all malformations in males, that we feel is ideally suited to a laparoscopic approach. For rectoprostatic fistulas, the approach should be based on which technique the surgeon feels most skilled to perform, laparoscopic or PSARP. For other malformations such as recto-urethral bulbar fistula, no fistula, or in females, we do not think laparoscopy is appropriate.

In general, babies with anorectal malformations look healthy unless they have a severe associated defect, mainly urologic, cardiac, or at another site of the gastrointestinal tract. The frequency of associated urologic defects in babies with anorectal malformation varies.[17–22] In our series, approximately half of the patients with anorectal defects had a significant associated urologic defect, and this frequency varies depending on the level of the fistula site. This, we believe, may help neonatologists and pediatricians suspect, detect, and treat these defects early. A constellation of associated findings (single kidney, absent scrotum, esophageal atresia, etc.) can also be detected prenatally.[23] Before the performance of the colostomy, every baby must have an abdominal ultrasound performed to rule out the presence of obstructive uropathy.

Concerning the passage of meconium, decisions should not be made during the first 16–24 hours of life since meconium often does not appear until after that period of time. Abdominal distension does not become a problem during the first 16–24 hours of life. Therefore, decisions as to whether the baby should undergo primary repair or a colostomy should wait for 16–24 hours for clinical evidence of the anorectal defect.

COLOSTOMY

Once the decision has been made to perform a colostomy, a nasogastric tube is placed in the stomach and i.v. fluids started. Prophylactic antibiotics are recommended.

Fig. 61.21a shows the type of colostomy that the authors recommend in the management of anorectal malformations. The advantages of this colostomy[24] over other types include:

- defunctionalizes only a small portion of the distal intestine, allowing better water absorption;
- is completely diverting;
- allows for an adequate length of bowel for the pull-through, a significant problem if the stoma is placed too distal in the sigmoid (Fig. 61.21b);
- allows decompression of urine that may pass from the urinary tract back into the rectum;
- simplifies cleaning of the distal intestine
- makes the distal colostograms easier than when dealing with a more proximal colostomy;
- reduces the incidence of prolapse to virtually zero.

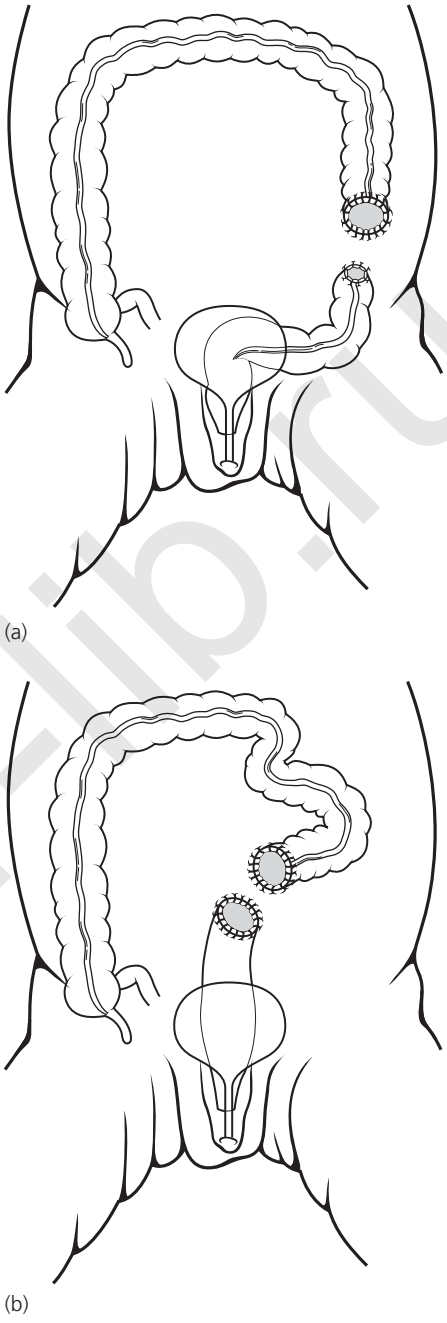

Figure 61.21 (a) Ideal colostomy. (b) Too distal colostomy.

Loop colostomies are problematic because they allow feces to pass into the distal stoma provoking fecal impaction, megarectum, and urinary tract infection. There is also a risk of contamination and infection after the main repair.

The recommended incision measures approximately 6 cm, is made in the left lower quadrant and is oblique. The proximal functional stoma is placed in the upper and lateral portion of the incision and the mucous fistula (non-functional) distal stoma is made small and placed in the lower and medial portion of the incision. The two stomas must be far enough apart so that the stoma bag does not

cover the mucous fistula. The distal bowel must be irrigated with saline solution during the operation to evacuate all of the meconium. In this way, the bowel remains completely clean, does not get distended, and the patient does not need any preparation prior to the main repair.

A colostomy must be considered a serious, delicate procedure. The surgeon must carefully identify the piece of intestine that they are going to exteriorize to avoid serious mistakes. The most frequent errors in performing colostomies seen by the authors include:[25]

- A colostomy placed too distal in the sigmoid.
- Opening of a right upper sigmoidostomy. The surgeon thought they were opening a transverse colostomy and actually grabbed the sigmoid colon and exteriorized it in the right upper quadrant. This interferes with the pull-through.
- Retracting colostomies. In these cases the bowel was probably handled poorly and may suffer from ischemia and retraction. In addition, the bowel is poorly fixed to the abdominal wall. To avoid this, the authors' suggestion is to fix the bowel to the peritoneum and to the anterior fascia.
- Prolapsed colostomies. Choosing the very proximal sigmoid for the functional end avoids prolapse because of the left colon's attachment to the retroperitoneum.

After the colostomy, once feedings are advanced, the baby can be discharged. If the baby is growing well, the main repair can be performed 4–8 weeks post-op. Prior to the final repair, it is mandatory to perform a distal colostogram in order to determine the precise type of anatomic defect that one is dealing with. This has important prognostic and therapeutic implications. This study must be done under fluoroscopy. A Foley catheter is introduced into the distal stoma, its balloon is inflated and water-soluble contrast material (never barium) is injected under enough hydrostatic pressure to overcome the contraction of the funnel-like muscle structure that surrounds the lowest part of the rectum. The dye injection is done by hand with a 60cc syringe. Failure to observe these principles will most likely show the dye staying above the pubococcygeus line, erroneously indicating the presence of a very high defect and not showing the fistula, simply because of the lack of hydrostatic pressure.[9] Figs 61.22–61.24 show distal colostograms in a case of recto-urethral bulbar fistula, rectoprostatic fistula, and rectovesical (bladder neck) fistula. Having this information, the surgeon will be able to plan the surgical procedure. When dealing with a case of rectovesical (bladder neck) fistula, the surgeon will be able to predict that the prognosis in terms of bowel function will not be as favorable as in other types of defects.[5] In addition, the main repair will take approximately 3–4 hours. A laparotomy or laparoscopy will also be necessary in order to mobilize the rectum. Most importantly, the surgeon will avoid looking for the rectum through a posterior sagittal incision where it will not be found, because that would risk injury to the urinary tract, vas deferens, seminal vesicles, and ectopic ureters. The posterior sagittal approach in this case will be used only to show the trajectory of the pull-through after its mobilization

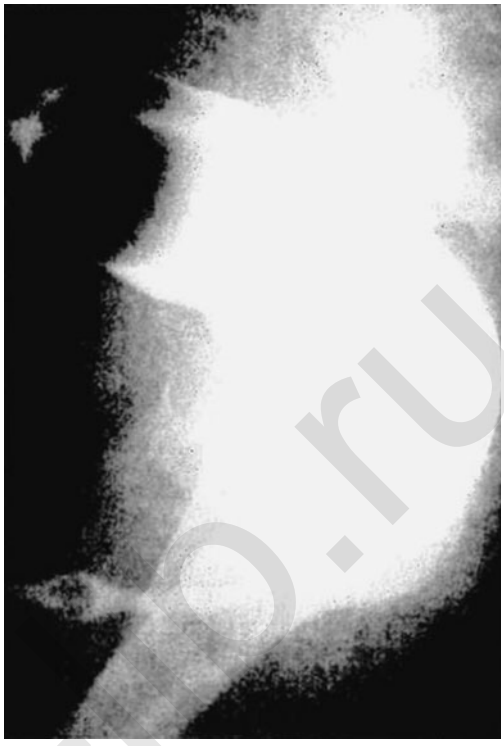

Figure 61.22 Distal colostogram in a recto-urethral bulbar fistula.

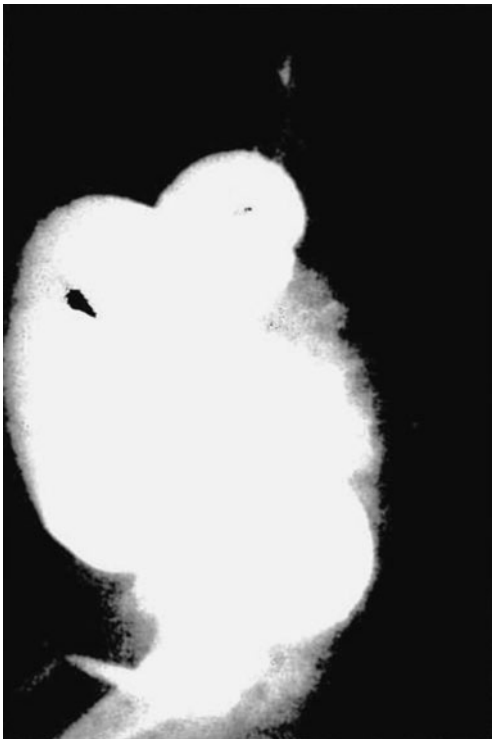

Figure 61.23 Distal colostogram in a recto-urethral prostatic fistula.

Figure 61.24 Distal colostogram in a rectovesical (bladder neck) fistula.

through laparoscopy or via laparotomy, and to allow tacking of the rectum to the muscle complex.

DEFINITIVE REPAIR

Minimal posterior sagittal anoplasty

This operation is done in all the so-called 'low' defects, including rectoperineal (cutaneous) fistulas in both males and females. In cases of male newborns it is important to place a Foley catheter in the bladder during the operation. The rectum and urethra are very close together despite not having a communication. The incision is very small and divides the posterior sphincter mechanism and continues around the fistula in a 'racket-like' fashion (Fig. 61.25a). Multiple 6-0 sutures are placed taking the mucocutaneous junction of the fistula. This serves the purpose of exerting uniform traction which helps in the dissection. The distal fistula is mobilized, as well as part of the rectum, sufficiently to be relocated comfortably within the limits of the sphincter without tension (Fig. 61.25b). The rectum is anchored to the muscle complex and then a 16-stitch anoplasty is done, as shown in (Fig. 61.25c).

Limited posterior sagittal anorectoplasty

This procedure is performed in cases of rectovestibular fistula in female newborns. The incision is very similar to the one just described but it is extended more cephalad, as far as necessary to achieve enough bowel mobilization. The main difference to the previous defect is the fact that the rectum and vagina share a rather long common wall. The most vital part of the operation consists of separating the rectum and vagina by creating a plane of separation without injuring either one (Fig. 61.26). The separation is carried out all the way up until both structures have a full-thickness normal wall. Lack of adequate rectal mobilization is the main cause of dehiscence after this repair. The separation of the rectum from the vagina requires a meticulous and delicate technique and is performed with a

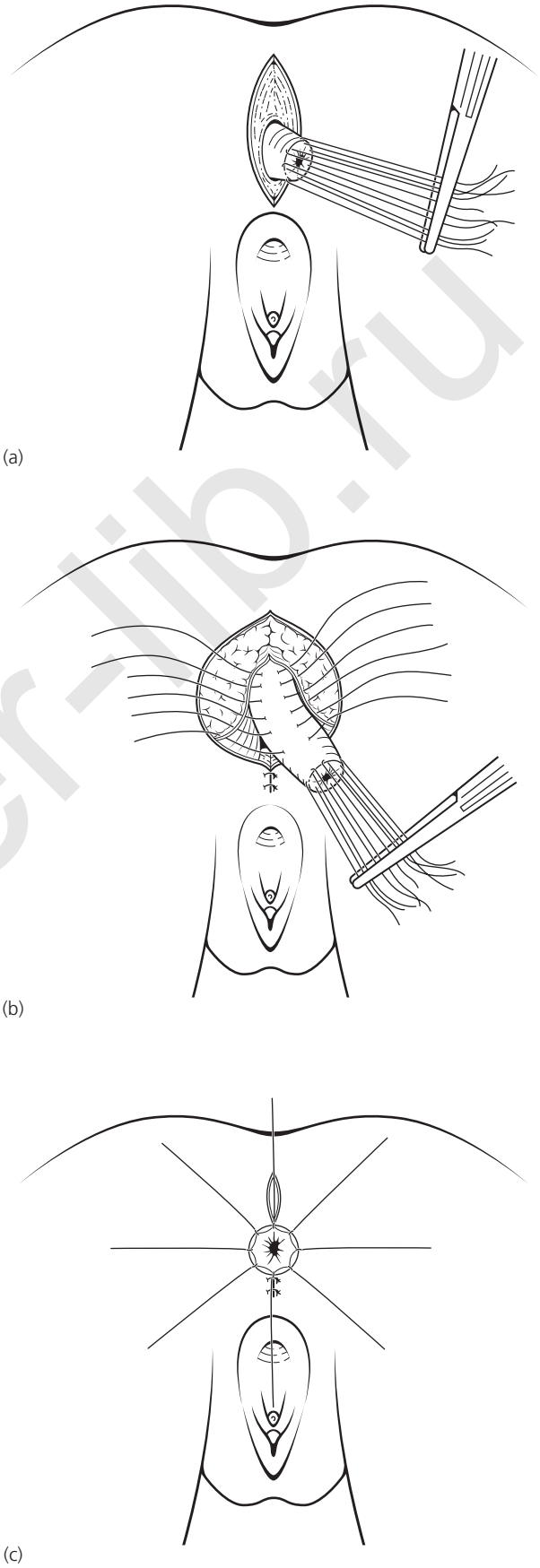

Figure 61.25 Rectoperineal fistula repair: (a) incision; (b) reconstruction: (c) anoplasty.

needle-tip cautery, changing from cutting to coagulation where necessary to provide meticulous hemostasis. Once the rectum has been completely separated, the limits of the external sphincter are determined by electrical stimulation. This will indicate where the rectum should be placed. The perineal body is then reconstructed with long-term absorbable sutures (Fig. 61.27a). The rectum is anchored to the posterior edge of the muscle complex (Fig. 61.27b) and then a 16-stitch anoplasty is performed in the same way as previously described (Fig. 61.27c,d). If a colostomy is present, these patients can have oral feedings on the same day as surgery and can go home the following day. If undiverted, our routine is to keep them NPO and on i.v. nutrition for 7–10 days. Antibiotic ointment is applied to the wound three times a day for 1 week.

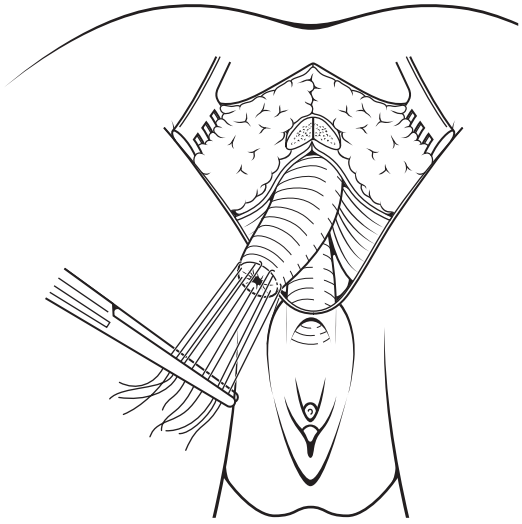

Figure 61.26 Rectovestibular fistula repair. Separation of rectum.

Posterior sagittal anorectoplasty

This technique is used for the repair of a recto-urethral fistula or a rectovaginal fistula. The patient is placed in the prone position as previously described, with the pelvis elevated and with a Foley catheter in the bladder. Electrical stimulation of the perineum will allow the surgeon to identify the anal dimple. The incision runs from the lower portion of the sacrum down and through the sphincter mechanism, staying exactly in the midline, leaving equal amounts of muscle on both sides. After opening of the skin and subcutaneous tissue, the parasagittal muscle fibers can be identified. The incision is deepened and after another area of fat (the ischiorectal space) the levator muscle is found. The levator muscle flows

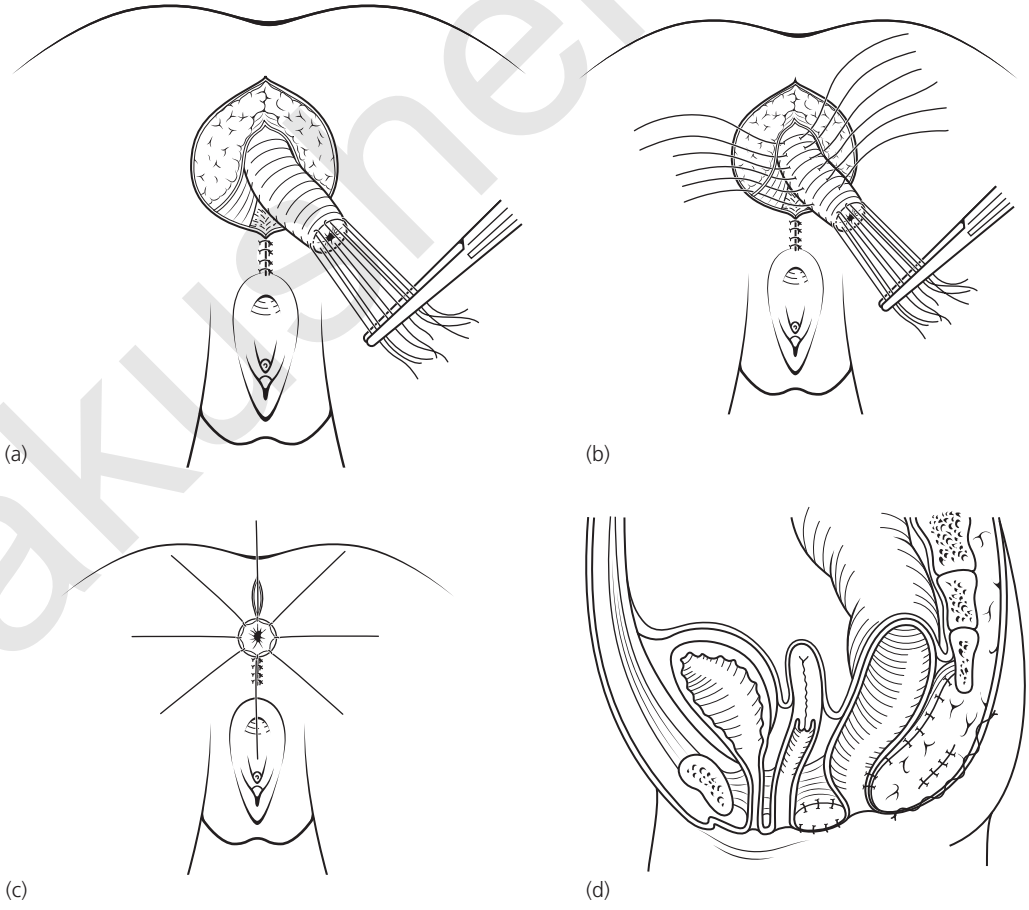

Figure 61.27 Rectovestibular fistula repair: (a) perineal reconstruction; (b) anchoring rectum to muscle complex; (c) anoplasty; (d) operation completed.

into the muscle complex up to the skin of the anal dimple, forming a funnel-like structure. Parasagittal fibers that run on both sides of the midline will close the lumen of the anus once this is reconstructed. Muscle complex fibers run perpendicular to the parasagittal ones and also medially. The muscle complex and parasagittal fibers cross perpendicularly, forming the posterior and anterior limits of the new anus (Fig. 61.28). The contraction of the muscle complex and levator pulls in the anus. The levator muscle is opened exactly in the midline. The rectum is then opened along its posterior wall between two traction sutures. Once the rectum is opened, the fistula site can be visualized. It must be remembered that the rectum and urethra share a common wall immediately above the fistula. Accordingly, a submucosal dissection must be carried out above the fistula site (Fig. 61.29). After approximately 1 cm of submucosal dissection, the dissection continues taking the full thickness of rectal wall. Once the rectum has been separated from the urethra, the fistula is closed with interrupted long-term absorbable sutures. The rectum is then dissected in a circumferential manner, so as to gain enough length to reach the perineum without tension (Fig. 61.30).

Tapering, as shown in Fig. 61.31 is rarely needed, but if necessary must be carried out in the posterior aspect of the rectum. The bowel must then be closed in two layers of interrupted sutures. The rectum is then placed in front of the levator muscle within the limits of the sphincter mechanism, and is also anchored to the posterior edge of the muscle complex to prevent prolapse (Fig. 61.32). The anoplasty is done as previously described (Figs 61.33 and 61.34).

Following the operation, the Foley catheter must remain in place for 7 days. If the catheter comes out accidentally, it is better to leave it out rather than trying to pass it back into the bladder and thus risking a urethral perforation at the urethral

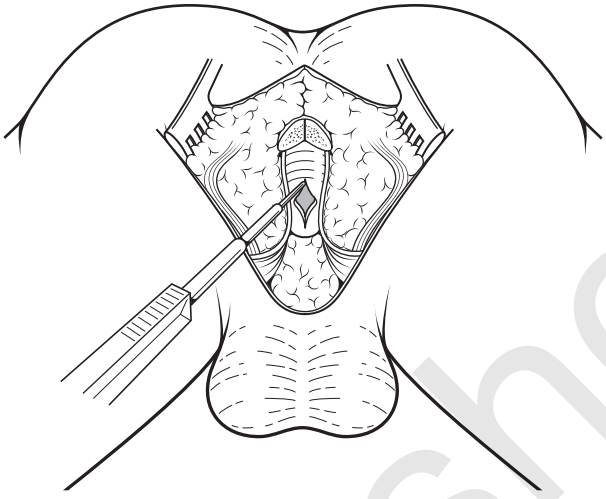

Figure 61.28 Anatomy exposed. Parasagittal fibers, muscle complex, and levator muscle have been split in the midline. The rectum is open in the midline.

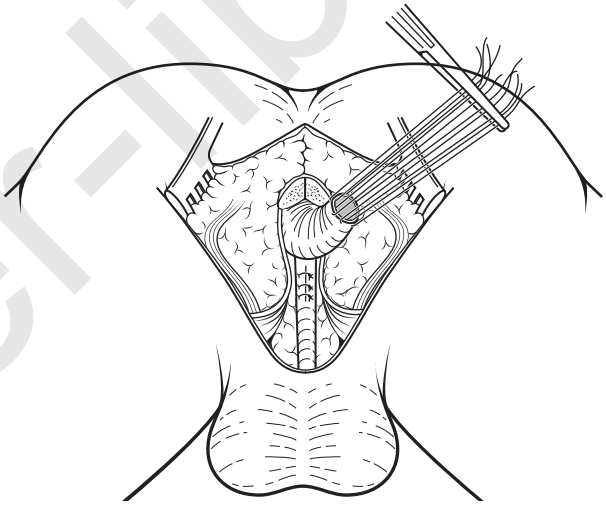

Figure 61.30 Rectum separated from urethra.

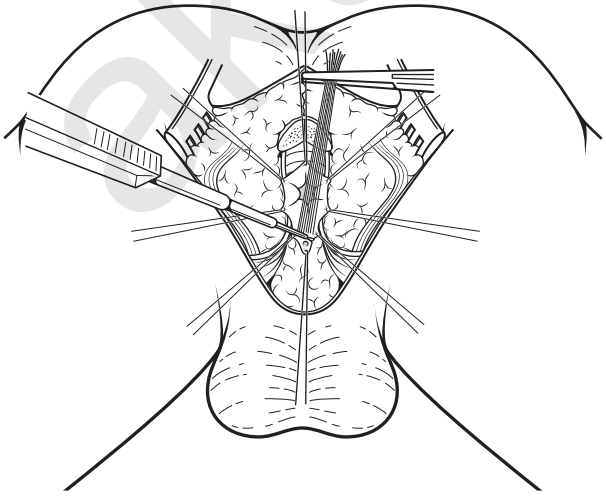

Figure 61.29 Separation of rectum from urethra.

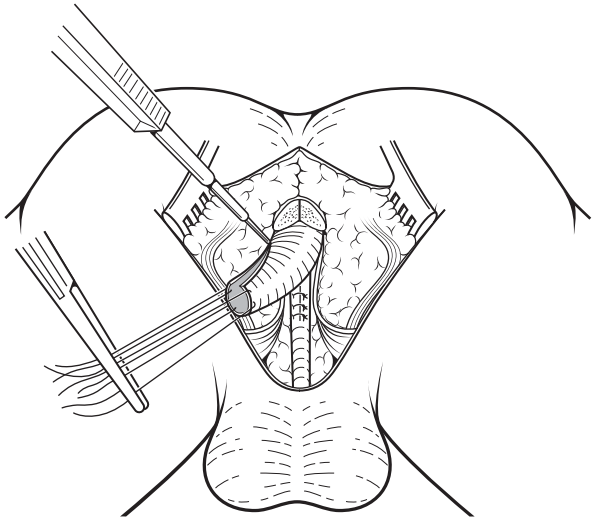

Figure 61.31 Tapering the rectum.

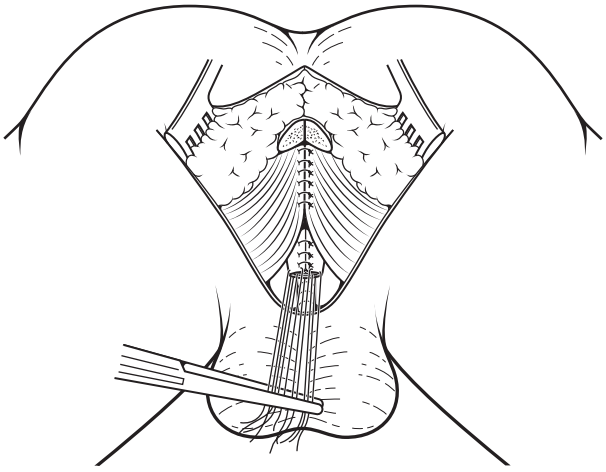

Figure 61.32 Rectum placed in front of the levator. Anchoring sutures from muscle complex to the rectum.

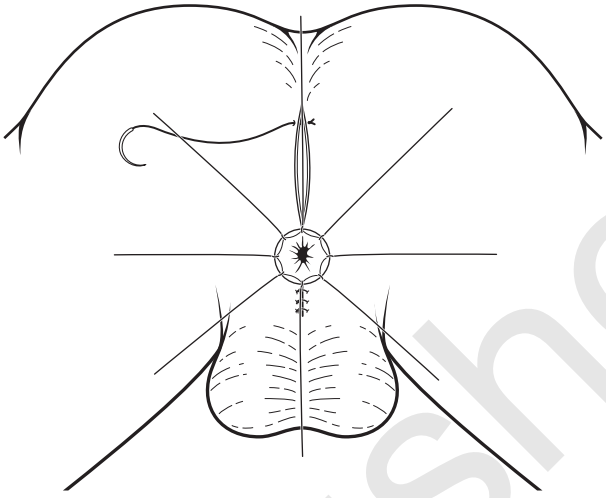

Figure 61.33 Anoplasty.

suture site. Most of the time, babies will be able to void with no difficulty. If this is not the case, which luckily is rare, then a suprapubic cystostomy is recommended.

Posterior sagittal anorectoplasty and laparoscopy or laparotomy (recto bladder neck fistula or high prostatic fistula)

This technique is used in cases of very high defects, the recto bladder neck or high rectoprostatic fistulas in males.

The operation is started with the patient in the supine position. The baby is prepared with a total body preparation from the nipples down. A Foley catheter is placed in the bladder. The abdomen is entered with laparoscopy, the peritoneal reflection is opened and the sigmoid colon is dissected down to the fistula site where it is ligated and divided. The rectum in these cases opens into the bladder neck in a 'T' fashion with no common wall, and therefore the

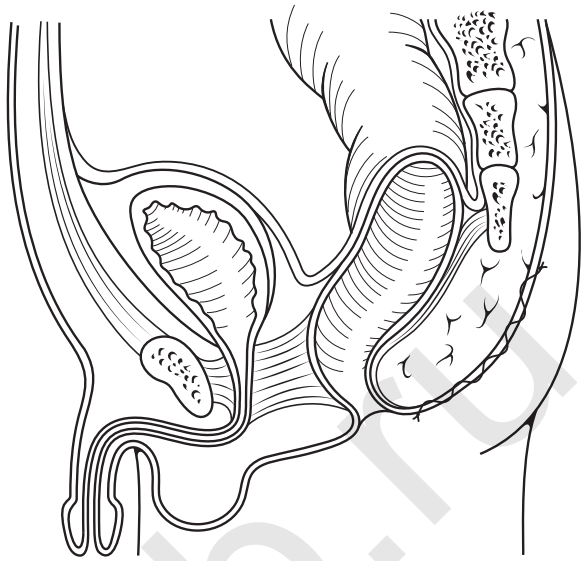

Figure 61.34 Anoplasty – operation completed.

separation from the bladder is relatively easy. Care must be taken to avoid damage to the vas deferens which are close in proximity. The perineal incision is the same as previously described for the posterior sagittal anoplasty but can be done in the supine position with the patient's legs elevated. The muscle structures are divided in the midline and the presacral space is identified. Getting a high rectum to reach the perineum is challenging and requires a meticulous dissection along the rectal wall, which is dependent on the rectum's excellent intramural blood supply. A colostomy placed too distal in the sigmoid may interfere with the rectal mobilization. Also, if the distal rectum requires tapering this may need to be done with an open incision or via the posterior sagittal incision. Once mobilized, the rectum is pulled-through to the perineum. The rectum is tacked to the posterior edge of the muscle complex and the anoplasty is done as previously described. The Foley catheter remains in the bladder for 7 days.

The posterior sagittal approach has also been used since 1982 to repair cloacas.[13] Since cloacas represent a spectrum, the operations to repair these defects may last from 3 to 14 hours and should be carried out by surgeons with significant experience. The technical maneuver that is called the total urogenital mobilization has greatly facilitated the repair.[26] Using the total urogenital mobilization, the rectum is separated from the vagina and then both the urethra and vagina are mobilized together down to the perineum. This maneuver also avoids the formation of urethrovaginal fistulas as well as vaginal stenosis. The more complex cases with common channels of 3 cm or greater require a variety of surgical maneuvers including specialized vaginal mobilizations or replacements to complete the repair.[13]

TWO WEEKS POSTOPERATIVELY

After 2 weeks, the anus is calibrated and the parents are taught to dilate, which they do twice a day. They are instructed to go up in size each week until the desired size is reached, at which

point the colostomy can be closed. Dilations are continued thereafter with a tapering protocol:

- once a day for a month
- every other day for a month
- every third day for a month
- twice a week for a month
- once a week for a month
- once a month for three months.

The ideal sizes of Hegar dilators are:

- number 12 for 1–4 months old
- number 13 for 4–8 months
- number 14 for 8–12 months old
- number 15 for 1–3 years old
- number 16 for 3–12 years old

Results

Each defect has a different prognosis. The patients with lower defects usually have excellent results, except when technical errors have been made or if they have associated sacral or spinal problems.

Table 61.1 shows the results obtained in our series. The patients with a sacral ratio (Fig. 61.35) of less than 0.3 and flat perineums have fecal incontinence regardless of the type of malformation or quality of the repair. Normal sacral ratios (>0.7) usually correlate with good functional prognosis.

Because persistent cloacas themselves represent another spectrum of defects, the potential for bowel and urinary control will vary. The length of the common channel seems to be the most important prognostic factor.

For patients suffering from fecal incontinence as a sequelae of their anorectal malformation (25% of patients), we implement a bowel management program that is used after the child reaches three years of age.[27] The goal is to send these children to school in normal underwear. The program is implemented by trial and error over a period of 1 week. It consists of teaching the family to clean the patient's colon once a day with an enema tailored to the specific child. This implementation is radiologically monitored every day during the week until the specific type of enema is found that is capable of cleaning the colon and keeping it completely clean

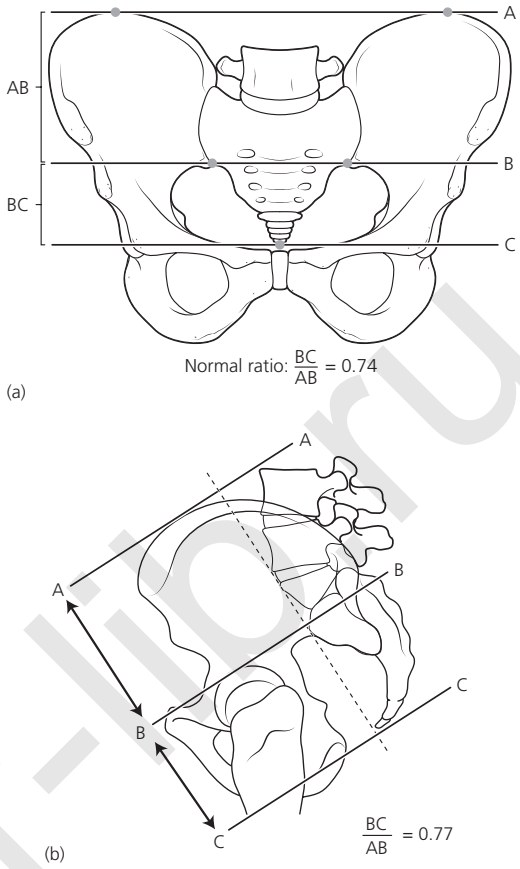

Figure 61.35 Sacral ratios: (a) AP sacral view; (b) lateral view.

Table 61.1 Global functional results. Our series of primary cases, evaluated after the age of potty training (age 3–4 years).

	Voluntary bowel movement		Soiling		Totally continent[a]		Constipated	
	No. patients	%	No. patients	%	No. patients	%	No. patients	%
Rectoperineal fistula	34/35	97	4/33	12	29/34	85	19/37	51
Rectal atresia or anal stenosis	8/8	100	2/8	25	6/8	75	5/8	63
Rectovestibular fistula	84/94	89	34/94	36	60/84	71	53/93	57
Imperforate anus without fistula	27/34	79	15/33	45	18/27	67	18/35	51
Recto-urethral bulbar fistula	69/85	81	45/84	54	36/69	52	54/85	64
Recto-urethral prostatic fistula	57/86	66	69/89	78	17/57	30	41/89	46
Cloaca: short common channel (<3 cm)	49/76	64	52/76	68	23/49	47	31/77	40
Cloaca: long common channel (>3 cm)	17/44	39	37/40	93	3/17	18	14/43	33
Rectovaginal fistula	3/4	75	3/4	75	1/3	33	1/4	25
Rectobladder neck fistula	8/39	21	37/39	95	2/8	25	7/40	18
Total	356/505	70	298/500	60	195/356	55	243/511	48

[a]Totally continent is voluntary bowel movements with no soiling.

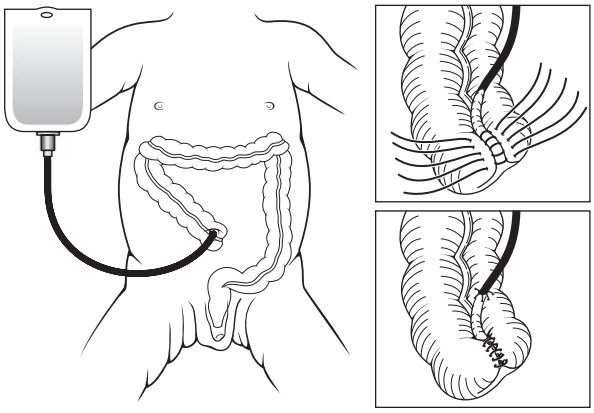

Figure 61.36 Malone appendicostomy.

for 24 hours.[28] Every year, during vacation time, the patient is subjected to a laxative trial; the enemas are stopped and the capacity of the patient to become toilet-trained without enemas is evaluated. If the patient is not successful, they go back to the enema program. Patients sometimes express dissatisfaction with rectal enemas; they want more privacy and do not want their parent giving them enemas. In order to further improve their quality of life, the family is offered a procedure called 'continent appendicostomy' (Malone procedure) (Fig. 61.36).[29,30] This procedure allows patients to independently administer the enema through the umbilicus.

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62

Congenital pouch colon

AMULYA K SAXENA AND PRAVEEN MATHUR

INTRODUCTION

Congenital pouch colon (CPC) is a congenital malformation of the large bowel in which the entire large bowel or segments of varying lengths of the large bowel exhibit enormous dilatations in the form of a pouch and communicate distally through a fistula with the urogenital system. CPC is associated with a high form of anorectal malformation with large variations in the size of the dilatations of the affected large bowel segment. Although not included in the Wingspread classification of aorectal malformations, CPC has been recognized as a rare form of aorectal mlformation and has been included in the Krickenbeck classification.[1]

An unusal feature of CPC is the prevalence of this malformation in the Indian subcontinent with the highest incidence in the west and north of India. Despite the growing global awareness of CPC and the increase in reporting of this congenital malformation, contemporary literature shows that approximately >98% of the patients reported to present with CPC are managed at pediatric surgical centers in India. The increased awareness has also led to the better recognition and management of these neonates and children. Congenital pouch colon, which is the most appropriate terminology to describe this malformation, has been referred to with synonyms such as pouch colon, pouch colon syndrome, short colon, colonic reservoir, and congenital short colon in preliminary reports that emerged during the 1970s and 1980s.

HISTORICAL BACKGROUND

Although CPC is an extremely rare congenital malformation beyond the Indian subcontinent, this anomaly was initially recognized in the West at the beginning of the twentieth century. The first description of this anomaly was documented by Spriggs from a specimen he carefully observed at the London Hospital Museum in 1912.[2] Spriggs described the specimen with an absence of half of the large bowel and rectum, and considered the dilatation to be the result of a congenital occlusion of the gastrointestinal tract. The next description of this congenital malformation was almost half a century later in a report from Canada. In 1959, a more accurate account was provided by Trusler *et al.*[3] who reported more typical characteristics of this malformation, such as the pouch-like dilatation of the shortened large bowel and its association with a high form of anorectal malformation. Almost a decade later in 1967, El-Shafie[4] described this malformation in detail as a congenital shortening of the small intestines which accompanied a cystic dilatation of the colon associated with an ectopic anus.

The first report of this malformation from India emerged in 1972, when Singh and Pathak[5] coined the term 'short colon' after observing this condition in a series of six patients. In the same report, Singh and Pathak also speculated on the possible embryogenesis of the malformation. Later, in a successive report in 1977, Singh *et al.*[6] described the anatomy of this malformation. An important contribution to this congenital anomaly was made by Chiba *et al.* in 1976, who not only made the first attempts to classify this malformation but also reported the management of this malformation with the technique of 'coloplasty'.[7] The term 'colonic reservoir' was coined by Gopal in 1978 in a report of this malformation with the distal end of the reservoir terminating in the female genitals via a rectovaginal fistula.[8] A further effort to describe this malformation as a 'short colon malformation' associated with an atresia of the anus was done by Li in 1981.[9]

In 1984, Narasimha *et al.*[10] suggested the term 'pouch colon syndrome' and after observing variations in the presentation of this malformation proposed a classification based on the length of normal colon preceding the pouch dilatation. In 1987, Cloutier *et al.*[11] described the malformation as a 'rectal ectasia' in a newborn with a low anorectal malformation and reported an incidence of 5% of terminal bowel ectasia in their patients with low anorectal deformities. Elaborate nomenclatures were suggested by Wu *et al.* in 1991 with acronyms such as 'association of imperforate anus with short colon' (AIASC) or 'association of imperforate anus with exstrophia splanchnica' (AIAES).[12] However, in 1994 Chadha *et al.*[13] introduced the term 'congenital pouch colon' which is the nomenclature to aptly describe this anomaly.

INCIDENCE

There is an extreme variation in the incidence of CPC around the world with the large patient series being reported exclusively from India. Smaller series of patients have been emerging from the neighboring countries in the Indian subcontinent, such as Pakistan and Nepal; however, surprisingly, an extremely low incidence has been observed in Bangladesh.[14] Only sporadic cases of CPC have been reported from the Middle East, Far East, the European continent, and the North American continent.[15–18] The incidence of CPC is highest in the western and northern regions of India and is estimated to be in the range of 5–18% of the total number of neonates managed for anorectal malformations.

In India, the states of Rajasthan, Uttar Pradesh, Punjab, Kashmir along with the union territories of Delhi and Chandigarh account for the majority of cases of CPC. Despite the high density of population in all these states, the management of CPC is generally not performed at primary or secondary health care centers and most neonates are referred to tertiary university medical centers with specialist care teams and expertise in pediatric surgery, a trend that has better enabled the estimation of incidences. Among the Indian tertiary care centers reporting large series of CPC, Udaipur in the western state of Rajasthan has reported the highest incidence of CPC in India, accounting for 37% of the high forms of anorectal malformations (which is more than double reported in Delhi – 15.2%).[19]

CPC more frequently affects the male population with a male:female distribution of 4:1. The sex ratios of CPC reported in case reports or small series outside India predict equal gender distribution, which are not accurate since the sample size is too small to derive valid conclusions.

ETIOLOGY

The exact embryogenesis of CPC is not known and the etiology is still quite elusive. Since the majority of the patients with CPC belong to the rural population of agricultural families in northern India, environmental factors in this region have been speculated upon. The widespread use and direct contact with pesticides in these agriculture-based communities have been regarded as the possible factor in the triggering of events that lead to CPC. It is also important that the effect of these factors influences the fetus after conception at a time when the hindgut is differentiating into the urinary and colonic tracts. Additional environmental factors that could play a role in the development of CPC are the deficiency of iodine or vitamin B; however, the role of these factors is rather questionable since their deficiencies are encountered in many communities throughout the world.

Various theories have been hypothesized to explain the formation of the pouch. The chronic obstruction theory proposed that the expansion of the large bowel was a result of chronic obstruction of the distal colon.[3] However, this theory has been rejected since the dilated pouch does not return to assume normal proportions even after a colostomy has been placed to relieve the obstruction. The next hypothesis was the interference of hindgut growth and migration proposed by Dickinson.[20] This theory proposed that the interference in the longitudinal growth of the hindgut (distal to the allantois) and failure of its migration into the pelvis following the obliteration of the inferior mesenteric artery in the early embryonic life was responsible for the formation of the short colon. The altered hindgut stimulation theory was hypothesized by Chatterjee.[21] This theory proposed that the cecum and the right colon normal development was stimulated by the normal developing hindgut, and development alterations in the hindgut resulting from a primary disorder were responsible for the altered development of the cecum or the right colon. The faulty rotation and fixation theory proposed by Wu *et al.*[12] hypothesized that the faulty rotation and fixation of the large bowel were responsible for the disturbances in longitudinal growth. The vascular insult theory was proposed by Chadha *et al.*,[13] in which degrees of vascular insult at the time of the partitioning of the cloaca by the urogenital septum were deemed responsible for the malformation and could explain its variations. The vascular insult theory was also supported by Mathur *et al.*[19] in explanation of double pouch formation in CPC. At present, vascular insult best explains the formation of CPC, since vascular supply to the pouch is always abnormal. Also, the overwhelming vascular support provided by the superior mesenteric artery to the entire distal bowel emphasizes this point, since the inferior mesenteric artery has been identified only in few patients with CPC during surgery.

PATHOLOGY

CPC is recognized by certain pathological characteristics that are solely found to be associated with this congenital malformation (Fig. 62.1).

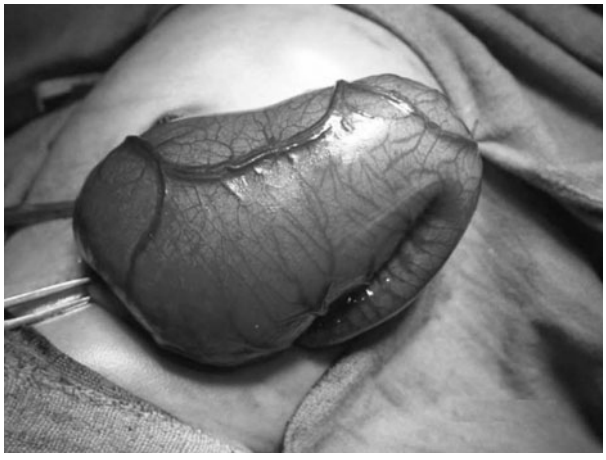

Figure 62.1 Operative view of the exteriorized grossly dilated congenital pouch colon segment visualized from a left lower quadrant 'hockey stick' incision.

Gross pathology

Characteristics are as follows:

- The most striking feature is the presence of anorectal malformations which differentiates this entity from segmental dilatation of the colon.
- Irrespective of the type of CPC, there is a decrease in the length of the large bowel due to the presence of the pouch.
- The pouch formations may differ in length and diameter and are fecal or meconium impacted at the time of surgery.
- The pouch wall is thick with a stiff consistency and is abruptly connected to the normal bowel without the presence of the transition zone.
- There is an absence of haustrations, taenia, and appendices epiploicae in the pouch colon.
- Furthermore, during surgery, an abnormal vascular supply to the pouch can always be identified.
- A fistula can occur in the urinary tract in male neonates (colovesical fistula) and the genito-urinary tract in females (colocloacal, colovaginal, or colovestibular fistula).
- Appendiceal anomalies are present which may vary from complete absence to the presence of double appendices.

Histopathology

Histological studies of resected pouch colon have demonstrated extreme variations in CPC. In the majority of patients, acute and chronic inflammation of the mucosal and submucosal layers are present with varying degrees of hemorrhage along with the presence of disorganized muscle layers in the colon wall (Fig. 62.2). Generalized hypotrophy of the muscle layers has also been observed which is more predominant in the outer muscle layer of the pouch.[22] Although, in other specimens, extreme variations in the muscle layer (both circular and longitudinal) have also be demonstrated that have ranged from fibrosis, atrophy to hypertrophy along with muscle disruption.[23] Investigations have also exhibited variations such as the presence of normal colon wall with normal ganglion cells in some patients, to a poorly developed colon wall musculature with decreased or absent ganglion cells in others.[6,10,13,24] Interestingly, heterotrophic tissue, such as gastric mucosa, small intestinal mucosa with characteristic villi, and pancreatic tissue have also been found in pouch specimens of CPC patients.[10,22]

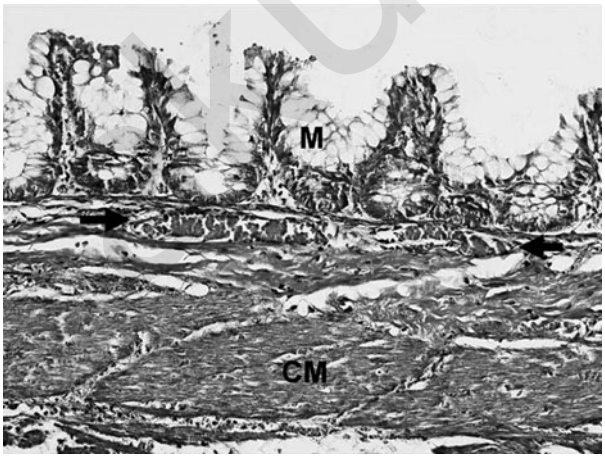

Figure 62.2 General features in the histopathology of pouch colon include inflammation of the mucosa (M) and disorganized colonic wall musculature (CM). Submucosal hemorrhage (arrows) is evident in this specimen. (Stain: Massom Trichome ×20 magnification.)

CLASSIFICATION

CPC can present as various types and efforts have been made to classify CPC in order to provide a basis for surgical management as well as for evaluating the outcomes.

The first efforts to classify CPC were made using a classification based on characteristics of short colon that grouped pouch colon into five types.[7] However, many features described in this classification were not associated with the CPC pathology. CPC was then classified by a classification based on presence of normal colon length proximal to the pouch into four types.[10] Although this classification identified the major forms of CPC, it had major drawbacks since the length of the normal colon was determined using terms such as 'short segment' and 'significant length' and appropriate parameters or anatomic landmarks to determine the normal colon length were absent. A further classification was proposed based on coloplasty which divided CPC into two types.[24] This classification was further modified into one based on pull-through which also broadly divided CPC into two types.[25] The last two classifications considered the surgical approach with regards to coloplasty or pull-through; however, neither offered any information about the length of the normal colon in CPC patients.

The Saxena–Mathur classification for CPC is based on anatomic morphology and divides CPC into five types (Fig. 62.3):[26]

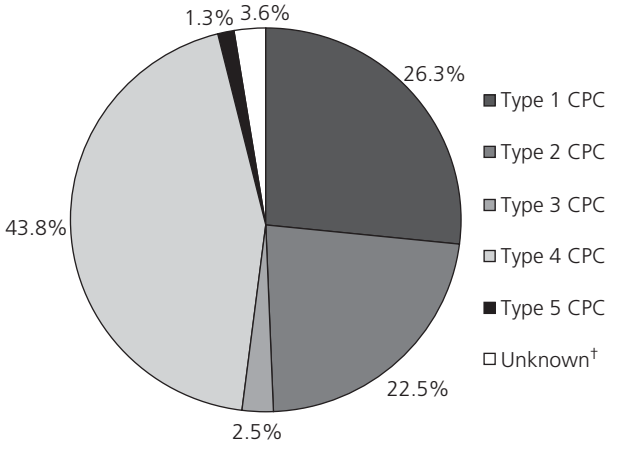

Figure 62.3 Distribution of patients ($n = 80$) into five types of congenital pouch colon according to the Saxena–Mathur classification. †In two patients with severe septicemia the type was not known due to fatal outcomes during resuscitation attempts prior to surgery.

Type 1: normal colon absent and ileum opens into pouch colon
Type 2: ileum opens into a normal cecum which opens into pouch colon
Type 3: normal ascending colon and transverse colon opens into pouch colon
Type 4: normal colon with rectosigmoid pouch
Type 5: double pouch colon with short normal interpositioned colon segment

This classification employs anatomic landmarks to determine the length of the normal colon, as well as identifies the relation of the pouch to the normal colon. It also includes rare forms of CPC such as double pouch colon and offers clear guidelines towards management of CPC.

HISTORY AND PHYSICAL EXAMINATION

The presence of an anorectal malformation with gross distention of the abdomen is the hallmark of the physical examination. In the male neonates, discharge of meconium (meconurea) or stool through the urethra via the colovesical fistula is evident and these neonates are generally referred for treatment in the immediate neonatal period. However, in female patients meconium and fecal discharge through a cloacal, uterine, or vaginal fistula may delay referral in a stable neonate. Furthermore, when a colocloacal fistula (common in females with CPC) is present, it is associated with a large fistula opening that permits decompression of the pouch colon contents, the presence of which can further delay presentation in female subjects for a period of several months after birth. At the time of referral, these patients with colocloacal fistulas are frequently obstipated and physical examination shows the discharge of stools from the ectopic site.

PRESENTATION

The majority of patients with CPC are presented in the immediate neonatal period due to the anorectal malformation. The absence of the anal canal and excessive distention of the abdominal cavity are the two characteristic signs that raise suspicion of CPC. Although in CPC the pouch ends through a fistula in the genitourinary tract, meconurea may be present or absent. Another symptom commonly observed in these neonates is serial episodes of bilious vomiting which is a major symptom that leads to referral. Delayed referrals or grossly distended pouch colon neonates are not uncommonly presented with colonic perforations, which present a major challenge in the management of the newborn with septicemia and peritonitis which further accentuates the respiratory distress already initiated by the massive abdominal distension. Delay in diagnosis and late referrals even in the neonatal period have been largely responsible for the high mortality in CPC. Awareness of the condition and development of proper management strategies especially through improvement in neonatal intensive care at the tertiary centers in India have drastically reduced the mortality from 40% to the present rate of 15%.[27]

DIAGNOSIS

Plain erect abdominal x-rays performed to diagnose patients with CPC demonstrate a classical solitary grossly dilated air fluid bowel loop that occupies more than 75% of the abdominal cavity with displacement of the small intestines (Fig. 62.4). The position of the pouch and the displacement of the intestinal loops depends on CPC type.[24] Although plain abdominal x-rays can predict the CPC type, the definitive diagnosis and CPC type can be determined only after surgical exploration. False diagnosis of CPC based on plain x-rays is possible in patients with (1) significant dilatation of the sigmoid colon, (2) pneumoperitoneum after perforation in anorectal malformations due to late presentation, and (3) in females neonates with recto-uterine fistula when severe dilatation of the meconium-filled uterus and gas exhibit the classical images of CPC x-rays.[28]

Although plain erect abdominal x-rays with the classical presentation of CPC are sufficient to establish the diagnosis, conventional invertograms used for the diagnosis in anorectal malformations are additionally performed. Prior to surgical management further investigations such as abdominal ultrasonography, i.v. pyelography, or voiding cysto-uretherography and echocardiography are mandatory since a wide range of genitourinary, gastrointestinal and other forms of associated anomalies are present in patients with CPC (Box 62.1).

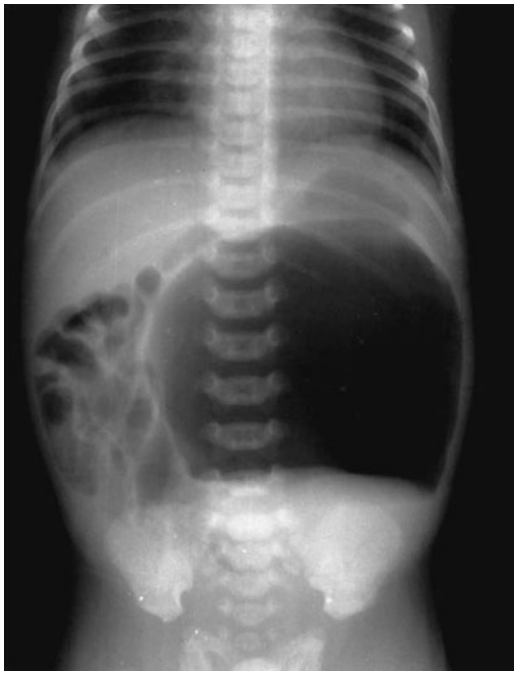

Figure 62.4 Plain abdominal erect x-ray demonstrating the classic grossly dilatated pouch colon segment occupying over 75% of the left abdomen, thereby displacing the small intestines towards the lower quadrant in the right abdomen.

Box 62.1 List of associated anomalies reported in congenital pouch colon patients

Genitourinary anomalies
- Hydronephrosis
- Vesico-ureteral reflux
- Bicornuate uterus
- Cryptorchidism
- Hydroureteronephrosis
- Hypospadias
- Renal aplasia/agenesis
- Renal dysplasia
- Double uterus
- Double vagina
- Septate vagina
- Ectopic kidney
- Urethera duplication (males)
- Uretheral diverticula
- Bifid penis
- Megalourethra
- Urethral strictures
- Bladder exstrophy
- Duplicate bladder exstrophy

Gastrointestinal anomalies
- Absent appendix
- Double appendix
- Malrotation
- Colon duplication
- Meckel's diverticulum
- Double Meckel's diverticulum
- Esophageal atresia
- Small intestinal duplication
- Rectal atresia

Other organ anomalies
- Sacral agenesis
- Congenital heart disease
- Myelomeningocele
- Prune belly syndrome
- Hemivertebrae
- Congenital talipes equinovarus
- Perineal teratoma
- Absent ribs
- Down syndrome

MANAGEMENT

Preoperative management

The preoperative management is broadly dependent on the condition of the pouch (intact versus perforated). In stable neonates, preoperative management includes gastric decompression using a wide bore nastrogastric tube, i.v. fluid replacement to correct the effects of dehydration and electrolyte imbalance, and placement of a urinary bladder catheter. Antibiotic therapy is commenced and extended depending on the state of the inflammation in the pouch colon evaluated during surgery. In neonates presenting with pouch perforations along with signs or either peritonitis or septicemia, aggressive intensive care management is necessary to stabilize the neonate for the emergency surgical procedure which is limited to evacuation of the meconium or stool from the peritoneal cavity, placement of a ileostomy or colostomy, and closure of the perforation site. The intention in surgical management in neonates with perforations is to perform the surgery with the smallest possible incision and to complete the procedure in a short time.

Operative management

The management algorithm of CPC is based on the type of pouch according to the Saxena–Mathur classification (Fig. 62.5).[29] An abdominal incision in the lower left quadrant in the shape of a 'hockey stick' has been found to offer optimal access to inspect the malformation with the primary intention of fistula ligation irrespective of CPC type. After the fistula has been exposed and ligated, the condition of the pouch dictates the further operative strategy. Staged procedures, employing the placement of a protective ileostomy or colostomy with ligation of the fistula in the first stage, followed by an abdominoperineal pull-through in the second stage, still offer the safest option when compared to one-stage surgery which is associated with a higher incidence of morbidity and even mortality. The intention of surgical management in CPC is to evaluate the amount of large bowel affected and to salvage its maximum length in order to restore or partially restitute the function of the large bowel, such as absorption, transportation, and containment.

In types 1 and 2 CPC a one-stage procedure (pouch excision and pull-through) or three-stage procedure (ileostomy, pouch coloplasty with pull-through and ileostomy closure), depending on the condition of the pouch (ischemic or healthy) can be performed. In the case of severe ischemia and perforations, resection of the pouch remains the only alternative. If the pouch is resected, either a direct pull-though of the ileum or placing a protective ileostomy with delayed ileum pull-through offer the best surgical options. However, if the pouch is healthy, the surgical approach is focused on attempts to rescue and taper the pouch and to perform a pouch coloplasty through pouch tubularization. Pouch tubularization is performed after pouch mobilization and longitudinal incision on the antimesenteric side (to preserve the vascular supply) with edge reapproximation over a cathether. Although tubularized pouch coloplasty is performed in both types 1 and 2 CPC, it is not uncommonly associated with increased morbidity in terms of incontinence and complications resulting from redilatation of the tubularized pouch.[30,31] Also, variations in the outcomes of surgery have been reported by various centers. [12,30,32,33] The function or the absorptive capability of the tubularized pouches is not understood; however, it is reported to be decreased since attempts to patch or augment healthy pouch colon onto normal pull-through ileum in type 1 CPC with the intention of rescuing the absorptive surface area have been reported with success.[34]

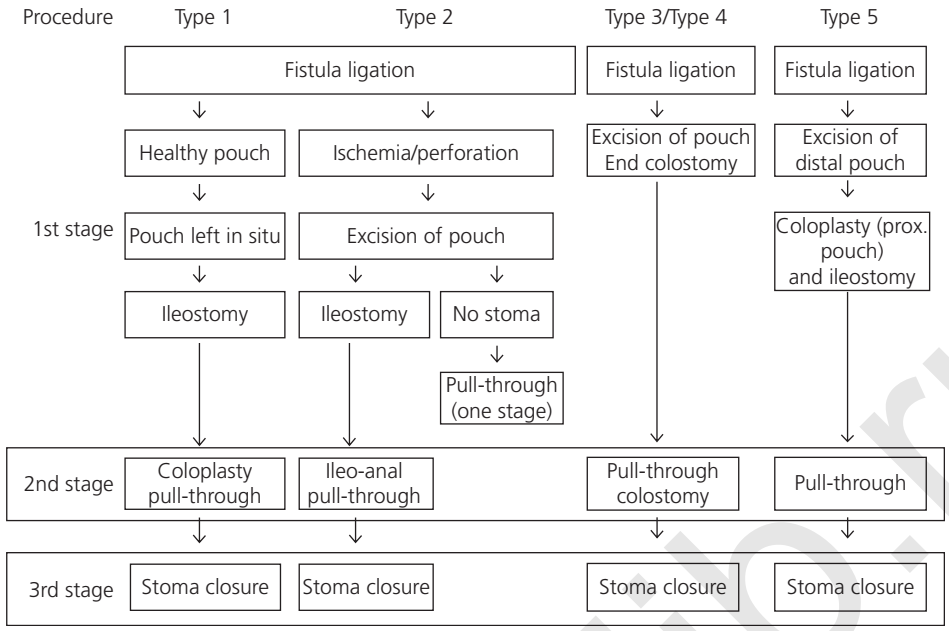

Figure 62.5 Management overview of the various types of congenital pouch colon with outline of the operative stages.

When referring to redilatations of tubularized pouches, the technique of 'window' colostomy needs to be addressed. This technique involves the placement of a stoma directly on the pouch colon, which is the most prominent part of the dilated bowel in an attempt to provide primary decompression in a sick neonate, when extensive surgical exploration is not possible. Window colostomies are more frequently performed by surgeons not well acquainted with this malformation, which are commonly associated with urinary complications when the fistula is left open. Furthermore, large prolapse of the pouch and failure to thrive have been also related to the placement of window colostomies.[35] Window colostomy is also associated with mortality in patients who have been managed with this option. The option of window colostomy should not be considered in a stable infant.

The significance of the Saxena–Mathur classification in differentiating types 1 and 2 CPC (despite the similarities in surgical approach as proposed by Wakhlu *et al.*[24] and Gupta and Sharma[25] in classifications based on the need for coloplasty) is to recognize the presence of the normal cecum in type 2 CPC which is underestimated in the classifications on surgical approach. Various investigations and experimental studies have demonstrated the significance of the cecum and ascending colon or parts of the ascending colon in the absorption of sodium which influence the exchange of chloride and bicarbonate in these tissues.[36,37] However, investigations need to be performed to validate these differences in patients and compare type 1 and type 2 CPC patients. Similarly, the absorption of potassium, which is significant in the descending colon in experimental studies,[38,39] highlights the difference between type 3 and type 4 CPC since the normal functioning descending colon only present in type 4 CPC.

The presence of considerable lengths of normal colon in types 3 and 4 CPC enable total resection of the pouch and a staged abdominoperineal pull-through of normal colon. The approach to types 3 and 4 involve the ligation of the fistula, excision of the pouch, and placement of a stoma which is followed by a delayed abdominoperineal pull-through. Although it is debatable whether a protective colostomy should be placed, or a prior high colostomy be closed during the pull-through procedure, the authors prefer the first option and place a protective colostomy during the pull-through which is returned at a later point in time. In types 3 and 4 CPC, if the high colostomy is opted for (instead of the end colostomy) appropriate placement of the colostomy is advocated since improper placement of a high colostomy may interfere with the pull-through procedure, especially if the length of the colon to be pulled-through is too short.

Management of type 5 CPC requires the approach to two pouch colon segments that are separated by a segment of normal colon and is best treated by a three-stage procedure.[19] The first procedure involves the ligation of the fistula, excision of the distal pouch and tubularization of the proximal pouch, and the placement of a protective ileostomy. The second procedure involves the abdominoperineal pull-through, keeping the protective ileostomy. In the third procedure, the protective ileostomy is returned. Another option of type 5 CPC would be to tubularize both the proximal and distal pouch.

Surgical management of female neonates with pouch colon is complex due to the frequent association with the cloaca, as well as the associated anomalies of the genital system.[40,41] Depending on the complexity of the genital anomalies a one- or three-stage approach is preferred; however, there is no consensus on the approach to date. The pouch colon has been tubularized to create a neo-vagina

and reconstruct the anorectum with preserved vaculature also using the longitudinal incision technique.[16]

Postoperative

The postoperative management depends on the condition of the pouch. In patients with pouch perforation, intensive care support along with parenteral nutrition is necessary until complete recovery. The use of antibiotics and duration of treatment is also dependent on the surgical findings. In patients with protective colostomy feeds are commenced earlier than those who have undergone tubularization and pull-through procedures. Monitoring of bowel movements are necessary to achieve success in these patients.[42] Regular postoperative follow up is necessary to document the bowel movements which could range from diarrhea when the pouch is resected to obstipation which could result in tubularized pouch redilatation and necessitate further surgical procedures.

COMPLICATIONS

Complications in the management of CPC can be divided into five distinct categories which are related to: (1) window colostomy, (2) protective colostomy, (3) tubularized pouch colon, (4) complete pouch resection, and (5) pull-through procedure. Window colostomy leads to a wide range of complications, such as incomplete pouch decompression, prolapse, stoma recession, stoma stenosis, pouchitis, enetrocolitis, and failure to thrive. The complications of protective colostomy or pull-through procedures are general complications associated with these procedures and are not specific for CPC. Tubularization of the pouch colon could be associated with complications of leakage along the suture line with consequent rupture. Also, redilatation after tubularized colon has been observed with long-term follow up in patients with salvaged pouch colon.[31,43] Complete pouch resection is associated with complications of recurrent watery diarrhea, excoriation around the anus, perineum or genitals, and poor weight gain. Severe complications in neonates with pouch perforations are not only limited to septicemia and peritonitis but have also been found to negatively influence the respiratory status as well as the anesthesia efforts intraoperatively and postoperatively with lethal outcomes.[44]

LONG-TERM RESULTS

It should always be remembered that CPC is a complex form of high anorectal malformation and the muscle complex responsible for maintenance of continence directly influences the long-term outcome in these patients. Patients who present with a well-developed muscle complex attain variable degrees of continence and have better outcomes when compared to those with a poorly developed muscle complex with sacral agenesis and who are incontinent. Continence levels may vary in different reported series as it is dependent on the surgical expertise that a center can offer. Education of the parents as well as their socioeconomic status are also important factors that have a direct impact on the successful implementation of any bowel management regimes.

As well as the muscle complex, the types of pouch colon also influence the level of continence. When resection of the entire pouch is necessary in the absence of normal large bowel, watery diarrhea and loose stools are frequent. The frequency of stools decreases as well as the consistency increases over a period of time. In types of CPC where sufficient normal bowel is present (types 3 and 4), better results have been achieved in patients when the entire pouch has been resected and the normal large bowel is pulled through. This is because the pouch colon tissue investigated has demonstrated a lack of normal spontaneous contractions despite maintaining acetylcholine and histamine-induced contractility.[45] Also, fibrous tissue replaces the muscle layers of the pouch colon and affects motility adversely.[23,46] Hence, in cases where the pouch colon tissue is salvaged and a tubularized coloplasty performed, utilization of approximately 15 cm of tissue has been associated with a favorable outcome.

Complex malformations that are present as associated anomalies also influence the long-term outcome in these patients. Gastrointestinal anomalies that affect CPC patients do not add to long-term morbidity. Also, severe forms of cardiac defects are not common and do not influence long-term outcome. However, the severity of the genitourinary malformations may directly influence the quality of life in these patients as they reach adolescence and adulthood.

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63

Congenital segmental dilatation of the intestine

HIROO TAKEHARA AND HISAKO KUYAMA

INTRODUCTION

Congenital segmental dilatation of the intestine is a rare lesion defined as limited bowel dilatation with three- to four-fold increased size with an abrupt transition between normal and dilated bowel and no intrinsic or extrinsic barrier distally to the dilatation. This condition is complicated by obstruction of the intestines or chronic constipation from birth. Since Swenson and Rathauser first described three patients with segmental dilatation of the colon in 1959,[1] 59 cases (30 newborns, 25 children, and 4 adults) with this condition (41 in the small intestine and 18 in the colon) were reported in the world literature by 1996.[2] Since then, the number of case reports has increased greatly.

Despite the many reports, the etiology of the disease remains elusive. Although the current study attempts to evaluate the roles of interstitial cells of Cajal, enteric nervous system, and smooth muscle in segmental dilatation of small bowel, the causal relation is not clarified.

ETIOLOGY

The etiology of segmental dilatation of the intestine remains unknown. Some etiologic hypotheses have been proposed:

- An obstructive insult to the developing bowel[3]
- Presence of heteroplastic tissue in the bowel wall may result in primary dysplasia of the intestinal segment or may interrupt the myenteric plexus[4–11]
- Anomalous tortuous vessels on the mesenteric side of the dilated segment[12,13]
- Unequal proliferation or vacuoles in smooth muscle at the epithelial stage[8,14]
- Deficiency of interstitial cells of Cajal, pacemaking cells of non-neural crest origin in enteric nervous system, and smooth muscle of bowel segmental dilatation[15–17]

PATHOLOGY

The common morphological feature of congenital segmental dilatation of the intestine is the presence of a single, well-defined segment of dilated intestine with a more or less abrupt transition to normal bowel both proximally and distally, with no evidence of intrinsic obstruction or deficient innervation.

Cases can be divided into two groups according to histopathologic findings. One group has a hypertrophic muscular layer within the dilated segment and the other a very thin or absent muscular layer. From reviews of 39 neonatal cases,[3–9,12,14,18–40] there were five with hypertrophic muscular layer,[12,22,26,32,40] and eight with hypotrophic or atrophic muscular layer.[3,5,7,19,21,34] Abnormal prominent, tortuous vessels on the mesenteric side of the dilated segment were reported in 11 cases.[3,12,22,29,32,38,40] Heteroplastic foci were found in the resected segment in five cases.[5–7,31,38]

The congenital segmental dilatation of the intestine is associated with numerous other malformations. In these series, one or more malformations were reported in 36 cases (78.2%).[3–9,12,14,18–22,41]

Histological examination shows no abnormality in the enteric nervous system. There are a few reports describing deficiency of interstitial cells of Cajal, pacemaking cells of non-neural crest origin, in mesenteric plexus, and smooth muscle of bowel segmental dilatation.[15–17] However, they may not be of enteric nervous system in origin, or abnormality of small bowel pacemaking, but of possible localized myopathy of the smooth muscle.[14]

CLINICAL FEATURES AND DIAGNOSIS

Many cases of congenital segmental dilatation of the intestine localized in the small intestines often present intestinal obstructions during the neonatal period,[1,3,8,12,13,18,23,32,42]

and consequently this condition is diagnosed during the early period after birth. Neonates with missed and accordingly delayed diagnosis appear with abdominal pain, vomiting, and intermittent attacks of diarrhea. Chronic constipation and abdominal distension, similar to the presentation of Hirschsprung's disease, is more common when the colon is involved.[1,3,18,31,32,35,42,43] In segment dilatation of the colon, the findings on contrast enema are very similar to those in Hirschsprung's disease (Fig. 63.1), but the two conditions can be differentiated by anorectal manometry.[43] In addition, histochemical studies demonstrate no proliferation of cholinergic nerve fibers of the rectal mucosa.[43]

Rarely, the patient may present with peritonitis due to perforation of the dilated segment.[19]

MANAGEMENT

As congenital segmental dilatation is often confused with mechanical intestinal obstruction or Hirschsprung's disease, the surgeon must make every effort to establish the diagnosis as precisely as possible prior to initiating surgery. A thorough preoperative radiological evaluation is necessary to distinguish the two, as well as to determine the site of the dilated segment. Preparation for the laparoscopic surgery includes the administration of preoperative oral and i.v. antibiotics. It is necessary to empty the gut by using total parenteral nutrition.

Surgery for segmental dilatation of the small intestine or the colon should be performed with a laparoscopic procedure. The main advantage of laparoscopic surgery in children is that it is a minimally invasive procedure that provides safe and superior cosmetic results.[2]

For cases complicated by a segmental dilated lower rectum, rectum is pulled out by using the endorectal pull-through method following devascularization of the mesorectum laparoscopically (Figs 63.2–63.4). The oral feeding is begun 3 or 4 days after surgery when there is evidence of bowel function. The patient is discharged when an oral diet is tolerated. Rectal examination is performed 2–3 weeks after surgery.[44]

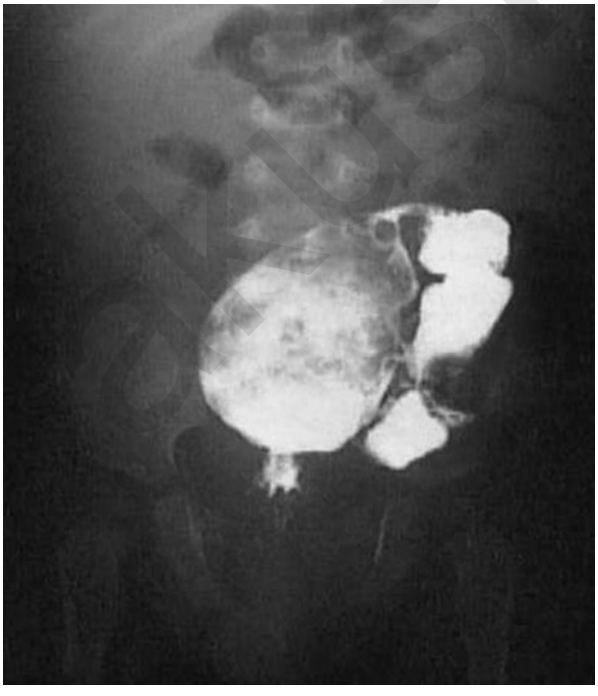

Figure 63.1 Barium enema shows segmental dilatation of the lower rectum.

LONG-TERM RESULTS

Most patients experience an uncomplicated postoperative course following cosmetic and minimally invasive intervention with laparoscopic surgery for congenital segmental

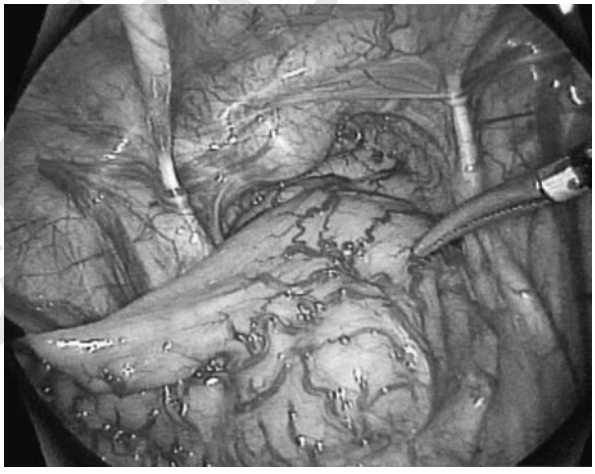

Figure 63.2 Laparoscopic photograph showing a segmental dilatation of the lower rectum with anomalous tortuous vessels on the mesenteric side.

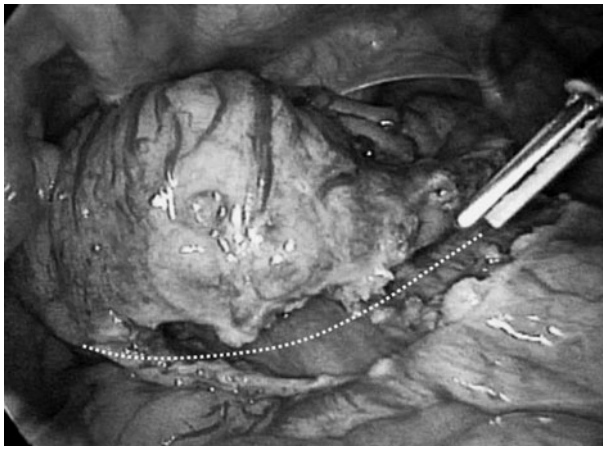

Figure 63.3 Devascularization (dotted line) of the dilated lower rectum was performed laparoscopically using an ultrasonic coagulation cutting device.

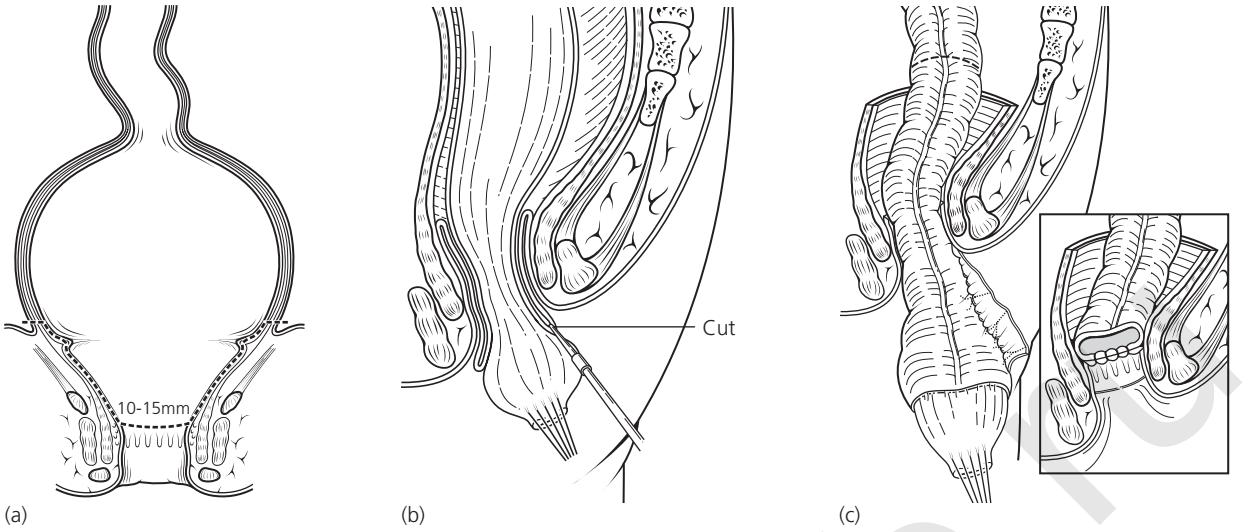

Figure 63.4 Transanal dissection of rectal mucosa begins 10–15 mm above the dentate line and the dotted line shows mucosectomy line (a). The submucosal plane is extended proximally until the colorectum is turned inside out, indicating that the transanal dissection has advanced to the level of the internal perirectal dissection (b). The segmental dilated rectum is pulled down to the anus and secured with interruped suture (c).

dilatation of the intestine. The survival rate is excellent unless other serious complications or anomalies exist.

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64

Intussusception

SPENCER W BEASLEY

PRENATAL INTUSSUSCEPTION

Prenatal intussusception is a recognized cause of intestinal atresia.[1,2] The presentation is that of a bowel obstruction at birth. Preoperative evaluation usually fails to yield a definite diagnosis[1] and the diagnosis is made at laparotomy.[2] Prenatal intussusception may be associated with fetal ascites[3] or meconium peritonitis.[4] Some cases are due to a Meckel's diverticulum.[5] Prenatal intussusception may result in an ileal atresia.[4]

NEONATAL INTUSSUSCEPTION

Although intussusception is common in the first year of life, it is rare in neonates and premature infants,[3,6] accounting for fewer than 1% of cases. The intussusceptions may be multiple[6,7] in which situation there may be no obvious pathological lesions at the lead points. Generally, however, when intussusception occurs in a neonate or infant, the possibility of a pathological lesion at the lead point must be entertained, and of these, a duplication cyst, inverted Meckel's diverticulum, or an ileal polyp are the most likely.[8] An early rotavirus vaccine (Rotashield®) was withdrawn from the market because of its association with intussusception. In contrast, the new live, oral, attenuated rotavirus vaccines (RotaTeq® and Rotarix®) appear to have no increased risk of intussusception.[9,10]

It is now well recognized that in the neonate and infant under three months of age, the likelihood of a pathological lesion at the lead point is significantly greater than in intussusception that occurs later in the first year of life.[1,11]

CLINICAL ASSESSMENT

When intussusception occurs in premature infants or in the neonatal period, its presentation may mimic neonatal necrotizing enterocolitis: the infant develops bile-stained vomiting, increased nasogastric aspirates, blood in the stools, and intestinal dilatation – but without evidence of intramural gas (pneumatosis intestinalis) that is pathognomonic of necrotizing enterocolitis.[12] It is not surprising that diagnostic confusion with necrotizing enterocolitis can lead to delay in appropriate treatment.[13] Similarly, in the neonate, the combination of bowel obstruction and rectal bleeding may lead to confusion with malrotation and volvulus; given the rarity of the condition in this age group, the diagnosis is often made only at operation.

In the older infant, vomiting, lethargy, pallor, and colic are the most common symptoms.[14] In long-standing cases, the infant may appear shocked and septicemic, with abdominal distension. Where abdominal distension and tenderness are not pronounced, an abdominal mass may be palpable and there may be evidence of blood mixed with the stool on rectal examination. Transanal protrusion of an intussusceptum is rare, but when it occurs it may be confused with rectal prolapse, and is associated with significant morbidity.[15]

NON-OPERATIVE TREATMENT

Indication for enema

When a diagnosis of intussusception is suspected and there is no clinical evidence of necrotic bowel (i.e. peritonitis or septicemia), reduction of the intussusception by gas enema should be attempted.[16] As alternatives, hydrostatic reduction under ultrasonographic control,[17] or in institutions where gas enemas are not available, a barium enema may be employed. Duration of symptoms, radiological evidence of small bowel obstruction,[18] and the position of the apex[19] per se are not contraindications to attempted enema reduction. Unfortunately, in the neonate, contrast enema is diagnostic in relatively few cases, mainly because the intussusception may not extend through the ileocecal valve, which may remain competent. Abdominal ultrasonography may assist in the

early diagnosis (Fig. 64.1) and in many centers is performed routinely where intussusception is suspected.[17]

Preparation for gas enema

There is considerable evidence that the gas enema is more effective and safer than the barium enema for reduction of intussusception that extends beyond the ileocecal valve (Fig. 64.2).[20–22] A gas enema should be performed in a pediatric surgical center by an experienced pediatric radiologist in the presence of a pediatric surgeon.[20] An i.v. line should be inserted and rehydration commenced before undertaking the enema. The child should be placed on a warming blanket during the procedure to prevent heat loss.

Technique of enema reduction

Gas (usually oxygen from a wall supply) is pressure controlled and run into the colon through a Foley catheter, which has been inserted through the anal canal, as with a conventional barium enema reduction.[20] The infant lies prone with buttocks taped and squeezed tightly together by the radiologist to avoid air leakage. The upper limit of pressure can be controlled by a manometer and the entire procedure is performed under continuous fluoroscopic control (Fig. 64.3).

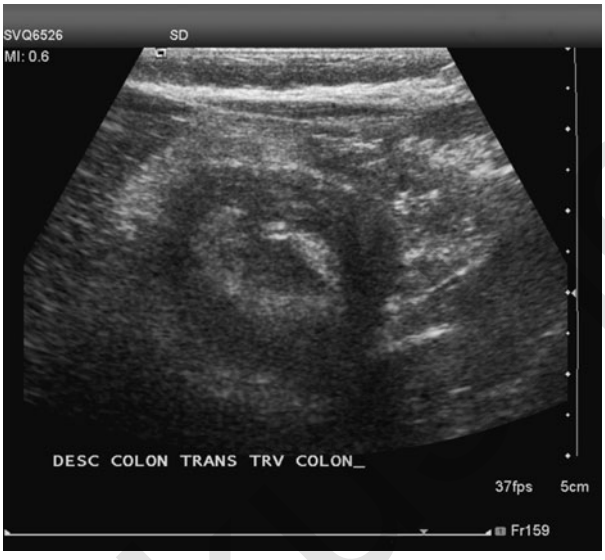

Figure 64.1 Ultrasonographic appearance of intussusceptum with the concentric rings of the intussesception within the intussuscipiens.

Cessation of gas enema

Flooding of the small bowel with gas signifies a complete reduction of the intussusception (Fig. 64.4). If free intraperitoneal gas is observed, the enema should be ceased immediately. If the initial attempt at reduction is unsuccessful and the infant remains in good condition, repetition of the gas enema after 2–3 hours is likely to be successful in about 50% of cases.[23] It is now our standard practice to repeat the enema after several hours if there has been partial reduction of the intussusception (as far as the cecum) in an infant whose clinical condition remains satisfactory.[23] Gas reduction tends to occur more rapidly than barium reduction. Both techniques have a similar recurrence rate[24] but the perforation rate may be more common after a gas enema than a barium enema.[25,26]

INDICATIONS FOR SURGERY

Clinical evidence of peritonitis or septicemia is an absolute indication for surgery, as it signifies that dead bowel is likely and resection is required (Box 64.1). Other indications for surgery include failure of repeated gas enemas to reduce the intussusception or early recurrence of intussusception after a successful enema (suggesting the presence of a pathological lesion at the lead point). Occasionally, a pathological lesion at the lead point may be seen during attempted enema reduction, but usually when a pathological lesion is present the intussusception cannot be reduced by enema. In the neonate who presents with an established bowel obstruction, the diagnosis is made when the intussusception is discovered at the time of laparotomy. Surgical management involves resection of non-viable bowel, and primary anastomosis. Until recent years, the mortality rate was over 20%,[6] largely because of delay in diagnosis. Recurrence is rare.

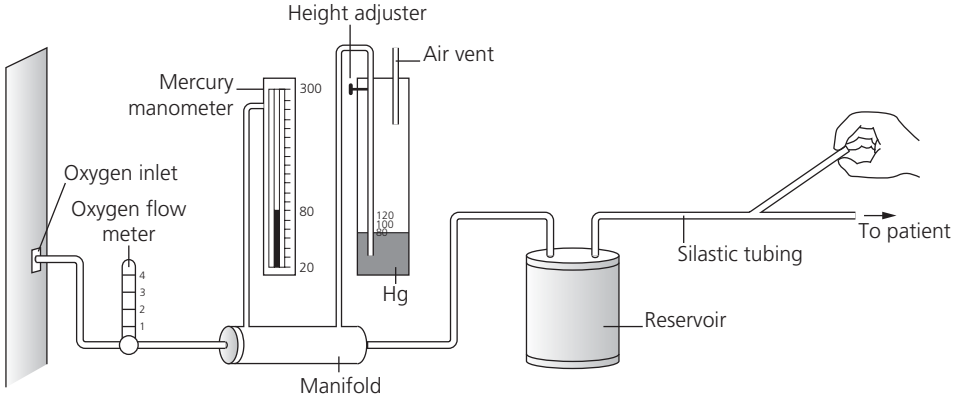

Figure 64.2 Schematic representation of the apparatus used to achieve gas (oxygen) reduction of intussusception.

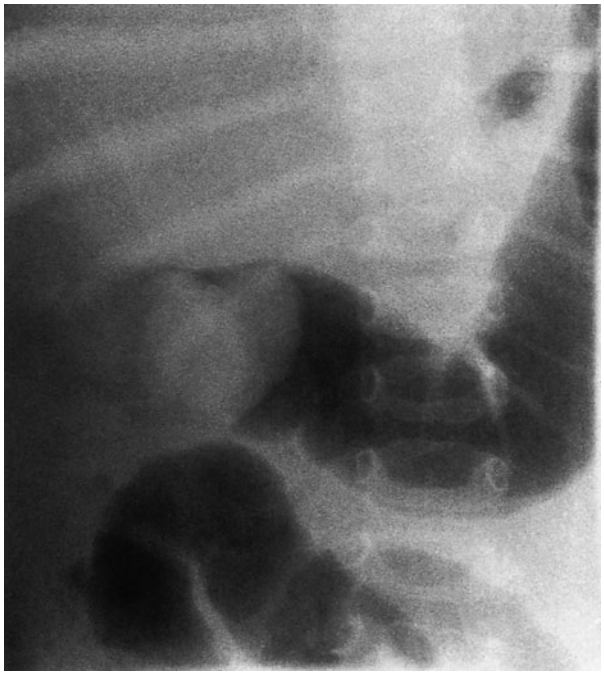

Figure 64.3 Gas reduction of intussusception: the pressure-controlled oxygen runs through the anus and outlines the intussusceptum in the transverse colon.

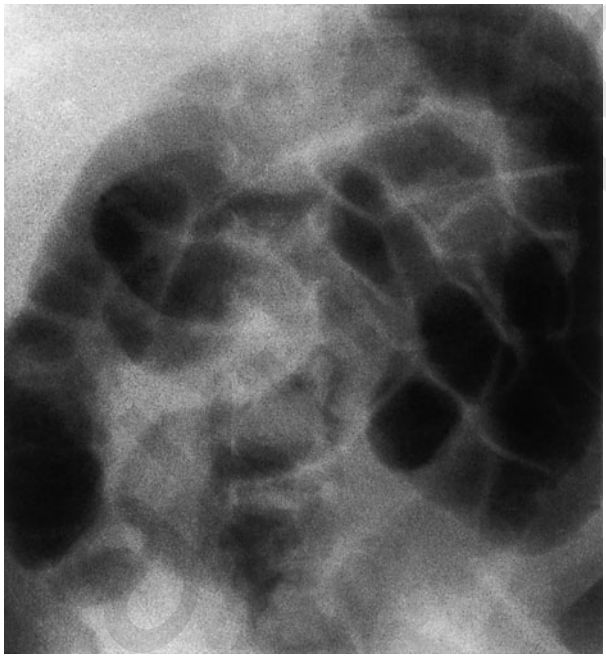

Figure 64.4 Sudden flooding of the small bowel signifies complete reduction of the intussusception.

Preparation for surgery

Prior to the general anesthetic, a nasogastric tube is inserted to empty the stomach. Prophylactic antibiotics are given intravenously at induction. The infant is paralyzed and intubated. A warming blanket must be used to prevent excessive heat loss, and temperature is monitored with a rectal or mid-esophageal probe. An oximeter monitors oxygen saturation.

Box 64.1 Indications for surgery

- Clinical evidence for dead bowel, i.e. peritonitis, septicemia
- Failure of enema reduction
- Early or multiple recurrences (relative indication)
- Evidence of pathological lesion at the lead point

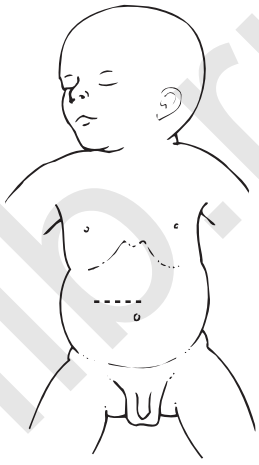

Figure 64.5 Right supra-umbilical transverse incision.

SURGICAL TECHNIQUE

Approach

A right, supra-umbilical transverse incision is made, dividing the ventral abdominal wall muscles in the line of the incision (Fig. 64.5). This gives good exposure, irrespective of the length of intussusception. Free peritoneal fluid is aspirated and the bowel is delivered into the wound.

Alternatively, a laparoscopic approach using a 5 mm umbilical port for the telescope and two 3 or 5 mm working ports is performed. The abdominal wall of the neonate is thin enough that a small incision may allow the 3 mm instruments to be introduced directly. A laparoscopic approach may be difficult in the presence of marked gaseous distension of the bowel, necessitating conversion to an open approach.

Manual reduction

The intussusception is carefully reduced by manipulation of the intussusceptum within the intussuscipiens in a proximal direction (Fig. 64.6). This is performed by gently squeezing the bowel between the fingers and in the cup of the hand. Time must be allowed to enable edema to dissipate. The intussusception is most difficult to reduce in the region of the

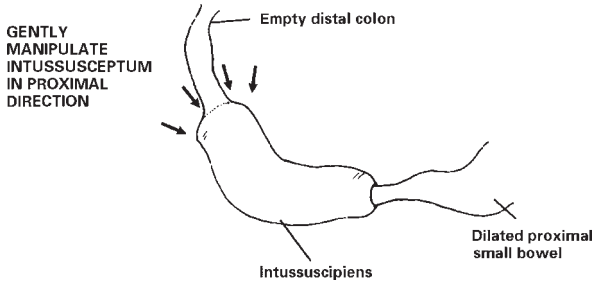

Figure 64.6 Gentle pressure on the distal limit of the intussusception coerces the intussusceptum proximally. Pulling on the bowel as it enters the intussuscipiens is not advised, as it tends to be more traumatic and less efficient at reducing the intussusception.

ileocecal valve. Care must be taken to avoid splitting the serosa. A similar technique is used in the laparoscopic approach, but reduction is completely reliant on instrumental manipulation.

Check for a pathological lead point

After full reduction of the intussusception, a dimple at the lead point is a common sight. Look for evidence of a duplication cyst, inverted Meckel's diverticulum, or another lesion at the lead point, because if these are present they should be resected.

Technique of resection

The indicators for resection are shown in Box 64.2. The aim should be to remove as little viable bowel as possible (Fig. 64.7). The small bowel mesentery is ligated and divided, and the bowel at the edges of resection is divided with scissors. A one-layer 4-0 Vicryl interrupted suture end-to-end anastomosis is performed. The defect in the mesentery is closed to prevent internal herniation.

Box 64.2 Indications for resection

- Inability to reduce intussusception manually
- Necrosis or gangrene of the bowel
- A pathological lesion at the lead point

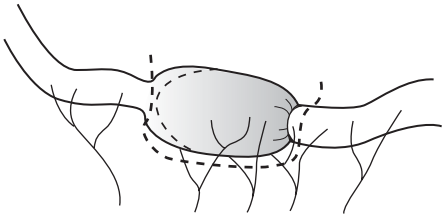

Figure 64.7 Line of resection of an irreducible intussusception.

Closure

The peritoneal cavity is irrigated with warm saline. The peritoneum and posterior rectus sheath and anterior rectus sheath are closed with continuous 3-0 sutures. The skin is closed with 5-0 subcuticular Monocryl. No drainage is required. When a laparoscopic approach has been used, the 5 mm umbilical wound should be sutured, but the 3 mm working ports do not need to be closed with sutures, and the risk of incisional hernia is low.

Postoperative instructions

A nasogastric tube is usually not necessary unless there has been severe obstruction or a prolonged ileus is anticipated. Oral fluids are resumed when the infant appears to be hungry and the abdomen is becoming soft to palpation.

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65

Inguinal hernia

THAMBIPILLAI SRI PARAN AND PREM PURI

INTRODUCTION

Inguinal hernia is one of the most common surgical conditions in infancy, with a peak incidence during the first three months of life. The diagnosis of inguinal hernia is made with increasing frequency in newborns; this period carries a particularly high risk of incarceration. The incidence of hernia is much higher in premature infants who survive in increasing numbers after sophisticated intensive care management. As a consequence, more and more indications for early surgical repair are proposed in a population in which there are additional surgical and anesthetic risks.

ETIOLOGY

Direct hernia is exceedingly rare at this age[1] and practically all congenital indirect inguinal herniae develop because the processus vaginalis remains patent after birth. This processus is an outpouching of the peritoneum through the inguinal canal that is first seen during the third month of intrauterine life. It accompanies the gubernaculum and the testis during their descent through the inguinal canal and reaches the scrotum by the seventh month of gestation. In the female, the processus extends along the round ligament. Obliteration of the processus vaginalis commences soon after the descent of the testis is completed and continues after birth. Most infants have a patent processus vaginalis several months after birth. Patency has been reported to be 80–94% in the newborn period, 57% in the 4–12-month age group, and 20% in adulthood;[2] this patency is not equivalent to an inguinal hernia and most often has no clinical relevance.

EPIDEMIOLOGY

The incidence of congenital indirect inguinal hernia in full-term neonates is 3.5–5%.[3] The incidence of inguinal hernia in preterm infants is considerably higher and ranges from 9 to 11%.[4] The incidence approaches 60% as birth weight decreases from 500 to 750 g.[2] Inguinal hernia is more common in males than in females. Most series report a male preponderance over females ranging from 5:1 to 10:1.[5] Of all inguinal hernias, 60% occur on the right side, 25–30% on the left, and 10–15% are bilateral.[2,6] Bilateral hernias are more common in premature infants and are reported to occur in 44–55% of patients.[4,7,8] The reported risk of a metachronous contralateral hernia is 7–10%.[9–12] There is a higher familial incidence and inguinal hernia has been observed with increasing frequence in twins and siblings of patients.[13] There is no geographic or racial predominance reported in the literature.

ASSOCIATED CONDITIONS

There is an increased incidence of inguinal hernia in patients with the following conditions:

- Undescended testis
- Ventriculoperitoneal shunts[14,15]
- Peritoneal dialysis[16,17]
- Cystic fibrosis
- Increased abdominal pressure[18] secondary to meconium ileus, necrotizing enterocolitis, chylous ascites, tight closure of gastroschisis, omphalocele
- Bladder exstrophy[19,20]
- Connective tissue disorders, such as cutis laxa,[21] Ehlers–Danlos and Marfan syndromes, or Hurler–Hunter mucopolysaccharidoses.[22]

CLINICAL FEATURES

Inguinoscrotal hernia can be diagnosed prenatally by ultrasonographic screening.[23] In the newborn, the presenting feature is a bulge in the groin which increases in size with

crying and which is usually noticed by the mother. This bulge may disappear spontaneously when the patient is quiet and relaxed but sometimes it remains visible and palpable for hours causing crying, obvious discomfort, and sometimes vomiting. When the lump in the groin is reduced, it is usually possible to feel thickening of the structures of the cord due to a hernial sac. A reliable clinical history along with palpation of a thickened cord is highly suggestive of inguinal hernia. In girls, the lump intermittently felt in the groin is usually less obvious and often a tender, non-reducible, ovoid-shaped mass corresponding to the ovary slided within the sac can be palpated.

Some premature infants with previous apneic episodes stopped having them after inguinal hernia repair. The obvious interpretation is that there can be some association between both clinical conditions.[24]

Although this eventuality is exceedingly rare, acute inflammation of the appendix within the hernial sac has been reported in premature and full-term newborns.[25–28]

INCARCERATED INGUINAL HERNIA

Incarceration occurs when the contents of the sac is blocked at its neck and cannot be easily reduced into the abdominal cavity. Strangulation occurs when there is vascular compromise of the contents of the sac because of the persistent constriction at its neck. The contents of the hernial sac may consist of small bowel, appendix, omentum, or ovary and Fallopian tube. If there is delay in treatment, incarceration rapidly progresses to strangulation and can lead to intestinal necrosis and even fecal fistula.[29]

The incidence of incarceration in neonates and young infants is reported to vary between 24 and 40%.[3,30,31] The incarceration rate is much higher in premature infants compared with full-term infants.

Testicular infarction has been reported in up to 30% of infants younger than three months of age with incarcerated inguinal hernia[32] and testicular atrophy following emergency operation for incarceration ranges between 10 and 15%. However, testicular volume in a group of children who had incarcerated inguinal hernia reduced by taxis during infancy and subsequently had elective herniotomy was not significantly different from age-matched controls, suggesting that this risk has been overemphasized.[30] Ovarian infarction is also possible after incarceration in females[4] and vaginal bleeding has been reported in an infant after uterine incarceration in the hernial sac.[33] The risks of gonadal damage when the slided ovary cannot be reduced justify the fact that most surgeons advise prompt operation in these cases.[34]

DIAGNOSIS

A newborn with incarcerated inguinal hernia usually presents with irritability, vomiting, a moderately distended abdomen, and a tender groin lump (Fig. 65.1). Occasionally, the infant may pass blood per rectum. Local examination reveals a tense, tender lump in the groin, the upper margin of which is not well defined. The homolateral testis may be normal or swollen and hard due to vascular compromise. Rectal examination usually is not necessary but, if done, the contents of the hernia can be palpated at the internal ring.

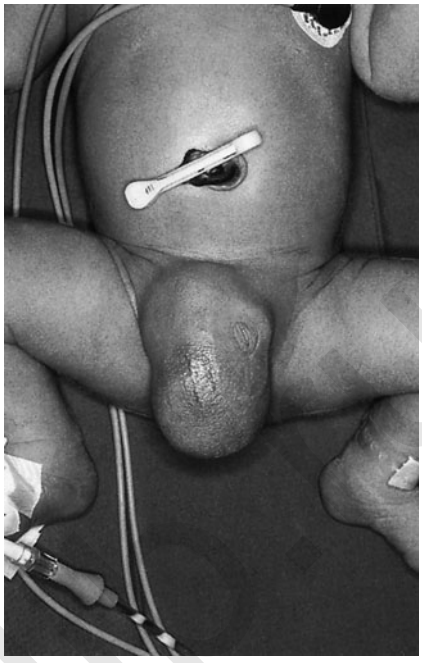

Figure 65.1 Large incarcerated right inguinal hernia in a 1-day-old infant. The hernia was reduced by taxis and herniotomy performed 2 days later.

The diagnosis of incarcerated inguinal hernia is usually made on clinical grounds. Abdominal x-rays may occasionally show bowel gas within the lump in the groin and confirm the diagnosis (Fig. 65.2). If intestinal obstruction is present,

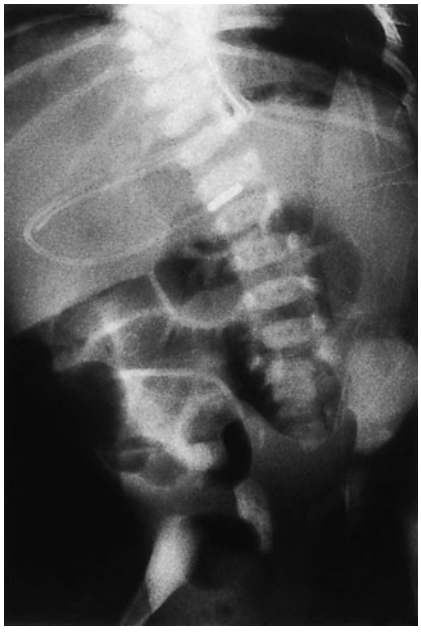

Figure 65.2 Supine abdominal film in a 10-day-old infant who presented with an irreducible lump in the right groin shows distended bowel loops extending into the right inguinal hernia.

plain abdominal films will show dilated loops of bowel with fluid levels. Ultrasonography can help diagnosis in some cases.[35]

DIFFERENTIAL DIAGNOSIS

Clinical diagnosis of incarcerated inguinal hernia is usually easy but it may be difficult to differentiate from the following conditions.

Hydrocele

It is possible to get above the swelling, which is non-tender. Transillumination is not a reliable sign in infants, as bowel can be transilluminant because of its thin wall.

Hydrocele of the cord or cyst of canal of Nuck is difficult to differentiate from incarcerated hernia. There is no previous history of reducible groin lump in these patients. Since the lower half of the abdomen is accessible to digital palpation through the rectum, rectal examination may be useful in excluding incarcerated hernia.

Inguinal lymphadenitis

The examination of the area of drainage will most often reveal the source of infection. The cord and testes are found to be normal.

Torsion of the testes

In a scrotal testicular torsion, it is possible to get above the swelling. The testis is tender and slightly higher than on the other side, while the torsion of the testes, which is situated in the superficial inguinal pouch, will be associated with an empty scrotum on the same side.

MANAGEMENT OF INGUINAL HERNIA

The treatment of inguinal hernia is surgery and, in our opinion, there is no place for the use of trusses or other so-called conservative procedures, even in low birth weight (LBW) infants.[36] The ideal time for surgery is as soon as possible after the diagnosis has been made not only because of the high risk of incarceration[37] but also because it has been shown that comfort and weight gain of premature infants with inguinal hernias improve after repair.[38] Nowadays, most inguinal hernia operations are done as day-case procedures,[34] although premature infants and children with cardiac, respiratory, or other conditions have an increased risk of anesthetic complications. However, most authors consider it reasonably safe to operate on these patients on a day-case basis.[39,40]

ANESTHESIA

General anesthesia with endotracheal intubation is preferred in small infants. Premature infants undergoing surgery have an increased risk of life-threatening postoperative apnea.[41] The use of spinal anesthesia in LBW infants undergoing inguinal hernia repair is associated with a lower incidence of postoperative apnea.[42,43]

OPERATION

Inguinal herniotomy is the procedure employed in the treatment of congenital persistence of processus vaginalis. The operation consists of simple ligation of the hernial sac without opening the external ring.

Position

The infant is placed in the supine position on a heating blanket.

Incision

A 1.5 cm transverse inguinal skin crease incision is placed above and lateral to the pubic tubercle (Fig. 65.3a).

Exposure of external ring

Hemostats are placed on subcutaneous tissue, which is cut or spread until the cord is seen to emerge from the external ring (Fig. 65.3b,c).

Separation of sac

The external spermatic fascia and cremaster are separated along the length of the cord by blunt dissection. The hernial sac is seen and gently separated from the vas and vessels (Fig. 65.3e). A hemostat is placed on the fundus of the sac.

Herniotomy

The sac is twisted so as to reduce its content into the abdominal cavity. The spoon can be used to keep vas and vessels away from the neck of the sac. The sac is transfixed with a 4-0 stitch at the level of internal ring, which is marked by an extraperitoneal pad of fat (Fig. 65.3b). The part of the sac beyond the stitch is usually excised, but there are no obvious advantages of removing the distal part of the sac after its division and closure, particularly if there is complete persistence of the peritoneovaginal duct, and therefore the operation should remain as simple as possible.[44] In girls, the operation is even more straightforward since there is no risk

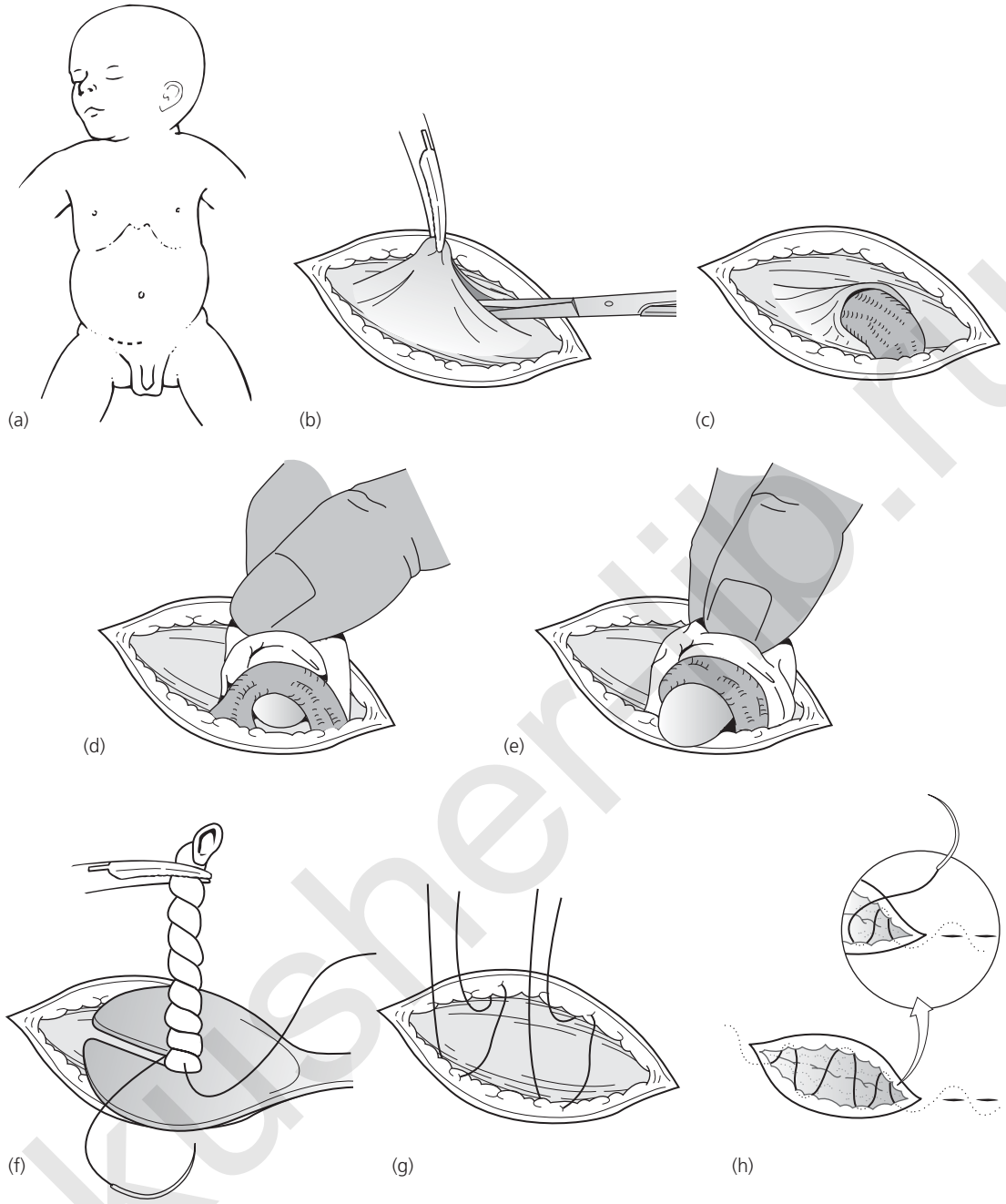

Figure 65.3 (a) Skin incision. (b,c) Exposure of external inguinal ring. (d) Isolation of the spermatic cord. (e) Separation of the hernial sac. (f) Transfixation of the hernial sac. (g) Closure of subcutaneous tissue. (h) Subcuticular closure of skin.

for the vas or the vessels and the external orifice can be closed after excising the sac.

Closure

Subcutaneous tissues are approximated using two or three 4-0 absorbable interrupted stitches (Fig. 65.3g) and the skin is closed with a 5-0 absorbable continuous subcuticular suture (Fig. 65.3h). A recent alternative is the use of cyanoacrylate adhesives for approximating the skin edges. A small dressing can be applied over the wound if necessary. At the end of the operation, the testis, always tractioned upwards during operative maneuvers, must be routinely pulled back into the scrotum to avoid iatrogenic ascent.[45]

Laparoscopic inguinal hernia repair

Laparoscopic hernia repair in infancy is still debatable. There are many techniques available for laparoscopic repair of inguinal hernia in infants. In recent years, several authors have reported that laparoscopic hernia repair in infants is feasible, safe, and effective.[46–49] However, it is associated with long operative time and higher recurrence rate compared to open herniotomy.

Contralateral exploration

Contralateral exploration is often performed in premature babies because of the high incidence of bilateral hernia in them, which ranges from 44 to 55% according to different authors.[4,7,8] Otherwise, contralateral exploration is not necessary as only around 10% of these children will subsequently proceed to develop a clinically apparent inguinal hernia on the other side.[10–12]

POSTOPERATIVE MANAGEMENT

Adequate postoperative analgesia is achieved by regional anesthesia, ilio-inguinal and ilio-hypogastric nerve block, which is administered either before or at the end of operation. Feeding is resumed as soon as the infant is awake. Most patients can be discharged home the same day. Postoperative apnea is a well-known risk of inguinal hernia operation in premature infants.[50] Although most episodes of postoperative apnea in these babies occur in the first 4 hours following the end of the procedure,[51] they are often admitted for 24 hours for observation in order to prevent this complication.[52] Postoperative apnea is inversely correlated with gestational and postconceptual ages[53] but absolute weight at operation and previous respiratory dysfunction are apparently the best independent variables to be correlated with such risks.[54]

MANAGEMENT OF INCARCERATED HERNIA

In a stable patient, there is no doubt that the preferred treatment for incarcerated hernia is reduction. This policy of non-operative reduction is based on the following facts: the likelihood of reducing strangulated bowel in infants is extremely rare and the complication rates are higher with emergency operations for irreducible hernia.[55]

The infant is placed in the Trendelenburg position, which helps to relieve the edema and allows mild traction of the hernial contents. Adequate sedation is given to the infant so as to relax the abdominal muscles. If the hernia is not reduced within 1 hour with these measures, an attempt is made to reduce it with gentle taxis, where constant gentle pressure is applied on the fundus of the sac in the direction of the cord. The vast majority of incarcerated hernias reduce with these non-operative techniques. After the hernia is reduced, the infant is kept in the hospital and observed. Elective operation is carried out after 24–48 hours, when edema and swelling have subsided.

Operative management

Failure to reduce the hernia and strangulation are indications for emergency operation. In girls, when the ovary is non-reducible, at least half of the surgeons in a recent US survey advise emergency operation.[34]

Preoperative support

Infants need to be stabilized prior to surgery. Nasogastric suction and correction of fluid and electrolyte imbalance are undertaken, and antibiotics are given, but this period should be kept to a minimum.

Operation

The patient is anesthetized. If the hernia is spontaneously reduced, the sac is opened and the intestine inspected. Herniotomy is performed if there is no evidence of intestinal ischemia. The bowel should be examined through the same incision or through right lower quadrant laparotomy on suspicion of reduction of non-viable bowel, as indicated by blood-stained fluid in the sac or if blue bowel is seen in the abdomen through the opened sac.

If the bowel does not reduce spontaneously when the patient is anesthetized, no attempts are made to reduce the hernia. The sac is opened and the contents are examined. If the bowel is viable, it is reduced. In case of difficulty in reducing the contents, the internal ring is either dilated or split superiorly. On the other hand, if viability of the bowel is questionable, it is delivered out and warm saline soaks are applied. The intestine is examined after 5–10 minutes. If its color returns to normal with adequate perfusion, peristalsis is visible and mesenteric arterial pulsations are seen, the intestine is returned to the abdomen and herniotomy is completed. If the bowel is nonviable, resection and anastomosis are performed, either through the same incision or through laparotomy. Testes are put in the scrotum irrespective of whether they are normal or ischemic. Only frankly necrotic gonads may be removed.

Postoperative care

If resection and anastomosis are carried out, nasogastric aspiration and i.v. fluids are continued in the infant until peristalsis returns and feeds are established. Antibiotics are continued for 5 days.

COMPLICATIONS

The overall complication rates after elective hernia repair are low at about 2%,[56] while these are increased to 8–33% for the incarcerated hernias requiring emergency operations.[4,55]

Complications of inguinal hernia repair include:

- Hematoma – can be avoided with meticulous attention to hemostasis. It is rarely necessary to evacuate wound, cord, or scrotal hematoma.
- Wound infection – low risk and should not exceed 1%.[3,57,58]
- Gonadal complications – occur due to compression of the vessels by incarcerated viscera. Though large numbers of testes look non-viable in patients with incarcerated hernia, the actual incidence of testicular atrophy is low[30] and

therefore, unless the testis is frankly necrotic, it should not be removed.

- Intestinal resection. This is necessary in about 3–7% of patients in whom the hernia is not reduced and it may cause some additional morbidity corresponding to resection itself and contamination of the field.[4]
- Iatrogenic ascent of the testes. This event is relatively rare since only slightly more than 1% of patients operated upon for inguinal hernia during infancy subsequently required orchidopexy.[45] This complication is probably due to entrapment of the testis in the scar tissue or failure to pull it down into the scrotum at the end of the operation and to maintain it there.
- Recurrence. The acceptable recurrence rate for inguinal hernia repair is less than 1%[56] but when operation is performed in the neonatal period this complication can occur in up to 8%.[58] The factors which predispose to recurrence are ventriculoperitoneal shunts, sliding hernia, incarceration, and connective tissue disorders.[59] Recurrence may be indirect or direct. Indirect recurrence is due to either failure to ligate the sac at high level, tearing of a friable sac, a slipped ligature at the neck of the sac, missed sac, or wound infection. Direct hernia may be due to inherent muscle weakness or injury to the posterior wall of the inguinal canal.
- Mortality. In a present-day situation, the mortality rate of inguinal hernia operation should be zero.

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66

Short bowel syndrome and surgical techniques for the baby with short intestines

MICHAEL E HÖLLWARTH

INTRODUCTION

The short bowel syndrome (SBS) in term neonates was defined by Rickham, in 1967, as an extensive resection of all but a maximum of 75 cm of the small gut.[1] This corresponds to 30% of the total jejuno-ileal length in term newborns. SBS in premature newborns also corresponds to 30% of the calculated intestinal length for the given gestational age.[2]

In the past, extensive loss of small bowel in newborns and babies used to be a catastrophic event nearly always followed by malnutrition and death. Reviewing the literature in 1965, Küffer found only nine surviving children with SBS.[3] In 1972, Wilmore reviewed 50 babies younger than two months with SBS and found survival was possible with 15 cm jejuno-ileum with the ileocecal valve, or with 38 cm jejuno-ileum without the ileocecal valve.[4] Recently, Dorney and colleagues reported that long-term nutritional support today allows survival in infants with as little as 11 cm of jejuno-ileum with the ileocecal valve (5% of the total), or with 25 cm of jejuno-ileum without the ileocecal valve (10% of the total).[5]

Intestinal adaptation is the term which characterizes the pathophysiology that follows intensive intestinal resection, and by which more than 80% of the babies with SBS do finally reach a normal life with entirely oral nutrition. Adaptation is characterized by an early increase of blood flow to the intestinal remnants[6] and by long-term stimulation of intestinal growth which enormously enlarges the absorptive surface area.[7] The latter includes an increase of villus height, crypt depth, intestinal length, intestinal thickness, and intestinal diameter. Additionally, water and solute absorption is enhanced in the colon, and colonic bacteria ferment undigested carbohydrates and proteins into short-chain fatty acids, which act as important energy providers and apparently, as additional promoters of adaptation.[8,9]

The precise mechanisms of adaptation are not clear, but intraluminal nutrients and endogenous intestinal secretions stimulate growth.[10–12] Recently it has been shown that ω-3 fatty acids from fish oil have a beneficial effect on liver function and ameliorate parenteral nutrition associated liver disease.[13] In general, the higher the workload required for digestion and absorption, the more potent is the stimulus for adaptation. In response to the nutrients and secretions, a large number of trophic polypeptides and other mediators are secreted. Over the years, some of them have attracted attention regarding their possible clinical value in promoting adaptation in SBS patients. First, gastrin was demonstrated to exhibit trophic effects on the small bowel.[14] Later, enteroglucagon was shown to stimulate the adaptive response on the intestinal tract in animal experiments and humans.[15] Since monoclonal antibodies failed to block this trophic effect, recently precursors of enteroglucagon are considered to be responsible for the intestinal effects. Glucagon-like peptide-2 is a trophic hormone that has an important role in controlling intestinal adaptation.[16,17] Human growth hormone (GH) in combination with epidermal growth factor, or with insulin-like growth factor-1 (IGF-I) have also been shown to regulate small intestinal growth and adaptation.[18–22] IGF-I receptors have been identified in all segments of the gastrointestinal tract, and IGF-I stimulates DNA and RNA synthesis and cellular amino acid uptake.[23] The endogenous GH-IGF-I system is an important regulator of small intestinal growth and adaptation.[21] Among the amino acids, glutamine (GL) plays an important role in the maintenance of intestinal structure and function by providing the energy required by cells with a rapid turnover, such as macrophages and enterocytes. Patients after major trauma or in chronic catabolic states benefit from GL supplementation.[24] In addition, Ziegler *et al.* have shown that human growth hormone increases glutamine uptake after intestinal resection, supporting the evidence that glutamine exerts trophic effects in the small intestine and the colon of patients with SBS.[19,25] More research however is needed, since studies by Vanderhoof *et al.* could not confirm a role for GL or GH as trophic agents for the intestinal tract.[26] Prostaglandin (Pg) E2 and polyamines have also been shown to stimulate cell

proliferation in animal experiments by increasing blood flow and DNA synthesis.[27,28] Experimental evidence exists that testosterone enhances adaptation after small bowel resection in cats.[29]

Within one year in more than 80% of the patients, adequate intestinal adaptation occurs and they can be weaned off parenteral nutritional support.[30,31] However, this process can cause significant embarrassment and psychological stress to the child and their family, as well as complications such as septicemia, cholecystitis, and chronic liver fibrosis.[32] Therefore, the ability to reliably predict whether a patient has the potential to be weaned from parenteral nutrition has gained significant attention. Citrulline is a free amino acid in plasma and is produced by the metabolism of glutamine and proline in small bowel enterocytes. It has been shown that plasma estimations of citrulline correlate well with the bowel length in children and adults and can be used as a predictor of whether weaning from parenteral nutrition will be possible or not.[33,34] The cut-off point distiniguishing children who reach independence of parenteral nutrition seems to be 15 μmol/L.[34]

While intestinal transplantation has still limited clinical applicability with long-term survivors, ongoing interest exists in surgical methods to enhance nutrient absorption. This chapter reviews current surgical techniques for patients with SBS, with special emphasis on their clinical applicability.

SURGICAL TACTICS IN SITUATIONS REQUIRING EXTENSIVE INTESTINAL RESECTION

Malformations, such as multiple intestinal atresias or gastroschisis with atresia can cause a congenital SBS in the newborn. Acquired conditions, such as intestinal strangulation by midgut volvulus or necrotizing enterocolitis, may require extensive intestinal resection. For patients at risk of SBS, surgery must be adapted to preserve as much small bowel as possible.

In intestinal atresias, dilated intestinal loops should be preserved instead of resected in the usual way. In volvulus, second-look procedures can help the surgeon decide which parts of the intestine are definitely lost. In extensive necrotizing enterocolitis, intestinal loops of questionable viability should be decompressed by an enterostomy, not resected. The ileum is more important than the jejunum, since it is the site of vitamin B_{12} and bile acid absorption. Also, the ileum has a much greater capacity for intestinal adaptation. When resection has been completed, the remaining jejunum and ileum should be measured from the ligament of Treitz all the way down to the ileocecal valve, with a thread laid along the antimesenteric border. Intestinal loops shrink considerably during manipulations, and the real intestinal length is difficult to measure *in vivo*. This may be one reason that survival does not seem strictly related to the length of the remaining bowel.

SURGICAL TECHNIQUES IN PATIENTS WITH SBS

General agreement exists that the therapeutic priorities in patients with SBS consist of the stabilization of patients' conditions, the evaluation of the adaptive capacities of the intestinal remnants, and the clarification of patients' special needs. Therefore, the primary surgical aim is restoration of the bowel continuity as soon as possible in order to allow all remaining intestinal segments to take part in the adaptation process. Additional surgical strategies come into play only if:

- the absorptive area is definitely too small to allow enteral feeding;
- dysmotility in grossly dilated loops entails stagnation of chyme;
- intestinal transit is too fast to allow sufficient absorption of nutrients (Table 66.1).

Intestinal transplantation (TPX) is, of course, the most effective method to increase the intestinal absorptive area immediately. Indications for TPX are patients after a catastrophic abdominal event with little or no small bowel remaining, and patients with SBS and irreversible liver failure due to progressive total parenteral nutrition-associated hepatic dysfunction. Until recently, the results of intestinal TPX had been poor, mainly due to a high rejection rate. With the introduction of new immunosuppressive drugs, such as tacrolism and OKT3, in addition to steroids, significant progress has been achieved with a one-year transplant survival rate approaching 75% in recent series. However, the adverse effects including lymphoproliferative diseases related to Epstein–Barr virus infections are reaching an incidence of 20%, and therefore much progress is still needed before transplantation can be recommended as a routine treatment replacing long-term home parenteral nutrition in a larger number of patients with SBS.[35–37]

Augmentation of the absorptive surface area has been attempted – almost exclusively in animal experiments – by autologous mucosal transplantation into demucosized intestinal loops and by patching surgically created intestinal defects with adjacent serosal surfaces which causes new intestinal mucosa to grow over the exposed serosal surface.[38–40] Digestive and absorptive function of this neomucosa is considerably lower compared to native mucosa and clinical experience with intestinal patching has not been reported.[41,42]

Therefore, current surgical procedures usually support only one or two of the above factors. The predominant problem in a given patient has to be evaluated carefully to choose the method most likely to enhance the absorptive capacity of the intestinal remnants. General agreement exists

Table 66.1 Surgical strategies in patients with short bowel syndrome.

To increase passage time	To increase absorptive surface area	To improve peristalsis
Antiperistaltic segment	Serosa patching	Tapering
Colon interposition	Mucosa transplantation	Tapering and lengthening
Intestinal valves	Small bowel intestinal transplantation	
Artificial invagination		

that most of such techniques are not indicated as a primary procedure. The priorities are: (1) stabilization of the patient's condition, (2) evaluation of the adaptive capacity of the intestinal remnants, and (3) clarification of the patient's special needs.

INEFFICIENT PERISTALSIS

Tapering

In a newborn with multiple intestinal atresias resulting in SBS, bowel which is congenitally enlarged due to chronic obstruction should be preserved. However, the low contraction pressure in such bowel segments results in inefficient to-and-fro peristalsis, easily demonstrated by radiological studies. Inefficient peristalsis can lead to stasis of the chyme, symptoms of obstruction, and a contaminated bowel syndrome caused by bacterial overgrowth. Tapering of dilated loops can be accomplished by a triangular resection of an antimesenteric segment (Fig. 66.1). The disadvantage of this type of tapering is that it reduces the available intestinal surface area. Thus, the technique can be recommended only for patients with sufficient intestinal length and absorptive area in whom inadequate peristalsis is the main problem.

Tapering can also be accomplished simply by turning in the redundant tissue (Fig. 66.1). This technique avoids reduction of intestinal surface area and results in normal bowel function.[43–45] Whichever method is used, effective and propulsive peristalsis takes at least 3 weeks to return.

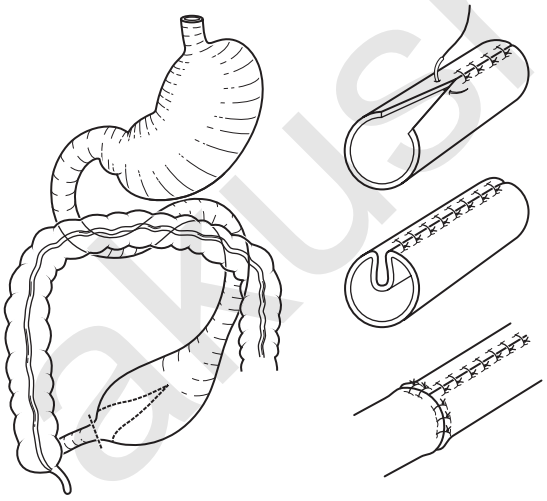

Figure 66.1 Tapering can be performed either by resection of a triangular antimesenteric segment or by turning in the redundant tissue. The latter method saves all the available resorptive surface area.

Tapering and lengthening

In 1980, Bianchi reported an experimental procedure combining the tapering of dilated loops with use of the redundant tissue for lengthening the bowel.[46] Anatomically, the mesenteric vessels from the last parallel arcade divide into anterior and posterior branches entering the bowel from either side of the midline. Especially in dilated segments, a relatively broad avascular plane in the midline can be used to separate the vascular layers. Longitudinal division of the bowel can be accomplished this way, while preserving sufficient nutrient vessels to either half of the intestine. Longitudinal closure of each intestinal segment and isoperistaltic end-to-end anastomosis doubles the intestinal length of this segment.

Bianchi in his experimental reports and Boeckmann and Traylor in the first clinical report used a GIA stapler to divide the intestinal parts.[47,48] Although the procedure using the GIA stapler is fast, it produces two rigid intestinal segments and consumes absorptive surface area. Aigrain *et al.* recommended division with scissors and a manually sutured anastomosis.[49] Seromuscular stitches guarantee a maximum of preserved mucosa (Fig. 66.2a). Since both sections of the bowel hang on the same mesenteric segment, a helix-like isoperistaltic anastomosis is easier to perform than an anastomosis with the two segments sliding one on the other. The helix technique avoids traction on the nutrient vessels, which is critical because necrosis of the divided segments has been reported (Fig. 66.2b).[50] Recent experimental studies in dogs showed that intestinal tapering and lengthening may impair nutritional status as well as intestinal adaptation and absorption.[51]

Bianchi's method has been used in more than 50 infants. Necrosis of half of the segments occurred in only one baby.[50] In some of these infants, the primary length of the intestinal segments was as long as 40–80 cm, which would question the indication of some of these procedures. According to Bianchi's own experience, the method has proved successful when performed not in newborns or the early phase of a short bowel problem, but in a later stage of the disease on so-called 'self selected survivors', i.e. patients in stable general conditions and free of severe complications, such as liver failure.[52] This statement can be confirmed by the author's experience with two SBS newborn babies with 15 cm and 20 cm small bowel remnants, no ileocecal valve, 40% of the normal colonic length. Although Bianchi's procedure was performed completely uneventfully and nearly doubled the intestinal length, both babies suffered from a poor peristalsis and died at the age of one year with progressive liver failure.

Another method of bowel tapering and elongation has been published by Kimura. This procedure consists of an initial coaptation of the small bowel remnant to a host organ (liver, abdominal wall) and, after collaterals have been developed, a secondary longitudinal split of the bowel is done to provide two loops, one from its antimesenteric half and the other from its mesenteric half. This procedure has been successfully used in two infants.[53,54]

A recently published procedure which can be used in cases with insufficient peristalsis due to dilated intestinal loops and also as a lengthening procedure is the so-called STEP (serial transverse enteroplasty).[55,56] The refashioning of dilated intestinal loops is achieved by serial alternating and opposite transsections of one-third or half of the intestinal lumen creating a zigzag-like figure (Fig. 66.3). The method has the

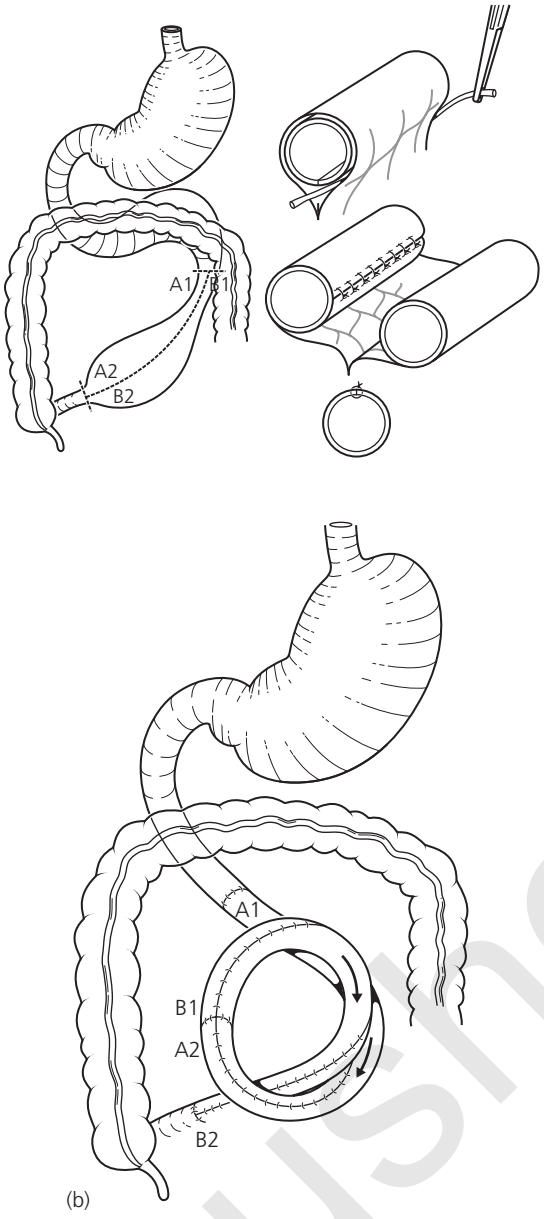

Figure 66.2 (a) Bianchi's tapering and lengthening is critical for the intestinal circulation. A Penrose drain facilitates the division of the segments. Seromuscular stitches save as much mucosal surface area as possible. (b) The helix-like arrangement of the two separated parts allows the anastomoses to be performed with minimal traction on the vessels.

advantage that it is technically much easier than Bianchi's procedure and the achieved lengthening is significantly longer. A retrospective analysis by a Canadian group for the improvement of intestinal function and treatment including 14 patients after a STEP procedure did not show significant differences when compared with an older group of patients except a lower mortality after liver failure, mainly as a consequence of an earlier referral and increased survival after transplant.[57] Long-term results including patients with comparable short bowel length are still unavailable, but the preliminary results in single patients are promising.

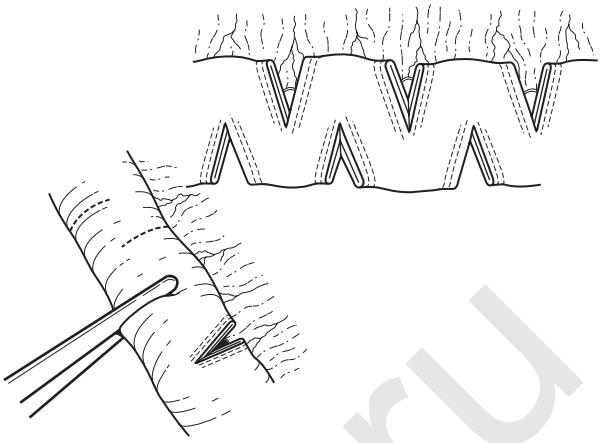

Figure 66.3 Serial transverse enteroplasty (STEP) consists of semicircular alternating incisions with the GIA stapler resulting in a zigzag-like elongation of the small bowel.

INADEQUATE INTESTINAL TRANSIT TIME

For a long time, the ileocecal valve was supposed to prolong intestinal transit time. Today, its beneficial role in patients with SBS has been challenged. A review by Dorney *et al.* showed that the presence of an intact ileocecal valve is crucial to survival of newborns after extensive loss of small bowel.[5] These findings have been confirmed by the author's experience: all babies with SBS and preserved ileocecal valve survived while all patients with fatal outcome did not have the valve.[58] In contrast, Coran *et al.*[59] and Kaufmann *et al.*[60] have not shown a difference in outcome of SBS patients with regard to the presence or absence of the valve. Furthermore, experimental evidence exists that bacterial translocation in SBS rats without ileocecal valve is significantly lower when compared to animals with preserved ileocecal valve.[61,62] While definite evidence of a beneficial role of the ileocecal valve in SBS patients is lacking, nevertheless, the valve should be preserved whenever possible; and it probably plays a role with regard to the prolongation of the intestinal transit time. Recently, Kosloske and Jewell[63] published a technique of appendiceal interposition that allowed preservation of a very short ileal stump with the ileocecal valve.

Antiperistaltic small intestinal segment

Reversal of distal small bowel loops has been studied experimentally for years. Since Gibson and colleagues' original report of the use of reversal of small intestine in an adult,[64] this has been the most commonly used method for patients with SBS (Fig. 66.4). The antiperistaltic small bowel segment acts as a physiological valve by causing retrograde peristalsis; therefore, it should always be located at the end of the intestinal remnants. The ideal length of the reversed segment appears to be 10 cm in adults and 3 cm in infants.[30,64,65] This may explain why the method has not consistently resulted in clinical improvement.[64,66] In a three-month-old patient in the author's department, a 3 cm antiperistaltic segment (out of a total of 11 cm small bowel)

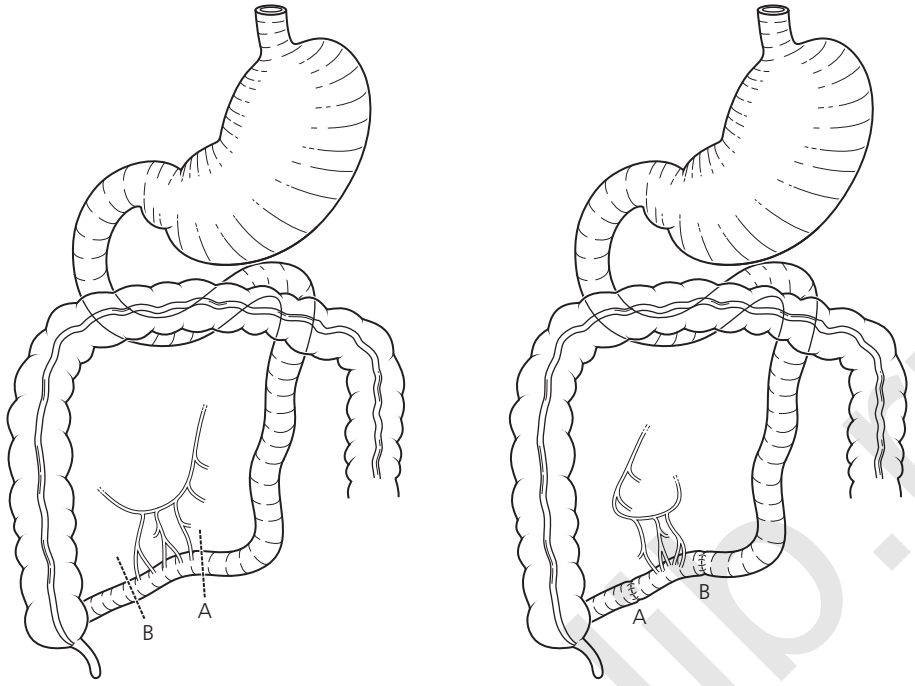

Figure 66.4 The antiperistaltic intestinal segment should be interposed close to the ileocecal valve or at the end of the small bowel. The optimal length in newborns is around 3 cm.

was helpful for intestinal adaptation. At four years of age, when the child was fed completely orally, the total radiological small bowel length had reached 1 m, with a swinging of the opaque meal at the probable location of the antiperistaltic segment.[30]

Colonic interposition

Isoperistaltic or antiperistaltic interposition of colon has the advantage of using none of the small intestinal remnants. The method was developed by Hutcher *et al.*[67,68]

The isoperistaltic segment should thus be interposed proximally either between the jejunum and ileum if the jejunal segment is short and the ileal segment long, or between the duodenum and jejunum if the latter is long and the ileum short (Fig. 66.5).[69] Isoperistaltic colonic interposition slows down the rate at which nutrients are delivered to the distal intestine by slowing peristaltic activity.[69] The optimal length of an interposed colon has not been defined. Glick *et al.*[70] used 10–15 cm-long segments in small babies, while Garcia and colleagues[71] used a 24 cm segment in a 14-month-old infant.

A reversed colonic interposition primarily causes a partial functional obstruction by delaying the emptying of the proximal bowel. It should therefore always be placed distally to the small bowel remnants.[69]

Besides the beneficial effect of slowing peristaltic activity, the interposed colonic segment increases the bowel length between the duodenum and cecum. Furthermore, colonic loops adapt to the function of the small bowel and can absorb water, electrolytes, and nutrients by active transport mechanism.[72] Experimental studies in rats have shown a significant increase in crypt depth, mucosal thickness, and maltase concentration of the interposed segment.[73]

Reported clinical results show that out of seven infants with isoperistaltic interposition four survived.[70,71] In two, the length of the intestinal remnants was not reported; in the other two they were 39 and 63 cm. An adult patient with 5 cm of jejunum and 7 cm of ileum after a midgut volvulus could be weaned from parenteral nutrition completely after interposition of an 18 cm-long isoperistaltic colon.[74] The sole reported infant with a reversed colonic interposition died.[75]

Recent experience in our department with proximal isoperistaltic colonic interposition and an additional distal STEP procedure in newborns with very short bowel, e.g. after gastroschisis with intrauterine volvulus and vanishing bowel, seems to be very promising.

Intestinal valves and pouches

As mentioned above under Inadequate intestinal transit time, while the benefits of the ileocecal junction on long-term outcome of babies with SBS has been questioned, there exists a large body of evidence as to its powerful impact on intestinal transit time by slowing the passage of intraluminal nutrients into the colon.[76] Therefore, a variety of experimental surgical procedures have been devised to slow down the intestinal transit time by creation of artificial valves. Constriction of the bowel by sutures and artificial sphincters,[77] mechanical or chemical denervation of segments,[66,78] and intussusception techniques have been studied extensively.[79–81] Clinical experience with intussuscepted valves is very limited. Waddell *et al.* performed a reversed intussusception of the colon into the jejunum in three adults, one of

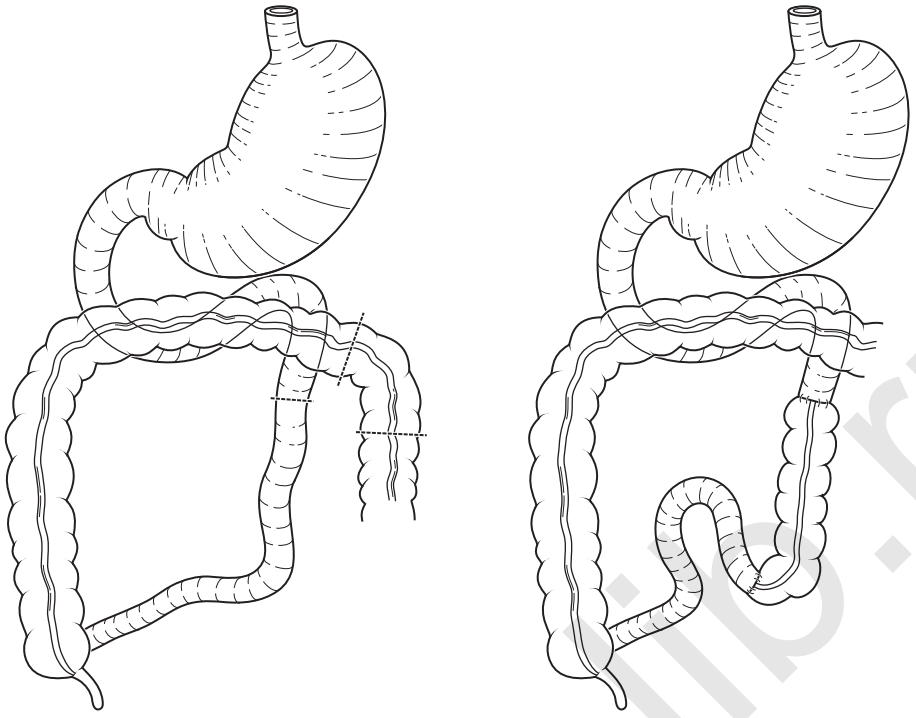

Figure 66.5 The isoperistaltic colonic interposition should be interposed proximally (while the reversed colonic interposition should be used distally). The length of an isoperistaltic interposition is recommended within 10–20 cm.

whom subsequently developed an obstruction.[82] Ricotta *et al.* constructed a 4 cm-long nipple-like ileocecal valve (Fig. 66.6) in a 15-year-old boy, which appeared to be helpful.[80] Cywes created a duodenojejunal pouch in a 21-month-old child who previously had 4 cm of jejunum reversed. The midsegment of the pouch acted as a reversed segment. While the transit time was prolonged at three months, late results were not encouraging.[40]

CONCLUSIONS

Despite the variety of surgical techniques designed to support intestinal adaptation after extensive loss of small bowel, none can be recommended unequivocally.[83,84] In the past, the overwhelming majority of babies with SBS have been treated exclusively by parenteral nutritional support until intestinal adaptation allowed entirely oral nutrition. Full enteral feeding has ultimately been attained in infants with originally as little as 15 cm of the small bowel with the ileocecal valve preserved, or 25 cm of jejuno-ileum when it was missing.[5,30,85] Survival rates of 75–83% are being reached in newborns, and 100% in children at or above two years of age.[55,86,87]

Surgery is indicated only in selected patients, either to achieve effective propulsive peristalsis or to prolong intestinal transit time. However, adjunctive surgical procedures should be postponed until the special needs of individual patients are evident. Approximately 10% will benefit from surgical interventions, either by prolongation of transit time or by remodeling parts of the intestine.[88]

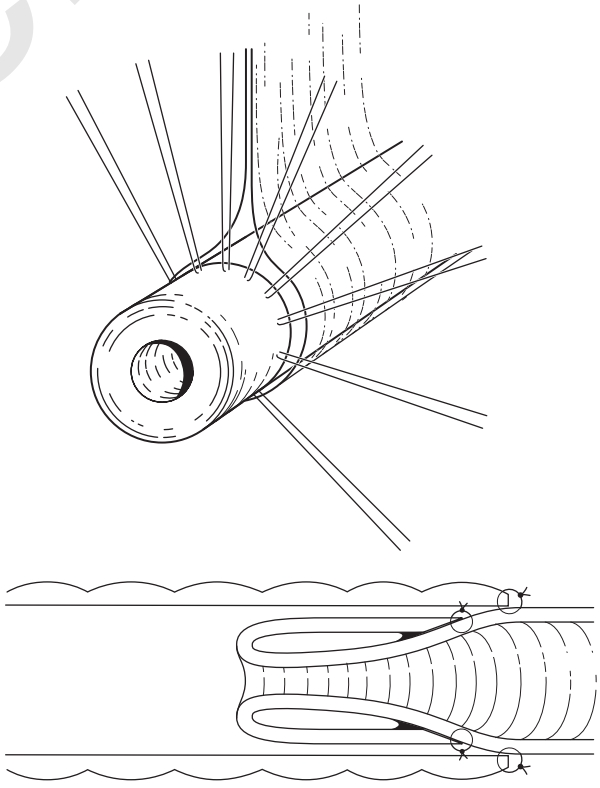

Figure 66.6 Nipple-like ileocecal valve according to Ricotta *et al.*[80] The optimal length in newborns is not defined, but will be around 1–2 cm. In a 15-year-old boy, a 4 cm-long valve worked well. Seromuscular stitches allow the precise adaptation of the mucosal layers.

Patients with total loss of small bowel or progressive liver failure may benefit from the progress made by intestinal TPX, although five-year survival rate does not lie much above 50%.[35] Survival rates after intestinal TPX as well as quality of life will hopefully significantly improve in the future. Most importantly, a reduction in adverse effects by finding new forms of immunosuppressive therapy in the future will be beneficial.

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Megacystis microcolon intestinal hypoperistalsis syndrome

PREM PURI AND JAN-H GOSEMANN

INTRODUCTION

Megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) is a rare congenital and generally fatal cause of functional intestinal obstruction in the newborn. The main characteristics of this syndrome are abdominal distension, caused by a massive enlarged non-obstructed urinary bladder, microcolon, and decreased or absent intestinal peristalsis.[1] MMIHS is usually associated with incomplete intestinal rotation and shortened small bowel.

PATHOGENESIS

MMIHS was first described by Berdon *et al.* in 1976.[1] To date, over 220 cases have been reported in the literature.[2–25] Although several hypotheses have been proposed to explain the pathogenesis of MMIHS (genetic,[26–33] neurogenic,[29,30,34–41] myogenic,[42–45] and hormonal[39,46] origin), the etiology of this syndrome remains unclear.

In the majority of MMIHS patients, histologic studies of the myenteric and submucosal plexuses of the bowel revealed normal ganglion cells. In some patients, decreased amounts of ganglion cells or hyperganglionosis together with giant ganglia were found.[29] In 1983, Puri *et al.* showed vacuolar degenerative changes in the smooth muscle cells (SMCs) with abundant connective tissue between muscle cells in bowel and bladder of patients with MMIHS.[44] This led to the suggestion that a degenerative disease of SMCs could be the cause of this syndrome. Several subsequent reports have confirmed evidence of intestinal myopathy in MMIHS.[42,43,45]

More recently, Piotrowska *et al.* reported absence of interstitial cells of Cajal (ICCs) in bowel and urinary bladder of patients with MMIHS.[43,47] ICCs are pacemaker cells which facilitate active propagation of electrical events and neurotransmission. Their absence may result in hypoperistalsis and voiding dysfunction in MMIHS.

Furthermore, absence or marked reduction in α-smooth muscle actin and other contractile as well as cytoskeletal proteins in the smooth muscle layers of MMIHS bowel have been reported.[43,45] Contractile and cytoskeletal proteins are important structural and functional components of SMCs and play a vital role in the interaction of filaments in smooth muscle contraction.

Rolle and Puri showed pathological changes within the bladder smooth muscle cells and markedly increased collagen deposits within the bladder wall of MMIHS patients. The authors concluded that the detrusor muscle is strikingly abnormal and this is the likely cause of voiding dysfunction in the affected patients.[48]

Other studies support the hypothesis that the absence of a functional α3 subunit of the neuronal nicotinic acetylcholine receptor (ηAChR) is responsible for the predominant intestinal manifestation of smooth muscle myopathy, leading to manifestation of MMIHS.[16,49,50] This lack of functional alpha 3 and the absence of smooth muscle actin in the circular layer of small bowel muscularis was recently suggested to be associated with a *de novo* deletion of the proximal long arm of chromosome 15 (15q11.2).[51]

The occurrence of MMIHS in 19 sets of affected siblings together with consanguinity in four sets of parents, reported by Puri and Shinkai, suggests an autosomal recessive pattern of inheritance.[2,31,32,52]

PRENATAL DIAGNOSIS

One hundred and eighty-two cases of MMIHS reported in the literature were reviewed by Puri and Shinkai.[2] The most frequent finding reported on fetal sonography ($n = 54$) associated with MMIHS was enlarged bladder (88%) together with hydronephrosis (57%). In 59% of the fetuses, normal amniotic fluid volume was detected, whereas 33% revealed increased volume and 7% had decreased volume. Only 5%

showed abdominal distension caused by dilated stomach. Three cases (5%) of oligohydramnios during the second and early third trimesters were reported, which may probably be related to the functional bladder obstruction (Table 67.1).

Enlarged bladder, detectable from 16 weeks of gestational age, was shown to be the earliest finding in MMIHS in serial obstetrical ultrasonography (Fig. 67.1). A later finding is hydronephrosis, caused by the functional obstruction of the bladder. Usually polyhydramnios develops late, appearing during the third trimester.

Recent reports have described prenatal magnetic resonance imaging (MRI) in patients with suspected genitourinary and gastrointestinal tract abnormalities following ultrasound examination.[10,14,25] In contrast to sonography, MRI not only demonstrated urologic abnormalities but identified also early stages of gastrointestinal pathology. Hence, the authors advocate MRI as an ancillary imaging technique whenever routine ultrasonography screening demonstrates genitourinary pathology with need for further investigation.

CLINICAL PRESENTATION

Review of the current literature reveals that females are more affected in MMIHS than males (2.4:1 ratio).[2–25] With regard to the duration of pregnancy, 59% of the reported patients were born at term, 26% at 36–39 weeks of gestation, 12% at 32–35 weeks, and 3% at 31 weeks and less. In four of the cases, reviewed by Puri and Shinkai,[2] pregnancy was terminated after ultrasonography detected MMIHS. Eight cases of dystocis delivery due to abdominal distention were reported and Cesarean section was required in four cases.

In four cases, paracentesis was needed because the bladder was so distended that the baby could only be delivered vaginally after removal of 250, 500, 650, and 500 mL of urine, respectively, from fetal bladder.[39,44,53,54] The mean birth weight was found to be normal (3 kg) for gestational age.

Clinical symptoms of MMIHS are similar to other neonatal intestinal obstructions. Abdominal distension is a constant and early finding. It is a consequence of the enlarged, unobstructed urinary bladder with or without upper urinary tract dilatation. The majority of patients were not able to void spontaneously. However, a distended, non-obstructed urinary bladder could be easily relieved by catheterization. Of 182 infants, 61 had bilious vomiting and 23 failed to pass meconium.[2] Other symptoms include bile-stained vomiting and absent or decreased bowel sounds.

Nineteen sets of siblings affected with MMIHS have been reported to date. Eighteen families had two affected siblings and one had three. Four sets of affected siblings occurred to consanguineous parents (Table 67.2). In another case, an affected child was born to a member of the family reported by Penman and Lilford,[32] and consanguinity was also present in these parents. In three further cases, an elder sibling of the affected child died just after birth because of intestinal obstruction or multiple abnormalities. In another case, a sibling of the patient was affected by prune belly syndrome.[2]

Table 67.1 Prenatal ultrasound findings.

Ultrasound findings	%
Enlarged bladder	88
Hydronephrosis	57
Normal amniotic fluid volume	59
Increased amniotic fluid volume	33
Decreased amniotic fluid volume	7
Dilated stomach	5
Oligohydramnion (2nd, 3rd trimester)	5

Data from Puri and Shinkai.[2]

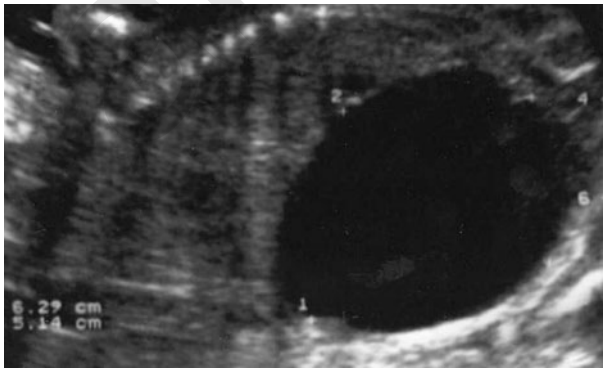

Figure 67.1 Massive enlarged fetal bladder: longitudinal view of abdominal ultrasound at 22 weeks' gestation, fetus in prone position.

RADIOLOGICAL FINDINGS

Radiological evaluation usually suggests the diagnosis of MMIHS. Plain abdominal films showed either dilated small

Table 67.2 Reported siblings with MMIHS.

Author	Consanguinity
Berdon *et al.* (1976)	–
Patel and Carty (1980)	–
Krook (1980)	–
Olivera *et al.* (1983)	–
Winter and Knowles (1986)	+
Farrell (1988)	–
Penman and Lilford (1989)	+
Young *et al.* (1989)	–
Gakmak (1989)	+
Garber *et al.* (1990)	–
Anneren *et al.* (1991)	+
Stamm *et al.* (1991)	–
Dewan (1995)	–
Kohler *et al.* (2004)	–

Data from Puri and Shinkai.[2]

bowel loops or a gasless abdomen with evident gastric bubble in the vast majority of 182 reported cases.[2] An enlarged urinary bladder was present in all patients who had cystography or ultrasonography (Fig. 67.2). Vesicoureteral reflux was found in eight patients and in 84 patients i.v. urography or ultrasonography detected unilateral or bilateral hydronephrosis.[29,55–58]

Barium enema showed microcolon in all 71 patients in whom this study was performed and in 39 cases malrotation was associated (Fig. 67.3).

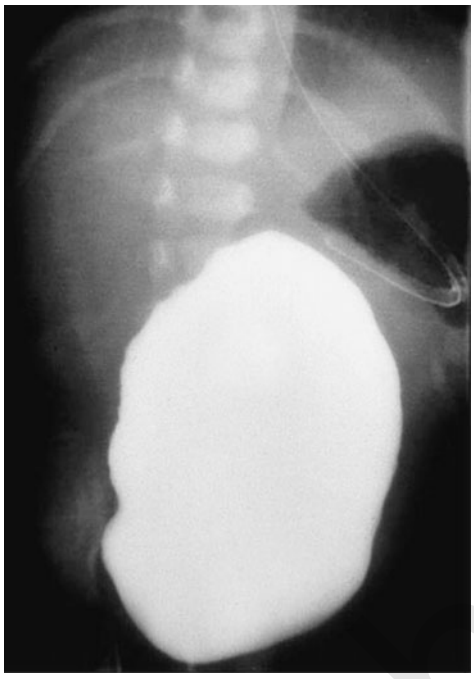

Figure 67.2 Voiding cysturethrogram showing massively enlarged bladder in a megacystis microcolon intestinal hypoperistalsis syndrome patient.

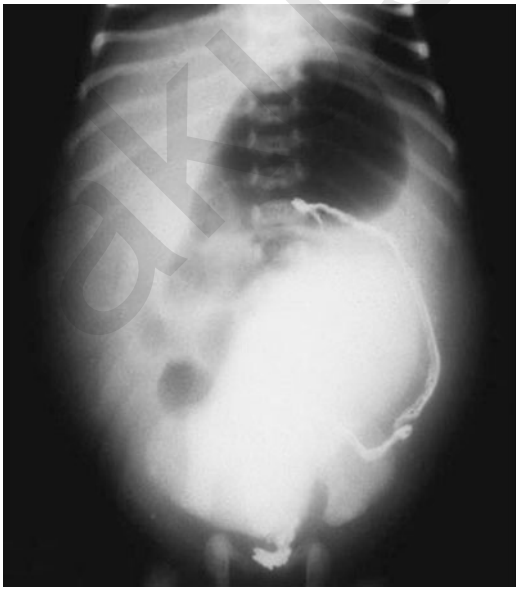

Figure 67.3 Contrast enema showing microcolon in a megacystis microcolon intestinal hypoperistalsis syndrome patient.

In patients who underwent an upper gastrointestinal series, both before and after laparotomy constantly revealed hypo- or aperistalsis in stomach, duodenum, and small bowel. Reverse peristalsis from small bowel into the stomach was observed in three cases, in two cases hypoperistalsis was associated with gastro-esophageal reflux and in one case the esophagus was aperistaltic.[2]

SURGICAL OR AUTOPSY FINDINGS

Megacystis and microcolon were the two most frequent findings at surgery or autopsy and were present in all patients (Fig. 67.4). Puri and Shinkai reported malrotation in a total of 81 cases.[2] Short bowel syndrome was found in 37 cases, dilated proximal small bowel in 19, segmental stenosis of the small bowel in 3, duodenal web in 1, and Meckel's diverticulum in 1.

Surgical management was not mentioned in several reports. Nevertheless, 70% of the reviewed patients underwent one or more surgical procedure. Various surgical interventions have been performed, such as gastrostomy, jejunostomy, ileostomy, cecostomy, segmental resections of jejunum and ileum, lysis of adhesions, and internal sphincter myectomy. In most patients, surgical manipulation of the gastrointestinal tract generally has been unsuccessful and in most patients total parenteral nutrition was required. Thirty-seven patients underwent vesicostomy to decompress the urinary tract and to preserve renal function.

HISTOLOGICAL FINDINGS

Histologic studies of the myenteric and submucosus plexuses were reported in 93 out of 182 cases. Ganglion cells were normal in appearance and number in 72 cases (77%). In the

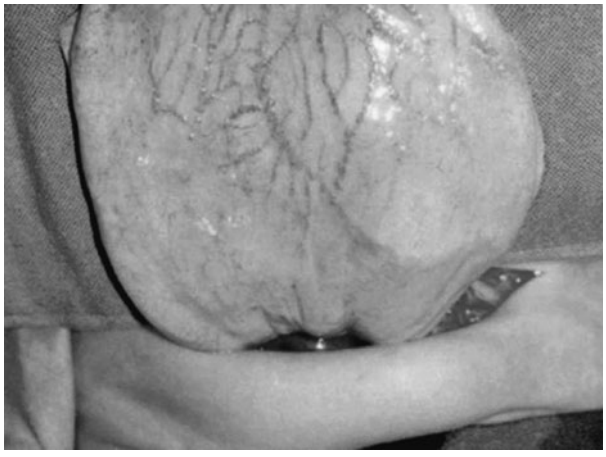

Figure 67.4 Operative photograph of a massively dilated urinary bladder in megacystis microcolon intestinal hypoperistalsis syndrome.

remaining 21 cases (23%), various neuronal abnormalities included hypoganglionosis, hyperganglionosis, and immature ganglia.[2,30,37,38,40,41,46,59]

The majority of reports do not mention histologic findings in the muscle layers of bowel and bladder wall. However, some authors found significant abnormalities in SMCs, such as thinning of the longitudinal muscle, seen in light microscopy.[2]

Vacuolar degeneration in the center of the smooth muscle of bowel (11 cases) and bladder (eight cases) was shown in electron microscopy (Fig. 67.5). Furthermore, connective tissue proliferation was found in the bowel (nine cases) and bladder (eight cases). In three cases, the bladder showed elastosis. Electron microscopy revealed vacuolar degeneration of smooth cells in muscle layers of bowel and bladder in addition to neuronal abnormalities in two more patients.[2]

Other investigators have reported absence or marked reduction in α-smooth muscle actin and other contractile and cytoskeletal proteins in smooth muscle layers of MMIHS bowel.[43,45]

OUTCOME

Management of patients with MMIHS is frustrating. A number of prokinetic drugs and gastrointestinal hormones have been tried without success. Surgical manipulations of the gastrointestinal tract have generally been unsuccessful. The outcome of this condition remains generally fatal with a survival rate of 19.7%.[60] The majority of the surviving patients are maintained by total or partial parenteral nutrition.[2]

In the recent literature, 12 cases of multivisceral organ transplant are described with various outcomes. Long-term survivors (50% at three years post-transplant) are reported to be free from total parenteral nutrition and seem to show adequate gastric emptying via Mikulicz stomata.[11,12,16,17,20,21,24]

The decision for surgical intervention should be made carefully, individualized and in most cases restricted to supportive interventions (such as feeding enterostomy and decompressing ostomy), since most explorations have not been helpful and probably are not necessary.

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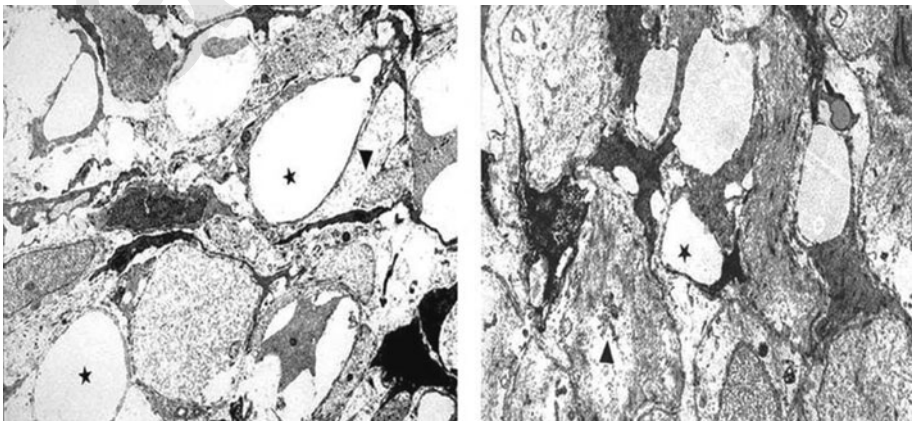

Figure 67.5 Electron microscopy: smooth muscle cells from ileum and bladder from a patient with megacystis microcolon intestinal hypoperistalsis syndrome showing vacuolar degeneration (*) in the center of smooth muscle cells.

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PART VI

LIVER AND BILIARY TRACT

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68

Biliary atresia

MARK DAVENPORT

INTRODUCTION

There is still much to learn about biliary atresia (BA); why it happens and how it happens being good examples of areas where there is too much speculation and not enough hard evidence. What is only too obvious is that if it is untreated it progresses to end-stage cirrhosis and is potentially fatal within the first 12–18 months. A treatment strategy has evolved, which in the best hands will give a 90% chance of long-term survival for all infants born with the disease, but, even in these survivors there is still significant morbidity and problems to overcome. Nonetheless, it is compatible with normal life.

HISTORY

The first documented case of biliary atresia was reported in English in 1891 by John Thompson.[1] He was a physician in Edinburgh and his newborn patient developed jaundice, passed only white-colored stool from an early age and ultimately died of liver failure with ascites at about six months. Her post-mortem showed a normally formed but empty gallbladder and an absence of the common hepatic duct.

Further reports followed, but no real treatment could be offered until surgeons began to operate on some of these infants. The most significant series published was that of Ladd in 1928, who reported his experience in ten cases of surgical jaundice – some of which were BA.[2] Fairly quickly afterwards, it was realized that only a small proportion (having 'correctable' BA) were suitable as surgical candidates as at exploration a patent part of the biliary tree could be found and a hepaticojejunostomy performed. The remainder, those with 'uncorrectable' BA, had an entirely solid biliary tract, certainly nothing that could be anastomosed to.

An alternative operation for the latter group was advocated by Morio Kasai (1922–2008), a surgeon working in Sendai, Japan.[3] He showed that a higher, more radical dissection was needed and if the entire extrahepatic biliary tract was removed, then even if it looked solid, still it would contain microscopic biliary ductules which connect to the intrahepatic biliary tract. If enough of these were uncovered then bile flow could be restored. The reconstruction advocated was termed a portoenterostomy to reflect this higher level of anastomosis. Once again, this proved not to be the complete answer with unpredictable results and a significant proportion that showed no effect whatsoever. Such was the skepticism that its value was only really recognized in North America and Europe during the 1970s. Most post-Kasai adult series as a consequence are therefore Japanese,[4] with some rare exceptions.[5] The alternative, if yet more radical, treatment for a terminally damaged liver also appeared in the 1960s – liver transplantation. Tom Starzl's first, albeit unsuccessful, attempt at human liver transplant took place in 1963 in Denver, Colorado in a three-year-old girl with end-stage liver disease due to BA.[6] During that period, the science of immunosuppression was in its infancy and transplant programs shut down having failed to come to terms with inevitable cellular rejection. The key discovery in the 1980s was an effective immunosuppressive agent – cyclosporine – which allowed transplant programs to flourish once more. From the 1990s, in most of the developed world and still today, the strategy for management has been an attempt to resuscitate the native liver with a Kasai portoenterostomy and if that fails – transplantation.[7]

ETIOLOGICAL HETEROGENEITY

Biliary atresia is not one disease, certainly not one with a single cause (Fig. 68.1). In all probability it is a phenotype resulting from a number of different etiologies. Three, perhaps four, groups can be defined clinically:

1. isolated BA
2. biliary atresia splenic malformation (BASM) syndrome[8,9]
3. cystic BA[10]
4. cytomegalovirus-associated BA.

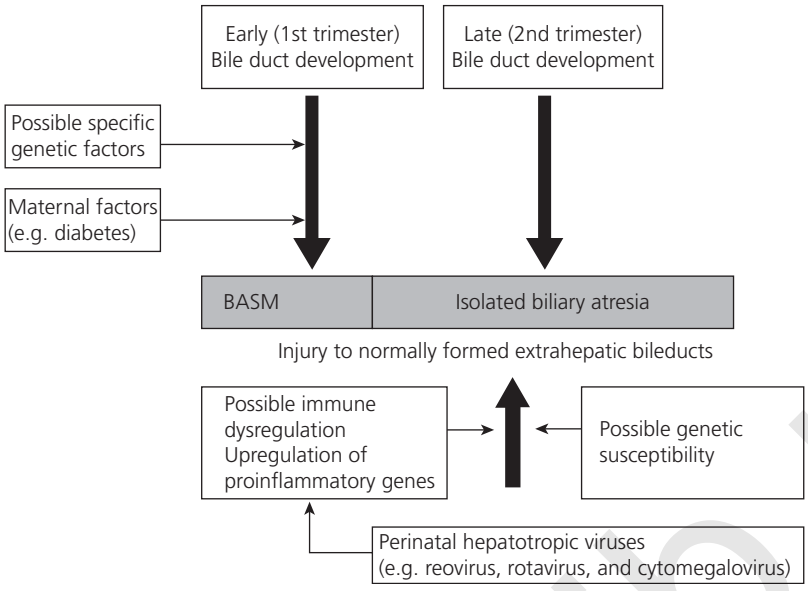

Figure 68.1 Schematic illustration of possible causes of biliary atresia: etiological heterogeneity.

There are other relationships, although these are much rarer. Some cases appear to have an association with other gastrointestinal anomalies, such as esophageal atresia and jejunal atresia (<2% of large series), and we have recently reported those with a defined chromosomal abnormality (e.g. cat-eye syndrome and chromosome 22 aneuploidy).[11]

We have now begun to use the term 'developmental biliary atresia'[12] for those cases where there is almost unequivocal evidence for a prenatal onset, and obstruction is evident by the time of birth. This would therefore include (2) and (3). The onset of occlusion in (4) is probably perinatal with occlusion of a patent biliary system by virally-mediated mechanism a possibility. The most prevalent group, isolated BA (1), is more difficult to categorize etiologically as it is simply defined by absence of anything else. Some could still be developmental in origin and others perinatal in timing.

BILIARY ATRESIA SPLENIC MALFORMATION SYNDROME

We first reported what became known as BASM in 1993,[8] recognizing that splenic anomalies (not just polysplenia) were related in some way to biliary atresia and that there was also a peculiar but consistent association with cardiac defects, situs inversus, pre-duodenal portal vein, and absence of the vena cava (Table 68.1). The reasons for this are still obscure, but it has been suggested that the common factor is simply an embryonic 'insult' in a critical window of the developing viscera – perhaps at 30–35 days' gestation. Whether this affects single specific genes or an array of developmental genes or proteins is not known.

There are genes that appear to be important in both bile duct development (e.g. *JAG1, HNF-6*[13] and visceral and somatic symmetry (e.g. *INV, CFC-1*[14,15]), although most work has been done in the mouse and actual correlation with mutations in humans is not that good. A possible genetic link was recently reported by Davit-Spraul *et al.*,[16] who found an increased frequency of mutations in the *CFC-1* gene (on chromosome 2) in patients with BASM, compared to controls.

A further interesting observation is that there is a definite link between maternal diabetes and BASM, in the same way that this condition can cause transposition of the great vessels, double outlet right ventricle and sacral agenesis (although these do not form part of the usual spectrum of BASM).[8,9]

Table 68.1 Spectrum of anomalies in biliary atresia splenic malformation syndrome.

Organ system	Malformation
Splenic	Polysplenia, double spleen (95%)
	Asplenia (5%)
Situs determination	Inversus (50%)
Venous	Preduodenal portal vein (40%)
	Portosystemic shunt (<2%)
	Vena cava (absence) (50%)
Intestinal development	Malrotation (60%)
Cardiac	Atrial septal defect, ventricular septal defect, Fallot's tetralogy, etc. (~40%)
Liver	Normal, 'mirror-image', or symmetrical in situs inversus
Biliary appearance	Solid and scanty gallbladder, may be absent. Gallbladder often a midline structure with solid, symmetrical proximal biliary ducts
Pancreas	Annular (<5%)
Miscellaneous	Immotile cilia syndrome (Kartagener's syndrome)
	Sacral agenesis

Finally, a small number of infants with BASM have immotile cilia syndrome (also known as Kartagener's syndrome) and this provides an interesting speculation as to mechanism. Certainly, dysfunctional cilia could be incriminated in determination of visceral situs – leaving it essentially to chance. But how cilial dysfunction interacts with the developing biliary tree is not known. Normally, only rats and squirrel monkeys have ciliated intrahepatic bile ducts, although there may be chemosensory cilia on cholangiocytes in humans. Cilia may occur in certain forms of biliary pathology – thus perhaps recapitulating its philogeny.

The macroscopic appearance of the biliary tree and liver is also somewhat different to isolated BA, with frequently absence of the common bile duct and a miniscule gallbladder and small proximal remnant. The liver is also usually symmetrical, whatever the nature of the abdominal situs.

PATHOLOGY OF BILIARY ATRESIA

This is best-described as an 'occlusive pan-ductular cholangiopathy' affecting both intra- and extrahepatic bile ducts.

The most common classification divides BA into three types based on the most proximal level of occlusion of the extrahepatic biliary tree (Fig. 68.2). In types 1 and 2, there is a degree of preservation of structure in the intrahepatic bile ducts but they are still irregular, deformed, and pruned – and do not dilate, even when obstructed. The most common variant, type 3, occurs where there is typically a solid, dense fibro-inflammatory proximal remnant at the porta hepatis. The distal duct may be atrophic, absent, or relatively well preserved. The latter typically seen in association with a mucocele of the gallbladder containing clear fluid. Type 3 intrahepatic bile ducts are usually grossly abnormal with myriad small ductules coalescing at the porta hepatis. Sometimes this can be visualized radigraphically as a 'cloud'.

Extrahepatic cyst formation may be evident and contains clear mucus or bile depending on preservation of the connection with intrahepatic bile ductules. We prefer the name 'cystic biliary atresia' for this entity, but the important thing is to distinguish it from simple obstruction in a cystic choledochal malformation.[10] The key to this is the cholangiogram which will show a distorted, deformed non-dilated intrahepatic duct system (if anything) in the former and a well-preserved and 'tree-like' dilated intrahepatic duct system in the latter. There should also be preservation of a decent epithelial lining in the latter on histology.

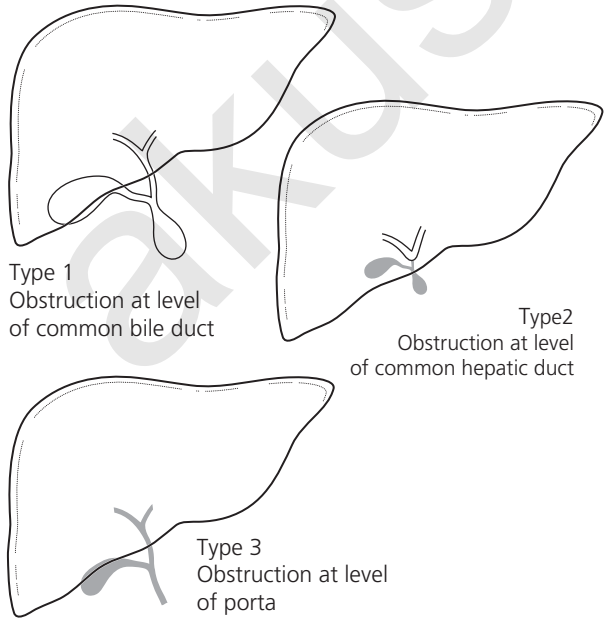

Figure 68.2 Classification of extrahepatic morphology in biliary atresia.

CELLULAR KINETICS AND INFLAMMATION IN BILIARY ATRESIA

That BA is not simply a mechanical obstruction of the biliary tree has been obvious for some time now. There is a marked inflammatory process that is present in most types (possibly with the exception of BASM) as evidenced by an obvious mononuclear infiltrate and expression of a variety of adhesion molecules on intrahepatic biliary and vascular epithelial surfaces.[17] Whether this is a primary or secondary phenomenon (to presence of bile outside biliary canaliculi for instance) is arguable but there is certainly evidence to support the former as a workable hypothesis.[17,18]

The infiltrate is largely composed of $CD4^+$ T-lymphocytes (specifically Th1)[19] and $CD56^+$ (natural killer) NK cells,[17,20] which exhibit markers for proliferation ($CD71^+$) and activation (particularly LFA-1^+ but also $CD25^+$). There is a distinct subset of $CD8^+$ cells, but many studies suggest these may be less important and lack various markers of activation, such as perforin, granzyme B, and Fas ligand.[21]

There is abnormal expression of cell adhesion molecules (proteins involved in cell–cell binding) with both ICAM-1 and VCAM-1 (but not E-selectin) being identifiable on epithelial structures in both liver, and to a lesser extent, the biliary remnant.[17,22]

We also identified increased levels of the soluble adhesion molecules ICAM-1 and VCAM-1 in the circulation at the time of Kasai together with rising levels of these and inflammatory cytokines (e.g. IL-2, TNFα) postoperatively.[23,24] After about six to nine months post-Kasai, these tend to come back down to more normal values (unpublished observation).

The resident (Kupffer cells) or recruited macrophages/monocytes appear to have a crucial role in the development of fibrosis seen in established BA. This may be as both the presenters of antigenic material in the first place and later as the initiating force for fibrosis in the development of chronic liver disease. Tracy *et al.*,[25] in 1996, first showed increases in resident macrophages ($CD68^+$) with marked expression of the lipopolysaccharide receptor $CD14^+$. Increased levels of both $CD68^+$ cells and its circulating markers (TNFα and IL-18) have been shown to impair prognosis post-Kasai.[24,26]

VIRUSES AND BILIARY ATRESIA

There have been a number of studies based on serology in infants with BA which initially suggested a causal link with perinatal viral infection (originally reovirus type 3[27]) but this was later disputed.[28] However, actual viral footprints within the bile ducts have been much harder to demonstrate and a causal link is still controversial.[29,30] Rauschenfels *et al.*,[31] in Germany, looked at wedge liver biopsies obtained from 74 infants at the time of Kasai portoenterostomy for a panel of DNA and RNA hepatotropic viruses. At least one virus was detected in about one-third of infants with the detection rate increasing with infant age. In some, multiple viruses could be found. They suggested this showed that viral infection was a secondary finding and unlikely to be the specific cause of BA. We have recently shown that it can be possible to distinguish clinically infants with cytomegalovirus IgM positivity with BA from other causes and that they do appear to have worse outcome (unpublished observation). Other series have suggested the opposite however.[32]

There is a mouse model of BA where just-born mice can be inoculated with rotavirus (or reovirus or cytomegalovirus) and who developed jaundice with intrahepatic histology similar to that of BA.[33,34] The nature of the cholangiodestructive pathway can be examined relatively easily and it can be shown that there is early upregulation of interferon inducers Irf7 and Irf9 genes (proinflammatory genes) with IFN-γ having greater expression at the time of bile duct obstruction.[35–37]

If no actual virally mediated damage, then it may be that we have to postulate another way of cholangiolar damage by suggesting that the virus acts as a trigger and that in some way there is an immune-mediated destructive process.[18] It could be speculated that this process would continue post-portoenterostomy, and that no native livers would ever drain bile in the long term. There is no real observational evidence that liver loss is inevitable though.

An interesting and novel mechanism of immune damage has been recently suggested based on the observation that male infants with BA have a three-fold increase in maternal-origin cells in their livers.[38] These have later been shown to be maternal-origin chimeric $CD8^+$ T cells and CD45 NK cells and certainly appear capable of initiating immune cholangiolar damage.[39] This is termed 'maternal microchimerism' and it may be the reason that the destructive process is time-limited.

EPIDEMIOLOGY

Given that BA appears a diverse disease, it is not surprising that its epidemiology also varies. Infants with developmental BA have a marked female predominance not seen in the isolated BA group.[8,9,12] Historically, there has been a suggestion of a seasonal variation in incidence,[40,41] though when examined in large national studies this has never been confirmed.[12,42] The implication is that if there were more infants with BA born during the winter months this might be related to the usual prevalence of viruses during this season.

The incidence of BA varies dramatically according to geography. Highest incidences are reported from Asia, with the highest from Taiwan (1 in 5000 live births).[43]

In the UK and Ireland (and much of Europe) there is an incidence of about 1 in 17 000–18 000.[12,42,44] We have recently reported significant regional differences within the UK with some areas having incidences usually seen in Japan for instance. We speculate that this may be as a reflection of the multiracial nature of the UK currently and variation of the different strands of BA (developmental BA was found to be more common in infants of Caucasian origin).[12]

CLINICAL FEATURES

Infants with BA are born smaller at birth (both developmental and isolated) and fail to thrive thereafter due to fat malabsorption.[12] Antenatal detection is possible in cystic biliary atresia and some syndromic cases may present very early because of their other malformations (e.g. malrotation).[45]

Otherwise, the key features are conjugated jaundice together with pale, unpigmented stools, and dark urine (bilirubinuria) in an otherwise healthy neonate. Liver fibrosis and cirrhosis are later developments even in infants with intrauterine BA and evident at birth,[45] and ascites and marked hepatosplenomegaly, are rare features not usually seen until about three months.

Some infants will present with a bleeding tendency which may be catastrophic, detectable with an elevated INR or prothrombin time, and caused by fat-soluble vitamin K deficiency.

LABORATORY FINDINGS

Liver biochemistry will show a conjugated jaundice (variable, but rarely $>250\,\mu mol/L$), modestly raised transaminases (AST >100 IU/L), and significantly raised γ-glutamyl transpeptidase (GGT >200 IU/L). None of this is specific.

The usual differential of a conjugated jaundice is medical and includes TORCH infections (e.g. toxoplasma, rubella, cytomegalovirus, hepatitis, etc.), genetic conditions (e.g. α-1-antitrypsin deficiency, Alagille's syndrome, progressive familial intrahepatic cholestasis (PFIC) disorders), metabolic conditions (e.g. cystic fibrosis, galactosemia), parenteral nutrition together with something termed 'neonatal hepatitis' which is fairly non-specific but none of the above.

The surgical differential is less common, and includes obstructed choledochal malformation, inspissated bile syndrome (usually preterm), and spontaneous perforation of the bile duct.[46] The key feature in these is that they all dilate their intrahepatic bile ducts when obstructed and should be distinguishable simply on ultrasound.

ULTRASONOGRAPHY

Ultrasound typically shows a shrunken, atrophic gallbladder with no evidence of filling between feeds. About 20% will show a 'normal' gallbladder – which turn out to be a

mucocele of the gallbladder in continuity with a relatively preserved common bile duct (CBD) and often absence of common hepatic duct (CHD).

Some centers appear able to actually diagnose BA, simply on ultrasound findings. A specific finding is said to be the 'triangular cord sign' described initially in Korean centers[47] and representing the proximal solid biliary remnant lying in front of the bifurcation of the portal vein. Accuracy rates of >80% have been reported.[48]

MISCELLANEOUS DIAGNOSTIC TECHNIQUES

In the author's unit, the pre-laparotomy diagnosis of BA is usually made by percutaneous liver biopsy showing histological features characteristic of large duct obstruction, and this is perhaps all that is needed in >80% of cases. It is less accurate the younger the liver though and does require an experienced and confident liver pathologist to distinguish these very subtle features.

Other investigations have been reported but are not necessarily essential in every case. Radio-isotope (technetium (Tc)-labeled iminodiacetic acid derivatives) hepatobiliary imaging has a role in some centers in showing the need for laparotomy by demonstrating absence of excretion, recognizing that severe forms of medical cholestasis also show this appearance.[49] A far simpler test is placement of a nasoduodenal tube and aspiration over 24 hours and is used in many Asian centers with undeniable accuracy, but has never really been used in UK centers.

Direct cholangiography is possible and is becoming more popular in those larger centers able to justify the small side-viewing endoscope necessary for infantile endoscopic retrograde cholangiopancreatography (ERCP).[49,50] Failure to cannulate the bile duct is a feature of BA but also may be the result of an inexperienced operator.[51]

Diagnostic laparoscopy and cholangiography (± liver biopsy) is a more widely available alternative to ERCP. Direct puncture of the gallbladder is straightforward to show the presence or absence of bile and a catheter or needle can then be used to outline the biliary tree. If an atrophic gallbladder is present without a lumen, this in itself is evidence of biliary atresia.

SURGERY – KASAI PORTOENTEROSTOMY

The preoperative management includes correcting the coagulopathy and may be an antibacterial bowel preparation. Perioperative antibiotics should be effective against aerobic and anaerobic bowel flora. The various stages in this operation can be broken down as follows below (Figs 68.3 and 68.4).

Cholangiogram

The diagnosis is always confirmed initially through a limited right upper quadrant muscle-cutting incision, allowing access

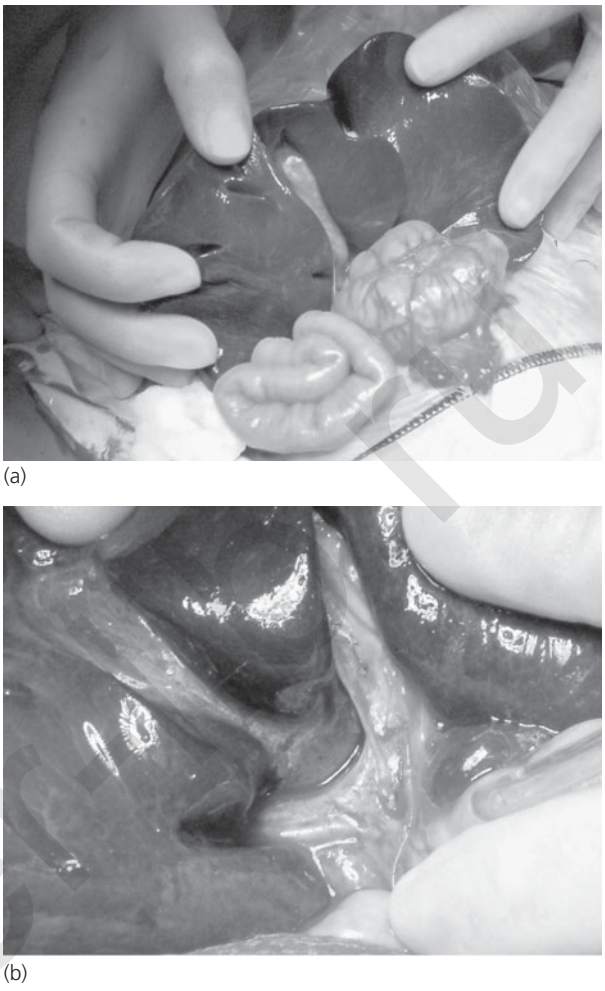

Figure 68.3 Operative appearance of liver in biliary atresia (BA). (a) The liver has been mobilized and is laid out on the anterior abdominal wall. The gallbladder is collapsed and contains no bile, consistent with a type 3 BA. (b) The biliary remnants and gallbladder have been removed, leaving a proximal transection of the portal plate flush with liver capsule.

to the gallbladder. To reiterate, the key observation, confirmed by needle aspiration, is the presence or absence of bile. Practically, the former can only be caused by a type 1 BA, but more likely it indicates one of the 'medical' causes of a conjugated jaundice listed above under Laboratory findings. A cholangiogram should be done to confirm. This may not be possible in some cases simply because the gallbladder has no lumen – but this in itself is indicative of BA. A 'normal' cholangiogram for completeness should show proximal intrahepatic ducts and sometimes this can be difficult; so a small vascular or 'bulldog' clamp on the CBD should aid reflux into the more proximal ducts. Neonatal sclerosing cholangitis and various hypoplastic biliary syndromes can then be detected.

Mobilization and eversion of liver

At this stage, portal venous pressure (via the umbilical ligament) is directly measured, as this may have prognostic

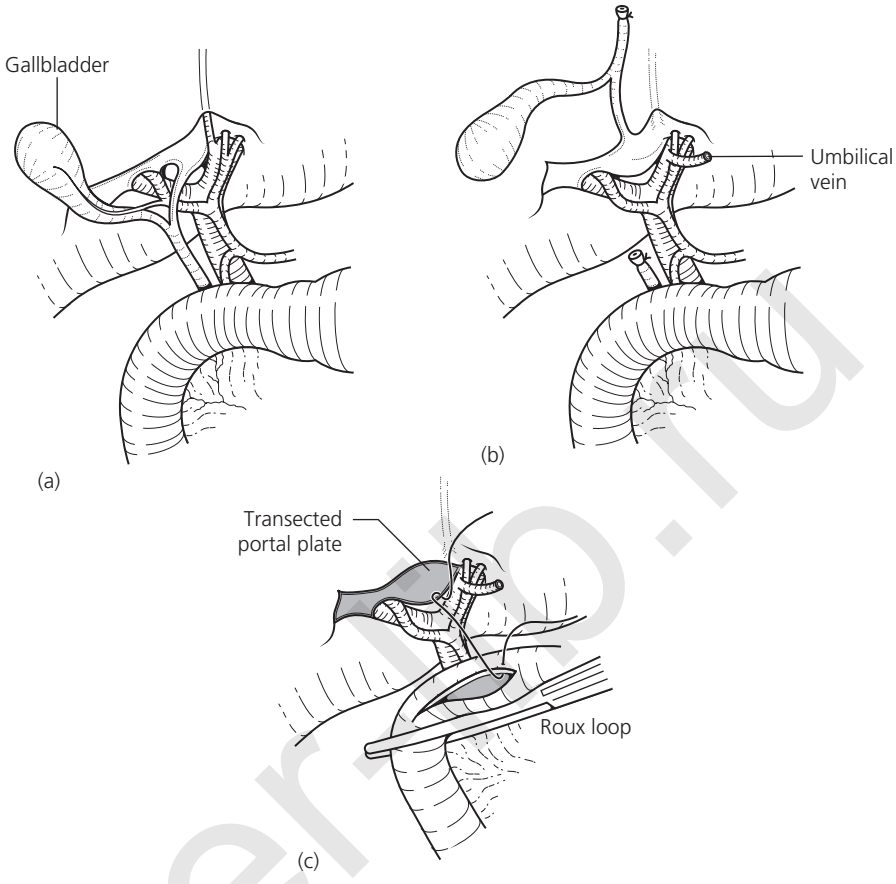

Figure 68.4 Schematic illustration of Kasai portoenterostomy. (a) Type 3 biliary atresia. (b) Mobilization of gallbladder and division of distal common bile duct. Elevation of biliary remnants and separation from vascular structures at level of porta hepatis (portal vein confluence, right and left hepatic arteries). (c) Transection of portal plate from 'umbilical point' on left, to around right portal pedicle. Portoenterostomy with 40–45 cm retrocolic Roux loop.

implications.[52] Then, the liver is mobilized fully by dividing the falciform, right and left triangular, and superior and inferior coronary ligaments. This allows the entire organ to be everted onto the anterior abdominal cavity, facilitating the portal dissection – the key part of the surgery. Care should be taken to warn the anesthetist as this maneuver kinks the cava and reduces venous return.

Portal dissection

The gallbladder should be mobilized off its bed and the distal CBD divided. This allows the more proximal biliary remnant to be dissected free from the vascular elements of the porta (right hepatic artery and bifurcating portal vein). Ligate or coagulate portal lymphatics to facilitate exposure. There are always small veins passing from the superior part of the U-shaped portal vein to the portal plate – these also need careful ligation – and then the liver tissue of the caudate lobe should be seen, opposite the undersurface of segment IV. The limit of the left-sided dissection is within the recessus of Rex where the umbilical vein joins the left portal vein**.** If this fossa is not open then the isthmus can be coagulated and divided. The right vascular pedicle divides into right anterior (base of gallbladder bed) and posterior (in a small innominate fossa) branches each with an accompanying bile duct remnant. All remnant biliary tissue needs excision and there is a definite plane of dissection which can be accessed using scissor dissection. Deeper dissection into liver parenchyma does not seem to achieve anything useful, possibly because of subsequent scarring and occlusion. Coagulation on the portal plate itself should be avoided; any bleeding from the edge should be tolerated as it will stop once the Roux loop is sutured in place.

Roux loop and portoenterostomy

Construct a retrocolic Roux loop measuring 40–45 cm with the jejunojejunostomy about 10–15 cm from the ligament of Treitz (to get mobility and reduce anastomosis tension). The portoenterostomy must incorporate all the denuded portal plate and should be quite wide (~2 cm). The author prefers an end-to-side arrangement using fine (e.g. 6/0 PDS) sutures, although other authors argue for an end-to-end arrangement.[53] A second layer can be added at the end posteriorly using adjacent periportal tissue.

Wound closure needs care as postoperative ascites can test its integrity and strength to the limit. A small drain may help to minimize ascites retention and allow the wound layers to heal. Significant bile leaks do not happen in Kasai operations –almost certainly because there is not that much bile around to leak!

CAVEATS TO SURGERY

Although a visible bile-containing duct may be evident in type 1 or 2 BA and a hepaticojejunostomy performed, it is

better that further proximal tissue is resected to the level of (and therefore needing) a portoenterostomy.

Sometimes on-table evidence of cirrhosis may seem to make a portoenterostomy futile. However, this is rarely absolutely predictable, although in infants of >100 days more likely.[54] A primary transplant may be a better option but is arguable.

At times it has been suggested that frozen section of the resected portal plate is useful to determine whether ductules are large enough (Fig. 68.5). In practice, the aim is to resect all visible bile duct remnant down to, but not encroaching on, parenchyma – thus there is nothing further to resect whatever the pathologist reports.

Portoenterostomy in BASM has a worse long-term outcome, and the outcome can be related to the age at which the surgery is performed.[8,55] The extrahepatic bile ducts are rarely florid, often non-inflammatory and atrophic in appearance. Great care should be taken with the preduodenal portal vein and any aberrant arterial vessels. A malrotation may require a Ladd's procedure and influence the construction of the Roux loop.

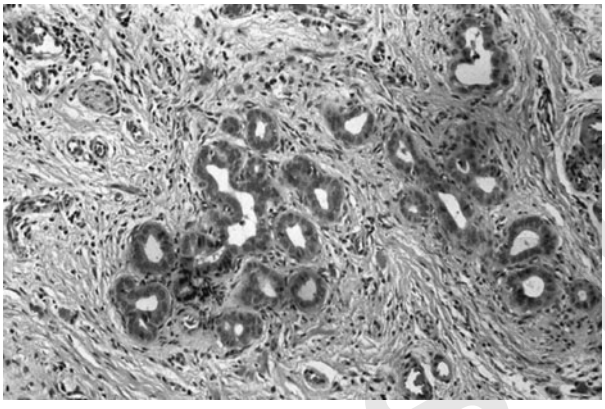

Figure 68.5 Hematoxylin and eosin microphotograph of transected biliary remnant showing multiple biliary ductules lined with relatively normal epithelium; within a fibrous stroma infiltrated by inflammatory mononuclear cells.

POSTOPERATIVE MANAGEMENT

Nasogastric drainage and i.v. fluids are required for 2–4 days before starting feeds. There is no clear advantage from continuing antibiotics beyond one month.

All infants require fat-soluble vitamin supplementation (both enteral and parenteral). All, even those rendered anicteric, will have a degree of fat malabsorption. They should also have an appropriate formula milk (e.g. containing medium-chain rather than long-chain triglycerides). Failure to thrive should be aggressively attended to with nasogastric overnight feeds if necessary. The medical management of the infant or child with serious underlying liver disease is complex, demanding, and absolutely crucial. Most centers achieve this successfully using a multidisciplinary team approach.

Pharmacological improvement in bile flow is possible, by ursodeoxycholic acid for instance but only when a degree of flow has been established by surgery and is one of the postulated mechanisms for steroids.[56] There is not much evidence for other medications, although a number of Japanese and Chinese centers use the Chinese herb, inchinko-to.[57]

The use of steroids is controversial, but appealing given the possible role of inflammation in the etiology of BA. Actual evidence beyond inevitably biased published small series is weak though[58,59] and a recent Cochrane review came to no great conclusions.[60] Our randomized, placebo-controlled trial of oral prednisolone (2 then 1 mg/kg/day in the first month) showed definite improvements in early clearance of jaundice but a lack of real effect on final results and need for transplant.[56] We have not been able to show any sustained effect on more subtle markers of the inflammatory response (e.g. sICAM-1) (unpublished observation). The only other prospective (but not randomized) trial of steroids (starting at 10 mg/kg/day) showed no difference whatsoever.[61]

OUTCOME FOLLOWING PORTOENTEROSTOMY

The actuarial five- and ten-year survival in England and Wales for infants born this century is about 90%.[7,62] There will still be deaths: most awaiting transplantation, some as postoperative complications due to transplant and some due to the effects of other anomalies (e.g. cardiac).

We would expect to restore enough bile flow to clear jaundice and achieve normal values for bilirubin in about 50–60% of infants with isolated BA.[7,55,56,62] Most (>90%) of these infants can expect to survive long term with a relatively normal childhood, but regular outpatient attendance to monitor progress. Their livers will however seldom be 'normal'; in fact, if ever biopsied they will be highly likely to show histological cirrhosis.[63] The five- and ten-year native liver survival will be about 45–50% therefore.[7,62,64] Care should be taken in the interpretation of such figures if they are from countries with no transplant option as their native liver survival equates to true survival.[65]

Effect of age at surgery

Cirrhosis and fibrosis are time-dependent phenomena and it is very reasonable to surmise that the earlier in the disease the cirrhotic process is abbreviated (by restoration of bile flow) then the better the outcome. However, as stated earlier, BA is a heterogenous disease and especially in isolated BA the time of onset is not known and trying to identify a real effect of age on a large series can be difficult.[7,64,66] This hypothesis is supported by the observation that in those where there is definite evidence of intrauterine pathology (i.e. developmental BA) a marked relationship can be seen while in those described as isolated (presumably much more chronologically heterogenous) this relationship is not seen (within 100 days at least).[55]

Large multicenter series with multiple surgeons have been unable to show a real statistically significant relationship.[7,66,67] Figure 68.6 illustrates this problem for isolated

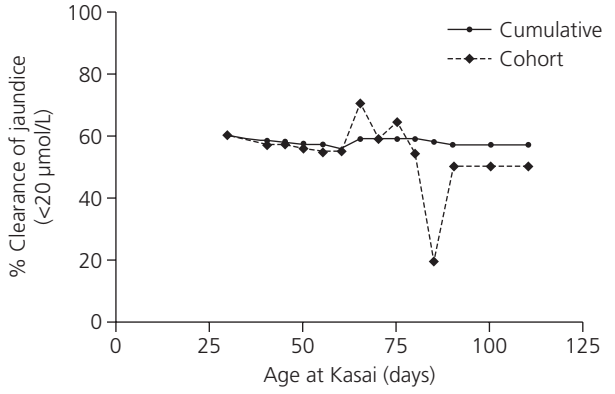

Figure 68.6 Relationship of age at surgery to clearance of jaundice in infants with isolated biliary atresia ($n = 177$). [Reprinted with permission from Ref. 55.] Note: the percentage to clear jaundice in each age-defined (e.g. 31–40 days) cohort is plotted as a solid diamond. The cumulative plots (black circles) are from 30 days and work from left to right, calculating percentage to clear jaundice for successive time points (<30, <40, <50 days, etc.). An essentially flat black line implies no real relationship with age at surgery. [Davenport M *et al.*, *Ann Surg* 2008; 247: 694–8.]

BA and is derived from a single center with two surgeons using the same technique and outcome measured with defined endpoints (clearance of jaundice). Statistically, as the compendium solid black line is virtually flat, implies no 'cut-off' and no effect of age within pragmatic limits. There is actually a gradual decline implying the truth of the original postulate (age worsens outcome) but statistically will require many more numbers to prove it.

Is there any benefit of surgery to those infants who come to surgery at >100 days? Though this is now relatively infrequent in developed countries it still occurs. That they are much more likely to have established cirrhosis is true and their prognosis is certainly less good. Nevertheless, a Kasai as the first step seems reasonable and has been associated with long-term jaundice-free survival in our series.[54] The alternative, of course, is a primary liver transplant.

COMPLICATIONS

Apart from end-stage liver disease in those where there is failure to restore bile flow with development of ascites, malnutrition, and deepening jaundice and which clearly can only be treated by transplantation, there are two major areas of complication.

Cholangitis

This probably occurs in relation to ascending organisms from within the Roux loop, as cholangitis is rare in those who never show any degree of bile flow post-Kasai. It is reported in up to 50% of large series, but seems only to be problematic in the first year postsurgery. It may be characterized by pyrexia, pale stools, increasing jaundice, and other signs of sepsis. Culture of organisms from blood or from liver biopsy is uncommon and judicious use of early, broad-spectrum antibiotics is advised (e.g. ceftazidime, gentamicin, etc.).

Recurrent cholangitis may occur possibly due to the formation of dilated biliary channels or cystic change within the liver and is detectable on ultrasound. In some cases, it occurs because there is a mechanical obstruction to bile drainage within the Roux loop and is detectable using radio-isotope scan.[68] The former is probably best treated by prolonged i.v. antibiotics via a Hickman line and the latter by laparotomy and Roux loop exploration. In older children, newer enteroscopes are now able to visualize the Roux loop directly and this may be an alternate mode of diagnosis.

Portal hypertension

The majority of infants at the time of Kasai will have portal hypertension (PHT), but whether this persists will probably depend upon degree of restoration of bile flow and other dynamic factors.[69] Esophagogastric varices take time to develop but will do so given sustained periods of PHT. The majority of long-term survivors will have endoscopic evidence of varices, although only a proportion will ever bleed. Surveillance endoscopy is recommended in these, although evidence is lacking for the role of prophylactic treatment (e.g. banding). Nonetheless, this is a possible option.

For those who have bled, they will require some form of endoscopic intervention initially, either sclerotherapy or banding. The former technique is well established but not without complications, such as ulceration, stenosis, and stricture formation, and currently should probably be reserved for infants and smaller children where it is not possible to actually pass the banding attachment. There will be a small proportion who have variceal bleeding of such magnitude to require immediate placement of a Sengstaken tube – this is fortunately unusual. Following endoscopic control of the varices an assessment needs to be made about overall liver reserve. There will be some with excellent restoration of liver function and clearance of jaundice where obliteration of varices is all that is needed; there will be others (typically infants and young children of less than two years) where this is simply one part of a failing system and these need to have an expedited transplant.

ROLE OF LAPAROSCOPIC KASAI PORTOENTEROSTOMY

The tsunami of minimally invasive surgery in the 1990s swept along pediatric as well as general surgeons and soon more and more adventurous operations were being described through smaller multiple port incisions, including the Kasai operation. Small series have been reported but none with good results and most with only limited outcomes.[70–72] At the present time, this operation may be the limit, and a number of enthusiasts are returning to the conventional open approach.[73] The reason may be self-evident – the dissection is unforgiving and meticulous precision is required and

therefore even with a robot the operations are simply not comparable. Others have suggested that it may be the effect of the paraphernalia of minimally invasive surgery. For example, Mogilner *et al.*[74] in an experimental model showed that the higher intra-abdominal pressures of the pneumoperitoneum may increase damage through effects on liver blood flow. A definitive answer has yet to be delivered but in its absence, practitioners should be cautious – this surgery has a high enough 'failure' rate without making it more difficult and promises of a better cosmetic result and short hospital stays are fatuous in the context of biliary atresia. The only person benefiting is the transplant surgeon who has a reduced number of adhesions to deal with!

LIVER TRANSPLANTATION IN BILIARY ATRESIA

This has now been available in North America and Western Europe for 'failed' Kasai children since the 1980s. It is still a major undertaking with a consistent risk of postoperative mortality of 6–15%.[75–77] The risk diminishes beyond the first year and an actuarial plateau is then reached, although the vast majority still require oral immunosuppression. A few do develop tolerance (perhaps up to 20%) with the possibility to withdraw medication.[78] Longer-term issues, such as Epstein–Barr-related post-transplant lymphoproliferative disease (up to 10% of some series) and chronic rejection, are still a cause of morbidity and potential mortality.

There are, within all countries and societies, problems coming to terms with ethical attitudes to both cadaveric and living-donor transplantation. Despite efficient use of donor organs, there are never enough of them. As a consequence, waiting-list deaths are still a major issue. There are also lingering technical issues related to size discrepancy, although organ reduction and split liver transplants ameliorate this in the larger centers.

In conclusion, biliary atresia in many respects remains a mysterious disease with its origins cloaked and obscure; in others, though the need for surgical intervention is straightforward, the outcome may be somewhat capricious and unpredictable.[79] Future needs include better pharmacological options to improve bile flow post-Kasai and modify or at least abbreviate the invariable tendency to liver fibrosis (and hence portal hypertension) – a characteristic that can be a real risk to the small infant on a transplant waiting list.

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69

Congenital biliary dilatation

HIROYUKI KOGA AND ATSUYUKI YAMATAKA

INTRODUCTION

Congenital biliary dilatation (CBD), or choledochal cyst, is a cystic or fusiform dilatation of the common bile duct that is uncommon in Caucasians. There is little doubt that CBD is a congenital lesion with a strong hereditary component, which may explain the higher incidence seen in Asia, and its familial occurrence in siblings and twins.[1–3] Traditionally, approximately half become symptomatic in infancy, and neonatal cases have been uncommon. However, with advances in diagnostic imaging techniques, its incidence is increasing, particularly in neonates.[4–11] In our series, about 20% of patients were detected either neonatally or antenatally, and interestingly, the ratio of cystic to fusiform-type CBD neonatally or antenatally is 20:1, in contrast to an overall ratio of 5:3.[12]

The treatment of CBD in early infancy has unique aspects that must be considered in relation to the risks of surgery itself and the size and physiological/immunological immaturity of the patient. Because CBD is commonly associated with pancreaticobiliary malunion (PBMU) involving concurrent anomalies of the common channel, pancreatic duct, and intrahepatic bile duct (IHBD), the importance of cholangiography both preoperatively and intraoperatively cannot be overemphasized. If these anomalies go unnoticed by surgeons, they may be injured during surgery and cause serious postoperative morbidity. Primary cyst excision (CE) with biliary reconstruction to avoid two-way reflux of bile and pancreatic secretions is now the standard procedure of choice.

ETIOLOGY

Various theories have been proposed for the etiology of CBD, but two factors are known to be causal: weakness of the wall of the common bile duct, and obstruction distal to it. Spitz[13] stressed an obstructive factor that appears early in development based on his experimental study in sheep, in which cystic dilatation of the common bile duct could be induced by ligation of the distal end of the choledochus only in neonatal lambs and at no other stages of development. The authors' animal research has confirmed this hypothesis,[14–18] and our radiologic and histologic studies on patients with CBD clearly demonstrate that distal stenosis is closely associated with cystic dilatation of the common bile duct, and that the site of stenosis is related to an abnormal choledochopancreatic ductal junction.[15–19] Jona *et al.*[20] purported that the pathogenesis of CBD-associated PBMU may be related to faulty budding of the primitive ventral pancreas. Wong and Lister[21] conducted research on human fetuses and demonstrated that the choledochopancreatic junction lies outside the duodenal wall before the eighth week of gestation, whereupon it moves inward towards the duodenal lumen, suggesting that an anomalous junction may be caused by arrest of this migration, while Tanaka[22,23] proposed that regression of the terminal choledochus and canalization of the ventral pancreatic duct (W1) caused by sinistral dislocation of the ventral pancreas are responsible for PBMU.

In recent years, cholangiography has identified anomalies of the pancreaticobiliary ductal system in association with CBD, which may allow reflux of pancreatic enzymes and subsequent dissolution of duct walls. This is known as the long common channel theory and was first proposed by Babbitt in 1969.[24] Since then, numerous abnormal arrangements of the pancreaticobiliary junction associated with CBD have been reported by others based on the results of endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), and intraoperative cholangiography (IC). This theory is further supported by the high amylase content of fluid aspirated from dilated ducts in patients with CBD. A dilated common channel and anomalous pancreatic duct are also frequently observed, which may be responsible for the formation of protein plugs or pancreatic stones, often associated with pancreatitis. It is generally recognized that a number of patients with an anomalous long common channel and high amylase level in the gallbladder, show no dilatation of the choledochus, although some had gallbladder carcinoma.[25] However, the authors' research in which choledochopancreatostomy was performed

in puppies to allow regurgitation of pancreatic fluid into the common bile duct, found that the chemical reaction of refluxed pancreatic fluid on the bile duct was extremely mild.[26] Interestingly, in this animal model, fusiform rather than cystic dilatation of the common bile duct was induced.

Although Babbitt[24] stressed that pancreatic fluid is the most likely factor causing edema and eventual fibrosis of the distal common bile duct as well as weakness of the choledochal wall, a diagnosis of CBD can be made antenatally as early as 15–20 weeks' gestation.[9–11,27] at which time pancreatic acini are only just beginning to appear, zymogen granules are immature, and there is no evidence of secretion seen on electron microscopy.[28] Thus, the chemical reaction of pancreatic fluid on the bile duct has not been clarified in the antenatal period, and even in the neonate, the pancreas has not matured enough to produce functional enzymes,[29] so the role of pancreatic fluid in CBD formation may be overrated.

In spite of these findings, controversy surrounds the cause of the stenosis distal to the dilated common bile duct. The authors believe that an anomalous choledochopancreatic duct junction combined with congenital stenosis are the basic causative factors of CBD at least in perinatal and young infants rather than weakness of the duct wall caused by reflux of pancreatic fluid. Both PBMU and stenosis are associated with abnormal development of the ventral pancreatic duct and biliary duct system.

CLASSIFICATION

Alonso-Lej *et al.*,[30] Todani *et al.*,[31] and Komi *et al.*[32] have described classifications for CBD based on anatomy and cholangiography of the hepatobiliary duct system or PBMU. Classification based on the association with PBMU is presented in Fig. 69.1.

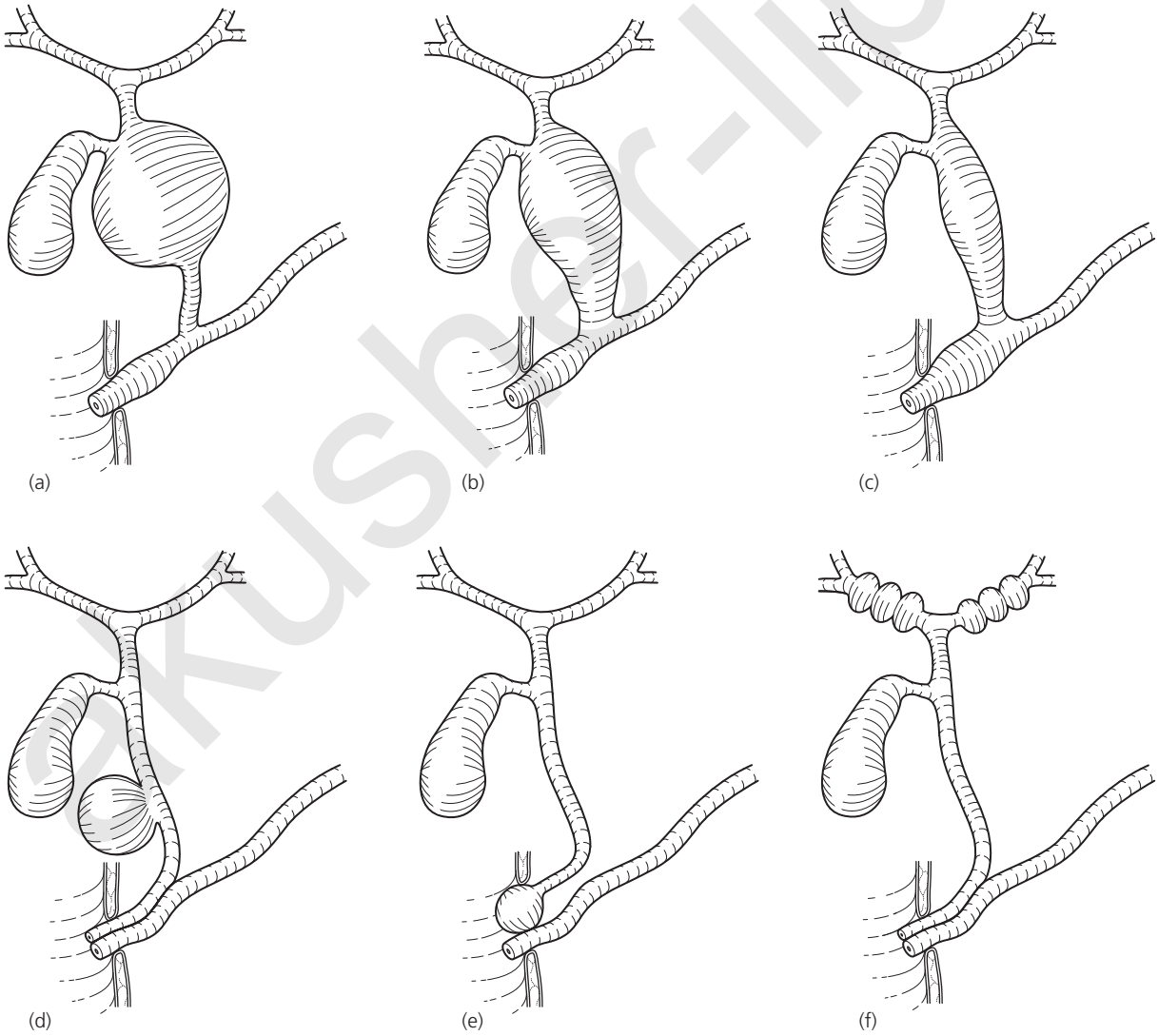

Figure 69.1 Classification of choledochal cysts with pancreaticobiliary malunion (PBMU): (a) Cystic dilatation of the extrahepatic bile duct. (b) Fusiform dilatation of the extrahepatic bile duct. (c) Forme fruste choledochal cyst. Without PBMU: (d) Cystic diverticulum of the common bile duct. (e) Choledochocele (diverticulum of the distal common bile duct). (f) Intrahepatic bile duct dilatation alone (Caroli's disease).

CLINICAL SIGNS AND SYMPTOMS

Clinical manifestations of CBD differ according to age. Neonates and young infants usually present with an abdominal mass, or obstructive jaundice, and acholic stools, depending on the degree of obstruction. Some present with a huge upper abdominal mass with or without jaundice. Some cases can even resemble correctable biliary atresia except that with CBD, there is a patent communication with the duodenum and a well-developed IHBD tree. In older children, the classical triad of pain, mass, and jaundice may be present. Fever and vomiting may also occur. The pattern of pain has been described as being similar to that of recurrent pancreatitis, in which a high serum amylase level is often present. However, in our series, there was little clinical evidence of pancreatitis in the neonate and amylase levels were not found to be elevated. CBD should always be considered in the differential diagnosis of a child with abdominal signs and symptoms; the essentials of management are the same.

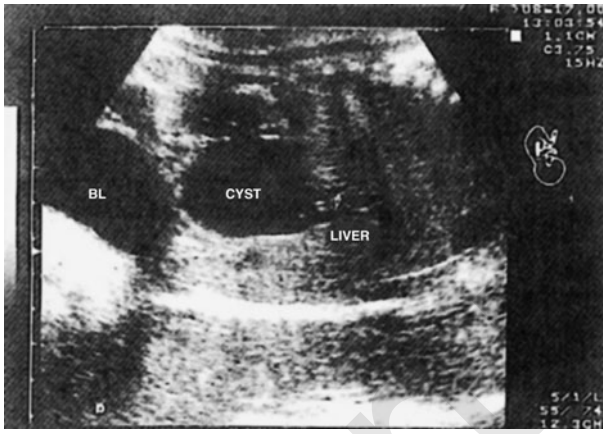

Figure 69.2 Antenatal ultrasound at 32 weeks' gestation. Sagittal view. A cystic structure is seen to be connected to the liver via a short duct (arrow). Bl, bladder.

DIAGNOSIS

Currently, abdominal ultrasonography (US) is the best method for detecting CBD, even though it does not permit visualization of the entire duct system and it is not sensitive enough to demonstrate an undilated common channel and pancreatic duct. However, routine antenatal US performed mainly for dating purposes has been of increasing value for detecting fetal anomalies,[4–11,27] and the number of neonates detected as having incidental CBD has increased significantly (Fig. 69.2).[33] CBD has been detected at routine prenatal ultrasound examinations as early as 15 weeks' gestation[9,10] and may be confused with duodenal atresia, biliary atresia, ovarian cysts, duplication cysts, and mesenteric cyst.

For thorough assessment of CBD, it is important to investigate for coexisting PBMU, anomalies of the pancreatic duct, intrahepatic ducts, and extrahepatic duct. ERCP can accurately delineate the configuration of the pancreaticobiliary duct system in detail, and is unlikely to be replaced by other investigations, especially in cases where fine detail is required preoperatively. ERCP is routinely performed for the diagnosis of biliary malformations in infants and neonates in many centers in Japan, with a reasonable success rate.[34] However, it is an invasive procedure and therefore is unsuitable for repeated use, and is contraindicated during acute pancreatitis.

The authors and others[35,36] have shown that magnetic resonance cholangiopancreatography (MRCP) can provide excellent visualization of the pancreaticobiliary ducts in patients with CBD allowing narrowing, dilatation and filling defects of the ducts to be detected with medium to high degrees of accuracy (Fig. 69.3). Because MRCP is non-invasive, it can partially replace ERCP as a diagnostic tool for the evaluation of anatomic anomalies of the pancreaticobiliary tract, where it is available, but there are limitations of patient size, weight, and age for the use of MRCP. Another advantage of MRCP over ERCP is that the pancreatic duct can be visualized upstream to an obstruction or area of stenosis. Once the quality of MRCP improves, ERCP may become optional.

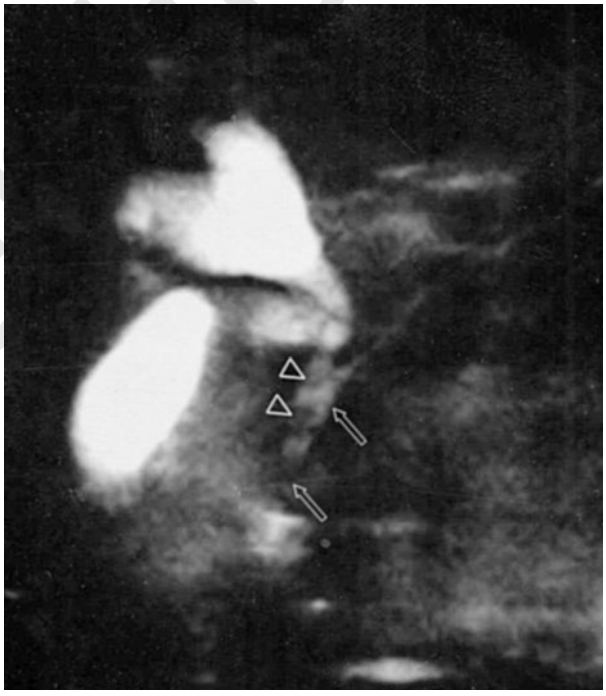

Figure 69.3 Magnetic resonance cholangiopancreatography in a patient with a choledochal cyst showing fusiform dilatation of the extrahepatic bile duct, long common channel (between arrows), protein plugs (arrowheads), and pancreatic duct.

If preoperative imaging can allow clear visualization of the entire biliopancreatic ductal system, including the intra- and extrahepatic bile ducts, and pancreatic duct in detail, intraoperative cholangiography is unnecessary; however, if sufficient information is not obtained, it must be performed. Furthermore, if the cyst is too large, intraoperative cholangiography via the gallbladder or directly via the common bile duct is useless. In such cases, intraoperative cholangiography should

be performed separately for the IHBD and distal common bile duct by a selective technique during excision of the cyst.

SURGERY

Choice of operative procedures

Cyst excision with Roux-en-Y hepaticoenterostomy (HE) is currently the definitive treatment for CBD regardless of age or symptomatology because internal drainage, a commonly used treatment in the past, is associated with high morbidity and high risk for carcinoma. Basically, the only difference between operative procedures available is the type of biliary reconstruction performed, although the level of transection of the common hepatic duct and the level of excision of the intrapancreatic bile duct are controversial. Although most surgeons use a Roux-en-Y hepaticojejunostomy, some[37,38] recommend a wide anastomosis at the level of the hepatic hilum to allow free drainage of bile in order to prevent postoperative anastomotic stricture and stone formation. The authors[39] recommend conventional hepaticojejunostomy, while others prefer hepaticoduodenostomy. Whatever type of biliary reconstruction is used, satisfactory surgical outcome with low early morbidity is to be expected, but postoperative complications after cyst excision, especially in the long term, generally occur more often if dilated IHBD are present. In our experience, hepaticoduodenostomy is not ideal for biliary reconstruction because of a high incidence of complications due to duodenogastric bile reflux.[39] Todani *et al.*[40] encountered a case of hilar bile duct carcinoma that developed 19 years after primary cyst excision and hepaticoduodenostomy. Although Todani's team preferred hepaticoduodenostomy because they believed it was more physiologic, they have since abandoned hepaticoduodenostomy after CE and now perform hepaticojejunostomy. Hepaticoenterostomy at the hepatic hilum is indicated in specific cases only, such as in patients with dilated IHBD with stenosis in the common hepatic duct, or adolescent patients with severe inflammation of the common hepatic duct.

Timing of surgery

Some pediatric surgeons recommend primary cyst excision soon after diagnosis.[6,8,10,41,42] In the authors' experience,[12,43] cyst excision need not be performed hastily if jaundice is not present. Rather, patients should be thoroughly assessed and surgery planned and performed by experienced, well-trained pediatric surgeons. In cases of bile peritonitis following perforation, severe cholangitis, poor general condition, or huge dilated CBD in neonates, external biliary drainage is recommended by either percutaneous transhepatic cholangiodrainage or direct percutaneous cyst drainage. Subsequently, delayed primary excision may be carried out three to six months later.

Neonates with choledochal cysts should receive standard medical management and nutritional support pre- and postoperatively; the importance of thorough preoperative assessment cannot be overemphasized. However, the timing of surgery for neonates is highly controversial because there are very few reports about the management of asymptomatic CBD detected in the antenatal or neonatal period. The authors believe that neonates should be treated by early surgery, particularly if they are jaundiced; for example, Dewbury *et al.*[4] reported that a laparotomy at 10 days of age confirmed a prenatally diagnosed CBD associated with severe hepatic fibrosis. Early surgery provides the opportunity to exclude biliary atresia, prevent biliary and hepatic complications, such as liver fibrosis which can progress rapidly in cases with biliary obstruction,[4,10,41] reverse fibrosis, reduce the risk for cholangitis, prevent accumulation of biliary sludge, relieve obstructive jaundice, as well as prevent cyst perforation.[6] The results of surgical treatment at this age are generally excellent.[42]

Complete excision

Complete (full-thickness) excision of the cyst is much easier in neonates and young infants, because the wall of the dilated common bile duct is generally thin and there are few adhesions to surrounding structures, such as the portal vein.[44,45] Aspiration of the cyst prior to dissection makes surgery easier if the cyst is large. The cyst should be incised in the middle portion close to the duodenum, because there is often an anomalous opening of the hepatic duct, i.e. a separate opening or opening into the distal part of the cyst. The cyst is then transected after careful circumferential dissection from the hepatic artery and portal vein. Subsequently, the distal portion is dissected and excised, taking care to completely remove the dilated segment at the level of the caliber change in order to prevent malignant transformation of the remaining cyst epithelium. If the cyst has no distinct caliber change (i.e. fusiform), the cyst should be excised just above the choledochopancreatic junction, and the stump double-sutured, ligated, and transected (Fig. 69.4). If protein plugs are found in the common channel, intraoperative endoscopy should be used to wash them towards the duodenum to avoid postoperative stone formation and pancreatitis. Finally, the common hepatic duct is transected at the level of distinct caliber change to leave an adequate length for HE.

Mucosectomy/biliary reconstruction

If CE of the distal portion is difficult due to inflammation or adhesions, mucosectomy[42,43] of the distal portion of the cyst is recommended, in order to avoid damage to the pancreatic duct, hepatic artery, and portal vein, and also to prevent the residual epithelium of the distal portion of the cyst from undergoing malignant transformation (Fig. 69.5). However, in neonates, mucosectomy is rarely indicated because there is little inflammation around the cyst wall. Biliary reconstruction in neonates and young infants is technically involved because anastomoses are often small and so should only be undertaken by experienced pediatric surgeons. Some surgeons overcome this problem by partially incising the mouth of the stoma of the anastomosis to widen it. On occasions,

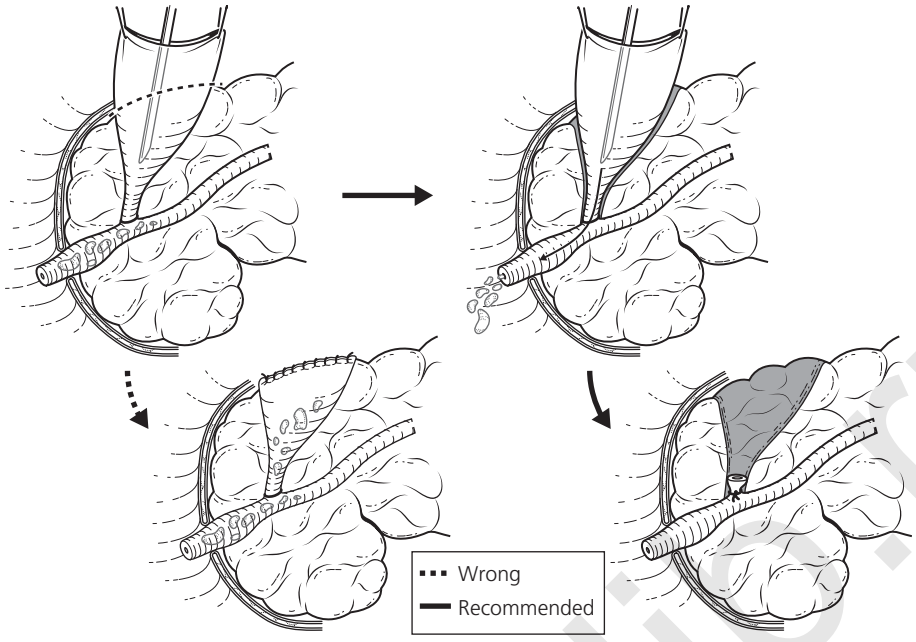

Figure 69.4 Diagram of intraoperative endoscopy of the bile duct distal to a cyst with debris and protein plug. If the distal common bile duct is resected along the dashed line, over time, a cyst will reform around the distal duct left within the pancreas, leading to recurrent pancreatitis, stone formation in the residual cyst, or malignant changes in the residual cyst. In contrast, if the distal duct is resected along the solid line, that is, just above the pancreaticobiliary ductal junction, cyst reformation due to residual duct within the pancreas is unlikely.

Figure 69.5 Mucosectomy of distal portion of choledochal cyst.

the authors have encountered luminal stenosis of macroscopically normal common hepatic ducts at the time of CE, which was considered to be secondary to fibrosis, probably as a consequence of inflammation associated with previous perforation.

Although an end-to-side anastomosis was initially used, the authors now prefer end-to-end anastomosis during Roux-en-Y hepaticojejunostomy, because drainage is more streamlined, with less possibility of bile stasis (Fig. 69.6). With end-to-side anastomosis, there was overgrowth of the blind end, causing adhesive bowel obstruction between the blind pouch and jejunum in one case, and stone formation in the blind pouch in another (Fig. 69.7).[46] Bile stasis in the blind pouch can also cause stone formation in the IHBD dilatation at the porta hepatis. If end-to-side anastomosis is unavoidable, the common hepatic duct should be anastomosed as close as possible to the closed end of the blind pouch so there will be no blind pouch at the anastomosis site; if an end-to-side anastomosis is performed far from the closed end of the blind pouch, elongation of the blind pouch will occur later in life as the child grows.

The authors have seldom performed other procedures, such as HE at the hilum or valved jejunal interposition hepaticoduodenostomy to prevent reflux of digested food into the IHBD.[38] Although these procedures are appealing theoretically, there is no significant difference in morbidity. HE at the hepatic hilum is more difficult than conventional HE, particularly in neonates and young infants without IHBD dilatation, and valved jejunal interposition hepaticoduodenostomy is a complicated procedure.

ASSOCIATED ANOMALIES REQUIRING TREATMENT

Intrahepatic bile duct dilatation

Recently, more attention has been paid to the treatment of IHBD anomalies, such as dilatation with downstream stenosis, which is strongly associated with late postoperative

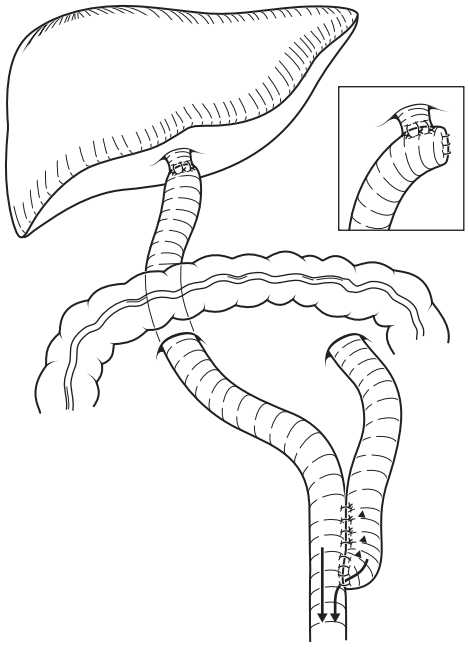

Figure 69.6 Adequate Roux-en-Y (RY) hepaticojejunostomy at the time of cyst excision. Arrowheads indicate approximated native jejunum and distal Roux-en-Y limb. Arrows indicate smooth flow without reflux of small bowel contents.

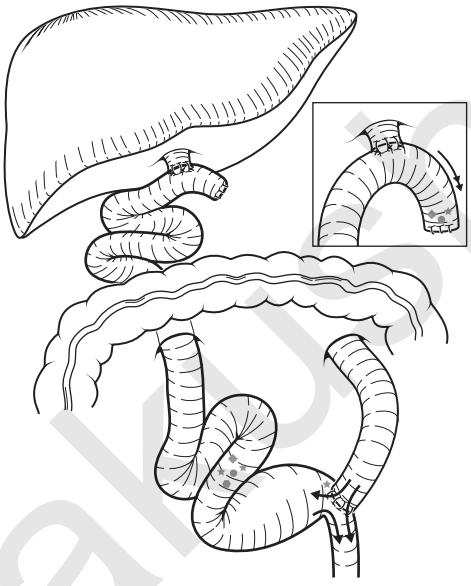

Figure 69.7 Inadequate Roux-en-Y (RY) hepaticojejunostomy at the time of cyst excision. Note hepaticojejunostomy far from the closed end of the blind pouch (arrowhead). Double arrowheads in the inset indicate elongation of the blind pouch. Arrow with an asterisk indicates reflux of jejunal contents into the RY limb through a T-shaped RY jejunojejunostomy.

complications.[31,38,46–52] In our series,[12] eight of 21 neonatal patients (38.1%) had IHBD dilatation (in one it was severe, and was still persistent at follow up 14 years later), which is remarkably less than the incidence in older children (53.3%).[46] IHBD dilatation can be treated by segmentectomy of the liver, intrahepatic cystoenterostomy, or balloon dilatation of the stenosis at the time of CE.[31,49,50] The authors have treated stricture of the IHBD at the hepatic hilum by intrahepatic ductoplasty and cystojejunostomy or hepaticojejunostomy at the hepatic hilum in three cases, [46,51]creating a wide stoma by incising along the lateral wall of the hepatic ducts following excision of the narrowed segment of the common hepatic duct (Fig. 69.5). By using intraoperative endoscopy, the ideal level of resection of the common hepatic duct can be safely determined without injuring the orifices of the hepatic duct or leaving a redundant duct.

Anomalies of the pancreatic duct and common channel

Anomalies of the pancreatic duct and common channel are only rarely symptomatic in neonates and young infants, and can include pathology such as stenosis of the papilla of Vater, stricture of the pancreatic ducts, protein plugs, or even a septate common channel.[32,52–54] Stone debris in the common channel and IHBD can also be responsible for postoperative abdominal pain, pancreatitis, stone formation, or jaundice and should be removed at the time of radical surgery. The authors have found intraoperative endoscopic examination of the common channel and intrahepatic duct to be of enough value to include it as a routine procedure during standard surgical treatment of CBD, because it is extremely efficient for examination and irrigation, and allows all distal pancreatic duct stone debris and stone debris in the common channel to be removed. If stenosis of the major papilla with a dilated common channel is found, a transduodenal papilloplasty or endoscopic papilloplasty should be performed.[52]

INTRAOPERATIVE ENDOSCOPY

Since 1986, the authors have routinely performed intraoperative endoscopy of the common channel, pancreatic duct, and IHBD to examine the duct system directly for stone debris and duct stenosis, and to remove stone debris by irrigation with normal saline (Fig. 69.8).[46] The authors use a pediatric cystoscope or fine fiberscope with a flush channel to view the pancreatic and biliary duct systems directly at the time of cyst excision.[51,52] In other cases, a neonatal cystoscope, a fine flexible scope (1.9–2.0 mm) with a flush channel is required. Recently, we found there was a high incidence of IHBD debris not detected by preoperative radiographic investigations,[55] and some cases where IHBD debris identified on preoperative radiography was overlooked when the case was reviewed retrospectively. These facts indicate that intraoperative endoscopy is necessary at the time of CE even if preoperative radiography does not indicate the presence of IHBD debris. Another striking finding was that debris can be present in the absence of IHBD dilatation, although debris was more common when the IHBD were dilated. Thus, we believe inspection using intraoperative endoscopy is mandatory even when there is no IHBD dilatation. In a recent

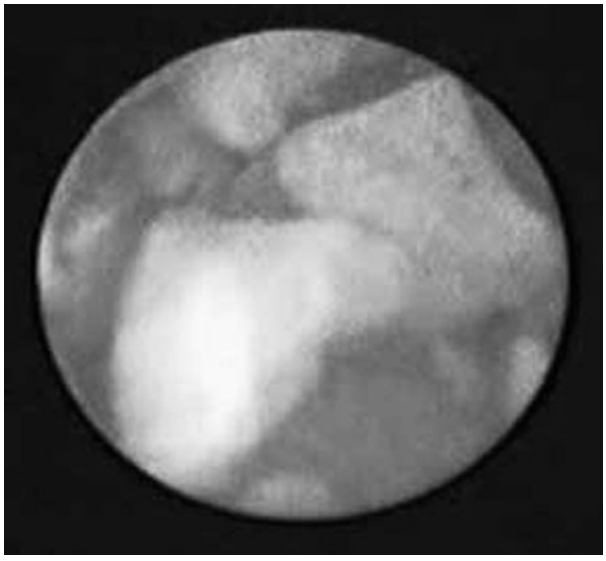

Figure 69.8 Massive debris in the common channel observed through the pediatric cystoscope.

review of the long-term follow up of our intraoperative endoscopy patients, the incidence of postoperative stone formation was lower than reported in the literature,[56] evidence of the clinical benefit of performing intraoperative endoscopy during CE.

LAPAROSCOPIC SURGERY

Recent advances in laparoscopy technology have enabled pediatric/hepatobiliary surgeons to perform minimally invasive surgery for CBD.[57] In 1995, the first laparoscopic CE in a child was reported.[58] Since then, several authors have reported the safety and feasibility using minimally invasive techniques for advanced hepatobiliary surgery in children.[59–62] Although technically more challenging, the general concepts are the same as for open surgery. The authors' approach is to use conventionally placed trocars (right upper quadrant, left paraumbilical, left upper quadrant; scope in the umbilicus) to free the cyst and transect it at mid level. An additional 3.9 mm trocar in the left epigastrium is used for a fine ureteroscope. Under laparoscope guidance, the tip of the scope is inserted into the common channel through the distal cyst to remove any protein plugs (Fig. 69.9).[63] Another two trocars are added for the hepaticojejunostomy; lateral right subcostal, and between the lateral right subcostal and right upper quadrant trocars. Hepaticojejunostomy is then performed using 5/0 absorbable sutures with the right upper quadrant trocar as a needle holder in the right hand; a 5 mm trocar between the lateral right subcostal and right upper quadrant trocars for the scope; and the 3 mm subcostal trocar as a needle receiver in the left hand. Both the right and left edge sutures are exteriorized and used as traction sutures during anastomosis of the anterior wall.

Although long-term follow-up results have yet to be collated, experienced laparoscopic surgeons would appear

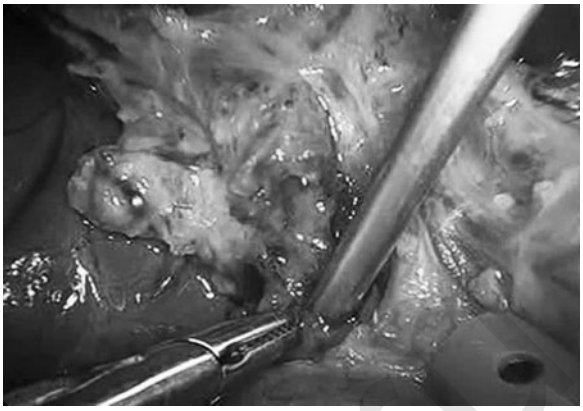

Figure 69.9 Under laparoscope guidance, the tip of the scope is inserted into the common channel through the distal cyst to remove any protein plugs.

to obtain results as good as those for open surgery. In a report comparing laparoscopic CE and Roux-en-Y reconstruction with open surgery in children,[64,65] operating time was found to be longer, and overall costs higher, but there was significantly less blood loss and duration of hospitalization was shorter. There were no significant differences for the incidence of bile leakage or wound infection rates.

Most recently, robot-assisted laparoscopic resection of CBD has been reported.[66,67]

POSTOPERATIVE COMPLICATIONS AND MANAGEMENT

Surgical outcome is better and early morbidity lower in younger children than in older children. The authors[68] reviewed 200 children and 40 adults who underwent CE and HE cyst excision hepaticoenterostomy (CEHE) and found that 18 out of 200 (9.0%) children developed complications post-CEHE. No stone formation was seen in the 145 children who had CEHE before the age of five years in our series, and there were 18 children who had 25 episodes of complications post-CEHE including cholangitis, IHBD stone formation, pancreatitis, stone formation in the intrapancreatic terminal choledochus or pancreatic duct, and bowel obstruction. There were no complications in the 70 children who had intraoperative endoscopy in our series.[68] Stones developed in seven (12.7%) of 55 children who had CEHE when they were more than five years old. For management of complications, reoperation was required in 15 children – revision of HE in four, percutaneous transhepatic cholangioscopic lithotomy in one, excision of intrapancreatic terminal choledochus in two, endoscopic sphincterotomy of the papilla of Vater in one, pancreaticojejunostomy in one, and laparotomy for bowel obstruction in six.

Careful long-term follow up is required, particularly in patients with IHBD dilatation and also dilatation of the remaining distal bile duct, pancreatic duct, and common channel, because there is a risk for chronic inflammation, stone formation, as well as the possibility of carcinoma arising at a later stage.

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Hepatic cysts and abscesses

STEPHANIE A JONES, FREDERICK M KARRER, AND DAVID A PARTRICK

INTRODUCTION

Cysts and abscesses of the liver in the neonatal period are uncommon. Hepatic cysts presenting in infants are usually simple, unilocular cysts, with polycystic liver diseases presenting later in childhood or in adults. Most abscesses in infants are pyogenic with parasitic infections occurring in older children or adults. Cross-sectional imaging studies (ultrasound, computed tomography, magnetic resonance imaging) can typically make work up and localization relatively straightforward. Antenatal diagnosis of liver cysts is now more common with improving scanning technology. Treatment, however, still requires experience and judgment to prevent recurrences or complications.

SIMPLE HEPATIC CYST

Simple or solitary cysts in infants can be congenital or acquired in origin. Parasitic cysts (from hydatid disease) are rare in children and have never been reported in infancy.

Congenital cysts probably arise from defective fusion or obstruction of intrahepatic bile ducts during development, or possibly originate from peribiliary glands.[1,2] These cysts are usually single and unilocular, but septation has been reported.[3] Although one or two thin septa are regarded as normal for a simple cyst, more septae should prompt consideration of other pathologies. Simple cysts are well encapsulated with a smooth surface. There is a 2:1 female preponderance.[4] Most common in the right lobe, they abut or hang down from the liver edge.[5] The liver almost never completely covers the cyst, especially the pedunculated cysts, so the presenting portion has a bluish hue. The internal cyst wall is lined by simple cuboidal or columnar epithelium.[6] Most contain clear fluid, but it may be brownish because of remote hemorrhage. Bilious cyst fluid indicates communication with a biliary radical.

Acquired or post-traumatic cysts may result from blunt trauma or birth trauma causing an intrahepatic hematoma. The hematoma reabsorbs leaving behind a cyst cavity. These cysts are lined by granulation tissue and fibrosis and rarely communicate with the biliary tree.

Differential diagnosis of complex cystic structures in the liver

Cystic structures in the neonatal liver also include ciliated hepatic foregut cysts, choledochal cysts, and mesenchymal hamartomas, and cystadenomas.[2,4,7,8] Simple, ciliated and choledochal cysts usually are unilocular, whereas mesenchymal hamartomas and cystadenomas are multilocular. Ciliated hepatic foregut cysts (CHFC) are rare cystic structures in the neonatal liver thought to originate from remnants of embryonic foregut buds that are trapped in the liver during development. They are most often seen in the left lobe of the liver. Common imaging characteristics of CHFC are uni- or bilocular, sediment containing cysts with calcifications in the cyst wall. Fine needle aspirate of the cyst will show ciliated columnar epithelial cells in a mucoid background.[4] Mesenchymal hamartoma (MH) is an uncommon tumor of the liver usually presenting before two years of age. A characteristic finding in MH are cysts of different sizes, with a variable solid component to the mass. MH may thus be cystic, solid, or mixed in presentation. Although MH is pathologically benign, reports of malignant generation to angiosarcoma and progression to an aggressive clinical course have been described.[8] Complex cysts should be completely excised because of the reported risk of malignant degeneration of these structures.[2]

Choledochal cysts are described in Chapter 69 of this textbook.

Presentation

Most congenital cysts do not have any clinical manifestations in infancy and are not diagnosed until an older age (fourth or fifth decade of life). Some are discovered prenatally or incidentally during work up of unrelated problems.[9] When they are symptomatic in infancy, it is usually because of a

visible or palpable upper abdominal mass.[10–12] They rarely cause symptoms from compression of other structures, but infants can present with abdominal distension, feeding difficulties, respiratory distress, and duodenal obstruction secondary to a large cyst.[2] Hemorrhage, secondary infection, rupture, or torsion can lead to an acute abdominal condition, but such complications are extremely rare.[13]

Diagnosis

Cysts large enough to be detected on physical examination are easily distinguished from solid tumors by ultrasonography. Liver function is typically normal in spite of the impressive size of these cysts. Plain x-rays may show diaphragmatic elevation or a soft tissue mass displacing the gas pattern in the abdomen. Computed tomography (CT) is useful to identify the exact location and number of cysts. Other preoperative imaging techniques (cholangiography, angiography, nuclear scans) may provide additional information but are usually unnecessary. With improving imaging technology, many hepatic cysts are being discovered antenatally. In some series, small asymptomatic simple cysts comprised the majority of the prenatal hepatic findings, and these regressed spontaneously. Only one in seven required postnatal surgery secondary to increasing size or symptoms.[2] On prenatal ultrasound, placental pathology in conjunction with hepatic cysts has been linked to mesenchymal hamartomas.[14] If such a finding is noted prenatally, early resection of the liver cyst should be considered.

Treatment

Small asymptomatic cysts (<5 cm) discovered incidentally should be left alone. Large or symptomatic cysts should be treated surgically. Percutaneous cyst aspiration may rule out biliary communication or abscess, but is not definitive therapy because of a high recurrence rate.[15] Complete resection is optimal and can be accomplished easily when the cyst is pedunculated. Many of these may be amenable to minimally invasive surgical techniques. If complete excision cannot be accomplished by simple enucleation, formal lobectomy is not typically indicated. These are benign lesions, therefore the risk of treatment should not exceed the risk of the disease. Under these circumstances, partial excision is preferred. By unroofing at least one-third of the cyst cavity, any serous drainage will be reabsorbed by the peritoneal cavity.[16] The edges of the cyst can be managed by oversewing with a running absorbable suture or by electrocautery. If the cyst contains bile and cholangiography confirms communication of the cyst with the biliary tree, then internal drainage via Roux-en-Y cystojejunostomy is indicated. Infected cysts should be drained externally (see below under Treatment, p. 646).

Prognosis

The prognosis for infants with simple hepatic cysts is excellent. Mortality and cyst recurrence should approach zero.[9,17,18]

POLYCYSTIC LIVER DISEASE

When liver cysts develop throughout the liver in high number, it is usually in association with an inherited polycystic disease. The two main variants of polycystic disease are autosomal dominant (adult type) and autosomal recessive (childhood type).[19] Both are associated with polycystic disease of the kidney. Autosomal dominant polycystic kidney disease (ADPKD) is the most common form (90%). Symptoms of renal involvement (pain, hypertension, renal failure, urinary tract infection) usually do not develop until adulthood. Liver cysts in autosomal dominant polycystic disease are exceptionally rare in childhood and have not been seen in infancy.

Autosomal recessive polycystic kidney disease (ARPKD) presents in childhood. There are four subgroups (perinatal, neonatal, infantile, juvenile), with varying degrees of involvement of the kidneys and liver.[20] The most severe cases present perinatally with oligohydramnios, Potter's syndrome, pulmonary hypoplasia, and usually die shortly after birth. Patients with lesser degrees of renal involvement present at an older age with renal failure and hypertension. In some children, renal involvement is minor and they do not present until adolescence with symptoms of portal hypertension such as variceal bleeding.[21]

In all forms of ARPKD, the liver is not usually grossly cystic. The liver abnormality is termed congenital hepatic fibrosis. Microscopically, there is bile duct proliferation with irregular broad bands of fibrous tissue containing multiple microscopic cysts formed by disordered terminal bile ducts, chiefly in the portal areas. The incidence of portal hypertension in ARPKD increases with longevity and appears to be inversely related to the severity of the renal disease. Treatment for portal hypertension is not required in infancy since it takes time for esophageal varices with the tendency to bleed to develop. If portal hypertension leads to esophageal bleeding, endoscopic treatment or portosystemic shunting is preferred. Hepatic synthetic function is usually preserved and the portal hypertension may improve in adolescence as other collaterals develop. Therefore, liver transplantation is usually not needed. Rarely, fibrosis is accompanied by cystic dilation of intrahepatic biliary ducts like Caroli's disease. This rare variant does not require treatment in infancy.[22]

The named subgroups of ARPKD aid discussion but are far from distinct. There is, in fact, considerable overlap among individuals and within families. In infancy, the treatment of ARPD only addresses the renal and consequent pulmonary insufficiency. No treatment is required for the hepatic lesion.

HEPATIC ABSCESSES

Incidence and etiology

The most common source of hepatic abscess in children has historically been perforated appendicitis (Fig. 70.1), but the incidence in this population has decreased since the introduction of antibiotics. It is now more commonly seen in

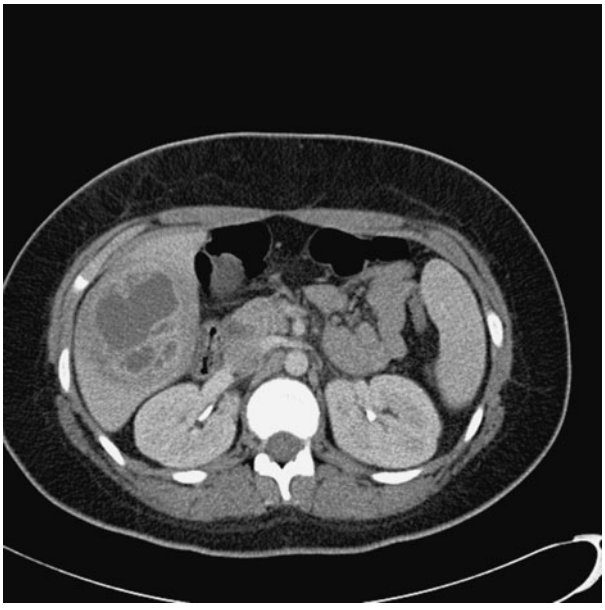

Figure 70.1 Computed tomography abdomen of a 12-year-old girl with a post-appendicitis right lobe liver abscess.

children with an underlying immune deficiency.[23] Although approximately 50% of children with pyogenic hepatic abscess are less than six years old, neonatal hepatic abscesses are rare. One study reported only three cases of hepatic abscesses out of 11403 neonatal admissions.[24] Even though rare, they can definitely be lethal in this vulnerable population. In this review, only 18 neonatal cases of solitary hepatic abscess were identified in the English literature from 1900.[24] In an earlier review, 24 cases were identified historically (including cases of multiple abscesses), to which the authors added an additional 13.[25] Neonatal liver abscess seems to differ considerably from the disease in older children. The patent umbilical vein in neonates provides ready access for bacteria to the liver, and umbilical vessel catheterization is a significant predisposing factor in hepatic abscess formation.[26,27] In hospitalized infants, umbilical vein catheters allow bacteria colonizing the umbilical stump a direct route to the liver. Less common sources of liver abscesses are inoculation via the portal vein from necrotizing enterocolitis,[28] isolated bowel perforations, and other intra-abdominal infections of the newborn. Bacteremia from meningitis or another septic insult can also result in hepatic abscesses via the hepatic artery.[29] Multiple pyogenic hepatic abscesses can complicate neonatal sepsis. Hepatic abscess has also been reported as a rare complication of ventriculoperitoneal shunts (six cases have been reported in the literature, primarily in older patients).[30] More recently, the majority of neonatal cases of hepatic abscess have occurred in premature neonates who are relatively immunosuppressed and have undergone umbilical vessel catheterization (Box 70.1).[24,31] There are reported associations of hepatic abscesses in infants exposed to HIV from the mother, misplaced umbilical catheters (right-sided abscesses), or the use of hypertonic glucose solutions via an umbilical catheter.[31]

The infecting organisms in neonates are more often Gram-negative than Gram-positive. Kays[18] reviewed the infectious causes of pyogenic liver abscesses, and in 22 neonates (less than one month of age) Gram-positive aerobes accounted for only 27% of abscesses whereas Gram-negative aerobes were responsible for 73%. Fungus was the infectious source in 5% (one patient, although an additional case has since been reported[24]), and anaerobic organisms have not been isolated from any neonatal liver abscess reported in the literature. This is in contrast to older children with hepatic abscess where up to 50% of infecting organisms isolated are Gram-positive, 25% are Gram-negative, 10% are anaerobic, 6% are fungus, and the remainder are unknown (cryptogenic). Others have noted polymicrobial infections in up to 50% of hepatic abscesses.[32]

Box 70.1 Predisposing factors for neonatal hepatic abscess

- Prematurity (immunocompromised)
- Umbilical vein catheterization (colonizing organisms, hypertonic glucose solution, misplaced catheter)
- Omphalitis
- Intra-abdominal infection (necrotizing enterocolitis, bowel perforation)
- Bacteremia (meningitis)

Presentation and diagnosis

The clinical diagnosis of neonatal hepatic abscess remains difficult. The classic findings of fever, hepatomegaly, and right upper quadrant pain are seldom obvious in the neonate. Signs and symptoms of sepsis may be present, but many infants are simply noted to be irritable with only mild abdominal distention or tenderness. A rapidly enlarging and tender liver is characteristic for a hepatic abscess, but this is not commonly found on clinical examination. Fever, leukocytosis, elevation of the sedimentation rate, as well as the C-reactive protein may be present. In the majority of patients, liver function tests are normal, but direct and indirect hyperbilirubinemia, elevation of the alkaline phosphatase, elevation of serum transaminase, anemia, and hypoalbuminemia have all been reported.[23] Therefore, to make the diagnosis in neonates, a high index of suspicion is necessary in conjunction with appropriate imaging techniques.

Radiographic evaluation

Plain films may suggest the diagnosis of hepatic abscess by the presence of an elevated right hemidiaphragm and right pleural effusion. Sometimes, a gas shadow can be visualized in the liver itself corresponding to the abscess cavity. Improvements in abdominal ultrasound and CT scanning now allow for a more rapid and accurate diagnosis in neonates.[33] Ultrasound has the advantage of lower cost, no radiation exposure, relative convenience, and ease of repeating the examination (no sedation, portable).[34,35] A hepatic abscess typically shows low or variable echogenicity by ultrasound, and cystic lesions as small as 1 cm can be

identified separate from liver parenchyma. A pyogenic abscess may have more irregular margins on ultrasound compared with an amebic liver abscess, which may be round and well-defined.[36] CT scanning has demonstrated increased sensitivity compared with ultrasound and it gives a clearer definition of the abscess.[23] The abscess margins variably enhance with the use of i.v. contrast. Figure 70.2 demonstrates the appearance on CT scan of a large hepatic abscess in a 5-day-old full-term baby. This neonate had an umbilical venous catheter in place with progressive hepatomegaly on physical examination. Included in the differential diagnosis of this cystic mass were hepatoblastoma, infantile hemangioendothelioma, mesenchymal hamartoma, and other rare liver tumors. Any neonate with persistent fever and suggestion of upper abdominal tenderness or an enlarged liver should undergo radiographic examination, especially if risk factors are present. If the ultrasound appears normal but clinical suspicion remains high, CT scanning should be performed. Specific diagnosis requires aspiration of the lesion with Gram stain and culture leading to subsequent identification of the infecting organism.

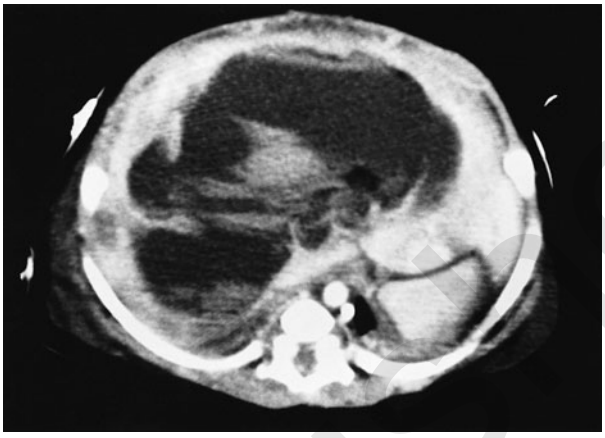

Figure 70.2 Computed tomography scan of a large hepatic abscess in a 5-day-old neonate.

Treatment

Systemic antibiotic therapy remains the mainstay of therapy for neonatal hepatic abscess. Initial antibiotic treatment should be started aggressively and include broad coverage. In neonates, empiric treatment should specifically be directed against Gram-negative bacilli and *Staphylococcus aureus*, although anaerobic abscesses have been reported and specific antibiotics covering anaerobes should be considered if the patient does not respond to initial therapy. After cultures identify the infecting organism, antibiotics can be narrowed according to the reported sensitivities. Percutaneous aspiration of smaller neonatal hepatic abscesses can be done for diagnostic purposes,[37] but larger abscesses require therapeutic drainage of the purulent fluid collection for adequate treatment.[38] Percutaneous drainage techniques have been demonstrated to be safe and efficacious in children with hepatic abscesses,[39] and recent experience in neonates has shown similar good results.[24,40] If indicated, an open abdominal exploration allows investigation and possible treatment of an intra-abdominal source of the infection. Laparoscopy may have a role in these patients in this regard. The neonate depicted in Figure 70.2 was treated aggressively with open surgical drainage and i.v. antibiotics (vancomycin to cover coagulase negative staphylococcus species cultured from the abscess cavity). This aggressive treatment resulted in nearly complete resolution of the process, documented by CT within 6 weeks (Fig. 70.3). Investigators have variably recommended 2–3 weeks of drainage with a total antibiotic course of 3–6 weeks.

Once drained and treated with antibiotics, follow up should include serial ultrasound examination. Most cases should have complete resolution, but chronic, partially calcified foci in the abscess site and portal vein thrombosis have been described after treatment.[40] Prevention of hepatic abscesses may not be possible in neonates given the many potential risk factors they may encounter. According to a recent Cochrane review,[41] there is no evidence to support the use of prophylactic antibiotics for umbilical vein catheterization to prevent sepsis or liver abscess.

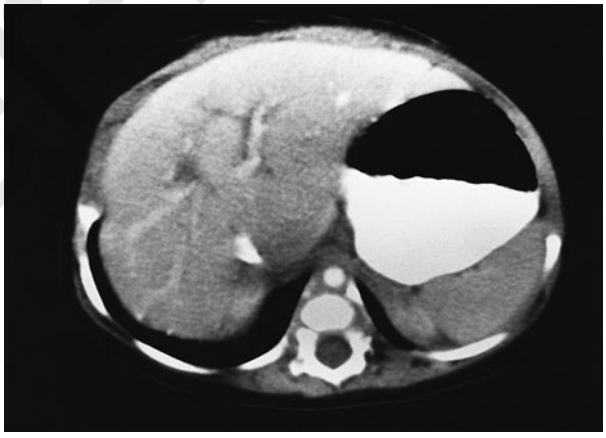

Figure 70.3 Repeat computed tomography scan 6 weeks following open surgical drainage and i.v. antibiotic treatment demonstrating complete radiographic resolution of the hepatic abscess.

AMOEBIC LIVER ABSCESS

The parasite *Entamoeba histolytica* is generally considered a possible causative organism in older children with hepatic abscess,[42,43] but it has rarely been documented to occur in newborns.[44] Hepatic abscesses due to *E. histolytica* usually follow a one- to two-month course of amoebic dysentery.[36] Due to non-specific signs and symptoms, the diagnosis again rests on clinical suspicion. Serologic testing via indirect hemagglutination or complement fixation assays can be a useful diagnostic tool. Even though investigators have tried to differentiate the radiographic appearance of amoebic versus pyogenic liver abscesses,[36,45] fine needle aspiration of the

abscess cavity is typically required. Return of characteristic 'anchovy paste' appearing material is suggestive of amoebic infection. Presence of trophozoites in stool and positive amoebic serology confirm the diagnosis.[45] Rather than drainage as the standard of therapy, amoebic liver abscesses can often be treated successfully with metronidazole and iodoquinal over a 30-day course.[46,47]

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PART VII

ANTERIOR ABDOMINAL WALL DEFECTS

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71

Omphalocele and gastroschisis

STEVEN W BRUCH AND JACOB C LANGER

INTRODUCTION

Omphalocele (also known as exomphalos) consists of a central abdominal wall defect that permits herniation of abdominal viscera into the umbilical cord. A membrane that is made of Wharton's jelly, from which the umbilical cord emerges (Fig. 71.1), covers the viscera. Pare provided the first description of an omphalocele in 1634. Hey reported the successful treatment of an omphalocele by primary repair in 1803, and Ahlfeld described the escharotic treatment using alcohol in 1899. In 1814, Scarpa observed that omphaloceles were often associated with other congenital anomalies.

Gastroschisis is a smaller abdominal wall defect to the right of a normally positioned umbilical cord, which permits herniation of intestine (Fig. 71.2), as well as occasionally liver, testis, or ovary. There is never an associated sac, and other than non-rotation and intestinal atresia, there are few associated congenital anomalies. Gastroschisis was first described by Calder in 1733, and the first surgical treatment for gastroschisis was described by Fear in 1878.

The surgical repair of abdominal wall defects has evolved over many years, with advances in diagnostic ability, neonatal intensive care, and anesthetic techniques. Although Gross popularized the skin flap closure of large omphaloceles in 1948,[1] it was Olshausen who first described this technique in 1887.[2] In 1966, Izant *et al.*[3] introduced manual stretching of the abdominal wall to make more room for primary closure. Schuster created the first mesh silo in 1967 to temporarily house the herniated viscera until primary closure could be accomplished.[4] Recently, a spring-loaded silo was developed which permits placement of the silo without the need for fascial sutures.[5]

Two additional advances in the medical management of infants with abdominal wall defects have had a significant impact over the past 30 years. Raffensperger and Jona[6] were

Figure 71.1 Omphalocele. The viscera (in this case liver and small bowel) are covered by a sac that is composed of Wharton's jelly, and the umbilical cord enters the top of the sac.

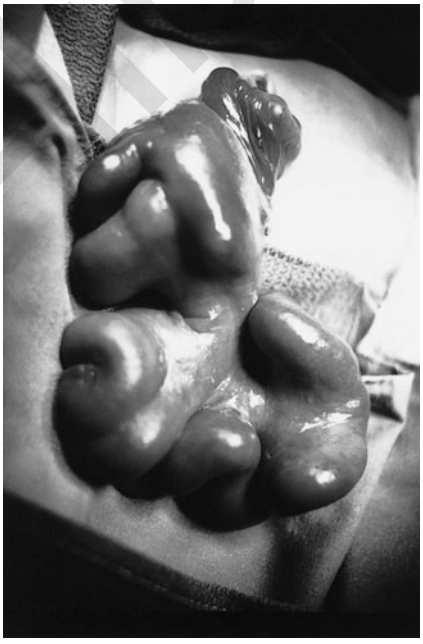


Figure 71.2 Gastroschisis. The defect is to the right of the umbilical cord and the entire intestinal tract is exteriorized. There is no sac. The bowel wall and mesentery are thickened and foreshortened.

the first to use postoperative paralysis and ventilator support in the neonatal intensive care unit to hasten abdominal wall closure, either primarily or after silo placement. Filler *et al.*[7] introduced the use of total parenteral nutrition (TPN) to the neonatal population, which has become a crucial component in the high survival rate of infants with abdominal wall defects.

EMBRYOLOGY AND ETIOLOGY

During the 6th week of embryonic development, the intestines begin to grow rapidly and migrate out of the umbilical ring into the umbilical cord.[8] By the tenth week, the intestines return to the abdominal cavity, rotating 270° counter-clockwise to attain their normal position. An omphalocele results from failure of the bowel to return to the abdomen, possibly due to delayed closure of the lateral folds with persistence of a large umbilical ring. The defect is centrally located on the abdomen, varies in size, and has a sac covering the abdominal contents that consists of peritoneum, Wharton's jelly, and amnion. Because the process of intestinal rotation normally occurs after return of the viscera to the abdomen, infants with omphalocele usually have non-rotation or malrotation. In addition to the intestine, some or all of the liver may also be present in the sac. The liver is often round and globular in appearance, central in location, and has an abnormal fixation to the diaphragm. The hepatic veins appear tortuous and wander close to the skin edge at the superior aspect of the defect. The spleen and ovaries or testes may also be found in the sac. Failure of the cephalic fold to close leads to lower sternal abnormalities and an epigastric omphalocele, which is commonly associated with cardiac defects, pericardial absence, and an anterior diaphragmatic defect, together known as 'pentalogy of Cantrell'. Failure of the caudal fold to close leads to a hypogastric omphalocele often associated with bladder or cloacal exstrophy.

Gastroschisis results in bowel herniation through a small defect to the right of the normally formed umbilical cord. There are several hypotheses to explain the development of the gastroschisis defect. In 1980, DeVries hypothesized that abnormal involution of the right umbilical vein results in adverse effects on the surrounding mesoderm and eventual body wall rupture.[9] One year later, Hoyme *et al.*[10] proposed that disruption of the omphalomesenteric or vitelline artery supplying the yolk sac near the umbilicus results in infarction and necrosis at the base of the umbilical cord followed by rupture of the abdominal wall. In 2007, Feldcamp *et al.*[11] theorized that defective closure of one or more of the embryonic body wall folds results in the gastroschisis defect. In 2009, Stevenson *et al.*[12] proposed that failure of the yolk sac and related vitelline structures to be incorporated into the umbilical stalk results in perforation of the abdominal wall that acts as an egress point for the intestine. Although a small number of cases may result from rupture of an omphalocele *in utero*, the exact mechanism for the development of gastroschisis remains unclear.[13] Despite this, the clinical scenario is well described. The entire intestinal tract is usually eviscerated, floating free in the amniotic cavity without an enveloping sac. Ovary, testis, and liver are less often involved. The intestines may develop a thick inflammatory peel, are foreshortened, and have a thickened mesentery – findings that correlate with functional impairment of motility and nutrient absorption. These changes result from a combination of factors, including contact with the amniotic fluid and constriction at the abdominal wall defect.

The cause of both omphalocele and gastroschisis is unknown. Omphalocele may have a genetic component, as suggested by the high incidence of structural and chromosomal anomalies, and also by the high incidence of omphalocele in several knockout models in mice.[14] Although gastroschisis is thought not to have a genetic component to its origin, Torfs *et al.*[15] described four gene polymorphisms associated with an increased risk for gastroschisis: intracellular adhesion molecule 1 (ICAM 1), endothelial nitric oxide synthase (eNOS), atrial naturetic peptide (NPPA), and alpha adducin (ADD1).[15]

INCIDENCE

The incidence of gastroschisis has been increasing worldwide over the past two decades. During that same time, the incidence of omphalocele has remained relatively constant. The EUROCAT working group reported that the incidence of gastroschisis increased from 0.60 per 10000 births in 1980–4 to 2.33 per 10000 births in 2000–2.[16] From 1987 to 2003, the overall birth prevalence for gastroschisis increased 3.2-fold in a population-based study from California.[17] The reason for this increase in gastroschisis, but not in omphalocele, is not well understood. Rasmussen and Frias[18] reviewed the currently available literature on non-genetic risk factors for gastroschisis, including sociodemographic factors, maternal therapeutic and non-therapeutic drug exposures, chemical exposures, and other factors. They found that the only factor to be definitively identified as a risk factor for gastroschisis is young maternal age. Other factors that require further confirmation include maternal exposure to certain medication including, aspirin and pseudephedrine, cigarette smoking, and illicit drugs, maternal nutritional factors, recent change in paternity, and short cohabitation time.

ASSOCIATED ANOMALIES

Omphalocele is associated with other anomalies up to 74% of the time.[19–21] Of these anomalies, 20% are cardiac, with tetralogy of Fallot and atrial septal defects being the most common.[22] Other common anomalies include:

- chromosomal anomalies (trisomy 13, 14, 15, 18 (most common), and 21), which occur in 20% of omphaloceles, and are more common in those without liver in the sac;
- Beckwith–Wiedemann syndrome (omphalocele, macroglossia, gigantism, pancreatic islet cell hyperplasia, and predisposition to Wilms' tumor and other pediatric solid tumors), which occurs in 12% of omphaloceles;
- pentalogy of Cantrell (epigastric omphalocele, anterior diaphragmatic hernia, sternal defect, pericardial defect, cardiac anomaly);

- lower midline syndrome (bladder or cloacal exstrophy, imperforate anus, colonic atresia, sacral vertebral anomalies, and meningomyelocele);
- multiple congenital anomalies, with malformations of the musculoskeletal, urogenital, cardiovascular, and central nervous systems being most common.

Gastroschisis occurs in association with other abnormalities much less frequently. The majority of the associated abnormalities involve the gastrointestinal tract. Intestinal atresia occurs in 10–15% of cases, and is thought to be secondary to a vascular accident or from constriction of the blood supply to the intestine at the defect. Meckel's diverticulum and intestinal duplications have also been noted.

FUNCTION OF EXTERIORIZED VISCERA

Because of the presence of a sac in most omphaloceles, the exteriorized viscera usually function normally. In infants with gastroschisis, however, the exteriorized intestine becomes thickened and shortened, and suffers from impaired motility and nutrient absorption.[23] A number of experimental studies have been done to investigate the etiology of this bowel damage. The results of these studies suggest that:

- intestinal damage arises from both amniotic fluid exposure and constriction of the bowel at the abdominal wall defect;[24,25]
- the damage occurs late during gestation;[26]
- amniotic fluid exposure causes injury because of meconium, rather than urine, in the fluid;[27]
- amniotic fluid exposure results in changes in collagen composition and in the production of mucosal enzymes;[28–30]
- levels of inflammatory cytokines in the amniotic fluid of fetuses with gastroschisis are elevated.[32]

Although there is a significant amount of variability in the severity of these abnormalities, intestinal transit and absorption tend to return to normal by six months in most infants.

PRENATAL DIAGNOSIS AND MANAGEMENT

The unique anatomic characteristics of omphalocele and gastroschisis allow them to be identified and differentiated using prenatal ultrasound. The diagnosis of omphalocele cannot be made definitively prior to the tenth gestational week, as the intestines are normally located in the umbilical cord up until that time. Although it is usually possible to sonographically differentiate omphalocele from gastroschisis, prenatal rupture of an omphalocele may make this more difficult. An abdominal wall defect is often suspected on routine screening because of elevation of the maternal serum alphafetoprotein (MSAFP), which is elevated in 90% of mothers carrying fetuses with omphalocele and 100% of those with gastroschisis.[33] Using a combination of maternal serum screening and ultrasound, the sensitivity and specificity for prenatal diagnosis of abdominal wall defects should approach 100%.[34]

Once an abdominal wall defect is identified, a search for additional anomalies should be carried out. If the problem is clearly gastroschisis, this can be limited to a careful anatomic ultrasound. For fetuses with omphalocele, both structural and chromosomal problems should be sought. Karyotype analysis by amniocentesis or chorionic villous sampling, and an anatomic ultrasound, including fetal echocardiography, should be completed. In most series, approximately two-thirds of associated abnormalities are detected prenatally in these fetuses.[35]

Currently, *in utero* repair is not recommended for either gastroschisis or omphalocele. Based on the principle that amniotic fluid exposure results in intestinal damage, several authors have advocated amniotic fluid exchange or amnioinfusion for the fetus with gastroschisis. Animal experiments suggest that bowel damage may be ameliorated with this technique,[36] and preliminary clinical experience was encouraging.[37–39] However, Midrio *et al.*[40] evaluated the effectiveness of serial amnioexchange in eight fetuses and failed to show reduced concentrations of inflammatory mediators and digestive substances in the amniotic fluid. In cases of gastroschisis with severe oligohydramnios, amnioinfusion may be lifesaving.

Serial ultrasound examination of herniated bowel in fetuses with gastroschisis is standard. Although prenatal ultrasound findings including bowel wall thickening, bowel dilation, presence of an associated peel, matting of the bowel, loss of peristaltic activity, changes in bowel wall echogenicity, attenuation of mesenteric blood flow, and changes in stomach position have been correlated with postnatal outcomes in some studies,[41–43] more recent studies have suggested that none of these findings predicted a worse postnatal course.[44,45] A large systematic review by Tower *et al.*[46] suggested that prenatal bowel dilation does not predict an increased risk of adverse postnatal outcome.

The timing, location, and mode of delivery may impact the outcome of infants with omphalocele and gastroschisis. Most infants with omphalocele should be delivered at term. In contrast, infants with gastroschisis may benefit from early delivery to minimize the damage from exposure of the bowel to amniotic fluid. Many centers choose to deliver at 37 weeks' gestation after documenting lung maturity, although this remains controversial.[47–49] Most studies looking at this question use historical controls to compare early to spontaneous delivery, and report both improved[50,51] and worse[52] outcomes for early delivery. Hadidi *et al.*[53] reported outcomes from two obstetric groups delivering infants into the same neonatal intensive care unit over the same time period, one preferring early Cesarean delivery at 36 weeks and the other preferring later spontaneous vaginal delivery. The results were mixed. They found that infants with gastroschisis born by early elective Cesarean delivery had a higher incidence of primary closure, fewer complications, mostly septic in nature, and they began enteral feeds sooner. However, they reported no difference in ventilator days, or overall length of stay in the two groups.[53] Early delivery does not necessarily need to be done by Cesarean section, as it has been shown that the average gastroschisis pregnancy goes into spontaneous labor around 37 weeks.[54]

Use of routine Cesarean delivery for both omphalocele and gastroschisis also remains controversial. There is general agreement that infants with a very large omphalocele should be delivered in this manner to prevent injury to the exteriorized liver; however, infants with smaller defects should probably be delivered vaginally unless there are obstetric indications for Cesarean section.[55] Many retrospective studies have been carried out comparing Cesarean and vaginal delivery for infants with gastroschisis, with most demonstrating no benefit of Cesarean delivery.[55–58] In most of the studies in which a benefit was found, the delivery was carried out before term, suggesting that it was the early delivery rather than the Cesarean section which conferred the benefit.[49,59,60]

With very few exceptions, all infants with an abdominal wall defect should be delivered at a perinatal center, where immediate neonatal and surgical expertise is available.[47,61]

NEWBORN MANAGEMENT

The initial treatment of a newborn with omphalocele or gastroschisis consists of fluid resuscitation, nasogastric decompression, avoidance of hypothermia, and local care of the exteriorized viscera. In infants with gastroschisis, the bowel should be inspected to ensure its blood supply is not compromised by twisting of the mesentery or constriction at the abdominal wall defect. If the size of the abdominal wall defect in gastroschisis is causing vascular compromise, the defect should be enlarged immediately. The bowel should be wrapped in warm saline-soaked gauze and covered with a waterproof dressing (Fig. 71.3). A bowel bag or cellophane works well for this purpose. Children with gastroschisis should be transported and nursed on their right side to avoid kinking of the mesenteric vessels. In infants with omphalocele, the sac should be inspected for leaks before placing the dressing.

Newborns with abdominal wall defects should be placed in a temperature-controlled environment, as they lose a great deal of heat through the exposed bowel. Babies with gastroschisis require up to two to three times the amount of fluid a normal term infant would require. Isotonic solutions should be used for resuscitation, and the child should be well hydrated prior to going to the operating room for repair. Once fluid resuscitation has been accomplished, parenteral nutrition, preferably through a central venous catheter, should be initiated.

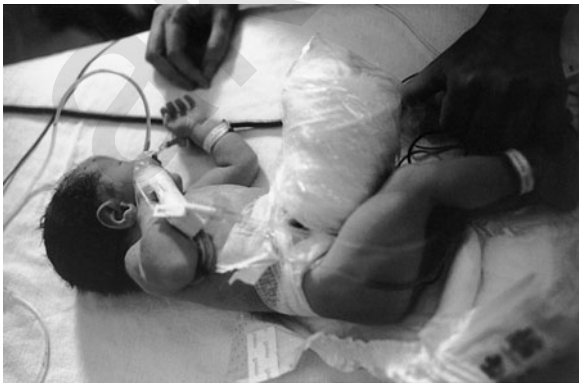


Figure 71.3 Appropriate dressing of an abdominal wall defect in the delivery room. The viscera are covered with warm saline-soaked gauze, supported on the anterior abdominal wall and covered with a waterproof dressing.

All infants should be carefully examined clinically and radiologically to ensure adequate pulmonary, cardiac, and renal function are maintained. Associated anomalies must be diligently searched for, particularly in those infants with omphalocele.

SURGICAL MANAGEMENT

The goal of surgical management for both omphalocele and gastroschisis is to place the herniated viscera back into the abdomen and to close the fascia. In many cases, this can be done in a single operation. Strategies to help accomplish this include: (1) stretching of the abdominal wall; (2) using normal saline or *N*-acetylcysteine enemas to clear the meconium from the colon; and (3) milking the small bowel contents toward the stomach and aspirating with a nasogastric tube. For omphalocele, the sac is usually removed after ligating the umbilical arteries and vein. Areas of the sac that are firmly adherent to a portion of the liver must be left in place to avoid hepatic injury. Careful dissection is required at the superior aspect of the omphalocele to avoid the malpositioned hepatic veins which are often very superficial. In some cases, the abdominal wall defect may require enlargement in order to fit the viscera back inside the abdomen. In all cases of abdominal wall defects, the bowel should be inspected to look for associated atresias and for evidence of a rotation abnormality. If an atresia is identified and the bowel appears to be healthy, the atresia should be repaired with a primary anastomosis. If the bowel is too thickened or inflamed, a stoma may be performed or the abdominal wall defect repaired with the plan for repair of the atresia at another laparotomy several weeks later.[62,63] Ideally, the intestine should be arranged in a position of non-rotation, although in most cases of gastroschisis it is difficult to assess for the presence of malrotation at the time of abdominal wall closure. In infants with omphalocele, the diaphragm should be inspected to ensure there is no defect that would only become apparent after the intestines are placed back into the abdomen.

If the viscera do not fit into the abdomen without a significant increase in intra-abdominal pressure, a silastic 'silo' can be placed and the herniated contents gradually reduced back into the abdomen over the next 1–10 days (Fig. 71.4). Parenteral antibiotics should be continued until the silo is removed. The contents of the silo should be reduced every 12–24 hours as tolerated by the baby. The bowel in the silo needs to be carefully observed during the reduction to avoid mechanical injury usually due to pushing a large amount of bowel through a small defect leading to vascular compromise and bowel necrosis.[64] When the viscera have been successfully returned to the abdomen, the infant is taken to the operating room, the silo is removed, and the fascia is closed along with the overlying skin.

The decision whether to do a primary repair or to place a silo can be difficult. Excessive intra-abdominal pressure may result in abdominal 'compartment syndrome', with intestinal

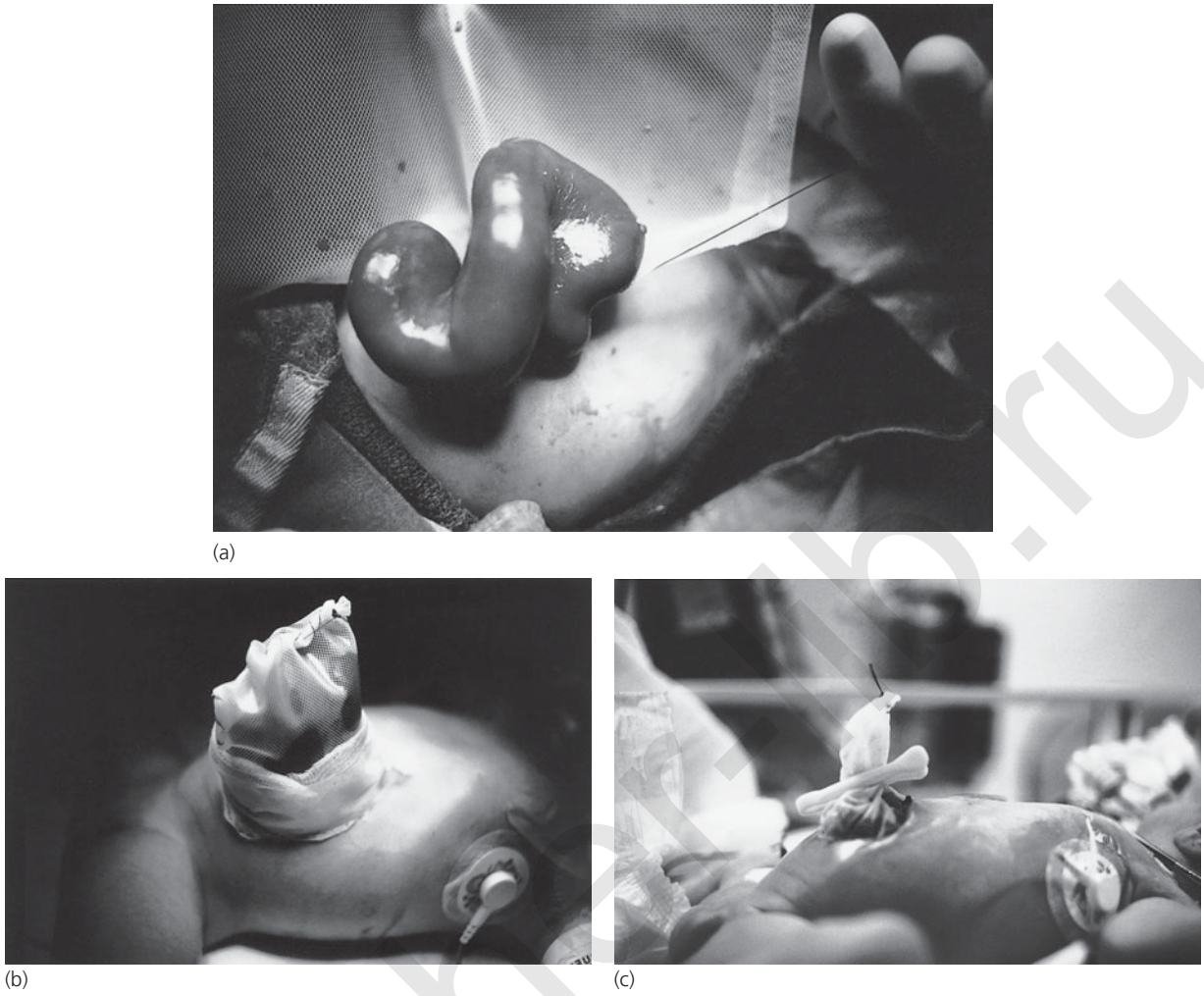
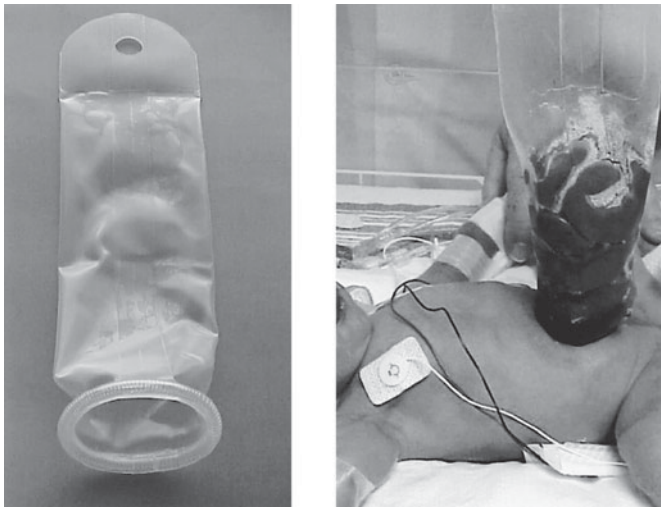


Figure 71.4 The use of a silo in a child with gastroschisis. (a) The silo is sewn to the abdominal wall, over the bowel. (b) The bowel is slowly reduced once or twice per day. (c) The abdominal wall is ready to be definitively closed.

ischemia leading to perforation and fistulization, reduced hepatic and renal blood flow, and reduced circulation to and from the lower extremities. Peak airway pressures have been used for many years as an indicator of excessive intra-abdominal pressure. Experimental and clinical studies have demonstrated that intravesicular or intragastric pressures of <20 mmHg, in combination with a rise in central venous pressure of <4 mmHg correlate with a lower incidence of abdominal compartment syndrome.[65–68] These parameters may also be followed postoperatively, and during silo reduction. Elevation of pressures would suggest that the abdomen should be reopened and a silo placed.

Several innovations have been introduced that may improve the outcome for infants with gastroschisis. Immediate repair in the delivery room, as initially reported by the Detroit group[69] and now practiced by some South American surgeons, is thought to allow easier abdominal wall closure, earlier extubation, less time to initiation of feeds, and a shorter hospital stay. However, this approach has not been validated in any prospective studies. Bianchi and Dickson[70] reported a technique for closure of gastroschisis at the bedside without the use of anesthesia or a silo. Although this approach may be useful in selected patients with relatively healthy bowel, some authors have reported poor results using the Bianchi approach.[71] Several groups have advocated routine bedside placement of a spring-loaded silo, which can be introduced into the defect without the need for a general anesthesia (Fig. 71.5). After gradual reduction of the viscera over the next 0–7 days, closure of the fascia is accomplished either in the operating room, or by placing a dressing and allowing the wound to granulate.[72] In retrospective studies, this technique was associated with improved outcomes when compared to the standard approach.[5,73] However, a recent multicenter randomized controlled trial of 54 infants with gastroschisis, and a recent review of 99 cases of gastroschisis by the Canadian Pediatric Surgery Network both failed to reveal any association between abdominal wall closure technique and functional outcome.[74,75]

Occasionally, an omphalocele is so large that it is unlikely that the abdominal cavity will accept the herniated contents over a reasonable period of time, even with the use of a silo. In other cases, the infant may have severe pulmonary hypoplasia or prematurity, or associated anomalies that preclude an attempt at closure. In these cases, the omphalocele sac may be left intact and allowed to slowly granulate and eventually epithelialize.[76] In the past, this was accomplished by painting



(a) (b)

Figure 71.5 (a) Spring-loaded silo. (b) This device can be placed at the bedside without an anesthetic and permits gradual reduction of the viscera in every case, with only one trip to the operating room.

with mercurochrome or iodine,[77] but mercury or iodine poisoning was reported in some cases and these agents have been largely abandoned. The use of OpSite has also been described.[78] The authors currently advocate the use of silver sulfadiazine for this purpose, which forms an eschar on the sac. The eschar begins to granulate, then epithelializes, and eventually a pseudo-skin forms from the edges of the wound and covers the entire sac (Fig. 71.6). The resulting ventral hernia is ultimately repaired electively when the child's other medical problems have improved. Newborns with omphalocele associated with life-threatening structural or chromosomal anomalies have a poor prognosis, and a frank discussion with the neonatologists and parents should precede any aggressive treatment.

POSTOPERATIVE MANAGEMENT

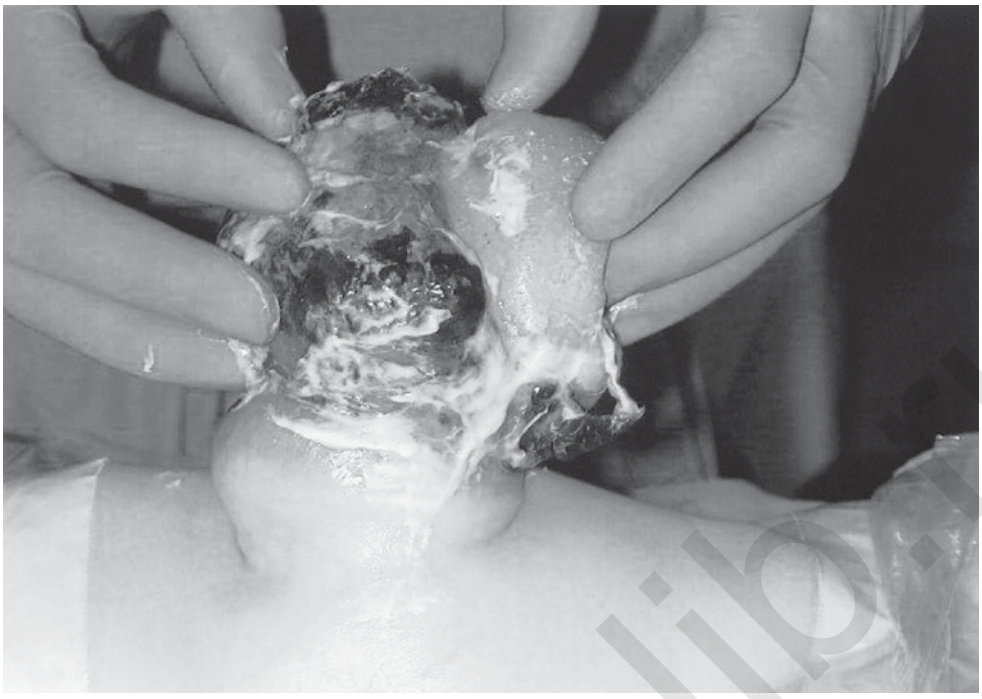
Postoperatively, feeding is started when gastrointestinal function returns; this usually takes much longer for infants with gastroschisis than with omphalocele, and can take weeks to months. If feeding is not proceeding well, the possibility of a missed atresia must be considered, and both upper and lower intestinal contrast studies should be carried out. Prokinetic agents are often used in this situation. Cisipride, which is no longer available, has been shown experimentally and clinically to improve intestinal motility.[79] Erythromycin, another prokinetic agent, however, has been shown not to have an effect on motility in infants with gastroschisis.[80]

Necrotizing enterocolitis is relatively common in infants with gastroschisis,[81] but the risk may be decreased by prevention of excessive intra-abdominal pressure during reduction of the viscera.[5,82] In addition, both omphalocele and gastroschisis are accompanied by an increased incidence of gastro-esophageal reflux, especially in the first year of life.[83] Although this can often be managed medically, some children require fundoplication or jejunostomy tube placement.[84] For many infants with an abdominal wall defect, long-term TPN must be used through a central venous catheter, which may be accompanied by complications related to line infections, metabolic disturbances, and liver injury.[85]

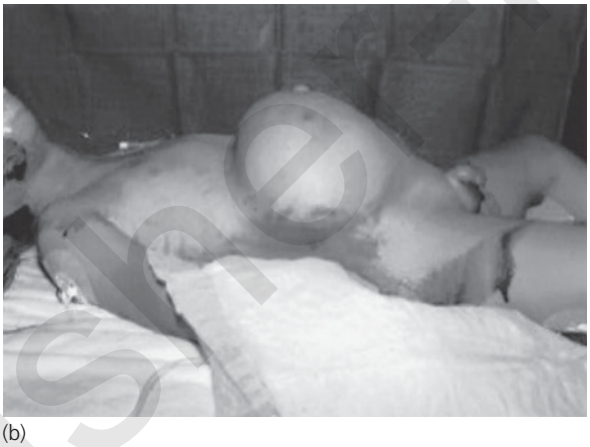
Functional bowel issues may be exaggerated in the subset of infants with gastroschisis who have intestinal atresia. In a review by Phillips *et al.*,[86] 12% of their gastroschisis population had an intestinal atresia. Of these, 29% did well following repair, 28% died of short bowel syndrome, necrotizing enterocolitis, or midgut infarction. The remaining 43% developed massive intestinal dilation and stasis despite having adequate bowel length. The majority of these infants required additional operations aimed at rescuing their dysfunctional bowel. These included tapering enteroplasties, diverting stomas for decompression, and anastomotic revisions.

LONG-TERM OUTCOME

The outcome of infants born with gastroschisis depends on the condition of the intestine. In uncomplicated cases of gastroschisis, the overall survival is greater than 90%.[87–90] However, the group of infants with gastroschisis that require home TPN due to loss of bowel length or inability to tolerate enteral feeds despite normal bowel length have a 50% mortality rate in the first two years of life.[90] A significant number of these patients require additional surgery, usually for adhesive intestinal obstruction, and a small group of children suffer from short bowel syndrome or long-term motility disorders which ultimately require small bowel transplantation.[91] In fact, gastroschisis is the most frequent indication for pediatric small bowel transplantation.[92] The outcome for infants with omphalocele is more dependent on the presence and severity of associated malformations. In the absence of chromosomal abnormalities, or severe pulmonary or cardiac anomalies, the majority of these children survive to live normal lives.[87,88] Henrich *et al.*[93] looked at several aspects of long-term quality of life in children with gastroschisis and omphalocele. These are depicted in Table 71.1. The results are



(a)



(b)

Figure 71.6 Escharotic management of a large omphalocele. The sac is covered with silver sulfadiazine (a). This results in granulation tissue and ultimately in epithelialization. The resulting ventral hernia (b) can be repaired at any time, when the child's medical condition improves.

Table 71.1 Long-term quality of life.

		Gastroschisis (%)	Omphalocele (%)
Gastrointestinal issues	Frequent	7	10
	Rarely or never	77	75
Physical limitations		9	7
Cosmetic results	Good or excellent	82	73
	Umbilical reconstruction	23	35
	Troubled by lack of umbilicus	24	11
Abdominal wall hernia		14	20
Delayed sitting or walking		32	27
Began school at usual age		77	93
Growth	Weight $<$3rd percentile	9	20
	Height $<$3rd percentile	14	13

similar in the two groups, and reveal a satisfying overall quality of life for these children after long-term follow up.

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Omphalomesenteric duct remnants

KENNETH KY WONG AND PAUL KH TAM

INTRODUCTION

The omphalomesenteric duct is a long narrow tube that joins the yolk sac to the digestive tube in the human embryo. Normally, the duct undergoes complete obliteration during the 7th week. Incomplete obliteration results in omphalomesenteric remnants, which may be apparent in the newborn infant.[1]

ETIOLOGY

Development of the midgut in the embryo is characterized by elongation of the gut at the end of the 4th week of gestation. At the apex, the intestinal loop remains connected and open to the yolk sac via the omphalomesenteric (vitelline) duct.[2] In some people, the duct persists due to incomplete obliteration and resorption, thus giving rise to various anatomical anomalies.

PATHOLOGY

Omphalomesentric remnants can be classified into various types according to the underlying anomaly (Fig. 72.1):

- persistent omphalomesenteric duct (patent or obliterated);
- omphalomesenteric duct cyst;
- Meckel' diverticulum;
- umbilical mucosal polyp/umbilical cyst.

HISTORY, PRESENTATION, AND DIAGNOSIS

Persistent omphalomesenteric duct

The omphalomesenteric duct may be patent and present as an omphalo-ileal fistula. The fistula may contain ectopic gastric, colonic, or pancreatic tissue. After birth, the infant presents with umbilical discharge, which resembles small bowel content. An umbilical 'polyp' consisting of intestinal mucosa may also be present. In the newborn, the discharge can often result in peri-umbilical excoriation. The diagnosis is confirmed by passing a catheter through the fistula into the small intestine and aspirating small bowel content, or by injecting radiographic contrast medium into the fistula.

Rarely, the ileum may even prolapse through the omphalo-ileal fistula, giving rise to the so-called 'steer-horn' abnormality.

For obliterated omphalomesenteric duct, it may persist as a fibrous cord attaching the ileum to the umbilicus internally. The infant who has this anomaly is usually asymptomatic. However, there is a risk of small bowel volvulus occurring around such a band.

Omphalomesenteric duct cyst

The obliterated omphalomesenteric duct may contain one or more cysts. The clinical presentation of this is similar to obliterated duct, with a risk of small bowel volvulus. Sometimes, the cyst can become infected and the child may present with pain and fever.

Meckel's diverticulum

The most common omphalomesenteric remnant seen is the Meckel's diverticulum, which is the persistence of the enteral end on the anti-mesenteric side of the small intestine (Fig. 72.2). This anomaly occurs in around 2% of the population, with its location usually within 60 cm of the ileocecal. Complications of the diverticulum include bleeding, diverticulitis, and intussusception. Asymptomatic ones are usually found incidentally at laparotomies for other conditions. A recent study showed that resection of incidentally detected Meckel's diverticulum had a significantly higher postoperative complication rate than leaving it *in situ*, and that 758 resections would need to be performed to prevent

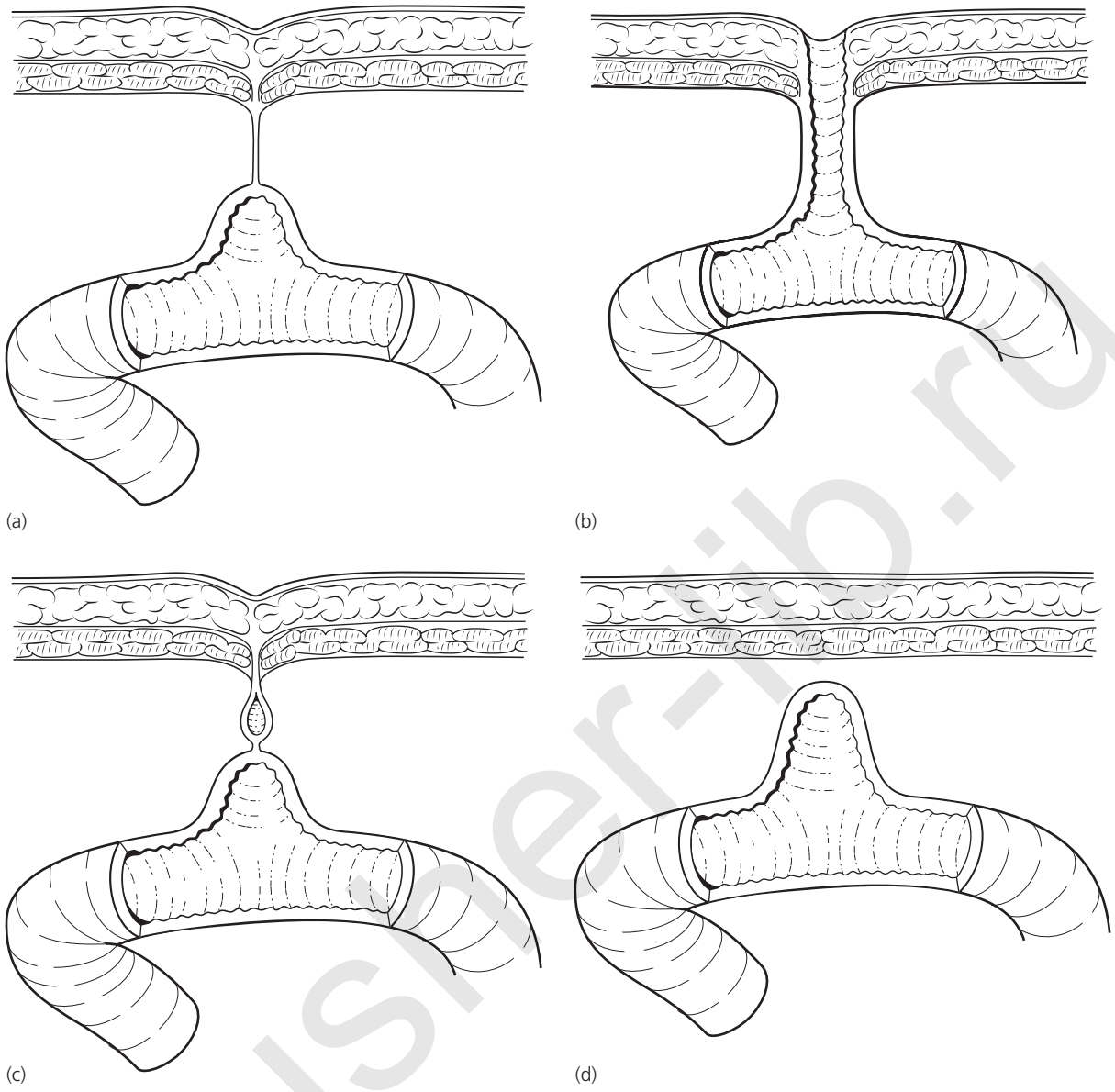

Figure 72.1 Schematic diagrams showing the various anatomical variations of omphalomesenteric remnants: (a) obliterated omphalomesenteric duct; (b) patent omphalomesenteric duct; (c) a cyst in an obliterated omphalomesenteric duct; (d) Meckel's diverticulum.

one death from the condition. As a result, there is no evidence to support the resection of incidentally detected Meckel's diverticulum.[3]

For diagnosis, the presence of ectopic gastric mucosa with the secretion of gastrin can be detected using Tc-99 radioisotope scanning (Fig. 72.3), although a negative result does not exclude the presence of Meckel's diverticulum (sensitivity of Tc-99 around 80–85%).[4]

Umbilical polyp

An umbilical polyp is a remnant of intestinal mucosa at the umbilicus. The pink, polypoid tissue produces a persistent discharge which may be blood-stained. The other differential diagnosis is an umbilical granuloma, which should respond to simple cauterization treatment. The diagnosis of an umbilical polyp may be confirmed by biopsy to look for the presence of intestinal or gastric mucosa.

OPERATIVE MANAGEMENT

Omphalomesenteric remnants are best managed operatively[5] and the approaches for the various anomalies are described below.

Excision of a patent omphalomesenteric duct

The orifice of the fistula is mobilized using a circumferential incision, preserving the surrounding umbilical skin (Fig. 72.4).

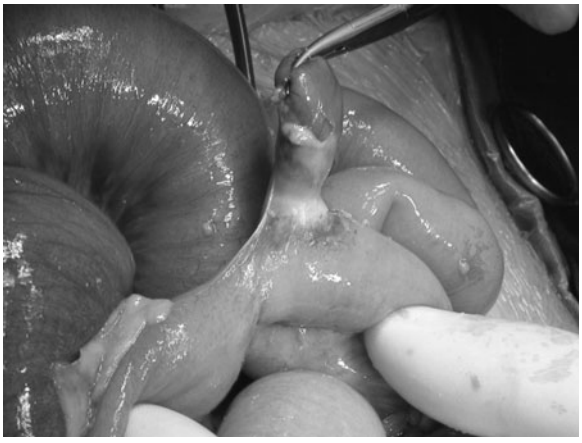

Figure 72.2 An intraoperative photograph showing a Meckel's diverticulum delivered out through an umbilical incision.

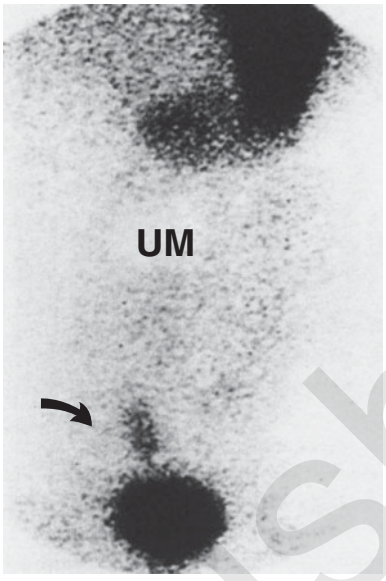

Figure 72.3 A photograph of a Tc-99 radio-isotope scan taken at 20 minutes, showing the presence of gastrin secreting mucosa in a Meckel's diverticulum.

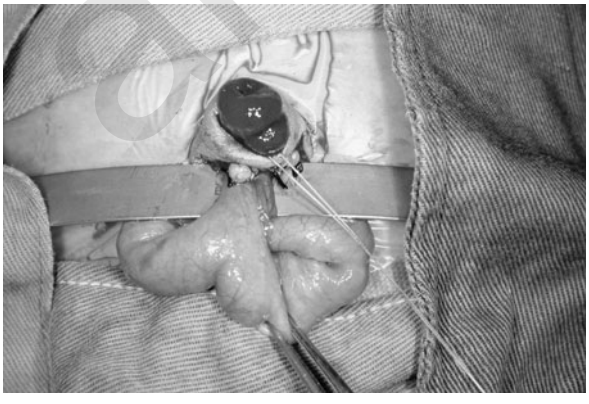

Figure 72.4 An intraoperative photograph taken after dissection of a patent omphalomesenteric duct.

A separate skin-crease incision is made below the umbilicus. The superior skin flap, which includes the umbilicus, is elevated and the fistula is brought out through the subumbilical incision. The abdominal wall fascia is incised transversely on either side of the fistula. The umbilical vessels and the urachus are individually ligated and divided and the peritoneal cavity is entered. The fistula is traced to its termination on the distal ileum.

The blood supply to the fistula runs across the ileum, and should be ligated and divided near its origin on the mesentery. The fistula is excised with a margin of ileum using a transverse elliptical incision. The ileal defect is repaired transversely with a single interrupted layer of absorbable 4-0 sutures. The linea alba is then repaired and the subumbilical incision closed with subcuticular 5-0 suture. The circular defect in the center of the umbilicus may be left to heal by secondary intention if small, or may be loosely closed with a purse-string suture. The healed wound should resemble the umbilicus.

Meckel's diverticulectomy

Symptomatic and confirmed Meckel's diverticulum should be excised. For those patients who are asymptomatic, it is not essential to remove them. Nowadays, the procedure is assisted or even performed wholly laparoscopically in many centers. Laparoscopy is also useful in helping to diagnose symptomatic patients with negative isotope scans. The principles of laparoscopic resection remain the same as open surgery and it is the authors' preference to resect a short segment of ileum together with the diverticulum to ensure that all abnormal mucosa is removed.[6,7] For open surgery, a 2-cm peri-umbilical incision is used to gain access to the peritoneal cavity. This will ensure an excellent cosmetic result postoperatively.

The Meckel's diverticulum is situated on the anti-mesenteric border of the distal ileum, and may be bound to the adjacent small bowel mesentery by a covering of peritoneum. These adhesions are divided to mobilize the diverticulum. Occasionally, the diverticulum is attached to the umbilicus, from which it must be separated. The blood vessels on the mesenteric side are ligated and divided. Ileal resection with primary end-to-end anastomosis with single-layer, interrupted absorbable 4-0 sutures is carried out. This ensures the removal of all ectopic tissue. The fascia of the subumbilical incision is closed using 3-0 absorbable sutures, and the skin is approximated with subcuticular 5-0 sutures reinforced with adhesive strips.

Excision of an umbilical polyp

A circumferential incision is made around the polyp, preserving as much of the normal umbilicus as possible. The skin defect is repaired using an absorbable purse-string suture. Because of the possibility of an underlying connection to the ileum by a remnant of the omphalomesenteric duct, limited exploration of the peritoneal cavity is advisable. A subumbilical incision is made as described above. The abdominal wall is opened transversely and the peritoneal cavity entered. If an omphalomesenteric duct remnant is present, it is resected.

COMPLICATIONS

For conditions which involve peritoneal access (either open or laparoscopic) and intestinal resection, early postoperative complications include anastomotic leak, adhesion formation, postoperative ileus and wound infection. These are, however, rare (<5%). Intestinal obstruction from adhesions may present as a late event.

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Bladder exstrophy: considerations and management of the newborn patient

ANDREW A STEC AND JOHN P GEARHART

INTRODUCTION

In this chapter, the techniques for managing the newborn with classical bladder exstrophy are discussed based on the authors' experience and data derived from more than 940 patients with bladder exstrophy, epispadias, and cloacal exstrophy from an institutional approved database at the authors' institution.

The primary objectives of modern surgical management of classic bladder exstrophy are: (1) a secure abdominal closure, (2) reconstruction of a functional and cosmetically acceptable penis in the male and female external genitalia in the female, and (3) urinary continence with the preservation of renal function and volitional voiding.

Currently, several techniques exist to reconstruct the newborn with bladder exstrophy. Regardless of the technique chosen, placing the posterior vesico-urethral unit into the pelvis combined with a successful primary closure gets the child in the best position for bladder growth and eventual voided continence. In the authors' experience, these objectives can best be achieved with newborn primary bladder and posterior urethral closure, early epispadias repair, and finally, bladder neck reconstruction when the bladder reaches an appropriate volume for an outlet procedure. This chapter will be limited to discussion on the early management and initial primary closure of these infants.

INCIDENCE AND INHERITANCE

The incidence of bladder exstrophy has been estimated to be between one in 10 000 and one in 50 000 live births.[1] However, data from the International Clearinghouse for Birth Defects monitoring system estimated the incidence to be 3.3 in 100 000 live births.[2] Two series have reported a 5:1 to 6:1 ratio of male-to-female exstrophy births.[1,2] The risk of recurrence of bladder exstrophy in a given family is approximately one in 100.[2] Shapiro *et al.* determined that the risk of bladder exstrophy in the offspring of individuals with bladder exstrophy and epispadias is one in 70 live births, a 500-fold greater incidence than that in the general population.[3] In reviews of exstrophy patient cohorts, three interesting trends have been found: (1) bladder exstrophy tended to occur in infants of younger mothers; (2) an increased risk at high parity was seen for bladder exstrophy and epispadias;[2] (3) an increased incidence occurs with *in vitro* pregnancies.[4]

EMBRYOLOGY

Bladder exstrophy, cloacal exstrophy, and epispadias are variants of the exstrophy–epispadias complex. The etiology of this complex has been attributed by Muecke to the failure of the cloacal membrane to be reinforced by ingrowth of mesoderm.[5] The cloacal membrane is a bilaminar layer situated at the caudal end of the germinal disk, which occupies the infra-umbilical abdominal wall. Mesenchymal ingrowth between the ectodermal and endodermal layers of the cloacal membrane results in formation of the lower abdominal muscles and pelvic bones. After mesenchymal ingrowth occurs, downward growth of the urorectal septum divides the cloaca into a bladder anteriorly and rectum posteriorly. The paired genital tubercles migrate medially and fuse in the midline cephalad to the dorsal membrane before perforation. If the cloacal membrane is subject to premature rupture, its stage of development when membrane rupture occurs determines if epispadias, bladder exstrophy, or cloacal exstrophy, will result.[6]

While multiple explanations have been presented, Marshall and Mueke maintain that the basic defect is an abnormal overdevelopment of the cloacal membrane, preventing medial migration of the mesenchymal tissue and proper lower abdominal wall development. Classic exstrophy accounts for

60% of patients born with this complex.[7] Of these patients, 30% are epispadias variants and 10% are cloacal exstrophies or minor variants, such as superior vesical fissure, duplicate exstrophy, and pseudoexstrophy.

ANATOMIC CONSIDERATIONS

Exstrophy of the bladder is part of a spectrum of anomalies involving the urinary tract, genital tract, musculoskeletal system, and sometimes the intestinal tract. In classic bladder exstrophy, most anomalies are related to birth defects of the abdominal wall, bladder, genitalia, pelvic bones, rectum, and anus (Fig. 73.1).

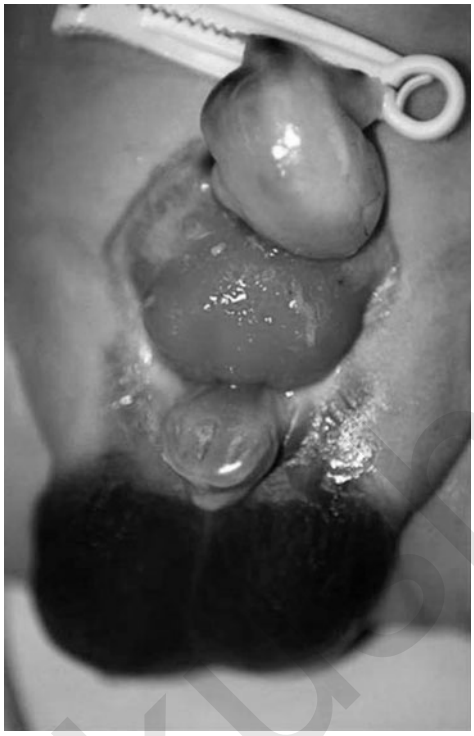

Figure 73.1 Newborn male infant with classic bladder exstrophy.

Musculoskeletal defects

Patients with classic bladder exstrophy have a characteristic widening of the pubic symphysis caused by malrotation of the innominate bones, in relation to the sagittal plane of the body along both sacroiliac joints. In addition, they display an outward rotation or eversion of the pubic rami at their junction with the iliac bones. Recently, new data by Sponseller *et al.*[8] utilizing computer tomography of the pelvis with three-dimensional reconstruction, have further characterized the bony defect associated with both classic bladder exstrophy and cloacal exstrophy. Sponseller *et al.* found that patients with classic bladder exstrophy have a mean external rotation of the posterior aspect of the pelvis of 12° on each side, retroversion of the acetabulum, and a mean 18° of external rotation of the anterior pelvis, along with a 30% shortening of the pubic rami. These rotation deformities of the pelvic skeletal structures contribute to the short, pendular penis seen in bladder exstrophy. Additionally, this rotation also accounts for the increased distance between the hips, waddling gait, and the outward rotation of the lower limbs in these children, which in itself causes little disability and usually corrects to some degree over time.

The most recent study using three-dimensional computed tomography (CT) has further increased our understanding of the pelvic anatomy in patients with bladder exstrophy.[9] In this paper, Stec *et al.*[9] showed that the sacroiliac joints are externally rotated, the pelvis is rotated inferiorly, and the pelvic volume in exstrophy patients is larger than normal controls. These new findings will hopefully serve to improve our understanding and surgical approach to pelvic osteotomy in these patients. One study was performed on fetal bony pelves with the exstrophy complex to determine histologic patterns and growth potential. Despite the abnormal gross architecture, histologically the exstrophic bones were identical to controls and completely normal; bone development was occurring at an expected rate with the potential for continued normal growth.[10]

In addition to the bony structures of the pelvis being laterally rotated, the large muscle groups constituting the pelvic floor are also flattened and laterally splayed. A fundamental tenet of bladder exstrophy repair is proper pelvic floor mobilization and placement of the vesicourethral complex deep within the pelvis. In 2001, Stec *et al.*[11] published the initial description using three-dimensional CT characterizing the pelvic floor in unclosed neonates with bladder exstrophy. This study found four primary findings that characterize the pelvic floor musculature in classic bladder exstrophy: (1) the pelvic floor covers a two-fold greater surface area in the exstrophy complex; (2) each levator ani half is outwardly rotated 38° from midline; (3) the levator ani is 31° flatter in the exstrophy complex thereby, forming much less of a supportive sling than controls; and (4) only 32% of the puborectal sling is located anterior to the rectum for pelvic support as compared to 50% in controls. Magnetic resonance imaging (MRI) studies on the pelvic floor musculature created more advanced three-dimensional models of the abnormal character of the pelvic floor muscle, demonstrating one additionally important caveat: the degree of pubic and bony diastasis does not account for all of the derangements in the pelvic floor anomaly in exstrophy.[12]

Abdominal wall defects

The triangular defect caused by the premature rupture of the abnormal cloacal membrane is occupied by the exstrophied bladder and posterior urethra. The fascial defect is limited inferiorly by the intrasymphyseal band, which represents the divergent urogenital diaphragm. This band connects the bladder neck and posterior urethra to the pubic ramus on anatomical study. The anterior sheath of the rectus muscles has a fan-like extension behind the urethra and bladder neck that inserts into the intrasymphyseal band. At the upper end of the

triangular fascial defect is the umbilicus. In bladder exstrophy, the distance between the umbilicus and the anus is always foreshortened. Although an umbilical hernia is usually present, it is usually of insignificant size. The umbilical hernia is repaired at the time of the abdominal wall closure. In a review of 181 children with bladder exstrophy, Connolly *et al.*[13] reported inguinal hernias in 81.8% of boys and 10.5% of girls.

Anorectal defects

The perineum is short and broad, with the anus situated directly behind the urogenital diaphragm, displaced anteriorly, and corresponding to the posterior limit of the triangular fascial defect. The divergent levator ani and puborectalis muscles and the distorted anatomy of the external sphincter contribute to varying degrees of anal incontinence and rectal prolapse. Anal continence is usually imperfect at an early age, but typically improves. Prolapse virtually always disappears after bladder closure. If the infant develops prolapse after closure, a bladder outlet obstruction must be ruled out.

Male genital defects

The male genital defect is severe and the most troublesome aspect of the surgical reconstruction, independent of the decision as to whether to treat by modern staged closure, combined closure, or by some form of urinary diversion. Formerly, it was thought that the individual corpus cavernosum was of normal caliber, but appeared to be shorter because of the wide separation of the crural attachments, the prominent dorsal chordee, and the shortened urethral groove. However, data by Silver *et al.*[14] have described the genital defect in bladder exstrophy in much greater detail. Utilizing MRI in adult men with bladder exstrophy and comparing this to age- and race-matched controls, it was found that the anterior corporal length in male patients with bladder exstrophy is almost 50% shorter than that of normal controls. A functional and cosmetically pleasing penis can be achieved when the dorsal chordee is released, the urethral groove lengthened, and the penis somewhat lengthened by mobilizing the crura in the midline. Potency is preserved in almost all exstrophy patients. Testis function has not been studied in a large group of post-pubertal exstrophy patients, but it is generally believed that fertility is not impaired by testicular dysfunction.

Female genital defects

Reconstruction of the female genitalia presents a less complex problem than in the male (Fig. 73.2). The vagina is shorter than normal, hardly greater than 6 cm in depth, but of normal caliber. The vaginal orifice is frequently stenotic and displaced anteriorly; the clitoris is bifid. The labia, mons pubis, and clitoris are divergent. The uterus enters the vagina superiorly so that the cervix is in the anterior vaginal wall. The Fallopian tubes and ovaries are normal. Female patients

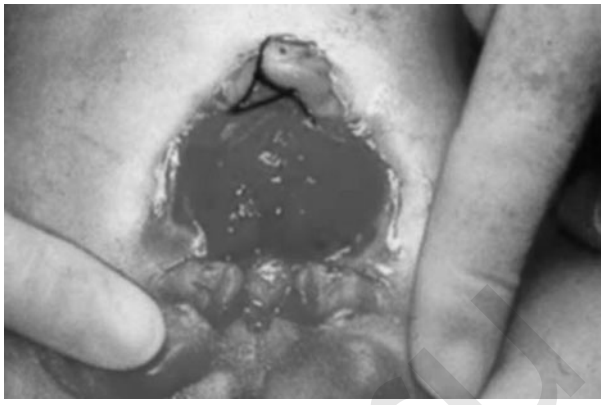

Figure 73.2 Female infant with classic bladder exstrophy.

are typically able to bear children. Most adolescents and young adults will undergo a vaginoplasty procedure in order to wear tampons and have intercourse.

Urinary defects

At birth, the bladder mucosa may appear to be normal, however, ectopic bowel mucosa or an isolated bowel loop or more commonly, a hamartomatous polyp may be present on the bladder surface. The size, distensibility, and neuromuscular function of the exstrophied bladder, as well as the size of the triangular fascial defect to which the bladder muscles attach, affects the decision to attempt repair. When the bladder is small, fibrosed, inelastic, and covered with polyps, functional repair may be impossible. The more normal bladder may be invaginated or may bulge through a small fascial defect, indicating the potential for satisfactory capacity after successful initial closure. It is not until examination under anesthesia that the true defect can be adequately evaluated, as bladders which appear to be small in the nursery may have a substantial amount of bladder sequestered below the fascial defect.

The upper urinary tract is usually normal, but anomalous development does occur. Horseshoe kidney, pelvic kidney, hypoplastic kidney, solitary kidney, and dysplasia with megaureter are all encountered in these patients. The ureters have an abnormal course in their termination. The peritoneal pouch of Douglas between the bladder and the rectum is enlarged and unusually deep, forcing the ureter down laterally in its course across the true pelvis. The distal segment of ureter approaches the bladder from a point inferior and lateral to the orifice, and it enters the bladder with little or no obliquity. Therefore, reflux in the closed exstrophy bladder occurs in 100% of cases and subsequent surgery is usually required at the time of bladder neck reconstruction.

PRENATAL DIAGNOSIS AND MANAGEMENT

Reports have indicated that it is possible to diagnose classic bladder exstrophy prenatally.[15,16] The absence of a normal fluid-filled bladder on repeat examinations suggested the

diagnosis, as did a mass of echogenic tissue on the lower abdominal wall.[16] In a retrospective review of 25 prenatal ultrasound examinations with the resulting birth of newborn classic bladder exstrophy, several observations were made: (1) absence of bladder filling, (2) a low-set umbilicus, (3) widening of the pubic ramus, (4) diminutive genitalia, and (5) a lower abdominal mass which increased in size as the pregnancy progressed and as the intra-abdominal viscera increased in size.[17] Prenatal diagnosis of bladder exstrophy allows for optimal management including delivery in a pediatric center and appropriate prenatal counseling of the parents.

DELIVERY ROOM AND NURSERY CARE

At birth, while the bladder mucosa is usually smooth, pink, and intact, it is also sensitive and easily denuded. In the delivery room, the umbilical cord should be tied with 2-0 silk sutures close to the abdominal wall so that the umbilical clamp does not traumatize the bladder mucosa and cause excoriation of the bladder surface. The bladder may be covered with a non-adherent film of plastic wrap (i.e. saran wrap (cling film)) to prevent the mucosa from sticking to clothes or diapers. In addition, each time the diaper is changed the plastic wrap should be removed, the bladder surface irrigated with sterile saline, and a new square of plastic wrap put in place.

The parents should be educated by a surgeon with a special interest and experience in managing cases of bladder exstrophy. An exstrophy support team should be available, which includes a pediatric orthopedic surgeon, pediatric anesthesiologists, social workers, nurses with special interests in bladder exstrophy, and a child psychiatrist with experience and expertise in genital anomalies. It is important to note that the need for changing the sex of rearing in classic bladder exstrophy is almost non-existent in the male child.

Cardiopulmonary and general physical assessment can be carried out in the first few hours of life. Radionuclide scans and ultrasound studies can provide evidence of renal structure, function, and drainage, even in the first few hours of life before the patient undergoes closure of the exstrophy defect. A thorough neonatal assessment may have to be deferred until transportation to a major children's medical center can be arranged. In these days of modern transportation, no child should be more than a few hours away from a neonatal center with full diagnostic and consultative services. During travel, the bladder should be protected by a plastic membrane to prevent damage to the delicate newborn bladder mucosa.

Occasionally, preoperatively, it may become evident that a small fibrotic bladder patch that is stretched between the edges of a small triangular fascial defect without elasticity or contractility cannot be selected for the usual closure procedure. Figure 73.3 shows a bladder that is too small for closure. Examination with the patient under anesthesia may at times be required to assess the bladder adequately, particularly if considerable edema, excoriation, and polyp formation has developed between birth and the time of assessment. Decisions regarding the suitability of bladder closure or the need for waiting should only be made by surgeons with a great deal of experience in the bladder exstrophy condition. A recent review by Dodson *et al.*[18] at one institution, found on initial judgment that the bladder was too small for closure in 20 patients. After a period of time, when the bladder had grown sufficiently, closure was undertaken. Long-term follow up revealed that 50% of these patients remained dry after bladder neck reconstruction and 50% required other adjunctive procedures.

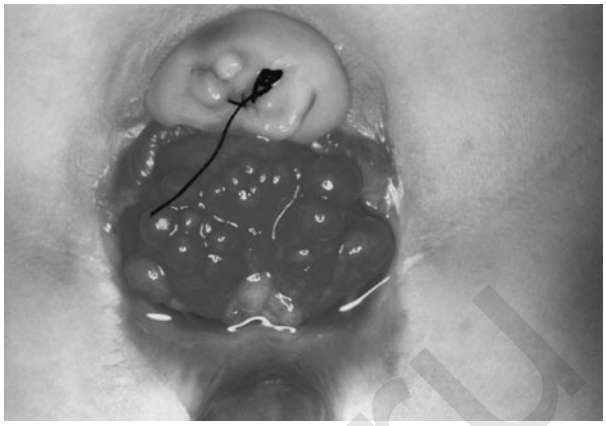

Figure 73.3 Patient with a small fibrotic bladder patch deemed too small for neonatal closure. Note the polypoid nature of the bladder mucosa.

PRIMARY BLADDER CLOSURE

Over the past two decades, modifications in the management of functional bladder closure have contributed to a dramatic increase in the success of the procedure. The most significant changes in the management of bladder exstrophy have been: (1) early bladder, posterior urethra, and abdominal wall closure; (2) the widespread use of pelvic osteotomy along with appropriate pelvic immobilization; (3) early epispadias repair at six to ten months of age; (4) reconstruction of a competent bladder neck and reimplantation of the ureters; and (5) most importantly, defining strict criteria for the selection of patients suitable for this approach.

The primary objective of functional closure is to convert the patient with bladder exstrophy into one with complete epispadias with incontinence and balanced posterior outlet resistance that preserves renal function. Typically, epispadias repair is now performed between six and ten months of age, after testosterone stimulation. Bladder neck reconstruction occurs when the child is four to five years of age, has an adequate bladder capacity, and is ready to participate in a postoperative voiding program.

Another type of staged exstrophy repair is the Kelly repair, or radical soft tissue mobilization. In this repair, the bladder and abdominal wall are closed without osteotomy after birth. Several months later, a radical soft tissue mobilization and the urogenital diaphragm and its periosteal attachments are dissected and used to allow closure of the pelvis and pelvic floor. The penis is made hypospadiac and later penile repair is

performed. Osteotomy is never used in this repair and so far continence results are modest with up to 71% of patient achieving either complete or partial continence in the largest cohort of patients reported in the literature.[19]

This offering will deal with the most common issue seen by the pediatric surgeon, that of obtaining a secure primary closure. Chan *et al.*[20] have shown that a successful closure of a good quality bladder template in a newborn is the single most important predictor of eventual voided continence.

Pelvic osteotomy

Pelvic osteotomies performed at the time of closure confer several advantages, including (1) easy re-approximation of the symphysis with diminished tension on the abdominal wall closure, eliminating the need for fascial flaps; (2) placement of the urethra deep within the pelvic ring enhancing bladder outlet resistance; and (3) bringing the large pelvic floor muscles near the midline, where they can support the bladder neck and aid in eventual urinary control.

After pubic approximation with osteotomy, some patients show the ability to stop and start the urinary stream, experience dry intervals, and in some cases become completely continent.[21] In a review article of a large number of patients referred to the authors' institution with failed exstrophy, a majority were referred with partial or complete dehiscence of the bladder, or major bladder prolapse, and had not undergone osteotomy at the time of initial bladder closure.[22]

The authors' recommendation is to perform bilateral transverse innominate and vertical iliac osteotomy when bladder closure is performed after 72 hours of age.[23] In addition, if the pelvis is not malleable or if the pubic bones are >4 cm apart at the time of initial examination under anesthesia, osteotomy should be performed, even if closed before 72 hours of age. A well-coordinated surgical and anesthesia team can perform osteotomy and proceed to bladder closure without undue loss of blood or risk of prolonged anesthesia in the child. However, one must realize that osteotomy, posterior urethral and bladder closure, along with abdominal wall closure, is a 5–7-hour procedure in these infants.

Combined osteotomy is performed by placing the patient in the supine position, preparing and draping the lower body below the costal margins and placing soft absorbent gauze over the exposed bladder. The pelvis is exposed from the iliac wings inferiorly to the pectineal tubercle and posteriorly to the sacroiliac joints. The periosteum and sciatic notch are carefully elevated and a Gigli saw is used to create the transverse innominate osteotomy, exiting anteriorly at a point halfway between the anterosuperior and anteroinferior spines (Fig. 73.4). This osteotomy is created at a slightly more cranial level than that described for a Salter osteotomy, in order to allow placement of fixator pins in the distal segments.

In addition to the transverse osteotomy, the posterior ileum may be incised from the anterior approach in an effort to correct the deformity more completely. This is important because anatomical studies have shown that the posterior portion of the pelvis is also externally rotated in patients with exstrophy, and as patients age they lose the elasticity of their sacroiliac ligaments. For this part of the osteotomy, an osteotome is used to create a closing wedge osteotomy vertically and just lateral to the sacroiliac joint. The proximal posterior iliac cortex is kept intact and used as a hinge. This combination of osteotomies easily corrects the abnormalities in both the anterior and posterior aspects of the pelvis.

Two fixator pins are placed in the inferior osteotomized segment and two pins are placed in the wing of ileum superiorly. Radiographs are obtained to confirm pin placement, the soft tissues are closed, and the urologic procedure is then performed. At the end of the procedure, external fixators are then applied between the pins to hold the pelvis in a corrected position. Light longitudinal skin traction is used to keep the legs still. The patient remains in the supine position in traction for approximately 4 weeks to prevent dislodgement of tubes and destabilization of the pelvis. The external fixator is kept on for approximately 6 weeks until adequate callus is seen at the site of osteotomy. Postoperatively, in newborns who undergo closure without osteotomy in the first 48–72 hours of life, the baby is immobilized in modified Bryant's traction in a position in which the hips have 90° flexion. When modified Bryant's traction is used, the traction is employed for 4 weeks.

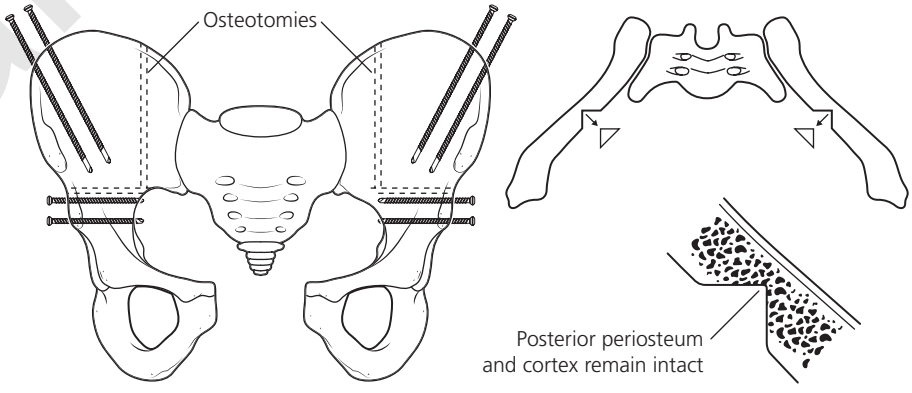

Figure 73.4 Combined transverse anterior innominate and anterior vertical iliac osteotomy with pin placement and preservation of the posterior periosteum and cortex.

Bladder, posterior urethral, and abdominal wall closure

The various steps in primary bladder closure are illustrated in Fig. 73.5. A strip of mucosa 2 cm wide, extending from the distal trigone to below the verumontanum in the male and to the vaginal orifice in the female, is outlined for prostatic and posterior urethral reconstruction in the male and adequate urethral closure in the female. The male urethral groove length is typically adequate and no transverse incision of the urethral plate needs to be performed for urethral lengthening. The diagrams in Fig. 73.5a–c show marking of the incision with a blue marker pen from just above the umbilicus down around the junction of bladder and the paraexstrophy skin to the level of the urethral plate. The approximate plane is entered just above the umbilicus and a plane is established between the rectus fascia and the bladder (Fig. 73.5c,d). The umbilical vessels are doubly ligated and incised allowing them to fall into the pelvis. The peritoneum is taken off the dome of the bladder at this point so that the bladder can be placed deeply into the pelvis at the time of closure. The plane is continued caudally down between the bladder and the rectus fascia until the urogenital diaphragm fibers are encountered bilaterally. The pubis will be encountered at this juncture and a double-pronged skin hook can be inserted in this bone and pulled laterally to accentuate the urogenital diaphragm fibers and help the surgeon radically incise these fibers between the bladder neck, posterior urethra, and the

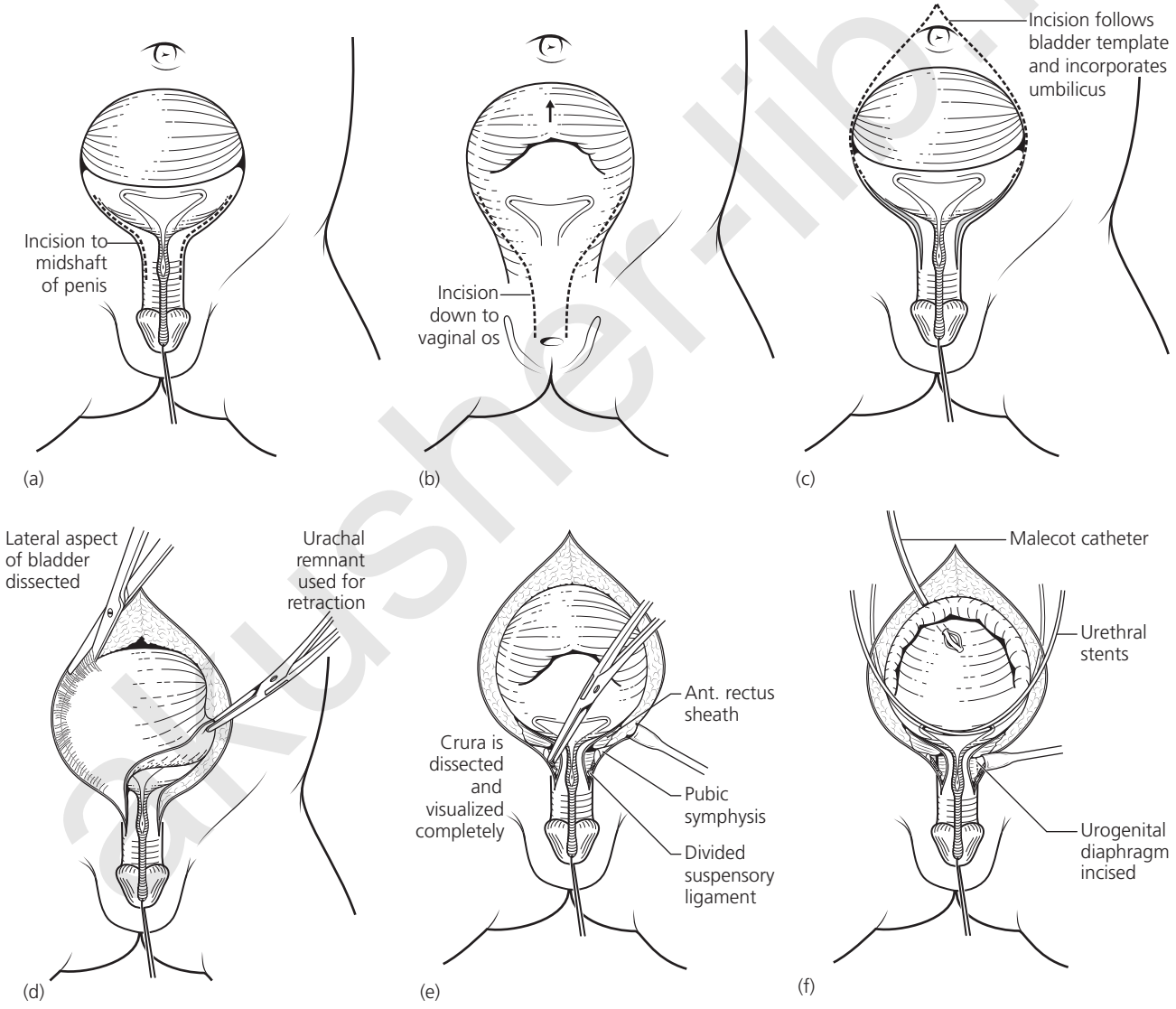

Figure 73.5 (a) Marking of the initial incisions for a male exstrophy patient from trigone around urethral plate. (b) Marking of comparable incisions for closure of a female exstrophy patient down to vaginal os. (c) Marking of the subsequent incision around the umbilicus and bladder, joining the initial dissection. (d) Development of the retropubic space and division of the lateral bladder attachments. (e) The urogenital diaphragm and anterior corpora are freed from the pubis in a subperiosteal plane. (f) Final deep incision of the remnant urogenital diaphragm fibers and insertion of a suprapubic tube. (g) Exit of the ureteral stents from the lateral sidewall of the bladder and the first layer of the bladder wall closure. (h) Closure of fascia is performed after placement of a No. 2 nylon horizontal mattress suture to approximate the pubis.

pubic bone. Gentle traction on the glans of the penis at this point will show the insertion of the corporal body on the lateral inferior aspect of the pubis. These urogenital fibers are taken down sharply with the electrocautery down to the pelvic floor in their entirety. If this maneuver is not performed adequately, the posterior urethra and bladder will not be placed deeply into the pelvis. Therefore, when the pubic bones are brought together, the posterior vesico-urethral unit will be brought anteriorly in an unsatisfactory position for later reconstruction.

The corporal bodies are not brought together at this juncture, as later Cantwell–Ransley epispadias repair will require the urethral plate to be brought beneath the corporal bodies. If the urethral plate is left in continuity, it must be mobilized up to the level of the prostate in order to create as much additional urethral and penile length as possible. Further urethral lengthening can be performed at the time of epispadias repair, at around six months of age.

Apparent penile lengthening is achieved by exposing the copora cavernosa bilaterally and freeing the corpora from their attachments to the suspensory ligaments on the anterior part of the inferior pubic rami. However, since Silver *et al.*[14] have shown that there is a 50% shortage of length in the corporal bodies in exstrophy patients versus normal controls, any penile lengthening that is obtained is more correction of chordee and changing the angulation of the penis, rather than true penile lengthening.

After their incision, the wide band of fibers and muscular tissue representing the urogenital diaphragm is detached subperiostally from the pubis bilaterally (Fig. 73.5e,f). Reluctance to free the bladder neck and urethral wall from the inferior ramus of the pubis moves the neobladder opening cephalad if any separation of the pubis occurs during healing. The mucosa and muscle of the bladder, and the posterior urethral wall on to the penis are then closed in the midline anteriorly. This orifice should accommodate a 12–14-Fr urethral catheter comfortably. The size of the opening should allow enough resistance to aid in the bladder adaptation and to prevent prolapse, but not enough outlet resistance to cause upper tract changes. The posterior urethra and bladder neck are buttressed to the second layer of local tissue if possible (Fig. 73.5g,h). The bladder is drained by a suprapubic non-latex Malecot catheter for a period of 4 weeks. The urethra is not stented in order to avoid necrosis with accumulation of secretions in the neourethra. Ureteral stents provide drainage for 10–14 days after closure, when swelling due to the presence of closure of a small bladder may obstruct the ureters and give rise to obstruction and transient hypertension. If there are no problems with the stents during healing, the current authors leave the stents in for as long as 2–3 weeks.

When the bladder and urethra have been closed and the drainage tube placed, pressure over the greater trochanters bilaterally allows the pubic bones to be approximated in the midline. Horizontal No. 2 mattress sutures are placed in the pubis and tied with a knot away from the neourethra (Fig. 73.5h). Often in a good closure, the author is able to use another stitch of No. 2 nylon at the most caudal insertion of the rectus fascia onto the pubic bone. This maneuver will add to the security of the pubic closure. A V-shaped flap of abdominal skin at a point corresponding to the normal position of the umbilicus is tacked down to the abdominal fascia and the drainage tubes exit this orifice. The method described by Hanna[24] is the author's most commonly performed procedure. Before and during the procedure, the patient is given broad-spectrum antibiotics in an attempt to convert a contaminated field into a clean surgical wound. Non-reactive sutures of polyglycolic acid (Dexon/Vicryl) and nylon are used to avoid an undesirable stitch reaction or stitch abscess.

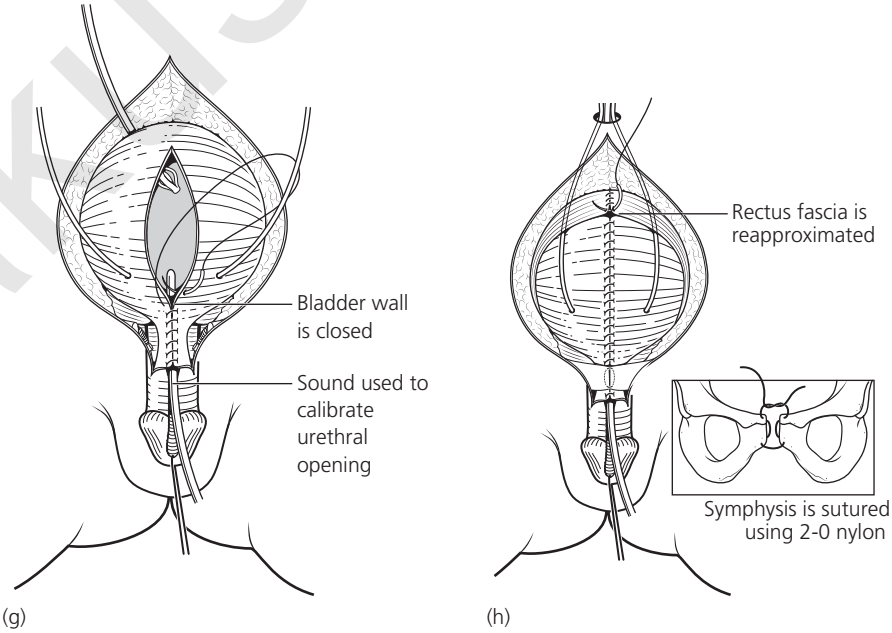

Figure 73.5 *Continued*

Combined bladder closure and epispadias repair

The modern staged closure of bladder exstrophy has yielded consistently good cosmetic and functional results, and the utilization of osteotomy has improved the potential for successful initial closure and later continence. In an effort to decrease costs, the morbidity associated with multiple operative procedures, and possibly to effect continence, there is current interest in performing single-stage reconstruction or combining procedures in appropriately selected patients. This technique was first described by Lattimer and Smith[1] for primary closures and Gearhart and Jeffs[25] in 1991 for failed exstrophy closures. Grady and Mitchell[26] have renewed interest in its use in newborn patients and results have now been reported in groups of boys undergoing single-stage reconstruction (bladder closure and epispadias repair) in infancy.

The complete primary repair of bladder exstrophy is now being performed in neonates at several centers worldwide. The basics steps of the procedure have been outlined by Grady and Mitchell.[26] The initial dissection begins superiorly and is carried inferiorly to isolate the bladder template. This is carried down in a continuous fashion to then begin the penile dissection ventrally. The penile dissection will progress medially with care being taken to preserve the urethral plate for later tubularization. As previously described by Mitchell and Bagli,[27] the penis will be completely dissembled into individual corporal bodies and urethral plate with supporting spongiosum tissue. Deep proximal dissection is undertaken to free the vesco-urethral unit from the intersymphyseal ligaments to provide deep placement of the unit into the pelvis. Once the dissection is complete, the bladder is closed, the penis is reassembled anatomically with a hypospadiac urethra and the abdominal wall and skin closure is completed.[26]

Long-term results of 39 children have been published that show in experienced hands, this procedure produces comparable success rates.[28] Of children aged four years or older who underwent complete primary repair, 74% are continent in daytime with volitional voiding. Importantly, only 20% of boys and 43% of girls achieved primary urinary continence without the need for bladder neck reconstruction. Complication rates were comparable at 18%, with five urethrocutaneous fistulae and two patients with fascial dehiscence. However, there are published reports of significant complications from the complete primary repair. At least two cases of complete loss of a corpora and hemiglans have been reported, as well as several cases of prolapse and dehiscence.[29]

In the authors' opinion, this technique should be limited to boys of older age (older than six months of age) because recent experimental evidence indicates that newborn exstrophy bladders differ from bladders in older infants in the level of maturity of the muscle and connective tissue components. The senior author believes that these patients should be carefully selected, especially newborns, because of the reasons given earlier. Otherwise, boys presenting after failed initial closure and/or older than six months of age, may be candidates for a combination of epispadias repair with bladder closure. Children should be carefully selected based on phallic size, length, and depth of the urethral groove, size of the bladder template, and perivesical and urethral plate scarring in children who have undergone a previous failed closure.

CONCLUSION

The modern staged approach to treatment in patients with bladder exstrophy is able to provide a satisfactory outcome both cosmetically and functionally in most cases. This approach consists of: (1) initial bladder closure, (2) repair of epispadias, and (3) bladder neck reconstruction. Bladder neck reconstruction is the recommended management based on the authors' and institutional experience with over 941 cases of the exstrophy–epispadias complex. Recent reports of a single-stage repair by other authors have proposed successful outcomes, however follow up is limited and numbers of patients in these series is small. In the modern staged repair, the continence rate for males with exstrophy voiding per urethra is 80.6%, with 70% dry around the clock and 10.6% dry during the day, but damp at night.[30] In females, 74% were voiding per urethra and continent 24 hours a day with an additional 10% being continent during the day while wet at night.[31] While recent developments in tissue engineering hold promise to improve outcomes for patients requiring genitourinary reconstruction in the future, staged functional closure remains the gold standard for patients with class bladder exstrophy at the turn of the millennium.

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Cloacal exstrophy

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INTRODUCTION

Cloacal exstrophy is the most severe anomaly in the exstrophy–epispadias spectrum. It is a rare and complex malformation that affects between one in 200 000 and one in 400 000 live births, with a male to female ratio of 1:2.[1] Despite its complexity, survival is expected, with nearly 100% of patients now surviving. Management has become focused on patient outcomes and the achievement of an optimal quality of life. This has been born out in the last three decades where the shift for improving the quality of life has included appropriate gender assignment, urinary and fecal social continence independent from stoma appliances, improved physical and social independence, and mobility.[2–5]

HISTORY

Cloacal exstrophy, also known as vesico-intestinal fissure, ileovesical fistula, or extrophia splanchnica, was first described by Littre in 1709 and again by Meckel in 1812.[1] The era of operative correction began with Rickham's 1960 report of a three-stage procedure performed over eight months.[6] Although only 17 of 34 patients survived correction during the years 1968–76, survival of 13 of 15 patients at a single institution was reported in the early 1980s;[1] and since that time, survival has ranged from 90 to 100% in a variety of reported series.[3–5]

Today, survival from cloacal exstrophy is nearly universal, mortality being a product of associated renal or cardiac disease and occasionally secondary to short bowel syndrome. The focus of care has now shifted to urinary, gastrointestinal, and genital reconstruction, designed to render the patient appliance-free. Considerable attention is now paid to appropriate gender assignment.

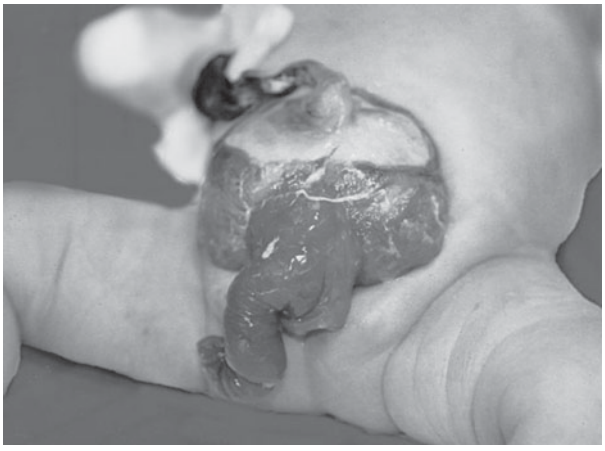
EMBRYOGENESIS

The classic description of cloacal exstrophy is that it results from incomplete coverage of the infra-umbilical wall by the secondary mesoderm of the primitive streak, resulting in a 'rupture' of the midline structures during the 5th embryonic week.[7] Were this developmental defect to occur after fusion of the genital tubercles in the 7th week, bladder exstrophy would result. If, however, the rupture occurs before the 5th week, the genital tubercles will have not fused and the urorectal septum will have not descended to separate the future bladder from the future large bowel. The result is a large midline defect with exposure of both bowel and bladder elements and separation of the genitalia. Furthermore, the absence of the urorectal septum may cause a marked retardation in the development of the colon, resulting in the blind-ending, foreshortened distal hind gut typically seen in these patients.

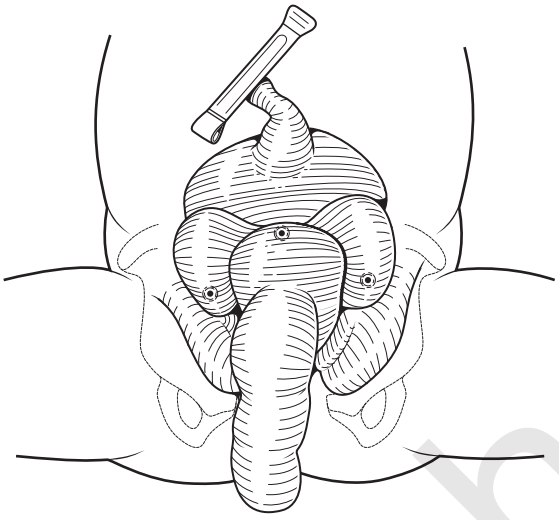
However, challenge to this classic explanation has occurred from three fronts: studies in twins,[8] the diagnosis of cloacal exstrophy in the fetus,[9] and the development of a chick model that simulates this anomaly.[10] Twin studies include reports in which cloacal exstrophy was present in one of two monozygotic twins, while the twin sibling was normal. This same finding has occurred in a set of conjoined twins. In two additional reports of the fetal diagnosis of cloacal exstrophy, rupture of the cloacal membrane occurred as late as 18–24 weeks and 22–26 weeks, a contrasting observation that may account for the broad scope of anatomic variations seen in this anomaly.[9,11] The chick studies suggest a role for space occupation by the swollen dorsal aorta that produces a widening of pelvic structures and a secondary stretching or thinning of the infra-umbilical abdominal wall before eventual rupture.[12]

SPECTRUM OF ANATOMIC VARIABILITY

Cloacal exstrophy is the most severe form of abdominal wall defect (Fig. 74.1). An omphalocele of variable size is present. Inferior to the omphalocele is a complex midline lesion with exposed mucosal surfaces. Laterally are the right and left hemi-bladders, and typically a ureteral orifice is present and identifiable in the lower portion of each, and the rudimentary



(a)



(b)

Figure 74.1 (a) A patient with cloacal exstrophy and (b) a diagram depicting the component parts of the deformity: a prolapsing terminal ileum (elephant trunk deformity), a cephalad membrane-covered omphalocele, two separated bladder halves, orifices depicting an appendiceal lumen and two ureteral orifices. It can also be observed that the pubic rami are separated and along their superior margin can be seen bifid corporal bodies.

trigone can often be seen. The central mucosal plate is composed of intestinal epithelium and represents an open ileocecal plate. Up to five orifices may be present on this surface. The most superior orifice belongs to the terminal ileum, which may be prolapsed as an 'elephant trunk' deformity. In the middle of the bowel plate is one or two orifices, representing the single or duplicated appendix. Finally, the most inferior orifice, which may also be single or duplicated, represents the distal colon or hind gut, and it is almost always of shortened length and ends blindly.

Genital abnormalities are usually present. For male infants, testes are often undescended and located intra-abdominally and an inguinal hernia is frequently seen. The penis is bifid with one corporal body each laterally positioned on the separated pubic rami, the urethra is epispadic, and the vas deferens may be normal, absent, or duplicated. In the female, the clitoris is bifid and separated or it may be absent, the vagina is typically duplex, although it too could be exstrophied or even absent, and the uterus is bicornuate in type.

The pelvis is also affected with the pubic symphysis widely separated and the hips are externally rotated and somewhat abducted. Additionally, within the anatomic spectrum, between 30 and 75% of patients also present with an associated spina bifida.[13]

PREOPERATIVE MANAGEMENT

Associated anomalies

Anomalies of organ systems remote from the basic cloacal exstrophy defect are common, occurring in as many as 85% of cases.[14,15]

Genitourinary anomalies

Abnormalities include the upper urinary tract (42–60%): hydronephrosis, hydroureter, ureteral atresia, ureteral duplication, pelvic kidney, renal agenesis, multicystic kidney, and crossed fused renal ectopia. These anomalies are often associated with, or can lead to, renal function impairment.

Frequently, in boys, the testicles are undescended and there are known vasal anomalies with the vas being normal, absent, or duplicated. In girls, there is frequently duplication of the whole or all of the internal genitalia, and in postpubertal girls there is an association of ovarian cysts, and secondary severe pelvic pain or urinary obstruction has been reported.[16]

Gastrointestinal anomalies

Associated gastrointestinal anomalies include malrotation, duodenal atresia, Meckel's diverticulum, and intestinal duplications.[17,18] Congenital short bowel syndrome has been noted in nearly 25% of patients; therefore, ileal as well as colon preservation is a very important strategy for long-term intestinal rehabilitation.[17]

Spinal–orthopedic anomalies

Vertebral anomalies occur in 48–75% of cases, with myelodysplasia syndromes present in 30–75%.[15] The tethered cord anomaly must also be excluded. Associated orthopedic anomalies (26–30%) include club foot, congenital dislocation of the hips, and other potentially severe deformities.[13]

Cardiac anomalies

Cardiac anomalies are frequently seen in patients with cloacal exstrophy and need to be evaluated with an echocardiogram

prior to surgical reconstruction. Cardiac anomalies are a common cause of death in these patients.[19]

Prenatal diagnosis

Prenatal ultrasound has become commonplace for the diagnosis of cloacal exstrophy. Major diagnostic criteria include the following: non-visualization of the bladder, a large midline infra-umbilical anterior abdominal wall defect or cystic abdominal wall structure, the protruding proboscis (ileum), an omphalocele, or myelomeningocele.[20] Less frequently defined minor criteria include lower extremity defects, renal anomalies, ascites, widened pubic arches, a narrow thorax, hydrocephalus, and a single umbilical artery. This diagnostic prepartum information allows appropriate education of the parents, planning for the pregnancy, timing, and location of the delivery, as well as optimal newborn management, preferably in a center experienced in the multidisciplinary medical and surgical care of this complex anomaly.

Postnatal management

At birth, immediate management is stabilization of the baby, protection of the exposed omphalocele, bladder, and bowel, and if present, protection of the myelomeningocele. After a screening physical examination, baseline laboratory studies include an evaluation of renal function and serum electrolytes (although initially this will be a more accurate indicator of the mother's renal function), as well as chromosomes and blood to assist in future cross-matching. An ultrasound of the genitourinary tract and spine along with chest/abdominal radiographs is done to complete the initial screening for associated anomalies. A cardiac echo is also recommended. Normal body temperature is maintained either by covering the exposed mucosa and membranes with a plastic wrap, or by enclosing the lower half of the torso in a plastic saline-containing bag warmed to ideal body temperature. A prenatal or postnatal chromosome study would be useful in determining the genetic sex of the baby.

At this time, it is imperative to assemble the team of pediatric surgeon and urologist, and if other organ system involvement has been identified, e.g. myelomeningocele, the appropriate additional consultants.[3,4,20,21] It is also prudent to add an endocrinologist to the evaluative team, as well as a psychiatrist/psychologist versed in gender assignment issues.[22] At that time, a team meeting with the family, if not done prenatally, must be arranged, and the magnitude of the problems and their potential solutions discussed. It is then important to prioritize and define a step-wise management plan that defines all of the issues, including gender (Table 74.1). All parties should be in agreement with the plan.

This complex anomaly requires the combined efforts of both pediatric surgeon and pediatric urologist. The team leader must also coordinate input from a variety of ancillary personnel, including a stoma therapist, physical therapist, social worker, psychiatrist or psychologist, and endocrinologist. A neurosurgeon or orthopedic surgeon may also need to be involved if indicated.

Table 74.1 Step-wise management plan for cloacal exstrophy.

Management phase	Patient age	Therapeutic procedures
Phase 1	Newborn	Meningocele coverage Closure/coverage of omphalocele Separation of bowel/bladder plates Ileal reconstruction End colostomy Hemi-bladder approximation/closure Pubic bone approximation
Phase 2	1–6 months	Feeding access Manage short bowel syndrome
Phase 3	6 months–2 years	Bladder closure if not done Phase 1: Iliac osteotomy First-stage genital reconstruction Tethered cord release Midline sagittal anorectoplasty
Phase 4	2–8 years	Bladder augmentation Construction of catheterizable urinary reservoir Second-stage genital reconstruction/gender decision
Phase 5	5–18 years	Completion of genital reconstruction Exogenous hormone therapy

Gender assignment

Gender assignment is frequently a complex and controversial decision. In 46,XX patients there is no debate, since all of these children should be raised as females. The problem occurs in 46,XY patients. When the phallic structures are of adequate length, and clearly this is a subjective data point, then most pediatric urologists would recommend that the child be raised as male; however, when the phallic structures are very diminutive, the decision is more difficult. Historically, the majority of these children were gender reassigned and raised as female. However, with increasing evidence of the potential of testosterone imprinting of the brain and the more frequent use of free flap phallic reconstruction, the contemporary trend is to raise these children as males, a strategy agreed to by two-thirds of polled pediatric urologists. If, however, it is decided to change the sex of rearing to female, then most surgeons would advocate early gonadectomy prior to the infant testosterone surge to minimize further brain imprinting.[23]

This decision involves many complex problems that include fertility, psychological, sexual ability, and gender-specific problems. Consequently, it is important that this

decision is made as part of a multidisciplinary team with significant family input.

OPERATIVE MANAGEMENT

The sequence

The successful therapy of this complex anomaly requires an orderly approach of both sequential and simultaneous steps.[13,14] If a myelomeningocele is present, it must first be covered, and attention to a possible tethered cord can be delayed. The next focus is a multistep procedure that includes coverage/closure of the omphalocele, take-down of the exposed ileal plate and exstrophied hemi-bladders, establishment of gastrointestinal continuity by tubularizing the bowel plate and salvaging all of the small and large bowel length, including the appendices, and creation of an end-colostomy that should exit the left upper abdomen. The hemi-bladders are connected in the posterior midline, and if possible tubularized into a reservoir. The separated pubic rami are approximated in the midline, a maneuver that facilitates both omphalocele closure, as well as bladder closure. The gonads and external genitalia are often addressed as the final step or at a subsequent procedure. Attention to the undescended and typically intra-abdominal testes can also be delayed until a time of further reconstruction. The subsequent phases of therapy are individualized and planned in a discussion with the family led by the care team.

STEP 1. OMPHALOCELE CLOSURE

In cases with a huge omphalocele, it is practical to consider leaving the intact membrane in place as a barrier for a potential staged closure. However, since in dissecting out the exstrophied bladder and bowel the peritoneal cavity will be entered, the usual approach is to open the abdomen extending the incision vertically with removal of the omphalocele membrane. This will facilitate eventual primary fascial closure of the omphalocele, aided by approximation of the pubic rami. This same exposure is optimal for staged closure techniques, including the application of a prosthetic silo. Newer approaches to abdominal wall coverage and closure include application of an expanded thoraco-epigastric myocutaneous flap or application of an absorbable matrix on which a mobilized skin flap can be laid.

STEP 2. BOWEL RECONSTRUCTION

The central bowel plate is then separated from the two lateral hemi-bladders. Intestinal reconstruction including the blind-ending colon segment should emphasize bowel conservation. The exstrophied ileocecal junction should be tubularized to restore continuity of the ileocolonic lumen. Appendices, single or duplicated, should always be considered as potential catheterizable conduits for achieving urinary dryness and thus should not be sacrificed. Similarly, duplicated colon segments, even though blind ending, can be used as interposed properistaltic and anti-peristaltic colon conduits to potentially prolong intestinal transit time. This is especially beneficial in the usual circumstance of a foreshortened colonic length or in the unusual circumstance of a concomitant limited small bowel length. An extra colon may also prove to be useful in urinary conduit reconstruction later in the child's life, and for these reasons it should never be sacrificed. After mobilizing the blind-ending colon, the tubularized bowel must then be exited as an end colostomy. The placement of this fecal stream stoma will optimally be exited more lateral and more cephalad than is usual, especially if a prosthetic pouch is used to close the omphalocele.

STEP 3. BLADDER RECONSTRUCTION

The free hemi-bladders are then reapproximated into a single midline posterior bladder wall plate by suture technique, taking care to identify and protect the ureteral orifices. If sufficient bladder surface exists from which to construct an adequate capacity reservoir, then the bladder is also closed anteriorly, forming a closed bladder. The tubularized bladder is then positioned behind the approximated pubic rami. The bladder neck and/or the reconstructed rudimentary urethra will drain inferiorly onto the perineum.

Primary abdominal closure is possible in most patients. Such primary closure can be performed most easily in the first 48 hours of life, with the benefit of circulating 'relaxin' and permanent high-tensile strength suture material placed into either end of the separated pubis. However, if the abdomen is too tight to allow for complete primary closure, a number of options is available. If the skin is sufficient but the muscle wall will not close then a material (mesh, durabond) can be inserted between the two recti to allow abdominal closure and the skin is then closed over the top. If the skin cannot be closed, then two options may be considered. First, close the bladder and bowel and then place a silo. This has the advantage that closure can be performed slowly in the neonatal intensive care unit as the abdominal cavity enlarges, but it also raises concerns about the fecal stream contaminating the silo. The second option is to approximate the bladder only posteriorly and then use the bladder plate to create a bladder exstrophy, hence using the plate to provide extra-abdominal space. The main problem with this is that it can cause damage to the bladder mucosa and it will require a significant later operation.

STEP 4. GENITAL RECONSTRUCTION

For genetic XY babies with a microphallus or a bifid phallus, gender conversion would previously have been accomplished at the neonatal procedure by assigning a female phenotype. However, current practice would not proceed to that decision until exploration of the options had occurred with a team that would include a urologist, endocrinologist, psychologist, and the baby's parents.[24–26] The discussion would include the role of prenatal as well as pubertal genetic male imprinting, as well as the options for phallic reconstruction that even might include total replacement phalloplasty.[27,28] Corporal and glandular tissue should always be preserved for eventual reconstruction, and the separated hemi-scrota should be

preserved and reapproximated in the midline. Completion orchiopexy should be delayed until a definitive gender decision is made. Vaginal reconstruction should be deferred to a later age for genetic XX babies to permit full evaluation and correction of double systems, potential vaginal atresia, or potential vaginal exstrophy, the latter located caudal to the exstrophied bladder mucosa. This will also allow an informed decision to be made about which tissue might best be used to augment any deficiency in vaginal tissue.[29,30]

POSTOPERATIVE CARE

Postoperatively, the patient should receive fluid and electrolyte management which takes into account a potentially diminished renal reserve. Many methods are available to minimize tension at the closure by preventing lower extremity movement that include: maintaining muscle relaxation and having the baby ventilated for a number of days; placement of a circumferential wrap that encircles the lower extremities from ankles to mid-abdomen to 'strap' together the upper thighs, minimizing pelvic tension and possible distraction of the closed pubic rami;[31] suspension in a modified Bryant's traction can also be done; and in some centers modified Salter osteotomies are performed to help with pelvic closure.[32] Staged closure of the omphalocele should follow in those cases with an applied prosthetic silo. The fecal and urinary stream should be isolated, either by temporary bladder or ureteral catheters or by permitting free drainage of urine onto the bladder exstrophied plate. An appliance should cover the colostomy.

After completion of the newborn repair, the associated anomalies should be prioritized and addressed. Orthopedic assessment of extremity, pelvis, and spinal deformities is necessary, and a long-range treatment plan should be outlined. If the pelvis was not primarily reapproximated, the eventual plan for pelvic osteotomy can be made so that at the time of reoperation, pelvic closure becomes a reality.[32]

LONG-TERM MANAGEMENT

Gender assignment/genital reconstruction

Although there is a genetic male predominance in cloacal exstrophy, the commonly found inadequate corporal structures associated with a bifid penis make adequate penile reconstruction difficult. Historically, therefore, most such patients underwent a female gender assignment. Despite their genetic sex, they were reared as a girl, and an eventual reconstructive operation was designed to develop phenotypic female anatomy complemented by female hormonal replacement.[3,23] However, in recent years, there has been a call to re-examine genotypically congruent sex assignment, even in those newborns with an inadequate phallus, both because of a high frequency of sexual dysfunction in gender-converted children and adolescents, as well as a realization of the potential for penile reconstruction.[23,29,33,34] Certainly, genetic males with adequate bilateral or even unilateral phallic structures should receive a male gender assignment. In any case where gender reassignment or conversion is considered, there is a considerable need for parental counseling, endocrinology input, and input on a longitudinal basis from a trained psychiatrist/psychologist for both the parents and child. All corporal and scrotal/labial tissue needs to be preserved. The corporal tissue, typically bifid, becomes critical whether reconstructing a penile shaft or a clitoris. In the phenotypic male, penile reconstruction and orchidopexy will be the two steps of significance, and they can be delayed beyond the neonatal period. In genotypic males with cloacal exstrophy, the testes are often located intra-abdominally. If a genotypic congruent sex assignment is maintained, orchidopexy will be needed. Fortunately as a group, the testes, despite their location, retain near-normal histology. In contrast, when gender conversion to the female phenotype is considered, orchiectomy should be performed early to prevent further masculinization of the brain. Penile reconstruction will likely need to be deferred to an older age if the bifid phalli are inadequate for simple reapproximation.

In genetic females, the bifid clitoris and labia are initially preserved and reapproximated in the midline. As the child grows, staged operations are used to create an adequate appearance. Failure of midline fusion, a key characteristic of cloacal exstrophy, is frequently manifested in the female reproductive system by duplication of the vagina, uterus, and Fallopian tubes. Atresia and exstrophy of the vagina are also possible. The latter is difficult to distinguish in the newborn period, due to the large exstrophic bladder above or anterior to the exposed vaginal tissue. However, diagnosis of this entity is important in planning the eventual staged vaginal reconstruction. An atretic vagina will require reconstruction with a combination of perineal skin flaps and a small or large bowel pull-through. Increasingly, a buccal mucosa free graft is instead being done (Baker L, personal communication).[30] An intact vagina may contain a septum or be duplicated, and it is most prudent to resect the more rudimentary of the two, attaching the remaining uterus to the vaginal vault. Other than the propensity for cyst formation, the ovaries should be normal.[16]

Continence and stomas

The goal for most children with cloacal exstrophy is a stoma-free existence. At a delayed interval, we prefer to use pelvic magnetic resonance imaging or computer tomographic imaging, coupled with electrical stimulation of the perineum, to define the presence of an anorectal pelvic muscle complex. If such muscle is present, a midline sagittal anorectoplasty is feasible in selected patients who also have an adequate small and large bowel length and sacral spinal structures for establishing a continent anorectum. Others have advocated a primary rectal pull-through procedure performed in the newborn period following the anterior approach used for abdominal wall reconstruction. Although anorectal reconstruction is an attractive and preferred outcome, those children amenable to this plan who also have a good outcome are few.[3,4,17] As a result, either a permanent colostomy or a colostomy or pull-through aided by an antegrade continent enterostomy (ACE) procedure may be preferred.[35] More

recently, a catheterizable continent stoma system has been described that may remove the need for a stoma appliance.[36]

Urinary 'dryness' is frequently accomplished utilizing the principle of a catheterizable stoma in a urinary reservoir. Using a 'continent nipple valve' of the Mitrofanoff principle with an appendix or a tubularized portion of small bowel, a catheterizable conduit is attached to the reservoir. The reservoir itself could be bowel or bladder augmented with stomach, small or large bowel. These procedures are typically deferred until the child has grown out of infancy.[21,22]

PATIENT OUTCOMES

With the progressively improving survival of cloacal exstrophy patients, attention has shifted to optimizing bowel, bladder, and sexual function. Historically, these children were at best committed to a chronic bowel as well as a chronic urinary stoma, and when that was coupled with a degree of genital ambiguity, short-bowel syndrome, or spinal dysraphism, the quality of life was best described as unfortunate. What has now been realized is that the majority of such children have a preserved intellect, and also an anatomy that lends itself to imaginative but real 'continent' outcomes.

A bowel pull-through procedure is feasible in selected patients, and only in the face of an absent gluteal cleft, poor response of muscle to perineal stimulation, severe sacral deformity, a lipomeningocele, or a 'rocker-bottom' should a permanent bowel stoma be considered. The remainder of the patients can undergo a pull-through procedure, and if a degree of incontinence exists, a bowel management program or application of the ACE procedure will be an adjunct.[4,35] The most challenging of the group are those children who also have a short small bowel, and in that circumstance various nutritional, pharmacologic, and operative manipulations may be in order.[17] In one series of 26 patients with cloacal exstrophy, four had colon duplication, one a duodenal web, and one had malrotation. Of six patients with short bowel syndrome, five were eventually weaned from parenteral nutrition. Interestingly, two of the four patients who underwent abdominal–perineal colon pull-through were continent of stool.[16] In another series of 22 patients, ten had an ileostomy, seven a colostomy, three were stoma free, and two had died. In this series, an association of spinal dysraphism increased intestinal morbidity, and the presence of an ileostomy, as opposed to a colostomy, increased dependence on parenteral nutrition and its inherent morbidity.[16] In a third series of 50 patients, 25 had a colon pull-through, and of these, four were failures, two were continent, and 19 were managed by a colon wash-out regimen.[3]

The reconstructed urinary reservoir is typically of small volume and it is non-dynamic. Bladder augmentation has been a process in evolution and includes the use of stomach, large and small bowel, or a potential combination thereof, that include ileal urinary conduits. To enhance bladder continence mechanisms, the bladder neck can be tightened, a bowel nipple valve can be added, bladder neck bulking agents can be injected, and these changes coupled with intermittent catheterization can render the majority of patients dry.[3,5] A catheterizable conduit attached to the urinary reservoir has also been proven to be effective. Spontaneous voluntarily controlled perineal voiding is currently an unrealistic outcome expectation. The magnitude of urinary reconstruction is indicated in one series of 50 patients, where 21 had narrowing of the bladder neck, 7 had a bowel nipple constructed, 12 a Mitrofanoff procedure, 4 a ureterostomy, and 35 had a bladder augmentation. Dryness was achieved 75% of the time.[3]

The outcomes from genital reconstruction in females are satisfactory, but the ability of a bifid uterus and reconstructed vagina to permit fertility has, as of yet, not been reported.[23,29] The greater controversy arises in a genetic male who has a penile reconstruction. Since the testes, even if located intra-abdominally, appear to be histologically normal, fertility may be preserved; however, to date, a fertile male has also not been reported.[23] More than 30% of males have a diminutive or absent penis. If an inadequate phallus is the result of a series of failed operative reconstructions, reported emotional disasters are common. More controversial yet are those genetic males who have undergone reassignment to the female phenotype. Acting-out male behavior imprinted genetically or hormonally has been witnessed. At adolescence, such 'phenotypically assigned females' have declared their 'maleness' and have emotionally struggled with their sexual identity. This has been reported to be improved if the testicles are removed early in the first year of life to prevent further masculinization.[23] In one assessment of quality of life, child behavior, and social cognition, no difference was reported for the gender-ambiguous children who underwent a gender reassignment when they were compared to the control exstrophied group who had no gender issue.[37] However, in another series of 29 genetic males with cloacal exstrophy reassigned to the female phenotype, all patients in adolescence had declared themselves male.[26]

Although staged management has the inherent difficulty of multiple operative procedures, the expectations for an excellent outcome should remain high. Many of these children can be rehabilitated to have a meaningful and functional quality of life through a careful, individualized, staged reconstruction accomplished by a team experienced in the care of this complex anomaly.

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75

Prune belly syndrome

PREM PURI AND HIDESHI MIYAKITA

INTRODUCTION

Prune belly syndrome is characterized by a triad of abnormalities, including an absence or deficiency of abdominal wall musculature, cryptorchism, and anomalies of the urinary tract. The characteristic deficiency of the abdominal wall musculature was first described by Frohlich in 1839.[1] Parker first reported the association of the genitourinary anomalies with the deficient abdominal musculature.[2] The term 'prune belly syndrome' was coined for this complex by Osler in 1901.[3] In 1950, Eagle and Barrett further defined the triad of absent abdominal wall musculature, undescended testes, and urinary tract abnormalities.[4] The incidence of prune belly syndrome is estimated to be one in 29 000 to one in 50 000 live births.[5–13] This syndrome occurs almost exclusively in boys.[13] It is very rare in females;[13] only 5% of cases described in the world literature have been reported to occur in females.[4–6,14]

ETIOLOGY

The pathogenesis of prune belly syndrome remains controversial and many theories have been proposed to explain it.[3,4] One theory proposes that prenatal obstruction or dysfunction of the urinary tract causes urinary tract dilatation, fetal abdominal distension, and subsequent muscle wall hypoplasia and cryptorchism in males.[5,6,15–17] An embryological theory proposes that failure of primary mesodermal differentiation leads to defective muscularization of both the abdominal wall and the urinary tract.[6,15–17] Although both theories explain some elements of the syndrome, they fail to explain others. Reinberg *et al.*[18] recently suggested that the two theories should be regarded as complementary mechanisms, both operating in any given case. They theorized that teratogenic agents produce abnormal development of derivatives of the lateral plate mesoderm and abnormal epithelial–mesenchymal interactions, resulting in abnormal organ development and mechanical or functional obstruction of the urinary tract. Recently, Stephens and Gupta proposed a theory of abnormal development of the intermediate mesoderm as a key factor in the pathogenesis of prune belly syndrome.[5,19] This theory has two features: the first is that the terminal part of the Wolffian duct is incorporated into both the prostatic and membranous urethra, and the second is that during incorporation, the ducts including their ureteric buds overexpand. Abnormal ectasia of the terminal Wolffian duct occurring between 6 and 10 weeks' gestation may produce saccular dilatation of the prostatic urethra, prostatic hypoplasia, and the valve-like obstruction in the membranous urethra. The ectasia could explain the attenuated bladder trigone and laterally placed wide ureteric orifices. Involvement of ureteric buds may also produce irregular megaureters. Renal dysplasia can be explained as a result of primary dysplasia of the metanephros or secondary to ureteric ectopia.

A single-gene abnormality or chromosomal defect has been suggested as the cause of this syndrome. There is an especially high incidence of prune belly syndrome associated with trisomy 21,[20] trisomy 13,[21,22] and trisomy 18.[23,24] Ramasamy *et al.*[25] reviewed 11 cases of familial prune belly syndrome and suggested a sex-influenced autosomal recessive mode of inheritance. Reports of prune belly syndrome in siblings and cousins, and reports of the syndrome associated with the 45X0 karyotype of Turner syndrome, support this proposal.

PATHOLOGY

Abdominal wall

Prune belly syndrome represents a spectrum of disease severity, ranging from those that die within the first few days of life to those that survive with relatively stable renal function in childhood. The most obvious defect in newborns with the syndrome is the shriveled prune-like appearance of the abdominal wall due to a deficiency in the abdominal wall musculature (Fig. 75.1). The affected muscles in decreasing order of frequency are the transversus abdominus, rectus abdominus below the umbilicus, and internal oblique,

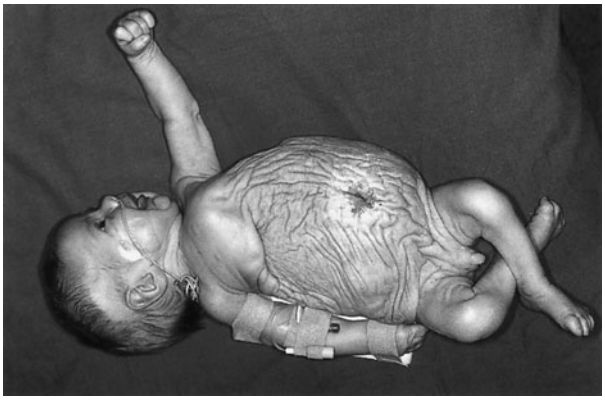

Figure 75.1 A newborn with typical features of prune belly syndrome. Note the shriveled prune-like appearance of the abdominal wall and patent urachus.

external oblique, and rectus abdominus above the umbilicus.[26–28] Biopsy from the abdominal musculature shows that major functioning or recoverable muscle exists in the lateral and upper sector of the abdomen, but that little or no muscle exists in the lower central abdomen.[29] Light microscopy shows a thin mass of muscle tissue with an irregular pattern of fatty infiltration interdigitated with the muscle. Electron microscopy shows a loss of coherence and internal orientation.[30] Z-bands are shattered and disarranged, and glycogen granules are clumped in various areas. The abdominal wall defect may result in chronic constipation and respiratory infection. In addition, this defect increases the risk of postoperative pulmonary complications in patients who undergo general anesthesia. It is also impossible for the patient with a complete manifestation of the triad syndrome to raise himself from the supine position to the sitting position without using the arms or rolling over and pushing up. However, the defect itself does not have prognostic significance.

Urinary tract

Abnormalities of the urinary tract are the major factors affecting the prognosis of patients with prune belly syndrome. Patients are at high risk for developing renal failure in infancy and childhood. As many as 30% of patients, typically those with impaired renal function at initial evaluation, develop chronic renal failure in childhood or adolescence.[6]

Kidney

The kidney in prune belly syndrome has many ranges of disorders from total agenesis (rare) or dysplasia, to no significant aberration.[6,31–38] Patients who have severe renal dysplasia usually have severe abnormalities of the bladder and urethra at birth and may even have another malformation, such as imperforate anus.[39] The degree of renal dysplasia or hydronephrosis does not appear to be related to the degree of abdominal wall deficiency.

Ureter

The ureters are characteristically markedly elongated, dilated, and tortuous. This is the most common urinary tract abnormality, and is present in 81% of patients with prune belly syndrome.[32] The lower end of the ureter is more severely affected than the upper one, and there are occasional saccular dilatations of the middle segment. The orifices are usually patent and obstruction is rare. Vesico-ureteral reflux is common and present in up to 85% of patients (Fig. 75.2).[32] The ureteric smooth muscle is replaced by fibrous tissue in the affected areas and there is scarcity of muscle bundles on histologic examination.[33] Ehrlich and Brown[34] studied the structure by electron microscopy and reported a marked decrease in nerve plexuses with irregularity and degeneration of non-myelinated Schwann fibers. These findings are in keeping with the poor peristalsis of the affected ureters.

Figure 75.2 Micturating cystourethrogram showing grade V vesico-ureteral reflux into left dilated tortuous ureter.

Bladder

Bladder abnormalities are common in prune belly syndrome. The typical bladder is large, irregular in shape and thick walled. Although the bladder wall is thickened, trabeculation is rare. Histologically, the intrusion of fibrous tissue between sparse muscle layers is similar to the ureters.[31] Commonly, there is a patent urachus or urachal cyst in prune belly syndrome. The trigone is surprisingly large, with very widely spaced, usually large and abnormal-appearing ureteric orifices which can be expected to reflux.[35] The bladder neck is often wide and ill-defined. Pelvic innervation and bladder ganglion cell distribution has been found to be normal.[6]

Urethra

The prostatic urethra is usually wide and elongated at the bladder neck (Fig. 75.3). It tapers to a narrow point at the level of the urogenital diaphragm, even though most patients do not demonstrate true obstruction at this point.[36] Often there is a posterior urethral diverticulum formed by a large prostatic utricle. The reduced musculature and prostatic hypoplasia cause a 'functional obstruction' to bladder outflow.[37] The membranous and anterior urethra are sometimes atretic or extremely hypoplastic. There are also reports of abnormalities of the penis, including ventral and dorsal chordee, hypospadias and hypoplastic, or absent corpora cavernosa. Other urethral lesions occur with hypospadias, and ventral and dorsal chordee.[36] Ejaculation is possible, but usually is retrograde due to the open bladder neck.

In females, the prune belly syndrome triad consists of lax, aplastic, or hypoplastic abdominal musculature, urinary tract anomalies, and genital anomalies, most commonly bicornuate uterus and vaginal atresia. Six of the seven female cases reported by Reinberg *et al.*[18] had vaginal atresia or uterine duplication and frequently coexisted in the same patient. Other urogenital anomalies include urogenital sinus and ambiguous genitalia.

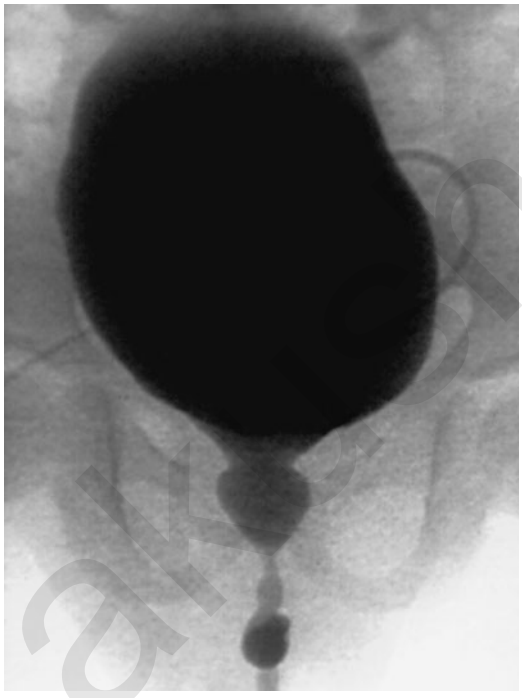

Figure 75.3 Micturating cystourethrogram showing ill-defined bladder neck with enlarged prostatic urethra. No urethral obstruction was demonstrated in the 2-week-old infant.

Testes

Bilateral cryptorchidism is an essential characteristic of prune belly syndrome. The testes may be located anywhere from just inferior to the lower pole of the kidney to near the ureterovesical junction.[31,38] Maldescent of the testes is believed to be related to absence of the abdominal muscles and the gubernaculum. In fetuses with prune belly syndrome, testicular histology revealed reduced spermatogonia and Leydig cell hyperplasia.[40,41] Testicular biopsy samples of infant testes in prune belly syndrome demonstrate atypical germ cells with large nuclei and prominent nucleoli and intense alkaline phosphatase staining localized to the cytoplasmic membrane.[41] The similarity of histological appearance of these testes to those in intratubular germ cell neoplasia suggests that long-term follow up of these patients for the development of invasive germ cell tumors is important. A few cases of malignancy in the testes of patients with prune belly syndrome have been reported.[42–44]

ASSOCIATED ANOMALIES

There is a high incidence of associated anomalies in patients with prune belly syndrome. Non-urological-associated anomalies in patients with prune belly syndrome occur in 65–73% of patients.[6,45–50]

Gastrointestinal anomalies are observed in about 30% of patients. Malrotation of the gut with a single mesentery and the occasional sequelae of volvulus and obstruction is the most common gastrointestinal anomaly. The other gastrointestinal anomalies are gastroschisis and omphalocele, imperforate anus, Hirschsprung's disease, and duodenal atresia.[39,48,49]

Cardiovascular anomalies, such as atrial and ventricular septal defects and tetralogy of Fallot, have been reported in about 10% of cases.[50] Pulmonary anomalies are common, the most severe of which is hypoplasia of the lungs associated with *in utero* oligohydramnios.

Orthopedic problems have frequently been reported in patients with prune belly syndrome.[39] The most common abnormalities are talipes deformities, congenital dislocations of the hip, and compression deformities of the limbs.

Antenatal diagnosis

With improved quality of antenatal scans, major renal tract abnormalities are being diagnosed as early as 13 weeks' gestation.[51] Differentiating between posterior urethral valve and prune belly syndrome could be difficult. Unfortunately, fetal detection of prune belly syndrome has not led to an improved outcome.[52,53] Fetal vesico-amniotic shunts have been used in the hope of preventing renal parenchymal damage in children with enlarged bladder and upper renal tract dilatation.[54–56] However, studies have failed to document a beneficial effect of fetal intervention on subsequent renal function or pulmonary development.

Newborn assessment and investigations

The prune belly appearance of the abdominal wall together with bilateral undescended testes allows easy diagnosis of this condition in a newborn. When antenatal oligohydramnios is

evident, pulmonary complications should be anticipated, and an immediate chest x-ray to exclude pneumothorax and pneumomediastinum is necessary.

Initial creatinine measurements reflect maternal renal function and repetitive sampling is necessary. A serum creatinine >1.0 mg/dL in a term infant or >1.5 mg/dL in a preterm infant after 72 hours indicates poor renal function and poor overall outcome. On the other hand, if initial creatinine is <0.7 mg/dL, then subsequent renal failure is unlikely. Urine should be checked for any infection and antibiotic prophylaxis to prevent urinary tract infection started. Renal ultrasound will provide information regarding kidneys, cortical thickness, renal tract dilatations, and bladder volume and post-micturition residue. A micturating cystourethrogram (MCUG) will provide information regarding vesico-ureteric reflux and rare presence of posterior urethral valve. However, contrast medium should be sparingly used in the presence of poor renal function and impaired glomerular filtration rates to avoid a rapid rise in serum osmolality and subsequent intraventricular hemorrhage. Mercaptoacetyltriglycine (MAG3) and dimercaptosuccinic (DMSA) studies are requested as indicated to assess the differential renal filtration and drainage.

Management

Based on the severity of renal disease, patients with prune belly syndrome could be classified into three groups:[57]

- Group 1 is characterized by oligohydramnios, pulmonary hypoplasia, possible urethral obstruction or patent urachus. These children also have very poor renal function and will usually die in the immediate postnatal period due to pulmonary complications. Aggressive surgical approach in these children should be avoided.
- Group 2 children have mild impairment of renal function and may progress to renal failure. During early infancy, a cutaneous vesicostomy may improve drainage of urine and allow time for definitive reconstructive surgery later. Definitive surgery is better postponed until one year of age.
- Group 3 consists of the majority of children with prune belly syndrome with normal renal function and dilated renal tracts. Surgical intervention is not necessary, as long as the renal function is maintained and no infection is seen. When problems are encountered, a urodynamic study is needed to evaluate bladder emptying and unbalanced voiding. When deterioration is noted, these children should be managed as the children in group 2, with early vesicostomy.

Definitive surgery includes abdominoplasty, bilateral orchidopexies and a suitable antereflux procedure around one year of age. Abdominoplasty for the cosmetic improvement should be performed around one year of age.[58–60] The surgical management strategy of the urinary tract should be tailored to suit individual cases. Surgical options include internal urethrotomy (when obstruction to outflow is evident on urodynamics study), ureteral tailoring and ureteric reimplantations, reduction cystoplasty with concomitant excision of a dilated urachal diverticulum, and/or intermittent catheterization. Approximately 30% of the long-term survivors will develop renal failure as a result of renal dysplasia, recurrent pyelonephritis or obstructive nephropathy. These children go on to have renal transplantation and are reported to have a graft survival rate of 66.7% at five years. However, good bladder emptying must be achieved prior to transplantation to avoid the significant risk of infection in the presence of immunosuppressant therapy.

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Conjoined twins

JUAN A TOVAR

INTRODUCTION

Genetically identical individuals joined by a part of their anatomy and often sharing one or more organs are known as 'conjoined twins'. This event occurs in 1:50 000 to 1:100 000 live births[1] and it is one of the more difficult challenges of pediatric surgery.

Mythologic creatures like two-faced Jano or multiple-headed Hydra were probably inspired by observation of conjoined twins.[2] Although representations of conjoined twins from ancient cultures were relatively frequent, they became popular after the original siamese twins Chang and Eng Bunker were sent to the United States in the nineteenth century for exhibition in a circus.[3] The complexity of the technical problems involved in separations of conjoined twins explains why the first attempts are relatively recent (seventeenth century).[4]

ETIOLOGY

Conjoined twinning is due to incomplete division of a primitive embryonal disk destined to produce identical twins. These are, of course, monozygotic, monochorionic, isosexual, and share the same genome and fingerprints.[5,6] The causes for this incomplete division are unknown but, interestingly, two-thirds of the cases are females. Spencer[7] pointed out in her monography that the twins are always joined by central parts of their anatomies and that they are always homologous in the sense that they never have the head or the lower limbs on opposite sides. This seems to confirm that the mechanism is a missed cleavage of the primitive embryonal disk along the longitudinal axis.

Some ancient experiments in amphibians and a few modern molecular genetic observations suggest that fusion of two originally separated embryos may be the explanation for some rare cases in which there is sex discordance.[8–10]

CLASSIFICATION

The location, extent, and nature of the bridge between both twins varies widely and this complicates description of the anatomy of each set. Several classifications attempt at simplifying description. Conjoined twins were divided into ventrally and dorsally joined and subdivided according to the level of fusion.[7,11] They are divided by taking into account their asymmetric or symmetric nature and the level of the fusion which followed by the suffix 'pagus'.

Asymmetric twins include 'fetus *in fetu*', acardius acephalus, and heteropagus parasitic twins. The description of the first variety of organoid teratomata to the family of conjoined twins is only acceptable when they are 'organoid' and contain a more or less rudimentary spine.[12] Acardius acephalus is a variety of parasitic twin devoid of heart and head that is connected by marginal placental vessels with the healthy twin (the 'autositus') who is in charge of the circulation and nutrition of both.[13] Heteropagus twins are usually attached to the abdominal wall of an anatomically normal autositus twin, without or with exomphalus, as organoid parasitic masses containing various organs and limbs unable to sustain independent circulation by themselves.[14,15]

Symmetric conjoined twins may be joined by the head (craniopagus), the thorax (thoracopagus), the abdomen (omphalopagus), the spine (rachiopagus), or by the caudal pole (ischiopagus and pygopagus). Occasionally, they are laterally fused along the body axis (parapagus).[16,17]

CLINICAL PRESENTATION

Nowadays, most conjoined twins are prenatally diagnosed by ultrasound in the advanced countries preventing serious obstetric problems. Except in thoracopagus with a common heart and in asymmetric twins, both fetal heart tones can be identified as in regular twins. The heads and limbs of

conjoined twins are on the same side ('homologous') in contrast with regular twins which are usually arranged in opposite directions. This allows fetal ultrasonographic diagnosis that leads to detailed ultrasound (US) and/or magnetic resonance imaging (MRI) studies aimed at defining the anatomy of the fusion and the chances of separation.[18,19]

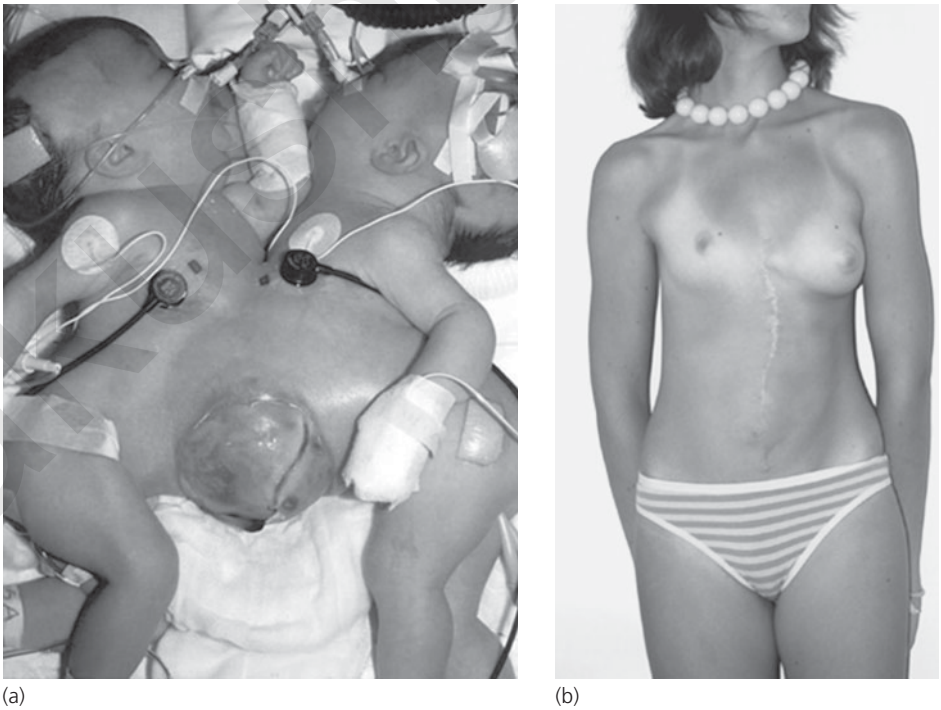
Most sets of twins are delivered by Cesarean section and can be taken care of by interdisciplinary teams from the beginning. In cases delivered vaginally, it is frequent for signs of obstetric trauma to be present at birth: long bone fractures, rupture of exomphalos, etc. The anatomy varies widely according to the modality of joining. Thoracopagi with common hearts have almost constantly severe cardiovascular and arterial anomalies that produce early symptoms and may be rapidly lethal.[20,21] The most frequent forms, omphalopagi and thoracopagi, often have an omphalocele membrane as part of the joining bridge (Figs 76.1 and 76.2). The livers are often fused and the intestines are usually connected or shared. The bladder may be common and sometimes opens at the lower part of the bridge as an exstrophy (Fig. 76.3). In cases joined by the rump (Figs 76.4 and 76.5, pages 690 and 691), the anatomical varieties in terms of gastrointestinal and urogenital openings are multiple.

Serious malformations or trauma suffered by only one of the twins may create difficult clinical situations because crossed circulation creates a single internal environment which is hard to manipulate: the healthier twin can compensate in part for the problems of the diseased one, but the latter may expose the former to disbalances, toxins, or medications.[22]

DIAGNOSIS

A comprehensive understanding of the anatomy of the organs and the distribution of their functions is necessary for planning viable separation strategies. Plain x-rays, gastrointestinal or urogenital tract contrast studies may depict the points of junction and other features of the corresponding organs but, due to the atypical anatomy,[23] incomplete understanding leads to unexpected surprises. Ultrasonography helps at every diagnostic step.[19,24] Angiography, that was widely used in the past for depicting the nature of the blood supply of the shared organs[25] is being replaced by computed tomography (CT) or magnetic resonance angiography.[26] CT angiography is the best way for depicting the vascular arrangement. MRI better depicts the fused neural and meningeal tissues in craniopagus, rachiopagus, ischiopagus, pygopagus, or parapagus.[27] Both CT and MRI are crucial for imaging the anatomy of conjoined hearts.[28] Helical CT reconstruction of the bony junctions may help in preparing strategies of skeletal separation (Figs 76.4 and 76.5, pages 690 and 691).[29] Nuclear imaging may help to define the functional anatomy of the liver, kidney, or other organs.[30]

Hematologic and biochemical studies are often misleading due to cross-circulation. When the vascular channels are large, parabiosis is complete, but when only minor territories are in connection, both twins maintain some internal environmental differences that can be relevant in cases in which blood tests are necessary for diagnosis. Other tests, like electrocardiogram (ECG), are challenging when the hearts are



(a) (b)

Figure 76.1 (a) Set of omphalopagus twins. Severe brain hemorrhage in twin on the right after vaginal delivery prompted neonatal separation. Only the twin on the left survived. Fourteen years later (b), she is a bright, normal girl whose only concern is breast asymmetry.

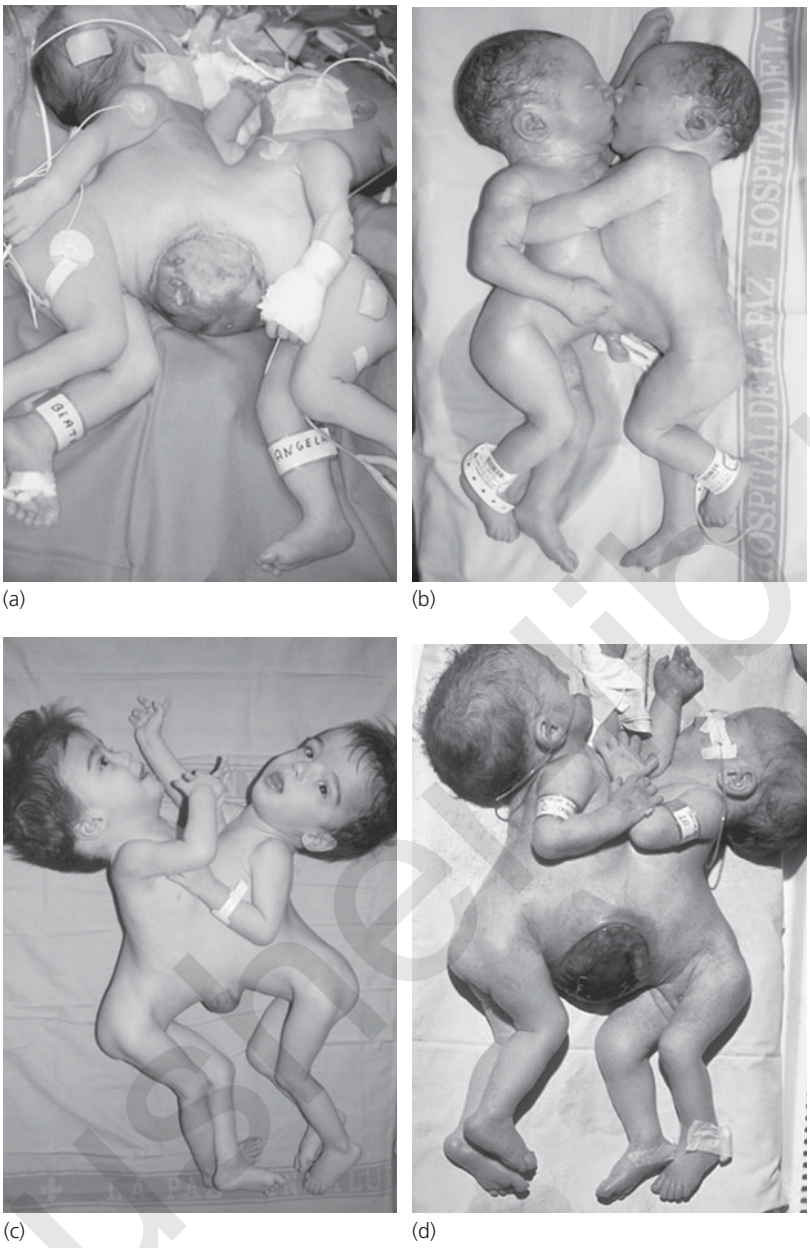


Figure 76.2 Four sets of thoracopagus twins with common hearts. Separation was undertaken only in set shown in panel (a) because they were joined only by a narrow atrial bridge. Unfortunately, the twins did not survive.

connected.[31] Metabolic rate may show considerable differences between twins upon calorimetry.[32]

TREATMENT

Preoperative ethical issues

The principles that regulate the medical profession are particularly difficult to respect in conjoined twins and serious ethical dilemmas are to be expected:[18,33,34]

- **Autonomy**. The principle of autonomy (the decisions of the patient should be respected), is usually exerted by proxy by the parents in children, and this may be a source of conflicts among them or with doctors or the courts if unanimous decisions are not agreed upon.
- **Justice**. The principle of justice (similar chances for both patients) is obviously at risk when it comes to separation that may involve mutilation or sharing of organs.
- **Beneficence and non-maleficence**. The principles of beneficence and non-maleficence (the benefit of the patients should be sought and no harm should be inflicted to them), that are considered as the ethical backbone of the medical decision-making process, are also difficult to

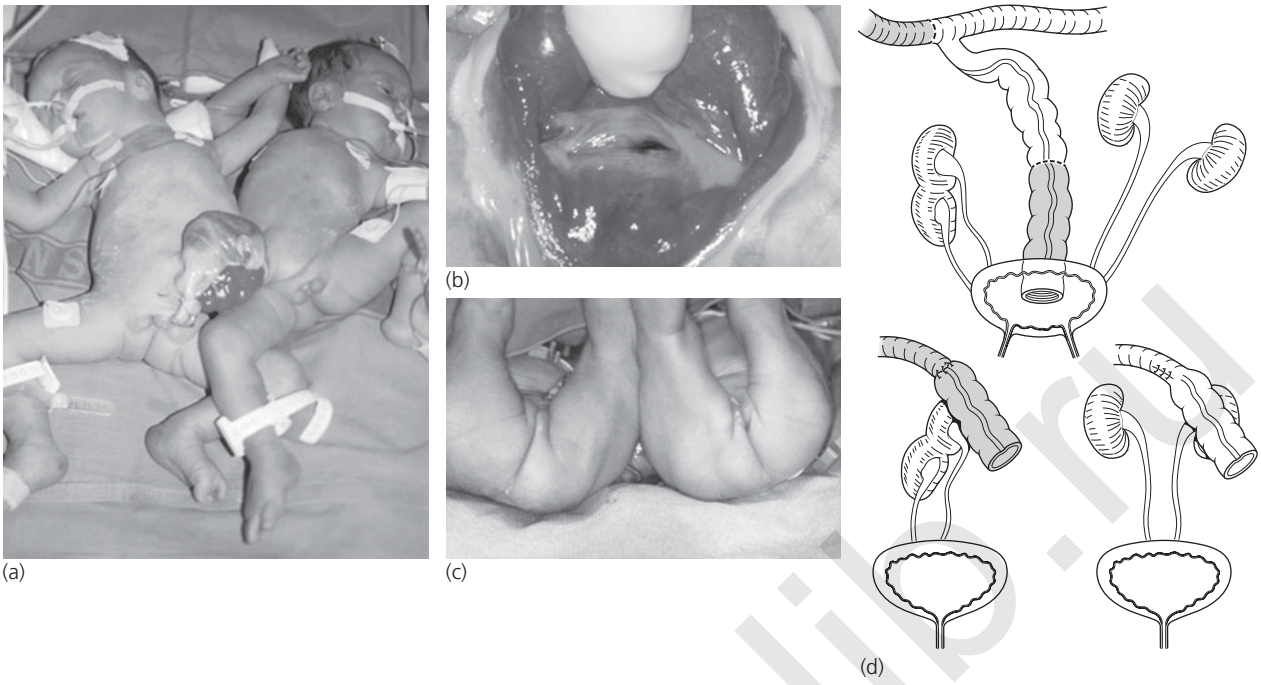


Figure 76.3 Omphalopagus twins with incomplete cloacal exstrophy. The single bladder opened under the exomphalos (a). A single colonic opening was visible in the middle of the bladder plate (b). Both had anorectal agenesis with one single urogenital canal and double uterus and vaginas (c). Separation involved division of the colon with colostomies and bladder closure (d). Later on, sagittal anorectoplasty with colonic and vaginal pull-through were performed.

apply if separation is necessary for the survival of only one twin, if distribution of organs is uneven, and if separation involves, as is usually the case, loss of some functions that might be preserved without separation.

When separation of conjoined twins is considered, the patients are usually too young for deciding by themselves, the parents are heavily influenced by information delivered by doctors and the team involved is usually so large and often ethically discordant, that keeping a unified line of decision becomes difficult. Acknowledgement of a strong moral leadership after open discussion of every issue is required before providing the parents with information about the chances and the consequences of separation. In case of serious discrepancies among all participants in the process of decision, the courts might be involved.

Furthermore, new difficulties may be created by the media (whose interference is difficult to avoid due to the large number of people involved). The twins and their family should be protected from these agents and, if possible, the entire process of decision-making and even the separation should be kept private.

Preoperative meetings

When separation has been decided upon, one or more meetings with scrub nurses, nurses, anesthesiologists, and surgeons of the required specialties (general pediatric, orthopedic, plastic, urologic, neurologic, and cardiovascular surgery) should be scheduled.[35] Technical aspects should be discussed and the operation itself should be rehearsed, because installation of the set of twins on the table, skin prep and draping, and transport of one twin with the corresponding anesthetic equipment to another table for reconstruction after separation should be carried out according to a previously established protocol. The expected order and extent of the participation of each specialist team in the separation should also be scheduled. The surgeon in charge of the direction of the operation acts as an orchestral conductor and his/her coordinating activity extends well beyond the end of the separation itself.

Separation

Anesthesia is a serious challenge not only because of the obvious anatomical difficulties for intubation, insertion of lines, and invasive monitoring, but mainly because of the previously mentioned situation of parabiosis, in which one single internal environment is shared to variable extents by the twins. The drugs administered to one pass on into the other one and biochemical and gas monitoring may be confusing.[36–38]

In general, asymmetric conjoined twins represent surgical challenges that are not unlike other ones met in this specialty. The acardius-acephalus parasitic twin is unviable and dies upon clamping the umbilical cord of the host (autositus) twin. The fetus *in fetu* is treated as a tumor and heteropagus asymmetric parasitic twins are removed with attention at preserving as much tissue as possible in order to respect the organs and allow wall reconstruction of the host.

The separation of craniopagus may be extremely difficult or even impossible, given the complexity of the neural,

arterial, and venous connections involved. Modern imaging and sophisticated neurophysiologic monitoring are particularly useful in these cases. The final amount and nature of the brain tissue and the vascular network shared by the twins set the limits for separation.[39–41]

Separation of omphalopagus twins involves variable difficulties depending on the extent of organ sharing. These twins more often have fused livers and gastrointestinal tracts. A small liver bridge without major vascular connections is relatively easy to take down, but a large mass of anatomically atypical liver with wide arterial, venous, and biliary connections[42] may be a serious undertaking. Perioperative ultrasonography and parenchyme-dividing devices used for liver resection are very useful for this purpose. The most common form of gastrointestinal tract connection involves fusion of the small bowel from the upper jejunum down and divergence near the distal ileum. Separation consists in most cases of allocating half the available gut to each twin. Additional problems may be met when atresia of one of the tracts or a common cystic dilatation of the mid bowel are present.[16–18,43,44]

Thoracopagus twins without connected hearts are separable in contrast with those with common myocardium. Only a few of them are amenable to surgery under cardiopulmonary bypass. In addition, these twins often have cardiovascular defects that may further complicate or preclude the separation. The aorta and the pulmonary arteries may be hypoplastic and the infradiaphragmatic aortas are often largely connected by thick collaterals. Of those who cannot be separated, most die of the associated heart dysfunctions in the first months or years of life.

Rachiopagus, ischiopagus, pygopagus, and parapagus twins share to different extents parts of the spine, central nervous system, gastrointestinal and genitourinary tracts and they may represent formidable challenges. The separation of the bony parts requires highly skilled orthopedic surgeons. In some cases, the reconstruction of the pelvic rim requires bilateral iliac osteotomies and pubic fixation (Fig. 76.4). In some cases, even refashioning a bony pelvis is impossible and the subsequent prosthetic treatment is difficult (Fig. 76.5).[45,46] The spine often has some malformations at other levels, and scoliosis has to be taken into account during follow up.[47,48]

Neurosurgical separation may involve dividing a common spinal cord with reconstruction of the dural sacs on each side.[46] Since fusion of neural tissue is usually distal, the motor and sensitive effects tend to be limited.

The distribution of a common lower gastrointestinal tract between both twins entails the loss of continence for one or both of them. In frontally joined twins, there is usually ileal confluence near the ileocecal valve and a single colon. The functional reconstruction of the pelvic organs is therefore

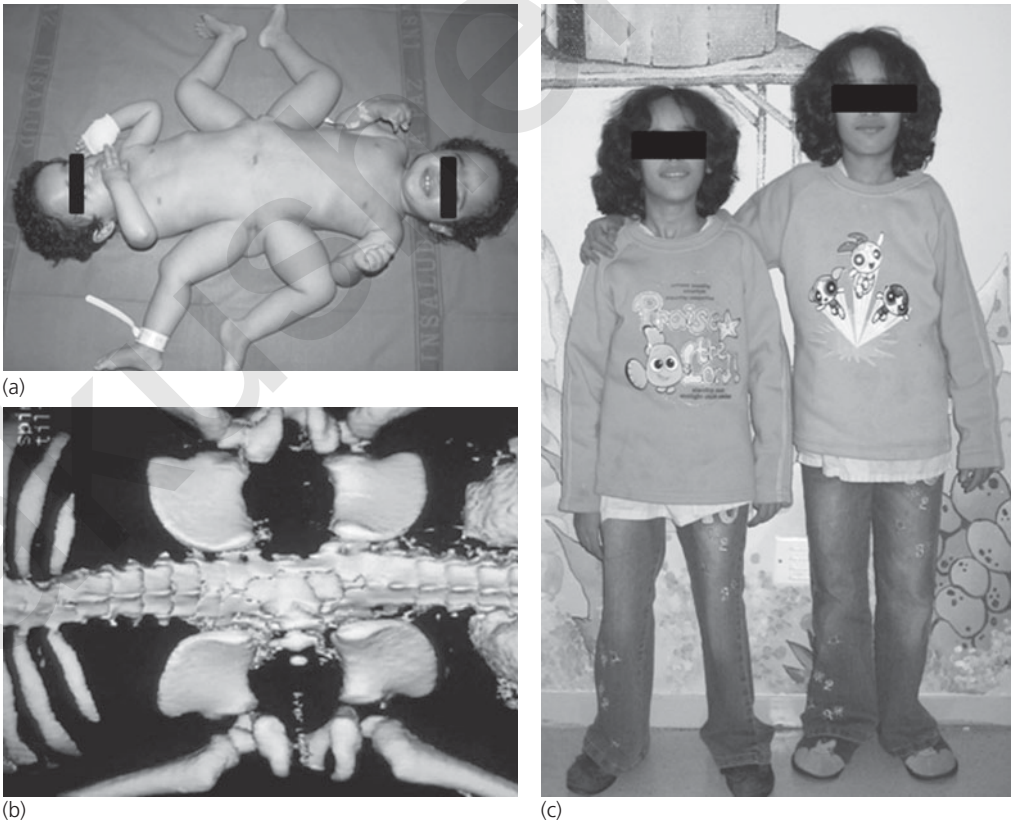
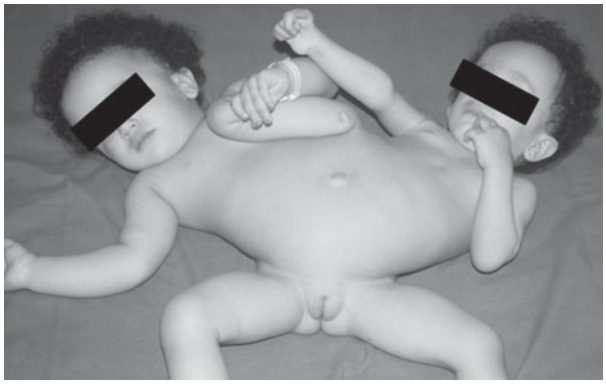


Figure 76.4 (a) Ischiopagus tetrapus (four legs) twins. (b) The spines and the spinal cords were joined at the caudal end as shown by helicoidal computed tomography reconstruction. During separation, the spines were divided, the meningeal sacs were reconstructed, a quadruple iliac osteotomy was performed for joining both pubic bones in each twin, the urogenital system was reconstructed, and colostomies were fashioned. (c) Patients at the age of 12 years. They deambulate normally and enjoy relatively normal lives with permanent colostomies and intermittent bladder catheterization.



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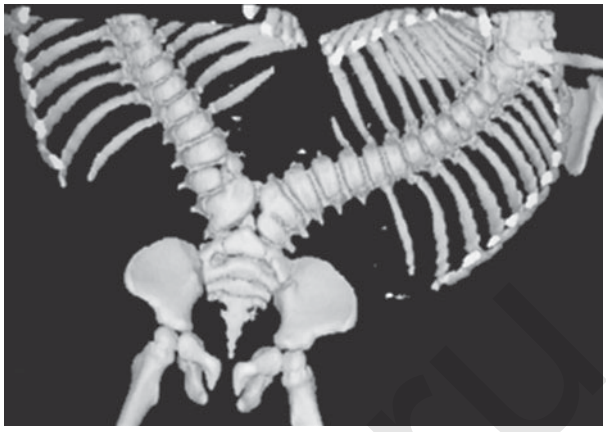

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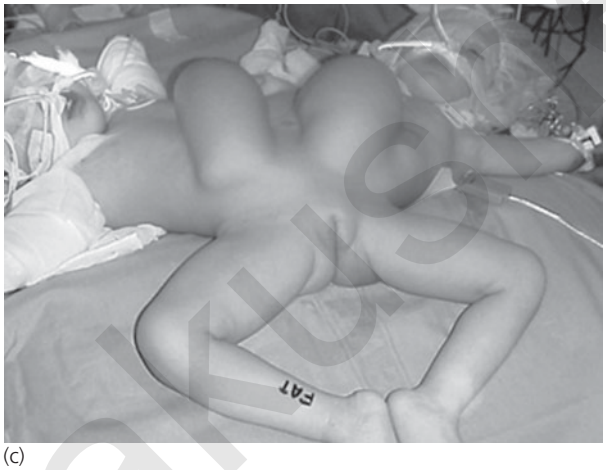

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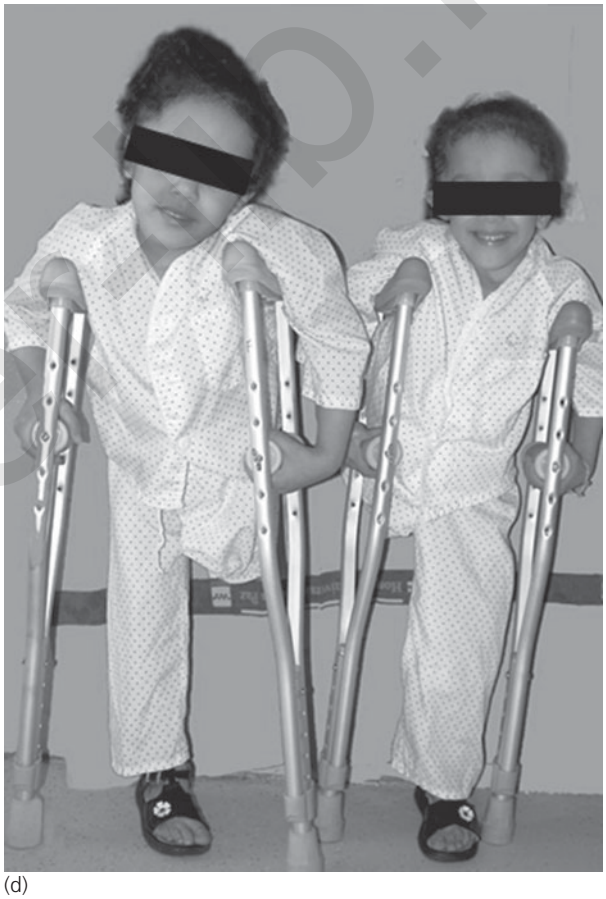

(d)

Figure 76.5 (a) Caudal parapagus twins with an extrathoracic limb irrigated from the abdominal aorta of twin A. (b) There was a single pelvis with two lower limbs and two spines with communicating spinal canals and joined cords. Separation involved two surgical steps. First, the spinal cords and meningeal sacs were separated and subcutaneous expanders were inserted (c). Second, the sacrum, the gastrointestinal and genitourinary tracts were divided and the parietal defects were closed. In twin A, the skin and muscle of the additional limb were used as a vascularized flap. In twin B, a synthetic mesh was used for this purpose. Colostomies were fashioned. Both twins are able to deambulate with braces (d).

rarely possible. Occasionally, the rectal function can be preserved in one twin, but more often this is impossible, and ostomies have to be fashioned at some stage. All refinements of advanced bowel management are necessary to obtain subsequent adaptation of these patients to a more or less normal life.[45]

The same can be said about distributing the urogenital tract structures between the twins. Keeping a bladder and urethra for one twin is rarely possible in most frontally united sets. Again, all refinements of reconstructive urology, bladder augmentation, clean intermittent catheterization, and continent urinary diversion may help to readapt these

patients.[49,50] The native genital tract can be reconstructed if duplicated, but sometimes vaginal replacement is necessary.

One of the major technical problems posed by separation of conjoined twins is the coverage of the huge parietal defects left. When only one survives, part of the wall of the other one can be used to bridge the defects, but in other cases, the skin can be expanded with subcutaneous expanders prior to separation[51–53] and various flaps or biologic[54] or synthetic materials[55,56] may be necessary. Since they have to be inserted in contaminated operative fields, the risks of bacterial colonization and infection are increased.

COMPLICATIONS

The nature of these risky operations involves a large number and variety of possible complications. Perioperative hemorrhage and damage to vital structures is always possible due to the often atypical anatomy. Bone division or meningeal membrane opening simultaneous to gastrointestinal or the genitourinary procedures increase the risk of serious infection. Wound closure avoiding compartment syndrome may necessitate synthetic materials that are also exposed to contamination. Wound disruption and infection are therefore not rare. Finally, a wide range of complications not unlike those seen after other major operations may occur: internal hemorrhage, abscesses, vascular thromboses, or postoperative intussusception among others are possible.

EARLY AND LONG-TERM RESULTS

Overall mortality in conjoined twinning is high. When diagnosis is made during early pregnancy, interruption of gestation is common practice in developed countries, particularly for the forms with bad prognosis.[1] Fetal mortality or stillbirths are also frequent. Obstetric mortality or severe birth trauma remain a real risk when prenatal diagnosis is missed and this happens more often in undeveloped countries in which pregnancies are not monitored. A considerable proportion of twins have multiple malformations that cause demise in the first hours or days of life.[39] When separation is deemed possible, it must be reminded that neonatal operations involve higher mortality not only because they are better performed later when most anatomical and functional features of the set have been ascertained, but also because neonatal separation is only indicated for life-threatening reasons (for instance, one twin may be very ill or develop intestinal obstruction).[57]

Thoracopagus twins with a common heart rarely survive because most have severe malformations. Of those sets in which separation is attempted, only a few individual twins survive.[58,59] However, thoracopagus without shared heart can be successfully separated.

Most omphalopagus twins can be separated and survive if no obstetric trauma or severe associated malformation are present (Fig. 76.1). In all other forms of conjoined twinning, a high proportion of the twins can be separated and survive, although with more or less extensive deficits that require follow up for life and often additional operations.

In the long term, separation of conjoined twins rarely produces independent individuals without sequelae. Some cases of asymmetrical twins and omphalopagi may survive separation facing a normal life. Most other cases have orthopedic or neurologic sequelae or have fecal and urinary continence problems that become predominant problems with the passage of time. Orthopedic and motor deficits may require prolonged rehabilitation and/or prosthetic appliances. Permanent enterostomies are not rare and the most sophisticated procedures for obtaining urinary continence or dryness are necessary.[16,60,61]

It is particularly discouraging that these pregnancies are often terminated in advanced medical and social environments able to provide lifelong assistance for rehabilitation and social integration, whereas twins from less privileged countries that are diagnosed at term are eventually separated and lack all the necessary facilities.

Separation of conjoined twins is a major test for the quality of pediatric surgical care. Only institutions with highly sophisticated pediatric surgical specialties can undertake these operations with a reasonable chance of success.

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PART VIII

TUMORS

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77

Epidemiology and genetic associations of neonatal tumors

SAM W MOORE AND JACK PLASCHKES

INTRODUCTION

Fifty percent of childhood cancer occurs under the age of five years[1] and clear evidence of inheritability exists in many childhood tumors. Although benign tumors and masses are not uncommon, malignant tumors are rare during the perinatal period.[2] Their behavior is variable and certain apparently benign neonatal masses (e.g. teratomas) may undergo malignant change if untreated. On the other hand, others (e.g. neuroblastoma) may behave relatively benignly and even mature in the neonatal period. Many of these tumors respond to therapy and have a good prognosis, but the mortality rate is estimated to be 6.26 per million live births.[3,4]

The hypothesis that tumors (and even adult cancer) may be linked to or even initiated during fetal development[5–7] is supported by an ever-increasing number of animal experimental studies. This makes the study of neonatal tumors particularly interesting as a possible explanation of their early (as opposed to later) appearance may lie in the developmental processes still active in the host. Possible reasons for this are based on the hypothesis that either genetic or environmental (e.g. nutrition and exposures to environmental toxins) factors (or both) may act as oncogenic promotors during gestation.[8]

This hypothesis is currently supported by an ever-increasing body of evidence and places the emphasis firmly on the developmental period as a focus of disease prevention and intervention. In this context, tumors occurring in the developmental and perinatal period can be regarded as a 'window of opportunity' in cancer research,[9,10] and may lead to the identification of potential therapeutic molecular targets.

INCIDENCE OF NEONATAL TUMORS

Neonatal tumors (NNT) or perinatal tumors comprise 2% of childhood malignancies, but from an epidemiological point of view, there is little clarity as to the real prevalence, sites of origin, and pathological nature of neonatal tumors and reported series vary from unit to unit (Table 77.1) varying from 17 to 121 per million live births (Table 77.2).[11–17] The reported incidence in the UK and United States, respectively, is approximately one in every 12 500–27 500 live births.[2] The Manchester Children's Registry estimated the incidence to be 121.29 per 10^6 child-years when all children under one year of age, including those with leukemias and lymphomas, are counted.[13] Overall, the highest incidence has been reported in Japanese children and the lowest in black children in the United States.[1]

AGE AND SEX

The majority of tumors are diagnosed when the infant is between 1 and 4 weeks of age. Fewer malignant tumors are diagnosed at birth, although benign or potentially malignant tumors are frequently encountered then.

The male-to-female ratio is equal in the majority with the exceptions of retinoblastoma (male preponderance) and teratoma (female preponderance).

PRENATAL DIAGNOSIS

With the advent of routine prenatal ultrasonographic screening and the considerable recent advances in technology, many neonatal tumors are now diagnosed antenatally. This is particularly true of patients with mixed germ cell tumors of the sacrococcygeal region and patients with renal tumors.

One of the difficulties in assessing the true incidence of neonatal tumors is the non-reporting of tumors occurring in stillborn babies and babies dying in the neonatal period.

The advent of neuroblastoma screening programs has brought more to light, but does not appear to affect the prognosis. The biological characteristics of neuroblastomas

Table 77.1 Published series of 'neonatal' tumors since 1980.

	Author	Country	Time span	No. of cases	Per year	Source
1978	Barson[13]	UK	N/I	270	?	Pathology review
1982	Gale *et al.*[14]	USA (Philadelphia)	N/I	22	?	Hospital series
1985	Isaacs[112]	USA (Los Angeles)	1958–82	110	4.4	Pathology review
1986	Las Heras and Isaacs[15]	USA (Los Angeles)	1964–78	42	3.0	Hospital registry
1987	Campbell *et al.*[12]	Canada (Toronto)	1922–82	102	1.7	Hospital series
1987	Davis *et al.*[16]	Scotland (Glasgow)	1955–86	51	1.6	Hospital series
1988	Crom *et al.*[11]	USA (Memphis)	1962–88	34	2.1	Hospital series
1989	Plaschkes and Dubler[19]	Switzerland (Bern)	1973–87	39	2.6	Hospital series
1989	Mur[113]	Argentina	1967–90	51	2.2	Hospital series
1990	Werb *et al.*[114]	Australia (Melbourne)	1939–89	46	0.9	Autopsies
1992	Borch *et al.*[17]	Denmark (Copenhagen)	1943–85	76	1.8	National cancer registry
1992	Parkes *et al.*[22]	UK (Birmingham)	1960–89	149 (+21 leuk)	5.0	Population-based registry
1994	Tenturier *et al.*[115]	France (Paris)	1975–86	75	7.5	Hospital series
1994	Moore *et al.*[21]	South Africa (Cape)	1957–91	60	1.8	Hospital series
1995	Xue *et al.*[116]	USA	1956–95	35 (<1 month)	0.9	Hospital series (35/225 < 1)
1995	Plaschkes[20]	International – SIOP	1987–91	192	38.5	International Tumor registry
1996	Chakova and Stoyanova[117]	Bulgaria	15 yrs	30	2.0	Hospital series
1996	Zhou and Du[118]	China	N/I	15	?	Hospital autopsy series
1997	Gurney *et al.*[119]	USA (SEER data)	1973–92	175 (12%)	8.76	NCI Registry
1998	Halperin[120]	USA (Durham, NC)	1930–98	23	0.33	Hospital series
2000	Rao *et al.*[121]	UK (Glasgow)	1955–99	83	1.84	Hospital series
2001	Sbragia *et al.*[122]	USA (San Francisco)	1993–00	64 (Antenatal)	9.1	Hospital series
2003	Hadley *et al.*[123]	South Africa (KZN)	1982–02	42 malignant, +39 'benign'	4.05	Hospital series
2003	Pinter *et al.*[124]	Hungary	1975–83	142 (+ <1 yr)	15.7	Hospital Series
2003	Buyukpamukcu *et al.*[125]	Turkey (Ankara)	1972–00	123	2.9	Hospital series
2006	Berbel Tornero *et al.*[126]	Spain (Barcelona)	1990–99	72	7.2	Hospital series
2009	Yeap and Zahari[127]	Malaysia	2000–06	28	4.6	Hospital series

SIOP, International Society of Pediatric Oncology.

Table 77.2 Incidence of neonatal tumors – published series.

Country	Author	Incidence	Source
UK	Barson[13]	70 per million live births	National survey by pathologists (UK)[a]
UK	Oxford Children's Cancer Group[128]	17 per million live births	Cancer Registry
UK	Manchester Children's Tumor Registry[41]	121.29 per 10^6 child-years	Tumor Registry, population based[b]
USA	Bader and Miller[2]	36.4 per 10^6 child-years	Third National Cancer Survey (USA)
Switzerland	Plaschkes and Dubler[19]	93 per million live births	Hospital activity analysis
Hungary	Pinter *et al.*[124]	100.5 per million live births	Hospital activity analysis[c]
Denmark	Borch *et al.*[17]	23 per million live births	Danish Cancer Registry (ICD)

[a]Benign–malignant.
[b]Less than one year (including neonates), includes leukemia and lymphoma.
[c]Less than three months.

detected by screening in Japan have been shown to be mostly favorable.[18] Few of these tumors have N-myc amplification, although 10–20% have unfavorable histological features.

CLINICAL PRESENTATION

Although many NNT present with benign masses, 34% of 192 patients reported by the International Society of Pediatric Oncology from 12 different centers presented with metastatic disease.[13] Some may be incidental findings and some larger masses may be diagnosed with antenatal ultrasonography.

PATHOLOGY

A particular problem exists in classifying neonatal tumors in that histological features of malignancy do not always correlate with clinical behavior. As a result, there are at least four clinical groupings of neonatal tumors:[19,20]

1. Tumors that are clearly malignant by all the usual criteria, but:
    a. behave more like those occurring in older children;
    b. behave better than expected;
    c. behave worse than expected;
    d. demonstrate unpredictable or uncertain behavior.
2. Tumors that show local invasiveness, but have no metastatic potential.
3. Benign tumors that are either:
    a. life threatening because of size and location;
    b. have a known tendency towards malignant transformation.
4. Extreme rarities, e.g. malignant carcinomas which are similar to adult-type tumors.

TUMOR TYPES

The distribution of the various histological types of tumors appears to be relatively constant when compared to other published series (Table 77.3). In a study of 192 cases collected from 12 different countries by the International Society of Pediatric Oncology 1987–91, 33 different types of tumor were reported to occur within the neonatal period.[20] Teratoma was the most frequently encountered type in our own,[21] as well as other large series,[20,22] and is followed by neuroblastoma, leukemia, and soft-tissue tumors. Certain tumors (e.g. retinoblastomas and brain tumors) vary in incidence, depending on hospital referral patterns. Renal and liver tumors occurred less frequently in the neonatal period.[13] Other types of tumor tend to be largely rarities. True carcinoma as seen in adults remains extremely rare in childhood, making up only 1–2% of patients.[23]

Table 77.3 International Society for Paediatric Oncology (SIOP) tumor registry 1987–1991.

Diagnosis	No. cases
Neuroblastoma	85
Teratoma	24
Rhabdomyosarcoma	13
Retinoblastoma	10
Mesoblastic nephroma	8
Hepatoblastoma	6
Undifferentiated sarcoma	5
Histiocytosis	4
Fibromatosis	3
Hemangiopericytoma	3
Renal (unclassified)	3
Yolk sac tumor	3
Brain tumor	2
Choriocarcinoma	2
Fibrosarcoma	2
Liver tumors	2
Primitive neuroectodermal tumor (PNET)	2
Angiofibroma	2
Arterioventricular malformations	1
Embryonal tumors	1
Ependymoblastoma	1
Glioma grades III–IV	1
Infantile myofibromatosis	1
Juvenile xanthogranuloma	1
Leiomyosarcoma	1
Melanoma	1
Neurofibroma	1
Oligodendroglioma	1
Rhabdoid tumor	1
Testicular carcinoma	1
Wilms' tumor	1
Total	192

ETIOLOGY AND CARCINOGENESIS

The etiology of cancer in children is multifactorial and includes both genetic and environmental factors. It seems likely that genetic factors predominate in heritable tumors, whereas a more involved multistep process is involved in those occurring spontaneously.

Genetic factors in neonatal tumors

Following the first report of the Philadelphia or Ph1 chromosome,[24] in affected cells of patients with chronic myeloid leukemia (CML), genetic mechanisms have been implicated in the etiology of many cancers, thus opening new areas for diagnosis and prognosis. Tumors are accepted as being a largely genetically based disorder at the cellular level and have been implicated in both non-hereditary and hereditary forms of malignancy in children and adults.[25] This is particularly true of neonatal tumors where most cancer cells are monoclonal, have a high incidence of chromosomal changes and some specific genetic mutations, as well as a clear inherited predisposition to malignancy.

As such, neonatal tumors provide a unique opportunity to study familial and genetic associations because minimal interactions between genetic and environmental factors have occurred that soon after birth. Modern genetic surveillance techniques offer potential opportunities for prevention, in contrast to most malignancies encountered in older patients.

Apart from explaining how tumors may present in the perinatal period, genetic control may also partly explain the variable behavior of certain tumors within the perinatal period.[10]

There are essentially three groups of genetic abnormalities involved in the epidemiology of neonatal tumors:

1. Genes resulting in a high risk of malignancy (e.g. in retinoblastoma)
2. Genetically determined syndromes, where an increased risk of malignancy exists
3. Genes which confer a higher risk by conferring an increased susceptibility to environmental factors.

The incidence will be influenced by the incidence of these abnormalities in the population/family at risk.

GENES RESULTING IN A HIGH RISK OF MALIGNANCY

Accumulating research over the past two decades have seen many significant advances in understanding the mechanisms of the heritability of cancer (5–10% of all cancers). This is of particular interest in the field of neonatal tumors.

The best example of this group is the *RB1* gene, which confers a risk of retinoblastoma. Other examples include Li–Fraumeni syndrome, where there is an association of rhabdomyosarcoma, soft tissue tumors, breast carcinoma adrenocortical carcinoma, brain tumors, and leukemia.

As many of the genetic mutations associated with malignancy in children appear to occur spontaneously, a double 'hit'[26] is a likely mechanism.

THE 'TWO-HIT' OR MULTISTEP MODEL OF TUMOR DEVELOPMENT

Whereas it is generally recognized that tumors are a genetically related disease, tumorigenesis can mostly be attributed to a multistep process whereby each step probably correlates with one or more distinct genetic variations in the major regulatory genes. Knudson,[26] in an attempt to understand the pathogenesis of neonatal retinoblastomas, proposed that the tumor resulted from a combination of a prezygotic (germinal) mutation, as well as a postzygotic (somatic) event on the basis of extrapolated statistical data. This so-called 'two-hit' theory, was later confirmed by Comings[27] who suggested that both of these events could apply to mutations of the *RB1* gene. It is now widely accepted that inherited or *de novo* chromosomal mutations or deletions may result in a susceptibility to cancer.

Knudson's 'two-hit' model is particularly applicable to inherited cancer models (and possibly neonatal tumors), whereby an inherited susceptibility occurs on the basis of an identified germline mutation. The tumor development then rests on the further inactivation of a second allele (often tumor suppressor genes) which gives rise to early activation of the oncogenic pathway.

This theory provides the basis for understanding the pathogenesis of a number of tumors occurring in the neonatal period and has since been validated for a number of other tumor types (e.g. retinoblastoma, Wilms' tumor (WT), neuroblastoma, and other tumors).

In sporadic tumors (as opposed to hereditary tumors), a multistep process is more likely and the mutational activation of oncogenes is often correlated with non-mutational inactivation of tumor suppressor genes. As this is probably an early event, it is then followed by a number of independent mutations in other genes to allow neoplastic growth.

How this applies to special circumstances, such as neonatally occurring tumors, beyond these known examples is still unclear. These tumors feature a number of host-specific features which include the potential of spontaneous regression in some, a greater capacity for cell repair, as well as a comparatively good prognosis when compared to histologically similar tumors occurring later in childhood. It is therefore reasonable to assume that further study of the genes controlling childhood cancer and particularly cancer occurring early in life, warrants further attention.

Genetically determined high-risk syndromes

The identification of a genetic association of a specific tumor may be hampered due to the fact that the precise genetic mechanisms may not be recognized by the current genetic testing methods. Etiological factors involved in the pathogenesis of certain tumors (e.g. Wilms' tumor) appear to be more complicated than those of others (e.g. retinoblastoma). Increases in familial occurrence or an increased risk in monozygotic twins may be present and an association between a specific malignancy and a set of alleles at a specific locus thus identified. This may not be exclusive to the particular tumor under study and may be associated with the pathogenesis of other types of tumors. Examples of this are the associations between leukemia, lymphomas, central nervous system (CNS) neoplasms, and soft-tissue tumors, as well as the *RB1* and *WT1* genes among others. The evaluation of clinical associations and syndromes linked to specific tumor types is therefore of considerable importance.

Mendelian single gene-related syndromes

Syndromes arising from defects in chromosomal breakage or disorders of sexual differentiation may lead to malignancy. A number of examples of Mendelian single-gene malignancy-related syndromes are described in Box 77.1.

These may be autosomal dominant, recessive, or X-linked. In addition, certain disorders of sexual differentiation may

Box 77.1 Inherited syndromes and childhood malignancy

- Chromosome breakage syndromes
  - Bloom syndrome
  - Fanconi's anemia
  - Ataxia telangiectasia
  - Xeroderma pigmentosa
- Neurocristopathies
- Neurofibromatosis
  - Tuberous sclerosis
  - Turcot's syndrome
  - Multiple mucosal neuroma syndrome
  - Basal cell nevus syndrome
- Metabolic disorders
  - Tyrosinemia (hereditary)
  - Alpha-1 antitrypsin deficiency
  - Glycogenolysis (type 1)
- Immune deficiency disorders
  - Sex-linked lymphoproliferative syndrome
  - Wiskott–Aldritch syndrome
  - Severe combined immunodeficiency
  - Bruton's agammaglobulinemia

also be associated with cancer in the pediatric age group. Autosomal dominant syndromes include familial colonic polyposis, neurofibromatosis, and the nevoid basal cell carcinoma syndrome (Gorlin syndrome), as well as the blue rubber bleb and Sotos syndromes. Skeletal abnormalities, such as multiple exostoses, polyostotic fibrous dysplasia, and Mafuccis syndrome are also associated with a higher incidence of tumor formation. These tumors do not normally present in the neonatal period and are added for completeness, but are extremely interesting from a genetic point of view (i.e. in tracing the affected individuals in family groups).

Autosomal recessive syndromes associated with tumors include xeroderma pigmentosum, Fanconi's anemia, Bloom syndrome, and ataxia telangiectasia syndromes. Bloom syndrome includes a sensitivity to ultraviolet light, growth retardation, and immunodeficiency which is associated with a higher rate of associated malignancy occurring at an earlier age,[28] e.g. leukemias and gastrointestinal malignancies. Fanconi's anemia is also linked to leukemia and liver tumors. Tumors associated with an autosomal recessive familial inheritance, as well as those associated with immunodeficient X-linked recessive syndromes occur outside the neonatal period, suggesting some degree of an initiating environmental influence.

The Epstein–Barr virus has been suggested as a possible pathogenetic factor[29] in the X-linked lymphoproliferative syndrome. Of particular interest are the fragile chromosomal syndromes, where fragile sites associated with breakage and repair of chromosomal defects are transmitted through families. A high percentage of the inheritable and constitutive fragile sites have been mapped to genetic sites associated with human cancer.[30] These chromosomal rearrangements have been associated with malignancy in at least six out of the 16 inheritable fragile chromosome sites and have also been identified in other non-inherited fragile chromosome sites.[30] As a result of the chromosome fragility in these cases, deletions and chromosomal fragments may occur. Should the fragile sites break close to a proto-oncogene location, the activation of the oncogene may result in the malignant transformation of the cells. In several disorders in sexual differentiation, the incidence of gonadal tumors has been increased.

Familial associations with cancer

Although loss of a chromosome segment of a specific chromosome pair (heterozygosity) may be involved in the pathogenesis of certain tumors,[31,32] a specific chromosome from one of the parents appears to be given preference in particular situations.[31] Examples of this are the loss of a maternally derived gene on chromosome 11 in sporadic Wilms' tumor[32] and the successive loss of function of both alleles of RB (retinoblastoma susceptibility gene) in the development of retinoblastoma, as well as certain sarcomas such as osteosarcoma.[31] Genetic processes other than chromosome anomalies may also be involved in the familial transmission of a tendency to develop certain tumors.

Large cohort studies of the offspring of parents with cancer have failed to show an overall increased risk for tumors.[33] There is also little evidence to suggest that cancer treatment confers an additional risk. In a separate study of 36 survivors of 82 neonatal tumors, the authors found no familial increase in the incidence of malignancy, although chromosomal abnormalities were identified in three patients.[34] One patient had a chromosome 21 abnormality, one had trisomy 13, and in the other a distinctive familial translocation pattern was located on the 9th chromosome in a girl with a neuroblastoma.[35] The lack of increase in incidence agrees with the findings of previous studies,[11,36,37] where no inherited effects of childhood tumors or tumor therapy were identified in survivors of childhood neoplasms.

Other syndromes associated with an increased genetic risk of cancer

Although a family history may be observed in the group of neurocristopathies associated with neural crest abnormalities, the associated tumors appear outside the neonatal period. Examples of this are pheochromocytoma, von Recklinghausen's disease, Sturge–Wreber syndrome, tuberous sclerosis, and von Hippel–Lindau disease, as well as the MEN II tumor syndrome.

Other congenital syndromes which confer an increased risk of malignancy include the WAGR and Denys–Drash syndromes in Wilms' tumors, the Beckwith–Wiedemann and Down syndromes, and neurofibromatosis (*NF1* gene). There is an increased risk of leukemia and other tumors in patients with Down syndrome.[38] Leukemoid reactions may be more difficult to distinguish in the neonatal period.[39] Abnormalities of the neurofibromatosis 1 gene (*NF1*) have been identified in patients with von Recklinghausen's disease and a number of different mutations on the tumor suppressor gene have been described in chromosome 17q. An additional NF2 suppressor gene has been identified on chromosome 22q, leading to tumors such as acoustic schwannomas and other neural tumors.

There is a certain amount of overlap in phenotypic expression in syndromes such as the Beckwith–Wiedemann, Denys–Drash, Simpson–Golabi–Behmel, and Perlman, as well as other overgrowth syndromes. Nephroblastomatosis may be a feature of a number of these syndromes and long-term survey is required as these could put patients at risk for embryonic tumors.

There are additional associations between Wilms' tumor, aniridia, urogenital malformations, and mental retardation (WAGR) and the Denys–Drash syndrome.[40] This latter syndrome includes features of intersex disorders, nephropathy, and Wilms' tumor. Although initially described only in males with pseudohermaphroditism,[40,41] this syndrome has been extended to include female children with ambiguous genitalia, nephropathy, and Wilms' tumor.[42] An observed constant association with genetic mutations located at chromosome 11p13 (*WT1* or Wilms' tumor gene) and the Denys–Drash syndrome indicates a possible molecular marker for this syndrome. The exact site of the point mutation which was identified in the majority of cases was located on the *WT1* exon 9, which affects the amino acid residue 394 arginine.[42] There is also an association between other tumors, such as hepatoblastoma or adrenocortical

carcinoma and Wilms' tumor, which may coexist in 6–10% of patients.

Genetic factors which are involved in an increased risk of tumors include tyrosinosis, the MEN II and III syndromes, congenital adrenal hyperplasia, the basal cell nevus and Li–Fraumeni syndromes.[43] Genetic mutations predisposing to malignant disease include the Wilms' tumor 1 gene. In this instance, an 11p13 chromosomal defect is often typical. A further example is the neurofibromatosis type 1 gene, which is common in certain tumors. Gene amplifications have been reported in certain tumors. Amplified N-myc and N-ras oncogenes have been observed in neuroblastomas. This N-myc amplification has been shown to be associated with the more severe form of the malignancy.

Association with congenital malformations

There is also a fairly clear relationship to congenital abnormalities which have been reported to occur in as much as 15% of neonatal tumors. The role of genetic factors in development and the link between congenital malformation and tumors (e.g. neuroblastoma[44]) is also becoming clearer. In one recent study, 15 out of 72 patients with a neonatal tumor had associated congenital abnormalities.[45]

Increased susceptibility to environmental factors

In addition to genetic factors, environmental exposure is also a strong contender for promoting oncogenesis. Although it is true that neonates have a limited exposure to environmental toxins having just been 'born', so to speak, but environmental influences which affect the mother (e.g. environmental exposure to ionizing radiation, drugs taken during pregnancy, infections and tumors in the mother, and congenital malformations) may also affect the unborn baby. As a result, events occurring during pregnancy could be of key significance in the development of neonatal tumors. Both the environmental and genetic factors may thus influence the development of a neonatal tumor in the offspring. It is therefore conceivable that both genetic and environmental factors may be operating (possibly in tandem) at this stage giving rise to a 'unifying hypothesis' linking ontogeny to oncogenesis.

Environmental exposure quite possibly influences vital signaling cascades which occur during development. These noxious influences would, however, have to occur during a period when normal developmentally specific mechanisms are influenced by multiple genetic and environmental factors which may influence the epigenetic processes taking place during that period.[6] Such influences on epigenetic factors have already been identified from patients exposed to certain environmental toxins in certain adult tumors.[6] More recently, the importance of disturbances in epigenetic programming which regulate both normal and neoplastic growth and development have been explored.[46,47]

It stands to reason, therefore, that a study of those genetic and environmental factors with the potential to influence this process has the potential to provide considerable information about both cancer etiology and the natural history of tumors, including their development and progression.

This molecular epidemiological approach in investigating childhood tumors is enhanced by the current available technology which may permit the characterization of connections between exposure and subsequent health effects in newborns by means of biomarkers (e.g. mutations in cord blood DNA).[48]

Radiation-induced tumorigenesis

Ionizing radiation has been clearly implicated in the etiology of a number of tumors in children. This may involve prenatal, as well as postnatal exposure. There is a dose-related increase in tumor incidence or a tendency for tumors to occur at a younger age following prenatal or neonatal radiation exposure.[49] This is also true of internally deposited radionucleotides administered in the prenatal or neonatal periods.[50] It is clear from experimental evidence that deletions, point mutations, translocations, and other genetic abnormalities occur as a result of ionizing radiation. As a result a state of genomic instability may occur, which may in turn result in malignant transformation. There does appear to be an increased susceptibility to ionizing radiation in the Li–Fraumeni syndrome mouse model (p53-deficient mice), which suggests some environmental influence in the development of tumors.[51]

Effect of drugs in pregnancy

It is becoming clearer that fetal exposure to endocrine disruptors and hormonally active substances (e.g. diethylstilboestrol) affect the prevalence of reproductive abnormalities, metabolic disorders and thus influence cancer.[52]

Drugs may act as carcinogens or co-carcinogens in association with other agents or a particular genetic background. There is also clear evidence that tumors may arise in the children of mothers taking medication. One of the best examples of this is the fetal hydantoin syndrome.[53] There is some evidence of tumors arising from estrogens taken during pregnancy, and sacrococcygeal tumors have also been associated with maternal intake of acetazolamide.[54] This may be a greater problem than was initially thought. Satge *et al.*[55] showed a history of medications being taken in 39 out of 89 (44%) neonatal tumor patients. Out of the 39 tumors, nine were malignant, of which the main types were neuroblastomas and teratomas. Three groups of drugs were identified: IARC group 1 diethylstilboestrol and oral contraceptives, IARC group 2 possibly carcinogenic to humans, and IARC group 3, where no association has been proven. To date the association of vitamin K with carcinogenesis remains unproven.[56]

Environmental exposure

Results of epidemiological studies are inconsistent as far as environmental exposure is concerned, but only weak

associations with risk factors such as smoking have been identified.[57] Other environmental factors such as exposure to electromagnetic radiation have proved to be difficult to determine from an epidemiological point of view.

SPECIFIC CLINICAL ASSOCIATIONS OF NEONATAL TUMORS

Retinoblastoma

Much of the understood relationship between genetics and tumors of childhood really lies in the seminal work of Knudson[26] who in 1971 developed the 'two-hit theory' of oncogenesis in retinoblastoma based on an analysis of the age of presentation of hereditary as opposed to the non-hereditary cases. Knudson's hypothesis that these tumors resulted from two separate genetic events was extended to suggest that these events could be mutations of the same *RB1* gene. It has subsequently been shown that 90% of individuals with the *RB1* gene will develop a retinal tumor. A small number of these patients (5%) have additional associated genetic disturbances (e.g. deletions or translocations at 13q14).

Retinoblastoma remains the most common intraocular tumor of childhood, with the average age of diagnosis being at 11–12 months of age for bilateral disease and 23 months for unilateral tumors. In cases with a strong family history and a high index of suspicion, diagnosis may be made in the perinatal period.

The retinoblastoma protein (pRB) is part of the control of genes involved in the cell cycle and, as such, interacts with a number of transcriptional factors by modulating their activity. Inactivation of the *RB1* gene can therefore also be involved in the development of other malignancies and patients with *RB1* mutations carry a risk of developing other tumors, such as osteogenic sarcomas, fibrosarcoma, and melanomas in early adult life. The cloning of the *RB1* gene[58] indicated an association with other tumors such as osteosarcoma and breast carcinoma, in addition to retinoblastoma. Deregulations and/or mutations of the retinoblastoma protein (RB/RB1) pathway have been observed in many human cancers suggesting a fundamental role in oncogenesis.

To date, deregulated expression in more than 260 genes has been associated with retinoblastoma. An understanding of the function of these genes, not only provides valuable insights into oncogenesis in retinoblastoma but has yielded possible therapeutic target sites (e.g. MCM7 and WIF1) currently under investigation.[59]

Wilms' tumor

Wilms' tumor is the most common pediatric renal tumor with a peak age of incidence of three to four years. Although rare in the neonatal period, patients with synchronous bilateral Wilms' tumor, familial cases, and those with abnormalities are noted to be significantly younger. Predisposing associations with aniridia, congenital abnormalities of the genitourinary tract, and hemihypertrophy may be associated with nephroblastomatosis, which may lead to an early Wilms' tumor (Box 77.2).

The genetic factors involved in Wilms' tumor are much more complex than those involved in other tumors, such as retinoblastoma. The familial associations have been shown to be part of an autosomal dominant trait and are of the order of 1% with a somewhat slight female preponderance, particularly in multicentric and bilateral tumors.

Wilms' tumor has been associated with at least two genetic variations (11p13 and 11p15). Associations between Wilms' tumors and aniridia, urogenital malformations and mental retardation (WAGR) and the Denys–Drash syndromes[40,41] led to the identification of a constitutional chromosomal deletion in the short arm of one copy of chromosome 11 p13 (the *WT1* gene). The *WT1* gene appears to act as a tumor suppressor gene with its deletion resulting in development of a Wilms' tumor.[60] The gene encodes a zinc finger transcription factor which binds GC-rich sequences and acts as either an activator or repressor of transcription for a number of growth factors (including Igf-2) which may be a possible explanation of its mechanism of action. In addition to the *WT1* gene at 11p13, there is evidence of a second WT gene at 11p15 (*WT2* gene). A high reported frequency of LOH at 1p35–p36 (DIS247) suggests that this may be involved in the pathogenesis of Wilms' tumor.[61] The Knudson and Strong model for Wilms' tumor has been validated through molecular identification of the *WT1* gene.[62,63]

The *WT1* gene variations are only present in approximately 20% of Wilms' tumors, however, suggesting further genetic associations. Further genes (e.g. *WT3* and *WT4*) also appear to be implicated in the oncogenesis of Wilms'

Box 77.2 Syndromes associated with Wilms' tumor

1. Aniridia (0.75–1%)
2. Hemihypertrophy (3.3%)
3. Beckwith–Wiedeman syndrome (3.7%)
4. Musculoskeletal abnormalities (2.9%)
5. Genitourinary abnormalities (5.2%)
6. Other syndromes associated with Wilms' tumors
   - Denys–Drash syndrome
     - Nephroblastoma
     - Male pseudohemaphroditism
     - Glomerulonephritis
     - Nephrotic syndrome
     - Renal failure
   - WAGR syndrome (11p13 deletion)
     - Nephroblastoma
     - Anorectal malformation
     - Genitourinary anomalies
     - Mental retardation
   - Beckwith–Wiedemann syndrome
   - Klippel–Trelaunay syndrome
   - Other associated tumors
     - Hepatoblastoma (6–10% of Wilms' tumors)
       - Adrenocortical carcinoma

tumors as are gains of 1q and deletions of chromosome 22 associated with a worst prognosis. The 11p15 variation is also associated with the Beckwith–Wiedemann syndrome. More recently, the *WTX* gene (Xq11.1) was reported to be mutated in Wilms' tumors. It is of interest that these two genes appear to occur with similar regularity and despite some overlap with the *WT1* gene, a combination could account for up to a one-third of Wilms' tumors.[64] An association between the WNT/beta-catenin signaling pathway (the *CTNNB1* gene encoding beta-catenin) and the *WTX* gene is also known. This and other reports[65,66] of beta-catenin mutations in Wilms' tumors suggests that Wnt signaling pathway dysregulation also plays an oncogenic role in certain Wilms' tumors.

As the most critical factor in the Wnt signal transduction pathway, beta-catenin appears to be involved in the development of a number of malignant tumors. This is not surprising as the Wnt signaling pathway is involved in kidney development and pathway activation being involved in beta-catenin protein stabilization, intracellular accumulation, and nuclear translocation. It is clear that beta-catenin gene mutations (identified in $\pm$15% of Wilms' tumors) may lead to nuclear beta-catenin accumulation in cells.[65] One recent report observed a highly significant ($p = 3.6 \times 10^{-13}$) association between *WT1* and beta-catenin mutations in Wilms' tumors.[66] Further studies have reported overexpression of beta-catenin/TCF target genes in *WT1*-mutant tumors with gain-of-function mutations of the *CTNNB1* gene being identified elsewhere in the gene on complete sequencing, increasing the overall mutation rate to 75%.[67]

In addition, a loss of heterozygosity (LOH) for 16q is a structural alteration identified in 20–30% of Wilms' tumors. p53 alteration also appears to be required for the progression to the anaplastic subtype. Further associations with p53 analogs (p73 and p63/KET) suggests that association with the p53 family may be important to cell growth and differentiation.[68] Haploinsufficiency in the *PAX6* gene is also strongly associated with aniridia.[69] Familial Wilms' tumor does not, however map to the 11th chromosome as FWT1 is on 17q12-q21 and FWT2 on 19q13. Other susceptibility genes still remain to be identified.

Neuroblastoma

Neuroblastoma is one of the most commonly occurring malignant solid tumors in childhood which is often being advanced at diagnosis, commonly metastasizing widely to bone marrow, bone cortex, liver, lymph nodes, and lung. The tumor arises from the neural crest origin and can originate from any site along the distribution of the sympathetic chain. More than 90% are active in secreting biochemical substances which helps in diagnosis as catecholamine metabolites may be measured in the urine.

Genetic factors play a major role in development and the link between maldevelopment and tumors. A positive association between congenital malformation and neuroblastoma has been reported in at least one recent study (odds ratio (OR) = 2.2, 95% confidence interval (95% CI): 1.1–4.5),[44] being particularly linked to those tumors presenting at under one year of age (OR = 16.8, 95% CI: 3.1–90), as opposed to those presenting at over one year of age.

Neuroblastomas demonstrate a unique clinical behavior within the perinatal period. Certain tumors, although malignant in appearance, may undergo spontaneous regression whereas others metastasize widely and aggressively. Studies have shown a favorable outcome for neuroblastoma in the majority of mass-screened perinatal patients[18,70] suggesting either a better biological profile or operative developmental signaling pathways which still function in the perinatal period. In addition, stage IVS neuroblastomas although widely spread (including a massively enlarged liver and extensive subcutaneous (blueberry muffin) lesions), have a relatively good clinical prognosis.

Neuroblastoma tumor cells are associated with molecular genetic features in up to 80% of cases, many of which are of biological and clinical significance as prognostic factors and are currently of value in directing treatment.

The most important of these are MYCN amplification, deletion of chromosome 1p, ploidy, additional copies of chromosome 17q, and the expression of the gene for the neurotrophin nerve growth factor gene *TRKA*. Multiple areas of LOH and copy number gain were seen. In many cases, the defect is found to be on chromosomes 1, 11, and 17. Gain of copy number on 17q has recently been reported in 95% of cases studied and one of the most consistent changes being a deletion on the short arm of chromosome 1 (1p36.1–1p36.3). Whereas 1p LOH is encountered in one-third of cases,[71] inactivation of the tumor suppressor gene at 11q23.3 has been found to be an even more frequently encountered element of malignant progression being identified in up to 68%.[72] LOH on both chromosomes 11q and 1p were mostly accompanied by copy number loss, indicating homozygous deletion. It is also highly associated with occurrence of chromosome 3p LOH.

Additional chromosomal abnormalities have been identified at 4p, 6q, 9q, 10q, 12q, 13q, 14q, 16q, 22p, and 22q.[73] Amplification of the n-Myc oncogene (usually found on chromosome 2) has been associated with a more advanced form of the malignancy and is a poor prognostic sign. Few of the perinatal neuroblastomas have n-myc amplification, although 10–20% have unfavorable histological features. Recent research into high-risk neuroblastomas without MYCN amplification has shown that other oncogenic genes may deregulate MYC via altered beta-catenin signaling (a transcriptional target of beta-catenin) indicating some degree of interdependence with other signaling pathways.[74] Recent reports of the downregulation of activin-A by MYCN offers an explanation for this as deprived neuroblastoma cells experience a decrease in growth-inhibitory signal transduction leading to excessive cell growth.[75] In addition, the expression of TrkA has recently been shown to inhibit angiogenesis and tumor growth in neuroblastomas suggesting possible new treatment options.[76] It is also interesting to note that *p53* gene mutations are absent in neuroblastomas,[77] although present in other tumors of childhood.

The association of the Wnt signaling cascade with cancers in young children, provides a further potential candidate

signaling pathway with the potential for therapeutic down-regulation and indicates the existence of an underlying mechanism which may result in dysregulation of the Wnt/beta-catenin transcription pathway.

TERATOMA

Germ cell tumors account for approximately 3% of pediatric malignancies worldwide and occur in gonadal (male and female) and extragonadal sites. Epidemiology should include abortions and stillbirths, as the related mortality rate is high. The majority of teratomas are located in the sacrococcygeal region and gonads in childhood. Sacrococcygeal tumors are mostly benign at birth and the majority do not develop to malignancy if adequate surgical removal is carried out before the infant is three months of age. After this time, the risk of malignancy increases if residual tumor is present and older children may require chemotherapy along with delayed surgical excision.

Teratomas are thought to arise from the primordial germ cells as the result of an early event. A genetic tendency towards spontaneous gonadal teratomas is seen in a specific strain of experimental mice (strain 129).[78] An association with autosomal dominant familial recurrence has been reported and there also appears to be a Mendelian dominant genetic predisposition to the development of a presacral mass in association with anorectal, sacral, and urogenital abnormalities.[79] Patients with an imperforate anus and a hemisacrum have a high incidence of presacral masses which are teratomas and may occasionally be malignant.[79] Recent evidence points to an association with the long arm of chromosome 7 and Currarino's triad.[80] Mediastinal teratomas have been shown to develop in the second trimester.[81] Their sensitivity to chemotherapy and the existence of reliable tumor markers are important prognostic factors.

SOFT-TISSUE TUMORS

Soft-tissue tumors (STS) are not uncommon in childhood and whereas the majority are benign lesions of connective tissue, a number of extremely aggressive tumors exist. There are arguably three separate clinical groups of soft-tissue tumors encountered in childhood (that is, congenital fibrosarcoma (CFS), rhabdomyosarcoma (RMS), and non-rhabdomyosarcoma (NRSTS)).[82]

Spicer[83] classified congenital fibrosarcoma separately to differentiate it from the more aggressive-type fibrosarcomas with similar histopathologic features seen in adults as they mostly have a favorable outcome and metastasize rarely. Classifying STS on prognosis and outcome, he considered that tumors of intermediate prognosis included rhabdomyosarcomas, peripheral neuroectodermal tumors (PNET), undifferentiated sarcomas, and malignant melanomas, whereas tumors with a uniformly bad prognosis included Kaposi sarcoma, malignant schwannoma, Triton tumors, and juvenile hyaline fibromatosis, as well as visceral fibromatosis.

Rhabdomyosarcoma

Rhabdomyosarcoma accounts for 10% of neonatal malignancies,[84] being the most common malignant STS even in the perinatal period.[20] It has a number of genetic associations which differentiate the histological subtypes and is associated with a number of genetic syndromes (Beckwith–Wiedemann, Li–Fraumeni, and WAGR syndromes, and neurofibromatosis (type 1)). This suggests a genetic basis for its early appearance in the neonatal period.

Associated genetic variations include loss of heterogeneity of the short arm of chromosome 11 (11p15 locus 12) in embryonal tumors which leads to an overexpression of the insulin growth factor II (*IGFII*) gene. Equally, a subset of alveolar RMS has a unique chromosomal translocation between chromosomes 2 and 13, that is, (t[2;13]) (q35;q14)).[85,86] This is close to the junction of the *PAX3* gene which controls neuromuscular development[87] and the *PAX/FKHR* fusion gene is found in as many as 60% of alveolar RMS. A further 10% of patients with particularly poor prognosis may also carry the Ewing's sarcoma (*EWS/ETS* fusion genes (occasionally along with the *PAX/FKHR* gene)).

Numerous other genetic variations have been reported, including frequent gains of chromosomes 2, 7, 8, 11, 12, 13q21, and 20, as well as losses of 1p35–36.3, 6, 9q22, 14q21–32, and 17.[88] A further loss of 1p36[89] corresponds to the locus for the paired home box PAX 7 which is characteristically altered in alveolar RMS tumors. The 1p region is interesting as it is also associated with neuroblastomas. Additional associations between mutations in the p53 tumor suppressor gene are also associated with adverse outcome.

STS and the Beckwith–Wiedemann syndrome

The Beckwith–Wiedemann syndrome (macrosomia, macroglossia, omphalocele, and hemihypertrophy) is associated with genetic and/or epigenetic alterations that modify imprinted gene expression on chromosome 11p15.5. There is an increased risk of soft tissue sarcomas (approximately 7.5%), especially if hemihypertrophy is present. Oncogenesis is associated with the detection of abnormal myogenic transcription factors (MyoD, Myogenin, and Myf5) and the PAX/FHKR chimeric transcription factors. Detection of other fusion genes, such as EWS/WT1, in desmoplastic small round cell tumors, EWS/ATF in clear cell sarcoma, SSX/SYT in synovial cell sarcoma, or the TLS/CHOP in liposarcoma have also been described. An overexpression of MyoD in RMS is thought to inhibit the development of muscle cells and characteristically marks these tumors.[90]

The increased tumor risk in the Beckwith–Wiedemann overgrowth syndromes (BWS) and the associated Wilms' tumor, hepatoblastoma, and hemihypertrophy, are probably due to the complex genetic/epigenetic abnormalities of

the imprinted 11p15 region.[91,92] A specific cancer risk is associated with specific areas of the gene[93] with the most common constitutional abnormalities currently appearing to be epigenetic, with aberrant methylation occurring at H19 or LIT1. As a result, untranslated RNAs are recorded on the gene at 11p15. Variations in H19DNA methylation were found to be significantly increased in at least one report (that is, 56% (9/16) versus 17% (13/76; $p = 0.002$), but not LIT1 alterations.

Ewing's family tumors

Although the cell of origin of Ewing's sarcoma is unknown, the Ewing's family of tumors most frequently has a specific translocation that results in expression of the EWS/FLI1 fusion protein responsible for malignant transformation.[94] Although a number of EWS/FLI1 downstream targets have been identified, the exact details of the oncogenic mechanism remains uncertain. It is currently thought that the *FLI*, *ERG*, *FEV*, *ETV1*, and *ETV4* genes appear to be involved in chimera formation which all upregulate EAT-2 (a previously described EWS/FLI1 target). EWS/FLI1 dysfunction appears to then result in functional activation of the retinoblastoma (pRB) family proteins which are key mediators of the resulting probable oncogenic transformation.[95]

HEPATOBLASTOMA

Hepatoblastoma (HB) is the most common malignant liver tumor particularly in the younger child. Although up to one-third of hepatoblastomas are associated with congenital abnormalities, familial recurrence is extremely rare with the exception of families with adenomatous polyposis coli.[96] There is also considerable support for associations with trisomies 2, 8, and 20 in the development of HB.[97] It has also been associated with a low birth weight in the neonate.[98]

Congenital hepatoblastomas appear to have a poorer prognosis than those occurring in the older child with metastatic lesions being reported at unusual sites (brain,[99] iris and choroid,[100] and placenta[101]). The latter may indicate tumor seeding during pregnancy via the fetal circulation.

There is relatively little known about the molecular basis of hepatoblastoma in infancy and the common tumor markers, such as CTNNB1, APC,[102] and IGF-2, are variable, particularly in the sporadic tumors. Some support exists for associations with trisomies 2, 8, and 20.[103] Multiple deletion or point mutations have been described in hepatoblastoma, but gains on chromosomes 1q and 2 are typical with 2q24 being viewed as the critical chromosomal band. In addition, gains on 8q and 20 have been shown to have a significantly higher association with poor outcome.[103]

There is a clear association with the Beckwith–Wiedemann syndrome[104] and hemihypertrophy. It has been postulated that the mechanism of tumorigenesis is similar to that of Beckwith–Wiedemann syndrome-associated tumors, such as Wilms' tumor, RMS, and hepatoblastoma, which suggests a common genetic pathway involving LOH at the 11p site.[105]

The chief APC gene function is to downregulate beta-catenin by phosphorylation sites on exon 3. Beta-catenin is a transcription-activating protein with the potential to promote tumorigenesis. APC mutation and dysregulation has been shown to lead to accumulation of beta-catenin protein in the cellular nucleus, thus activating a number of tumor-related events.[102] Current data suggest that activation of beta-catenin signaling may be an important step in hepatoblastoma pathogenesis. In a separate study, mutations in beta-catenin were only detected in 19% of cases, although beta-catenin protein accumulation was identified in 67% and microsatellite instability in 81% confirming that beta-catenin dysfunction is involved in sporadic hepatoblastoma;[106] chromosomal variations were observed in 88% of cases in a genome-profiling study.[107] Gains in chromosomes 1q, 2 (or 2q), 8, 17q, and 20, and losses in chromosomes 4q and 11q occurred frequently, as well as high-grade amplifications at 7q34, 14q11.2, and 11q22.2. LOH at 11p15 was identified in a subgroup and is of considerable interest due to the location of the insulin-like growth factor II (*IGFII*) and *H19* genes within this region.[107]

OTHER TUMORS

Other genetic aberrations associated with tumors, such as the loss of heterozygosity on chromosome 5q, in identifying the gene for familial polyposis of the colon, defects in tumor-suppressive genes on 17q (p53) and 18q (DCC) in carcinoma of the colon, and translocation of the end of the long arm of chromosome 8 with chromosome 14, or an alteration in C-myc regulation or p53[108] in Burkitt's lymphoma, are interesting associations with pediatric tumors, but are not particularly associated with the neonatal period.

ANTENATALLY DIAGNOSED TUMORS

Clinical approach to antenatally diagnosed tumors

The reasons for highlighting neonatal tumors are manifold, but include the following:

- increased diagnosis of neonatal tumors due to routine ultrasonography during pregnancy brings to light tumors whose natural history and optimal management is unclear;
- increased knowledge and understanding of pathophysiology and biological behavior of tumors may reduce unnecessary harmful forms of therapy;
- molecular genetics in these tumors identifies risk factors and provides models for understanding carcinogenesis in other tumors;
- environmental and teratogenic factors may be identified.

All evidence points toward the fact that the natural history of neonatal tumors is different (mostly better) than that of comparable tumors in older children. The basis of this

behavior is largely unknown and hard epidemiological and etiological data in this group are lacking.

It is important that the identification of the genetic associations of these tumors continues and the cancer-producing genes to identify the genetic alleles associated with malignancy are investigated further. In addition, it is important that families with a genetic susceptibility to malignant tumors be investigated in order to identify specific genetic loci which may or may not be related to a specific allele. Because of the rarity of these tumors, it is clear that international collaborative studies and research projects are necessary to achieve this goal.

THERAPEUTIC CONSIDERATIONS

There is a paucity of objective information on the optimal treatment and long-term outcome of neonatal tumors[11] and the impact of therapeutic measures to be taken into consideration.[12,109–111]

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78

Hemangiomas and vascular malformations

ARIN K GREENE AND STEVEN J FISHMAN

INTRODUCTION

Vascular anomalies are disorders of the endothelium that usually present during childhood. These lesions affect all parts of the vasculature: capillaries, veins, arteries, or lymphatics. Although nearly always benign, vascular anomalies may involve any location. In addition to disfigurement, local complications include obstruction, bleeding, infection, and pain. Systemic sequelae can include thrombocytopenia, pulmonary embolism, congestive heart failure, sepsis, and even death.

A biologic classification of vascular anomalies has clarified the difference between vascular anomalies based on physical findings, natural history, and cellular characteristics.[1] Vascular anomalies are broadly divided into two groups: tumors and malformations (Table 78.1). Vascular tumors are characterized by endothelial cell proliferation (Fig. 78.1). Vascular malformations, in contrast, arise from dysmorphogenesis and have normal endothelial cell turnover (Fig. 78.2).

Table 78.1 Biological classification of vascular anomalies.

Tumors	Malformations	
	Slow flow	Fast flow
Infantile hemangioma (IH)	Capillary (CM)	Arteriovenous (AVM)
Congenital hemangioma (CH)	Venous (VM)	
Kaposiform hemangioendothelioma (KHE)	Lymphatic (LM)	
Pyogenic granuloma (PG)		

VASCULAR TUMORS

Infantile hemangioma

CLINICAL FEATURES

Infantile hemangioma (IH) is a benign tumor of the endothelium that affects approximately 4–5% of Caucasian infants.[1–3] It is more frequent in premature children and females (3:1 to 5:1).[4] IH typically is single (80%) and involves the head and neck (60%), trunk (25%), or extremity (15%).[2] The median age of appearance is 2 weeks, although 30–50% of lesions are noted at birth as a telangiectatic stain or ecchymotic area.[5] IH grows faster than the rate of the child during the first nine months of age (the proliferating phase).[6] When IH involves the superficial dermis it appears red. A lesion beneath the skin may not be appreciated until three to four months of age when it has grown large enough to cause a visible deformity; the overlying skin may appear bluish. By 9–12 months of age, the growth of IH plateaus to approximate that of the infant.[6] After 12 months of age, the tumor begins to shrink (the involuting phase); the color fades and the lesion flattens. Involution stops in approximately 50% of children by five years of age (the involuted phase).[5] After involution, one-half of children will have an abnormality: residual telangiectasias, scarring, fibrofatty residuum, redundant skin, or destroyed anatomical structures.

DIAGNOSIS

Ninety percent of IH are diagnosed by history and physical examination. Diagnosis is facilitated using a hand-held Doppler device showing fast-flow. Ultrasonograpy (US) is the first-line confirmatory study to differentiate IH from other lesions. IH appears as a soft-tissue mass with fast-flow, decreased arterial resistance, and increased venous drainage.[7] On magnetic resonance imaging (MRI), IH is isointense on T_1, hyperintense on T_2, and enhances during the proliferating phase.[8] Involuting IH has increased lobularity and adipose tissue; the number of vessels and flow is reduced.[8] Rarely,

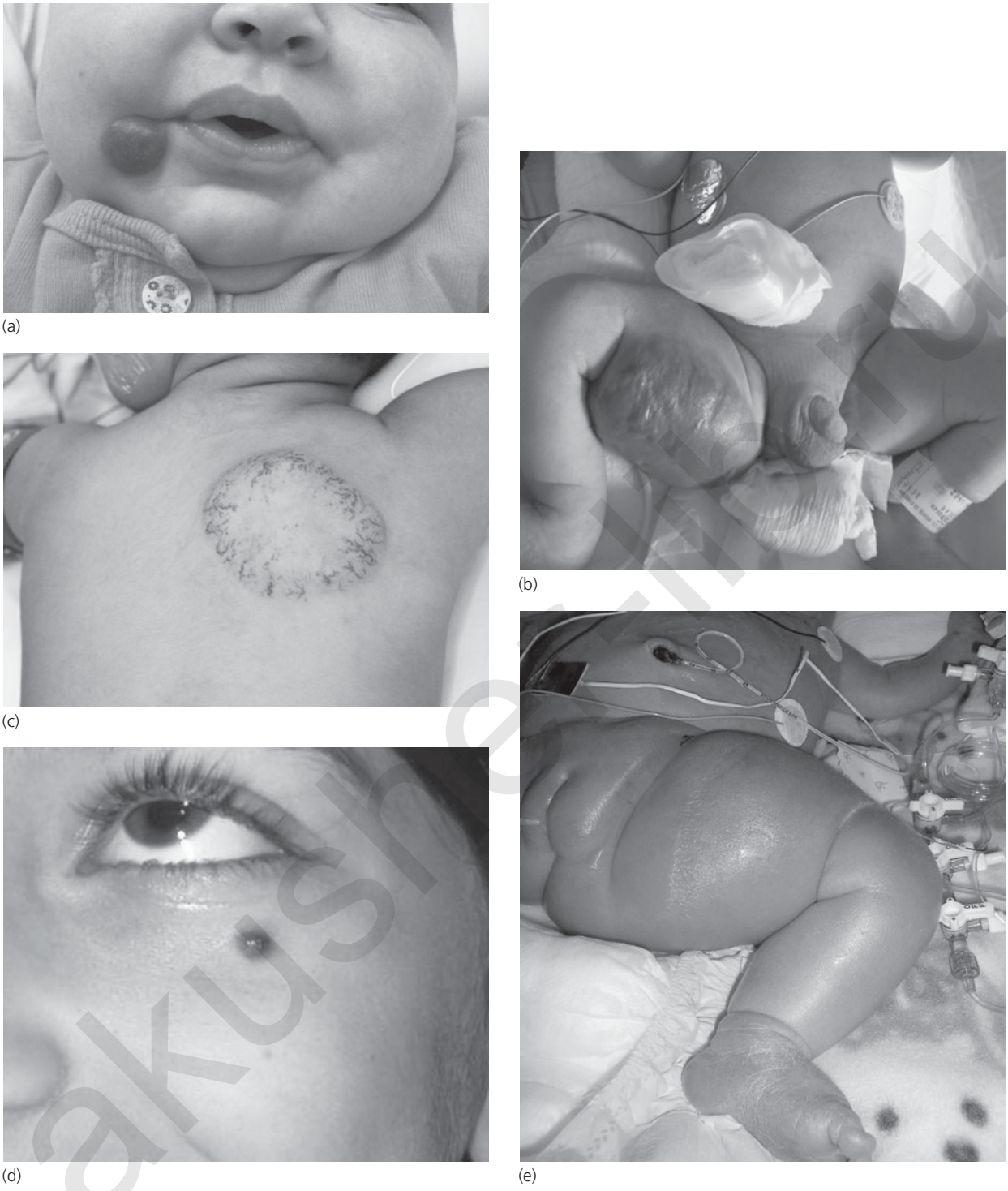


Figure 78.1 Vascular tumors of childhood. (a) Infantile hemangioma (IH) in a three-month-old female. The lesion was noted 2 weeks after birth and subsequently enlarged. It was treated with corticosteroid injection. (b) Rapidly involuting congenital hemangioma (RICH) in a 3-week-old male. The lesion was fully grown at birth and rapidly involuted over the first year of life. (c) Non-involuting congenital hemangioma (NICH) in a 2.5-year-old male; the vascular mass had not changed since birth. (d) Pyogenic granuloma in an eight-year-old female with a three-month history of a bleeding lesion. (e) Kaposiform hemangioendothelioma (KHE) in a 5-week-old neonate treated with vincristine.

biopsy is indicated if malignancy is suspected or if the diagnosis remains unclear following imaging studies. Because an erythrocyte-type glucose transporter (GLUT1) is specifically expressed in proliferating IH, immunostaining for GLUT1 can differentiate IH from other lesions.[9]

CLINICAL CONSIDERATIONS

Head and neck hemangiomas

Ten percent of proliferating IH cause significant deformity or complications, usually when located on the head or neck.[10]

Ulcerated lesions may destroy the eyelid, ear, nose, or lip. IH of the scalp or eyebrow can result in alopecia. Periorbital hemangioma can block the visual axis or distort the cornea causing amblyopia. Subglottic hemangioma may obstruct the airway; tracheostomy rarely may be necessary.

Multiple hemangiomas

Although 20% of infants will have more than one IH, occasionally a child will have five or more small (<5 mm), dome-like lesions termed 'hemangiomatosis'.[5] These children are at increased risk for IH of internal organs. The liver is most commonly affected; the brain, gut, or lung are rarely involved. US should be considered to rule out hepatic IH.

Hepatic hemangiomas

The liver is the most common extracutaneous site for IH, which may be focal, multifocal, or diffuse (Fig. 78.3).[11] Although most hepatic IH are non-problematic and discovered incidentally, some tumors can cause heart failure, hepatomegaly, anemia, or hypothyroidism. Ninety percent of fast-flow hepatic lesions are hemangioma; arteriovenous malformation, hepatoblastoma, and metastatic neuroblastoma are less common and do not demonstrate significant shunting on imaging.[11] Focal hepatic IH are usually asymptomatic unless they have associated direct macrovascular shunts (hepatic artery to hepatic vein and/or portal to hepatic vein). These direct shunts can lead to high output cardiac failure. Focal hepatic lesions are not associated with cutaneous lesions. They are not typical infantile hemangiomas, but rather the hepatic presentation of rapidly involuting congenital hemanangioma (RICH). Multifocal hepatic IH are typical infantile hemangioma, immunopositive for GLUT1, and may be associated with cutaneous lesions. Although usually asymptomatic, multifocal lesions can also have associated macrovascular shunts which can cause high-output cardiac failure. In either focal or multifocal variants, shunts may close with tumor involution, which may be hastened pharmacologically. Embolization of the shunts, although technically demanding, will quickly control cardiac failure.[12] Diffuse hepatic IH can cause massive hepatomegaly, respiratory compromise, or abdominal compartment syndrome. Infants are also at risk for hypothyroidism and subsequent irreversible brain injury because the tumor expresses a deiodinase which inactivates thyroid hormone.[13] Patients require thyroid-stimulating hormone monitoring and, if abnormal, thyroid replacement, often in massive doses, until the IH undergoes involution.

Lumbosacral hemangioma

Large, superficial, plaque-like, or reticular IH may rarely be associated with underlying spinal, urogenital, or anorectal malformations when it is located in the lumbosacral midline (tethered spinal cord, anorectal and genital malformations, renal anomalies, lipomyelomeningocele).[14,15] US is obtained to rule out associated spinal anomalies in infants less than four months of age. MRI is indicated in older infants or when US is equivocal.

PHACES association

PHACES association affects 2.3% of patients with IH, and consists of a plaque-like IH in a 'segmental' or trigeminal dermatomal distribution of the face with at least one of the following anomalies: posterior fossa brain malformation, hemangioma, arterial cerebrovascular anomalies, coarctation of the aorta and cardiac defects, eye/endocrine abnormalities, sternal clefting or supraumbilical raphe.[16] Ninety percent of infants are female and cerebrovascular anomalies are the most common associated finding (72%).[17] Because 8% of children with PHACES have a stroke in infancy, patients should have an MRI to evaluate the brain and cerebrovasculature.[18] Infants are referred for ophthalmologic, endocrine, and cardiac evaluation to rule out associated anomalies.[18]

NON-OPERATIVE MANAGEMENT

Most IH are managed by observation because 90% are small, localized, and do not involve esthetically or functionally important areas. During the proliferative phase, 16% of lesions will ulcerate; the lips, neck, and anogenital region are the most common areas to break down.[19] Other complications include bleeding and infection.[19] To reduce the risk of ulceration, the IH is kept moist during the proliferative phase with hydrated petroleum to minimize desiccation, as well as to protect against incidental trauma. IH may be further protected by using a petroleum gauze barrier. If an ulceration develops, it is managed with local wound care.

Topical corticosteroid

Topical corticosteroid has minimal efficacy; especially against IH involving the deep dermis and subcutis. Ultrapotent agents may be effective for small, superficial IH; however, their efficacy is inferior to intralesional corticosteroid. Although lightening may occur, if an underlying mass is present it likely will not be affected.[20] Adverse effects include hypopigmentation, skin atrophy, and possible adrenal suppression.

Intralesional corticosteroid

Small, well-localized IH that obstruct the visual axis or nasal airway, or those at risk for damaging esthetically sensitive structures (i.e. eyelid, lip, nose) are best managed by intralesional corticosteroid. Triamcinolone (3 mg/kg) stabilizes the growth of the lesion in at least 95% of patients, and 75% of tumors will decrease in size.[21] The corticosteroid lasts 4–6 weeks and thus infants may require additional injections during the proliferative phase. Intralesional corticosteroid may cause subcutaneous fat atrophy. Blindness has been reported following injection of periorbital hemangioma, possibly due to embolic occlusion of the retinal artery.[22,23]

Systemic corticosteroid

Problematic IH that is too large to treat with intralesional corticosteroid is managed by daily oral prednisone. The patient

is started on 3 mg/kg per day for one month which then is tapered every 2–4 weeks until it is discontinued between 10 and 12 months of age when the tumor is no longer proliferating. Recently, propranolol has been described for the treatment of IH, but its efficacy and safety, compared to corticosteroid, has not been studied.[24,25] Corticosteroid, in contrast, has been used to treat IH for over 40 years and has proven to be very safe and effective.[26–29] Overall, 84% of patients treated with different doses of corticosteroid will have (1) stabilization of growth or (2) accelerated regression.[28] Almost all patients, however, will respond to 3 mg/kg per day.[28] Treatment response is usually evident within 1 week of therapy by signs of involution: decreased growth rate, fading color, and softening of the lesion. The location of the hemangioma does not affect the response rate.[30] For the rare lesion that fails to stabilize with corticosteroid, the dose may be increased up to 5 mg/kg per day which may improve treatment response.[31] Alternatively, the child may be switched to vincristine; interferon is not advocated in children less than 12 months of age because it may cause spastic diplegia.[32,33]

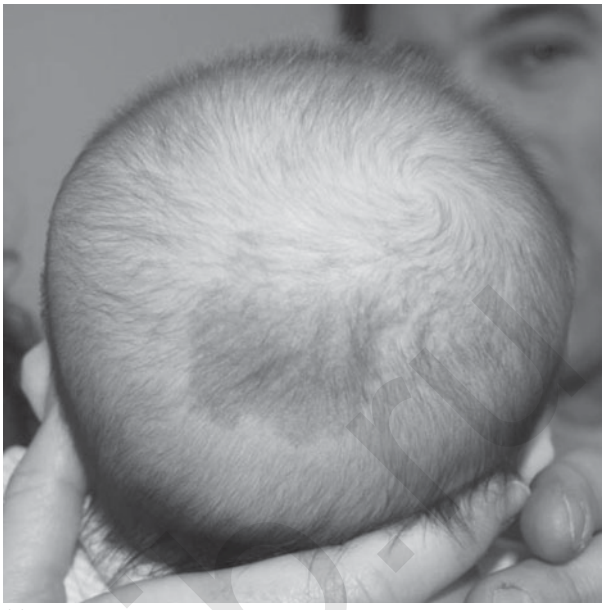
Complications of systemic corticosteroid for the management of IH have been studied and no adverse effects on neurodevelopment have been found.[29] Short-term morbidity includes: cushingoid face (71%), personality change (29%), gastric irritation (21%), fungal (oral or perineal) infection (6%), myopathy (1%), decreased gain in height (35%), and decreased gain in weight (43%).[27] These findings resolve after the completion of therapy. For example, over 90% of children return to their pretreatment growth curve for height by 24 months of age.[27] Long-term complications of corticosteroid, such as aseptic necrosis of the femoral head, diabetes, osteoporosis, long-term adrenal insufficiency, cataracts, and glaucoma, have not been noted in patients treated with corticosteroid for IH.[27,34,35]

Embolic therapy

High-output congestive heart failure may be caused by macrovascular shunts seen with focal or multifocal hepatic lesions, or very rarely large non-hepatic IH. Embolization may be indicated for the initial control of heart failure, while the therapeutic effects of systemic corticosteroid are pending. Cardiac failure can recur even after initial improvement, and continued drug therapy after embolization may be indicated until the child is approximately 12 months of age when natural involution begins.

Laser therapy

Pulsed-dye laser treatment for proliferating IH is contraindicated. The laser penetrates only 0.75–1.2 mm into the dermis and thus only affects the superficial portion of the IH. Although lightening may occur, the mass of IH is not affected and accelerated involution does not occur.[36,37] Instead, patients have an increased risk of skin atrophy and hypopigmentation.[37] The thermal injury delivered by the laser to the ischemic dermis increases the risk of ulceration, pain, bleeding, and scarring.[38] The pulsed-dye laser is indicated, however, during the involuted phase to treat residual telangiectasias. Destructive laser therapy may be useful in airway hemangioma to avoid tracheostomy while awaiting successful response to pharmacotherapy.



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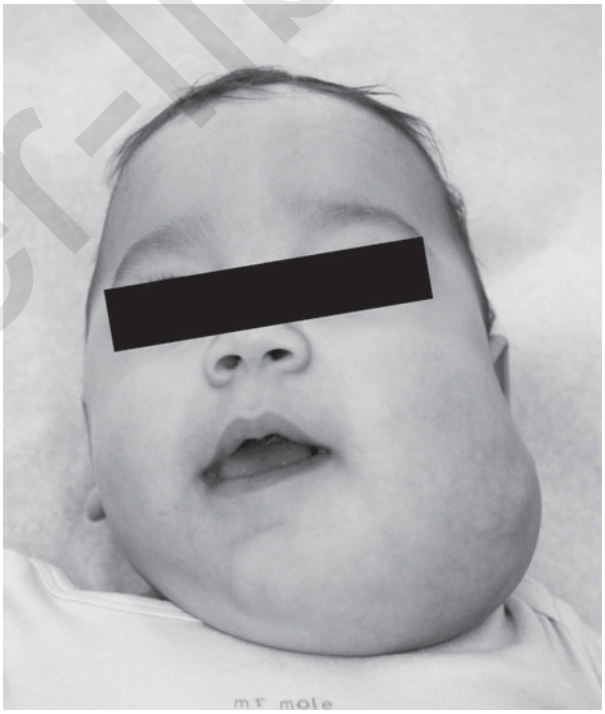
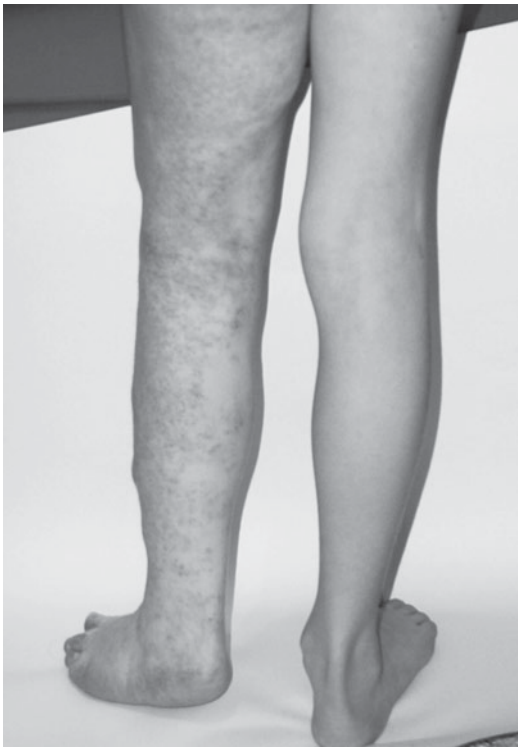


(b)

Figure 78.2 Vascular malformations of childhood. (a) Capillary malformation (CM) of the scalp of a two-month-old female. (b) A seven-month-old female with a macrocystic lymphatic malformation (LM) of the left face treated with sclerotherapy. (c) A seven-year-old female with a diffuse venous malformation (VM) of the left lower extremity managed with compression stockings. (d) A 16-year-old male with an arteriovenous malformation (AVM). (e) A one-year-old female with a combined capillary–lymphatic–venous malformation (CLVM) of the right lower extremity with overgrowth (Klippel–Trenaunay syndrome).



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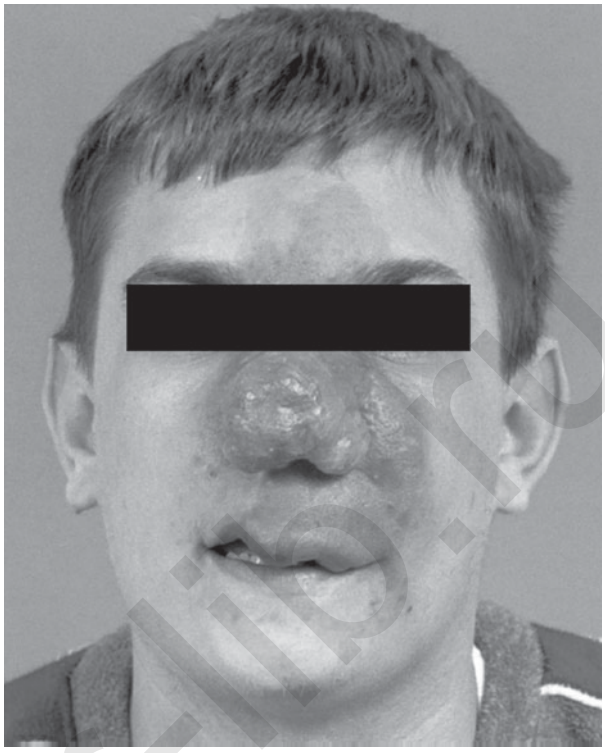

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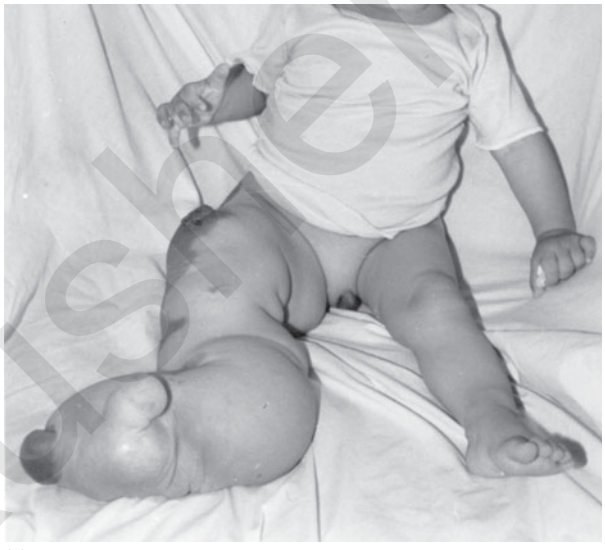


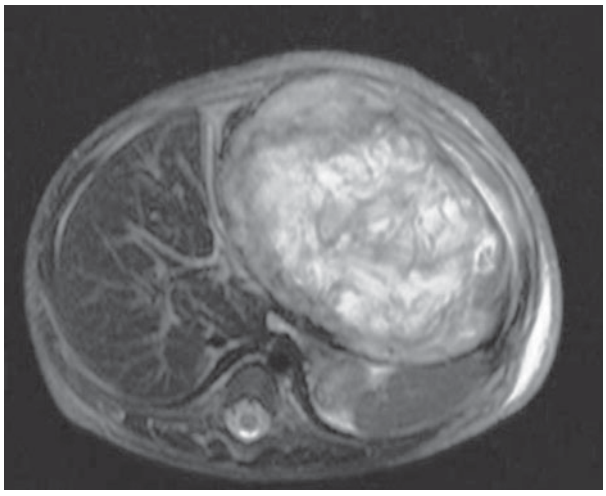
(e)

Figure 78.2 *Continued*

OPERATIVE MANAGEMENT

Proliferative phase (infancy)

Operative treatment in infancy is generally not recommended. The tumor is highly vascular during this period and the patient is at risk for blood loss, iatrogenic injury, and an inferior esthetic outcome, compared to excising residual tissue after the tumor has regressed.[30] Factors that lower the threshold for resection of a problematic proliferating IH include (1) failure or contraindication to corticosteroid, (2) well localized in an anatomically safe area, (3) complicated reconstruction is not required, (4) resection will be necessary in the future and the scar will be the same. Circular lesions located in visible areas, particularly the face, are best treated by circular excision and purse-string closure.[39] This technique minimizes the length of the scar, as well as distortion of surrounding structures. A lenticular excision of a circular hemangioma will result in a scar as long as three times the diameter of the lesion, while a two-stage circular resection followed by lenticular excision 6–12 months later will leave a scar approximately the same length as the diameter of the original hemangioma.[39]



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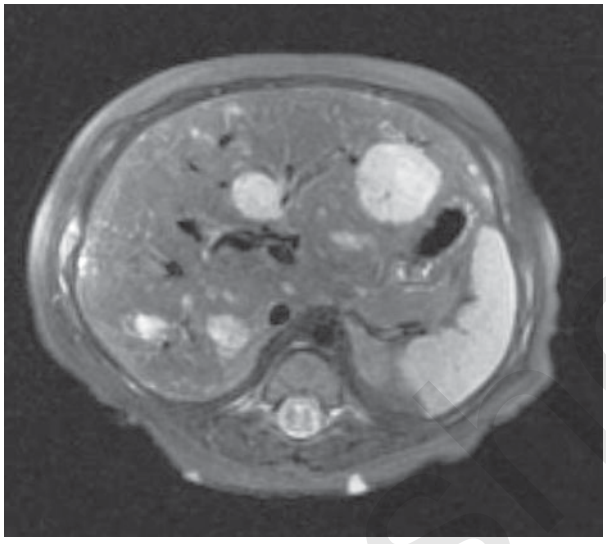

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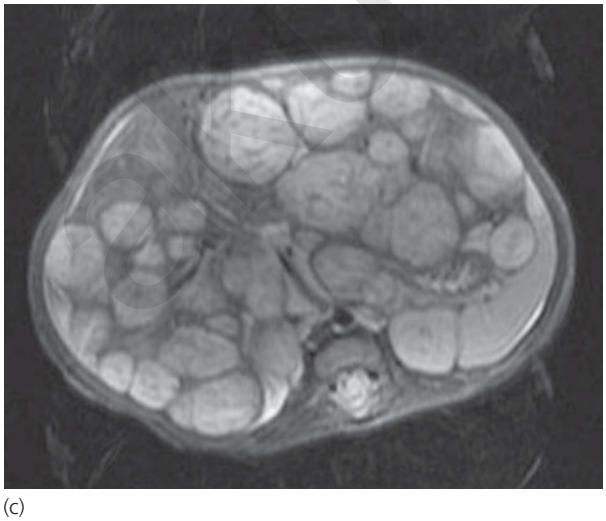

(c)

Figure 78.3 Types of hepatic hemangioma in infancy. Axial T_2 MRI showing three patients with focal (a), multifocal (b), and diffuse (c) hepatic hemangiomas.

Involuting phase (early childhood)

While operative management of IH is generally avoided during the proliferative phase, resection during involution is much safer because the lesion is less vascular and smaller. Because the extent of the excision and reconstruction is reduced, the esthetic outcome is superior. Approximately 50% of IH leave behind fibrofatty tissue or damaged skin after the tumor regresses, causing a deformity.[5] Less often, children require reconstruction of damaged structures (i.e. nose, ear, lip). Staged or total excision should be considered during this period, rather than waiting for complete involution if (1) it is clear that the patient will require resection (i.e. post-ulceration scarring, destroyed structures, expanded skin, significant fibrofatty residuum), (2) the length of the scar would be similar if the procedure was postponed to the involuted phase, (3) the scar is in a favorable location. Advantages of operative intervention during this period, compared to late childhood, is that reconstruction is performed prior to the child's development of memory or awareness of body differences.

Involuted phase (late childhood)

Waiting until IH has fully involuted prior to resection ensures that the least amount of fibrofatty residuum and excess skin is resected, giving the smallest possible scar. Allowing full involution to occur, however, must be weighed against the psychosocial morbidity of maintaining a deformity until late childhood. Allowing full involution is advocated for lesions when it is unclear if a surgical scar would leave a worse deformity than the appearance of the residual hemangioma.

Congenital hemangioma

CLINICAL FEATURES

Congenital hemangioma (CH) is fully grown at birth and does not illustrate postnatal growth.[40–42] CH has a different appearance to IH: it is red-violaceous with coarse telangiectasias, central pallor, and a peripheral pale halo. Unlike IH, CH is more common in the extremities, has an equal sex distribution, and is almost always solitary with an average diameter of 5 cm.[40–42] Two types of CH exist: rapidly involuting congenital hemangioma RICH and non-involuting congenital hemangioma (NICH). RICH involutes rapidly after birth and 50% of lesions have completed regression by seven months of age.[40,42] RICH affects the head or neck (42%), limbs (52%), or trunk (6%).[40–42] RICH does not leave behind a significant adipose component, unlike IH.[42] NICH, in contrast, does not undergo involution.[41] It involves the head or neck (43%), limbs (38%), or trunk (19%).[41]

MANAGEMENT

RICH does not require operative management in infancy because it undergoes accelerated regression; tumors are observed. Occasionally, RICH is complicated by congestive heart failure which is treated by corticosteroid or embolization

as the lesion involutes. Since RICH undergoes such rapid natural involution, it is not clear whether corticosteroid hastens involution. After regression, RICH may cause a residual deformity, usually atrophic skin and subcutaneous tissue. Operative intervention for RICH must not create a more obvious deformity than the lesion. Reconstruction with autologous grafts (fat, dermis) or acellular dermis may be indicated. NICH is rarely problematic in infancy and is observed. Because NICH is benign, asymptomatic tumors do not require excision. Symptomatic lesions in infancy are managed with embolization or resection. Resection may be indicated to improve the appearance of the affected area, as long as the surgical scar is less noticeable than the lesion. Pulse-dye laser therapy may improve the late appearance of CH by eliminating telangiectasias.

Kaposiform hemangioendothelioma

CLINICAL FEATURES

Kaposiform hemangioendothelioma (KHE) is a rare vascular neoplasm that is locally aggressive, but does not metastasize.[43,44] Although one-half of lesions are present at birth, KHE may develop during infancy (58%), between the ages of one and ten years (32%), or after 11 years of age (10%).[45] KHE has an equal sex distribution, is solitary, and affects the head/neck (40%), trunk (30%), or extremity (30%).[45] The tumor is often greater than 5 cm in diameter, and thus larger than the typical IH.[44] KHE causes a visible deformity, as well as pain. In addition, 50% of patients have Kassabach–Merrit phenomenon (KMP) (thrombocytopenia $<25\,000/mm^3$, petechiae, bleeding).[43,44] KHE partially regresses after two years of age, although it usually persists long term, causing chronic pain and stiffness.

DIAGNOSIS

KHE is diagnosed by history and physical examination. Unlike IH, it is usually present at birth as a flat, reddish-purple, edematous lesion that does not exhibit rapid postnatal growth; it is also associated with KMP. MRI is indicated for diagnostic confirmation or to evaluate the extent of the tumor. MRI shows poorly defined margins, small vessels, and invasion of adjacent tissues.[8] KHE shows T_2 hyperintensity and postgadolinium enhancement; signal voids may also be present.[8] Histologically, KHE has infiltrating sheets or nodules of endothelial cells lining capillaries.[43] Hemosiderin-filled slit-like vascular spaces with red blood cell fragments, as well as dilated lymphatics, are present.[43]

MANAGEMENT

Most lesions are large and involve multiple tissues preventing complete extirpation. Patients with KMP require systemic treatment to prevent life-threatening complications. Large, asymptomatic tumors are also managed with pharmacotherapy to minimize fibrosis and subsequent long-term pain and stiffness. KHE responds best to vincristine (90%), which is the first-line therapy.[46] KHE does not respond as well to second-line drugs, interferon (50%), or corticosteroid (10%).[44,46] Thrombocytopenia will not be significantly improved with platelet transfusion because the platelets are trapped in the lesion. Transfusion can worsen swelling and should be avoided unless there is active bleeding or a surgical procedure is planned. By two years of age, the tumor often undergoes partial involution and the platelet count normalizes. Excision rarely may be indicated for symptomatic patients with well-localized lesions or who have failed chemotherapy. Resection is not required for large lesions that are not causing functional problems because KHE is benign. The risks of the resection and the resulting deformity should be weighed against the appearance of the tumor.

Pyogenic granuloma

Pyogenic granuloma (PG) has been called 'lobular capillary hemangioma'.[47] PG is a solitary, red papule that grows rapidly, forming a stalk. It is small, with an average diameter of 6.5 mm; the mean age of onset is 6.7 years.[48] The male:female ratio is 2:1. PG is commonly complicated by bleeding (64.2%) and ulceration (36.3%). PG primarily involves the skin (88.2%), but can involve mucous membranes as well (11.8%). PG is distributed on the head or neck (62%), trunk (19%), upper extremity (13%), or lower extremity (5%). Within the head and neck, affected sites include: cheek (28.8%), oral cavity (13.5%), scalp (10.8%), forehead (9.9%), eyelid (9.0%), or lips (9.0%).[48] PG should be treated after diagnosis to prevent likely ulceration and bleeding. Numerous treatment methods have been described for PG: curettage, shave excision, laser therapy, or excision. Because the lesion can involve the reticular dermis, it may be out of the reach of the pulsed-dye laser, cautery, or shave excision. Consequently, these modalities have a recurrence rate of 43.5%.[48] Definitive treatment requires full-thickness skin excision.

VASCULAR MALFORMATIONS

Capillary malformations

CLINICAL FEATURES

Capillary malformation (CM) consists of dilated capillaries in the superficial dermis. CM is most often solitary, but can be small or extensive. It may occur in any location and over time darkens and develops fibrovascular overgrowth. It can be associated with soft tissue and skeletal hypertrophy. Sturge–Weber syndrome consists of CM in the ophthalmic (V1) trigeminal dermatome associated with ipsilateral ocular and leptomeningeal vascular anomalies.[49] Leptomeningeal anomalies can lead to seizures, contralateral hemiplegia, and delayed motion and cognition. Patients are at risk for retinal detachment and glaucoma and should be followed by an ophthalmologist.[5]

MANAGEMENT

Pulse-dye laser (585 nm) therapy can improve the appearance of CM by lightening the color; the head and neck region has a better response compared to the extremities.[50] Outcome is also superior for smaller lesions and those treated at a younger age.[51] Fifteen percent of patients achieve at least 90% lightening, 65% improve 50–90%, and 20% respond poorly.[52] Multiple treatments, spaced 6 weeks apart, are often required until the CM fails to improve with additional treatments. After laser treatment, CM often redarkens over time.[53] CM can also be associated with soft-tissue and skeletal overgrowth.[49] Enlargement of the maxilla or mandible can result in an occlusal cant and malocclusion. CM of the trunk or extremity may be associated with fatty overgrowth causing asymmetry. Because overgrowth may be progressive, most patients do not require contouring, usually labial, until adolescence or adulthood. Malocclusion may be corrected in adolescence with orthodontic manipulation. If orthodontics is insufficient, an orthognathic procedure is considered when the jaws are completely grown. Severe cutaneous thickening and cobblestoning can be resected and reconstructed by linear closure, skin grafts, or local flaps. Facial asymmetry caused by overgrowth of the zygoma, maxilla, or mandible can be improved by contour burring.

Lymphatic malformation

CLINICAL FEATURES

Lymphatic malformation (LM) results from an error in the embryonic development of the lymphatic system. LM is characterized by the size of the malformed channels: microcystic, macrocystic, or combined.[1,2] Macrocystic lesions are defined as cysts large enough to be treated by sclerotherapy.[54] Because the lymphatic and venous systems share a common embryological origin, lymphatic-venous malformation (LVM) can also occur. LM is usually noted at birth or within the first two years of life. LM is most commonly located on the head and neck; other frequent sites include the axilla, chest, and perineum. Lesions are soft and compressible. The overlying skin may be normal, have a bluish hue, or contain pink-red vesicles.

LM typically causes a deformity and psychosocial morbidity, especially when it involves the head and neck. The two most common complications associated with LM are bleeding and infection. Intralesional bleeding occurs in up to 35% of lesions causing bluish discoloration, pain, or swelling.[55] Infection complicates as many as 71% of LMs and can progress rapidly to sepsis.[55] Cutaneous vesicles can bleed, cause malodorous drainage, as well as wounds. Swelling due to bleeding, localized infection, or systemic illness may obstruct vital structures. Two-thirds of patients with extensive cervicofacial LM require tracheostomy to maintain the airway.[55] Secondary bony overgrowth is another complication; the mandible is most commonly involved and patients can develop a malocclusion. Jaw contouring or orthognathic procedures may be required.[55] Oral lesions can cause macroglossia bleeding, pain, poor oral hygiene, and caries.[56] Thoracic or abdominal LM may lead to pleural, pericardial, or peritoneal chylous effusions. Periorbital LM leads to a permanent reduction in vision (40%) and 7% become blind in the affected eye.[57] LM may be diffuse or multifocal; patients can have splenic or osteolytic bone lesions.

DIAGNOSIS

Ninety percent of LM are diagnosed by history and physical examination.[1,2] Small, superficial lesions do not require further diagnostic work-up. Large or deep lesions are evaluated by MRI to (1) confirm the diagnosis, (2) define the extent of the malformation, and (3) plan treatment. LM appears as a cystic lesion (macrocystic, microcystic, or combined) with septations of variable thickness.[58] It is hyperintense on T_2-weighted sequences and does not show diffuse enhancement.[58] Although US is not as accurate as MRI, it may provide diagnostic confirmation or document intralesional bleeding. US findings for macrocystic LM include anechoic cysts with internal septations, often with debris or fluid-fluid levels.[58] Microcystic LM has ill-defined echogenic masses with diffuse involvement of adjacent tissues. Histological confirmation of LM is rarely necessary. LM shows abnormally walled vascular spaces with eosinophilic, protein-rich fluid, and collections of lymphocytes.[59] Immunostaining with the lymphatic markers D2-40 and LYVE-1 are positive.[59]

MANAGEMENT

LM is a benign condition and intervention is not mandatory; small or asymptomatic lesions may be observed. Often, an infected LM cannot be controlled with oral antibiotics and i.v. antimicrobial therapy is usually required. Intervention for LM is reserved for symptomatic lesions that cause pain, significant deformity, or threaten vital structures.

Sclerotherapy

Sclerotherapy is first-line management for large or problematic macrocystic/combined LM. It involves aspiration of cysts followed by the injection of an inflammatory substance which causes scarring of the cyst walls to each other. Sclerotherapy has superior efficacy and a lower complication rate than resection.[60] Resection of macrocystic LM is generally not necessary unless (1) the lesion is symptomatic and sclerotherapy is no longer possible because all of the macrocysts have been treated, (2) resection may be curative because the lesion is small and well-localized, or (3) the lesion is so massive or has a large microcystic component, such that a significant mass will remain after sclerotherapy.

Several scleroscants may be used to treat LM: doxycycline, sodium tetradecyl sulfate (STS), ethanol, bleomycin, and OK-432. We prefer doxycycline because it is very effective (83% reduction in size) and safe (less than 10% risk of skin ulceration).[58,61] STS is our second-line agent. Ethanol is an effective scleroscant, but has the highest complication rate. It can be used for small lesions but large volumes should be

avoided to reduce the risk of local and systemic toxicity. Ethanol can injure nerves and thus should not be used in proximity to important structures. The use of OK-432 is limited because it is not widely available in all countries.[60]

The most common complication of sclerotherapy for LM is skin ulceration (10%).[58,61] Ethanol is associated with additional systemic toxicity: central nervous system (CNS) depression, pulmonary hypertension, hemolysis, thromboembolism, and arrhythmias.[58] Extravasation of the sclerosant into muscle can cause atrophy and contracture.[54] LM often re-expands over time; 9% recur within three years following OK-432 treatment and most will re-expand with longer follow up.[60,62] Consequently, patients often need repeat sclerotherapy over the course of their lifetime. If a problematic LM recurs and macrocysts are no longer present in the lesion, then resection is the only treatment.

RESECTION

Extirpation of LM can be associated with significant morbidity: major blood loss, iatrogenic injury, and deformity.[55,56,63] For example, resection of cervicofacial LM can injure the facial nerve (76%) or hypoglossal nerve (24%).[55] Excision is usually subtotal because LM involves multiple tissue planes and important structures; 'recurrence' is thus common (35–64%).[62,64] Consequently, sclerotherapy is the preferred treatment for macrocystic/combined lesions. Nonproblematic microcystic lesions can be observed. Resection is reserved for (1) symptomatic microcystic LM causing bleeding, infection, obstruction/destruction of vital structures, or significant deformity, (2) symptomatic macrocystic/combined LM that no longer can be managed with sclerotherapy because all macrocysts have been treated, (3) small, well-localized LM (microcystic or macrocystic) that may be completely excised for cure. When considering resection, the postoperative scar/deformity following removal of the LM should be weighed against the preoperative appearance of the lesion.

For diffuse malformations, staged resection of defined anatomic areas is recommended. Subtotal resections of problematic areas, such as bleeding vesicles or an overgrown lip, should be carried out rather than attempting 'complete' excision of a benign lesion which would result in a worse deformity than the malformation itself. Macroglossia may require tongue reduction to return the tongue to the oral cavity or to correct an open-bite deformity. Bony overgrowth is corrected by osseous contouring and malocclusion may require orthognathic correction, usually at the time of skeletal maturity.

Bleeding or leaking cutaneous vesicles may be managed by resection if they are localized and the wound can be closed by direct approximation of tissues. Vesicles often recur through the scar. Large areas of vesicular bleeding or drainage are best managed by sclerotherapy or carbon dioxide laser; alternatively, wide resection and skin graft coverage is required. Microcystic vesicles involving the oral cavity respond well to radiofrequency ablation.[65] Patients and families are counseled that LM can expand following any intervention, and thus additional treatments may be required in the future.

Venous malformation

CLINICAL FEATURES

Venous malformation (VM) results from an error in vascular morphogenesis; veins are dilated with thin walls and abnormal smooth muscle.[66] Consequently, lesions expand, flow stagnates, and clotting occurs. Lesions are blue, soft, and compressible; hard calcified phleboliths may be palpable. VM may range from small, localized skin lesions to diffuse malformations involving multiple tissue planes and vital structures. VM is typically sporadic and solitary in 90% of patients; 50% have a somatic mutation in the endothelial receptor TIE2.[67,68] Sporadic VM is usually greater than 5 cm (56%), single (99%), and located on the head/neck (47%), extremities (40%), or trunk (13%).[67] Almost all lesions involve the skin, mucosa, or subcutaneous tissue; 50% also affect deeper structures (i.e. muscle, bone, joints, viscera).[67]

Approximately 10% of patients with VM have multifocal, familial lesions; either glomovenous malformation (GVM) or cutaneomucosal venous malformation (CMVM).[67,69] GVM is an autosomal dominant condition with abnormal smooth muscle-like glomus cells along the ectactic veins. It is caused by a loss-of-function mutation in the glomulin gene.[70] Lesions are typically multiple (70%), small (two-thirds <5 cm), and located in the skin and subcutaneous tissue; deeper structures are not affected.[67] GVM involves the extremities (76%), trunk (14%), or head/neck (10%). Lesions are more painful than typical VM. CMVM are small, multifocal mucocutaneous lesions caused by a gain-of-function mutation in the TIE2 receptor.[71] The condition is autosomal dominant and less common than GVM. Lesions are small (76% <5 cm), multiple (73%), and located on the head/neck (50%), extremity (37%), or trunk (13%).[67] Blue rubber bleb nevus syndrome (BRBNS) is a rare condition with multiple, small (<2 cm) VM involving the skin, soft tissue, and gastrointestinal tract.[72] Morbidity is associated with gastrointestinal bleeding requiring chronic blood transfusions or recurrent, usually self-limited, intussusceptions.

Complications of VM include psychosocial morbidity, pain, and swelling. Head and neck VM may present with mucosal bleeding or progressive distortion leading to airway or orbital compromise. Extremity VM can cause leg-length discrepancy, hypoplasia due to disuse atrophy, pathologic fracture, hemarthrosis, and degenerative arthritis.[63] VM of muscle may result in fibrosis and subsequent pain and disability. A large VM involving the deep venous system is at risk for thrombosis and pulmonary embolism. Gastrointestinal VM can cause bleeding and chronic anemia. Stagnation within a large VM results in a localized intravascular coagulopathy (LIC) and painful phlebothromboses.

DIAGNOSIS

At least 90% of VMs are diagnosed by history and physical examination.[1,2] Dependent positioning of the anomaly can help confirm the diagnosis; VM will enlarge because of reduced venous return. Small, superficial VM do not require

further diagnostic work-up. However, large or deeper lesions are evaluated by MRI to (1) confirm the diagnosis, (2) define the extent of the malformation, and (3) plan treatment. VM is hyperintense on T_2-weighted sequences.[58] In contrast to LM, VM enhances with contrast, often shows phleboliths as signal voids, and is more likely to involve muscle. US may be used for some localized lesions; findings include compressible, anechoic–hypoechoic channels separated by more solid regions of variable echogenicity.[7] Phleboliths are hyperechoic with acoustic shadowing.[58] CT is occasionally indicated to assess osseous VM. Histological diagnosis of VM is rarely necessary, but may be indicated to rule out malignancy or if imaging is equivocal.

MANAGEMENT

Patients with large extremity lesions are prescribed custom-fitted compression garments to reduce blood stagnation in the lesion and thus the risk of expansion, LIC, phlebolith formation, and pain.[73] Patients with recurrent pain secondary to phlebothrombosis may find relief from prophylactic daily aspirin (81 mg) to prevent thrombosis. Large lesions are at risk for coagulation of stagnant blood, stimulation of thrombin, and conversion of fibrinogen to fibrin. Fibrinolysis results in LIC.[73] The chronic consumptive coagulopathy can cause either thrombosis (phleboliths) or bleeding (hemarthrosis, hematoma, intraoperative blood loss).[73] Low molecular weight heparin (LMWH) is considered for patients with significant LIC or at risk for disseminated intravascular coagulation (DIC).[73] Patients who develop a serious thrombotic event require long-term anticoagulation or a vena caval filter.

Sclerotherapy

Intervention for VM is reserved for symptomatic lesions that cause pain, deformity, or threaten vital structures. First-line treatment is sclerotherapy, which is safer and more effective than resection.[54,58,74] Diffuse malformations are managed by targeting specific symptomatic areas, because the entire lesion is too extensive to treat at one time. Sclerotherapy is continued until symptoms are alleviated or when vascular spaces are no longer present to inject. Although sclerotherapy effectively reduces the size of the lesion and improves symptoms, it does not remove the malformation. Consequently, patients may continue to have a mass or visible deformity after treatment that may be improved by resection. In addition, VM usually re-expands after sclerotherapy, and thus patients often require additional sclerotherapy treatments over the course of their lifetime.

Our preferred scleroscants are STS and ethanol; STS is most commonly used.[58] Although ethanol is more effective than STS, it has a higher complication rate. Most patients, especially children, are managed under general anesthesia using US or fluoroscopic imaging. The most common local complication of sclerotherapy for VM is skin ulceration (10–15%).[54,74] Extravasation of the scleroscant into muscle can cause atrophy and contracture.[54] Post-treatment swelling may necessitate close monitoring. Systemic adverse events from sclerotherapy, including hemolysis, hemoglobinuria, and DIC, are more common if large lesions are treated. Patients with low fibrinogen levels are given LMWH 14 days before and after the procedure.[73] Anticoagulation is held for 24 hours perioperatively (12 hours before and after the intervention) to prevent bleeding complications.[58,73]

RESECTION

Extirpation of VM can be associated with significant morbidity: major blood loss, iatrogenic injury, and deformity. In contrast to sclerotherapy, resection is not favorable because: (1) the entire lesion can rarely be removed, (2) resection may cause a worse deformity than the lesion, (3) the risk of recurrence is high because channels adjacent to the visible lesion are not treated, (4) the risk of blood loss and iatrogenic injury is greater. Resection should be considered for (1) small, well-localized lesions that can be completely removed or (2) persistent mass or deformity after completion of sclerotherapy (patent channels are not accessible for further injection). When considering resection, the postoperative scar/deformity following removal of the VM should be weighed against the preoperative appearance of the lesion. Subtotal resections of problematic areas, such as an overgrown lip, should be carried out rather than attempting 'complete' excision of a benign lesion which would result in a worse deformity than the malformation itself. Patients and families are counseled that VM can expand following excision, and thus additional operative intervention may be required in the future.

Many VMs should have sclerotherapy prior to operative intervention. After adequate sclerotherapy, the VM is replaced by scar and thus the risk of blood loss, iatrogenic injury, and recurrence is reduced. In addition, fibrosis facilitates resection and reconstruction. Because GVM are usually small and less amenable to sclerotherapy, first-line therapy for painful lesions is often resection. Nd:YAG photocoagulation may be an adjuvant to sclerotherapy for the management of difficult airway lesions.[75] Gastrointestinal VM with chronic bleeding, anemia, and transfusion requirements are typically managed by resection. Solitary lesions can be treated by endoscopic banding or sclerotherapy.[76] Multifocal lesions (i.e. BRBNS) require removal of as many lesions as possible through multiple enterotomies, instead of bowel resection, to preserve bowel length.[72,76] Diffuse, problematic colorectal VM may require colectomy, anorectal mucosectomy, and endorectal pull-through.[77]

Arteriovenous malformation

CLINICAL FEATURES

Arteriovenous malformation (AVM) results from an error in vascular development during embryogenesis. An absent capillary bed causes shunting of blood directly from the arterial to venous circulation, through a fistula (direct connection of an artery to a vein) or nidus (abnormal channels bridging the feeding artery to the draining veins).[66] Genetic abnormalities cause certain types of familial AVM. Hereditary hemorrhagic telangiectasia is due to mutations in endoglin and activin receptor-like kinase 1 (ALK-1), which

affect transforming growth factor-beta (TGF-β) signaling.[78] Capillary malformation–arteriovenous malformation (CM-AVM) results from a mutation in RASA1.[79] Patients with PTEN mutations also can develop arteriovenous anomalies.[80]

The most common site of extracranial AVM is the head and neck, followed by the limbs, trunk, and viscera.[5] Although present at birth, AVM may not become evident until childhood. Arteriovenous shunting reduces capillary oxygen delivery causing ischemia; patients are at risk for pain, ulceration, bleeding, and congestive heart failure. AVM also may cause disfigurement, destruction of tissues, and obstruction of vital structures. AVM worsens over time, and can be classified according to the Schobinger staging system (Table 78.2).[81]

Table 78.2 Schobinger staging of arteriovenous malformation.

Stage	Clinical findings
I (quiescence)	Warm, pink-blue, shunting on Doppler
II (expansion)	Enlargement, pulsation, thrill, bruit, tortuous veins
III (destruction)	Dystrophic skin changes, ulceration, bleeding, pain
IV (decompensation)	Cardiac failure

DIAGNOSIS

Most AVMs are diagnosed by history and physical examination.[1,2] If AVM is suspected, the diagnosis should be confirmed by US with color Doppler examination showing fast-flow and shunting. MRI is also obtained to (1) confirm the diagnosis, (2) determine the extent of the lesion, and (3) plan treatment. MRI shows dilated feeding arteries and draining veins, enhancement, and flow-voids on T_2-weighted imaging.[82] If the diagnosis remains unclear after US and MRI, angiography is performed. Angiography is also indicated if embolization or resection is planned to determine the flow dynamics of the lesion. AVM shows tortuous, dilated arteries with venous shunting and dilated draining veins on angiogram.[82] Often, a blush illustrates the nidus of the lesion. Histopathological diagnosis of AVM is rarely necessary, but may be indicated to rule out malignancy or if imaging is equivocal.

MANAGEMENT

Because AVM is often diffuse, involving multiple tissue planes and important structures, cure is rare. The goal of treatment is usually to control the malformation. Intervention is focused on alleviating symptoms (i.e. bleeding, pain, ulceration), preserving vital functions (i.e. vision, mastication), and improving a visible deformity. Management options include embolization, resection, or a combination. Resection offers the best chance for long-term control, but the re-expansion rate is high and extirpation may cause a worse deformity than the malformation itself. Almost all AVM will re-expand after embolization. Consequently, embolization is most commonly used preoperatively to reduce blood loss during resection, or for palliation of unresectable lesions.[83]

Asymptomatic AVM should be observed unless it can be completely removed for cure with minimal morbidity; embolization or incomplete excision of an asymptomatic lesion may stimulate it to enlarge and become problematic. Intervention is determined by (1) the size and location of the AVM, (2) the age of the patient, and (3) Schobinger stage. Although resection of an asymptomatic stage I AVM offers the best chance for long-term control or 'cure', intervention must be individualized based on the degree of deformity that would be caused by excision and reconstruction.[83] For example, a large stage I AVM in a non-anatomically important location (i.e. trunk, proximal extremity) may be resected without consequence, before it progresses to a higher stage where resection is more difficult, and the recurrence rate is greater.[83] Similarly, a small, well-localized AVM in a more difficult location (i.e. face, hand) may be excised for possible 'cure' before it expands and complete extirpation is no longer possible.

In contrast, a large, asymptomatic AVM located in an anatomically sensitive area is best observed, especially in a young child not psychologically ready for major resection and reconstruction. First, resection and reconstruction may result in a more noticeable deformity or functional problem than the malformation itself. Second, although the recurrence rate is lower when stage I AVM is resected, it is still high and thus even after major resection and reconstruction the malformation can recur. Third, some children (17.4%) do not experience significant morbidity from their lesion long term, into adulthood.[83]

Intervention for stage II AVMs is similar to stage I lesions. However, the threshold for treatment is lower if an enlarging lesion is causing a worsening deformity or if functional problems are expected. Stage III and IV AVMs require intervention to control pain, bleeding, ulceration, or congestive heart failure.

Embolization

Embolization involves the delivery of a substance, through a catheter to the AVM, to occlude blood flow and/or fill a vascular space. Reduced arteriovenous shunting and ischemia improves symptoms and may shrink the lesion. Embolization is used either as a preoperative adjunct to resection or as monotherapy for lesions not amenable to extirpation. Because the AVM is not removed, almost all lesions eventually will expand after treatment.[66,81–84] Stage I AVM has a lower recurrence rate than higher-staged lesions. Most recurrences occur within the first year after embolization, and 98.0% re-expand within five years.[83] Despite the high likelihood of re-expansion, embolization can effectively palliate an AVM by reducing its size, slowing expansion, and alleviating pain and bleeding. Preoperative embolization also reduces blood loss during extirpation.

Substances used for embolization may be liquid (n-butyl cyanoacrylate (n-BCA), ethanol, Onyx (ethylene-vinyl alcohol

copolymer)) or solid (polyvinyl alcohol particles (PVA), coils). The goal of embolization is occlusion of the nidus and proximal venous outflow.[82] The embolic material is delivered to the nidus, not the arterial feeding vessels. Occlusion of inflow will cause collateralization and expansion of the AVM; access to the nidus will also be blocked preventing future embolization. For preoperative embolization, temporary occlusive substances (gelfoam powder, PVA, embospheres) that undergo phagocytosis are used. Permanent liquid agents capable of permeating the nidus (ethanol, n-BCA, Onyx) are used when embolization is the primary treatment. The most frequent complication of embolization is ulceration.

Resection

Resection of AVM has a lower recurrence rate than embolization and is considered for well-localized lesions or to correct focal deformities (i.e. bleeding or ulcerated areas, labial hypertrophy).[83] Wide extirpation and reconstruction of large, diffuse AVM should be exercised with caution because (1) cure is rare and the recurrence rate is high, (2) the resulting deformity is often worse than the appearance of the malformation, and (3) resection is associated with significant blood loss, iatrogenic injury, and morbidity. When excision is planned, preoperative embolization will facilitate the procedure by reducing the size of the AVM, minimizing blood loss, and creating scar tissue to aid the dissection. Multiple embolizations, spaced 6 weeks apart, may be required prior to resection. Excision should be carried out 24–72 hours after embolization, before recannalization restores blood flow to the lesion.

Surgical margins are best determined clinically, by assessing the amount of bleeding from the wound edges.[81] Most defects can be reconstructed by advancing local skin flaps. Skin grafting ulcerated areas has a high failure rate because the underlying tissue is ischemic; excision with regional flap transfer may be required. Free-flap reconstruction permits wide resection and primary closure of complicated defects, but does not improve long-term AVM control.[63,81,83–85] Despite subtotal and presumed 'complete' extirpation, most AVMs treated by resection recur.[83] The majority of recurrences occur within the first year after intervention, and 86.6% re-expand within five years of resection.[83] Patients and families are counseled that AVM is likely to re-expand following resection, and thus additional treatment may be required in the future.

PTEN-associated vascular anomaly

The PTEN (phosphatase and tensin homolog) gene encodes a tumor suppressor lipid phosphatase.[86] Patients with PTEN mutations have PTEN hamartoma-tumor syndrome (PHTS). This autosomal dominant condition had previously been referred to as Cowden syndrome or Bannayan–Riley–Ruvalcaba syndrome (BRRS).[80,87] Males and females are equally affected, and approximately one-half (54%) of patients have a unique fast-flow vascular anomaly with arteriovenous shunting, referred to as a PTEN-associated vascular anomaly (PTEN-AVA).[80] Unlike typical AVM, PTEN-AVA may be multifocal, is associated with ectopic adipose tissue, and has disproportionate, segmental dilation of the draining veins.[80,82] Patients with PHTS have macrocephaly, and males have penile freckling.[80] Histopathology shows skeletal muscle infiltration with adipose tissue, fibrous bands, and lymphoid aggregates. In addition, tortuous arteries with transmural muscular hyperplasia and clusters of abnormal veins with variable smooth muscle are present.[80] Genetic testing is confirmative; the mutation is associated with multiple benign and malignant tumors which require surveillance.

COMBINED VASCULAR MALFORMATIONS

Capillary malformation–arteriovenous malformation

The prevalence of CM-AVM is estimated to be 1 in 100 000 Caucasians.[79,88] Patients have atypical capillary malformations that are small, multifocal, round, pinkish-red, and surrounded by a pale halo (50%).[79,88] Thirty percent of individuals also have an AVM: Parkes–Weber syndrome (PWS) (12%), extracerebral AVM (11%), or intracerebral AVM (7%).[88] PWS describes a diffuse AVM of an overgrown extremity with an overlying CM.[5] PWS involves the lower extremity approximately twice as often as the upper extremity.[88] CM-AVM is an autosomal dominant condition caused by a loss-of-function mutation in the *RASA1* gene.[79] A patient presenting with multiple CMs, especially with a family history of similar lesions, should be evaluated for possible AVMs on physical examination. Because 7% of patients with CM-AVM will have an intracranial fast-flow lesion, brain MRI should be considered.[69] Exploratory imaging of other anatomical areas is not necessary because extracranial AVM have not been found to involve the viscera.[88] Although the CM is rarely problematic, associated AVMs can cause significant morbidity.

Klippel–Trenaunay syndrome

Klippel–Trenaunay syndrome (KTS) is an eponym denoting a slow flow, capillary-lymphatico-venous malformation (CLVM) in association with soft tissue and/or skeletal overgrowth.[89] KTS affects the lower extremity in 95% of patients, the upper extremity in 5% of patients, and least commonly the trunk.[89] Leg-length discrepancy is followed by plain radiographs and MRI is used to confirm diagnosis as well as determine the extent of the anomalies. The deep venous system is commonly malformed. The marginal vein of Servelle is often located in the lateral calf and thigh and communicates with the deep venous system.[90] Complications include thrombophlebitis (20–45%) and pulmonary embolism (4–24%).[91] KTS of the lower extremity can involve the pelvis causing hematuria, hematochezia, constipation, and bladder outlet obstruction. Unlike some other hemihypertrophy syndromes, patients with KTS are not at increased risk for Wilms' tumor and screening ultrasounds are unnecessary.[92] Severe enlargement of the foot requires ray, midfoot, or Syme amputation to allow the use of footwear. Management of the VM component of KTS is conservative with compressive

stockings for insufficiency and aspirin to minimize phlebothrombosis. Symptomatic varicose veins may be removed or sclerosed if a functioning deep system is present. Occasionally, sclerotherapy and surgical excision are necessary for the LM component. Staged contour resection of the extremity can be performed.

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79

Congenital nevi

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INTRODUCTION

Pigmented lesions represent a common congenital diagnosis encountered by the pediatric surgeon. Congenital nevi represent a group of skin lesions occurring at birth or becoming apparent within the first few years of life, and are characterized by ectopic rests of dermal elements. Although most commonly melanocytic in nature (such as the congenital melanocytic nevus, nevi of Ota, nevi of Ito, nevus spilus, café-au-lait spots, and Mongolian spots), nevi can also originate from sebaceous (nevus sebaceous of Jadassohn), neural or epidermal elements. Lesion characteristics vary according to the type of cell involved, location within the skin, and level of cell differentiation. Knowledge of the differential diagnosis and natural history of these lesions can help balance the plan of care, so as to address the potential risk of malignant degeneration while accounting for functional and esthetic concerns encountered during excision and reconstruction.

CONGENITAL MELANOCYTIC NEVI

Congenital melanocytic nevi (CMN) are the most common congenital nevi composed of nevus cells of melanocytic origin that carry a varying amount of pigment. These nevi can be classified based on their expected size at adulthood into small (<1.5 cm), intermediate (1.5–19.9 cm), and large (>20 cm) lesions with some describing a separate giant (>50 cm) classification for very extensive or garment-like lesions.[1,2] These classification groups are important not only when determining treatment options, but when stratifying the potential risk of malignant change. When evaluating a lesion in a baby, body surface area changes between infancy and adulthood can be used to predict if a lesion falls into the large category. As a general rule, a 9-cm lesion on the head or neck or a 6-cm lesion on the body of an infant will grow to meet the large nevi classification.[2] Another cited definition of large congenital nevi includes lesions >2% total body surface area.[3] Incidence of CMN decreases with increasing size of the lesion with the relatively common small lesions occurring in 1:100 births, intermediate lesions in 1:1000, large lesions in 1:20 000 births, and giant lesions in 1:500 000.[3–5]

Etiology

Embryologically, melanocytes originate from neural crest cells as melanoblasts. During early gestation, these melanoblasts migrate to the basal layer of the epidermis at which time they differentiate into dendritic melanocytes and associate into melanosomes that produce pigment for transfer to keratinocytes. Congenital melanocytic nevi result from a disturbance in this migration and differentiation process resulting in ectopic rests of immature cells along their course of migration. Because of this, nevus cells often extend deep into the subcutaneous tissues and can even involve fascia, muscle, periosteum, or the leptomeninges. They usually require excision at the fascial level for adequate removal, while retaining function.

When nevus cells are found within the central nervous system (leptomeninges, brain, or spinal column), the condition is called neurocutaneous melanosis (NCM). The clinical presentation of NCM can range from asymptomatic to progressive, severe neurologic deterioration with developmental delay, hydrocephalus, and seizures often with fatal outcomes. Symptoms are produced by either the benign proliferation of nevus cells within the central nervous system which block the circulation of cerebral spinal fluid and lead to hydrocephalus and increased intracranial pressure, or from their malignant degeneration. If NCM is to become symptomatic, the vast majority of cases will do so before age three years. The prognosis of symptomatic NCM is poor with >90% dying usually within three years of onset of neurologic symptoms.[6] Although it is difficult to know the true incidence of NCM in association with large congenital melanocytic nevi (LCMN) because screening of asymptomatic patients is not universally performed, a study of an internet registry found NCM on magnetic resonance imaging

(MRI) in approximately 5% of cases of LCMN/GCMN (giant congential melanocytic nevi) of which only 5–6% became symptomatic.[7] Large CMN of the posterior midline and those found in association with multiple satellite nevi (>20) have the highest risk of NCM and should be strongly considered for MRI screening (Fig. 79.1a,b).[8]

Pathology

Nevus cells differ from melanocytes histologically as they group together in clusters rather than arrange as individual melanosomes. In addition, nevus cells assume a rounded rather than dendritic shape, and keep their pigment within their cytoplasm instead of transferring it to the surrounding keratinocytes.[9]

Because of the higher risk of malignant transformation found in CMN compared to acquired nevi, efforts have been made to identify histologic characteristics specific to CMN. When nevus cells are found within eccrine ducts, follicular epithelium, or blood vessels, it indicates a congenital lesion; however, not all CMN display this finding.[10] Furthermore, only congenital lesions demonstrate nevus cells within the deeper subcutaneous tissues, fascia, and muscle. Clinically, examination of small CMN with a dermatoscope or under loupe magnification will reveal small pigment granules at the peripheral aspect of the lesion which is another specific finding to CMN.[11] Discovery of more specific markers for

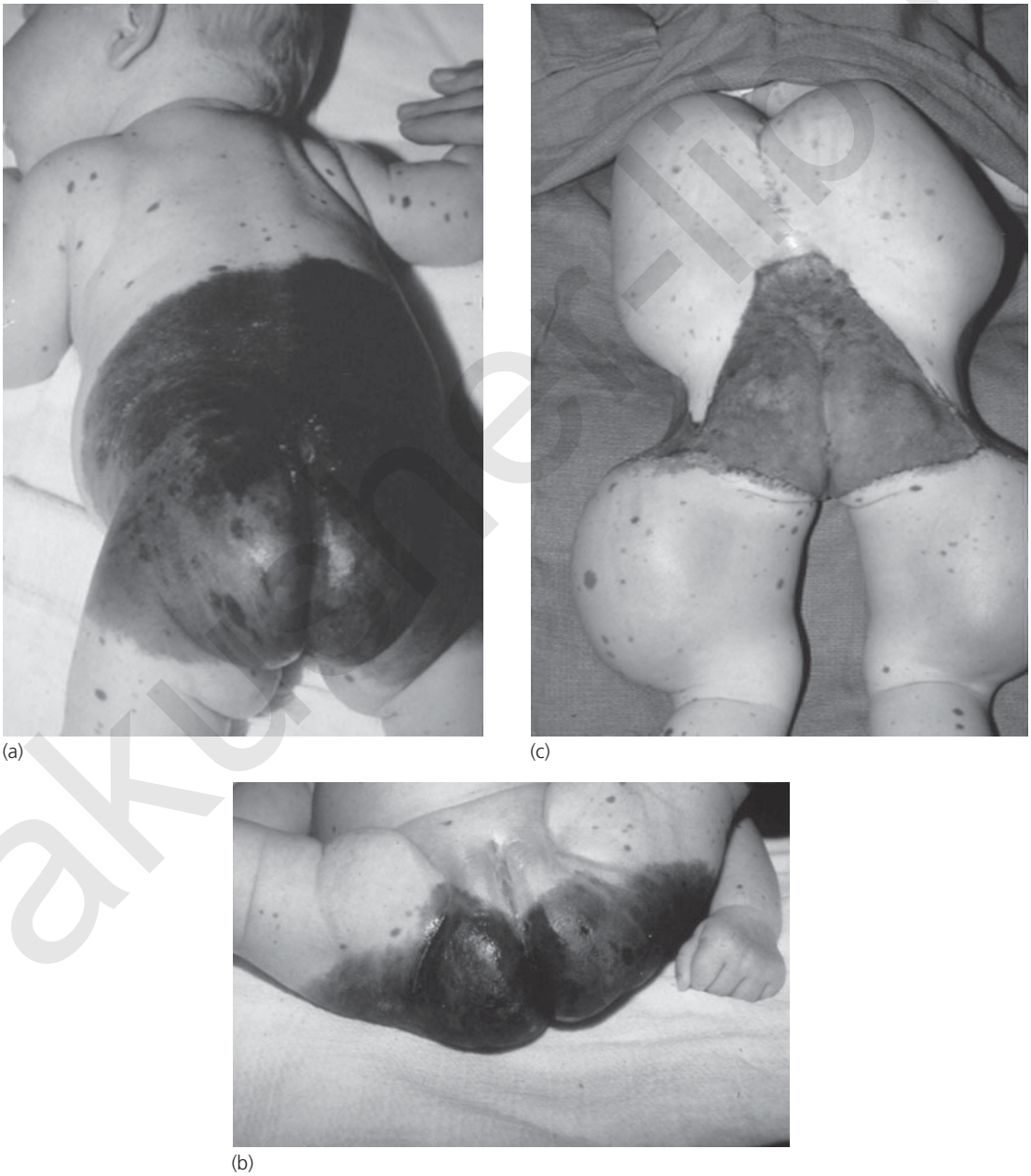
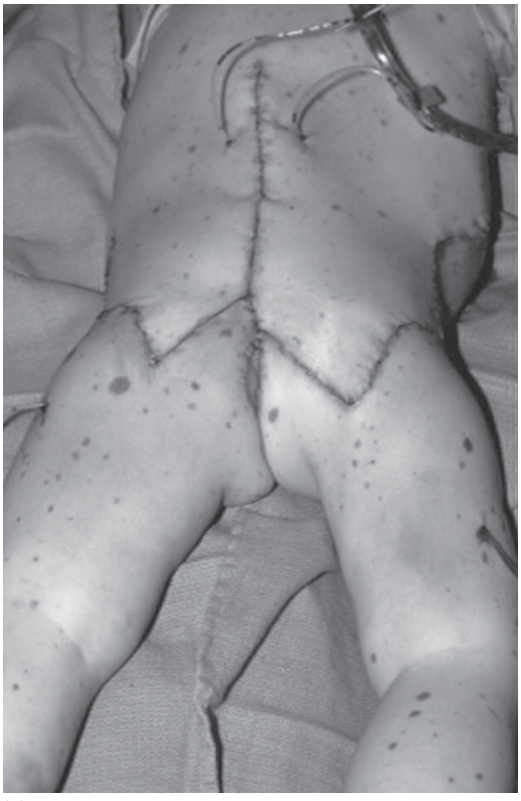


Figure 79.1 (a,b) Giant melanocytic nevus of the perineum and buttocks and multiple satellite nevi, both independent predictors of underlying neurocutaneous melanosis. (c,d) Using serial expansion and excision techniques with transposition-designed flaps, total excision of the lesion was accomplished without loss of urinary or fecal continence with a reasonably normal appearance (e) on long-term follow up.



(d)

(e)

Figure 79.1 *Continued*

CMN will help to more clearly determine the true rate of melanoma associated with these lesions.

Presentation

CMN can differ greatly in their size and appearance. Although often obvious at birth, some lesions can be quite faint, and seem to appear with time over the first year of life as they increase in pigmentation. Coloration varies from pale tan to a deep bluish black, and may be uniform or extremely variegated. The lesions are often thickened in texture with increased skin markings compared to surrounding normal skin. They often have hair which can range from fine light fuzz to coarse thick follicles. When large lesions are present, they may be accompanied by smaller peripheral satellite lesions of different sizes and numbers which may appear for the first two to three years of life.

Over time, the surface of CMN may change to become verrucous and irregular with darkening of pigmentation, but lightening of color can be seen in as many as 30% of patients with large and giant nevi. Erosion or breakdown is not uncommon in the neonatal period, but may also occur later. This does not necessarily indicate malignant change, but warrants further investigation.

Management

The management strategy of CMN can be stratified based on size of the lesion and potential risk of malignant change.

SMALL CONGENITAL MELANOCYTIC NEVI

Most CMN fall into this small category and can usually be addressed with simple or staged excision. The lifetime risk of melanoma occurring in small CMN has been quoted at 4.9% when based on patient-reported history of a congenital lesion which lowers to 2.6% for lesions determined to be CMN on histologic criteria of melanoma specimens.[12] However, the risk of melanoma arising within small CMN before puberty is extremely unlikely.[13] For this reason, most defer the removal of these lesions until the patient reaches an age at which comfortable excision can be performed under local anesthesia to avoid the associated risks of general anesthesia. However, if the lesion falls in a cosmetically sensitive area or is located in an area that will require general anesthesia regardless of age, consideration should be given to earlier removal to avoid potential psychologic sequelae of delaying treatment. From a practical point of view, these procedures are best performed either before the patient begins toddling or just prior to school entrance in order to avoid potential complications from falls, heightened anxiety, and lack of patient cooperation.

LARGE CONGENITAL MELANOCYTIC NEVI

Management of large CMN is a more complex involved process that again strikes a balance between addressing the risk of malignancy with functional and esthetic concerns of the lesion and its reconstruction.

At this time, large CMN are not able to be diagnosed prenatally. The appearance of dark, extensive, hairy lesions of the face, trunk, or extremities is by nature devastating for parents who have been anxiously awaiting the birth of their child. Because of this, the infant with large congenital melanocytic nevi should be referred early to a dermatologist and surgeon familiar with the management of these lesions to allow parents to be counseled about the nature of these lesions, risks of malignancy, potential for excision, and reconstructive options. If presented in a compassionate manner, even the news of a multiple-stage reconstruction over many years can be well accepted by families. In over 25 years of experience, the senior author has developed treatment plans for the management of these lesions with the tenet that esthetic and functional outcome are as important as removal of the nevus itself.

An immediate concern of the family and doctors involved with the care of these patients is the potential risk of malignancy. Review of the literature reports a wide range for the rate of melanoma occurring in patients with LCMN, anywhere from 2 to 31%.[1–4 14,15] This variance is explained in part by differences in study design and patients (with an increasing number undergoing surgical interventions), and can lead to confusion in how to counsel patients' families. A retrospective study of patients with LCMN defined as $>2\%$ total body surface area (TBSA) found an 8.5% risk during the first 15 years of life.[3] Sandsmark *et al.*[14] quoted a risk of 6.7% in childhood. A more recent prospectively followed patient cohort registry reported a five-year cumulative life-table risk of 2.3%; however $>50\%$ of these patients had undergone partial to complete excision of their nevi, with all reported melanomas arising in extracutaneous locations.[15] The timing of melanoma diagnosis in patients with LCMN has also been studied with a trend towards development of malignancy early in life. It has been reported that 50% of LCMN that develop malignancy do so in the first three years of life, with 60% by childhood and 70% by puberty.[16] Although the true incidence of malignant melanoma arising in untreated LCMN is unlikely to be clearly defined, these numbers encourage early removal.

History and physical examination

On initial history, any changes in the appearance of the nevus or satellite lesions should be elicited along with any family history of melanoma. Documentation of developmental milestones and presence of any neurologic symptoms should be noted. Serial examination of the lesion(s) should be undertaken every three to six months, depending on the character and variability in the appearance of the lesions. Often patches of darker color or raised nodules develop within a large CMN that may represent neural nevus. This is a form of intradermal nevus with melanocytes that appear histologically similar to Schwann cells and contain nerve organelles, such as Meissner's and Pacinian corpuscles. The patches may also represent local areas of proliferation that do not necessarily behave in an aggressive manner. Certainly biopsy of any suspicious raised, ulcerating, or atypical areas can be used to exclude malignancy (Fig. 79.2). Histologic findings of low mitotic rate, lack of necrosis, evidence of maturation in the cell population and lack of high-grade nuclear atypia are clues to a benign course. The best description of these areas is melanocytic tumor of uncertain potential, and these unusual areas are best addressed earlier in the course of reconstruction.

In the case of large nevi in an axial location especially of the posterior midline scalp or back or when numerous satellite lesions (>20) are present, MRI is recommended to document the presence of neurocutaneous melanosis (NCM). Asymptomatic patients can be identified specifically by T_1 shortening on the MRI. For increased sensitivity, the MRI should be obtained before age four months, because after then increasing myelinization of the central nervous system (CNS) can potentially obscure visualization of nevus cells.[17] Foster *et al.*[18] reported that 23% of at-risk patients had NCM on MRI, with only one patient developing neurologic sequelae of hypotonia, developmental delay, and seizures during the five-year follow-up period. More recent studies report a lower 5% incidence of NCM in patients with LCMN.[7]

It is important to convey that the finding of NCM on MRI does not necessarily imply the future development of neurologic symptoms. It does, however, indicate a risk for later development of benign or malignant melanotic tumors. In the cases of symptomatic NCM, the associated poor prognosis should deter the surgeon from aggressive management of the cutaneous lesion. At this point, the low incidence of symptom development reported in asymptomatic patients with a positive screen for NCM would certainly caution against applying that same philosophy to this patient population. Further study will help to fully ascertain the true predicted course of disease in asymptomatic, scan-positive patients and help guide both surgical planning and the role of serial scanning. At this time, if the initial MRI is positive, we proceed with reconstruction as planned and feel that further scans are unnecessary unless neurologic symptoms develop.

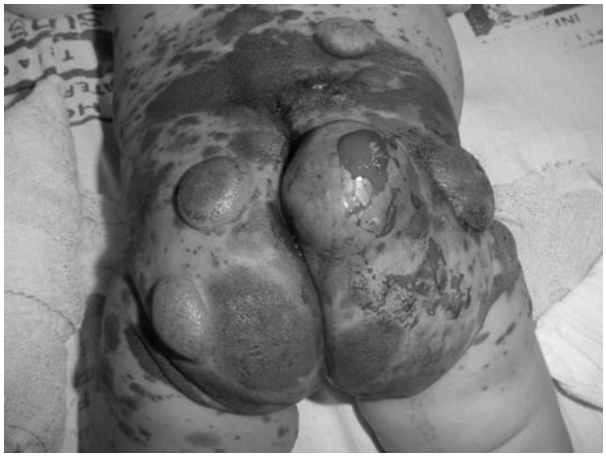


Figure 79.2 Sarcoma arising within a giant congential melanocytic nevus at birth.

Other congenital nevi

BLUE NEVI

Blue nevi are smooth, bluish-black lesions that can be present at birth but more likely appear during childhood and puberty (Fig. 79.3). They occur more frequently in females and are usually found on the head or extremities. Two variants exist: common and cellular. The common blue nevus is a relatively small (<1 cm), sharply demarcated, dome-shaped benign lesion. Histologically, it is composed of intradermal and possibly subcutaneous dendritic melanocytes with normal overlying epithelium. The cellular blue nevus is larger (1–3 cm) with less regular borders and is frequently found in the lumbosacral area. The lesion tends to be wider at the surface than the base, and is composed of spindle-shaped melanocytes in aggregates mixed within dendritic melanocytes. Unlike the common form, malignant transformation has been reported within the cellular variant, and therefore excision is recommended.

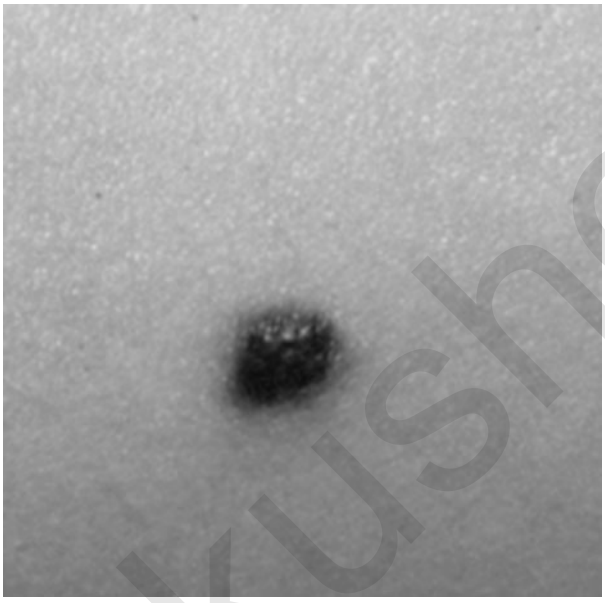


Figure 79.3 Blue nevus.

MONGOLIAN SPOTS

Mongolian spots are blue-gray macules usually overlying the lumbosacral area of otherwise healthy infants (Fig. 79.4). They are more common in Asian and darker-skinned individuals. Mongolian spots are most often present at birth, but may appear within the first weeks of life, and usually regress spontaneously by the age of three to four years. Lesions are made up of widely scattered dendritic melanocytes within the lower two-thirds of the dermis.[19] No treatment of these benign lesions is necessary, however, laser can be effective for management of a persistent lesion.[19]

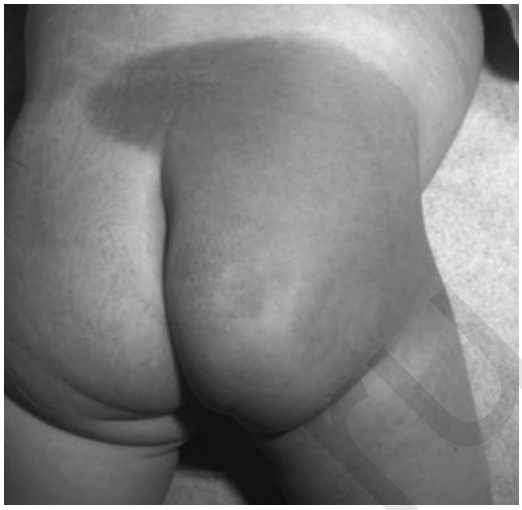


Figure 79.4 Mongolian spot of the posterior trunk.

NEVUS OF OTA/NEVUS OF ITO

The nevus of Ota is a blue-gray facial discoloration characterized by speckled or mottled coalescing macules appearing at birth or in childhood in the V1–V2 distribution (Fig. 79.5). Unlike Mongolian spots, these lesions do not regress, and can become hyperpigmented in puberty. The lesion may extend to involve the mucosal membranes of the nose and mouth, as well as sclera, conjunctiva, and retina, and occular pathology and glaucoma have been associated. Nevus of Ota displays a female predominance, and is found most commonly in Asian and Indian populations. In 10% of cases, the nevus is bilateral and associated with extensive Mongolian spots.

The nevus of Ito is a blue-gray macular lesion similar to the nevus of Ota that affects the shoulder (scapula, deltoid, supraclavicular) area and is sometimes associated with sensory changes. It is rarer than nevus of Ota, and more common in Asians.

Both of these lesions represent field defects of dermal melanocytosis, histologically characterized by elongated dendritic melanocytes scattered within the collagen bundles

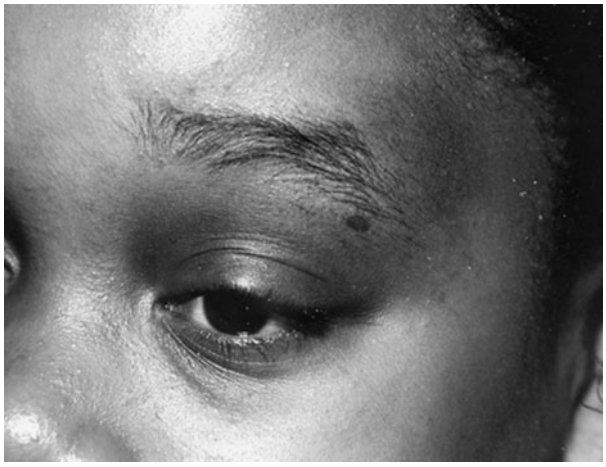


Figure 79.5 Nevus of Ota in its typical V1–2 distribution.

mostly in the upper third of the reticular dermis. They may contain raised areas within the lesion which are indistinguishable from blue nevus.

Although considered benign, there have been a few reported cases of malignant change, especially in areas similar to cellular blue nevus, and may require biopsy to distinguish them from melanoma.[19] Historically, cryotherapy and non-selective destruction with CO_2 laser has been used with mixed esthetic results. Current laser technology allows the surgeon to take advantage of selective photothermolysis to direct laser energy to destroy the melanocytes without damaging the surrounding tissues with excellent cosmetic results. Multiple treatments with a Q-switched ruby laser, Q-switched alexandrite laser, or Q-switched Nd:YAG laser is effective to fade the lesion.[19] For the nevus of Ota, an ophthalmologist should be consulted due to the risk of ocular pathology.

CAFÉ-AU-LAIT SPOTS

Café-au-lait spots are benign sharply demarcated macules of light tan to brown regular pigmentation. They can present in normal individuals or when multiple can be associated with syndromes such as neurofibromatosis. Histologically, lesions are caused by increased pigment in macromelanosomes within the keratinocytes in the basal layer. Laser ablation can be used to successfully treat lesions that are of cosmetic concern, but recurrence is common.[20]

NEVUS SPILUS

Nevus spilus are light tan to brown macules that resemble café-au-lait spots, but with areas of darker speckling within it (Fig. 79.6). On histology, there are both areas of increased pigment within the keratinocytes of the basal layer, as well as an increased number of melanocytes. The specked areas represent a mixture of findings from freckling, to congenital melanocytic nevi, to blue nevi. Suspicious areas within the lesion should be excised for biopsy as the nevocellular areas do carry some malignant potential. If the entire lesion is in a cosmetically sensitive area, it can be removed surgically.

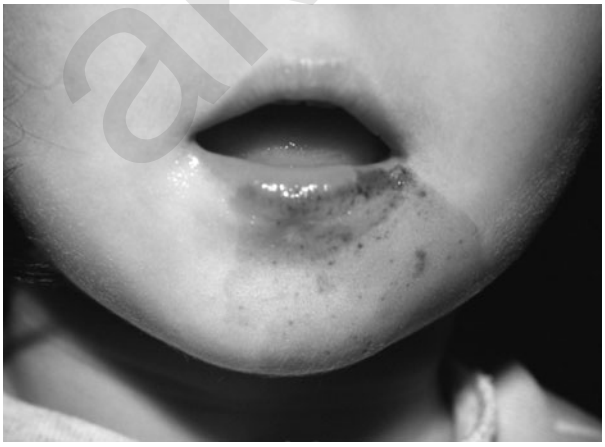


Figure 79.6 Nevus spilus of the lower lip.

SEBACEOUS NEVI

Sebaceous nevi present at birth as a waxy, hairless, yellow-orange plaque usually on the scalp, head or neck (Fig. 79.7). Over time, they can become more nodular, verrucous, and itchy, and are most pronounced at puberty. Sebaceous nevi are hamartomas of sebaceous glands. They carry a risk of malignant transformation (well documented at 15–20%) into basal cell carcinoma, making removal by excision with reconstruction recommended. Sebaceous nevus syndrome is the combination of large sebaceous nevi of the scalp and face associated with developmental delay, seizures, ophthalmologic and bony abnormalities.

Extensive linear sebaceous nevus is mostly seen in the head and neck and presents some unique challenges to the reconstructive surgeon. For the larger lesions involving scalp and face, tissue expansion can be applied in a similar fashion which will be described for LCMN. Narrow linear lesions can be excised in stages, often timed so a partial excision is performed at the same time. A tissue expander is placed elsewhere and further excision done when the expander is removed for distant flap reconstruction. Lesions on the ear are addressed with either staged excision or excision and full-thickness skin graft. Those involving the helical rim should be grafted only after full growth of the ear to avoid distortion of the cartilage. It is not uncommon to see linear nevi involving the lower lip, chin, and adjacent neck. Given the linear orientation, it is important to design the reconstruction to minimize tension on the repair while breaking up the scar line to avoid scar hypertrophy and contracture. The senior author's surgical approach has been described in detail in a previous publication.[21]

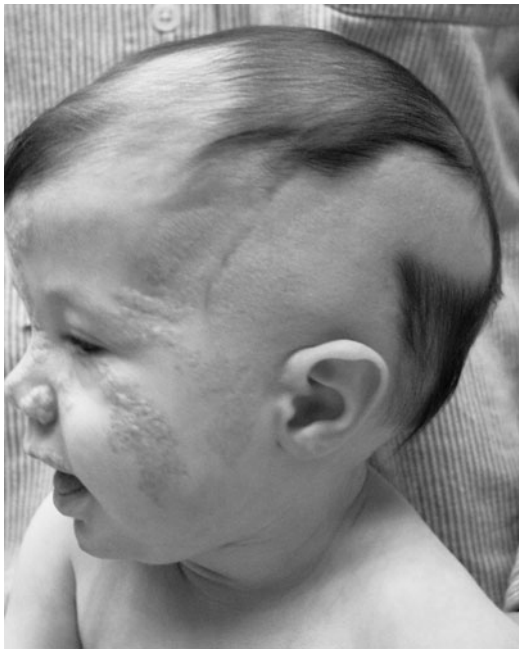


Figure 79.7 Extensive sebaceous nevus of the face and scalp.

SPITZ NEVI

Although not usually congenital, Spitz nevi are another commonly encountered pediatric skin lesion. They present as pink, raised, firm lesions that on occasion can be pigmented (Fig. 79.8). At times, they may be confused with pyogenic granulomas because of their appearance and rapid growth at onset. Originally termed 'benign juvenile melanoma', these lesions display a bizarre pathology beneath the microscope, and can be confused with malignancy if the pathologist is not provided with the history of the lesion and patient's age. In fact, these lesions are benign, but do grow rapidly and tend to recur aggressively if not completely excised. Because of that, these lesions should be excised with a generous 3–4-mm border of normal tissue to decrease the chance of recurrence.

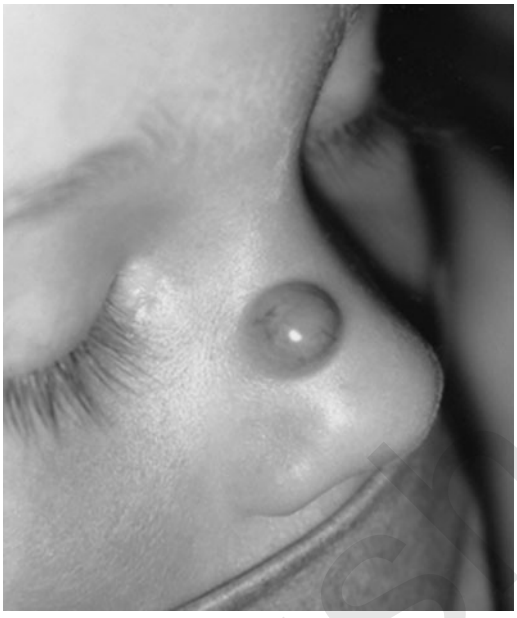


Figure 79.8 Spitz nevus of the nose.

MANAGEMENT OF LARGE AND GIANT CONGENITAL MELANOCYTIC NEVI

Treatment for LCMN and GCMN remains controversial to some, as they feel the risk of malignant degeneration within these lesions is too low to warrant the extensive number of surgeries and potential scar burden associated with removal. Others feel the potential for non-cutaneous melanoma to develop in nevus cells not amenable to surgical removal (such as in NCM) represents a remaining risk that negates the effectiveness of cutaneous excision for reduction of melanoma risk.[6] However, the significant deformity and associated psychological impact caused by these lesions often tip the scales toward attempted intervention. Management plans should always strive to balance removal of the nevus with a functional and esthetic reconstruction, and lesions that cannot be effectively addressed in this manner should be considered for conservative management by serial observation by an experienced dermatologist.

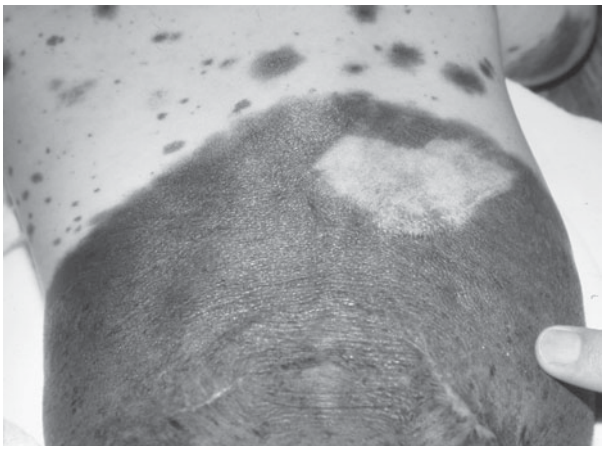
Treatment options are most often surgical with excision and reconstruction using either adjacent or expanded skin or skin grafts/substitutes, but can include dermabrasion, curettage, and laser.

Dermabrasion, curettage, and laser therapy

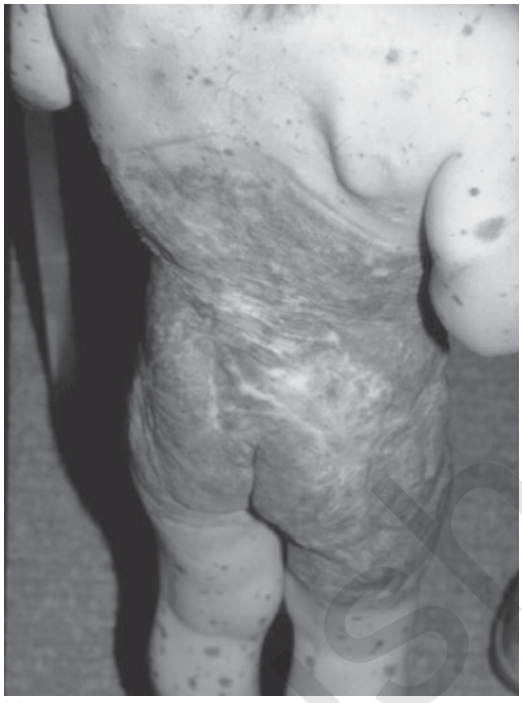
Non-excisional methods of treatment for CMN, including dermabrasion, curettage, and laser, have been reported as effective methods of reducing the cell burden of the nevus without completely removing it to improve appearance. The success of dermabrasion and curettage relies on the finding that early in infancy, the skin nevus cells lie in a more superficial location histologically within the upper reticular dermis and epidermis. Dermabrasion works to abrade away these surface cells, whereas curettage separates the cells at the natural cleavage plane between the superficial and deep dermis. Using either method, the number of nevus cells within a lesion is reduced, but not eliminated. Therefore, as lesions may be lighter initially, they may darken with time as described in a long-term study (Fig. 79.9a,b).[22] In addition, any associated hypertrichosis is not affected, as hair follicles are found much deeper extending into the subcutaneous fat. Finally, malignant potential theoretically remains for the remaining nevus cells, and scarring from these interventions may make follow-up examination difficult. Nonetheless, good cosmesis has been reported using both methods, despite biopsy-proven persistence of nevus cells within the lesions throughout the field of the original defect. In order to be effective, these treatments must be performed at less than 15 days of life.

Laser offers another potential treatment strategy attractive to both the patient and doctor as a simplified method to reduce the pigmentation of a lesion without scarring. Laser therapy is well suited for the treatment of lesions characterized by superficial dermal pigmentation, such as the nevi of Ota and Ito, persistent Mongolian spots, café-au-lait macules, and some elements of nevus spilus due to their minimal thickness, location of pigment within the dermis, and low potential for malignancy. Effective treatment relies on proper wavelength and pulse-width selection to allow penetration of the skin and photoselective destruction of melanin, while preserving the remaining elements to avoid scarring.[19,20] Serial treatments are required. Scarring can occur with aggressive treatment or improper setting selection. Hypo- and hyperpigmentation have also been reported which may be temporary or permanent. Exposure to sunlight in the perioperative period can cause significant burning, scarring, and hyperpigmentation.

Unfortunately, because CMN display nevus cells within all layers of the skin, as well as within the deeper structures, it is unrealistic to think that a laser could effectively penetrate to the depths necessary to eliminate all pigment-producing nevi cells without significant secondary damage and scarring. In addition, laser treatment vaporizes the specimen, therefore eliminating histologic evaluation of the lesion to determine its nature. Finally, the impact of the exposure of nevus cells to the radiant energy associated with laser therapy is unknown, and may not be apparent for many years into the future.



(a)



(b)

Figure 79.9 (a) The pale area within the nevus was curetted immediately after birth. Seeing this result, the rest of the lesion was curetted. (b) As a toddler, this typical result shows recurrence of pigmentation and scarring, making clinical and histological surveillance of the lesion difficult.

Although dermabrasion, curettage, and laser offer a relatively simple approach to improving the appearance of CMN, they present many drawbacks. Leaving residual nevus cells within CMN imparts a continued risk of malignancy, and scarring may make monitoring the lesions more difficult after treatment. In addition, scarring from these therapies may complicate ultimate excisional treatment options in the future. Finally, the delay of more definitive reconstruction may have its own psychological effects on a child. Although limited use of these therapies may be useful in certain areas of reconstruction (such as lightening of a thin lesion in the cosmetic and functionally sensitive eyelid area), thoughtful consideration is warranted prior to widespread implementation of these modalities in a treatment algorithm for LCMN.

Surgical excision and reconstruction

The benefits of surgical excision of LCMN include complete removal of involved skin and subcutaneous tissue. Although some have focused on skin grafts, skin substitutes, or cultured epithelium for reconstruction, when possible, use of tissue expansion allows the most functional and esthetic result by allowing replacement with full-thickness normal tissue. Goals of treatment include complete excision at an early age, minimization of scarring and functional impact with a low requirement for future procedures. Early excision is emphasized for four reasons: (1) The greatest risk for malignancy is reported in childhood, most notably in the first three years of life. (2) The elasticity and healing capacity of the skin is better the younger the patient. (3) Patients operated on in infancy tolerate surgery better both physically and emotionally than their older counterparts. (4) By completing reconstruction early, the psychological impact of the lesions and surgical interventions can be reduced.

In 1988, Bauer *et al.*[23] presented a coordinated approach to the management of these lesions in 78 patients. This report outlined the spectrum of treatment options from skin graft to tissue expansion, and assessed the effectiveness of excision and reconstruction with each technique in each body region. Since then, further experience with over 300 patients has allowed further development and refinement of approach.[24–28] Although a full discussion of the nuances of management of each of LCMN is beyond the scope of this chapter, the following provides a summary.

SCALP

Scalp reconstruction is complicated by its relatively inflexible quality and the unique esthetics of maintaining hair quality and direction. Because of this, tissue expansion remains the workhorse for scalp reconstruction during excision of LCMN. Scalp lesions are best reconstructed in stages, with placement of one or more tissue expanders in a subgaleal plane beneath the normal scalp skin. Following adequate expansion (generally from 10 to 12 weeks), the expanders are removed, lesions excised, and the defect closed using both advancement and transposition flaps designed to preserve hair direction and hairline.[24] Serial expansions are often necessary, and flaps should be carried out and checked before nevus excision (Fig. 79.10a–g). Safe expansion of the infant scalp can be carried out at six months of age with careful attention given to the fontanel during expander placement and reconstruction. Although temporary cranial molding is common, there were no infants with permanent skull deformities noted with spontaneous correction occurring generally within three to four months.

FACE

LCMN of the face present some of the greatest reconstructive challenges. By dividing the face into esthetic units, tissue expansion of available adjacent areas of normal skin in the neck and forehead can provide skin of excellent quality match, while allowing scars to lie at the junction of esthetic units rendering them less obvious (Fig. 79.10d–e). When advancing tissue from the neck into the cheek area, a

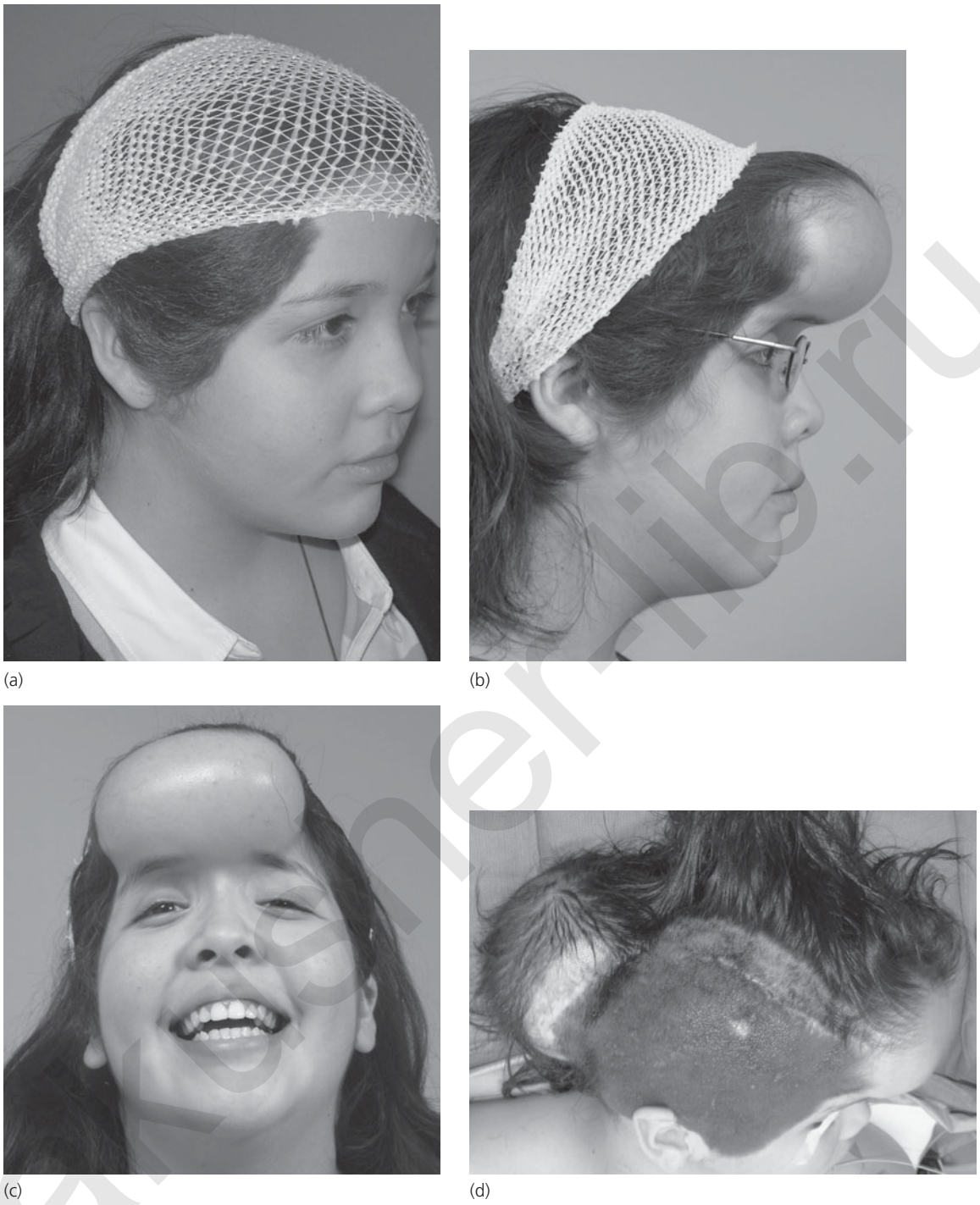


Figure 79.10 (a) Large congential melanocytic nevus of the scalp and forehead after the first round of expansion. (b) Result after first stage. (c) Re-expansion of the forehead. (d–f) Final reconstruction of esthetic units with scars well concealed at hairline and along the browline.

transposition design can help improve flap movement while aligning the scars optimally. Whether transposed with the flap based laterally (most common) or medially, the transposition minimizes the risk of late downward drift of the flap and ectropion of the lower eyelid.[24] Lesions of the nose are best resurfaced by an expanded forehead flap carried on a superficial temporal artery pedicle when possible or with an expanded supraclavicular full-thickness skin graft. The periorbital area is also best addressed with expanded full-thickness skin grafts to allow preservation of the thin nature of the tissue, while decreasing incidence of ectropion.[25] LCMN of up to 75% of the forehead can be managed with tissue expansion (often serial) and requires careful planning to minimize distortion of the eyebrow position and maintain a normal distance from brow to hairline. Nevi extending into the temporal area must be treated by expansion of both scalp

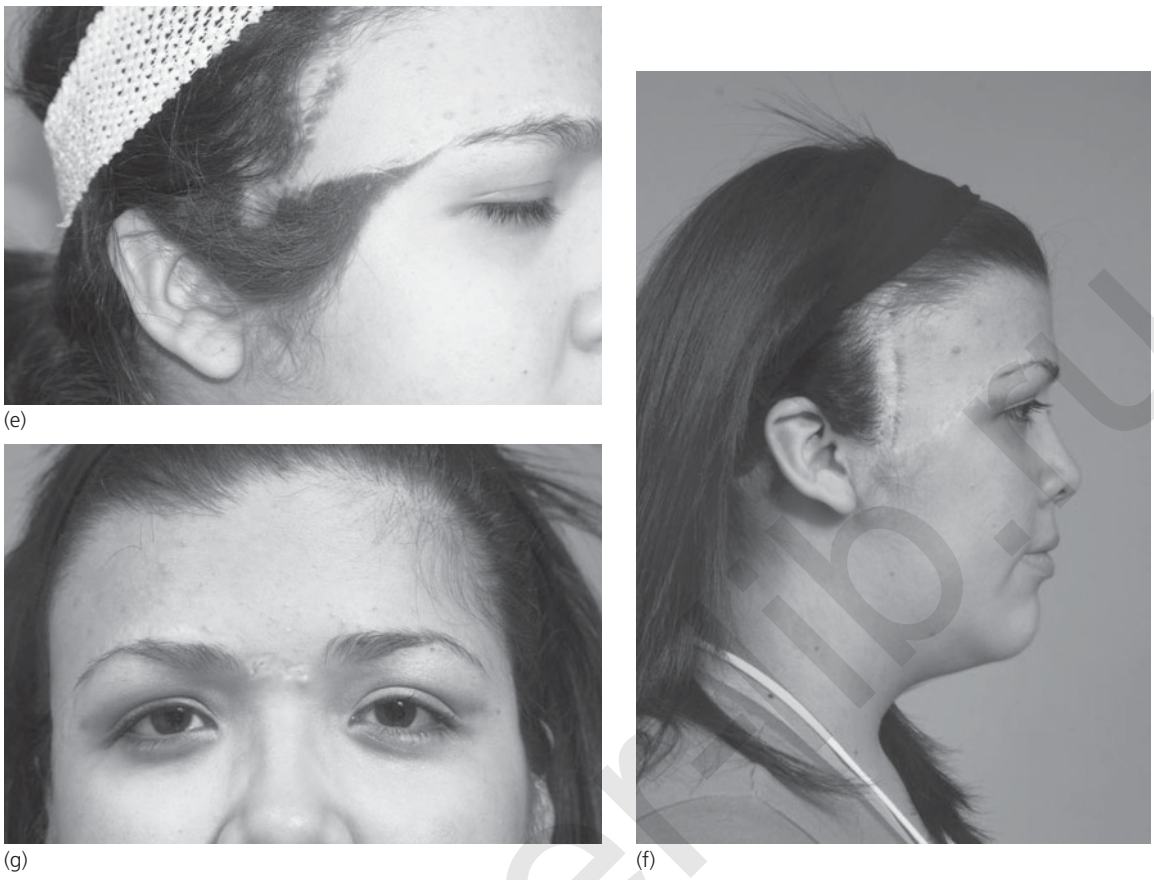


Figure 79.10 *Continued*

and forehead, with flaps designed to establish both normal position and hair direction for the temporal region.[26]

TRUNK

The often extensive involvement of GCMN of the trunk with relative lack of normal donor skin presents a daunting challenge to the reconstructive surgeon, leading many to resort to split-thickness skin graft-based reconstruction. The inferior functional and esthetic results achieved call into question whether excision should have been undertaken at all in favor of conservative observation. With better expanded flap design carried out in series, or use of expanded distant flaps with microvascular transfer, superior trunk reconstruction can be achieved.

The posterior trunk is the most common location of GCMN often extending anteriorly in a dermatome distribution. These lesions are best reconstructed with serial tissue expansion and subsequent transposition flap closure (Fig. 79.1a–e). By utilizing flap transposition over simple advancement, excision and reconstruction of bathing trunk and large thorax nevi previously felt to be treatable only with skin grafting has become possible.[24] Anterior trunk lesions can be treated with an abdominoplasty technique with or without expansion depending on lesion size. When adjacent donor sites are unavailable for expansion, excision and reconstruction of shoulder, upper back, and posterior neck nevi can be accomplished using microvascular transfer of a free expanded TRAM (transverse rectus abdominal muscle) flap (Fig. 79.11a–d). With increased use of expanded flaps over skin grafting for trunk reconstruction, late contour deformities seen at junction points between grafted and ungrafted areas can be significantly reduced. These modified techniques have resulted in esthetic benefits far beyond what could be accomplished with alternative treatments.

EXTREMITIES

LCMN of the extremities continue to present a considerable challenge due to the limitations of local expansion techniques in these areas and the relatively poor esthetic outcome experienced with skin grafting. The current authors' prior approach utilized both split-thickness and expanded full-thickness skin grafts for most lesions, but the long-term soft-tissue contour defect and pigment abnormalities in the grafted skin have led to the use of alternative approaches when possible. In upper extremity lesions, use of transposition flaps from the upper back and shoulder has effectively eliminated contour defects to the proximal upper extremity. In addition, three-stage, expanded pedicled flaps from the abdomen and flank can be designed to provide complete coverage of a circumferential nevus from elbow to wrist with excellent contour and acceptable scarring achieved at both donor and recipient sites (Fig. 79.12a–d).[27] A similar

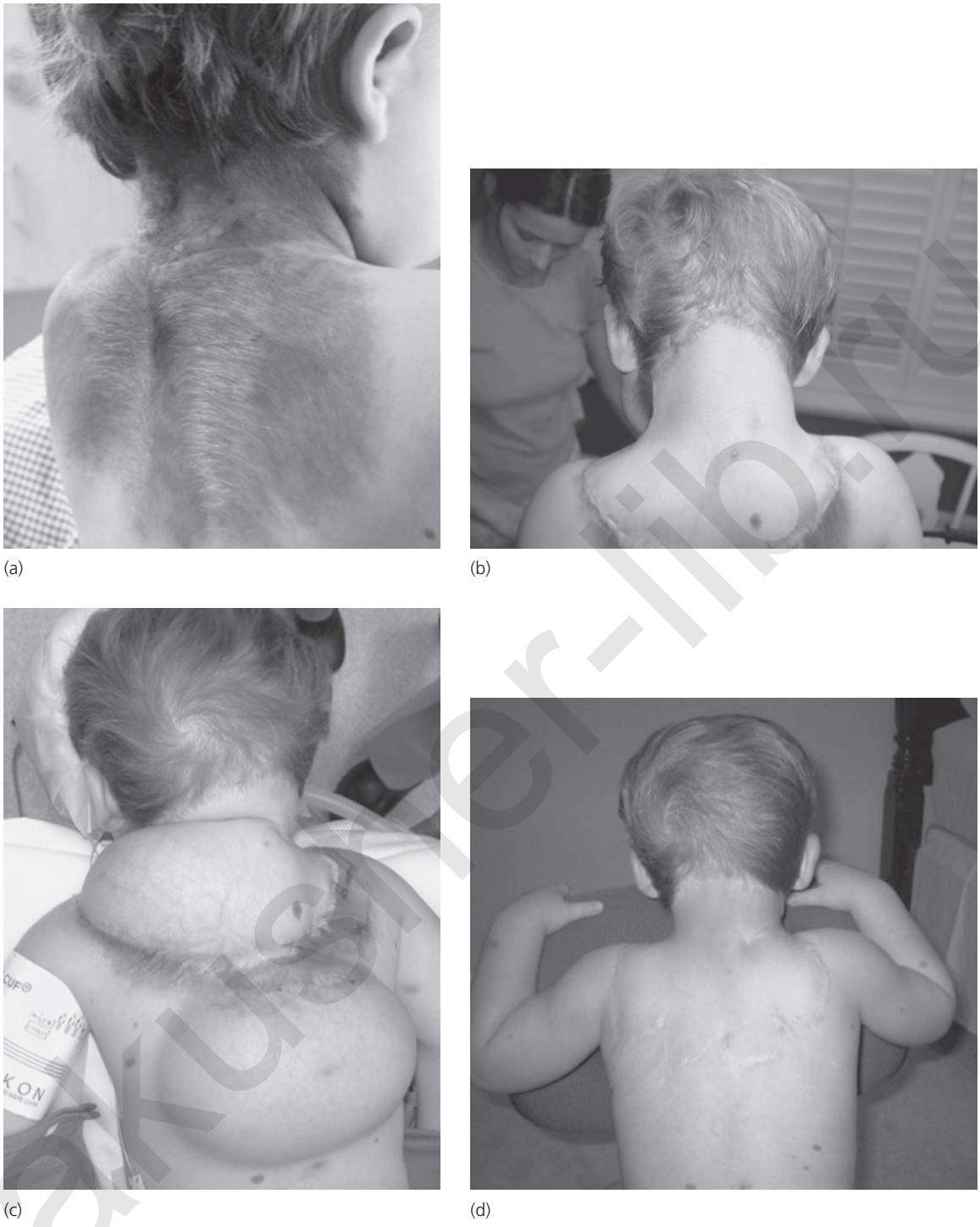


Figure 79.11 (a) Extensive large congential melanocytic nevus of the upper back and neck. (b) Reconstruction with expanded free transverse rectus abdominal muscle (TRAM) flap. (c) Re-expansion of free TRAM flap. (d) Final result with good contour and flexibility of the shoulders and neck.

pedicled approach has been successful in providing coverage for a lower leg lesion after ipsilateral thigh expansion in the young infant when lower extremity flexibility is at its peak with excellent results.[28] Finally, expanded free flaps offer another alternative for coverage of larger lesions of the extremities with improved functional and esthetic results.

COMPLICATIONS

Complications of surgical excision of LCMN with expanded flap reconstruction are uncommon despite the complex nature of these procedures and include expander infection/exposure, flap compromise, incisional dehiscence, and scarring. The

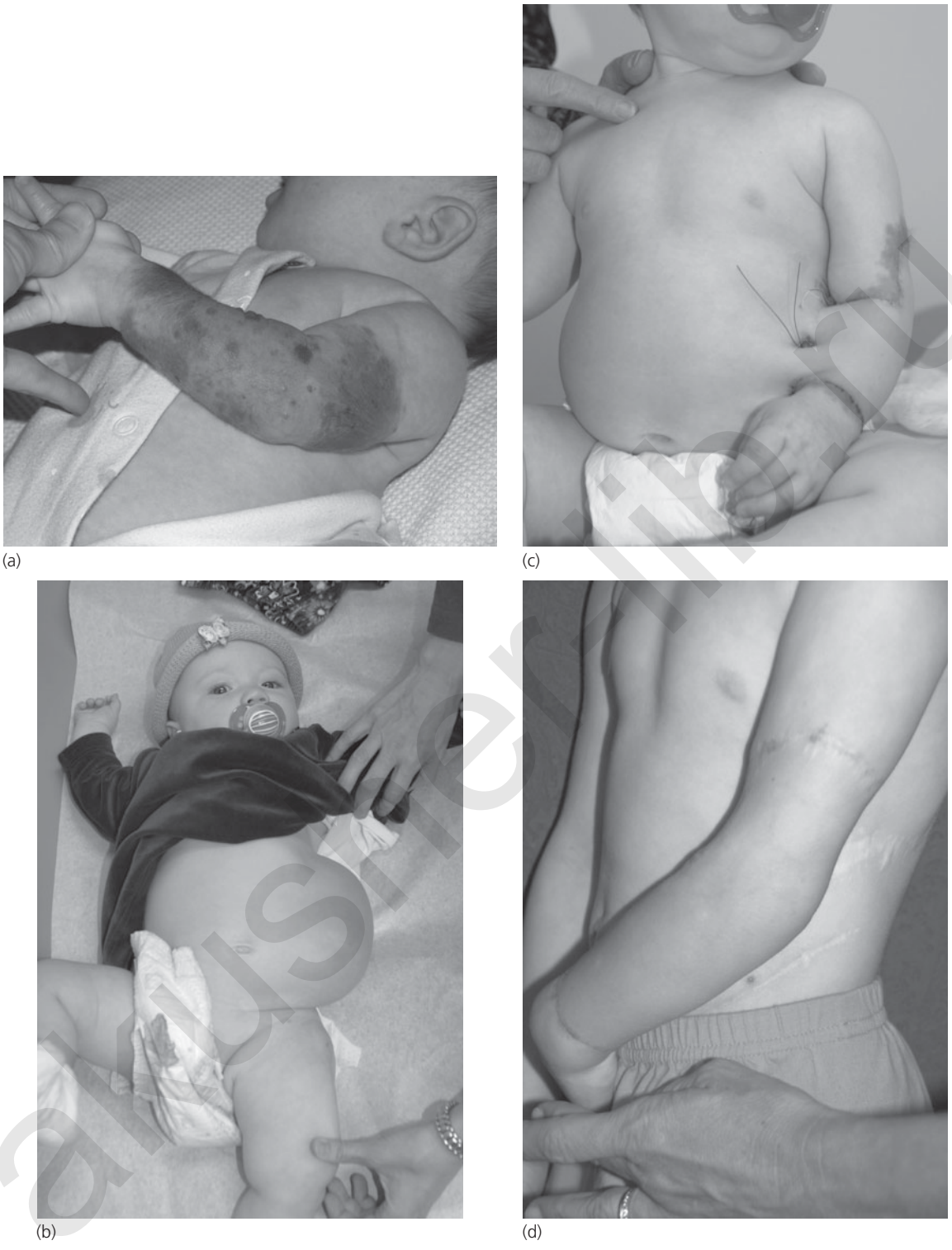


Figure 79.12 (a) Extensive nevus of the arm. (b) Expansion of abdominal donor site. (c) Attachment of pedicled abdominal flap for circumferential arm reconstruction. (d) Final result with good contour of arm and acceptable abdominal scarring.

incidence of expander infection has been reported at 5%, which can be due to inoculation during expander insertion or repeated expansions, after exposure of the expander or by hematogenous seeding from a distant infection.[29] These infections can usually be managed conservatively by antibiotic administration with completion of expansion and successful reconstruction. A low threshold for placement on oral antibiotics during healing problems or illness occurring during expansion may help minimize risk.

Expansion effectively increases the vascularity of a flap through the delay phenomenon making flap ischemia rare. Preservation of the capsule and avoidance of excessive

tension during closure can prevent this potentially devastating complication. Finally, meticulous closure and postoperative scar management help achieve optimal results.

CONCLUSIONS

The treatment of congenital large and giant nevi presents a continuing challenge to all individuals involved with these patients. The ability to present an organized discussion of current views on risk of malignant change to parents, patients (when old enough), referring physicians, and other allied health-care workers is critical. Treatment strategies should take into consideration the varied opinions regarding malignant risk, emphasize the benefits of early excision on lowering that risk, and most importantly, provide a means of dealing with these often devastating lesions in a manner that optimizes the functional and esthetic outcome and minimizes the need for major reconstruction in later life.

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Lymphatic malformations (cystic hygroma)

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INTRODUCTION

Lymphatic malformations (LMs) constitute one subset of a larger group of so-called vascular malformations which may affect any segment of the vascular tree including arterial, venous, capillary, and lymphatic vessels. All vascular malformations can be considered to be the result of errors of embryonic development and can be categorized according to the particular vascular component involved, as well as by physiologic flow properties. Thus, there exist slow-flow lesions (which include lymphatic, venous, and capillary malformations), fast-flow anomalies (which contain an arterial component) and complex, combined vascular malformations.

Commonly referred to as 'cystic hygroma' or 'lymphangioma', lymphatic malformations consist of a group of developmental anomalies of the lymphatic system. They are slow-flow anomalies which range in clinical presentation from small masses to large and sometimes debilitating, disfiguring, or invasive lesions. Structurally, they may be characterized as microcystic, macrocystic, or combined lesions, and these properties have significant clinical implications for treatment. The most common presentation of a LM is a ballottable mass beneath normal skin, although a large LM may transilluminate causing the overlying skin to attain a blue hue. Occasionally, dermal lymphatic involvement causes puckering, dimpling, or vesiculation.[1] Most commonly found in the neck and shoulder, LMs may also occur in the mediastinum, retroperitoneum, groin, and other areas. This chapter will provide an overview of the diagnosis and management of these often difficult lesions with emphasis on those involving the head and neck region.

EMBRYOLOGY AND ETIOLOGY

Most lymphatic malformations are sporadic, but some exhibit classic Mendelian inheritance. Although our understanding of lymphatic development (and, by extension, errors in lymphatic development) remains rudimentary, recent strides in the the field of vasculogenesis have opened the door for greater insight into observed aberrancies.

According to early work by Sabin,[2] development of the lymphatic system begins in the 6th to 7th week of embryonic life, approximately 4 weeks after the onset of vasculogenesis with the formation of five primitive 'lymph sacs': originating as a set of paired sacs lateral to the jugular vein, a retroperitoneal sac at the root of the small bowel mesentery, and paired sacs posterior to the sciatic veins. This process is thought to result from the migration of a specialized subset of endothelial cells from the anterior cardinal vein in response to mesenchymal expression of vascular endothelial growth factor C.[3] These sacs produce buds which arborize centrifugally to form the peripheral lymphatic system. Additional recent data suggest that there is a role of *in situ* differentiation of lymphangioblasts from mesenchymal cells into lymphatic endothelial cells with subsequent recruitment of these cells into developing lymphatic vessels.[4]

Lymphangiogenesis, like its counterparts – vasculogenesis and angiogenesis – is subject to an extraordinarily precise choreography of growth factors and signaling molecules. Important regulators include VEGF and the VEGF receptor families, angiopoietins and the Tie-2 receptor, TGF-β and its receptor, PDGF-B and its receptor, the Notch and Jagged families of membrane-associated molecules and the integrin family of cell surface receptors.[4–7] Overexpression of the isoforms VEGF-C and VEGF-D in transgenic mice induces the formation of hyperplastic lymphatic vessels.[8] Kinase-inactivating mutations in the human *VEGFR3* gene result in Milroy's disease.[9] Tie-2-deficient mouse embryos demonstrate normal initial vasculogenesis, but have a disorganized vascular network lacking appropriate hierarchical organization.[10] Tie-1-deficient models demonstrate decreased endothelial cell integration leading to embryonic edema, hemorrhage, and death, and the Tie-1 receptor has recently been shown to be required for normal embryonic lymphangiogenesis.[11,12] Ang1-4, members of the angiopoietin family, likely have roles in vessel stabilization and lymphatic development.[13] Mutations in the *Fox* family of transcription factors have been associated with congenital

lymphedema, and this family is thought to play a role in the formation of lymphatic valves.[14] Not surprisingly, the integrins, which mediate interactions within the extracellular matrix both as cellular adhesion molecules and as signal tranducers, appear to be important in formation of the vascular and lymphatic systems. Mutations or deletions in specific integrin subtypes can lead to abnormal lymphatic development.[15] Recently, integrin-α9 was found to be necessary for normal lymphatic valve morphogenesis and may be implicated as a candidate gene for primary lymphedema caused by valve defects.[16]

PRENATAL DIAGNOSIS

Lymphatic malformations are often diagnosed by prenatal ultrasound in the late first trimester.[17] The differential diagnosis of a cystic lesion in the fetus is extensive,[18] but in experienced hands the correct diagnosis can be made in most cases.[19] Although most lymphatic malformations presenting to the pediatric surgeon have an excellent prognosis, prenatal sonography has revealed a high 'hidden mortality' among fetuses with this condition.[20–23] The majority of fetuses with a lymphatic malformation develop hydrops fetalis or diffuse lymphangiomatosis prior to fetal demise (Fig. 80.1). There is often either an associated chromosomal abnormality (usually Turner syndrome,[24] although many others have been reported[25]), or a familial syndrome associated with other structural anomalies, such as multiple pterygium syndrome[26] or Robert syndrome.[27] Although most of these fetuses die *in utero*, spontaneous regression has occasionally been observed.[28–30]

Lymphatic malformations presenting in the fetus have a different natural history and prognosis from those presenting postnatally.[28,31] The natural history of cervical lesions detected prenatally varies according to the gestational age at which nuchal thickening appears and is further influenced by the presence or absence of hydrops or abnormal karyotyping. The cases diagnosed in the first trimester without any other abnormality usually have good prognosis with spontaneous resolution in the majority.[32–34] Conversely, those with hydrops and abnormal karyotype have a poorer outlook. The prognosis of patients detected in the second trimester is usually poor.[35] Lymphatic malformations diagnosed in late gestation appear to belong to a different spectrum of disease with a much more favorable prognosis. These cases are comparatively rare,[36–38] and likely to represent an etiologic mechanism occurring during the latter half of pregnancy. Prenatal diagnosis should be followed by delivery and aggressive surgical management at a perinatal center.

Occasionally, a fetus may be identified with a large anterior cervical lymphatic malformation which causes airway obstruction. These pose a challenge at the time of delivery, and are best managed using the *ex-utero* intrapartum (EXIT) procedure to gain access to the airway prior to dividing the umbilical cord (Fig. 80.2).[39,40] In severe cases, a tracheostomy can be performed or the child can be placed on

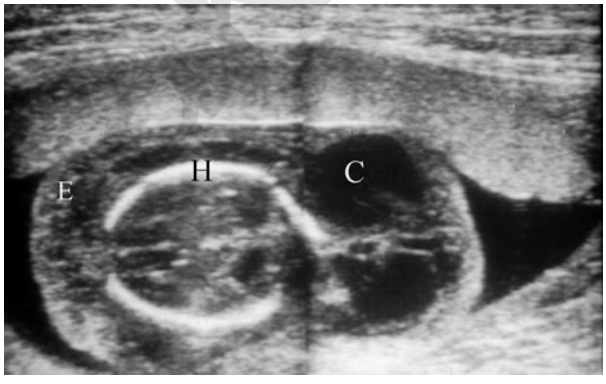
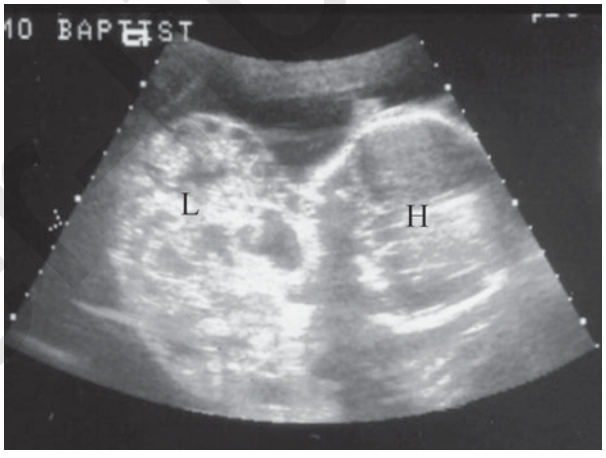
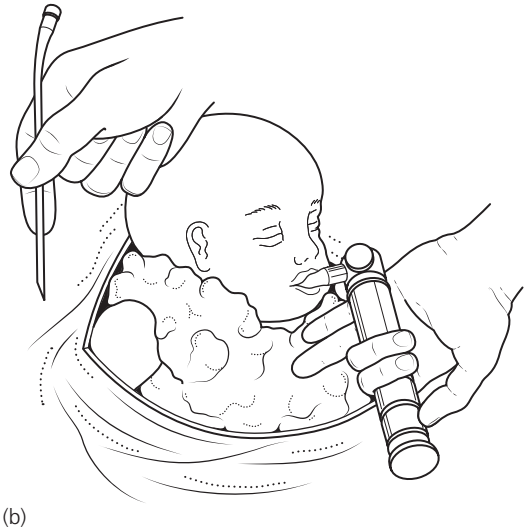


Figure 80.1 Prenatal ultrasound of a fetus with Turner syndrome and a large posterior cervical cystic hygroma. Note the diffuse subcutaneous edema (E), which is indicative of hydrops fetalis. C, cystic hygroma; H, fetal head.



(a)



(b)

Figure 80.2 (a) Prenatal sonogram showing a large pretracheal lymphatic malformation. H, fetal head; T, lymphatic malformation. (b) The *ex-utero* intrapartum (EXIT) procedure, in which intubation is accomplished prior to delivery while still on placental support.

extracorporeal membrane oxygenation as part of the EXIT procedure.

Those LMs not diagnosed prenatally are generally evident at birth or before the age of two years; however, occasionally, they can manifest suddenly in older children and adults.

Clinical presentation and imaging

The majority of lymphatic malformations occur in the head and neck, axilla, or retroperitoneum; involvement of the mediastinum, groin, extremities, or face are less common (Table 80.1).[41,42] Approximately 80% are diagnosed before the age of five years, and over half present in the newborn period. Lymphatic malformations of the neck typically present as a soft, fluctuant swelling in the lateral or anterior neck. These lesions are frequently asymptomatic and age-related growth is variable (Fig. 80.3). LMs in the forehead and orbit cause localized overgrowth and proptosis. Cervicofacial LM can be associated with mandibular overgrowth causing an underbite.[43] LMs in the floor of the mouth and tongue are characterized by vesicles, intermittent swelling, and bleeding. Occasionally, huge malformations involving the floor of the mouth or the larynx will present at birth with airway obstruction (Fig. 80.4). Rapid increases in size or sudden pain may be due to hemorrhage into the tumor, or to infection. Cervical LMs involving the supraglottic airway may necessitate tracheostomy. Diffuse thoracic lymphatic anomalies or rare abnormalities of the thoracic duct or cisterna chyli can manifest as recurrent pleural and pericardial chylous effusion or chylous ascites. Anomalous lymphatics in the gastrointestinal (GI) tract can cause chylous ascites or present with a (typically asymptomatic) cystic abdominal mass (Fig. 80.5). Both congenital chylous ascites and chylothorax may be associated with the development of hypoalbuminemia as the result of chronic protein-losing enteropathy. Lymphatic malformations of the extremities may be small and localized, or may involve the entire extremity in an infiltrative and debilitating fashion associated with both soft tissue and skeletal overgrowth. Pelvic LMs can be accompanied by bladder outlet obstruction, constipation, or recurrent infection.

Table 80.1 LMs of the head and neck at the Hospital for Sick Children (1988–2000).[65]

Sites of involvement (130 patients)	No. cases
Neck[a]	97
Posterior	40
Anterior	38
Submandibular	37
Face and oropharynx[b]	46
Tongue	14
Floor of mouth	14
Cheek	17
Parotid	14
Larynx	5
Mediastinum and chest wall	14

[a]Neck only, 69; entire neck (all three sites), 17.
[b]Face and oropharynx only, 19.

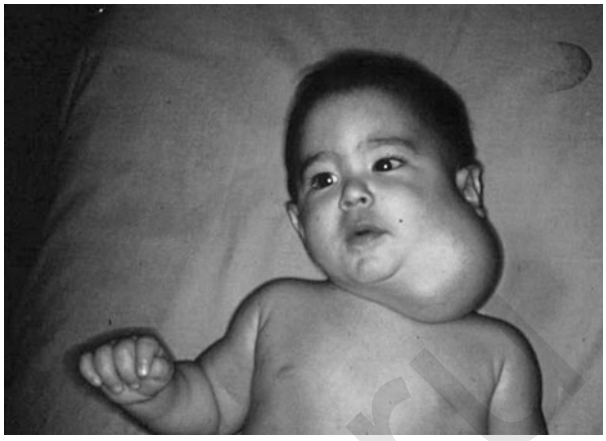
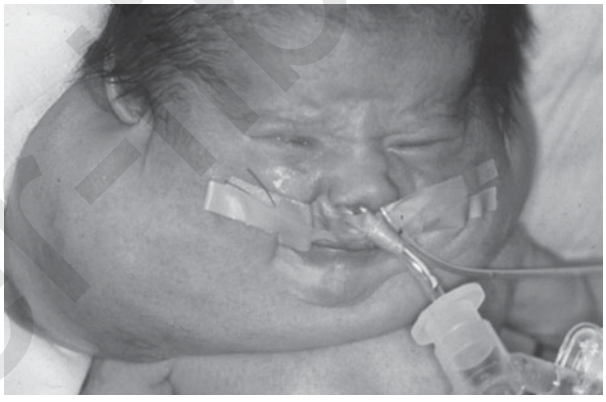


Figure 80.3 Five-month-old child with moderate-sized lymphatic malformation, which was relatively asymptomatic.



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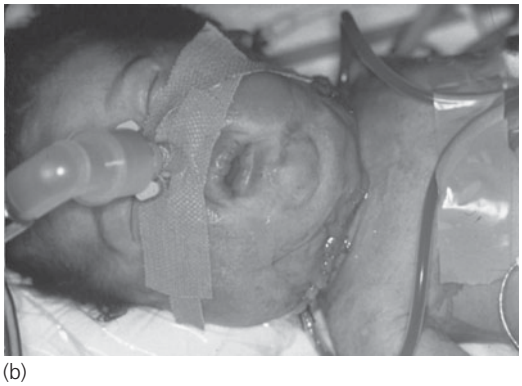

(b)

Figure 80.4 Newborn with large lymphatic malformation and airway obstruction. (a) Preoperatively; (b) postoperatively.

Occasionally, LMs occur in the constellation of a well-described phenotype. The eponym 'Gorham-Stout syndrome' has been applied to a phenomenonon involving progressive osteolysis, caused by diffuse soft tissue and skeletal LM. Alternative names include 'disappearing bone disease' or 'phantom bone disease'.[44] Klippel–Trenaunay syndrome is a well-described combined capillary–lymphatic–venous

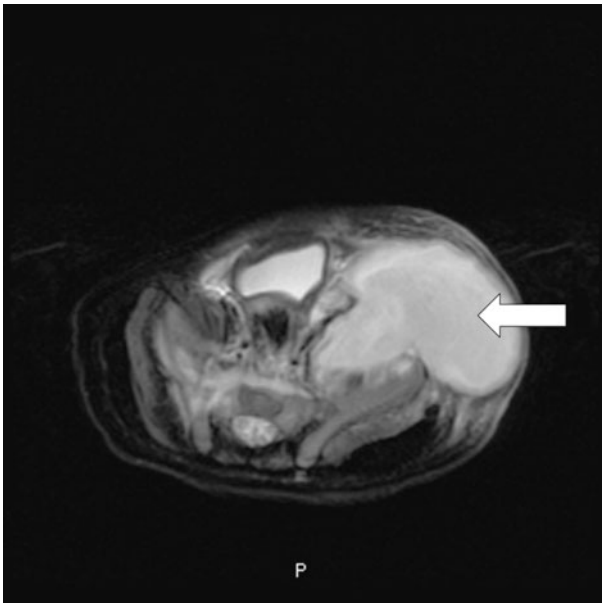

Figure 80.5 Magnetic resonance image of a retroperitoneal lymphatic malformation presenting as an asymptomatic abdominal mass in a newborn (arrow).

malformation associated with soft tissue and skeletal hypertrophy. The capillary malformations are multiple and typically arranged in a geographic pattern over the lateral side of the extremity, buttock, and/or thorax. Lymphatic hypoplasia is present in greater than 50% of patients with associated lymphedema or isolated lymphatic microcysts. The Parkes Weber syndrome shares many similarities with Klippel–Trenaunay syndrome, but should be distinguished by a component of an additional capillary–arteriovenous malformation. Lymphedema should also be included as a type of LM. Type I hereditary lymphedema (Milroy disease) is an autosomal dominant disorder presenting early in life with localized areas of edema. Affected areas are characterized by absent or hypoplastic superficial lymphatics. Linkage analysis demonstrated the locus of mutation on chromosome 5q35.3 corresponding to the gene encoding VEGFR-3.[45,46] Type II hereditary lymphedema (Meige disease) is a late-onset autosomal dominant disorder attributed to a mutation in the *FOXC2* gene with variable penetrance and phenotype. Associated features include distichiasis (a double row of eyelashes), ptosis, cleft palate, yellow nails, and congenital heart disease. The disorder is thought to arise from an impairment of lymphatic drainage, and lymphoscintigraphy demonstrates numerous dilated lymphatic vessels.[14]

INVESTIGATIONS

Magnetic resonance imaging (MRI) is the most useful imaging modality for lymphatic malformations, aiding in the classification of macrocystic and microcystic lesions, as well as defining anatomic relationships including important neurovascular structures (e.g. brachial plexus and carotid artery).[47–49] Lymphatic malformations demonstrate hyperintense signal intensity in T_2-weighted and turbo-STIR images, as well as rim enhancement after contrast application.[50] Microcystic lesions have an intermediate signal in T_1 sequences and an intermediate to high signal in T_2 sequences. Macrocystic lesions show low intensity in T_1 and high intensity in T_2. The new generation of ultrafast MRI scanners has permitted this technique to be used more frequently in small infants, and even in affected fetuses.[51]

Ultrasound may be a helpful adjunct in confirming the presence of macrocystic LM, and Doppler studies may be of additional assistance in looking at flow properties.[52–54] Computed tomography (CT) is extremely useful for assessing relationships to adjacent structures, especially within the mediastinum and retroperitoneum.[55,56] Coronal CT imaging may provide better visualization of neck and mediastinal masses in the newborn.[57]

Conventional contrast lymphangiography is rarely performed, but may be of help in establishing the location of a lymphatic or chylous leak in a patient with a diffuse thoracic lymphatic anomaly.[1,58] Boxen *et al.*[59] described the use of lymphoscintigraphy to define the lymphatic supply of a large lymphatic malformation.

Often a combination of techniques must be used to completely define the anatomic relationships of a large or complicated lesion.

DIFFERENTIAL DIAGNOSIS

The diagnosis of lymphatic malformation is usually straightforward and can be easily differentiated from lymphadenopathy, teratomas, and other solid tumors based on the clinical examination and imaging studies. Lipomas may also be confused with superficial lymphatic malformations, but will not have a cystic appearance on ultrasound examination. Hemangiomas may be present in the same location, but do not transilluminate and tend to collapse on compression. However, there are some patients who have features of both lymphatic and vascular malformation within the same lesion.

COMPLICATIONS

The two principal complications of LMs are intralesional bleeding and infection. Bleeding may occur spontaneously or as a consequence of trauma. It is associated with rapid, painful enlargement of the lesion with attendant ecchymosis. Analgesia and observation are generally sufficient. Prophylactic antibiotics are recommended in the setting of a large bleed. Hemorrhage and infection can transform a macrocystic lesion into a microcystic and scarred lesion.

It is not uncommon for LMs to increase in size in the event of a viral or bacterial infection. This is typically self-limited and thought to be related to changes in lymphatic flow. Nonetheless, bacterial superinfection of the malformation can be fatal and cause an ascending cellulitis and septicemia. Additionally, an infection in a cervicofacial LM can cause obstruction of the upper airway and dysphagia. Prolonged i.v. antibiotic therapy is frequently indicated, with choice of broad-spectrum antibiotic agents directed against

oral pathogens in the head and neck or enteric organisms in the trunk or perineum.

MANAGEMENT

The two strategies for treating lymphatic anomalies are sclerotherapy and surgical resection. Historically, irradiation,[60] incision and drainage, or injection of sclerosing agents,[61] or boiling water,[62] have all been used as non-surgical treatments of lymphatic malformations. With the exception of sclerotherapy, none has demonstrated reproducible success. Sclerotherapy uses a variety of agents to induce obliteration of the lymphatic lumen by chemical destruction of the endothelium with subsequent sclerosis/fibrosis. Success parallels the degree of damage inflicted upon the endothelial and deeper muscular and connective tissue layers. In general, macrocystic LMs are more amenable to sclerotherapy than microcystic as it is possible to drain the entirety of the cyst cavity and induce endothelial apposition prior to administration of a sclerosant. Of the available sclerosing agents, ethanol is often considered a first-line choice, although it has experienced greater success with venous than lymphatic malformations. Ethanol injection is quite painful, often requiring general anesthesia and subsequent pharmacologic pain relief. Local side effects include necrosis, blistering, and a self-limited neuropathy. Systemic side effects, although uncommon, result from the absorption of ethanol and include cardiac arrest, pulmonary vasoconstriction, and systemic hypotension. Ethibloc, a sclerosing solution of ethanol, amino acids, and contrast agent, available in Europe, has been used with reported success rates of 20–65%.[63,64] OK-432, a bacterial product derived from *Streptococcus pyogenes*, induces a significant local inflammatory response and has reported success rates of 60–100%.[65,66] The mechanism of action of OK-432 is not completely understood, but likely reflects a multi-tiered activation of the immunologic system, including neutrophils, macrophages, NK cells, and T cells.[67] No significant toxicity has been recorded. Antineoplastic agents, such as bleomycin[68] or cyclophosphamide,[69] and fibrin sealant[70] have also been attempted with limited success.

Resection is the only way to potentially 'cure' LM. Because of this, most authors advise early surgical excision of lymphatic malformations, to avoid the complications of infection, hemorrhage, and continued growth with further infiltration of surrounding tissues.[62] Spontaneous regression of these lesions after birth is thought to be rare.[71] Although safe surgical excision is now possible in most cases, some reports in the past decade have advocated injection sclerotherapy for cases which are located in regions where resection would be too hazardous, for cases which have been incompletely resected, and for recurrent tumors. Our own experience would suggest that the lesions that are reportedly responsive to agents such as OK-432, namely moderate- to large-sized cystic malformations, are those that can be safely excised with a single operative intervention. These 'easier' lesions also form the critical mass of cases required for gaining the surgical experience necessary for the successful surgical management of the more complex lymphatic malformations. In such lesions, staged excision is often necessary. In each resection a surgeon should focus on a defined anatomic region, attempt to limit blood loss, perform as thorough a dissection as possible, and be prepared to operate as long as necessary. Even with such an intensive approach to resection, subsequence 'recurrence' is as high as 40% after an incomplete excision and 17% after a macroscopically complete excision.[72]

SURGICAL MANAGEMENT

Most lymphatic malformations are easily resected without undue mortality or morbidity, as long as the following principles are adhered to:

- Adequate exposure must be obtained.
- Meticulous dissection must be used in order to preserve vital structures, including nerves, vessels, trachea, and esophagus. We have had success with the exclusive use of a microbipolar dissection technique.[73] This technique is of particular advantage when dissecting close to important neurovascular structures.
- Since this is a benign disease, it is not justifiable to sacrifice a vital structure in order to completely excise the lesion.
- Whenever possible, the lymphatic supply to the lesion should be ligated to prevent postoperative accumulation of lymph. In the head and neck region, the lymphatic supply to a lymphatic malformation is usually not visible, but it is possible that the microbipolar dissection technique may 'weld' these channels shut.

Lymphatic malformations of the neck can usually be approached through a transverse cervical incision under general intratracheal anesthesia. Perioperative antibiotics should be employed. After division of the platysma muscle, the mass is carefully dissected from all surrounding structures (Fig. 80.6). The large cystic malformations are usually well encapsulated, and every attempt should be made not to rupture the cysts. The fluid within the cyst aids the surgeon in defining the cyst wall, and therefore in finding the correct plane in which to dissect. Particular care must be taken to avoid injury to the carotid artery and its branches, or to the internal jugular vein. Preservation of other large venous channels, if possible, may also be beneficial in promoting regional drainage. A number of nerves are often closely associated with the lesion, including the facial nerve, the spinal accessory nerve, the vagus nerve, and the brachial plexus. Although pathological studies have shown that microscopic tumor is often left behind, recurrence is rare when all gross tumor is removed.[72] Once the malformation has been removed, and, if possible, the lymphatic supply to the malformation ligated, a closed-suction drain should be left in the tumor bed to prevent early accumulation of fluid. Dietary restriction of long chain triglycerides in the postoperative period may be of some benefit in reducing the amount of chylous lymph production.

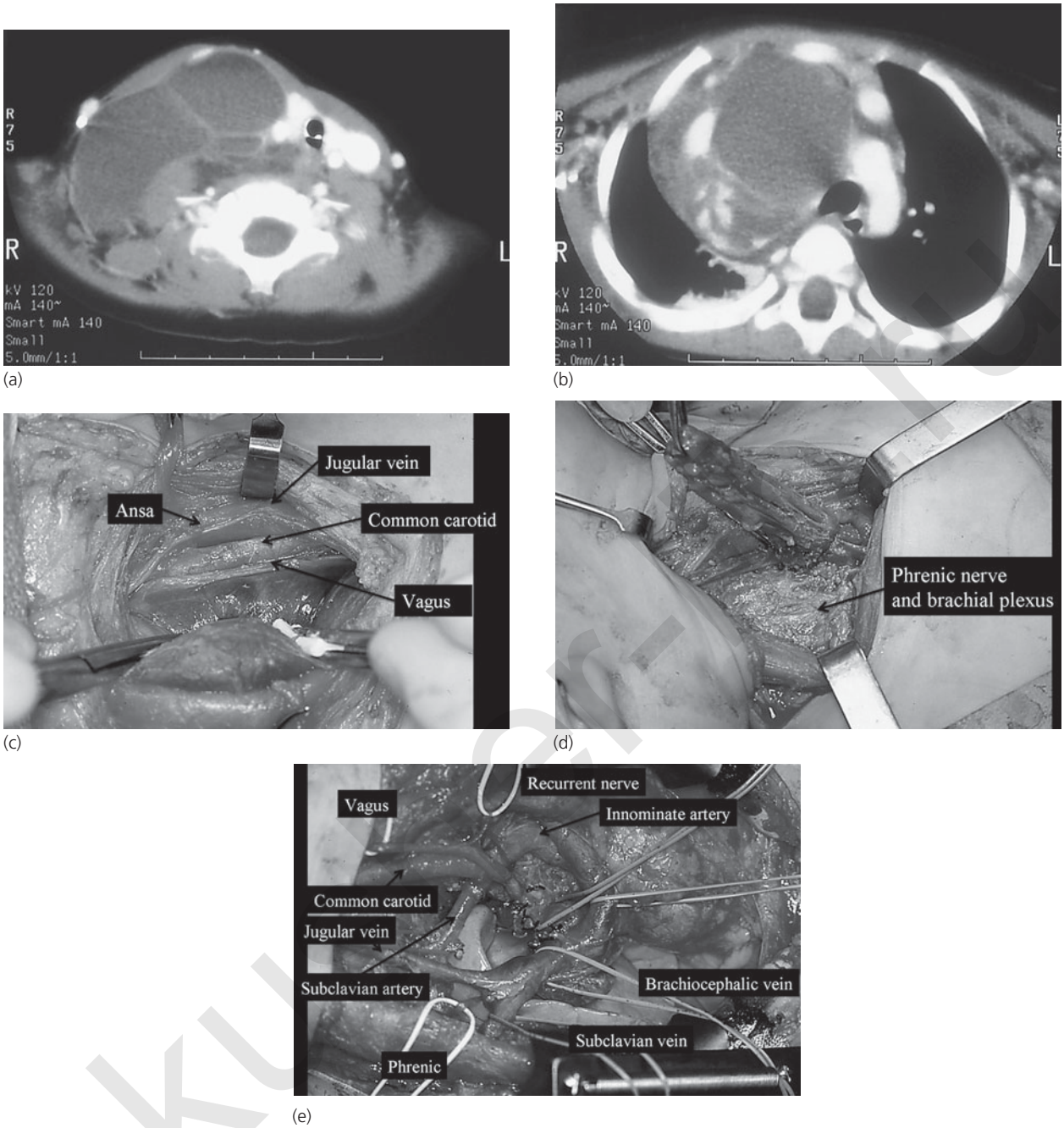

Figure 80.6 Surgical exposure of a cervico-mediastinal lymphatic malformation. Note location of vital neurovascular structures, which must not be damaged during the dissection. (a,b) Computed tomography scan demonstrating the lesion; (c,d) dissection of the cervical portion; (e) completed mediastinal dissection after extension of the incision and sternotomy.

A small number of cervical lesions extend into the axilla or the mediastinum. For axillary extension, the child should be elevated 15–20° on the involved side, with the arm draped free, and both cervical and axillary crease incisions should be used.[62] The cervical component is approached first, separating the lesion away from the brachial plexus until the cysts are seen to pass below the clavicle. The axillary portion is then dissected free. The most difficult aspect of the operation is removing the lesion from the brachial plexus behind the clavicle, where it is often densely adherent. Only careful, meticulous dissection will permit complete removal of the malformation without injury to the nerves.

Extension into the mediastinum also presents a difficult technical challenge. The best approach is one-stage resection through an 'inverted hockey-stick' incision, as described by Grosfeld *et al.*,[74] where a transverse neck incision is extended inferiorly into a midline sternotomy. Modifications of the Grosfeld approach, by either leaving a bridge of skin between the horizontal cervical and midline sternotomy incisions or by performing a partial upper sternotomy through the

cervical incision, may provide a cosmetically superior result without significantly compromising exposure. These approaches provide adequate exposure to safely dissect the lesion away from the jugular, carotid and subclavian vessels, and the aortic arch, esophagus, and pericardium, with preservation of the phrenic, vagus, and recurrent laryngeal nerves. The rare lymphatic malformation which is confined to the mediastinum can be approached through a lateral thoracotomy, a midline sternotomy,[75] or a thoracoscopic approach (Fig. 80.7).

Perhaps the most difficult lesions to approach surgically are the massive lesions which involve tongue, floor of the mouth, and larynx. These lesions are usually present at birth, and may result in early airway obstruction, either by sheer mass effect or as a result of hemorrhage into the tumor. In many cases, a tracheostomy is necessary as a life-saving procedure, followed by multiple extensive operative procedures.[76] For prenatally diagnosed cases, access to the airway can be achieved at the time of Cesarean section before clamping the umbilical cord (EXIT procedure).[39,77,78] The same surgical principles are employed as outlined above, but the strategy for each patient must be individualized. Recurrence rates in these patients are higher, but do not seem to correlate with the removal of all macroscopic tumor.[79] Historically, repeated or staged surgical approaches seemed to offer the best hope for palliation. Currently, if at all possible and feasible, our first choice is an aggressive, single-staged resection to avoid the need for tracheotomy or gastric tube feeding. The option of a more aggressive surgical approach has been made possible by advancements in anesthetic techniques, improved specialized neonatal and pediatric postoperative care units, and the use of the microbipolar dissection technique. Also, the use of laser technology for controlling airway obstruction from laryngeal or tracheal involvement has been highly successful in this group of patients.[79,80]

Lymphatic malformations involving the tongue pose a very difficult problem. As a general principle, direct surgical treatment of the tongue should be avoided if possible. Intermittent swelling of the tongue can be effectively controlled with systemic steroids. Capillary lymphatic malformations involving the mucosal surface of the tongue (also known as simplex), can cause blistering, bleeding, and pain, and are best handled with laser resurfacing techniques.[81,82] Persistent, symptomatic macroglossia involving the intrinsic muscles of the tongue may require reduction glossoplasty. Lymphatic malformations involving the floor of the mouth and tongue may also lead to bony malformations of the growing mandible, which may require subsequent surgical correction.[83]

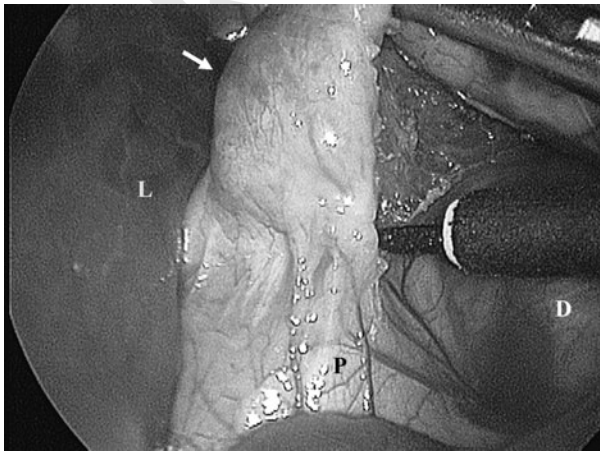

Figure 80.7 Thoracoscopic approach to a small mediastinal lymphatic malformation (arrow). D, diaphragm; L, lung.

Lymphatic malformations in the abdomen usually originate in the retroperitoneum or the intestinal mesentery. Either a laparotomy or a laparoscopic approach can be used. In either case, resection should be done using meticulous technique. Although a complete resection is sometimes possible, often some of the lesion must be left behind. The remaining cysts should be unroofed, since complications, such as postoperative ascites, are rarely seen. Image-guided laser coagulation has also been reported for unresectable lesions.[84] Primary intestinal lymphangiectasia presenting as a protein-losing enteropathy, has been reported in case studies to be successfully treated with segmental resection of involved small bowel.[85] Occasionally, a lymphatic malformation will present with scrotal swelling, and may be misdiagnosed and operated upon as a hydrocele. Once the diagnosis has become clear, these lesions should undergo complete resection if possible.

Lymphatic malformations of the extremities range from small, easily resected cysts to large, infiltrating lesions. The large malformations are often accompanied by poor lymphatic drainage, which predisposes the limb to edema, infection, and inhibition of function. Complete excision of these lesions may be impossible, and amputation may ultimately be necessary.

Surgical complications

In the modern era, the mortality associated with surgical resection of a lymphatic malformation should approach zero. Early intervention before infectious complications or airway obstruction, and strict adherence to the principles described above, permit safe removal with little morbidity in the majority of cases. The complications of surgery include seroma, infection, and neurological sequelae, such as Horner's syndrome, facial nerve palsy, or spinal accessory nerve injury. Although these problems are usually transient, surgical intervention may occasionally be required.[86] Table 80.2 outlines the perioperative complications seen in 130 consecutive surgical cases at our center.[87]

Recurrence can occur after surgical excision, especially if the first resection has been incomplete. These recurrences may represent fluid refilling cysts which had been decompressed, or may be due to filling of more distal cysts whose drainage has been interrupted by the surgical procedure. Ultrasound, computed tomography, and magnetic resonance imaging may all be useful for demonstrating these recurrent lesions.[87] Options for management include further resection or injection sclerotherapy, depending on the anatomic location and the likelihood of injury to neurovascular structures.

Table 80.2 Perioperative complications, 120 cases.[65]

Complication	No.
Infection	6
Bleeding[a]	5
Cranial neuropathy	12
Marginal mandibular branch VII[b]	10
Cranial nerve XI	1
Cranial nerve XII	1
Horner's syndrome	1
Seroma	4
Salivary fistula	1
Wound dehiscence	3
Tongue edema	3

[a]Requiring blood transfusion.
[b]Paresis resolved completely.

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81

Cervical teratomas

MICHAEL WL GAUDERER

INTRODUCTION

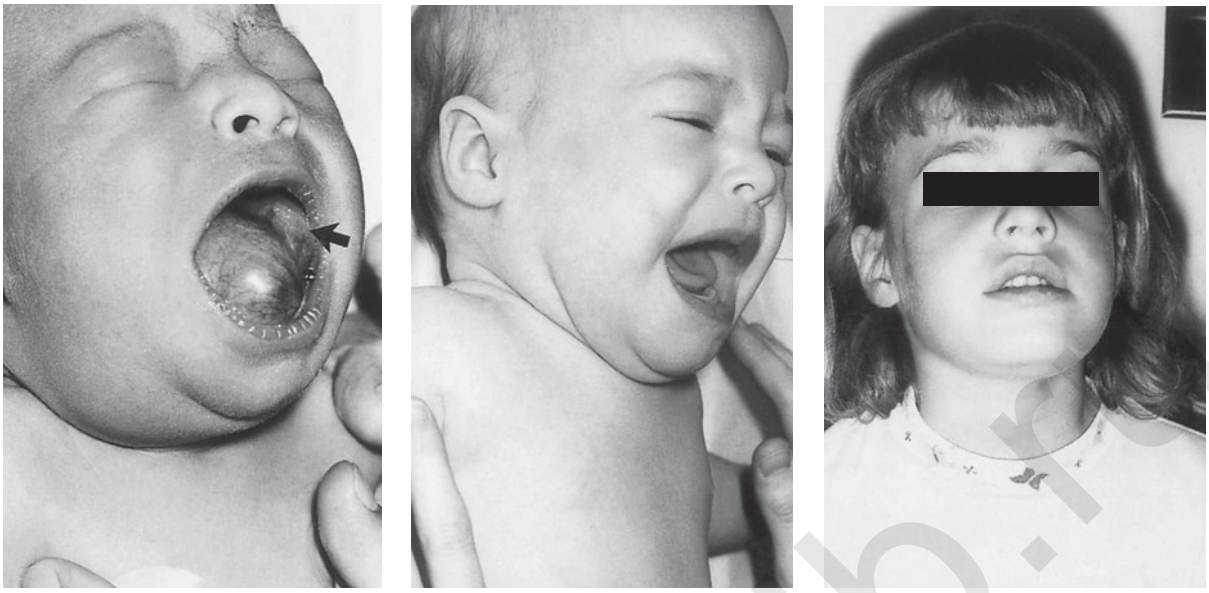
Cervical teratomas, although rare, are an important cause of neck masses in newborns and children. Because these lesions are often quite large, they can lead to precipitous airway obstruction necessitating prompt recognition and surgical intervention. Antenatal diagnosis and new techniques of multidisciplinary intrapartum management have contributed to an improved outlook for the survival of newborns at greatest risk of airway compromise.

PATHOLOGY

Teratomas are neoplastic lesions composed of tissues foreign to the anatomical site of origin, including all three germ layers. It is believed that most cervical teratomas arise from the embryonic thyroid anlage, although frequently clear association with the gland cannot be demonstrated.[1–4] In 1974, Roediger *et al.*[5] presented a comprehensive discussion of the histogenesis of this lesion. Although a wide variety of tissues from all three germinal layers have been found in cervical teratomas, there is a 68% incidence of neural tissue, which in many cases predominates in the solid portion of the tumor.[2–4,6] Thyroid tissue is present in 30% of specimens. The majority of cervical teratomas in the pediatric age group are benign (Fig. 81.1a–c); however, malignancy with and without distant metastases has been reported.[3,7–9] Conversely, the incidence of malignancy in adults with cervical teratomas is reported to be as high as 70%.[10] Although cervical teratomas are generally located anteriorly to the major neck structures (Fig. 81.2), significant distortions of normal anatomy are frequently encountered (Fig. 81.3).[3,4,9,11,12] Teratomas are usually single lesions, however they may occur in more than one site in the head and neck.[13] The presence of a teratoma arising in one fetus of a twin pregnancy has been described.[14] Associated anomalies are rare.[2–4]

INCIDENCE AND CLINICAL MANIFESTATIONS

In four large series of teratomas in infancy and childhood, the incidence of cervical location ranged from 2 to 9.3%.[15–20] Cervical teratomas are reported to occur in all races and there is a slight female preponderance.[2–4] There is a high incidence of prematurity, polyhydramnios, and birth dystocia. Polyhydramnios is probably secondary to inability of the fetus to swallow amniotic fluid.[2] Stillbirth is usually associated with giant cervical lesions and due to a combination of compression of vital structures and congestive heart failure.[21] The most common clinical presentation, in addition to the mass, is respiratory difficulty.[1,4,12,22] Respiratory symptoms may vary from total apnea to mild dyspnea or coughing with feedings. The dyspnea may also be positional. Although airway compression may not be noted at birth, it may progress rapidly over several hours to a life-threatening obstruction. These cervical teratomas clearly represent a spectrum. Some children are referred beyond the neonatal period,[23] while in others it only becomes manifest in adulthood.[3,10] A classification of cervical teratomas,[3] taking into consideration the age and clinical presentation (Table 81.1), clearly shows that almost half of the patients are newborns with respiratory distress (group II). Operative and non-operative management is accompanied by a 43% mortality in this subgroup.[3] The mortality rates in groups I and III will probably remain unchanged. However, establishment of an adequate airway followed by prompt excision of the tumor should lead to improved survival in group II, the most common presentation. Therefore, once such a lesion is diagnosed after birth,



(a) (b) (c)

Figure 81.1 (a) One-day-old, full-term female newborn born with right cervical teratoma that extended into the oral floor, displacing the tongue to the left (arrow). The lesion was firm, partially cystic and limited to the right anterior cervical triangle. She had mild respiratory distress, worsening when placed in the supine position. On the second day of life, the $6.5 \times 5.5 \times 4.5$-cm mass was excised through a transverse cervical incision, combined with intraoral dissection. The thyroid gland was not involved. Analysis of the specimen revealed a benign cystic teratoma containing neuroglia, choroids plexus, smooth muscle, respiratory and squamous epithelium, and pancreas. Transient difficulty with oral feedings occurred in the immediate postoperative period. (b) Same child at three months of age. Notice the well-healed scar following the natural skin crease and the normal position of the tongue. (c) Same child at six years. The scar is no longer discernible. Tongue motion and dentition are normal.

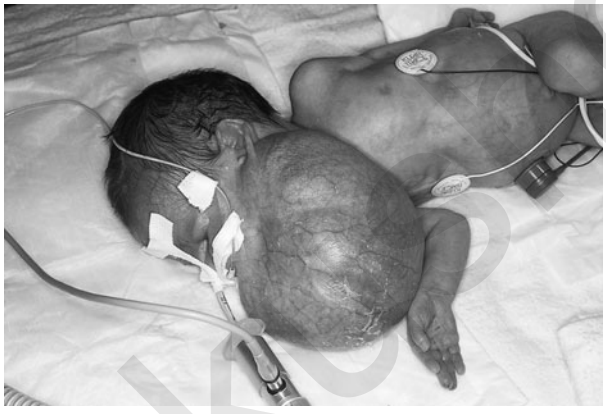


Figure 81.2 Very large cervical teratoma in a premature child.

prompt excision is mandatory. If diagnosed antenatally, recently developed intrapartum airway establishment techniques may be applied effectively;[12,24–27] this has changed the prognosis of select patients in group II (Table 81.1).

DIAGNOSIS

Cervical teratomas can accurately be diagnosed antenatally[3,4,28] using ultrasonography,[28] which is also the most useful immediate postnatal imaging study. Plain radiographs demonstrate calcification within the lesion in 16% of pediatric cases.[3,29] Tracheal deviation is common. Other imaging modalities, such as radioisotope scans, computed

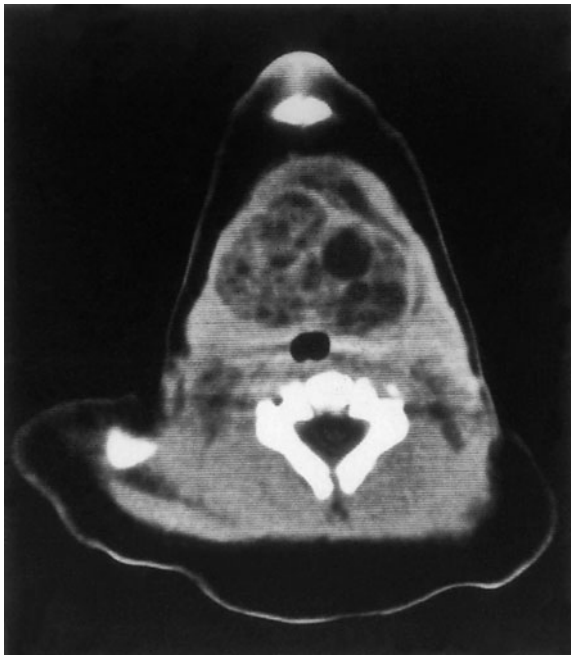


Figure 81.3 Computed tomography scan of the neck of a five-month-old female patient. The lesion was initially thought to be a hemangiolymphangioma. Fortunately, this child had minimal or no airway compression, in spite of the location of the mass. The removed specimen was a benign teratoma containing neuroglia, choroid plexus, respiratory epithelium, pancreas, muscle, and cartilage.

Table 81.1 Classification of cervical teratomas by age and clinical presentation based on the review of 217 cases.[3]

Group		No. cases	Total cases (%)	Malignant (%)	Mortality (%)
I	Stillborn and moribund live newborn	27	12.4	2 (7.4)	100
II	Newborn with respiratory distress	99	45.6	2 (2)	43.4[a]
III	Newborn without respiratory distress	37	17.1	0	2.7
IV	Children age one month to 18 years	31	14.3	0	3.2
V	Adult	23	10.6	16 (69.6)	43.5[b]

[a]Includes operative and non-operative treatment.
[b]Incomplete follow up for six malignant cases.

axial tomography (Fig. 81.3), and magnetic resonance imaging (MRI) are helpful in more complex cases, but should be used with great caution because sedation for longer exposure times may be needed. MRI can be helpful in planning the operation, as it demonstrates planes of dissection and position of vital structures that have been displaced by tumor growth.[7] It is also useful in prenatal evaluation in preparation for operating on placental support.[30]

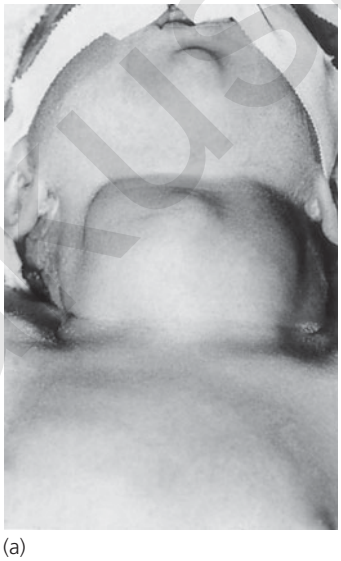
Differential diagnosis

Differential diagnoses should include cystic hygroma, lymphangioma, branchial cleft abnormalities, congenital goiter, thyroglossal duct cyst, dermoid cyst, neuroblastoma, and duplications.

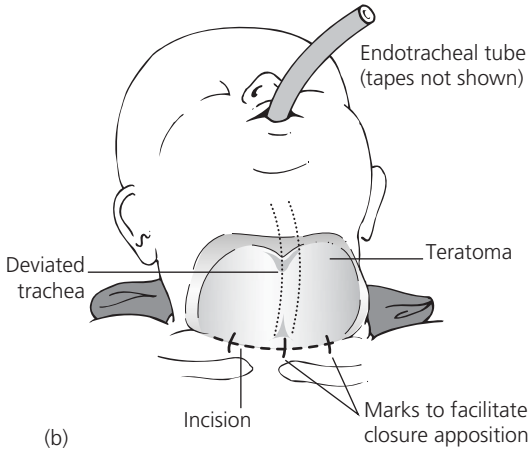
MANAGEMENT

The most difficult aspect of the management of orocervical teratomas is the establishment and maintenance of an adequate airway.[3,9,12,22] Orotracheal or nasotracheal intubation requires skill and patience in these infants due to tracheal deviation and/or compression. A useful adjunct is nasotracheal intubation with the aid of a flexible fiberoptic scope. The endotracheal tube is slipped over the scope and the endoscope is then inserted. Once the tip of the flexible scope reaches the carina, the endotracheal tube is advanced and positioned. The distance between the carina and the end of the tube can then easily be determined by direct visualization. Tracheostomy, as an emergency procedure, has obvious limitations, although it may be necessary in extreme situations.[22,26] Whenever possible, a tracheostomy should be avoided because it increases operative, as well as postoperative, morbidity.[3] If the teratoma is composed of one or more large cysts, emergency aspiration may be employed to reduce tumor size and alleviate pressure on the airway.

An exciting advance in the management of fetuses with a high probability of upper-airway compromise at or immediately after birth, is the development of the *ex utero* intrapartum treatment (EXIT).[12,24–27] This technique permits the establishment of a secure airway while the child is on placental support. The procedure requires a



(a)



(b)

Figure 81.4 Operative approach to the case in Fig. 81.3a. The intubated child's neck is elevated over a roll. Wide draping with adhesive plastic sheets allows for excellent exposure and helps prevent temperature loss. The incision is drawn with a marking pen on one of the skin creases, if possible. To facilitate proper apposition of the redundant skin following resection, multiple small cross-hatches are drawn with the pen. Following the skin incision, the marks are replaced by guy sutures that are helpful for traction on the flaps, as well as the final approximation. It must be remembered during the dissection that the trachea may not be in the center. Other vital structures may also be markedly displaced.

multidisciplinary approach of team members from the involved specialties: obstetrics, anesthesia, pediatric surgery, and neonatology.[24–27]

The incision for cervical and orocervical teratomas should be carefully planned to allow access not only to the neck, but also to the upper mediastinum or oral cavity, if needed. As opposed to lymphangiomas, teratomas can be usually be dissected without great difficulty (Fig. 81.4a,b). The lesion is often attached to one of the lobes of the thyroid. When dissection reaches this level, every attempt should be made to preserve the thyroid and parathyroids. Dissection around the trachea and the esophagus must be carried out with great care to avoid injury to the recurrent laryngeal nerves (Fig. 81.5). Tracheal, as well as esophageal, deviation should be constantly kept in mind. In the small neck of the newborn, deep dissection can lead to injury to the phrenic nerves. Once the tumor is removed, a soft, fine silicone rubber drain is placed and attached to a closed drainage system. The musculoaponeurotic layers are approximated with fine synthetic absorbable sutures and the skin is closed with subcuticular stitches. Postoperatively, vocal cord and diaphragmatic function should be assessed and recorded. Calcium levels are measured in the immediate postoperative period and thyroid function tests are obtained after a few weeks. Careful histological examination of the entire excised specimen is mandatory (Fig. 81.6). If the alphafetoprotein levels were initially elevated, follow-up determinations should be sought.

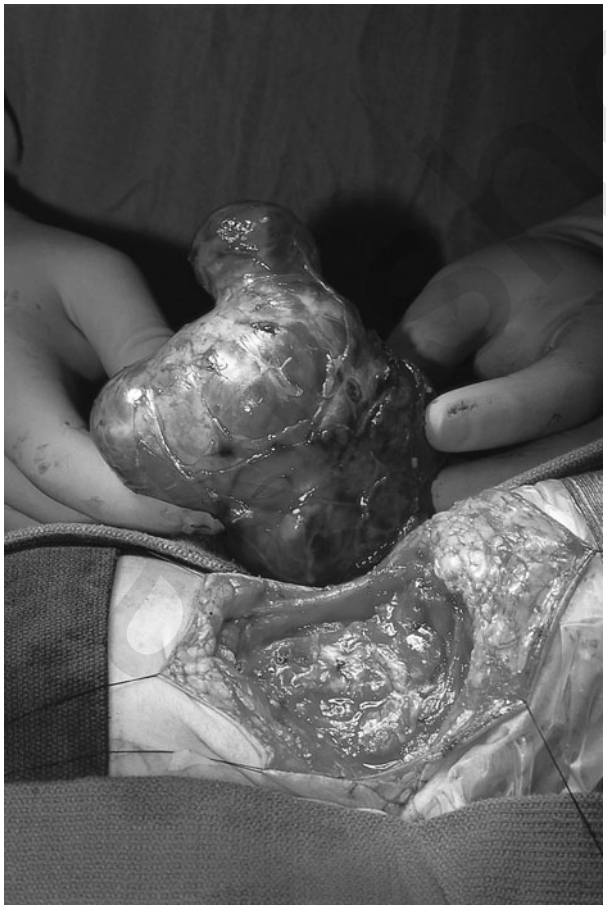


Figure 81.5 Complete excision of a large cervical teratoma. Notice the smooth surface of the removed specimen and retraction of the redundant skin flaps by the guy sutures.

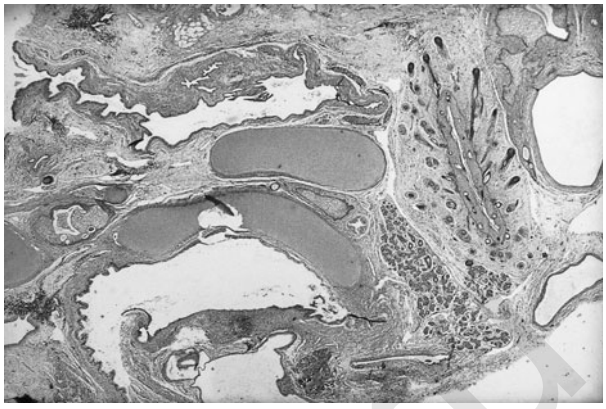


Figure 81.6 Histological section of a cervical teratoma demonstrating an array of various tissues.

CONCLUSION

The overall prognosis for cervical teratomas is good, particularly in the newborn, with little or no respiratory distress (Table 81.1).[3,4,9,17,23] If the lesion is diagnosed *in utero*, appropriate preparations can be made to assure prompt establishment of a good airway immediately at or following birth. Carefully planned excision is then possible. This should increase the survival in the newborn with significant respiratory compromise.

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82

Sacrococcygeal teratoma

KEVIN C PRINGLE

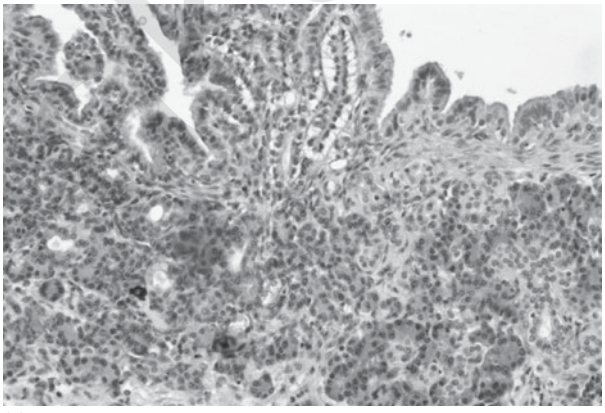
INTRODUCTION

A sacrococcygeal teratoma is a neoplasm arising from the caudal end of the spine, usually protruding from the inferior end of the infant's spinal column and displacing the anus forwards. These tumors have a female-to-male ratio of at least 3:1.[1–9] The incidence is approximately one in 40 000 live births.[10,11] There is general agreement that sacrococcygeal teratoma (SCT) is the result of continued multiplication of totipotent cells from Hensen's node which fail to apoptose at the end of embryonic life.[7,12,13] This concept has recently received support from the work of Busch *et al.*[14] who have identified histochemical markers in SCTs supporting an origin from caudal embryonic stem cells. This provides convincing evidence against the theory that these tumors arise from migrating germ cells traveling from the yolk sac to gonad. Most authorities reject the concept that these are suppressed twins or parasitic fetuses. Pantoja and Rodriguez-Ibanez[15] reviewed the conflicting theories as to the origin of these tumors. A familial distribution of sacrococcygeal teratoma has occasionally been reported.[16–18]

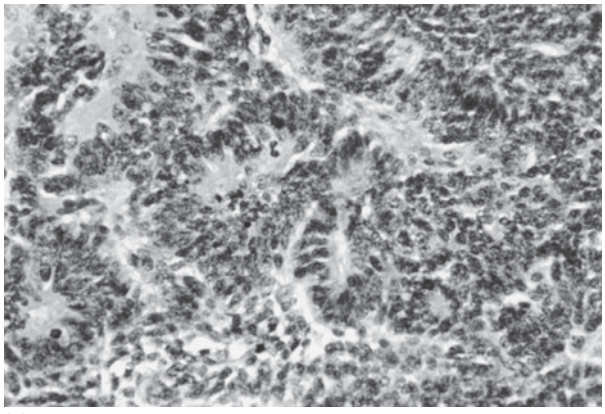
PATHOLOGY

Willis defined the term teratoma as follows: 'A teratoma is a true tumor or neoplasm composed of multiple tissues of kinds foreign to the part in which it arises'.[13] The sacrococcygeal teratoma was second on Willis' list of sites where teratomata are found, but in almost all pediatric surgical series, the sacrococcygeal site is the most common site.[1–4,19] By definition, then, sacrococcygeal teratomata are composed of several types of tissue, usually derived from two or three germ layers. Robbins[20] defines a teratoma as 'a tumor composed of cells representing more than one germ layer'. In fact, however, in any tumor consisting of an epithelial component and a supporting stroma, at least two germ layers are represented. Most carcinomata, therefore, would meet Robbins' definition of a teratoma.

Within any one tumor, the cells can vary from totally benign (even forming well-formed teeth, hair, or other organs) to cells that appear frankly malignant (Fig. 82.1). However, many sacrococcygeal teratomata contain malignant-looking cells (usually described as 'immature'), but if



(a)



(b)

Figure 82.1 Histology of two areas of the tumor from the patient shown in Fig. 82.3. (a) Apparently well-formed epithelium; (b) an area of primitive neuroglial tissue that could be diagnosed as being consistent with an aggressive neuroblastoma, were it not for the context in which it was found.

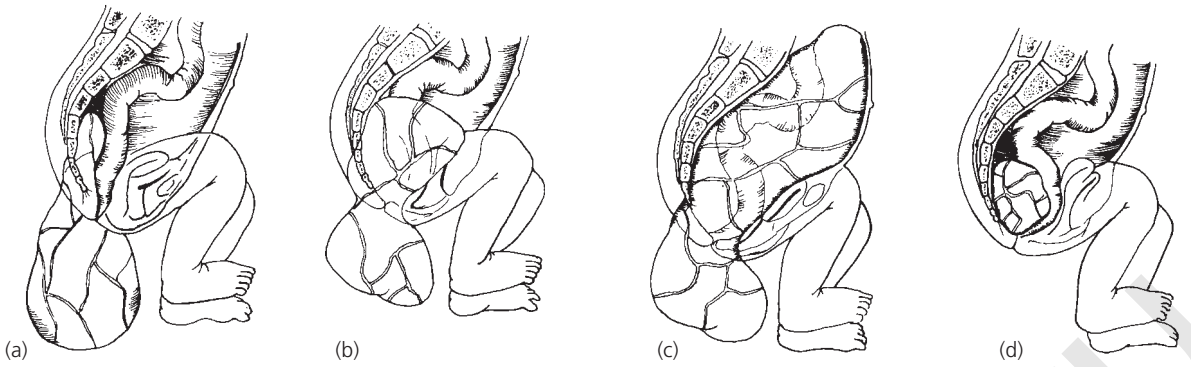


Figure 82.2 Sacrococcygeal tumors as classified by Altman *et al.*[19]

they are completely excised they do not recur. For this reason, the diagnosis of malignant sacrococcygeal teratoma can only be made if there are distant metastases.[19]

The risk of malignancy depends on two factors: (1) the site and the extent of the tumor and (2) the age at diagnosis. Tumors diagnosed after two months of age have a high risk of being malignant. An exception to this statement is the relatively rare presacral 'dermoid' tumors, which often present in adolescence or adult life with constipation or urinary obstruction, but if excised completely appear to be totally benign. Altman *et al.*[19] classified sacrococcygeal teratomata into four groups when they reported the results of the American Academy of Pediatrics (AAP) Surgical Section Survey. Type I tumors are almost exclusively exterior with a minimal pelvic component (Fig. 82.2a). They are rarely malignant (0% in the AAP survey). Type II tumors have a significant pelvic component. In the AAP survey, 6% of type II tumors were malignant (Fig. 82.2b). Type III tumors have an intrapelvic and intra-abdominal component greater than the external component (Fig. 82.2c). The intra-abdominal component can usually be palpated on abdominal examination. In the AAP survey, 20% of type III tumors were malignant. The type IV tumors are exclusively presacral; they had an 8% incidence of malignancy in the AAP survey (Fig. 82.2d).

PRESENTATION

Before routine antenatal ultrasound examinations became widely accepted, the most common presentation was as a large sacral mass that is immediately obvious at birth.[1–5,12,19,20] The malignant tumors tend to present as a swelling of the buttock at five to six months of age. However, with the advent of routine antenatal ultrasound, the most common presentation is now antenatal diagnosis by ultrasonography.[21–30] Series reporting the antenatal diagnosis of sacrococcygeal teratomata have revealed that many of those fetuses diagnosed as having a sacrococcygeal teratoma are likely to die before delivery.[21,23,31–33] Most of the fetuses reported to have died following antenatal diagnosis had tumors with a mass as great as or greater than the rest of the fetus. It is, therefore, entirely possible that these fetuses die of heart failure as the fetal heart is unable to pump sufficient blood to nourish both the tumor and the rest of the fetus. Certainly, in most of the antenatal series reported, fetal hydrops (non-immune hydrops) is very common, and is associated with an increased risk of fetal demise.[21,24,26,28–33] In 1990, Ikeda *et al.*[28] reported the characteristics of 20 cases of prenatally diagnosed sacrococcygeal teratomas. Six infants delivered at a gestational age of from 25 to 32 weeks died prenatally; 14 cases delivered after 32 weeks' gestation survived. Other articles, including three from the group in Chapel Hill (all reporting the same nine antenatally diagnosed sacrococcygeal teratomata[34–36]) also report a high mortality rate if fetal hydrops is noted or if the diagnosis is made early in gestation.[28–30,32,33] Wilson *et al.*,[37] from the Children's Hospital of Philadelphia, have recently emphasized the rate of growth of the tumor and the estimated fetal cardiac output as important prognostic indicators, with a growth rate of >150 mL/week and a combined cardiac output >650 mL/kg per min being associated with a worse prognosis. Benachi *et al.*[38] have similarly emphasized the prognostic importance of rapid fetal growth and high vascularity.

Recent improvements in magnetic resonance imaging (MRI) technology have enabled this modality to be used in the fetus without the need for fetal sedation or paralysis.[39–41] As more experience is gained with these techniques, it is becoming easier to define the anatomy of the tumor much more accurately, and it is sometimes possible to accurately determine the blood supply to the tumor *in utero*.

The improved diagnosis and the high mortality rate associated with fetal hydrops have provided a considerable impetus for some groups to consider fetal surgery for selected cases of antenatally diagnosed sacrococcygeal teratomata. The groups in San Francisco and at Children's Hospital of Philadelphia have had the greatest experience with this approach,[42–46] although other groups have also attempted fetal surgery[47] or percutaneous shunting or drainage to allow vaginal delivery[48,49] for these tumors. The results, so far, have been mixed.[42–49] A detailed discussion of this aspect of the management of sacrococcygeal teratomata is beyond the scope of this chapter, but it would be fair to say that the role of fetal intervention in the presence of this tumor has still not yet been defined.

One further presentation (not often reported) is when the tumor becomes impacted during delivery and either causes the death of the fetus by obstructing delivery, or the tumor

ruptures during delivery and the infant bleeds to death shortly after birth.[29,50–52]

CLINICAL FEATURES

Most cases presenting as neonates to pediatric surgeons will have a large skin-covered mass protruding from the coccygeal region, pushing the anus and vagina anteriorly (Fig. 82.3). There may be large veins visible on the surface and these usually drain into the surrounding structures. Large tumors may have ruptured (in which case they will bleed profusely) or may have an ulcerated area on the surface. Neonates with a tumor approaching the size of the rest of their body may be delivered prematurely and will often have some features of non-immune hydrops.[22,24–30,32,33]

Infants presenting with malignant tumors usually present with a rapidly growing buttock mass.[53,54] In such cases, distant metastases are usually present at diagnosis. With the increasing use of antenatal ultrasound in many countries in recent times, this should become an extremely rare presentation. The management of these tumors is beyond the scope of this chapter. Recent advances in multimodal therapy of these tumors has resulted in survival rates as high as 80%.[55] Children and adolescents with a benign presacral tumor usually present with constipation or urinary retention.[16,18,56–58] A retrorectal mass is easily recognizable on rectal examination. Again, management of these tumors is beyond the scope of this chapter.

In all cases, the tumor is firmly attached to, and may be said to arise from, the anterior surface of the coccyx. It may displace the coccyx posteriorly, but almost without exception, the sacrum is normal. The author has seen one infant who was delivered at 30 weeks' gestation with a large sacrococcygeal teratoma associated with agenesis of the coccyx and the last two sacral vertebrae.[26] Very rarely, however, the tumor can extend superiorly. In one reported case, the tumor extended within the spinal canal as high as T4.[59]

In most cases, the majority of the blood supply to the tumor is derived from the middle sacral artery[5,60] and during removal, once this vessel is controlled, blood loss is usually minimal. This is not always the case and a preliminary abdominal procedure to control the middle sacral artery in very large tumors, as suggested by some authors recently,[61–63] can occasionally yield very disappointing results, with only a very small vessel being identified.[64] In addition, on two occasions in the author's personal series, the bulk of the venous drainage from the tumor returned through the sacral hiatus and back to the azygous system via a large network of very friable epidural veins. This resulted in a frighteningly large loss of blood when the sacrum was divided. In both cases, the initial blood loss was controlled with pressure and the middle sacral artery was rapidly controlled, allowing the definitive control of the bleeding from the divided sacral canal with gelfoam on one occasion and bone wax on the other. With the improvement of the resolution of modern ultrasound machines and the introduction of color flow mapping using Doppler ultrasound, it may be possible to determine whether the venous return is via the sacral hiatus. The limited experience from the author's center suggests that this is possible. However, it should be stated that in the patients in whom preoperative color flow mapping has been used over the past five years, no sacral flow has been noted either on ultrasound or at operation. Clearly, more experience is needed. However, the simplicity of this examination with modern ultrasound machines makes this a useful addition to preoperative work-up.

Some authors have advocated laparoscopic procedures to divide the middle sacral artery.[63] This may be technically difficult if there is a large intra-abdominal component of the tumor.

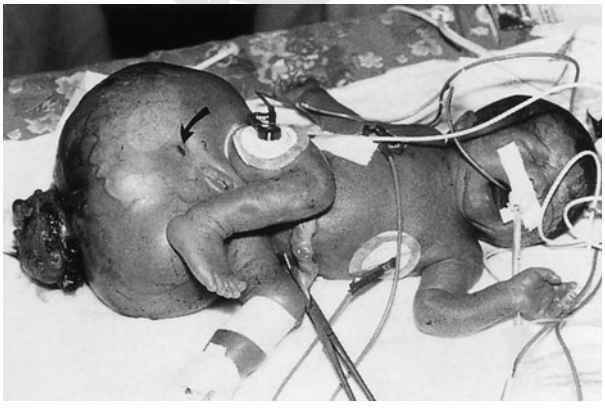


Figure 82.3 Premature infant with a large sacrococcygeal tumor that weighed almost as much as the rest of the infant. Note the displacement of the anus (arrow) and the vulva.

POSTNATAL DIAGNOSIS

The major differential diagnosis that should be considered is an anterior meningocele. This can usually be ruled out by physical examination, including rectal examination. In sacrococcygeal teratoma, the rectal examination will invariably reveal a solid presacral component. If an anterior meningocele is present, this will be cystic, and an anterior sacral defect will often be palpable. Dillard *et al.*[4] point out the need to observe the anterior fontanel during the rectal examination. In anterior meningocele, pressure on the sacral mass will result in a bulging fontanel. The diagnosis can be confirmed by radiography of the lumbosacral region, which will show a characteristic defect in the sacrum in a patient with a meningomyelocele. An MRI examination will confirm the diagnosis.

Another recently described addition to the list of differential diagnoses is a sacrococcygeal chordoma.[65] Lemire *et al.*[66] have produced a list of 20 different lesions that can possibly enter into the differential diagnosis. Most of these are extremely rare, but will usually be distinguishable from sacrococcygeal teratoma on careful physical examination. An abdominal ultrasound is useful to determine the size and consistency of any pelvic or abdominal component. It may be necessary to pass a catheter into the bladder and fill the bladder with water to allow it to be used as a sonic window.

With the rapid improvements in MRI technology, it is now possible to utilize MRI in neonates with minimal sedation, although in many cases a general anesthetic is still required for a detailed examination. Software packages allowing the use of MRI to delineate vascular anatomy are now available.[67–69] The use of gadolinium as a contrast medium has improved the delineation of the vascular anatomy. If oil is instilled into the rectum during the MRI examination while T_1-weighted images are gathered, then the oil can be used as a contrast medium during the scan,[70,71] although modern advances in MRI technology have now made this technique obsolete. MRI should clearly distinguish between sacrococcygeal teratoma and anterior meningocele, and may be able to detect the occasional extension of the tumor through the sacral hiatus into the spinal canal.[61]

PREOPERATIVE MANAGEMENT

If the lesion is intact and the infant is stable, then there is no need for immediate resection. However, a case can be made for resecting these lesions within the first 24 hours after birth, since the gut is not usually colonized in the first 24 hours after birth. Early resection, therefore, will reduce the risk of infection if the field is contaminated by stool during the resection. Perioperative antibiotics are advisable. They should be given immediately before surgery commences and be continued for 24–48 hours postoperatively. If the infant has been fed, or is several days old, then a case can be made for a formal bowel preparation prior to the operation.

Blood should be cross-matched, and adequate i.v. access is vital. An arterial line may also be useful during the operation. It is worthwhile to obtain blood for alpha-fetoprotein levels before surgery as a baseline, in order to confirm postoperatively that alpha-fetoprotein levels continue to fall at a normal rate.[26,72–74] It should be noted that in very rare cases, the alpha-fetoprotein level might not be elevated.[75]

If the tumor has ruptured, then a pressure bandage may stem the blood loss for a brief time. However, there is some concern that this may 'squeeze' immature cells into the venous drainage from the tumor. These cells will most likely lodge in the lungs. However, failure to slow the rate of blood loss in these infants may ensure that metastatic disease is not a problem for that infant. Obviously, emergency surgery is indicated in these circumstances.

In the past, there was often a reluctance to attempt the surgical removal of a tumor that might be as large as the rest of the baby. This is less common now, although there can be an understandable desire to let the baby grow before attempting the removal of the tumor, which will most likely be benign. This temptation should be resisted, however, as the risk of malignancy increases with age, suggesting that many of the tumors that were benign at birth become malignant after about two months.[3,5,7,8,12,16] If a surgeon in a peripheral hospital encounters one of these lesions, then transfer to a pediatric surgical unit is advisable, if this is possible.

OPERATION

The patient is anesthetized, intubated, and a catheter placed in the bladder to measure urine output throughout the procedure, before being positioned prone with a roll under the hips. The roll is positioned so that the infant's weight is taken on the anterior superior iliac spines. It is vital that the abdomen be left hanging free to ensure that respiration is not inhibited by the baby's weight. For this reason, the baby's shoulders should be supported either by a smaller roll lying transversely across the apex of the chest at the level of the medial ends of the clavicles, or by two rolls running parallel to the spine, each supporting the glenohumeral joints. The former option is illustrated in Figure 82.4. It is often useful to pack the rectum with Vaseline gauze to enable it to be readily recognized when the rectum is exposed later in the procedure. The packing also reduces the risk of stool contaminating the operative field. Many authorities state that the anus should be 'prepped' out of the field.[12,76] This author finds that approach both inconvenient and impractical, as access to the anus is often required during the procedure. The cautery pad can usually be placed across the shoulders. A clear plastic drape may conserve body heat and assist in prevention of hypothermia. The addition of a perforated blanket through which is pumped warmed, filtered air also helps to maintain body temperature.

A chevron incision is made in the skin over the dorsum of the mass (Fig. 82.5a,b) and is continued down to fascial layers. It is preferable not to dissect beyond the level of the deep fascia at this stage of the dissection. There are often several large veins in the subcutaneous tissue on either side of the midline; these should be cauterized, or if they are too large for that, they may be divided between ties. The incision should be placed so as to preserve as much normal skin as possible. Excess skin can always be trimmed later if necessary. The apex of the chevron should be over the lower sacrum. In the midline, the dissection should continue directly down to the sacrococcygeal junction, or even down to the fourth or fifth sacral vertebra. The edges of the sacrum are defined, and a clamp is passed across the sacrum at this level, keeping the tips of the forceps against the ventral surface of the bone (or cartilage) to ensure that the forceps pass between the sacrum and the underlying middle sacral vessels, which are usually substantial vessels, supplying the bulk of the blood supply to

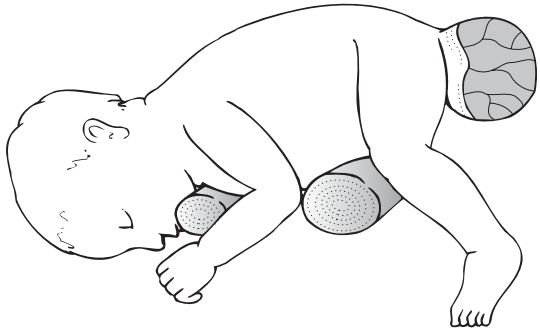


Figure 82.4 Infant with a sacrococcygeal teratoma positioned for surgical resection of the tumor. Note the large transverse roll under the pelvis and the smaller roll under the upper chest.

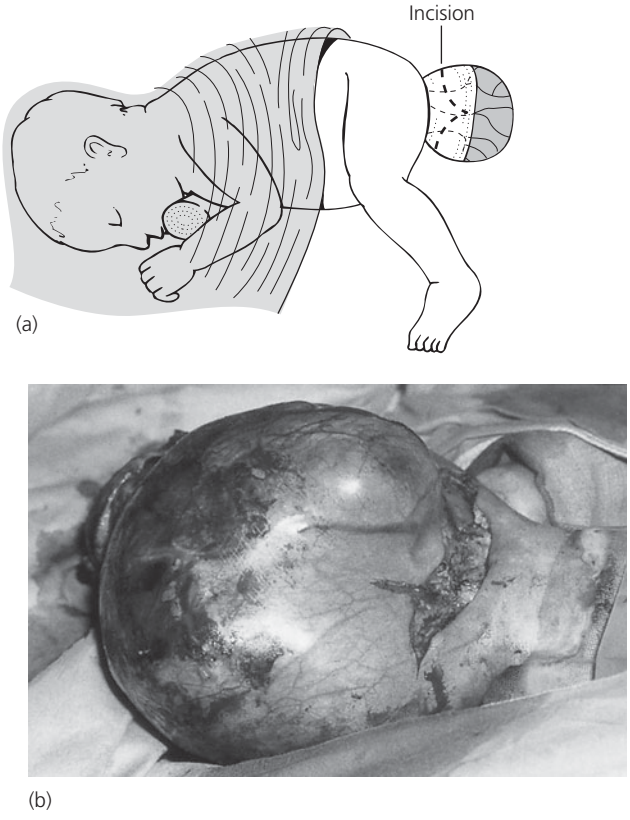


Figure 82.5 (a) Lateral view of the incision over the tumor. All normal skin that can possibly be preserved is retained, to be trimmed later if necessary. (b) Skin incision in the infant shown in Fig. 82.3. Her head is to the right.

the tumor. Once this maneuver is complete, the sacrum (which is usually completely, or at least largely, cartilaginous) can be divided with a scalpel and the severed section of the spine displaced slightly inferiorly to expose the middle sacral vessels (Fig. 82.6a,b). As mentioned earlier, this can very rarely result in catastrophic blood loss from the epidural veins, if the bulk of the venous return is passing back to the baby via the sacral hiatus. It may be necessary to divide some of the attachments of the thinned-out remnants of the levators to the edges of the lower end of the sacrum and coccyx to enable the distal portion of the sacrum and coccyx to be displaced caudally. The middle sacral vessels are then ligated in continuity and divided. This early division of the middle sacral vessels is essentially the same as the procedure advocated by Smith *et al.*[60]

This maneuver opens a plane of dissection that is outside the tumor capsule, but deep to the thinned-out remnants of the levators and gluteus maximus. The levators may be so thin as to be almost invisible (Fig. 82.7), but they will contract on stimulation, either with a muscle stimulator or the electrocautery. The dissection should continue laterally in this plane either side of the midline until the muscles are lost in the fascia of the tumor. At this point, they can be divided along a line parallel to the skin incision. This will allow the tumor to be further displaced in a caudal direction.

Attention is then directed to the pelvic extension of the tumor. Using blunt dissection with peanut swabs in the plane anterior to the middle sacral vessels, it is usually possible to displace the pelvic component of the tumor anteriorly until its upper extent is reached. This is normally an essentially avascular plane anterior to the sacrum, although some vessels feeding into the tumor from the internal iliac vessels may be encountered laterally. These can usually be controlled with cautery. In most cases, the tumor can be dissected out from the pelvis and rolled inferiorly over the patient's legs (Fig. 82.8).

This maneuver exposes the upper end of the rectum, which can be identified by a Vaseline gauze pack placed immediately before the operation is commenced or by passing a finger in through the anus. The tumor can be dissected off the rectum with a combination of sharp and blunt dissection, and rolled inferiorly until the plane of dissection moves away from the rectum and the anal canal. At all times during this dissection, it is best to try to maintain the plane of dissection on the capsule of the tumor and to preserve all normal structures no matter how distorted and thinned out they are. As the tumor is rolled inferiorly, it eventually becomes apparent that the plane of dissection has reached the subcutaneous tissue along the inferior surface of the tumor, posterior to the anus. Once the dissection has reached this point, the dissection can be terminated as long as the inferior skin flap that has been developed is of sufficient

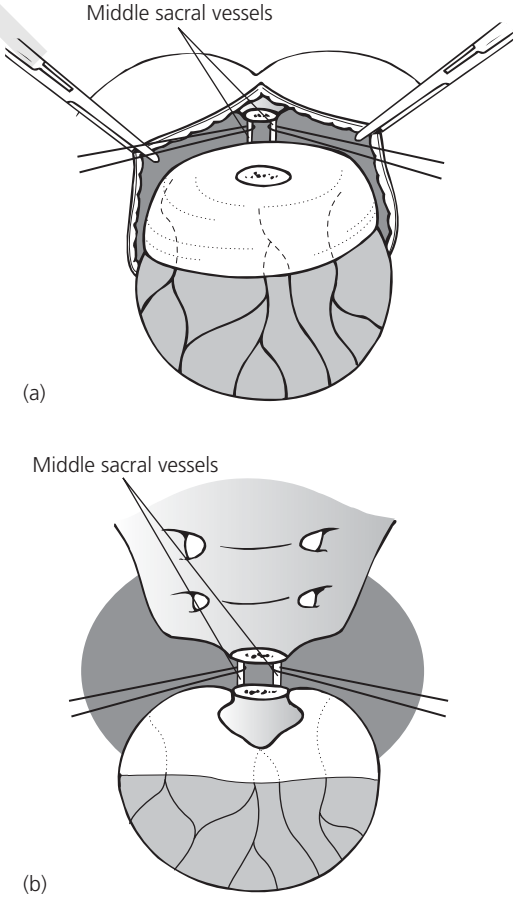


Figure 82.6 (a) Sacrum divided with the middle sacral vessels slung on ties. (b) The divided fifth sacral vertebral body, showing the tumor arising from the ventral surface of the coccyx.

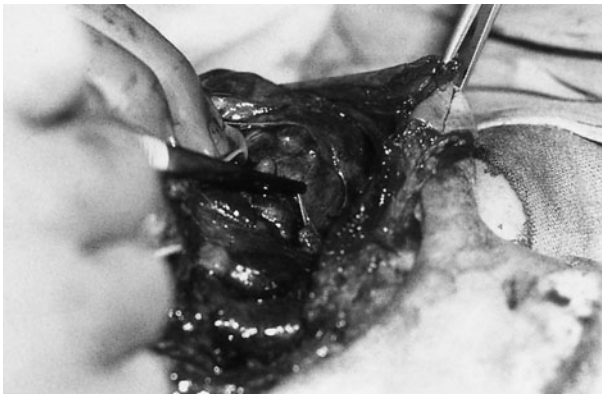


Figure 82.7 The sacrum has been divided and the forceps demonstrate the thinned-out levators (the head is to the right).

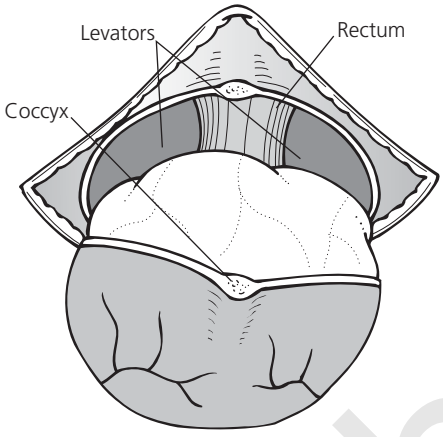


Figure 82.8 Completion of the pelvic dissection with the tumor rolled inferiorly, exposing the rectum.

length to allow easy closure of the wound (Fig. 82.9). The inferior skin flap can then be divided from the tumor and the tumor delivered from the field. A careful check of the tumor bed is carried out to ensure that meticulous hemostasis has been achieved. If the peritoneum has been opened during the pelvic dissection, then it is closed if possible.

Attention is then directed to reconstruction of the pelvic floor and closure of the wound. The remnants of the levator sling are identified and the central portion is sutured to the perichondrium of the anterior surface of the sacrum using 5-0 Maxon® (Cynamid Tyco Healthcare, Norwalk, CT, USA) (a monofilament absorbable suture) (Fig. 82.10a,b). This same suture is used for all subsequent muscle and fascial reconstruction. These initial fascial sutures, rather than the skin closure, should determine the siting of the anus. This aspect of the reconstruction, therefore, should be carried out with care to ensure both a functional and cosmetically pleasing result.

If a drain is to be placed, then it is placed at this stage, in the presacral space, led out through the gap in the levators and tunneled out through the subcutaneous tissue of the buttock. A closed-suction drain is preferred. If there are remnants of the levators recognizable lateral to the midline, these are repaired with interrupted 5-0 Maxon sutures. The medial edges of gluteus maximus are then closed in

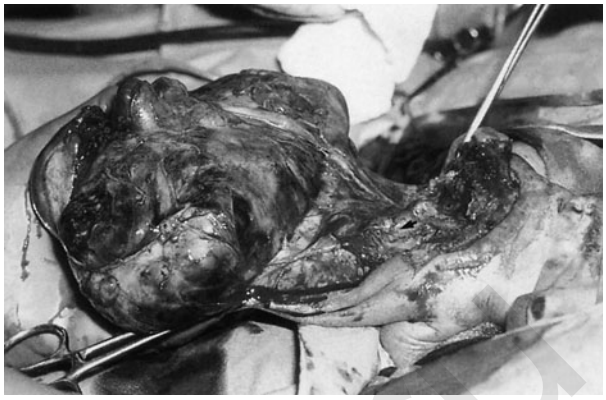
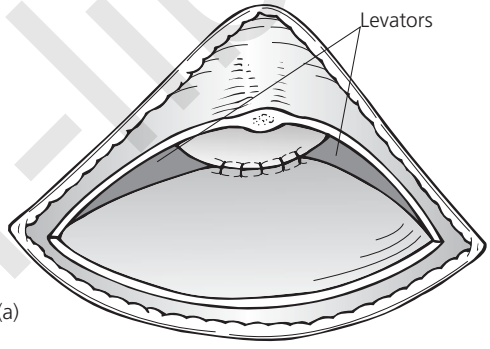


Figure 82.9 Completion of the pelvic dissection. The tumor has been dissected off the rectum (arrow) and the dissection has reached the stage where the division of the inferior skin flap can be contemplated. (Same patient as Fig. 82.3; the head is to the right.)



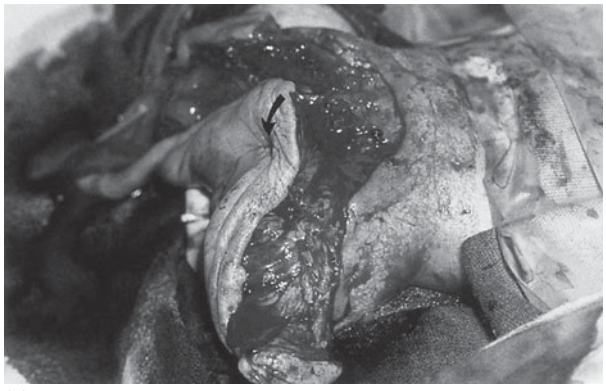


Figure 82.10 (a) Levators sutured to the perichondrium of the sacrum. These sutures set the anal position. (b) The levators have been sutured to the sacral perichondrium, resulting in the setting of the definitive anal position. (Arrow indicates the anus: same patient as in Fig. 82.3 the head is to the right.)

the midline over the sacrum and the lower part of the levator sling (Fig. 82.11). The skin flaps are then trimmed to length. If possible, the subcutaneous tissues are closed with a running 5-0 Maxon suture and the skin is closed with a running 5-0 Maxon subcuticular suture. A steristrip and collodion dressing is then applied. If it is not possible to close the subcutaneous tissue, then a subcuticular suture may not be adequate for skin closure. In this case, 5-0 nylon skin

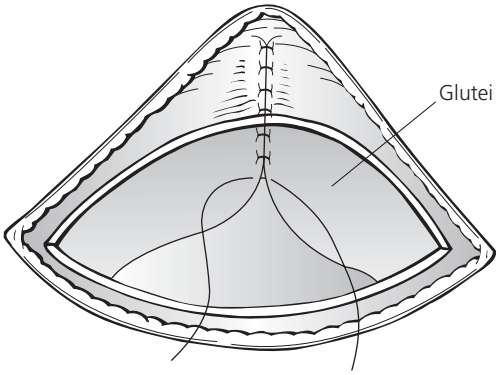
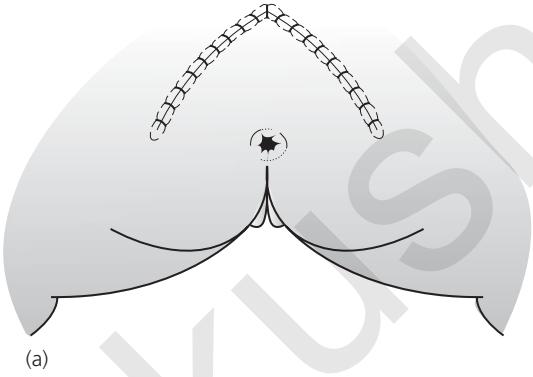


Figure 82.11 Closure of the glutei, posterior to the sacrum. This closure is continued inferior to the divided sacrum.

sutures are placed (Fig. 82.12a,b). The rectum is repacked with Vaseline ribbon gauze at the completion of the procedure in an attempt to obliterate dead space. It is useful to suture a 2-0 silk suture to the end of this pack to aid its retrieval, should the pack become displaced higher up the rectum in the immediate postoperative period.

Preliminary abdominal exploration is indicated in three circumstances: (1) if there is a large abdominal component,[76,77] (2) if the tumor has been ruptured and is actively bleeding,[64] and (3) in the rare case when a premature baby is delivered in a hyperdynamic state and preliminary devascularization is needed to stabilize the patient before proceeding to definitive resection.[30] In these cases, the abdomen is opened via a transverse infra-umbilical incision placed just below the upper limit of any intra-abdominal mass or just below the umbilicus if there is no abdominal component. In either case, the aim is to find and ligate and then divide the middle sacral vessels if at all possible. If this is not possible, then either an arterial occlusive sling[64] or a small vascular clamp is placed across the aorta below the origin of the inferior mesenteric artery. The abdomen is closed temporarily with a running 3-0 nylon mass closure and dressed with a clear plastic adhesive dressing. The patient is repositioned and the tumor is then resected from behind as outlined previously. When the pelvic portion of the dissection is completed, the patient is repositioned in the supine position and the clamp or aortic occlusive sling is removed before the abdomen is closed in layers with 4-0 Maxon sutures to the fascia and 5-0 Maxon subcuticular sutures to the skin.

Some authors[62] have advocated an abdominoperineal approach in all cases with routine devascularization of the tumor through an abdominal approach, followed by resection of the tumor (under the same anesthetic) with the patient in the supine position. Some surgeons in Melbourne (B Bowkett, personal communication) also advocate resection of the tumor in the supine position, with the initial incision being in the midline, extending from the sacrum down to the tumor. These authors cite the ability to devascularize the tumor from the abdominal approach and the ease with which external cardiac massage can be applied as the main advantages of this approach. The current author retains significant reservations about this approach. There is a need to control the blood supply to the tumor from above in a minority of cases and it is felt that if there is significant venous drainage through the epidural veins, then blood loss from this source would be extremely difficult to control with the patient in the supine position.


(a)

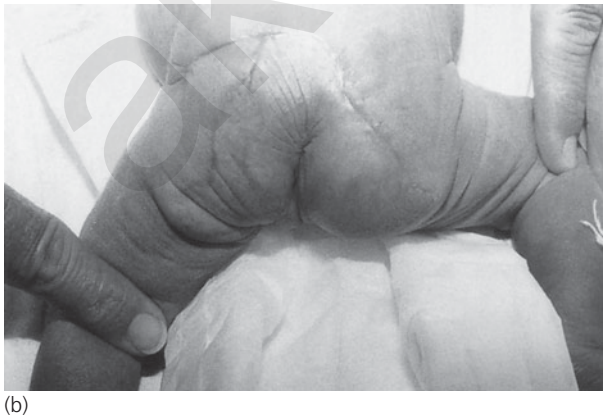

(b)

Figure 82.12 (a) Diagrammatic representation of the completed skin closure. (b) End result in the same patient illustrated in Fig. 82.3.

POSTOPERATIVE MANAGEMENT

The infant is nursed in a prone position for several days postoperatively. The urinary catheter can be removed as soon as the baby's condition is stable and the infant can be extubated as soon as its respiratory condition allows. The infant can usually be fed as soon as it is extubated. The Vaseline pack is usually removed in the first postoperative day by pulling on the 2-0 silk suture left attached to the distal end. Any drain can usually be removed within the first few days of the procedure.

Alpha-fetoprotein levels should be determined immediately postoperatively and on discharge. In spite of the fact that alpha-fetoprotein is stated to have a half-life of only 3 days, the levels usually take several months to return to normal. The infant should then be followed at monthly intervals for three months and then at three-monthly intervals for one year. At each visit, a rectal examination will detect any local recurrence and an alpha-fetoprotein level will detect any distant spread. The alpha-fetoprotein level is often very high (of the order of 100 000 IU or more[26,72])

and even in normal babies it may be over 100 000 IU.[72–74] These high levels usually take over a year to fall to normal adult levels. As long as the alpha-fetoprotein level continues to fall steadily, recurrence is thought to be unlikely. However, it is important to not rely solely on the alpha-fetoprotein levels, as in one patient in the author's series, a very large pelvic recurrence (sufficiently large to produce urinary obstruction) occurred in the presence of a continuously falling alpha-fetoprotein level. None of the other patients who developed recurrent tumors (including the patient who developed metastases in the inguinal lymph nodes) showed a rise in the alpha-fetoprotein levels.

Follow up should continue for at least five years, and preferably through puberty, if at all possible. It is important to obtain renal ultrasounds on an annual basis for the first few years, and vital to obtain one on an urgent basis if there are any new urinary symptoms. One patient in the author's series had a normal renal ultrasound close to her second birthday in April. In September of that year, she presented for routine follow up with a history of having had three urinary tract infections in the previous two months. A renal ultrasound obtained shortly after that visit revealed severe hydronephrosis bilaterally, and her serum creatinine level was significantly elevated, having been normal only a few months before. Urodynamic studies revealed that she had a hostile, high-pressure neurogenic bladder. The hydronephrosis resolved considerably with the introduction of clean intermittent catheterization, although this has placed a considerable strain on the family.

PROGNOSIS

In the absence of distant metastases at presentation, and if the excision is complete, then the life expectancy should be normal, although the appearance of the buttocks usually leaves something to be desired (Fig. 82.12b).

There are very few papers in the literature that focus on long-term outcome. One recent paper[55] reported the results in a series of 23 patients followed for up to 22 years. Four patients with malignant tumors had recurrence-free intervals ranging from nine to 14 years. There were two patients with nocturnal enuresis, one of whom had perineal anesthesia. There was one child with a patulous anus and one patient with a neurogenic bladder. The authors emphasized the need for long-term follow up and the need to be alert for the late appearance of urinary or fecal incontinence.

Another paper, from Liverpool, reports the results in 33 patients over 25 years treated in a single center.[78] Surprisingly, only one patient was described as having an immature teratoma and six patients were described as having malignant tumors, two of whom died of metastatic disease. Some of the other patients in this report appear to have been diagnosed as having malignant tumors on the basis of histology and were then treated with chemotherapy on the basis of that diagnosis. In the author's series, there have been local recurrences treated only by repeat resection, without any adjuvant therapy. The only patient treated with chemotherapy was the patient who presented two months after resection with evidence of spread to the inguinal lymph nodes. She is a long-term survivor 16 years after a course of intensive chemotherapy.

The prognosis for patients presenting with a malignant sacrococcygeal teratoma must still be guarded. Modern chemotherapy has produced a considerable improvement in survival.[52,79] The chemotherapy regimens are relatively toxic and these patients require close monitoring during their treatment. Survival rates as high as 80% have been recorded.[52]

Continence, surprisingly, is usually normal, although the cautionary tale mentioned earlier should be noted. However, other recent papers[78,80] have suggested that the incidence of problems with urinary and/or fecal incontinence may be as high as 30%.

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83

Nasal tumors

PETER LAMESCH

INTRODUCTION

Congenital masses of the nasal midline are very rare, occurring in one in every 20 000–40 000 newborns. Although benign, these masses may cause large facial deformities, such as hypertelorism, cerebrospinal fluid (CSF) fistulae, cerebral herniation, visual alterations, meningitis, and cerebral abscess.[1,2]

Nasal gliomas are typically diagnosed in newborn patients. However, the first report on a surgically treated nasal glioma published by Guthrie in 1924 concerned a 48-year-old patient.[3] In a second paper published in 1927, Guthrie wrote in the introduction, 'The cranial and nasal cavities lie in such close proximity to each other that one might naturally suppose that both are liable to be involved in the same disease process'.[4]

There are various types of congenital nasal tumors, which may be classified in accordance with their embryonic origin. The most common are dermoid cyst, glioma, and encephalocele (Box 83.1).[1,5,6]

Box 83.1 Differential diagnosis

Ectodermal
- Dermoid cyst
- Dermoid sinus

Neurogenic
- Meningocele
- Encephalocele
- Glioma
- Neurofibroma

Mesodermal
- Hemangioma
- Vascular malformation

Mixed origin
- Teratoma

EMBRYOLOGY

At an early stage of development during the third and fourth week, there is a protrusion of the forebrain and dura through the foramen cecum into the prenasal space, which is limited by frontal and nasal bones on the anterior aspect and posteriorly by a cartilaginous capsule. During further development, the dural process is sealed and the foramen becomes obliterated. Any failure of this obliterating procedure leaves a canal, a pathway favoring the extension of the glial tissue, hence the development of encephaloceles and gliomas.[5,7]

An encephalocele is a herniation of brain tissue into the prenasal space; a glioma is derived from an encephalocele sequestered from the brain. For some authors, glioma are hidden encephaloceles or sequestered encephalocele.[8]

The frontal and nasal bones are formed by intramembranous ossification. At this stage of development, there is a gap between these bones, the fonticulous nasofrontalis, filled by a membrane; the dura and the skin are in contact without interposition of bony tissue. Part of the ectoderm may fail to separate from the dura and so remain in the depths of the nasal space. This displaced ectopic ectodermal tissue is the origin of a dermoid cyst. If a connection does exist with the skin, a dermoid sinus will result.

All these tumors or heterotopias are located in the midline (nasofrontal) or asymmetric unilateral (naso-ethmoidal) position. They are present at birth. They often produce hypertelorism, telecanthus, and nasal deformity.

CONGENITAL TUMORS OF NEUROGENIC ORIGIN

Nasal glioma

Gliomas of the nose are rare, always benign heterotopias, and they should not be considered as tumors. Approximately 250 cases of nasal gliomas have been described in the literature.[9] Their incidence is one in 250 000 births with a

male-to-female ration of 3:1.[10,11] Nasal gliomas account for approximately 20% of all congenital nasal masses;[12] 60% of the tumors are extranasal, while 30% are intranasal and 10% both.[1,13,14] Although most gliomas are located around the midline region of the nose, there are reports with gliomas located in the scalp, cheek, soft palate, tonsils, tongue, leptomeninges, middle ear, orbit, and in limbal dermoids.

A nasal glioma is firm, gray-pink to purple, rounded or dome-shaped polypoid, non-compressible and non-pulsatile mass of glial tissue of congenital origin that may appear in an extra- or intranasal location at or near the root of the nose (Fig. 83.1). They show no impulse when the patient cries. The covering skin may look like a hemangioma. Gliomas are unilateral or in the midline, but are usually located at the side of the nasal bridge. The root of the nose is often enlarged; there may be an orbital hypertelorism. The diameter of the tumor varies from 1 to 3 cm. Their growth rate is usually the same as that of the surrounding tissue according to the infant's growth.

The intranasal type is located high in the nasal fossa. The septum may be displaced and the nasal passage may be obstructed. Increased lacrimation may result from compression of the lacrimal duct. These tumors may present as early neonatal respiratory distress.[15]

In intra-extranasal gliomas, there is a communication between the two components of the mass, usually through a defect in the nasal bone or at the lateral margin of the nasal bone.

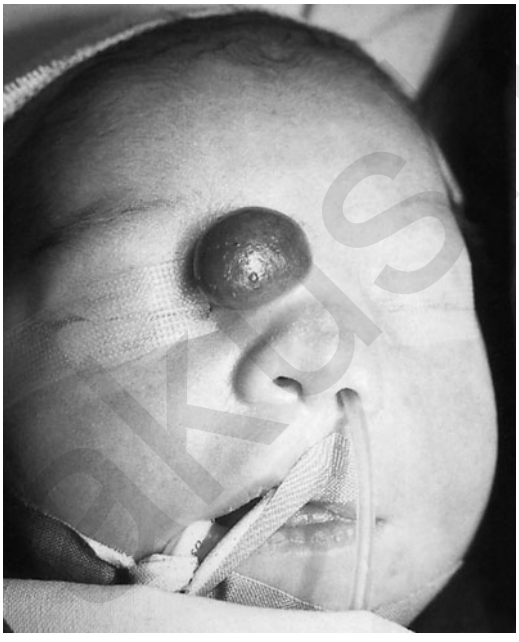

Figure 83.1 Nasal glioma in a newborn.

HISTOLOGY

A glioma consists of glial and fibrous tissue with an overlying flattened epidermis.[13] The specimens consist of fibrillary astrocytes and fibrous connective tissue. True neurons are seen rarely.[16] It does not contain a cerebrospinal fluid-filled space communicating with the ventricular system of the brain or the subarachnoid space. In two heterotopias, cellularity in places approached that of low-grade neoplastic glioma.[17]

DIAGNOSIS: IMAGING

Preoperative imaging is essential for an appropriate surgical approach by delineating the exact site and extension of the tumor.[13,18] It is important to distinguish nasal tumors or masses from basofrontal encephaloceles to avoid inadvertent exposure of the brain during the surgical removal of mass lesions.

Computed tomography (CT) scanning is useful to visualize bony defects, but is not reliable for soft-tissue contrast. Magnetic resonance imaging (MRI) is superior for imaging brain tissue; it should therefore be used preferentially for definition of the tumor mass and to disclose intracranial extension.[18]

De Biasio *et al.*[19] reported a case of fetal nasal glioma diagnosed at 21 weeks' gestation. The glioma appeared as a moderately hypoechoic mass near the junction of the medial aspect of the left orbit and the lateral aspect of the nose. It showed no internal vascularization on color and power Doppler ultrasonography. The glioma was resected after an uneventful pregnancy at the age of four months.

TREATMENT

Though benign and relatively slow growing, these heterotopias can cause disturbances of growth and subsequent deformity by encroachment upon the bony frameworks of the nose. Furthermore, they are unsightly and some of them, located at the root of the nose, such as encephaloceles and gliomas, may interfere with vision. Hence, early surgical excision is advisable.

Complete surgical excision of nasal gliomas (with repair of any hypertelorism) is the treatment of choice. The most conservative cosmetic surgical technique should be chosen after intracranial connection has been ruled out.

TECHNIQUE

An elliptical incision is made around the base of the tumor and the mass is removed *in toto*. In order to avoid recurrences, it is important to excise or coagulate the small deep stalk, which may pass upwards for a short distance under the nasal bone. This tract is exposed by splaying open the nasal bones through a midline nasal incision. In the case of a high-situated intranasal glioma, an extracranial extranasal approach may be necessary to provide wide access to the nasal cavity. A lateral rhinotomy is most often used. Burckhardt and Tobon[20] described an endoscopic approach in a case of intranasal glioma. In cases with intracranial lesion, craniotomy is mandatory.

COMPLICATIONS

Incomplete excision

Recurrences due to incomplete excision are rare (11%). In 13% of the cases, there is a connection with the intracranial

nervous system by a pedicle of fibrous tissue, passing through the cribriforme plate. Nasal gliomas with a cystic component seem to have a greater tendency for recurrence, however the reason for this remains unclear.[21] Levine *et al.*[16] reported a case in which a nasal glioma masqueraded as a capillary hemangioma with a subsequent inadequate treatment, which indicates the need for a preoperative histologic examination in some cases.

A recurrence can be avoided by a detailed evaluation of the preoperative imaging and a meticulous dissection in order to expose a stalk or a possible intracranial connection. Only a complete excision prevents recurrence.[21–23]

Dural defect

As normally there is no permeable communication with the subdural space, an accidental dural defect is theoretical. Should it occur, it must be promptly closed to prevent a CSF fistula. If such a defect is large, an epicranium graft may be needed for a safe and tight closure.

Hematoma

This can be avoided by careful hemostasis with bipolar coagulation.

Skin defect

In some cases, the skin defect is closed directly. Large defects can be covered by free skin grafting, by glabellar skin flaps, or by tissue expansion:

1. **Free skin graft**. This is an ideal method for covering skin defects, when there is a suitable recipient ground. Reconstruction is obtained without additional scars. The technique is easy and the cosmetic result is excellent. The graft takes in almost all cases. The best skin graft is a retroauricular full thickness skin graft.
2. **Flaps**. The skin in the glabellar donor area provides a good color and texture match for the resurfacing of the upper nasal defect. The glabellar flap can be transferred in three ways: as a classic glabellar flap, as a midline transposition flap, and as an island flap:
    a. Classic glabellar flap: the time-honored reconstructive technique in the upper nasal area. The drawback is that eyebrow hair may be moved down into the medial canthral area by rotation of the skin (Fig. 83.2a–c).
    b. Midline transposition or finger flap, which is a good method for reconstructing the glabellar region. The finger flap is reliable and suitable. The finger has a simple design and allows transfer of the thin non-hair-bearing skin. The harvesting area is closed directly. If the flap has any skin excess it will be exhibited by a standing cone in the inferior rotation area. This excess can be trimmed without any problem involving the blood supply. The result of this method is usually excellent (Fig. 83.3a–c).
    c. The glabellar island flap is an interesting, although more time-consuming procedure. The use of magnification is recommended. The main advantage of this technique is the lack of skin distortion, i.e. a standing cone. The harvesting defect is closed directly with excision of triangles of skin superiorly and inferiorly. There is no deformation of local morphology. The initial swelling due to the subcutaneous pedicle will subside with time (Fig. 83.4a–d).
3. **Tissue expansion** as described by Radovan[24] is a new method. This is a two-stage procedure based on the principle to develop donor tissue by expansion adjacent to the defect. Reconstruction can be performed with contiguous tissue of similar texture, color, thickness, and sensation.

Meningocele and encephalocele

The encephalocele is a protrusion of brain inside a dural sac through a skull defect. The tumor contains an ependyma-lined space filled with the CSF; it communicates with the ventricular system. Encephaloceles are located at the root of the nose, midline (nasofrontal) or asymmetric lateral (naso-ethmoidal); they are most frequently intranasal.[1,25] The bridge of the nose is broadened and often hypertelorism and nasal deformity are produced. Depending on the contents, meningoceles and encephaloceles are taut or soft, compressible and pulsatile tumors, enlarging when the patient cries (Fürstenberg sign).

PREOPERATIVE EXAMINATION

Evaluation should include a complete rhinologic and neurologic examination.[26] The dominant clinical sign of encephaloceles is an intermittent rhinoliquorrhea that can be distinguished from normal nasal secretion by the typically high glucose concentration in the liquor. The defect at the base of the skull is demontrated by radiological examination; an intracranial lesion is best disclosed with MRI and/or CT scanning.[18,27] Three-dimensional CT provides additional useful information in cases with significant bony abnormalities at little additional cost or time.[28]

TREATMENT

The treatment of choice is excision of the tumor with the herniated brain and closure of the dural defect. Usually there are no problems for closure of the wound the covering skin being normal. According to Macfarlane *et al.*,[29] primary and secondary hypertelorism regressed in most instances where patients were treated before the age of two years. In their series of 114 patients treated over a 15-year period, in 59% of the children the developmental outcome was normal, 18% had mild mental or physical disability, and in 23% severe impairment occurred.

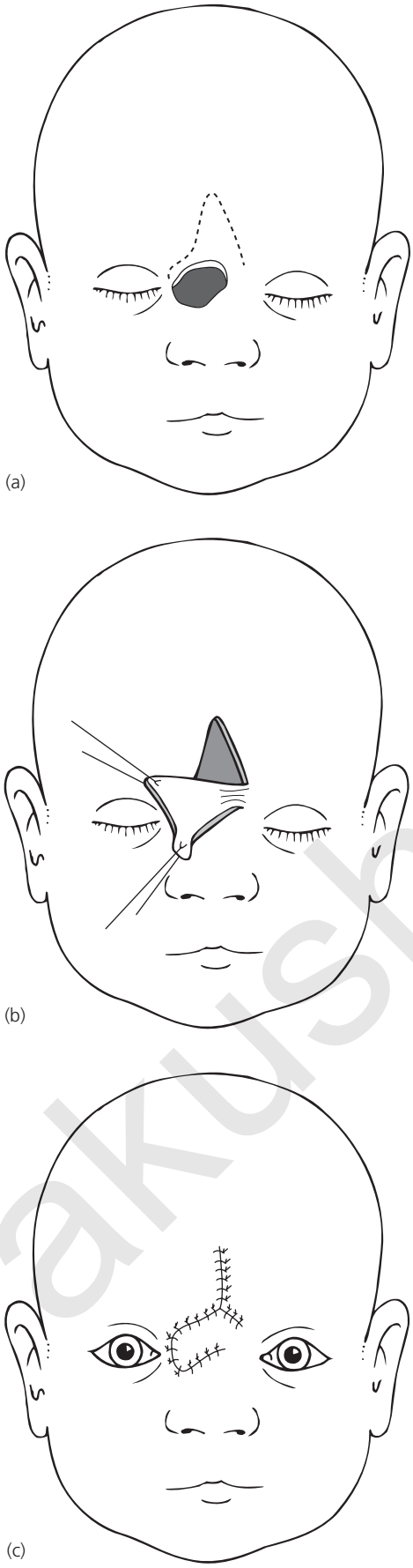

Figure 83.2 (a–c) Classic glabellar flap.

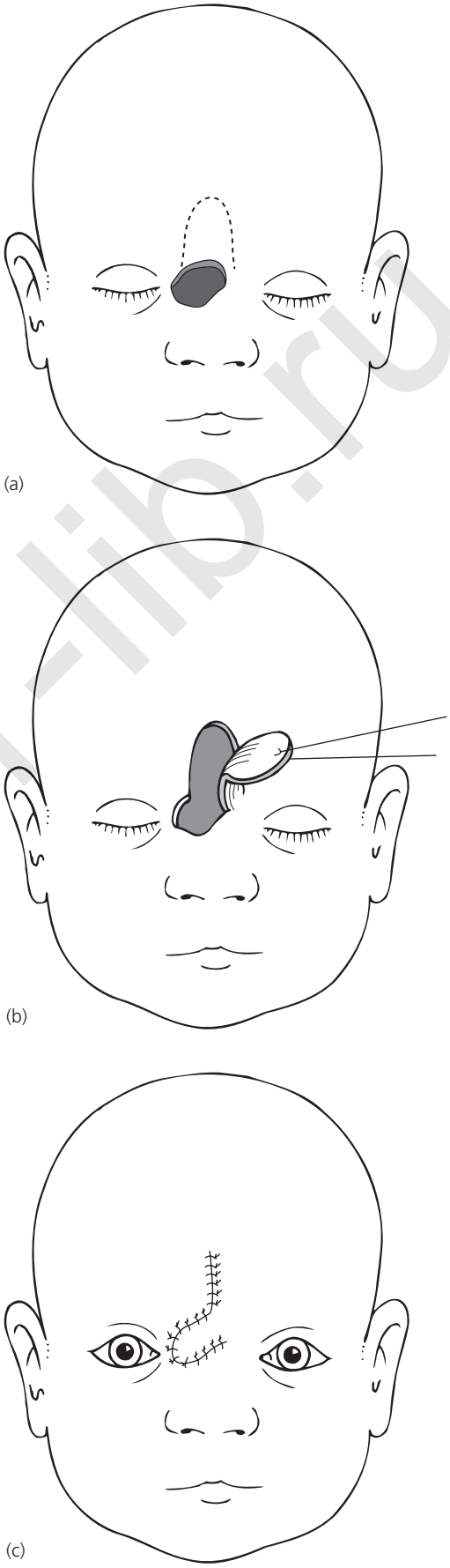

Figure 83.3 (a–c) Finger flap – midline transposition flap.

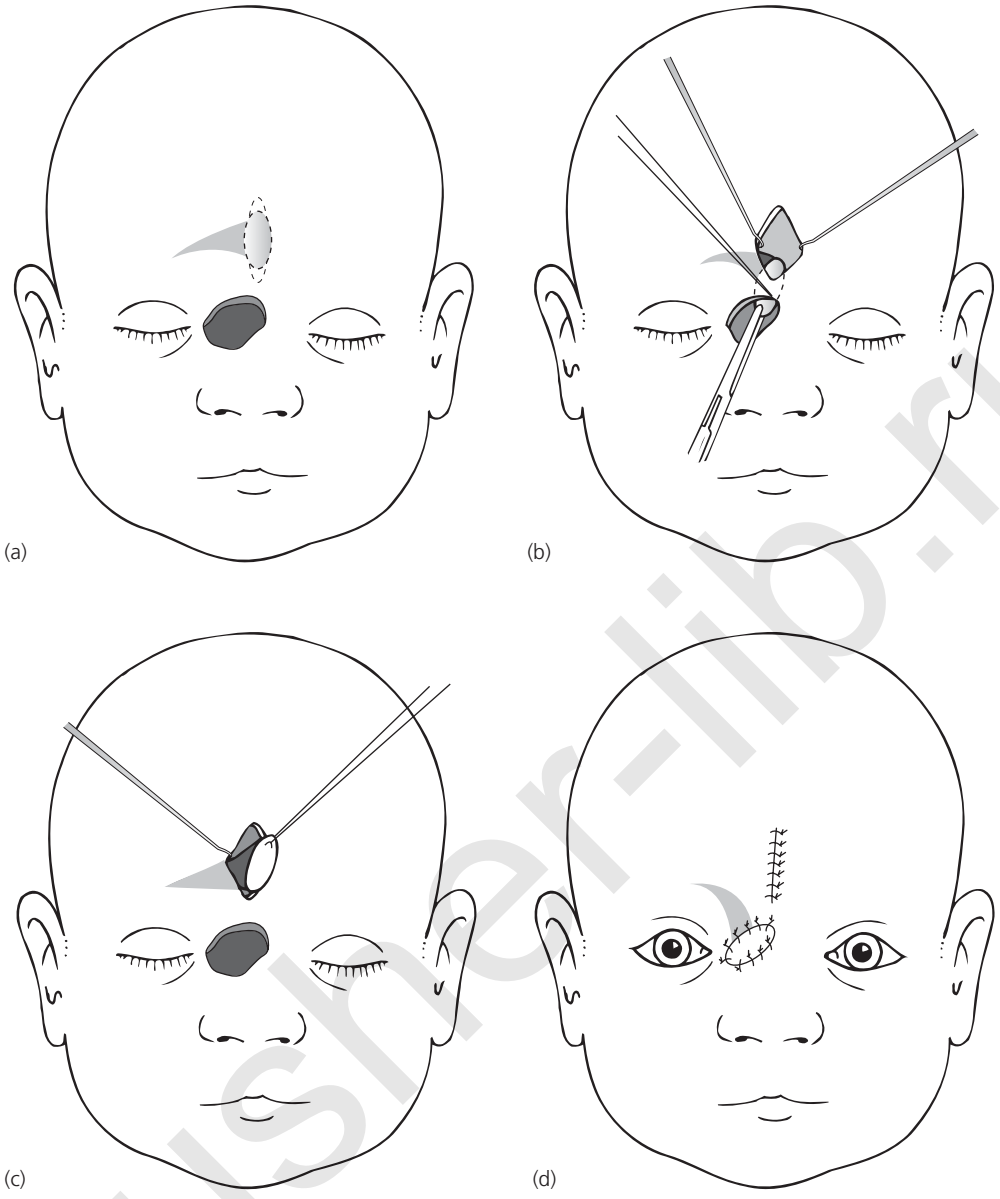

Figure 83.4 (a–d) Glabellar island flap.

COMPLICATIONS

The main postoperative complication is leakage of CSF because of a large dural defect.[26,29] In Macfarlane's series,[29] it occurred in one out of 114 patients. The dural defect must be closed tightly to prevent such a fistula. If the defect is too large for direct closure, an epicranial or a fascia lata graft may be a valid alternative.

CONGENITAL DERMOID CYSTS AND DERMOID SINUS

Congenital dermoid cysts are the most frequently found congenital nasal tumors. During early embryonic development, a portion of the dura begins to grow in close association with nasal skin. Eighty-four percent are found in the head and neck, 37% of these are located in the orbit and periorbit, and 10% are found in the midline of the nasofrontal region. External dermoid cysts present clinically as firm, non-fluctuating, and non-pulsatile mass. The Fürstenberg sign is negative.[1] The dermoid sinus appears externally, sometimes as a dimple with protruding hair; in these cases only a thorough examination will reveal the diagnosis. The dimple usually leads to a sinus tract which extends along the nasal septum, underneath the nasal bones, towards the base of the anterior cranial fossa; it may enter the skull (dumb-bell cyst).[5]

HISTOLOGY

Dermoid cyst and sinuses are both lined by squamous epithelium with various dermal appendages, such as glands and hair follicles.

COMPLICATIONS

Repeated infections may form multiple sinus tracts, making complete excision difficult. Sometimes, the mass of the cyst may erode nasal bones and associated sinuses, although rarely a liquorrhea may occur.

TREATMENT

The treatment of choice is operative removal, preferably before potentially chronic infections occur.

TECHNIQUE

A midline nasal incision and excision of the mass is the best technique. The tract passing into the nasal septum must be exposed after opening the nasal bones. All epithelial elements must be removed. The stalk is carefully dissected cephalad; if it enters the skull, a craniotomy is mandatory in order to remove the intracranial part of the lesion.

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Neuroblastoma

ANDREW M DAVIDOFF

INTRODUCTION

Tumors in the newborn are relatively rare, comprising only about 2.5% of all childhood malignancies.[1] The majority of these tumors are benign lesions, but malignancies can occur. Overall, neuroblastoma is the fourth most common cancer of childhood, comprising 7–10% of all malignancies diagnosed in children younger than 15 years of age. However, neuroblastoma is second only to teratoma as the most commonly diagnosed tumor in the neonate and is, overall, the most common malignancy in the newborn, accounting for 30% of all tumors in this age group, with an estimated prevalence of 2–6 per 100000 live births in the United States.[2,3] With the increasing use of perinatal imaging, this number is likely to increase.

Neuroblastoma is a heterogeneous disease; tumors can spontaneously regress or mature without treatment, or display a very aggressive, malignant phenotype. Although the specific reasons for these differences in biologic behavior are yet to be completely elucidated, certain clinical and biologic factors have been identified that predict, to a significant degree, the tumor phenotype. Among these, patient age at diagnosis is one of the most powerful, with age less than 1–1.5 years conferring a favorable prognosis.[4,5] It follows, then, that neuroblastoma diagnosed in the newborn period is associated with a very favorable outcome. The challenge in managing these patients is to maintain an excellent survival rate, while minimizing the toxicity of any therapy.

ETIOLOGY

Neuroblastoma is derived from cells of the neural crest. During normal development and renewal, neural crest cells migrate and evolve to perform highly specialized functions to meet the physiologic needs of the body. This involves tightly regulated processes that include continued cell proliferation, differentiation, and programmed death (apoptosis). An intricate system of checks and balances ensures proper control over these physiologic processes. For example, small nodules of primitive neuroblasts are routinely found in the developing adrenal gland and even during the early postnatal period. Beckwith and Perrin[6] first described these microscopic nodules that they termed 'neuroblastoma *in situ*' in the adrenals of infants undergoing autopsy following death from non-malignancy-related causes. The incidence of this finding was more than 200-fold greater than the clinical incidence of neuroblastoma, suggesting that perhaps many neuroblastomas spontaneously regress or mature into lesions that never become clinically apparent. Even clinically apparent neuroblastoma can regress or spontaneously mature. Although initially thought to be mediated by the immune system, this may be the result of the withdrawal of neurotrophic maintenance factors, such as nerve growth factor (NGF). Neuroblastoma probably represents failure of this process of regression. Although the precise etiology of neuroblastoma is currently unknown, as with all cancer, genetic, epigenetic, and environmental factors appear to contribute.

Inherited genetic factors

Neuroblastoma generally occurs sporadically, but familial neuroblastoma does occur in about 2% of the cases. Interestingly, however, substantial biologic and clinical heterogeneity is often observed in familial cases. Recently, the germline mutation associated with hereditary neuroblastoma has been identified – activating mutations in the tyrosine kinase domain of the anaplastic lymphoma kinase (*ALK*) oncogene on the short arm of chromosome 2 (2p23).[7] These mutations can also be somatically acquired although the prevalence of ALK activation in sporadic neuroblastoma remains to be determined.

Environmental factors

In addition to genetic factors, environmental factors may have a direct impact on cell phenotype and fate by causing DNA

damage that permanently alters the host genome, although few environmental factors have been convincingly linked to the development of neuroblastoma. Several case-control studies have examined the relationship between maternal and paternal occupation and exposure, and the risk of neuroblastoma in offspring.[8] Several other studies have also suggested a relationship between the use of certain medications just prior to and during pregnancy and neuroblastoma, specifically hormone use and fertility drugs, and phenylhydantoin for seizure disorders.[9,10] Similarly, the results for smoking, alcohol, illicit drug use, and the use of hair dye in some studies are suggestive but not conclusive.[11,12]

PATHOLOGY

Neuroblastoma is an embryonal tumor of the sympathetic nervous system. These tumors arise during fetal or early postnatal life from sympathetic cells (sympathogonia) derived from the neural crest. Therefore, tumors can originate anywhere along the path which neural crest cells migrate, including the adrenal medulla, paraspinal sympathetic ganglia, and sympathetic paraganglia, such as the organ of Zuckerkandl.

Neuroblastoma can be distinguished histologically by the presence of neuritic processes (neuropil) and Homer Wright rosettes (neuroblasts surrounding eosinophilic neuropil). Scattered ganglion cells or immature chromaffin cells may also be seen. The appearance of the tumor cells may vary from undifferentiated cells to fully mature ganglion cells. In addition, neuroblastomas have variable degrees of Schwannian cell stroma, reactive non-neoplastic tissue recruited by the tumor cells.

Shimada classification

In 1984, Shimada and colleagues first developed an age-linked classification system of neuroblastic tumors based on tumor morphology in which neuroblastomas were divided into two prognostic subgroups, favorable histology and unfavorable histology. In 1999, the International Neuroblastoma Pathology Classification (INPC) was devised and then modified in 2003,[13] and is an adaptation of the original Shimada system (Table 84.1). The INPC is an age-linked classification that depends on the differentiation grade of the neuroblasts, the cellular turnover index (mitosis–karyorrhexis index (MKI)), and the presence or absence of Schwannian stroma; and classifies neuroblastic tumors into three morphologic categories: neuroblastoma, ganglioneuroblastoma, and ganglioneuroma.

Neuroblastomas are, by definition, Schwannian stroma-poor (<50% of the tumor tissue) and can be subtyped as undifferentiated, poorly differentiated (<5% of tumor cells have features of differentiation), or differentiating (>5% of tumor cells show differentiation towards ganglion cells). Additional factors that contribute to the prognostic distinction of stroma-poor, neuroblastic tumors (neuroblastoma) as favorable or unfavorable subtypes include the MKI, which is defined as the number of tumor cells in mitosis or karyorrhexis per 5000 neuroblastic cells (i.e. low MKI, <100 cells; intermediate, 100–200 cells; high, >200 cells) and the patient's age (<1.5 years, 1.5–5 years, >5 years). It has been hypothesized that neuroblastic cells with maturational potential require an *in vivo* latent period before demonstrating histologic evidence of differentiation; therefore, there is a certain allowance for mitotic and karyorrhectic activities of neuroblastic cells in tumors in infants and younger children.[14] Thus, newborns with neuroblastoma are very likely to have favorable histology disease.

Table 84.1 Prognostic evaluation of neuroblastic tumors according to the International Neuroblastoma Pathology Classification.[14]

	Neuroblastoma pathology	Classification
Neuroblastoma	Schwannian stroma-poor	
< 1.5 years	Poorly differentiated or differentiating and low or intermediate MKI tumor	Favorable
1.5–5 years	Differentiating and low MKI tumor	
< 1.5 years	(a) undifferentiated tumor, or (b) high MKI tumor	Unfavorable
1.5–5 years	(a) undifferentiated or poorly differentiated tumor, or (b) intermediate or high MKI tumor	
≥ 5 years	All tumors	
Ganglioneuroblastoma, intermixed	Schwannian stroma-rich	Favorable
Ganglioneuroblastoma, nodular	Composite Schwannian stroma-rich/ stroma-dominant and stroma-poor	Unfavorable or favorable (based on nodule histology)
Ganglioneuroma	Schwannian stroma-dominant	
Maturing		Favorable
Mature		

MKI, mitosis–karyorrhexis index.

Molecular pathology

Although there is no single genetic abnormality or initiating event common to all neuroblastomas, a number of different genetic alterations have been identified that provide powerful

prognostic information and play crucial roles in risk assessment and treatment planning.

DNA CONTENT

Normal human cells contain two copies of each of 23 chromosomes; thus, a normal diploid cell has 46 chromosomes. The majority (55%) of primary neuroblastomas are triploid or 'near-triploid/hyperdiploid' and contain between 58 and 80 chromosomes; the remainder (45%) are either 'near-diploid' (35–57 chromosomes) or 'near-tetraploid' (81–103 chromosomes).[15] The 'DNA index' of a tumor is the ratio of the number of chromosomes present to a diploid number of chromosome (i.e. 46). Therefore, diploid cells have a DNA index of 1.0, whereas near-triploid cells have a DNA index ranging from 1.26 to 1.76. Importantly, patients with near-triploid tumors typically have favorable clinical and biologic prognostic factors and excellent survival rates, as compared with those patients who have near-diploid or near-tetraploid tumors.[16] This association is most important for infants with advanced disease;[17] the prognostic significance of tumor ploidy appears to be lost in patients older than two years.

AMPLIFICATION OF *MYCN*

Early studies of neuroblastoma cell lines showed the frequent presence of extrachromosomal double-minute (DM) chromatin bodies and chromosomally integrated homogeneously staining regions (HSRs) characteristic of gene amplification.[18] Since that time, it has been shown that the amplified region was derived from the distal short arm of chromosome 2 (2p24) and contained the *MYCN* proto-oncogene.

Overall, approximately 25% of primary neuroblastomas have MYCN amplification, being present in 40% with advanced disease, but only 5–10% with low-stage disease.[19] The copy number, which can range from 5- to 500-fold amplification, is usually consistent among primary and metastatic sites and at different times during tumor evolution and treatment.[20] This finding suggests that *MYCN* amplification is an early event in the pathogenesis of neuroblastoma. Amplification of *MYCN* is associated with advanced stages of disease, rapid tumor progression, and poor outcome; therefore, it is a powerful prognostic indicator of biologically aggressive tumor behavior.[19,21]

CHROMOSOMAL CHANGES

Approximately 20 to 35% of primary neuroblastomas exhibit 1p deletion, as determined by fluorescent *in situ* hybridization (FISH), with the smallest common region of loss located within region 1p36.[22] About 70% of advanced-stage neuroblastomas have 1p deletions.[23] Molecular studies have shown that there is a strong correlation between 1p deletion and *MYCN* amplification and other high-risk features such as age older than one year and advanced-stage disease.[22] A recent study has demonstrated that 1p deletions are independently associated with a worse outcome in patients with neuroblastoma.[24]

OTHER MOLECULAR ABNORMALITIES

Neurotrophins and their tyrosine kinase receptors are important in the development of the sympathetic nervous system and have been implicated in the pathogenesis of neuroblastoma. Three receptor–ligand pairs have been identified: TrkA, the primary receptor for nerve growth factor (NGF); TrkB, the primary receptor of brain-derived neurotrophic factor (BDNF); and TrkC, the receptor for neurotrophin-3 (NT-3). TrkA appears to mediate differentiation of developing neurons or neuroblastoma in the presence of NGF ligand, and apoptosis in the absence of NGF.[25] High TrkA expression is associated with favorable tumor biology and good outcome[26] and is inversely correlated with *MYCN* amplification.[27] Conversely, the TrkB/BDNF pathway appears to promote neuroblastoma survival through autocrine or paracrine signaling, especially in *MYCN*-amplified tumors.[28] TrkB is expressed in about 40% of neuroblastomas, usually advanced-stage disease. TrkC is expressed in approximately 25% of neuroblastomas and is strongly associated with TrkA expression.[29]

PRESENTATION

When symptomatic, children with neuroblastoma usually present with signs and symptoms that reflect the primary site and extent of disease. An abdominal mass may be detected on physical examination when the primary is adrenal or retroperitoneal. Respiratory distress may be a reflection of a thoracic tumor. Altered defecation or urination may be caused by mechanical compression by a pelvic tumor, or by spinal cord compression by a paraspinal tumor. A tumor in the neck or upper thorax can produce Horner syndrome (ptosis, miosis, and anhydrosis), enophthalmos, and heterochromia of the iris. Acute cerebellar ataxia has also been observed, characterized by the dancing-eye syndrome, which includes opsoclonus, myoclonus, and chaotic nystagmus. Two-thirds of these cases occur in infants with mediastinal primary tumors.[30] Additional signs and symptoms that reflect excessive catecholamine or vasoactive intestinal polypeptide secretion include diarrhea, failure to gain weight, and hypertension.

There are differences in the distribution of the primary site and extent of disease between newborns and all children with neuroblastoma. Newborns have a higher incidence of adrenal primaries (90 versus 50%) and a lower incidence of disseminated disease at presentation (20 versus 60%) with bone metastases, in particular, rarely occurring in newborns. Newborns with localized disease, especially those whose lesion was detected on routine perinatal imaging are almost always asymptomatic. Infants with metastatic neuroblastoma may have stage 4S disease, which, by definition, is a localized primary tumor in patients younger than one year, with dissemination limited to skin, liver, or bone marrow (<10% of nucleated cells). These patients may present with 'blueberry muffin' cutaneous lesions, respiratory distress secondary to massive hepatomegaly, and anemia secondary to bone marrow disease (see below under Stage 4S neuroblastoma).

Laboratory findings

LACTATE DEHYDROGENASE

Despite its lack of specificity, serum lactate dehydrogenase (LDH) can have great prognostic significance. High serum levels of LDH reflect high proliferative activity or large tumor burden, and an LDH level higher than 1500 IU/L appears to be associated with a poor prognosis.[31] Thus, LDH can be used to monitor disease activity or the response to therapy.

FERRITIN

High levels of serum ferritin (>150 ng/mL) may also reflect a large tumor burden or rapid tumor progression. Elevated serum ferritin is often seen in advanced-stage neuroblastomas and indicates a poor prognosis;[32] levels often return to normal during clinical remission.

URINARY CATECHOLAMINES

Measurement of homovanillic acid (HVA) and/or vanillylmandelic acid (VMA) in the urine is a critical component of the preoperative assessment. Together with a positive bone marrow, elevated levels can be used to make the diagnosis of neuroblastoma and, if elevated at diagnosis, can be used as a marker of disease status (e.g. progression or recurrence).

Diagnostic imaging

STANDARD RADIOGRAPHS

Chest radiography can be a useful tool for demonstrating the presence of a posterior mediastinal mass, which in an infant is usually a thoracic neuroblastoma. A Pediatric Oncology Group (POG) study demonstrated that a mediastinal mass was discovered on incidental chest radiographs in almost half of patients with thoracic neuroblastoma who had symptoms seemingly unrelated to their tumors.[33] Abdominal radiography is less often the modality by which a neuroblastoma is discovered; however, as many as half of abdominal neuroblastomas are detectable as a mass with fine calcification.

ULTRASONOGRAPHY

The vast majority of abdominal neuroblastomas in the newborn are diagnosed by ultrasonography, either in the prenatal period, as part of routine surveillance of the fetus, or in the postnatal period, to evaluate an abdominal mass. Although ultrasonography is the modality most often used during the initial assessment of a suspected abdominal mass, its sensitivity and accuracy are less than that of computed tomography (CT) or magnetic resonance imaging (MRI) for diagnosing neuroblastoma.

Computed tomography

CT remains a useful, commonly used modality for the evaluation of neuroblastoma. It can demonstrate calcification in almost 85% of neuroblastomas, and intraspinal extension of the tumor can be determined on contrast-enhanced CT. Overall, contrast-enhanced CT has been reported to be 82% accurate in defining neuroblastoma extent, with the accuracy increasing to nearly 97% when performed with a bone scan.[34]

Magnetic resonance imaging

MRI is becoming the most useful and most sensitive imaging modality for the diagnosis and staging of neuroblastoma. MRI appears to be more accurate than CT for detection of stage 4 disease: the sensitivity of MRI is 83%, and that of CT is 43%; and the specificity of MRI is 97%, and that of CT is 88%.[35] Metastases to the bone and bone marrow, in particular, are better detected by MRI, as is intraspinal tumor extension.[35]

METAIODOBENZYLGUANIDINE IMAGING

Metaiodobenzylguanidine (MIBG) is transported to and stored in the distal storage granules of chromaffin cells in the same way as norepinephrine. MIBG has been used for scintigraphic imaging of neuroblastoma. The MIBG scintiscan is the imaging study of choice in evaluating the involvement of bone and bone marrow by neuroblastoma, having largely replaced technetium-99m methylene diphosphonate (^{99m}Tc-MDP) bone scans.

MANAGEMENT

Diagnosis

In most instances where an adrenal or posterior mediastinal mass has been detected in a newborn, performing a biopsy before resection is unnecessary; most of these lesions will be localized, resectable neuroblastoma and will not receive adjuvant therapy. In the rare case of disseminated disease in the newborn, a biopsy is appropriate, rather than upfront resection, as all of these patients will receive chemotherapy, which, given in the neoadjuvant setting, may make resection of the primary tumor easier.

Staging

Current staging of neuroblastoma is based on the International Neuroblastoma Staging System (INSS) (Table 84.2).[36] Evaluation of the primary tumor and involvement of metastatic sites in the INSS system depend largely on the imaging studies described above (CT or MRI, and MIBG). In addition, children with localized neuroblastoma who are currently enrolled on a Children's Oncology Group (COG) protocol will also have 'image-defined risk factors' assessed by central review of diagnostic imaging studies. This will be performed to determine whether these factors are more prognostically relevant than INSS staging for patients with localized neuroblastoma. These image-defined risk factors (Table 84.3) were proposed by the European International Society of Pediatric Oncology Neuroblastoma Group and

Table 84.2 International Neuroblastoma Staging System.

Stage	
1	Localized tumor with complete gross excision, with or without microscopic residual disease; representative ipsilateral lymph nodes negative for tumor microscopically (nodes attached to and removed with primary tumor may be positive)
2A	Localized tumor with incomplete gross excision; representative ipsilateral non-adherent lymph nodes negative for tumor microscopically
2B	Localized tumor with or without complete gross excision, with ipsilateral non-adherent lymph nodes positive for tumor. Enlarged contralateral lymph nodes must be negative microscopically
3	Unresectable unilateral tumor infiltrating across the midline,[a] with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration (unresectable) or by lymph node involvement
4	Any primary tumor with dissemination to distant lymph nodes, bone marrow, bone, liver, skin, and/or other organs (except as defined for stage 4S)
4S	Localized primary tumor (as defined for stage 1, 2A, or 2B), with dissemination limited to skin, liver, and/or bone marrow[b] (limited to infants <1 year of age)

[a]The midline is defined as the vertebral column. Tumors originating on one side and crossing the midline must infiltrate to or beyond the opposite side of the vertebral column.
[b]Marrow involvement in stage 4S should be minimal, that is, $<10\%$ of total nucleated cells identified as malignant on bone marrow biopsy or on marrow aspirate. More extensive marrow involvement would be considered to be stage 4. The metaiodobenzylguanidine scan (if performed) should be negative in the marrow.

generally reflect the presence of encasement of major vessels or nerves, or the infiltration of adjacent organs/structures by locoregional tumor. Cecchetto *et al.*[37] reported in 2005, that the presence of one or more of these image-defined surgical risk factors was associated with a lower complete resection rate and a greater risk of surgery-related complications when attempting an initial resection of a localized neuroblastoma.

Risk stratification

As previously mentioned, one of the notable characteristics of neuroblastoma is the substantial heterogeneity of the disease. Increasing evidence indicates that the biologic and molecular features of neuroblastoma are highly predictive of clinical behavior. Current treatment is based on risk stratification that takes into account both clinical and biologic variables predictive of disease relapse. The most important clinical variables appear to be age[5] and stage[38] at diagnosis. The most powerful biologic factors at this time appear to be *MYCN* status,[19,21] ploidy[16] (for infants), and histopathologic classification.[39] However, additional biologic and molecular variables continue to be evaluated, and the allelic status at chromosomes 1p36 and 11q23 are currently being used to

Table 84.3 Objective surgical risk factors for primary resection of localized neuroblastoma.[37]

Site	
Neck	1. Tumor encasing major vessel(s) (e.g. carotid artery, vertebral artery, internal jugular vein) 2. Tumor extending to base of skull 3. Tumor compressing the trachea 4. Tumor encasing the brachial plexus
Thorax	1. Tumor encasing major vessel(s) (e.g. subclavian vessels, aorta, superior vena cava) 2. Tumor compressing the trachea or principal bronchi 3. Lower mediastinal tumor, infiltrating the costovertebral junction between T9 and T12 (may involve the artery of Adamkiewicz supplying the lower spinal cord)
Abdomen	1. Tumor infiltrating the porta hepatis and/or the hepatoduodenal ligament 2. Tumor encasing the origin of the celiac axis, and/or the superior mesenteric artery 3. Tumor invading one or both renal pedicles 4. Tumor encasing the aorta and/or vena cava 5. Tumor encasing the iliac vessels 6. Pelvic tumor crossing the sciatic notch
Dumb-bell tumors with symptoms of spinal cord compression: any location	
Infiltration of adjacent organs/structures: diaphragm, kidney, liver, duodeno-pancreatic block, and mesentery	

define the duration of therapy for certain patients. Taken together, these variables currently define the COG risk stratification (Table 84.4) for therapeutic approach, with children being categorized into three risk groups predictive of relapse: low, intermediate, and high risk. The probability of prolonged disease-free survival for patients in each group is $>95\%$, $>90\%$, and $<30\%$, respectively. The vast majority of newborns with neuroblastoma will have low-risk disease; rarely do they have high-risk disease. In particular, only 3% of all patients with stage 1 or 2 neuroblastoma have *MYCN*-amplification with the incidence in newborns being even lower.[40]

Treatment

LOW-RISK DISEASE

The treatment for patients with low-risk disease is generally surgical resection alone, even in the presence of microscopic residual disease (stage 1), gross residual disease (stage 2A), or gross residual disease with ipsilateral lymph node involvement (stage 2B), if the tumor has favorable biologic characteristics (i.e. is without *MYCN* amplification). Infants with stage 4S disease who are not experiencing substantial symptoms may undergo an initial biopsy and observation only, if the tumor has favorable biologic factors. Infants with an adrenal mass who meet certain imaging and biochemical

Table 84.4 Children's Oncology Group risk stratification for children with neuroblastoma.

Risk stratification	INSS stage	Age	Biology
Low			
Group 1	1	Any	Any
	2A/2B (>50% resected)	Any	*MYCN*-NA, any histology/ploidy
	4S	<365 days	*MYCN*-NA, FH, DI > 1
Intermediate			
Group 2	2A/2B (<50% resected or Bx only)	0–12 years	*MYCN*-NA, any histology/ploidy[a]
	3	<365 days	*MYCN*-NA, FH, DI > 1[a]
	3	≥365 days–12 years	*MYCN*-NA, FH[a]
	4S (symptomatic)	<365 days	*MYCN*-NA, FH, DI > 1[a]
Group 3	3	<365 days	*MYCN*-NA, either UH or DI = 1[a]
	4	<365 days	*MYCN*-NA, FH, DI > 1[a]
	4S	<365 days	*MYCN*-NA, either UH or DI = 1[a] or unknown biology
Group 4	4	<365 days	*MYCN*-NA, either DI = 1 or UH
	3	365–<547 days	*MYCN*-NA, UH, any ploidy
	4	365–<547 days	*MYCN*-NA, FH, DI > 1
High			
	2A/2B, 3, 4, 4S	Any	*MYCN*-amplified, any histology/ploidy
	3	≥547 days	*MYCN*-NA, UH, any ploidy
	4	365–>547 days	*MYCN*-NA, UH or DI = 1
	4	>547 days	Any

[a]If tumor contains chromosomal 1p LOH or unb11qLOH, or if data are missing, treatment assignment is upgraded to next group.
DI, DNA index; FH, favorable histology; *MYCN*-NA, *MYCN* not amplified; UH, unfavorable histology.

criteria may also be observed on a protocol (see discussion of ANBLP2, p. 777).

INTERMEDIATE-RISK DISEASE

Patients receive cycles of cyclophosphamide, doxorubicin, carboplatin, and etoposide given every 3 weeks on the current COG protocol, ANBL0531. The duration of therapy (i.e. the number of cycles), will depend upon which of three intermediate risk groups a patient is placed in, with group stratification again being based on clinical and biologic risk factors (Table 84.4). One of these biologic factors will include loss of heterozygosity (LOH – loss of one of two normally paired chromosomal regions) at chromosome 1p or 11q (unbalanced), as these events have been shown to be independently associated with decreased progression-free survival in patients with low- and intermediate-risk disease.[24]

The overall surgical goal in intermediate-risk patients is to perform the most complete tumor resection possible, consistent with preservation of full organ and neurologic function. This may necessitate leaving residual disease adherent to critical anatomic structures. It is no longer required that infants with 4S disease undergo resection of their primary tumor. In addition, if these infants are too unstable at presentation, it is no longer required that they even undergo an initial biopsy.

HIGH-RISK NEUROBLASTOMA

The general approach to treating patients with high-risk neuroblastoma includes intensive induction chemotherapy, myeloablative consolidation therapy with stem cell rescue, radiation therapy, and immunotherapy for minimal residual disease. Other approaches, such as targeted therapy and anti-angiogenic therapy, are also being evaluated. The role of surgery for control of locoregional disease is controversial. Several reports have suggested that patients with INSS stage 3 or 4 disease who undergo gross total resection of their primary tumor and locoregional disease experience improved local tumor control and increased overall survival;[41–43] however, other reports have not confirmed these observations.[44,45] Despite the uncertainty of the role of surgery, the COG high-risk protocol currently recommends attempting gross total resection of the primary tumor and locoregional disease in patients with high-risk neuroblastoma.

Surgical management

PREOPERATIVE PREPARATION

All patients, prior to surgery, should have a complete blood count, chemistry panel (to include liver function tests if the liver is involved), and a coagulation screen. Urinary catecholamines, and serum ferritin and LDH, should already have been obtained as part of the initial work-up (see above Laboratory findings). Blood pressure should be normalized with pharmacologic means if hypertension was present at presentation. Operations on neuroblastoma are often hazardous and hemorrhage is a frequent problem, hence packed red blood cells should be available for transfusion during or immediately after the operation.

OPERATIVE APPROACH (OPEN)

Tumor size, the extent of vascular encasement, and exact tumor location should be considered in selecting the approach for a retroperitoneal neuroblastoma. Options available for the abdominal incision include a transverse incision, bilateral subcostal (Chevron) incisions, or a midline incision (Fig. 84.1). A transthoracic (intercostal), transdiaphragmatic extension can be added for resection of neuroblastomas with either thoracoabdominal extension or extensive periaortic or celiac axis encasement. The tumor should be carefully exposed to determine the relation between the tumor and normal organs and vessels. If encasement of major vessels, such as the aorta, vena cava, or their branches, is found, tumor dissection must be performed to free the vessels completely. With deliberate dissection of the tumor from the mesenteric and renal vessels, injury to the liver, bowel, spleen, and kidneys can be avoided (Fig. 84.2), although this frequently results in piecemeal division and excision of the tumor.[45] For a more detailed description of extensive surgical resection of neuroblastoma, see Ref. 45.

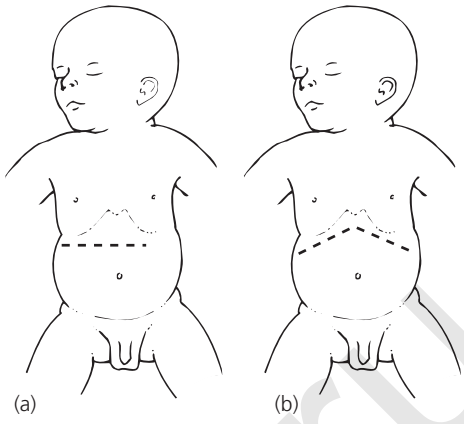

Figure 84.1 Incisions for retroperitoneal neuroblastoma resection. (a) Transverse abdominal incision (right-sided tumor); (b) bilateral subcostal incision.

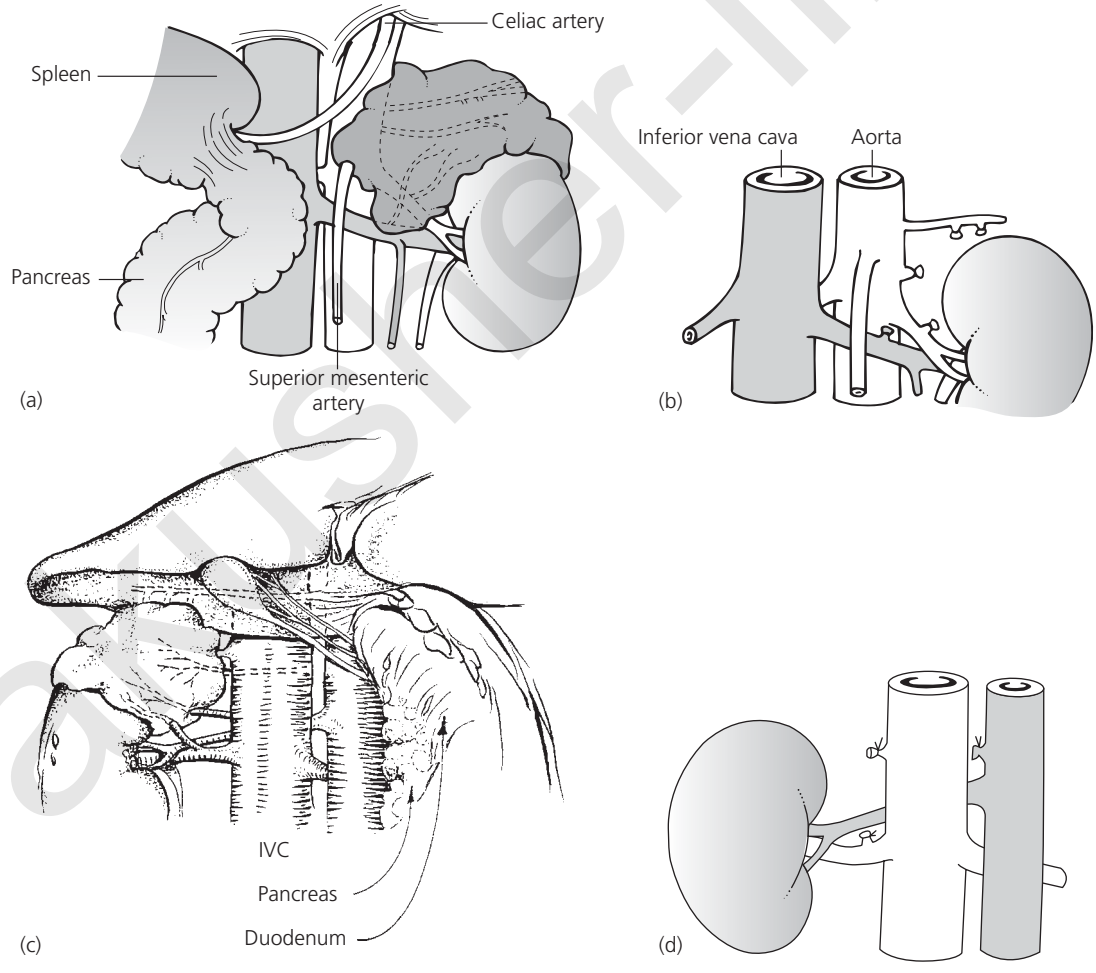

Figure 84.2 Right adrenal tumor. (a) The lienorenal ligament has been divided allowing mobilization of the spleen and pancreas to the right. The renal vessels are visible and dissected out – branches to the tumor are divided. Next, the tumor is dissected from the aorta dividing any vessels. (b) Tumor has been removed and the vascular supply divided. (c) The duodenum and head of pancreas with important structures in the lesser omentum mobilized to the left. The renal vessels are dissected out and branches to the tumor are divided. Medially, the tumor is juxtaposed to the inferior vena cava and sharp dissection may be needed to separate it. At least one vein will need to be secured and divided. (d) The tumor has been removed. Left adrenal tumor.

OPERATIVE APPROACH (LAPAROSCOPIC)

Laparoscopic adrenalectomy is feasible in children and may have some benefits (less pain, shorter hospitalization, improved cosmesis) compared to open adrenalectomy. Laparoscopy may be a reasonable approach in neuroblastoma, in particular, where negative margins, piecemeal removal of the specimen, and leaving residual tumor are not usually of concern. In addition, vascular encasement, characteristic of high-risk neuroblastoma in older children does not usually occur in newborns, making a minimally invasive approach feasible. However, an appropriate oncologic procedure, that currently still includes bilateral lymph node sampling for staging, is required. The surgeon also should consider that, as discussed previously, small adrenal masses discovered in the perinatal period and 4S neuroblastomas may not need to be removed.

Transperitoneal laparoscopic adrenalectomy is generally performed with the operative side up, but in such a fashion that allows rapid transition to an open procedure, if that becomes necessary. The table is tilted into the reverse Trendelenburg position and can be flexed to increase the distance between the costal margin and the iliac crest. Generally, four ports are used (Fig. 84.3). Dissection is performed in much the same manner as the open procedure with care being taken to secure the adrenal vein and to avoid the renal vessels. Bilateral retroperitoneal lymph node sampling is currently still required for appropriate neuroblastoma staging.

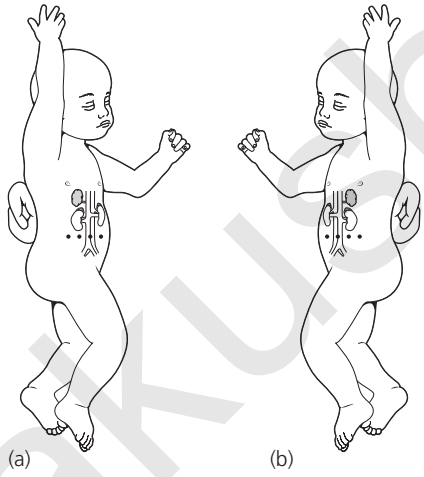

Figure 84.3 Trocar placement for laparoscopic adrenalectomy for (a) right- and (b) left-sided tumors.

Special management situations

SCREENING FOR NEUROBLASTOMA

Because the two most important clinical variables for predicting outcome in patients with neuroblastoma are tumor stage and patient age at the time of diagnosis, it was hypothesized that earlier detection of neuroblastoma through mass population screening might significantly impact neuroblastoma-associated mortality. In Japan in the 1980s, mass screening of neuroblastoma was performed in infants by quantitating urinary VMA and HVA; initially, the mass screening showed very encouraging results.[46] However, subsequent population-based studies with concurrent control groups performed in Germany and North America found that although the incidence of neuroblastoma increased, the additional cases were largely early-stage, favorable biology, low-risk tumors.[47] Because the overall mortality of patients with neuroblastoma was not affected, the implication of these studies was that mass screening most likely detected tumors that would have undergone spontaneous regression and not been detected clinically. Thus, there currently appears to be no role for screening infants for neuroblastoma.

EXPECTANT OBSERVATION OF PERINATAL ADRENAL MASSES

Small, localized neuroblastomas in young infants tend to regress spontaneously, particularly if the lesion is cystic. Based on this observation, the COG protocol, ANBLOOP2, evaluates the safety of expectant observation of patients with these lesions to further define their natural history. This study is designed to prove the hypothesis that close biochemical and sonographic observation can be used for safe clinical management of infants with small adrenal masses; surgical resection is reserved for those rare cases in which there is evidence of continued growth (or parent preference for surgical resection). To be eligible, infants with an adrenal mass must be less than six months of age when the mass is first identified; the mass must be <16 mL in volume, if solid, or <65 mL if at least 25% cystic; and disease must be limited to the adrenal gland. Eligible patients will then be placed on study and either be observed according to the schema detailed in Table 84.5 or have immediate surgery if that is the parents' preference. For those patients being observed, any increase in tumor volume or urine catecholamines will trigger more frequent surveillance, followed by surgical resection if the increase continues.

Table 84.5 Follow-up evaluations on ANBLOOP2.

Observation	Week of study								
Follow-up investigation	0	3	6	12	18	30	42	66	90
Abdominal sonogram	✓	✓	✓	✓	✓	✓	✓	✓	✓
Urine VMA/HVA	✓	✓	✓	✓	✓	✓	✓	✓	✓
Abdominal CT/MRI	✓		✓				✓		

CT, computed tomography; HVA, homovanillic acid; MRI, magnetic resonance imaging; VMA, vanillylmandelic acid.

STAGE 4S NEUROBLASTOMA

In 1971, D'Angio *et al.*[48] reported a number of patients with a 'special' variant of metastatic neuroblastoma, termed IV-S (now referred to as 4S). These patients were infants who

typically had a single, small primary tumor; however, these infants often had extensive metastatic disease in the liver, resulting in significant hepatomegaly, skin nodules ('blueberry muffin' lesions), and small amounts of disease in the bone marrow (<10% of the mononuclear cells). Patients with 4S neuroblastoma were quite remarkable, because the large amount of disease generally underwent spontaneous regression, even without treatment, and the infants ultimately had no evidence of disease.

Only supportive therapy has been recommended for this stage of neuroblastoma because of the high incidence of spontaneous regression and the resultant good prognosis.[49] Most of these patients have tumor with favorable biology (single-copy *MYCN*, favorable Shimada histology, and DNA index >1); therefore, they are assigned to the low-risk classification and receive no therapy. However, despite the generally benign course of their malignancy, these infants can die of complications caused by the initial bulk of their disease. Limited chemotherapy, local irradiation, or minimal resection can be used to treat infants with life-threatening symptoms of hepatomegaly. Operative placement of a Silastic pouch as a temporary abdominal wall may be a choice for those with significant liver enlargement that causes either respiratory compromise secondary to diaphragmatic elevation or obstruction of the inferior vena cava. This procedure may help to avoid life-threatening events until shrinkage of the liver is achieved by either spontaneous regression or therapy. The rare infant with 4S disease and either unfavorable Shimada histology or a DNA index of 1 (or if the biology is not known) will be treated for intermediate-risk disease (group 3), and those with 4S disease that is *MYCN* amplified will be treated for high-risk disease.

INTRASPINAL EXTENSION OF NEUROBLASTOMA

In a subset of patients with paraspinal neuroblastoma, tumor growth may extend into the spinal canal ('dumb-bell' tumors). If neurologic symptoms result, urgent treatment is required to prevent permanent injury caused by compression of the cord. Each of the three main therapeutic modalities (surgery, radiation therapy, and chemotherapy) has been used in the past; the POG report by Katzenstein *et al.*[50] showed similar rates of neurologic recovery in patients treated with surgery or chemotherapy, but significant orthopedic sequelae were seen more commonly in patients treated with surgery. Although chemotherapy is probably considered most appropriate for the initial management of these patients, improvements in neurosurgical techniques, including the use of laminotomy instead of laminectomy to access the intraspinal tumor, may necessitate reconsideration of this approach, especially in those patients with acutely progressive symptoms.

The appropriate approach for patients with asymptomatic intraspinal tumor extension is also uncertain. For patients with low- or intermediate-risk disease, the risks of attempting to remove the intraspinal component of a paraspinal tumor probably outweigh the benefits. This situation most commonly arises in patients with thoracic primary tumors. The intrathoracic component is resected and gross residual disease remains in the spinal canal. Because residual foraminal disease rarely grows to a symptom-developing size, the importance of conservative therapy in this circumstance should be emphasized. For patients with high-risk disease, the importance of resecting gross intraspinal disease is uncertain.

OPSOCLONUS–MYOCLONUS SYNDROME

The opsoclonus–myoclonus syndrome (OMS) consists of myoclonic jerks and random eye movements or progressive cerebellar ataxia. OMS occurs in as many as 4% of patients, usually infants with thoracic primary tumors. Although the exact etiology of this syndrome is not known, the presence of crossreactive autoantibodies to neural antigens in some of these patients suggests that it is it mediated by the immune system.[51] Although patients generally have a good prognosis with regard to their tumor, neurologic symptoms often persist after successful removal of the tumor and can be quite debilitating.[30] Some symptomatic relief may be attained by high doses of corticosteroids or adrenocorticotropic hormones and some studies have suggested that chemotherapy, i.v. IgG therapy, or both may improve the long-term neurologic outcome for these patients.[52] The COG is currently testing this approach in a prospective clinical trial.

COMPLICATIONS

Because extensive surgery is often required, intraoperative and postoperative complications are not uncommon.[53,54] As many as 80% of patients will experience significant blood loss during surgery that requires transfusion of blood and blood products either in the operating room or in the early postoperative period. Up to 10% will suffer an injury to a major vascular structure (aorta, vena cava, or renal vessels), and injury to other viscera (stomach, bowel, liver, spleen, or kidney) also occurs in approximately 5% of cases. On occasion, this necessitates removal of injured organs, with the kidney being the most common. As with all surgical procedures, there is also a risk for anesthetic complications, with infants being at higher risk. The overall mortality for young infants undergoing adrenal surgery for tumor resection appears to be about 2%.[55] Postoperative complications have a wide range. Wound complications occur in 1–5% of cases, as does postoperative bowel obstruction. In addition, hypertension, chyle leak, pleural effusion, infection and sepsis, diarrhea, and prolonged total parenteral nutrition (TPN) requirement can occur. Rarely, a patient will have to be urgently re-explored for postoperative hemorrhage or for bowel obstruction.

LONG-TERM RESULTS

Most newborns with neuroblastoma will have low-risk disease and be treated either with surgery alone or expectant observation. The treatment plan of surgery alone for patients with low-risk disease was established on the basis of the prior

experiences of each of the legacy children's oncology groups in the United States, the Pediatric Oncology Group, and the Children's Cancer Group (CCG). The POG 8104 study found that two-year survival was 89% for patients with POG stage A (INSS stage 1) disease despite microscopic residual disease, when patients were treated with surgery alone.[56,57] In a similar cohort of patients, the CCG 3881 study found three-year event-free survival (EFS) and overall survival to be 94 and 99%, respectively, for patients with Evans stage I disease.[58] That study also found that although patients with Evans stage II disease (similar to INSS 2A/2B) had a three-year EFS of 81% irrespective of the extent of surgical resection and subsequent treatment, the overall survival for these patients was 99%.[58] This finding suggests that even if these patients experience disease relapse, most can be salvaged with additional therapy. Therefore, neither adjuvant chemotherapy nor radiation therapy appears to be necessary for the initial management of most patients with low-risk disease.

On the basis of these data, a group-wide study (COG P9641: Primary surgical therapy for biologically defined low-risk neuroblastoma), was conducted from 1998 to 2006 to evaluate primary surgical therapy for biologically defined low-risk neuroblastoma. The overall strategy of this study was to treat patients with low-risk neuroblastoma with surgery and supportive care only; adjuvant therapy was given only when less than 50% of the tumor was resected or when symptoms that were life- or organ-threatening developed. A probability of three-year survival more than 95% was predicted for these patients with low-risk disease. Although the final published results from this study are still pending, the current recommendation continues to be that patients with low-risk neuroblastoma be treated with surgery alone.

The safety of expectant observation of adrenal masses in appropriate neonates is the primary study question of an ongoing clinical trial and so has yet to be answered definitively. However, there are significant published clinical data supporting this approach, emanating primarily from Japan.[13–15]

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85

Soft-tissue sarcoma

MARTIN T CORBALLY

INTRODUCTION

Solid tumors presenting in the neonatal or perinatal period are rare and usually benign. Malignant tumors at this extreme of life are rare and account for less that 2% of all malignant tumors in childhood with an approximate incidence of one in 30 000 live births. Their rarity and the complexity of surgery, chemotherapy, and radiotherapy in this age group make management complicated and challenging. Immature neonatal metabolism and physiology affect drug absorption and distribution and makes chemotherapy difficult to administer, complex, and challenging. Increasing awareness of the long-term effects of chemotherapy in both older children and neonates and the age-dependent sensitivity of their evolving physiological systems and evolving neural development underscore the need to modify treatment protocols to the particular needs of the neonate. In addition, some tumors such as sacroccygeal teratoma have certain malignant potential in the absence of radical surgery, whereas others such as fibrosarcoma, despite alarming histopathological features behave in a benign way and yet aggressive surgery is clearly not appropriate. In a biological sense, neoplasms such as neuroblastoma may undergo spontaneous resolution, while others may behave as typical neuroblastoma. Benign tumors by virtue of their location may pose a serious threat to survival, e.g. cervical fibrosarcoma may pose a threat to the child's airway and aggressive, urgent surgery is indicated.

GENETICS

The majority of malignant tumors in the neonatal period have significant genetic elements, either inherited or acquired, and multifactorial factors contribute to their development. Single gene mutations and more complex constitutional chromosome anomalies favor the development of neonatal neoplasms. Some are well known, e.g. the association of Down syndrome and leukemia and hepatoblastoma and rhabdomyosarcoma in familial Li–Fraumeni syndrome. Other well-described associations include 11p mutation and nephroblastoma, Wilm's tumor and the Denys–Drash syndrome (11p13 and WT1 mutations) and the T-chromosomal translocation involving the *ETV6* and *NTRK3* genes, which are more common in fibrosarcomas that occur in the neonatal period or earlier infancy and the allelic loss of the 11p15 region in embryonal rhabdomyosarcoma.

Soft-tissue sarcomas are a heterogenous group of tumors that are derived from mesenchymal cells and can therefore differentiate into muscle, fibrous structures, fat, etc. Although by its nature soft-tissue sarcoma is a rare disease in neonates and young infants, it is nevertheless an important differential diagnosis of any infant that presents with an unusual mass or obstruction. Other presentations that are or can be a cause of concern are unusual visceral bleeding or prolapse of the neoplastic mass from vaginal, urethral, or other orifice.

Soft-tissue sarcomas account for approximately 10% of all neonatal tumors and only 2% of all childhood sarcomas. In general, they fall into three different groups:

1. Congenital fibrosarcoma
2. Rhabdomyosarcoma
3. Non-rhabdosarcoma soft-tissue sarcomas.

OVERVIEW AND PRINCIPLES OF MANAGEMENT

It is important to stress that the management of soft-tissue sarcomas in the neonatal period involves significant early input at a multidisciplinary level, including histopathology, oncology, surgical oncology, radiotherapy, radiology, and nursing. Treatment is generally tailored to the needs of the individual patient with the aim of controlling the tumor, while limiting toxicity of therapy. While chemosensitivity and response to radiotherapy varies from patient to patient, it is modified to minimize the severity of myelosuppression and serious infection. In addition, the aggravated late effects of radiotherapy in this population make radiotherapy suitable only as a treatment of last

resort and proportionately greater emphasis is therefore placed on surgical removal. Clearly, histological diagnosis is generally surgical, although in some situations the diagnosis may be made on fine needle aspiration cytology (FNAC). Generally, localized soft-tissue sarcomas are best treated by wide local excision. This treatment option, however, should not be mutilating or interfere with growth and or function. Limited surgical resection (debulking) may be the only appropriate surgical procedure if surgical clearance was considered to be mutilating since chemotherapy may result in more manageable complete surgery after tumor shrinkage.

At presentation, it is important not simply to provide tissue for histological diagnosis, but also accurate tumor staging must be performed. This will include a variety of imaging, such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). These may or may not require sedation or anesthesia. In addition, bone marrow samples are taken to assess metastatic involvement. Pleural effusions may need aspiration or chest drain insertion if symptomatic. Accurate histology and clinical and radiological staging facilitates appropriate chemotherapy.

Histological diagnosis is made from either an open or through cut biopsy or in some cases by FNAC. It is most important that the biopsy is taken by (or following consultation with) the surgical oncologist, who should be ultimately responsible for the surgical care of the patient. An inappropriately sited biopsy site may compromise the subsequent surgical approach and make complete tumor clearance impossible. Essentially, the needle tract or open biopsy tract must be in the line of the ultimate incision for surgical clearance. The essence of biopsy is to secure enough tissue for accurate diagnosis and appropriate biological studies, if necessary. The biopsy, where possible, should minimize tumor spillage and this may be facilitated by the generous use of Hibitane sponges. The use of an argon diathermy may be useful in controlling any local spillage which occurs as a result of the biopsy. If it is possible to resect the tumor primarily, then this is always a superior option provided this does not cause any mutilating effect. Clearly, wide local excision is not considered if there is evidence of metastatic disease. Drains are best avoided if possible. All tissue should be sent fresh to the laboratory.

If complete excision is considered possible, then representative nodal sampling should be included to facilitate accurate staging. Primary excision demands clear margins both clinically and histologically and residual positive margins may indicate the need for a re-excision including the original skin incision and all tissue layers to the site of origin. A reasonable margin of 2 cm or so all around the tumor with en bloc resection should be adequate to ensure that capsular invasion does not compromise the completeness of the margin. It may, at times, be necessary to have frozen section confirmation that margins are negative and if not, then an additional excision should be performed.

SPECIFIC TUMORS

Congenital fibrosarcoma

There are two kinds of fibrosarcoma seen in childhood that share similar histological appearances (but different outcomes). The congenital infantile fibrosarcoma is a well-recognized tumor with a very low tendency to metastasize and an overall excellent cure rate of more than 90%. While more common on the extremities it may also occur on the back, retroperitoneum, head and neck. Spontaneous resolution has been described. The so-called adult-type fibrosarcoma is indistinguishable from the congenital type, but is differentiated on its clinical behavior and age at presentation (occurring more typically in children aged 10–15 years). Histologically, the tumor is composed of spindle-shaped fibroblasts, exhibits variable collagen production and no other differentiation (Fig. 85.1). A recurring translocation (t(12;15)) involving the *ETV6* and *NTRK3* genes has been documented in congenital infantile fibrosarcoma, but not in the 'adult type'. The presence of this translocation may confer a better prognosis. Relapse is common in both types and treatment is aimed at complete excision where possible or staged excision following cytoreduction with vincristine, cyclophosphamide, and actinomycin D. Local recurrence is possible and could be as high as 40%, but does not have an impact on survival as aggressive behavior and metastasis is rare.

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is an extremely rare tumor in the neonatal period. The Intergroup Rhabdomyosarcoma Study in 1994 reported on 14 patients with RMS out of a total of 3217 patients. The tumor can develop in any location where mesenchymal tissue other than bone is present and it typically can spread to nodes, lung, and marrow. It arises

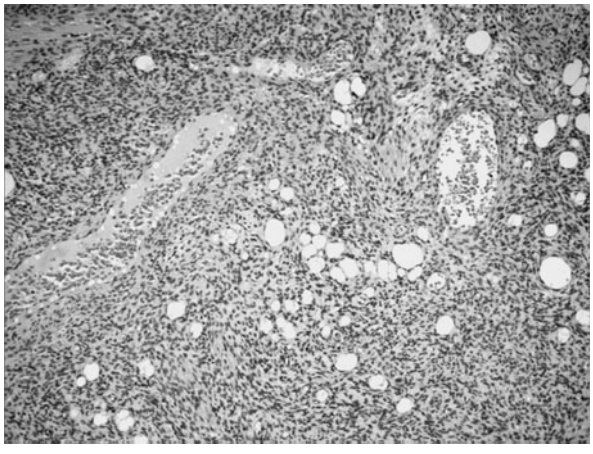

Figure 85.1 Congenital fibrosarcoma. Spindle cell proliferation infiltrating fat (adipocytes are the white blob-like cells) showing 'blood lakes' characteristic of this entity.

from mesenchymal tissue and has a strong tendency towards myogenesis. There is an association with RMS and the Li–Fraumeni syndrome and neurofibromatosis type 1.

There are two different histological subtypes, embryonal and alveolar, which exhibit different clinical outcomes and distinct chromosomal translocations (Fig. 85.2). Embryonal subtype is associated with the allelic loss of the 11p15 region. Histologically, the lesion is marked by degrees of myogenic differentiation that express desmin and muscle-specific actin. However, MyoD and myogenin are the most significant diagnostic markers.

While RMS can occur at any anatomic site, they are most common in the head and neck and genitourinary areas. Approximately 50% of RMS arises in the bladder, vagina, testicular and sacrococcygeal sites, and over 50% of RMS have metastatic disease at presentation, making it an aggressive tumor. Fortunately, the majority of these tumors are of the embryonal type (as distinct from alveolar RMS) and survival with this histology and complete resection is better than 90%. However, with metastatic disease, survival is less than 30%. While prognosis depends on histological characteristics and stage at presentation, it is also dependent on site of the primary lesion, with head and neck RMS (not parameningeal) and genitourinary having better than 90% survival.

Treatment is aimed at complete surgical resection if possible, but adjuvant chemotherapy is necessary in all, even where it appears that surgery has been complete. Chemotherapy includes cyclophosphamide, vincristine, and actinomycin D.

Aggressive surgical resection is not indicated in the presence of non-sterilized metastases or if such surgery would be associated with significant morbidity. Radiotherapy is reserved for loss of local control.

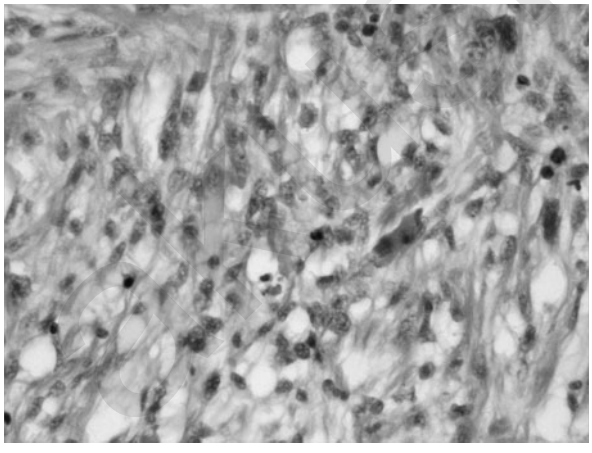

Figure 85.2 Embryonal rhabdomyosarcoma. Spindle cell sarcoma with elongated strap-like cytoplasmic processes and hyperchromatic nuclei showing considerable pleomorphism. The intensely eosinophilic cytoplasm is characteristic of skeletal muscular differentiation.

Non-rhabdomyosarcoma soft tissue sarcomas

These comprise an extremely rare group of neonatal sarcomas and include such entities as malignant mesenchymal sarcoma, primitive sarcoma, angiosarcoma, and rhabdoid sarcoma (Fig. 85.3), tending to arise on the trunk, extremities, and head and neck area. They clearly exhibit marked clinical histologic and biologic heterogenicity and usually present as painless growing mass. Only about 10% will have regional and or distant metastases at presentation. In general, the management of these rare neoplasms reflects that used in the treatment of RMS, with complete wide excision where possible being the mainstay of treatment. Chemosensitivity is less predictable than in RMS and radiotherapy more often needed.

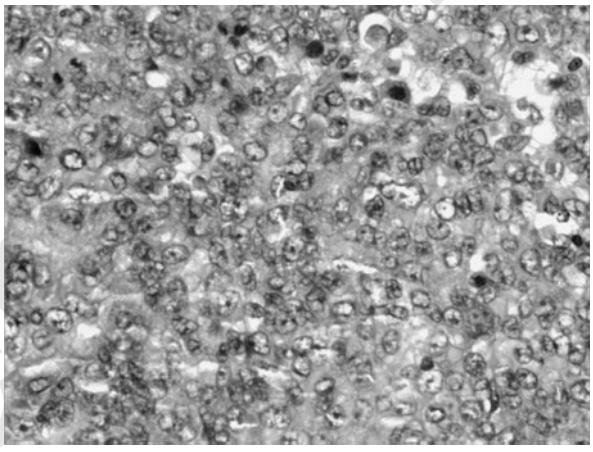

Figure 85.3 Rhabdoid sarcoma. The tumor cells are round with abundant eosinophilic cytoplasm and contain large, vesicular nuclei with prominent micronucleoli. Multiple mitotic figures are evident in the field imaged. The cytoplasm classically shows condensation of intermediate filaments, as seen here, which produces the 'rhabdoid' phenotype.

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86

Hepatic tumors

JAI PRASAD AND MICHAEL P LA QUAGLIA

INTRODUCTION

Benign and malignant liver tumors in infants are being detected perinatally with increasing frequency using ultrasound. The spectrum of such pathologic masses in newborns and infants is different from that in older children (see Fig. 86.1). With advances in the understanding of the biology of these tumors over the last decade, the approach to their treatment has also evolved. This chapter aims to describe the current and evolving approaches to the management of the most common benign and malignant liver tumors occurring in newborns (see Table 86.1).

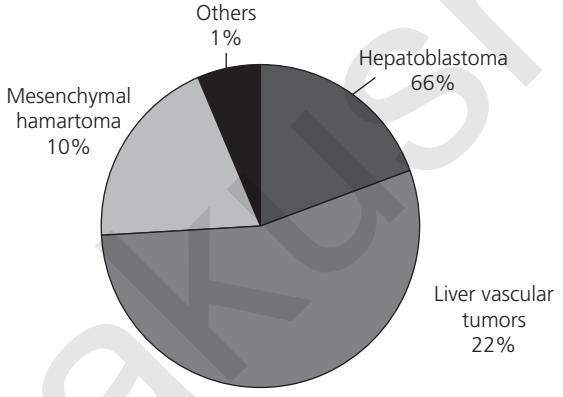

Figure 86.1 Distribution of neonatal liver tumors. Data from von Schweinitz D. Neonatal liver tumours. *Semin Neonatol* 2003; **8**: 403–10.

BENIGN LIVER TUMORS

Hemangiomas

Liver vascular tumors are the most common pediatric tumor, affecting 4–5% of white infants.[1] The exact incidence is difficult to calculate, as a large proportion of these lesions are asymptomatic and detected incidentally. This section describes the current classification, management, and outcomes for hemangiomas.

Table 86.1 Primary pediatric liver tumors.

Age group	Malignant (%)	Benign (%)
Infants, toddlers	Hepatoblastoma (43)	Hemangioma (14)
	Rhabdoid tumors (< 1)	Mesenchymal Hamartoma (6)
	Malignant germ cell tumors (< 1)	Teratoma (< 1)
School age/ adolescents	Hepatocellular carcinoma and transitional cell tumors (23)	Hepatic adenomas (2)
	Sarcomas (7)	Focal nodular hyperplasia (2)

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Hemangiomas are benign endothelial cell neoplasms characterized by proliferation of normal or abnormal blood vessels. While most infantile and congenital hemangiomas are cutaneous, liver lesions are fairly common.[2] Both visceral and cutaneous hemangiomas exhibit similar biologic behavior. Despite a landmark paper by Mulliken and Glowacki[3] that grouped vascular birthmarks into two major categories, hemangiomas and malformations, clinicians and pathologists do not agree about the descriptions of vascular lesions in the liver, using the term 'infantile hemangioma' interchangeably and inclusively for true hemangiomas, arteriovenous malformations, and hemangioendotheliomas.

TUMOR BIOLOGY

Infantile hemangiomas (also referred to in the literature as 'infantile hepatic hemangioendotheliomas') typically present

shortly after birth and are characterized by a rapid proliferation of capillaries in the first year of life (proliferative phase), followed by a gradual, inevitable regression of the tumor over one to five years (involuting phase), and continual improvement until resolution and replacement of the tumor with fibrofatty tissue (involuted phase). Histologically, in the proliferative phase, they are observed to have endothelial hyperplasia with incorporation of H-thymidine and large numbers of mast cells.[4] This phase is defined by high expression of proliferating cell nuclear antigen, type IV collagenase, and vascular endothelial growth factor. High expression of tissue inhibitor of metalloproteinase, TIMP-1, an inhibitor of new blood vessel formation, is found exclusively in the involuting phase.[5] In contrast, vascular malformations do not express any of these biologic markers or show signs of spontaneous regression, instead continuing to grow with the child.

Glucose transporter 1 (GLUT1) immunoreactivity is found in virtually all hemangiomas, except for a subgroup of solitary liver hemangiomas that shares characteristics with a recently described group of cutaneous hemangiomas called the 'rapidly involuting cutaneous hemangioma' (RICH). Vascular malformations do not express GLUT1.[6,7] Mutations in the *VHL* tumor suppressor gene in a family with pheochromocytomas and hepatic hemangiomas have recently been described.[8]

CLASSIFICATION

Hepatic hemangiomas in infancy and childhood have been widely referred to as 'hemangioendotheliomas' and divided into types 1 and 2. However, this term is misleading, as their behavior is different from epitheloid hemangioendotheliomas (with metastatic potential) and Kaposiform hemangioendotheliomas (associated with the Kasabach–Merritt phenomenon[9]), both of which are true neoplasms showing no signs of spontaneous regression.

The International Society for the Study of Vascular Anomalies (ISSVA) settled that cutaneous vascular tumors should be classified into two categories: hemangiomas (GLUT1-positive) and a heterogenous group of anomalies represented by vascular malformations (GLUT1-negative).[3,9] Drawing parallels from this, Mo *et al.* have suggested two groups for hepatic vascular tumors: hepatic infantile hemangiomas (GLUT1-positive and typically multiple, but may be focal) and hepatic vascular malformations with capillary proliferation (GLUT1-negative, solitary masses).[7]

Christison-Lagay *et al.*[1] and Dickie *et al.*[10] have proposed classifying hemangiomas based on imaging characteristics. Three types of lesions have been described: focal, multifocal, and diffuse (see Fig. 86.2a–c). Focal lesions are solitary and are usually GLUT1-negative. Multifocal lesions are discrete hypodense lesions with intervening normal hepatic parenchyma. Diffuse hepatic hemangiomas present with extensive hepatic involvement and near-total replacement of the hepatic parenchyma with innumerable lesions. Both multifocal and diffuse lesions are GLUT1-positive. Some authors have proposed that a subgroup of GLUT1-indeterminate or negative solitary hepatic vascular tumors may exhibit behavior and immunohistochemical characteristics similar to those of the RICH.[1,11,12] Table 86.2 presents the currently accepted ISSVA classification for vascular anomalies.

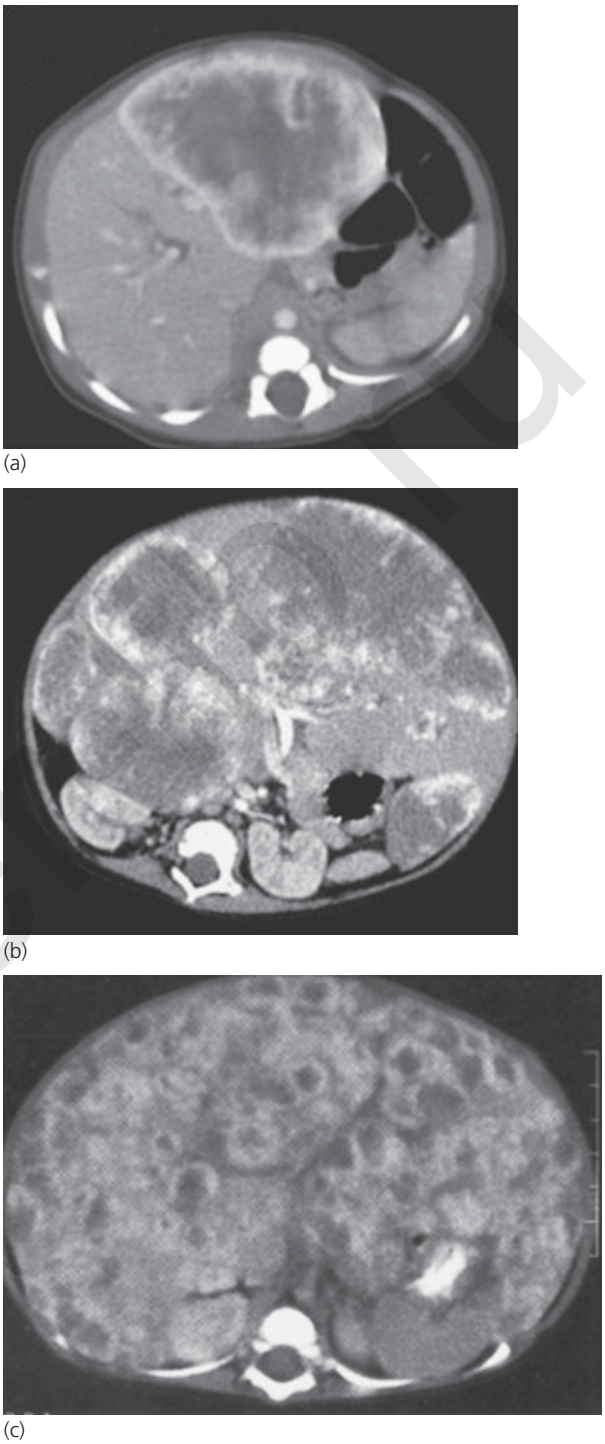


Figure 86.2 (a) Solitary infantile hepatic hemangioma; (b) multifocal hepatic infantile hemangioma; (c) diffuse infantile hepatic hemangioma. Reprinted from Meyers RL. Tumors of the liver in children. *Surg Oncol* 2007; **16**: 195–203. Copyright Elsevier.

Table 86.2 Vascular anomalies: International Society for the Study of Vascular Anomalies classification.

Vascular tumors	Vascular malformations
Infantile hemangioma	Slow flow vascular malformations:
Congenital hemangioma (RICH and NICH)	Capillary malformation
Tufted angioma	Port-wine stain
Kaposiform hemangioendothelioma	Telangiectasia
Spindle-cell hemangioendothelioma	Angiokeratoma
Other, rare hemangioendotheliomas (epitheloid, composite, retiform, etc.)	Venous malformation
Dermatologic acquired vascular tumors (pyogenic granuloma, targetoid hemangioma, etc.)	Lymphatic malformation
	Fast flow vascular malformations:
	Arterial malformation
	Arteriovenous fistula
	Arteriovenous malformation
	Complex combined malformations:
	CVM, CLM, LVM, CLVM, AVM-LM, CM-AVM

AV, arteriovenous; C, capillary; L, lymphatic; M, malformation; NICH, non-involuting congenital hemangioma; RICH, rapidly involuting congenital hemangioma; V, venous.

CLINICAL PRESENTATION

Clinical presentations of the various lesions described above overlap considerably. Infantile hepatic hemangiomas are frequently associated with cutaneous hemangiomas, the incidence of liver lesions being higher with multiple or large skin lesions.[2] Most liver hemangiomas may be clinically silent and escape detection. Some, however, remain asymptomatic and are discovered on routine prenatal or postnatal imaging performed for unrelated reasons. The most common presenting features are an abdominal mass, hepatomegaly, and anemia. Patients with large tumors can be critically ill at presentation with congestive heart failure (CHF), inferior vena cava compression, respiratory distress, and even abdominal compartment syndrome and multiorgan failure. Hypothyroidism may be present due to type III iodothyronine deiodinase activity in the liver hemangioma and may contribute to CHF. It is more common in the diffuse type, but has been noted in multifocal and large solitary hemangiomas. Screening with thyroid function tests at presentation is, therefore, advisable. Rarely, hemorrhagic shock with or without disseminated intravascular coagulation may follow a rupture of the lesion. Rupture can be precipitated by percutaneous needle biopsy.

INVESTIGATIONS

No serum marker is clinically useful for diagnosis, although elevations in alpha-fetoprotein (AFP) concentration have been reported.[13–15] These elevations are usually mild and call into question the importance of differentiating larger lesions from hepatoblastoma.

Liver hemangiomas are generally diagnosed using multi-detector-row computed tomography (CT) and magnetic resonance imaging (MRI) with contrast enhancement. These lesions are hypodense on CT scanning with centripetal (outside-in) enhancement. On MRI, they are hypointense on T_1- and hyperintense on T_2-weighted sequences. Imaging criteria used in the diagnosis include nodular peripheral enhancement followed by centripetal fill-in, change to isodensity on CT, or isointensity on MRI with the blood vessels and a complete fill-in in the late phase on contrast-enhanced images.

Contrast-enhanced ultrasonography (CEUS) is being increasingly used as the first-line imaging modality in the characterization of liver lesions.[16,17] The nodular peripheral enhancement expanding centrally is also seen with CEUS. This may offer a diagnostic advantage over CT and MRI in view of the low rate of adverse reactions from the microbubble contrast, allowing for multiple injections and assessments and its use in patients with decreased renal function.[17–19]

Angiography has been declining as a diagnostic modality in vascular anomalies of the liver. Endovascular modalities are now used to outline the vasculature of tumors in a subgroup of infants who present with high-output cardiac failure for whom a high-flow shunt amenable to embolization is suspected.

Infantile hemangiomas must be distinguished from epithelioid hemangioendothelioma, an intermediate-grade neoplasm that has the potential to metastasize. This is a tumor seen mostly in adults and rarely in older children.[20–22] It has not been reported in newborns. It consists of multifocal and confluent masses of homogenous liver nodules with peripheral enhancement. Treatment usually involves liver resection or transplantation.

MANAGEMENT

Asymptomatic focal lesions do not need treatment and may be followed with serial ultrasound examinations until resolution. This can be every one to two months until the lesion is stable, after which scans can be performed two to three times a year until involution is demonstrated. If there are signs of asymptomatic shunts, a closer follow-up schedule can be implemented. Multifocal lesions have a similar natural history to that of focal lesions and can be similarly observed. Patients with focal lesions or multifocal lesions large enough to cause shunts leading to CHF should undergo a careful assessment and work-up in an intensive care unit with electrocardiography, echocardiogram, and thyroid function tests. Congestive heart failure should be managed in consultation with a pediatric cardiologist. Diffuse liver lesions are the most difficult subgroup to manage. In addition to the

above, an early consultation with the transplant team should be considered for patients whose disease progresses despite medical management.

CORTICOSTEROIDS

Glucocorticoids at varying doses have been used for many decades as the first line of treatment for cutaneous and hepatic hemangiomas. A possible mechanism is the negative effect of steroids on angiogenesis. Administration of 2–5 mg/kg of oral prednisolone or an i.v. equivalent is commenced for patients with hemodynamically significant shunts or signs of CHF. Response rates in the literature vary, with good responses ranging from 30 to 75% for multifocal and diffuse disease.[1,23] Steroids may also be indicated for co-existing cutaneous lesions that may-threaten vision (e.g. eyelids) or be life-threatening (e.g. paratracheal or pharyngeal lesions). Lesions have been reported to stabilize between two and four months. The duration of therapy is guided by serial imaging and generally ranges from five to eight months.[1,10,23]

CHEMOTHERAPEUTIC AGENTS

Interferon-alpha has been used in corticosteroid-unresponsive cases with promising results. In a report by Ezekowitz *et al.*,[24] liver hemangiomas regressed by 50% or more in 18 of 20 patients receiving interferon alpha-2a (up to 3 million units/m^2 body surface area) after an average of 7.8 months with no long-term adverse effects. However, its use has been guarded since 6.1% of children younger than one year experienced spastic diplegia and motor developmental disturbances after receiving interferon.[24,25]

Vincristine is a mitotic inhibitor that inhibits the formation of tubulin microfibrils and arrests mitosis in the metaphase. It has been used in steroid-resistant, life-threatening hemangiomas at a dose of 1–2 mg/m^2. The high content of tubulin in the endothelial cells of hemangiomas makes this tumor particularly sensitive to vincristine.[26,27]

ENDOVASCULAR INTERVENTIONS

Use of angiography and embolization of arteriovenous shunts, although not curative, can provide major symptomatic relief from the hemodynamic effects of high-flow shunts in hemangiomas. Hemangiomas can derive collaterals from any of the hepatic, phrenic, intercostal, superior mesenteric, or adrenal arteries. It has been indicated primarily for CHF refractory to medical management, steroids, or additional chemotherapy. It has also been employed to shrink large hemangiomas, symptomatic by the mass effect causing caval compression or abdominal compartment syndrome. An angiographic classification has been proposed based on the number of lesions: flow characteristics (high versus low); presence; type of shunt (arteriovenous, arterioportal, or portovenous); and major anomalies of hepatic vessels (particularly venous varices).[28] The best response to embolization is found in patients with macroscopically visible shunts on angiography associated with single or multifocal lesions. Hemangiomas with extensive portal venous supply are more difficult to treat and may require multiple embolizations.[28] There is a risk of fatal hepatic necrosis after hepatic arterial embolization. The expertise required to perform and interpret angiography in this group of infants is generally found only in highly specialized referral centers.

SURGERY

Liver resections for hemangiomas have declined with better understanding of the biologic behavior of these tumors, improvements in pharmacotherapy, advances in endovascular techniques, and better pediatric intensive care. Recent reports have argued for surgery to be a last recourse after pharmacotherapy for the tumor, medical management of CHF, and endovascular interventions have all failed to achieve symptomatic control and tumor regression.[10,28,29] Kassarjian *et al.*[28] reported a series of 15 patients managed with endovascular interventions with one death in a patient who had diffuse liver hemangioma, severe CHF, and hypothyroidism. Dickie *et al.*[10] reported a series of 16 patients with no mortality and only two patients who required surgery (a left lobectomy and an orthoptic liver transplant). In contrast, Moon *et al.*[23] employed hepatic resection as a primary treatment modality for solitary, resectable, and symptomatic lesions. They used hepatic artery embolization as a second line of treatment, with one death from postoperative hemorrhage among nine patients who underwent surgery. Surgery and open biopsy are also indicated when a distinction cannot be made between a hepatoblastoma and a hemangioma.

LIVER TRANSPLANTATION

A small number of patients with diffuse hepatic lesions replacing most of the hepatic parenchyma develop life-threatening complications, including CHF, consumptive coagulopathy, abdominal compartment syndrome, and multiorgan failure. Because these patients may be those most likely to benefit from liver transplantation, early involvement of the transplant team has been advocated if there is a poor response to initial pharmacotherapy.[1] Embolization, even in the context of diffuse lesions, has been shown to prevent transplant.[29] The outcome following transplantation is varied, although some authors report good outcomes.[30–32]

FUTURE DIRECTIONS

The classification and treatment of hepatic hemangiomas will continue to evolve. Prospective characterization of patients will further the understanding of these uncommon tumors. While there is reasonable concordance about classification of GLUT1-positive multifocal or diffuse liver lesions, there remains a lacuna in the biologic, clinical, and radiologic characterization of certain solitary liver vascular tumors. The Children's Hospital Boston has proposed and created a worldwide web-based registry for longitudinal accrual of patients with liver hemangiomas.[1]

Anti-angiogenic drugs show potential in the treatment of liver hemangiomas. Bevacizumab, a recombinant monoclonal

antibody against vascular endothelial growth factor, was incidentally found to reduce the size of liver lesions significantly in a patient with colorectal adenocarcinoma initially suspected to be metastases, but later found on biopsy to be hemangiomas.[33] A similarly dramatic response was seen in a 41-year-old patient with pulmonary epitheloid hemangioendothelioma.[34] No trials of bevacizumab have yet been conducted in children or infants with hemangiomas, although a recent phase I trial in children 1–21 years with various solid tumors indicates that it is tolerated well in children.[35]

Recent reports have documented propranolol to be effective at reducing the size of hemangiomas. These reports show that fairly modest doses (3 mg/kg per day) of propranolol reduce the size of infantile hepatic hemangiomas. Indeed, propranolol has been suggested as a first-line therapy for high-risk hemangiomas.[36,37] A two-month-old infant with diffuse hepatic hemangioma with near-total replacement of the liver parenchyma had a dramatic response to propranolol at 2 mg/kg per day, after corticosteroids and vincristine had failed.[38] Possible mechanisms postulated are vasoconstriction, decreased expression of vascular endothelial growth factor, and apoptosis of capillary endothelial cells.

Mesenchymal hamartoma of the liver

Mesenchymal hamartomas (MHL) usually present as solitary hepatic lesions and are the second most common benign liver tumor after hemangiomas in newborns. They accounted for 6% of pediatric liver tumors in a series of patients compiled by Weinberg and Finegold in 1983.[39] The understanding of the biology of this tumor has evolved greatly since it was definitively described in 1956 by Edmondson.[40] More than two-thirds are diagnosed in children less than one year of age, although rarely can they be detected in adults.[41] A systematic review of the literature found that 85% of children presented before the age of three and that the tumor was slightly more common in boys.[42] Mesenchymal hamartomas must be distinguished from other congenital and infective cystic diseases, hemangiomas, and other liver tumors.

PATHOLOGY AND PATHOGENESIS

Right lobe tumors are three times more common than left, and 10–20% can be pedunculated. A small proportion of cases may involve both lobes.[42,43] Mesenchymal hamartomas usually contain both cystic and solid components, the proportion of which varies. Tumors can be very large, up to 20–30 cm in diameter and weighing up to 3 kg. The majority (about 50%) are multicystic, with the intervening myxoid stroma containing fibroblasts, blood vessels and lymphatics, collagen, bile ductules, and islands of hepatocytes. Less commonly, the cysts can be very small and sometimes absent, resulting in a predominantly solid tumor.[44,45] The cystic spaces are filled with a clear or mucoid liquid and may or may not be lined by epithelium, the latter seen more often in larger cysts. Mesenchymal hamartomas are usually well circumscribed and are surrounded by a rim of compressed hepatic parenchyma, but are devoid of a true capsule.[42] There have been a few reports of multifocal MHL. Small satellite lesions at the margins of the tumor have been described and may explain recurrent disease after excision of the main tumor.[46]

The pathogenesis of this tumor is not clearly defined. The prevailing opinion is that these tumors are developmental aberrations that arise from ductal plate malformations from the primitive mesenchyme late in the course of embryogenesis, trapping islands of hepatocytes and dysplastic bile ducts within their structure.[44] Some investigators have argued that they may be true neoplasms. The histopathologic and immunohistochemical similarities between undifferentiated embryonal sarcoma (UES) of the liver and MHL can be striking. It has been postulated that UES – with its onset in older children, benign bile ductular elements within a malignant mesenchyme, its predisposition to the right lobe, and occasional pedunculation – may be preceded by an MHL.[47,48] Several reports describe cases of UES arising within a previous MHL, two of which occurred after incomplete excision. Aneuploidy has been detected by flow cytometry in two out of eight MHLs in one study.[48] Cytogenetic abnormalities involving the same breakpoint on chromosome 19 (band 19q13.4) have now been reported in nine cases; three of which involved a UES originating within an MHL.[49–52] These karyotypic and cytogenetic abnormalities in at least some MHLs may indicate a clonal defect.

CLINICAL PRESENTATION

Mesenchymal hamartomas present most commonly as abdominal distention or an upper abdominal mass. Large tumors can cause respiratory distress or compression of the inferior vena cava with distended superficial abdominal veins or lower limb edema. Abdominal pain is unusual in children, but more common in adults. Examination reveals a large, smooth, non-tender mass in the upper abdomen. The tumor can be detected on prenatal ultrasound and may cause fetal hydrops, polyhydramnios, and fetal demise.[53,54] Case reports of MHL describe presentation with obstructive jaundice, vascular steal phenomenon, high-output cardiac failure, and perinatal tumor rupture in the newborn.

INVESTIGATIONS

Liver function tests are usually normal. Alpha-fetoprotein concentrations may be moderately elevated. Levels return to normal after tumor removal, but may take up to a year due to liver regeneration. Thus, MHL should be distinguished from hepatoblastoma and may require biopsy.

A CT or ultrasound examination is diagnostic in most patients. The typical finding of a multiseptate cystic tumor with distinct margins is rarely seen in other pediatric tumors and is diagnostic of an MHL. The cystic areas appear hypodense and hypovascular on imaging. Solid areas (within mixed solid-cystic or predominantly solid tumors), septae, and peripheral areas may show heterogenous enhancement

after i.v. contrast on CT.[45,55] The differential diagnosis in totally solid tumors in newborns and infants should include various hepatic tumors, such as hepatoblastoma, hepatocellular carcinoma, and hemangiomas.

On MRI, lesions typically have a low intensity on T_1-weighted sequences, but have variable signal intensity on T_2-weighted sequences. When diagnosis is in doubt, the pathology is usually confirmed after resection of the tumor or by an open or percutaneous tumor biopsy (see Fig. 86.3a,b).

TREATMENT

Mesenchymal hamartoma of the liver is best treated by anatomic resection of the involved liver segments. While the tumors themselves are not very vascular, the surrounding compressed hepatic parenchyma can be very vascular. However, in the rare case that a tumor is too large for an anatomic resection, enucleation can be performed. The tumor mesenchyme sharply demarcates the surrounding compressed hepatic parenchyma, allowing for this approach. However, incomplete excision and marsupialization result in a high rate of recurrent disease and are best avoided.[56]

Variable degrees of spontaneous regression have been noted. A systematic review of the literature by Stringer and Alizai[42] found nine such cases, four of which had a prominent vascular component. None, however, regressed completely, and the follow-up time in all was under three years. In view of the association between UES and MHL, the safety of this approach cannot be determined without long-term follow up.[42]

In the very rare case, a liver transplantation may be an option for recurrent or unresectable MHL. The United Network for Organ Sharing group reported two cases of transplants performed in children who had progressive liver failure after resection of MHL, one of whom died from postoperative bleeding. A third case was reported of a newborn girl who developed a diffuse hemangioma of the liver remnant four months after a resection for MHL.[22,57,58]

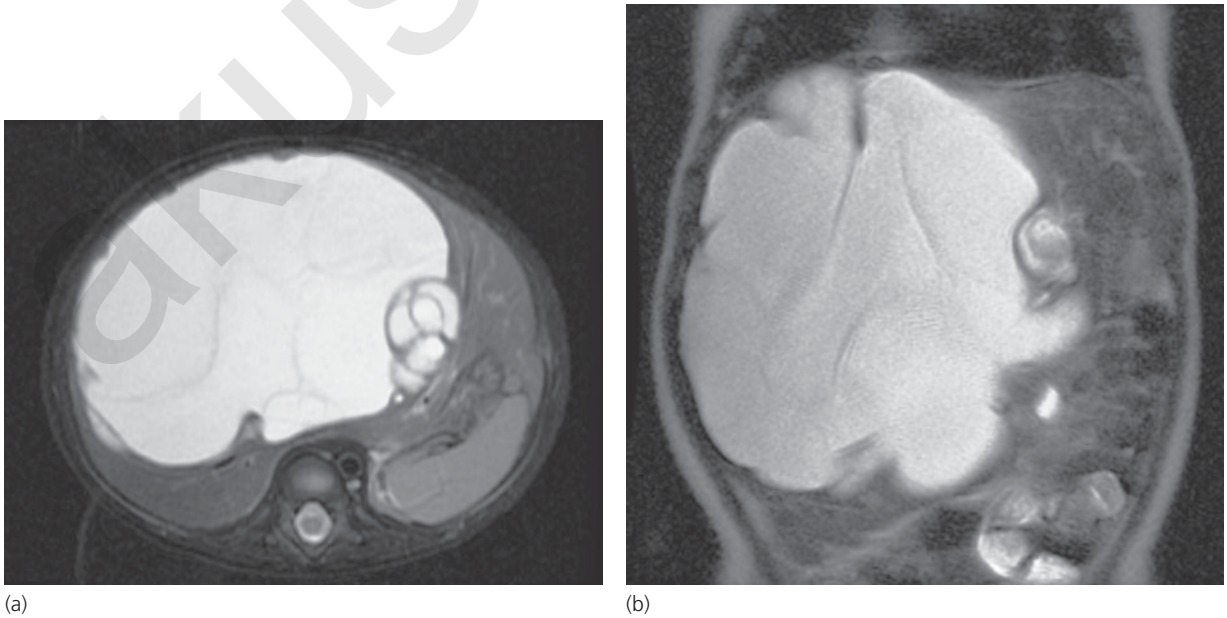
MALIGNANT LIVER TUMORS

Hepatoblastoma

The incidence rates for primary liver cancer, as published by the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute in Bethesda, MD, USA, are 5 per million in the 0–4 age group and 1 per million in the 5–9, 10–14, and 14–19 age groups. The incidence of hepatoblastomas in infants less than one year of age was 11.9 per million.[59] Five percent of all cancers and more than 95% of all hepatic cancers in this age group are hepatoblastomas. In the Pediatric Oncology Group series, 11% of hepatoblastomas occurred in the first six months of life. Of these, 50% were congenital, as evinced by their size at the time of diagnosis, usually at two to three months.[60] Hepatoblastomas accounted for 1% of all liver and bile duct tumors diagnosed in the United States between 2002 and 2006.

The Children's Tumor Registry in Manchester, UK, reported that the incidence of hepatoblastomas increased from 0.4 to 1.0 per million between 1971 and 1983. SEER reports an average annual increase of 5.2% from 1973 to 1992.[61] This may be due to the increase in survival of premature low- and very-low-birth-weight infants, a factor that has been associated with hepatoblastomas.[62–64]

Evidence for genetic or epigenetic origins of hepatoblastoma comes from its strong association with familial adenomatous polyposis (FAP), Gardner's syndrome, and Beckwith–Wiedemann Syndrome.[65] The risk of hepatoblastoma rises 1000–2000-fold in children with this family



(a) (b)

Figure 86.3 T_2-weighted magnetic resonance image of a large mesenchymal hamartoma showing a multiseptate cystic tumor. The patient underwent enucleation of the tumor. (a) Axial view, (b) coronal view.

history.[66–69] The risk of hepatoblastoma in patients with FAP is around 1%.

HISTOLOGY

Hepatoblastomas usually occur as a solitary mass in the liver, but are occasionally multicentric. Rarely is the tumor composed solely of one cell type. In a review of cases for the Pediatric Oncology Group, 5% were small cell undifferentiated and 7% were of the pure well-differentiated fetal type. The rest of the tumors were a mixture of diverse epithelial cell types in varying proportions. For this reason, both fine needle aspiration and needle biopsies may sample a non-representative section of the tumor. Among all cases, 85–90% contain both fetal and embryonal cells and 20% may have stromal components.[60]

The small cell type is particularly aggressive, especially when present in a significant portion of the hepatoblastoma (75% or so) as the sole cell type. This histology is more common in neonates and infants. AFP levels may not be raised.[70] It has a poor prognosis due to lack of response to current therapy. The significance of smaller proportions of small cells is not yet known. Occasionally, rhabdoid cell types are found intermixed with small cells. The rhabdoid tumor cells as an exclusive cell type are rare and probably represent a biologically different tumor (see below under Malignant rhabdoid tumors). The presence of mixed histologic features has no prognostic significance. In current Children's Oncology Group (COG) hepatoblastoma treatment protocols (see Table 86.3), tumors with pure fetal histology are designated as favorable histology; all other tumors are classified as unfavorable (see Fig. 86.4a–c).

Table 86.3 Classification of hepatoblastomas.

Major categories	Small cell, undifferentiated
Epithelial	Rhabdoid
Fetal, well-differentiated (mitotically inactive with minimal mitotic rate of $\leq$2 mitoses per 10, $\times$40 objective fields)	Mixed stroma having osteoid features; rarely striated muscle, cartilage, or minor components as follows:
Fetal, mitotically active ($>$2 mitoses per 10, $\times$40 objective fields)	Cholangioblastic (ductal)
Embryonal	Intestinal glandular epithelium (teratoid)
Macrotrabecular	Neuroid-melanocytic (teratoid)
	Rhabdomyoblastic
	Chondroid
	Blastemal

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GENETIC CHANGES

Hepatoblastoma is tightly linked to excessive Wnt/beta-catenin signaling. There is a high rate (50–90%) of mutations found in *CTNNB1,* which encodes β-catenin, placing hepatoblastoma among the most common human tumors with constitutive activation of β-catenin/Tcf signaling.[71–73] *APC* gene (involved in degradation of β-catenin) mutations have been characterized regularly in kindred of FAP and in a variable number of sporadic hepatoblastomas.

Cairo *et al.*[74] reported two major molecular subclasses of hepatoblastomas that evoke early and late phases of prenatal liver development. Using a 16-gene signature that correlated with the phase of liver development, they established a tight correlation between the stage of hepatic differentiation and clinical behavior – notably vascular invasion, metastatic spread, and patient survival. This demonstrated strong prognostic relevance compared to clinical criteria (tumor stage and predominant histotype) on multivariate analysis. Also, *Myc* repression in hepatoblastoma cell lines with constitutively activated β-catenin impaired tumorigenesis, suggesting that *Myc* genes may be the main effectors of the oncogenic Wnt/β-catenin pathway in aggressive hepatoblastomas.[74]

Other molecular mechanisms implicated in the growth of hepatoblastomas include the overexpression of insulin-like growth factor-I[75,76] and downregulation of a novel tumor suppressor gene, *RASSF1A*, by promoter methylation.[77,78] Methylation of the *RASSF1A*, gene was an independent risk factor on multivariate analysis. Upregulation of the *MAPK* pathway has also been noted in aggressive hepatoblastomas with a small cell component.[79]

Cytogenetic studies in HB have shown recurring patterns of chromosomal abnormalities. The most common involve trisomies, particularly of chromosomes 2, 8, and 20. Translocations involving chromosomes 1, more specifically bands 1q12–21, have been described as a recurring translocation in hepatoblastoma and were found in 20 of 55 patients in a series of hepatoblastomas.[80]

CLINICAL FINDINGS

The majority of infants with hepatoblastoma present with an asymptomatic abdominal mass noticed incidentally by a family member or a pediatrician. An array of non-specific symptoms, such as abdominal pain, fever, irritability, weight loss, or gastrointestinal disturbances, may occur in a small percentage of patients, especially those with advanced disease. Clinical examination usually shows an expansile solitary mass in the liver. Thrombocytosis, with the platelet count ranging in the millions, is a well- known, albeit uncommon, feature of hepatoblastoma. Thrombopoietin production by the tumor has been proposed as possible cause of the thrombocytosis.[81,82] Hormone elevations that lead rarely to symptoms are due to human beta-chorionic gonadotropin, testosterone, adrenocorticotrophic hormone, or parathormone-related peptide.[83,84]

The AFP level is markedly elevated in more than 90% of patients with hepatoblastoma, in whom it is used as diagnostic tool and as a tumor marker to monitor therapeutic response. The half-life of AFP in the first month of life is 5–6 days, increasing to approximately 42 days by six

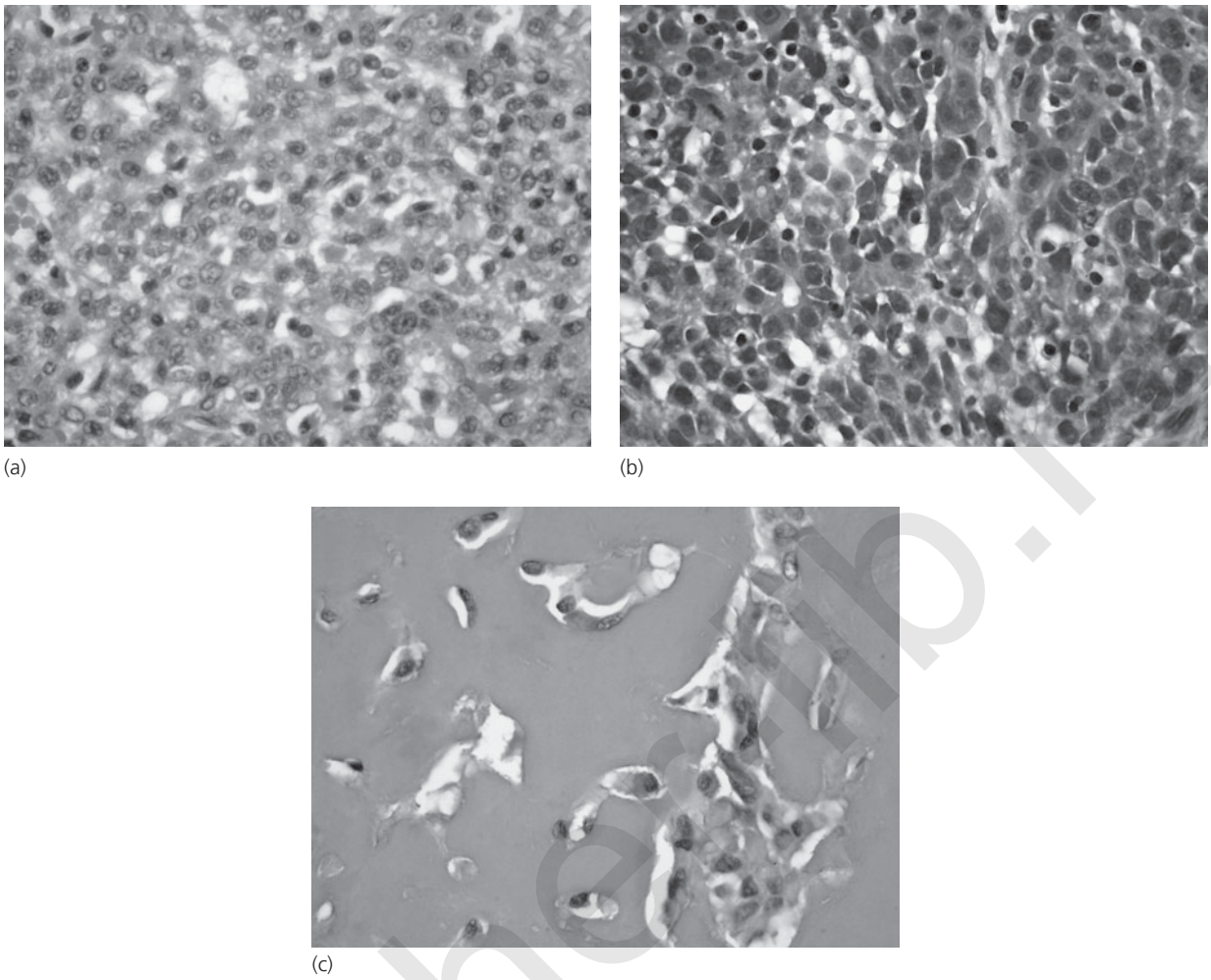

Figure 86.4 Histologic subtypes of hepatoblastomas. (a) Fetal type, (b) small cell undifferentiated, (c) mesenchymal type with osteoid. Courtesy of Julie Teruya-Feldstein, MD, Memorial Sloan-Kettering Cancer Center.

months of age. Levels in preterm babies (earlier than 37 weeks' gestation) are significantly higher with a negative correlation between gestational age and AFP levels.[85] AFP levels are usually less than 10 ng/mL by one year of age, although persistent elevations, especially in preterm babies without any known associated factors, have been observed (see Table 86.4).

Table 86.4 Physiologic alpha-fetoprotein level.

Age	Mean ± SD (ng/mL)
Premature	134 734 ± 41 444
Newborn	48 406 ± 34 718
Newborn to 2 weeks	33 113 ± 32 503
Newborn to 1 month	9452 ± 12 610
2 months	323 ± 278
3 months	88 ± 87
4 months	74 ± 56
5 months	46.5 ± 19
6 months	12.5 ± 9.8
7 months	9.7 ± 7.1
8 months	8.5 ± 5.5

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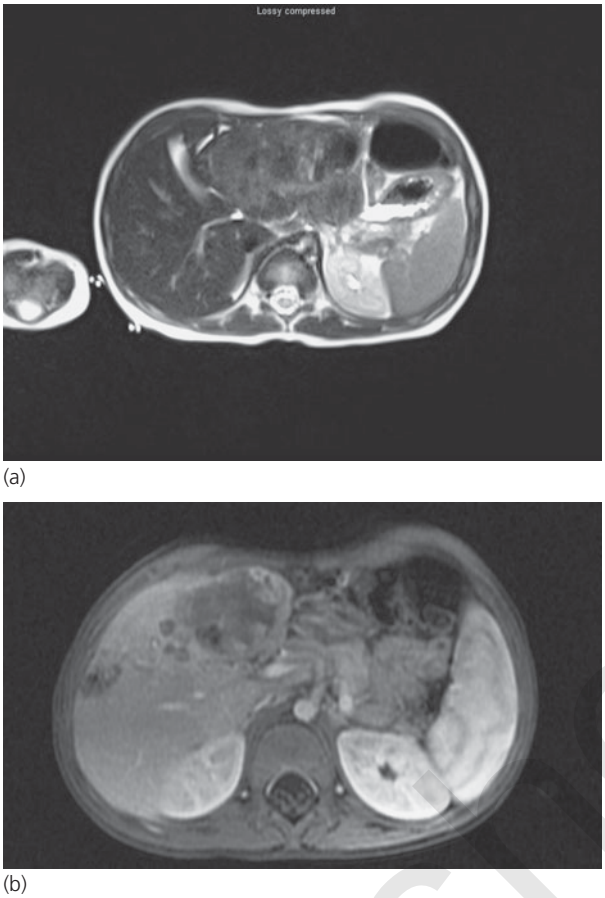
IMAGING

An abdominal CT (with and without contrast) or MRI and magnetic resonance angiogram (MRA) can be performed at presentation, according to the local practice. A Doppler ultrasound (if an MRA has not been performed) will define any involvement of the portal or hepatic veins and inferior vena cava. It can be difficult to distinguish direct involvement of the veins from external compression.

A CT scan of the chest (without contrast) and a posteriolateral chest x-ray should be performed on all patients with a primary liver tumor. Technetium-99m methylene-diphosphonate nuclear bone scintigraphy is not routinely recommended due to the rarity of bone metastasis in hepatoblastomas and is performed only if there is clinical suspicion.[86] The role of positron emission tomography has not been evaluated in hepatoblastomas. A small series showed fluorodeoxyglucose uptake in the primary tumor; however, larger studies need to confirm such findings and outline a

role for this modality.[87] As resection of the primary tumor is essential for survival, liver imaging must define the segmental involvement of the liver and associated vasculature, both of which are indicators of resectability (see Fig. 86.5a,b).



(a)

(b)

Figure 86.5 Focal and multifocal hepatoblastoma. (a) Focal hepatoblastoma involving the left lobe of the liver; (b) multifocal hepatoblastoma with largest lesion involving the left lobe with multiple satellite tumors in segments IV, V, and VIII. This patient underwent an extended left hepatectomy.

STAGING

The COG employs a staging scheme after applying the results of surgery (resection or biopsy) (see Table 86.5). Risk stratification in the current COG hepatoblastoma protocol is based on the predominant tumor histology, presence of gross residual disease, distant metastasis, and the presence or absence of a low AFP level (< 100 ng/mL) at diagnosis (see Fig. 86.7).

The Liver Tumor Strategy Group (SIOPEL 1) of the International Society of Pediatric Oncology (SIOP) introduced the PRETEXT (*Pre*treatment *Ext*ent of disease) system of staging liver tumors.[88,89] PRETEXT designates the following sections in the liver: (1) left lateral (Couinaud 2 and 3); (2) left medial (Couinaud 4); (3) right anterior (Couinaud 5 and 8); and (4) right posterior (Couinaud 6 and 7) (see Fig. 86.6). Risk stratification in PRETEXT is based on the number of contiguous tumor-free regions of the liver and

Table 86.5 The Children's Oncology Group staging system.

Stage	
I	Complete gross resection at diagnosis with clear margins, pure fetal histology (PFH) and unfavorable histology (all histology, except PFH)
II	Complete gross resection at diagnosis with microscopic residual disease
III	Biopsy only at diagnosis; or gross total resection with nodal involvement; or preoperative tumor spill/rupture
IV	Distant metastatic disease at diagnosis

the involvement of the caudate lobe; invasion of the vena cava or all three major hepatic veins; portal vein involvement; contiguous extrahepatic growth; tumor rupture or hemorrhage; and distant metastasis denoted by the letters 'C', 'V', 'P', 'E', 'H', and 'M', respectively (see Table 86.6). PRETEXT stage has been shown to be an independent predictor of five-year overall survival.[89]

In addition to small cell undifferentiated histology, the presence of a low AFP level (< 100 ng/mL) at diagnosis has been shown to be an independent predictor of a poor outcome. This fact likely indicates a more undifferentiated tumor and is more common in infants and newborns.[90,91]

The PRETEXT system has recently been validated by the COG, and future trials within the COG will use the PRETEXT staging system as an objective tool to monitor the effect of neoadjuvant chemotherapy and to determine the timing and extent of surgical resection.[92] It is hoped that this tool will allow better intergroup collaboration in the development of new therapeutic strategies for the highest-risk groups that continue to have a poor response to current treatment approaches.

TREATMENT

The treatment of hepatoblastomas is a success story in pediatric oncology. Overall survival has increased from 30 to 70% in the last 30 years.[93] Overall survival by COG stage I (with pure fetal histology), stage I (with unfavorable fetal histology), stage II, stage III, and stage IV is 100, 97.5, 100,

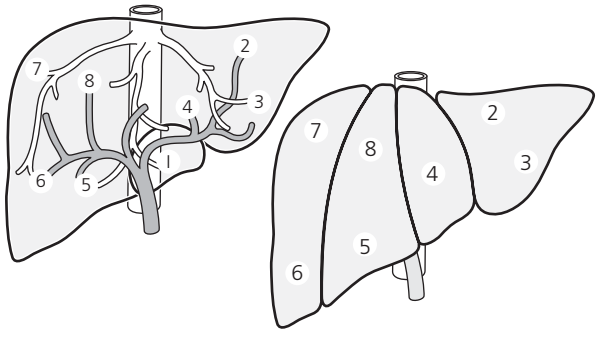


Figure 86.6 Liver segmentation, surgical anatomy and PRETEXT sections. Reprinted from Otte JB. Progress in the surgical treatment of malignant liver tumors in children. *Cancer Treat Rev* 2010; **36**: 260–71. Copyright Wolters Kluwer Health.

Table 86.6 PRETEXT number and its meaning.

PRETEXT No.	Definition
I	One section is involved and three adjoining sections are free
II	One or two sections are involved, but two adjoining sections are free
III	Two or three sections are involved, and no two adjoining sections are free
IV	All four sections are involved
Standard risk (SR-HB)	PRETEXT I–III, V-, E-, P-, M-, H-
High risk (HR-HB)	PRETEXT IV, V+, E+, P+, H+, M+, or AFP <100 ng/mL

E, extrahepatic disease; H, tumor rupture or intraperitoneal hemorrhage; M, distant metastases; P, portal vein involvement; V, involvement of the IVC and/or major hepatic veins.
Reprinted with permission from Roebuck DJ, Olsen Ø, Pariente D. PRETEXT: a revised staging system for primary malignant liver tumours of childhood developed by the SIOPEL group. *Pediatr Radiol* 2005; **37**: 123–32. Copyright Springer Science + Business Media.

70.2, and 39.3%, respectively.[92] The advent of 'platinum'-based chemotherapy protocols, along with advancements in surgical techniques, have spurred this progress. Various collaborative groups have researched and developed successful treatment strategies for hepatoblastomas.

Active agents against hepatoblastoma are cisplatin, 5-fluorouracil, vincristine, doxorubicin, ifosfamide, and irinotecan. The standard chemotherapy regimen in SIOPEL is cisplatin and doxorubicin. This is being evaluated against cisplatin monotherapy in standard-risk hepatoblastoma in the SIOPEL-3 trial (see Table 86.6). High-risk hepatoblastoma (HR-HB) patients are randomized to receive a more dose-intensified therapy with cisplatin, carboplatin, and doxorubicin than the HR-HB arm of SIOPEL-3 in the new SIOPEL-4 protocol.[94]

The COG uses C5FV as the standard chemotherapy regimen for low- and intermediate-risk tumors. The addition of doxorubicin to cisplatin offered no survival advantage for low-risk (COG stage I or II) tumors and was associated with increased incidence of adverse events. However, an improved event-free survival was noted in patients receiving cisplatin-doxorubicin compared with C5FV for stage III and IV patients.[93,95] The current COG study (AHEP-0731) randomizes intermediate-risk hepatoblastoma to cisplatin, 5-fluorouracil, vincristine, and doxorubicin against standard therapy. The use of irinotecan as window therapy for high-risk hepatoblastoma is also being evaluated for stage IV hepatoblastoma, for which outcome on current therapy continues to be dismal (see Fig. 86.7).

The key difference in approach between the COG and SIOPEL is the timing of surgery and the use of neoadjuvant chemotherapy. The COG's approach has been to primarily resect tumors when possible, then to administer adjuvant chemotherapy for tumors with histologies other than pure fetal histology. Neoadjuvant chemotherapy after open or percutaneous needle biopsy is given to infants who present with an unresectable tumor. The SIOPEL approach has been to treat all patients diagnosed with hepatoblastoma (based on imaging and image-guided percutaneous needle biopsy) with neoadjuvant chemotherapy. They have argued towards less extensive surgical resections and shown operations to be easier and safer in pretreated tumors. Biopsy of the tumor, as is a prerequisite for such an approach, has also been found to be technically safe with a very low risk of tumor spread.[96]

The timing of surgery after induction therapy is another consideration. The current COG and SIOPEL protocols recommend an assessment for resection after two cycles of chemotherapy followed by two further cycles if the tumor is unresectable. A recent study found no statistically significant decline in tumor volume after the second cycle of chemotherapy.[97] These findings were similar to those of a previous study from our institution on pediatric solid tumors that included three hepatoblastomas.[98] This may have implications for reduced toxicities with shorter regimens and early referral for transplant in the absence of a chemotherapeutic response.

For multifocal, PRETEXT IV tumors, liver transplant has emerged as a viable option. Six-year tumor-free survival of

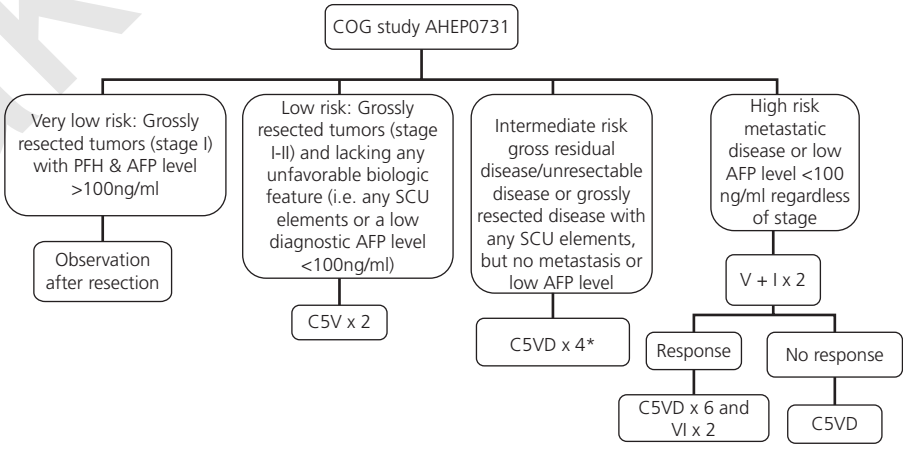


Figure 86.7 Children's Oncology Group hepatoblastoma current study: COG AHEP0731. Adapted from Otte JB. Progress in the surgical treatment of malignant liver tumors in children. *Cancer Treat Rev* 2010; **36**: 260–71. Copyright Wolters Kluwer Health.

82% was achieved with primary liver transplant, compared to 30% for rescue transplants due to either tumor recurrence or technical failures. Live-related donor and cadaveric liver transplantation had disease-free survivals of 82 and 71%, respectively. Macroscopic venous invasion, albeit a significant factor in overall survival, is not a contraindication to transplant, as long as the transplant can be performed without leaving gross tumor behind.[99]

The significance of pulmonary metastasis at presentation and later is currently being evaluated. The incidence of pulmonary metastatic disease can be as high as 40%. The outcome of this group of patients is markedly poorer.[100,101] The Children's Cancer Group reported long-term survival with resection of pulmonary metastasis and systemic chemotherapy where the lungs were the only site of metastatic disease and where the primary tumor had been successfully treated.[102,103] A recent study from the COG reports excellent outcome following pulmonary metastasectomy of lung metastasis detected at presentation (eight of nine patients were long-term survivors), but a poorer outcome for pulmonary recurrence after chemotherapy, where four of 13 were long-term survivors.[101]

EMERGING THERAPIES

Transcatheter arterial chemoembolization (TACE), which uses a percutaneously placed intra-arterial catheter, has recently emerged as an option for advanced, unresectable hepatoblastomas (see Table 86.7). It has the potential for making inoperable hepatoblastomas resectable or transplantable. Four series of hepatoblastomas, which included 36 patients ranging from 50 days to five years of age, have reported a resectability rate of 88.8%.[104–107] One of the 32 patients had a transplant, while all others underwent left/right hepatic resection or trisegmentectomy. The role of TACE is being evaluated prospectively in the second Japanese Study Group for Pediatric Liver Tumors (JPLT-2) trial.

Novel chemotherapeutic strategies are also being evaluated for the treatment of high-risk, especially small cell undifferentiated, hepatoblastomas, which respond poorly to current chemotherapy protocols. The COG and JPLT-2 are currently prospectively evaluating the use of irinotecan (a topoisomerase-1 inhibitor) in this subgroup of patients.

Gene-directed therapeutic strategies currently being investigated include Bcl-2 silencing and the targeting of *Myc* and *β-catenin* genes. The use of gene therapy to activate 5-fluorocytosine (an inactive prodrug) to 5-fluorouracil has been described in preclinical trials (see Table 86.7).

Malignant rhabdoid tumor

Malignant rhabdoid tumors of the liver are poorly understood extremely rare tumors, with a grave prognosis. Fewer than 50 cases have been reported in the literature.[108] They have sometimes presented with an abdominal mass, distention, or fever. Four of 19 patients in a series were three months old or younger.[109] More commonly, they present as central nervous system or renal tumors. Differentiating the tumor from a small cell undifferentiated-type hepatoblastoma can be difficult, as they share clinical and histologic features.[110] The tumor is very friable, can present with rupture, and can bleed uncontrollably following biopsy. There appears to be a strong correlation between the loss of *INI1* immunostaining and the presence of an INI1 mutation, suggesting that the former may be a reliable marker of rhabdoid tumors in children.[110,111] Confirmatory immunohistochemical stains for these tumors usually include expression of vimentin, cytokeratin, and epithelial membrane antigen and the absence of INI1 protein.

Malignant rhabdoid tumors are usually resistant to chemotherapy, with a median survival of only 15 weeks.[109] There are two reported cases of long-term survival: a 13-month-old girl following right hepatectomy and multiagent

Table 86.7 Reports of transcatheter arterial chemoembolization (TACE) in unresectable hepatoblastoma.

Reference	No. of patients	Age range	No. of treatments	Resectability	Overall survival	Complications of TACE
Han *et al.*[104] (1999)	4	8–22 months	2	4/4 underwent hepatic resections	100%, 16–52 months follow up	None
Li *et al.*[105] (2008)	16	50 days–60 months	1–3 (cisplatin/ adriamycin)	13/16 – complete resections (including one OLT); 3/16 – partial resection	1-yr OS: 87.5%; 3-yr OS: 68.7%; 5-yr OS: 50%	None
Xuewu *et al.*[106] (2006)	8	2–12 months	1–3 (adriamycin/ vincristine/ cisplatin)	6/8 – complete resection; 1/8 – no surgery as tumor completely regressed; 1/8 – died of pneumonia before surgery	15-49 months follow up	One case of pneumonia
Oue *et al.*[107] (1998)	8	4–26 months	1 (heterogenous group, 3, patients received pre- or post-TACE chemotherapy)	8/8 resected (one patient had pulmonary metastasis)	6/8 disease free at 46 months; 2/8 died of metastatic disease	Fever

chemotherapy with ifosfamide, vincristine, and actinomycin D;[112] and a three-year-old boy after combination chemotherapy with ifosfamide, carboplatin, and etoposide alternated with vincristine, adriamycin, and cyclophosphamide and liver transplantation.[113]

Germ cell tumors

While germ cell tumors in children are fairly common, their occurrence in the neonatal liver is quite rare. Large series of fetal and neonatal tumors spanning decades have documented only isolated cases in the liver. As a group, they account for around 2% of tumors in this age group.[43,114,115]

CHORIOCARCINOMA

Choriocarcinoma in the neonatal period is a rare, life-threatening malignancy, but one that is highly responsive to the appropriate early treatment instituted. However, it is generally recognized late in the neonate. Choriocarcinoma is a rapidly growing, hemorrhagic tumor of the trophoblastic tissues. It has been documented and treated successfully, both in the presence and absence of maternal or placental disease.[116–118] An obvious explanation would be that it could be metastatic disease from a placental primary, although a *de novo* origin cannot completely be ruled out in certain cases.[119] The absence of placental disease can be explained by the presence of even a microscopic focus of primary disease in the placenta missed on histopathology. A placental focus of choriocarcinoma is not always present in maternal disease.

Choriocarcinoma is detected easily in the newborn by the presence of an elevated serum β-HCG (human chorionic gonadotropin) level. The neonate usually presents with an abdominal mass, hepatomegaly, and anemia. This 'infantile choriocarcinoma syndrome' was first described by Witzleben and Bruninga[120] in 1968 in infants aged five weeks to seven months, although this can easily be applied to the newborn. The presence of choriocarcinoma in the mother who has delivered a live baby is rare and should prompt a screen for a neonatal tumor in the first month of life. Also, suspicion of choriocarcinoma in the neonate should prompt a search for the same in the mother. The tumor can metastasize rapidly to the lungs, brain, and skin, and usually is fatal within weeks owing to uncontrolled hemorrhage.[119]

If detected early, the choriocarcinoma is highly chemosensitive to methotrexate and agents used for other germ cell tumors, such as etoposide, bleomycin, and cisplatin. Paclitaxel can be used as second-line chemotherapy for cisplatin-unresponsive disease. Residual disease in the liver, lungs, or brain can be resected or observed as per the response monitored radiologically (CT/MRI) and biochemically (serum β-HCG). Not surprisingly, there has been an increasing number of reports of successful treatment since the 1990s.[117,121–126]

OTHER GERM CELL TUMORS

The few reported cases of teratomas of the liver in the newborn have been mature teratomas, although more examples of all kinds have been reported in infancy.[127–129] Interestingly, a large series of teratomas in children included two liver tumors, both of which occurred in newborns.[130] The AFP is usually elevated regardless of the presence or absence of malignancy. Treatment usually consists of resection and chemotherapy guided by the malignant cell type.

PRINCIPLES OF LIVER RESECTIONS

The details of individual major hepatic resections are beyond the scope of this chapter, and the reader is referred to a text on hepatobiliary surgery.[131] However, the general principles of liver resections in neonates and infants are similar to those in adults. The main hazards are of blood loss and bile leak. Eighty-five percent of the liver can be safely removed in small infants. Liver regeneration is rapid and almost complete within three months.[132] Central hepatectomy has also been shown to be a feasible, although technically challenging, operation in children with hepatoblastomas.[133] Values on liver function tests usually return to normal within a few weeks.

Bloodless hepatic dissection is crucial in newborns in whom the blood volume is no more than a few hundred milliliters. The surgical approach is based on a thorough understanding of the hepatic anatomy as described by Couinaud.[134] Skilled anesthetic management and maintenance of a low central venous pressure in the patient minimizes blood loss. Hepatic resections in children can be carried out through a transverse or subcostal incision, and vertical extension is unnecessary. After division of the ligamentum teres and the falciform ligament, a thorough examination of the liver is undertaken to identify the site or sites of tumor involvement. Further mobilization of the left or right lobe is undertaken with division of the respective peritoneal reflections on the diaphragm. The mobilization of the right lobe is completed once the fibrous tissue over the inferior vena cava is divided with scissors or the endoscopic gastrointestinal anastomosis vascular stapling device (Endo-GIA; United States Surgical, Norwalk, CT, USA). The use of intraoperative ultrasound at this stage is useful in identifying the location of hepatic vessels, particularly the hepatic veins.

The next stage is establishing inflow control and identifying and preserving the components of the biliary tree. Control of the branches of the hepatic artery and the portal vein supplying the part of the liver to be resected can be achieved individually by extrahepatic dissection or by transecting the relevant pedicle within the substance of the liver. During left hepatectomy, the left branch of the portal vein and left hepatic artery are divided within the umbilical fissure. Dissection of the extrahepatic biliary structures is not necessary and carries the risk of inadvertent bile duct injuries, especially in the presence of variant anatomy. Division of the biliary radicals can be achieved at the time of parenchymal transection by dividing them laterally within the pedicles.

Establishing control of the venous outflow is the aspect of the operation most fraught with the risk of blood loss and air embolism. This dissection is performed with the patient in the 15° Trendelenburg position and with the anesthesiologist

maintaining a central venous pressure of less than 5 mmHg. The individual hepatic veins are carefully dissected, divided within vascular clamps, and oversewn with 3-0 polypropylene sutures. Alternatively, they can be divided using the Endo-GIA vascular stapling device.

Division of the liver parenchyma should be considered to be more akin to fine dissection than a fracture and division. This may be accomplished by a simple crushing technique. The authors apply intermittent inflow occlusion (Pringle maneuver) for periods of up to 7 minutes with 1-minute windows when hemostasis is achieved on the cut surface. The Glisson's capsule is scored with cautery and a Kelly clamp used to fracture the liver substance. A combination of titanium hemoclips and the Endo-GIA vascular stapler is used to transect the liver substance. The authors employ a saline-linked radiofrequency ablation device called Tissue-Link (TissueLink Medical, Diver, NH, USA) and the argon beam coagulator to achieve hemostasis. Routine drainage of the abdominal cavity is not employed.[135]

CONCLUSION

The understanding of hepatic tumors in newborns and infants has evolved rapidly in the treatment of both benign and malignant disorders. Newborns and infants with these disorders present with a unique set of problems without parallel in other age groups. It is hoped that the increasing international intergroup collaboration will produce continued success and help develop novel therapeutic approaches in managing these rare disorders.

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87

Congenital mesoblastic nephroma and Wilms' tumor

ROBERT CARACHI

INTRODUCTION

Congenital mesoblastic nephroma (CMN) first described by Kastner in 1921,[1] is the most common renal tumor in the neonate, although rare cases present in later childhood. It is also known as a fetal renal hamartoma, mesenchymal hamartoma of infancy, or lipomyomatous hamartoma. It has an incidence of 2.8% of all renal tumors of childhood, with a mean age of presentation of 3.4 months in contrast to an average age of three years in Wilms' tumors.[2] It has been documented as being 22.8% of all primary tumors in children one year old or less.[3] A neoplasm in the kidney of a child less than three months old is usually a CMN. The majority of renal neoplasms originating in the fetus and found during the first weeks of life, differ in structure and in biological behavior from a nephroblastoma. In contrast to cystic lesions of the kidney, solid renal neoplasms are rare in the newborn and account for only 8% of neonatal tumors. In the Children's Cancer Group (CCG) Neonatal Study, there were 25 neonatal renal neoplasms, of which 17 were CMN and the rest were Wilms' tumors.[4] A review of neonatal Wilms' tumors in the national Wilms' tumor register identified 15 cases out of 6832 patients with an incidence of 0.16% demonstrating how rare malignant renal neoplasms are in neonates. Although prenatal ultrasound is capable of detecting renal neoplasms *in utero*, there are no specific sonographic characteristics that can differentiate a CMN from a Wilms' tumor. Both tumors present as a palpable abdominal mass in the neonate. Males outnumber females by 2 to 1 with CMN and both sexes are equally affected by Wilms' tumors.

PATHOLOGY AND CYTOGENETICS

In 1967, Bolande and colleagues[5] recognized CMN as a unique lesion that could be distinguished clinically and pathologically from true congenital Wilms' tumor by its benign clinical behavior, a preponderance of mesenchymal derivatives and lack of the malignant epithelial components typical of Wilms' tumor. A definite infiltrative tendency distinguishes CMN from hamartomas with more limited growth potential. CMN is usually solid, unilateral, and can attain a very large size like a uterine fibroid.

Histological differentiation is that of a spindle cell neoplasm with interlacing bundles of fibroblasts and myofibroblasts. Tumor types have irregular interdigitating margins in the perirenal fat and wide margins of excision are desirable for complete removal. Incomplete removal results in tumor recurrence which happens within a year of resection in most instances. No chemotherapy or radiotherapy is indicated here and a wide surgical resection is the treatment of choice.[6]

Atypical and more aggressive mesoblastic nephromas tend to be soft, fleshy tumors with areas of gross hemorrhage and necrosis and are more cellular without recognizable normal glomeruli or tubules.

Another variant is a congenital cystic mesoblastic nephroma (cellular variant) which can present as a unilocular hemorrhagic cyst. This can be detected antenatally and misdiagnosed as a hemorrhage into the kidney. The lining of the wall of this cyst shows a typical cellular rim comprising mitotically active small round and spindle-shaped cells giving the diagnosis of CMN (Murthi, Carachi, Howatson, personal communication). The treatment for this tumor is surgical.

Gaillard and colleagues[7] recently reported pathological and molecular characteristics of CMN in 35 cases. Based on cellular criteria, 14 were classified as classical, four as partly cellular, and 17 as cellular CMN. The mean ages were 24, 11, and 70 days, respectively. There were 13 intrarenal tumors (stage I), but nine classical, three partly cellular, and five cellular CMNs extended to the perirenal fat (stage II), and five cellular tumors ruptured (stage III). In order to assess cellular proliferative activity, silver staining of nucleolar organizer region (Ag-NOR) proteins was performed on 19 CMNs. The number of Ag-NOR dots per cell was significantly lower in

classical and partly cellular CMN than in cellular CMN, whatever the stage. Within the cellular CMNs, the mean number of Ag-NOR dots was statistically higher in the single case that recurred with fatal outcome. The number of Ag-NOR dots, DNA content measurements, the histological subclassification, and the presence or absence of tumor at the surgical margins, may be useful features in selecting those patients who will benefit from further treatment after nephrectomy.

A characteristic chromosomal translocation, t(12;15)-(p13;q25) has been described which results in fusion of the ETV6 (TEL) gene from 12p13 with the NRTK3 neurotrophin-3 receptor gene (TRKC) from 15q25. This results in a chimeric RNA which is characteristic of both infantile fibrosarcoma and the cellular variant of congenital mesoblastic nephroma. This suggests a close relation between these two conditions.[8]

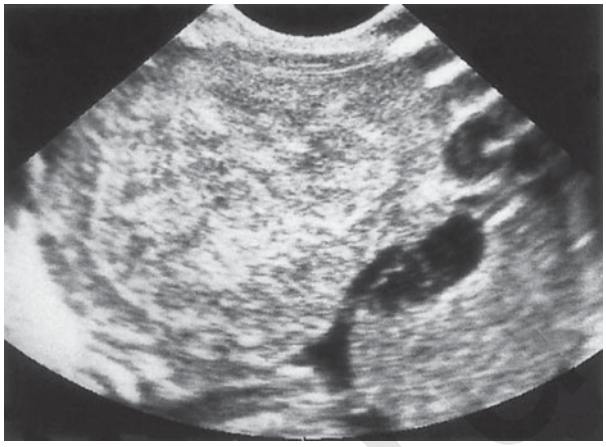
Human epidermal growth factor receptors (HER) play a critical role in the branching morphogenesis of renal tubules. In addition, HER2 expression in Wilms' tumor had been assessed and its role in tumorigenesis has been established. Amplification and overexpression increases the metastatic potential of a tumor and promotes chemoresistance.[9]

It has been reported that abnormal renin production and hypertension are common features of CMN. Several investigators have reported distinctive patterns of immunoreactive renin staining, suggesting that mesoblastic nephromas are a source of increased renin production producing hypertension.[10,11] The most intense staining for renin was observed within areas of recognizable cortex trapped within the tumor. Renin was localized in cells in the walls of vessels running up to the glomeruli.

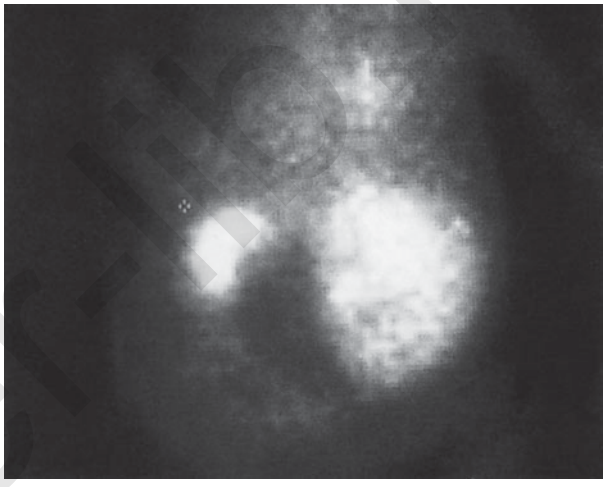
CLINICAL FEATURES

The newborn usually presents with a large, non-tender abdominal mass. Maternal polyhydramnios and prematurity are frequently seen, although the reason for this is unclear. Male to female ratio ranges from 1.8:1 to 3:1.[6,11] Hypertension has been recognized as a presenting feature, and there is an association between preoperative hypertension and cardiac arrest during surgery.[6] Some patients present with hematuria. In the congenital cystic mesoblastic nephroma variant, the patient may present with a hemorrhagic problem. Recently, mind maps have been introduced to explain in a didactic fashion the clinical features, investigations, differential diagnosis and management of CMN and Wilms' tumor.

Detailed antenatal ultrasound scans may pick up a solid tumor of the kidney. Plain films of the abdomen show a large, soft-tissue abdominal mass that is rarely calcified. Sonography demonstrates the solid nature and renal origin of the mass and most commonly shows a mixed echogenic intrarenal mass (Fig. 87.1a,b). CMN should easily be distinguished from more common renal masses in the newborn[12] – hydronephrosis or multicystic kidney – which are sonolucent. Magnetic resonance imaging (MRI) gives detailed imaging of the renal tumor and its surrounding structures.



(a)



(b)

Figure 87.1 (a) Sonography demonstrates a mixed echogenic mass. (b) ^{99m}Tc-DTPA renal scintigraphy shows function within the mass in the kidney.

TREATMENT

Nephrectomy of this benign tumor is curative without the need for supplementary radiation or adjuvant chemotherapy. Even when there has been intraoperative rupture, excisional surgery is curative, and local recurrence is rare. Distant metastasis has been reported, but is extremely uncommon[13] A review of 38 patients with the cellular variant of mesoblastic nephroma showed that seven children had recurrence and three died. According to the review, pathologically positive surgical margins were the only statistically significant predictor of recurrent disease. Frozen section may help in obtaining tumor-free margins during surgery. Recent studies on molecular biology may shed further light on tumor behavior and add criteria for further therapy after surgery.

PREOPERATIVE PREPARATION

Blood samples are obtained for a full blood count, group, and crossmatch. Tumor markers renin, active renin, and inactive renin should also be assayed because these tumors have been

documented as producing high levels of these hormones.[11] Erythropoietin levels should also be assayed. Careful monitoring and control of blood pressure is required to prevent dangerous perioperative fluctuations. A central venous cannula for i.v. infusion is inserted into the neck vein or subclavian vein, as well as an arterial cannula to monitor blood pressure.

OPERATIVE TECHNIQUE

Position

The patient is placed supine with a roll under the lumbar spine to create a lordosis.

Incision

An upper transverse muscle-cutting incision from the flank across the midline provides adequate exposure (Fig. 87.2a).

Laparotomy and exposure of the renal pedicle

The abdomen is entered, taking care not to cut into the tumor while incising the abdominal wall muscles. The small intestine is displaced towards the opposite side and covered with moist packs. The liver and the opposite kidney are inspected for the presence of any other disease. This is very rare in this condition. Free fluid is sampled and sent for cytology.

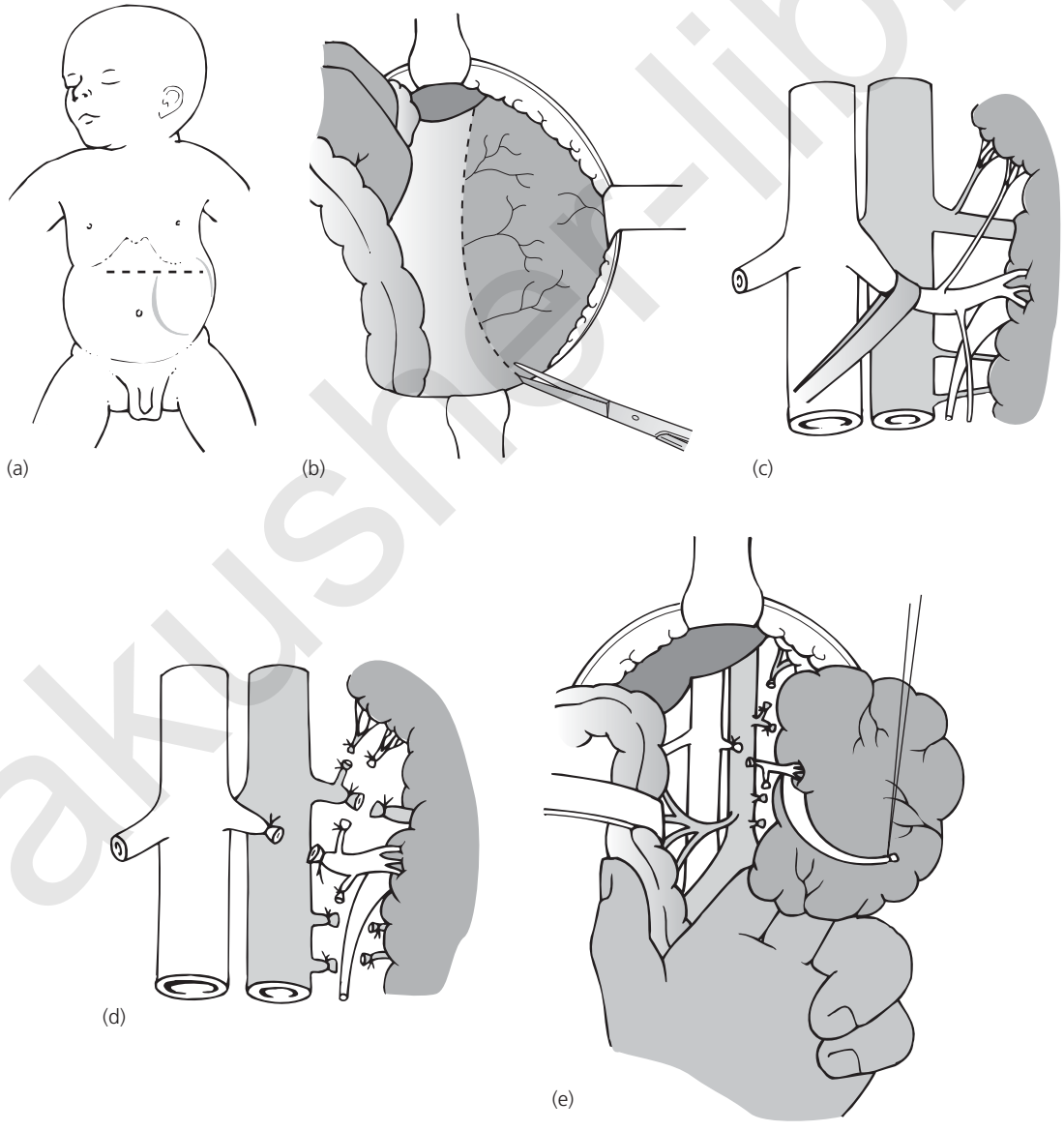


Figure 87.2 Resection of left mesoblastic nephroma: (a) incision; (b) colon retracted medially and posterior peritoneum incised; (c) ureter, gonadal vessels, and renal vessels identified; (d) ureter and gonadal vessels ligated and divided – this is followed by ligation and division of renal vein and artery; (e) tumor is removed from the posterior abdominal wall using sharp and blunt dissection.

The colon overlying the tumor is retracted medially and the posterior peritoneum lateral to the colon is incised and reflected forward to the midline (Fig. 87.2b). Tumor handling should be minimized in hypertensive patients to prevent excessive release of renin. The inferior vena cava and renal veins are both palpated for the presence of tumor. The ureter is identified (Fig. 87.2c) and a tape is passed around it. It is traced as far down as possible into the pelvis, ligated with 3-0 chromic catgut and divided. Next, the gonadal vessels are ligated and divided. Before mobilization of the tumor, abdominal packs are used to isolate the operative site from the rest of the abdominal cavity. This is to prevent any dissemination of tumor if there is spillage during the time of surgery. The renal vein is doubly ligated and divided (Fig. 87.2d). The renal artery is exposed and transfixed with non-absorbable sutures. The para-aortic lymph glands, together with surrounding tissue, are dissected off the aorta and inferior vena cava and labeled carefully. The tumor is removed from the posterior abdominal wall using finger dissection (Fig. 87.2e). The excised specimen should contain kidney, Gerota's fascia, fat from the lumbar fossa and para-aortic lymph glands.

After removal of the tumor, hemostasis is obtained with diathermy coagulation or suture ligatures. No drain is usually required.

POSTOPERATIVE CARE

Postoperative recovery following resection of mesoblastic nephroma is rapid. Nephrectomy of this benign tumor is curative. If on histology the tumor is found to be Wilms', it should be treated in accordance with the degree of involvement as outlined in the National Wilms' Tumor Study Programs.

COMPLICATIONS

The main complication of CMN is rupture of the tumor during surgery. Howell and colleagues[6] reported intraoperative rupture in 20% of their cases. In practice, this is extremely rare despite intraoperative rupture, excellent subsequent relapse-free survival has been reported.

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Neonatal ovarian tumors

CHAD WIESENAUER AND MARY E FALLAT

INTRODUCTION

For decades, ultrasound examination, both pre- and postnatal, has made it possible for clinicians to recognize ovarian cysts and other masses. True neoplasms are rare, simple ovarian cysts are common, and large or complex cysts often demand surgical attention. A variety of approaches including aspiration (both pre- and postnatal), surgical removal, or observation have been proposed and are acceptable depending on the radiographic and clinical circumstances.

ETIOLOGY

Although not fully understood, it is widely believed that ovarian cysts derive from ovarian follicles. Mature follicles can be found in up to 60% of newborn ovaries. It is widely cited that fetal follicle-stimulating hormone (FSH), fetal luteinizing hormone (LH), estrogens (maternal, placental, and fetal), and placental human chorionic gonadotropin (HCG) all stimulate the ovarian follicle.[1–3] At birth, HCG and estrogen levels fall precipitously, leaving only the fetal pituitary gonadotropins LH and FSH to stimulate or maintain the ovarian follicle. The newborn hypothalamus and pituitary become sensitive to negative feedback by about four to six months of age, decreasing secretion of LH and FSH. By this time, most if not all stimulation of the ovarian follicle halts, and fetal cysts should involute. Simple ovarian cysts are known to resolve spontaneously in most cases by one to six months.[1,4–6]

An alternative theory has been recently proposed by Enriquez *et al.*,[7] in which abnormal development of the primitive gonad, and not just hormonal stimulation, is the root cause of fetal cyst formation. Cyst formation becomes a consequence of germinal epithelial secretion in a dysgenetic gonad.

Incidence

The normal newborn ovary will demonstrate several scattered anechoic cysts from 4 to 5 mm in diameter. More than 80% of newborn ovaries will have ovarian cysts <9 mm in diameter, whereas cysts >9 mm occur in from 20 to 34% of ovaries.[8] There is general consensus that newborn cysts, less than 2 cm in maximal diameter, are considered normal and unlikely to cause problems.

Torsion

Torsion is believed to occur when a relatively large, mobile mass twists on a long, thin pedicle. Many authors consider cysts of diameter greater than 4 or 5 cm at high risk for complications, most commonly torsion.[1,4–6,8–10] Other authors use a more conservative diameter of 2.0 cm to direct management.[11] Three series report that between 27 and 53% of antenatally diagnosed ovarian cysts (both simple and complex) were found to be torsed at operation.[1,11,12]

PATHOLOGY

Pathologic examination, possible only if surgical removal is performed, will often confirm the diagnosis of an ovarian cyst. The vast majority of cysts are of follicular origin. Torsed ovaries will have suffered a variable period of ischemia, so examination may not reveal any identifiable ovarian follicles or parenchyma. Tumors, as stated above, are rare in the newborn, but careful examination of the literature reveals examples. In what appears to be the most extensive review in the English language, of 257 antenatally diagnosed ovarian cysts, Brandt and co-workers reported three cystadenomas and two teratomas out of 170 surgically removed ovaries.[1] Three other authors have reported antenatally diagnosed tumors including two germ cell tumors, one teratoma, and one serous cystadenoma.[11,13,14] There exist two reports of ovarian carcinomas found at fetal autopsy. These were bilateral ovarian cancer in a 30-week fetus, and a granulosa cell carcinoma in a stillborn fetus.[15,16] Juvenile granulosa cell tumor, a tumor that may be considered malignant due to its aggressive potential, is reported in children less than seven

months of age in three reports.[17–19] Finally, there exist reports of one endodermal sinus tumor and one teratoma in children under one year of age.[20]

HISTORY AND PHYSICAL EXAMINATION

Most newborns with ovarian cysts will have a normal physical examination at birth. Since the ovary is an intra-abdominal organ in an infant, large cysts will displace the intestinal tract and present as palpable, but generally non-tender, masses. These infants rarely have signs of intestinal obstruction if the mass reaches substantial size.

PRESENTATION

Most neonatal ovarian cysts are first diagnosed at prenatal ultrasound. Their appearance is almost exclusively in the third trimester, at around 28 weeks' gestational age.

DIAGNOSIS

Ultrasound is the modality of choice for both the child and mother, being quick, relatively inexpensive, and safe, compared to other imaging modalities. Magnetic resonance imaging (MRI) has been proposed as more reliable by some authors,[21] but discounted by others.[22] The basic criteria for ultrasound diagnosis are: (1) cystic structure in the lower or lateral abdomen and (2) normal urinary and gastrointestinal tracts.[22] Differential diagnoses include urachal cyst, enteric duplication, hydrometrocolpos, choledochal cyst, renal cyst, hydronephrosis, distended bladder, perforated meconium cyst, duodenal atresia, anterior myelomeningocele, mesenteric cyst, lymphangioma, and omental cyst; with the latter three entities being the most easily confused with ovarian cyst.[1,6,23,24] Nussbaum *et al.*[25] proposed useful criteria for simple and complex ovarian cysts in 1988. Simple cysts are completely anechoic with an imperceptible cyst wall (Fig. 88.1), whereas complex cysts demonstrate a fluid/debris level, have a retracting clot, are septated, or are solid (Fig. 88.2). Of all 'complex' cysts, Monnery-Noché *et al.*[11] found 89% to be torsed, with the remainder being hemorrhagic.

Evolution

Prenatal and postpartum sonographic observation has allowed investigators to determine how ovarian cysts are likely to behave. Anywhere from 44 to 70% of antenatally diagnosed simple cysts will convert to complex, presumably by torsion, by the first postpartum ultrasound.[6,11,12,26,27] These five studies considered simple cysts of all diameters. Some authors have correlated antenatal cyst size with risk of ovarian loss,[1,4,9] but more recent investigations have demonstrated no correlation between size and risk of ovarian loss.[11,12,26,28] The latter studies call into question the usefulness of cyst diameter in surgical decision-making.

Simple cysts (all diameters) are known to regress spontaneously postpartum in at least 82% of cases.[6,27] Sakala *et al.*[29] cite 50% resolution by one month, 75% by two months, and 90% resolution by three months. The remainder of these simple cysts are generally aspirated or operated upon for failure to regress in size after a period of observation.

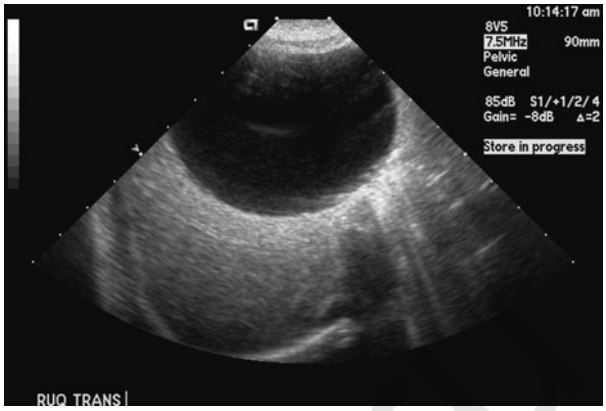

Figure 88.1 Transabdominal ultrasound of a simple ovarian cyst, 5.5 × 6 cm. Note the lack of internal echoes and no perceptible cyst wall.

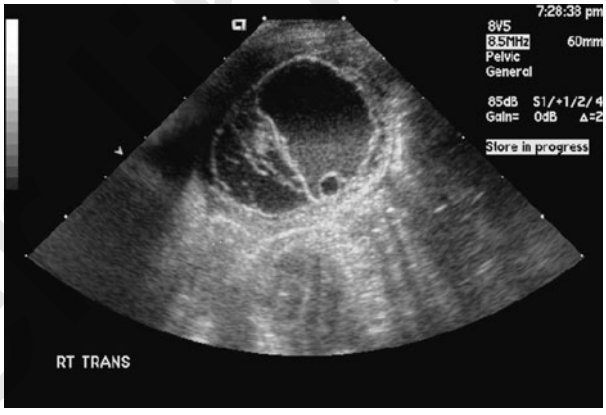

Figure 88.2 Transabdominal ultrasound of a complex ovarian cyst, 2.5 × 3.5 cm. Features include a relatively thick cyst wall, fluid/debris level, and multiple septations. This ovary was found to be torsed and non-viable.

Concerning complex cysts, three studies have observed them postpartum, with an involution rate of between 58 and 77% by one year.[6,26,27] Most ovaries that did not involute as witnessed by ultrasound were operatively treated with removal, if torsed and necrotic. Viable, follicular ovaries were detected by ultrasound in 16 to 25% of formerly complex cysts that were observed. In those cases where the complex cyst involuted and a viable ovary was not subsequently seen, it may be speculated that the gonad was torsed and necrotic, and eventually resorbed spontaneously. More reports are needed to know if observation in these cases is a legitimate therapeutic option.

MANAGEMENT

The treatment of newborn ovarian cysts remains controversial. Considering only simple cysts, the majority of authors still

selectively operate or aspirate (including *in utero* aspiration) based on a maximal diameter of 4 or 5 cm.[1,6,8,10,30,31] although other authors support close ultrasound observation for larger simple cysts with good results.[12,23,27] As for complex cysts, a growing number of authors support ultrasound observation, with surgical treatment only if they fail to demonstrate continuous regression over time.[6,7,12,23,26,27] Other surgeons prefer to definitively exclude malignancy by removal of the complex ovarian cyst.[1,3,10,31]

In utero aspiration

To avoid the 44–70% risk of *in utero* torsion of the simple cyst discussed above, some investigators have attempted *in utero* decompression of simple cysts. Bagolan *et al.*[31] appear to have published the largest series of 14 patients without complication. After two of these ovaries torsed despite aspiration, their ovarian preservation rate was 86% – clearly better than historical controls of waiting until birth (44–70% torsion). They, along with others, recommend *in utero* decompression for anechoic cysts $\geq$4 cm, cysts that are rapidly enlarging, or cysts that wander in the abdomen.[30] Of note, Bagolan *et al.*[31] did report two errant prenatal diagnoses among their *in utero* aspirations. These cases were two hydronephroses, and both fetuses suffered no untoward effects from these aspirations. This therapy deserves further study.

Postnatal aspiration

Proponents of postnatal aspiration point to maximal preservation of ovarian tissue coupled with cyst decompression to potentially prevent torsion. Also, many authors mention that the majority of operatively managed ovarian cysts involve oophorectomy, not cystectomy or fenestration, thereby removing any chance of viable ovarian tissue on the affected side. Opponents point out lack of a definitive diagnosis, i.e. risk of cancer. Kessler *et al.*[8] reported 17 aspirated ovarian cysts, both simple and complex (not widely supported), with a 67% ovarian preservation rate. No complications were reported, although three cysts recurred and responded to repeat aspiration. Other investigators have had similar success,[10] yet Puligandla *et al.*[32] report a case whereby an enteric cyst was mistaken for ovarian pathology, and aspiration led to a devastating complication.

Operative removal

The majority of large simple cysts and complex cysts are removed via laparotomy or laparoscopy. A large cyst is defined as greater than either 4 or 5 cm in maximal diameter, although at least one group operatively removed simple cysts greater than 2 cm in diameter.[11] Although the goal is always ovarian tissue preservation, more often than not the entire ovary is removed for lack of identifiable ovarian parenchyma.[2,7,8,12,13,23,29] Fenestration of the cyst wall is an option if the cyst wall cannot safely be entirely separated from ovarian tissue. Of course, operative removal is the only method to exclude neoplasia, and also the only method that results in no chance of viable ovarian tissue on the affected side. Proponents of operative removal also cite risk of adhesive bowel obstruction as potential complications of the unremoved ovarian cysts.[2,3,11] Surgeons have come up with many creative alternatives to suprapubic laparotomy (Fig. 88.3), including exteriorization-aspiration, transumbilical removal (Fig. 88.4), and modifications using the laparoscopic approach.[33–37] An ovarian-sparing cystectomy can be facilitated by injecting saline in the interface between the cyst and ovary, using a scalpel or electrocautery to begin the dissection, and then the cyst can often be peeled off the surface of the ovary using a moist cotton-tipped dissector or swab to facilitate the dissection (Fig. 88.5). Subsequent bleeding at the ovarian

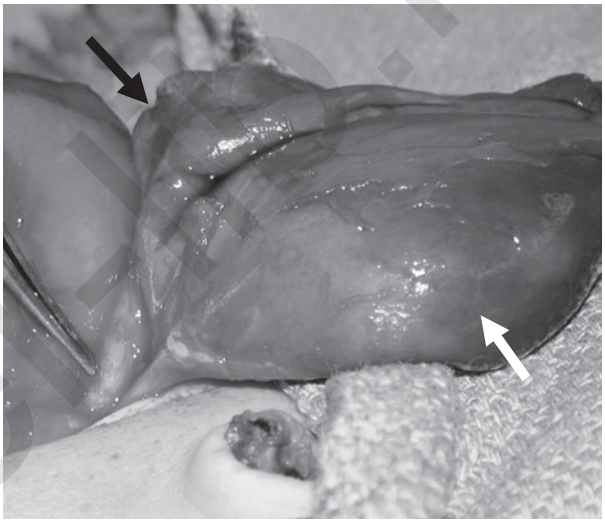

Figure 88.3 Torsed ovary with large attached cyst, exteriorized via a suprapubic transverse incision. White arrow points to cyst, black arrow to torsed and non-viable right ovary, forceps points to healthy uterus. Viable left ovary and tube are to left of uterus.

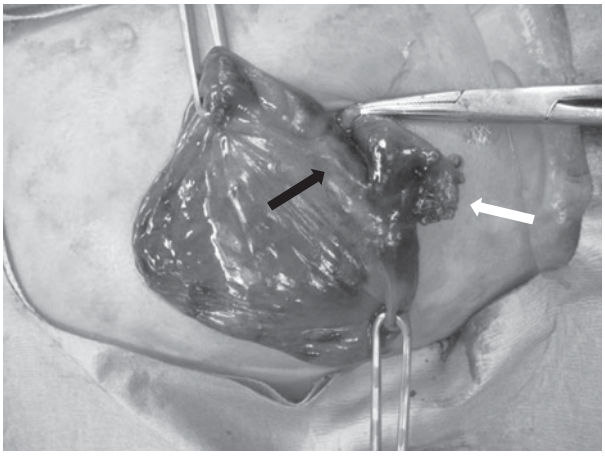

Figure 88.4 Simple ovarian cyst drained and exteriorized via umbilical incision. This is the cyst from Fig. 88.1. White arrow points to Fallopian tube, black arrow to thin rim of ovarian parenchyma.

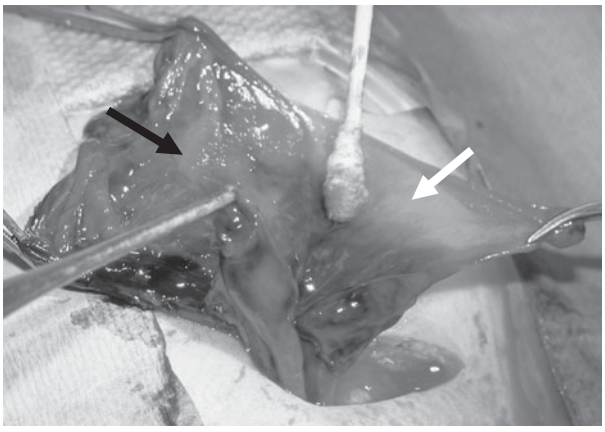

Figure 88.5 Dissection of ovarian cyst from viable ovarian tissue using a cotton-tipped applicator. White arrow points to cyst wall, black arrow to ovarian parenchyma, and forceps hold Fallopian tube.

surface can be controlled using electrocautery. It is not necessary to reapproximate ovarian tissue, but an absorbable small gauge absorbable suture, such as polyglactin 910 (Vicryl; Ethicon Inc.) should be used if this is felt necessary.

COMPLICATIONS

Complications of cyst observation include a missed malignancy, although this is very rare. As stated above, some authors believe that torsed, necrotic ovaries have the potential to cause adhesive bowel obstruction. Complications of cyst aspiration include misdiagnosis and any consequences of unintentional needle injury of another organ. Complications of operative removal include injury to viable ovarian tissue that might have been functional without intervention, and also the risk of adhesive bowel obstruction inherent to any transabdominal operation.

LONG-TERM RESULTS

No long-term studies to date have examined future fertility in the population of newborns and infants who had ovarian cysts or tumors subjected to a variety of therapeutic options.

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PART IX

SPINA BIFIDA AND HYDROCEPHALUS

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89

Spina bifida and encephalocele

MICHAEL D JENKINSON, MAGGIE K LEE, AND CONOR L MALLUCCI

INTRODUCTION

Neural tube defects (NTD) encompass a variety of congenital anomalies ranging from anencephaly to spina bifida occulta and arise due to defects in the morphogenesis of the neural tube. While spina bifida remains the most common congenital central nervous defect encountered in neurosurgical practice, the overall incidence of NTDs is in decline.[1–4] Multiple factors account for this change, including increased antenatal diagnosis, declining birth rates, changing social attitudes, and improved standard of living and diet. Nevertheless, a diagnosis of spina bifida can have devastating consequences and the 'correct' management of these patients is a continued source of medical, ethical, and legal controversy. A multidisciplinary team is required including neurosurgeons, pediatricians, neurologists, urologists, orthopedic surgeons, physiotherapists, social workers, psychologists, and nursing staff. At the center are the patient and family with the common goal being social integration and a meaningful life.

HISTORY

Caspar Baulinin is credited with the first accurate description of spina bifida in the early seventeenth century.[5] The term 'spina dorsi bifida' was coined by Nicholas Talpius (Tulp) in 1641[6,7] and Virchow introduced the term 'spina bifida occulta' in 1875.[8] The association of hydrocephalus and spina bifida was recognized by Morgagni in 1761, and he also described anencephaly and spina bifida as expressions of the same pathological process and attributed bladder, rectal, and limb abnormalities to the neuronal damage in the defective spinal cord.[5]

Aspiration of the lesion was the time-honored method of management, but had catastrophic consequences. Forestus ligated the sac,[9] and sac excision was attempted by Tulp with fatal results.[7] The Clinical Society of London[9] recommended the use of a local sclerosing technique as the preferred method of treatment, which was initially advocated by Morton.[10] Excision of the sac was again popularized by Bayer[11] and Frazier[12] in the early twentieth century, however, the mortality rate remained high. With the advent of antibiotics and the introduction of cerebrospinal fluid (CSF) shunts in the 1950s, the operative results encouraged more surgeons to introduce comprehensive, aggressive management. In 1963, Sharrard *et al.*[13] proposed emergency operative closure of the back lesion to decrease mortality and improve muscle function. This provided new hope for these patients. However, in the latter part of the decade, it became evident that the mortality remained high and those who survived had major handicaps. Lorber,[14] who was one of the supporters of the aggressive policy of the Sheffield group, reviewed 524 cases of myelomeningocele treated actively and concluded that there were four main criteria associated with a poor prognosis: gross hydrocephalus, severe paraplegia, kyphosis, associated gross congenital anomalies or major birth injury. He advocated that patients with one or a combination of these criteria should be managed conservatively as very few patients survived, and those who did would suffer severe mental and physical handicap. In recent years, the reliability and 'predictive value' of these four criteria have been questioned. It has been suggested that the management of these infants should be individualized and changed whenever necessary in the best interest of the patient and family.[15–17]

INCIDENCE AND EPIDEMIOLOGY

There are geographic variations in the incidence of spina bifida and neural tube defects worldwide, for example, the incidence of spina bifida cystica varies between 0.3 per 1000 live births in Finland, to 4.5 per 1000 live births in Ireland.[18] There is greater reported variation in the incidence of spina bifida occulta which ranges between 1 and 50% depending upon the age group.[19] Caucasians are at higher risk than black people of developing spina bifida[20] and lower socioeconomic groups also seem to have a higher incidence of the defect.[21]

EMBRYOLOGY

Neural tube defects are the results of an abnormality in the process of neurulation. The primitive streak and Hensen's nodes are present in the embryo at 2 weeks' gestation. The notochord starts extending rostrally from Hensen's node and this induces the process of neural tube formation. Thickening of the ectoderm cephalic to Hensen's node occurs and forms the neural plate. Folding and later fusion of these folds form the neural tube. This process continues caudally up to the somites, which have started to appear from the 3rd week. Other ectodermal tissue closes over this and buries the tube. The unfused rostral and caudal neural folds are called the anterior and posterior neuropores. These are closed at about 25 and 30 days, respectively. The process of neurulation is then completed. At this stage, there are about 21–29 somites. Four somites are incorporated into the occipital bone and 20 for the cervical and thoracic vertebrae. Caudal to this, the remainder of the tube forms the caudal cell mass. During the next 4–5 weeks, canalization of this cell mass occurs; this is followed by the regression of the most caudal part of the neural tube, which forms the filum terminale. The notochord separates from the neural tube dorsally and the gut ventrally forming sub- and epichordal spaces.

PATHOGENESIS

All developmental defects of the central nervous system are NTDs, while neurulation defects in a strict sense make up a subgroup of NTDs. These defects can involve:

- Brain
  - Anencephaly: a result of persistence of the anterior neuropore. This allows some part of the developing brain to remain in contact with the amniotic cavity. The types are holocrine, if the defect extends to involve foramen magnum, and mesoacrania, if the foramen is not involved.[22]
  - Encephalocele: the result of defective cephalic neurulation.
- Spinal cord
  - Meningocele: a post-neurulation defect.
  - Myelomeningocele: defective caudal neurulation results in myelomeningocele, which can occur anywhere from cervical to lumbar sites. There are various theories put forward to explain the precise mechanism of the defective neurulation. These are either due to failure of neural folds to fuse or a reopening of the normally fused neural tube. Defective neuroepithelium itself may be responsible for the failure of neural folds to fuse[23] or the defect may lie in the mesoderm, which deters the closure of neural folds. The normally fused neural tube may reopen because of increased intraluminal pressure[24] or a primary defect in the neuroepithelium.
  - Associated Arnold Chiari malformation may be secondary to failure of ascent of the cord within the spinal column because of tethering or as a result of descent secondary to increased pressure of hydrocephalus.
- Brain and spinal cord: craniorachischisis is the defect involving brain and spinal cord.
- Other defects occur secondary to various post-neurulation abnormalities involving the neural tube or mesoderm, or because of persistence of totipotent cells. These lesions are diastematomyelia, complete anterior and posterior spina bifida, butterfly vertebrae, lipoma, hemangioma, dermoid cyst, and sacrococcygeal teratoma. A partial duplication and separation of the notochord can result in herniation of the endoderm of the yolk sac, called 'split notochord syndrome'. If the hernia ruptures, it may result in ectopic bowel, sinus, or fistula.[25]

TERMINOLOGY AND CLASSIFICATION

The types of NTDs vary from anencephaly to spina bifida occulta. These lesions can be classified as shown in Table 89.1. Myelomeningocele is one of the most common congenital malformations.

Spina bifida occulta

The term 'spina bifida occulta' refers to the form of spinal dysraphism not accompanied by the extrusions of the contents of the vertebral column. Spina bifida occulta,

Table 89.1 Classification of neural tube defects.

Site	Lesion	Pathology
Craniospinal	Craniorachischisis	Involves brain and spine
Cranial	Anencephaly	Brain and skull poorly developed
	Exencephaly	Exposed brain without skin or bone cover
	Encephalocele	Brain herniation through congenital opening of skull and covered by meninges and skin
Spinal	Spina bifida cystica	
	Myelomeningocele	Open cord defect at any point from cervical to sacral
	Meningocele	Skin covered sac formed of meninges – defect in posterior arch
	Spina bifida occulta	Absent spinous process and varying amounts of lamina (may be associated with lipomyelomeningocele, tethered cord, dermal sinus tract, diastematomyelia, hemangioma)

without any external evidence, is rarely diagnosed in the newborn. Occasionally, it may cause neurological deficit because of a tethering of the cord, or some patients may have external evidence of spina bifida occulta. These lesions include a small dimple, sinus, tuft of hair (Fig. 89.1), or hamartomatous lesions, such as hemangioma, lipoma, and nevi. Neural involvement may manifest as urinary problems, e.g. recurrent urinary infection or enuresis, motor deficit with pedal deformity, pelvic tilt and muscle weakness, and sensory involvement in the form of trophic ulceration. All these patients warrant careful examination and investigation. Spinal x-ray will show evidence of spina bifida and other spinal abnormalities. Ultrasonography can be useful in the newborn period to diagnose diastematomyelia.[26] The common clinically relevant lesions are lipomyelomeningocele, tethered cord, dermal sinus tract, and diastematomyelia. All of these lesions need referral to a neurosurgical specialist and therefore when these lesions are noted, a craniospinal magnetic resonance image (MRI) is indicated. Many of these lesions require follow up and surgery at some point in the future. The increased incidence and treatment of these lesions over the last 10–20 years probably reflects increased diagnosis due to the more widespread availability of MRI.

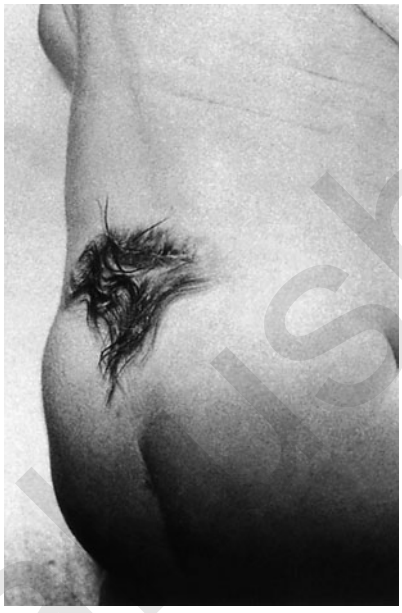

Figure 89.1 Spina bifida occulta. A large tuft of hair over the lumbosacral region in this baby was associated with spina bifida occulta and a tethered cord.

Spina bifida cystica: meningocele

A meningocele is an epithelial lined sac filled with CSF, which communicates with the spinal subarachnoid space. Meningocele, which comprises about 5% of all spina bifida cystica cases, is usually not associated with neurological deficit and hydrocephalus, and is most frequently observed in the lumbar region.

Spina bifida cystica: myelomeningocele

Myelomeningocele is the most common form of NTD (Fig. 89.2). A neural plaque is centrally placed, around which there is a cystic lesion with attenuated meninges and skin (Fig. 89.3). Although the pathological changes are obvious at the site of the lesion, additional changes involve the whole of the nervous system and other systems, especially genitourinary and skeletal.

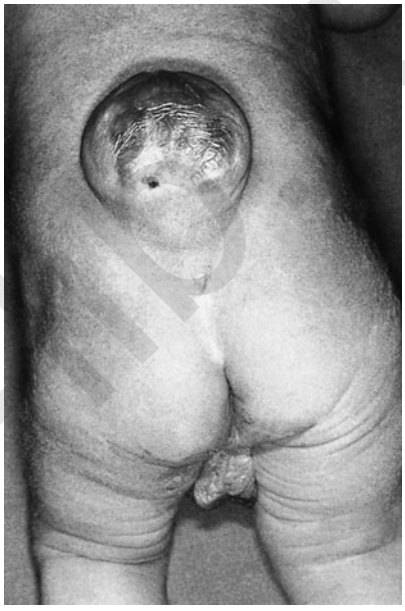

Figure 89.2 Dorsolumbar myelomeningocele. This infant had normal movement in both lower limbs.

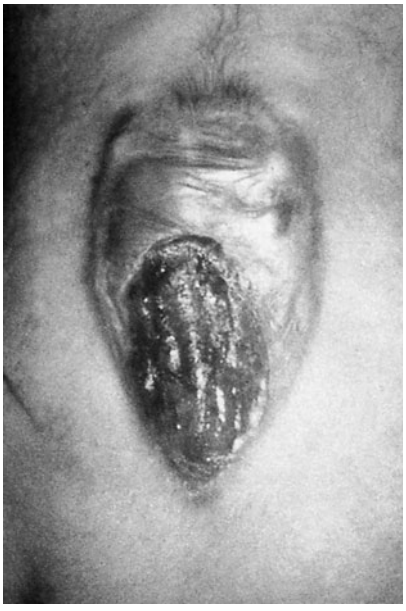

Figure 89.3 Myelomeningocele. Lesion showing neural plaque in the center covered by a thin membrane.

ETIOLOGY

The precise etiology of NTDs is not known, however genetic and environmental factors have been implicated.

Genetics

The exact mode of inheritance is not known, although ethnic variation, gender (females are more commonly affected than males), increased incidence with parental consanguinity and familial tendency, suggest a multifactorial hereditary predisposition. An individual's risk of having other children with spina bifida increases to one in 20–25 if there is one child with spina bifida in the family.[27,28] This risk is one in eight to ten if there are two children with NTDs.[28] The risk of having an affected child is of lesser magnitude (one in 200) if one of the parents had spina bifida than if a sibling had spina bifida.[27]

Dietary factors

Substantial data have been accumulated to suggest that myelomeningocele and other neural defects may be reduced by improved maternal nutritional status. Mothers of spina bifida patients were found to have an increased incidence of folate metabolism abnormalities[29] and it has since been suggested that folic acid might be involved. Several studies have reported a beneficial role of folic acid and other vitamins.[30–33] The Medical Research Council conducted a randomized double-blind prevention trial with factorial design at 33 centers in seven countries to determine whether supplementation with folic acid or a mixture of seven other vitamins (A, D, B_1, B_2, B_6, C, and nicotinamide) around the time of conception could prevent NTDs.[34] The women at risk were randomly allocated to various groups including a control group to avoid bias. This study found a significant reduction in the number of children born with NTDs to high-risk mothers who had taken folic acid in the periconceptional period. Periconceptional use of folic acid has been recommended to all women with or without risk. A concern that large doses of folic acid may delay the diagnosis of pernicious anemia has led to the fortification recommendations being limited to a level that may add, on average, only about 0.1 mg folic acid/day. However, others feel that a daily dose of 0.4 mg/day should be continued.[35] Indeed, recent studies published from Canada, the United States, and Australia have shown a decline in neural tube defects, especially in high-risk groups not only with folic supplementation, but also with food fortification.[3,36,37]

Teratogens

Many agents have been blamed as possible teratogens responsible for the occurrence of NTDs. Exposure to the antiepileptic drugs valproate[38,39] and carbamazepine[40] *in utero* carries a 1.2% risk of fetal NTDs, which have been reported to be more severe open defects with a high incidence of hydrocephalus.[41] Certain viruses[42] and hyperthermia have also been hypothesized to cause NTDs, and exposure to heat in the form of a hot tub, sauna, or fever in the first trimester of pregnancy has also been associated with an increased risk of NTDs.[43–45]

PRENATAL DIAGNOSIS

Prenatal diagnosis of myelomeningocele allows both improved obstetric care and, conversely, termination of an affected fetus if desired.[46]

Alpha-fetoprotein in maternal serum

Alpha-fetoprotein (AFP) can be detected in maternal serum in open NTDs. It is an effective method for mass screening to identify pregnancies requiring further evaluation. Elevated levels after 16 weeks' pregnancy are suspicious; the test is repeated a week later to confirm the presence or absence of NTDs. The sensitivity of this test is about 97% for anencephaly and 72% for spina bifida.[47] This second test requires further confirmation by amniocentesis and prenatal ultrasonography after appropriate counseling.

Ultrasonography

Prenatal ultrasonography may be used as a primary screening procedure. It is a safe and effective method of antenatal screening if the ultrasonographer is experienced,[48] and levels of up to 98% specificity and 94% sensitivity have been reported.[49] Within Europe, there are formal national ultrasound screening policies for structural anomalies.[50] However, detection rates are influenced by gestational age and type of NTD. Spina bifida has a higher detection rate of 92–95% in the second trimester compared to a lower rate of 44% in the first trimester.[51] Three-dimensional sonography has an advantage over conventional two-dimensional ultrasound in predicting the level of lesion and this may offer a predictive morbidity.[51] Prenatal MRI screening is not currently readily available due to limited resources and there is no evidence showing superiority over ultrasound.

Amniocentesis

While many now question the use of amniocentesis in the era of modern high quality ultrasonography, there remains a role in some cases for amniotic fluid biochemical markers for assessment of risk of neural tube defect and other anomalies.[52] Using ultrasound guidance, amniotic fluid is obtained transabdominally at about 16 weeks' gestation. Alpha-fetoprotein and acetylcholinesterase (ACE) levels are estimated to confirm the presence of NTD. The risk of an open NTD is 60% if the levels are $\geq +3$ standard deviations (s.d.) above normal, and rises to 86% if the levels are $\geq +5$ s.d. The combined analysis of AFP and ACE in amniotic fluid increase the accuracy of diagnosis.[53] Specimens contaminated

with fetal or maternal blood can cause potential problems with interpretation of results and repeat amniocentesis may be required.

CLINICAL MANAGEMENT

This section relates primarily to the management of myelomeningocele as this is the most common NTD that presents to pediatric neurosurgical practice.

Prenatal assessment and antenatal counseling

Once a prenatal diagnosis of myelomeningocele has been made, an MRI of the fetus is obtained to determine the level and extent of defect. This allows the neurosurgeon to predict the likely degree of neurological deficit and facilitates prenatal counseling. Antenatal counseling is undertaken in specialist clinics and involves fetal medicine specialists, obstetricians, neurosurgeons, and radiologists. Parents need to be given realistic expectations regarding the prognosis for intellectual development, ambulation and survival, as well as information on hydrocephalus and neurogenic bowel and bladder. In the UK, a review process is underway with a view to setting up a national standard.

It still remains controversial whether Cesarean section should be carried out if the prenatal diagnosis of myelomeningocele has been made. Some authors[54] report that Cesarean section offers advantages to those born by this route as compared to those born by vaginal delivery, although other authors do not support this.[55] Luthy *et al.*[54] reported that delivery by Cesarean section for the fetus with uncomplicated myelomeningocele before onset of labor may result in better subsequent motor function than vaginal delivery or Cesarean section after labor has commenced. While there is no clear evidence, either way, Cesarean section facilitates a timed delivery to allow planning for surgical closure of the myelomeningocele.[56]

In utero surgery

There is a potential role for fetal surgery as neural tube defects are diagnosed prenatally. It is estimated that just over 400 fetal operations have been performed for myelomeningocele worldwide. The techniques using endoscopy, percutaneous fetoscopic patch coverage, and recently via hysterotomy have been described. However, there is little evidence as to the benefit of fetal surgery itself.[57] Currently, the Management of Myelomeningocele Study (MOMS) is being conducted in the United States. This study is a three-center randomized prospective trial comparing prenatal (18–25 weeks' gestation) and postnatal repair of myelomeningocele. Outcomes assessed include death, the need for ventricular decompressive shunting by one year of life, and neurological function at 30 months of age. The results are expected in December 2011.[58]

Postnatal assessment

LOCAL EXAMINATION

The sites affected are the lower thoracic, lumbar, sacral, cervical, and upper thoracic regions. In about 80% of infants with myelomeningocele, the defect includes the lumbar region because this is the last region of the neural tube to close. Occasionally, more than one lesion can be found[56] and there is often marked kyphosis or scoliosis present. Most myelomeningoceles contain an enlarged subarachnoid space ventrally, with the neural tissue displaced dorsally; in combination, this creates a herniated sac on the infant's back.

MOTOR FUNCTION

Motor function is assessed when the infant is at rest. Sharp stimulation above the level of the meningocele is administered with careful observation of voluntary movement below the affected level. Varying degrees of paralysis below the level of the lesion are common, except in rarer cervical and upper thoracic lesions, which are usually spared. The paralysis is usually flaccid, indicating a complete neural lesion. It must be borne in mind that there are some abnormal reflex activities in the lower extremities that have no bearing on volitional motor function.

SENSORY LOSS

Sensory loss is determined by pinprick test from distal to proximal, looking for an upper limb or facial response characteristic of those experiencing a pain sensation. The level at which anesthesia starts indicates the myotome level of the lesion and predicts the degree of disability.[57] Proper care is necessary to avoid trophic changes in anesthetic areas.

BLADDER AND BOWEL INVOLVEMENT

Over 90% of patients with myelomeningocele have a form of neurogenic bladder. The vast majority of these patients have disturbances of detrusor and sphincter balance resulting in a large, trabeculated bladder with urinary stasis. The anal external sphincter and puborectalis are often involved, resulting in patulous anus and sometimes rectal prolapse. It is difficult to ascertain bladder involvement in the newborn, but steps should be taken to ensure the bladder is kept empty. The upper urinary tract is usually normal, but some affected patients will experience changes in the upper urinary tract at birth.[59] These patients need careful urological and renal follow up.

HYDROCEPHALUS

Approximately 85–95% of patients with myelomeningocele have some degree of hydrocephalus. Assessment of the anterior fontanelle, and occipito-frontal circumference are important to determine the timing of any CSF diversion procedures. In those infants with clear evidence of hydrocephalus, early CSF diversion is indicated. Delayed placement

of a ventriculoperitoneal shunt is not associated with a lower infection rate compared to placement at the time of myelomeningocele closure.[60,61] Almost half of meningocele patients shunted at birth require shunt revision in the first year of life, mostly due to mechanical failure.[62] Endoscopic third ventriculosomy (ETV) has also been used in some patients, although the failure rate is high when performed as a primary procedure.[63,64] In patients presenting with shunt malfunction, secondary ETV has a better success rate and is therefore best reserved for later management.[63]

CHIARI II MALFORMATION

Chiari II malformation is invariably associated with spina bifida. MRI demonstrates caudal displacement of the posterior fossa contents, the elongated brainstem, small fourth ventricle, aqueduct stenosis, and tectal 'beaking'. Between 25 and 33% of patients are symptomatic from the Chiari II malformation and in the infant this manifests as brainstem dysfunction associated with sleep apnea and lower cranial nerve palsies. Stevenson *et al.*[65] reported that apnea, stridor (vocal cord paresis), and swallowing difficulties in infancy were associated with a 15% mortality rate in those affected. Whether early decompression improves symptoms remains controversial as surgery-related morbidity and mortality is high in infants (up to 15–20%).[66,67] From a practical point of view, symptomatic Chiari II are rare in infants as long as the hydrocephalus is correctly managed. Chiari II can become a secondary problem in adult life with delayed deterioration.

SKELETAL ABNORMALITIES

Club foot is the most commonly occurring abnormality with spina bifida. Other deformities include dislocation of the hip, genu recurvatum, and kyphoscoliosis. Orthopedic assessment and specialist physiotherapy services are required to manage these problems and minimize the extent of deformity.

Investigations

A full blood count is obtained and blood is crossmatched with maternal serum. A plain x-ray of the spine will reveal the extent of the bony lesion and associated kyphoscoliosis. An ultrasound scan of the head and renal tract are carried out as baseline investigations. MRI of the entire craniospinal axis will determine the presence of associated congenital abnormalities.

Parental discussion

Babies born with NTDs deserve an ethical, humane program of management based on accurate background data involving the parents fully in the decision-making process.[15,68] The management of each child should be individualized and reviewed regularly. It has been observed that in spite of early closure and application of all measures available, there is still a significant rate of disability and mortality.[69–71] Historically, Lorber[14] outlined some adverse criteria for conservative management of these patients, including gross paraplegia, hydrocephalus exceeding the 90th centile by 2 cm or more, severe kyphosis, thoracolumbar lesions, and other associated congenital anomalies (Fig. 89.4). These criteria are based on the belief that these patients will die early in infancy; this type of management will also give some time for discussion with the parents, enabling them to make rational decisions. These severely affected babies were often managed conservatively with demand feeding and sedation. In the past decade with improved antenatal diagnosis and prenatal counseling, many of the severe defects are avoided with early termination and therefore the trend in the Western world is for active management as outcomes are improving. Parents are usually aware of the expected prognosis for intellectual development, ambulation, and survival after antenatal counseling.

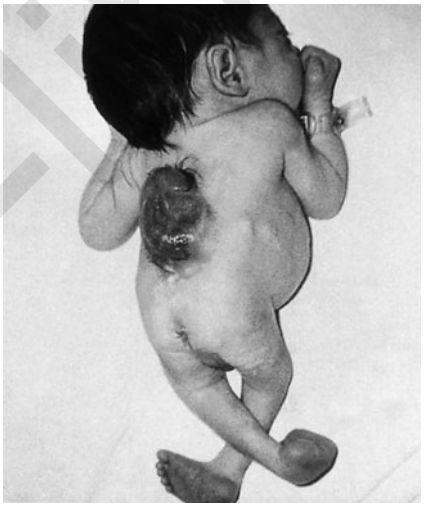

Figure 89.4 Large dorsolumbar myelomeningocele. This baby had bilateral lower limb paralysis, hydrocephalus, and bilateral dysplastic kidneys. The baby was managed conservatively.

Operative treatment and technique

All actively treated spina bifida patients should undergo closure of the defect within 24–48 hours of delivery. It was previously thought that early closure resulted in improved neurological outcome,[12] but this has not been supported by more recent studies.[72,73] Early defect closure prevents infection and further damage to exposed neural tissue – the aim being to preserve existing function. The principle of surgery is to reconstruct the spinal cord by five-layer closure of the pia and arachnoid, lumbar fascia, subcutaneous tissue, and skin. The vascular supply to the neuroplaque is maintained and unnecessary neural injury is avoided. The patient is placed in the prone position with a soft roll under the hips and shoulder, and with the head turned to the right through 90° (Fig. 89.5a). Swabs are taken from the lesion for microbial examination and culture. An antiseptic soak is placed over the anus. The lesion is covered with a warm swab

and the surrounding skin is cleaned and draped. The skin is incised at the junction of the arachnoid membrane and skin (Fig. 89.5b). The membrane between the edge of the skin defect and neural plaque is removed carefully to avoid inclusion cysts (Fig. 89.5c). The dura is freed laterally and then superiorly and inferiorly to normal intact dura (Fig. 89.5d). Dura is then sutured in the midline with continuous monofilament absorbable sutures (Fig. 89.5e). A suction drain may be placed extradurally, although this is not mandatory. The lumbodorsal fascia is incised laterally and dissected free from the posterior lilac crest. These are folded medially and sutured over the dorsal dural layer. The subcutaneous tissue is closed with absorbable interrupted sutures and then the skin is closed with interrupted nylon stitches (Fig. 89.5e). The infant is nursed in a prone position. Feeding is commenced once the bowel starts working. The wound is periodically inspected. The suction drain is removed 24–48 hours after operation.

Postoperative management and complications

Infection is common[74] and treatment is with appropriate antibiotics and local drainage. Wound dehiscence may occur and is usually secondary to undue tension on the skin edges or skin necrosis. If the involvement is deep to the lumbodorsal fascia, it may cause meningitis or ventriculitis. These are vigorously treated with local dressings, systemic antibiotics, and external ventricular drainage if hydrocephalus is present and CSF leak occurs. With meticulous closure of the dura, CSF fistula should be rare, however if it does occur, immediate repair is preferred rather than conservative treatment. Hydrocephalus may be present in about 15% of patients with myelomeningocele at birth, while it eventually develops in 85% of these patients. The exact reason for this is not clear; it may be aggravated by a shift in the brainstem after repair, which produces changes in the aqueduct or the Chiari malformation, leading to a further alteration in the

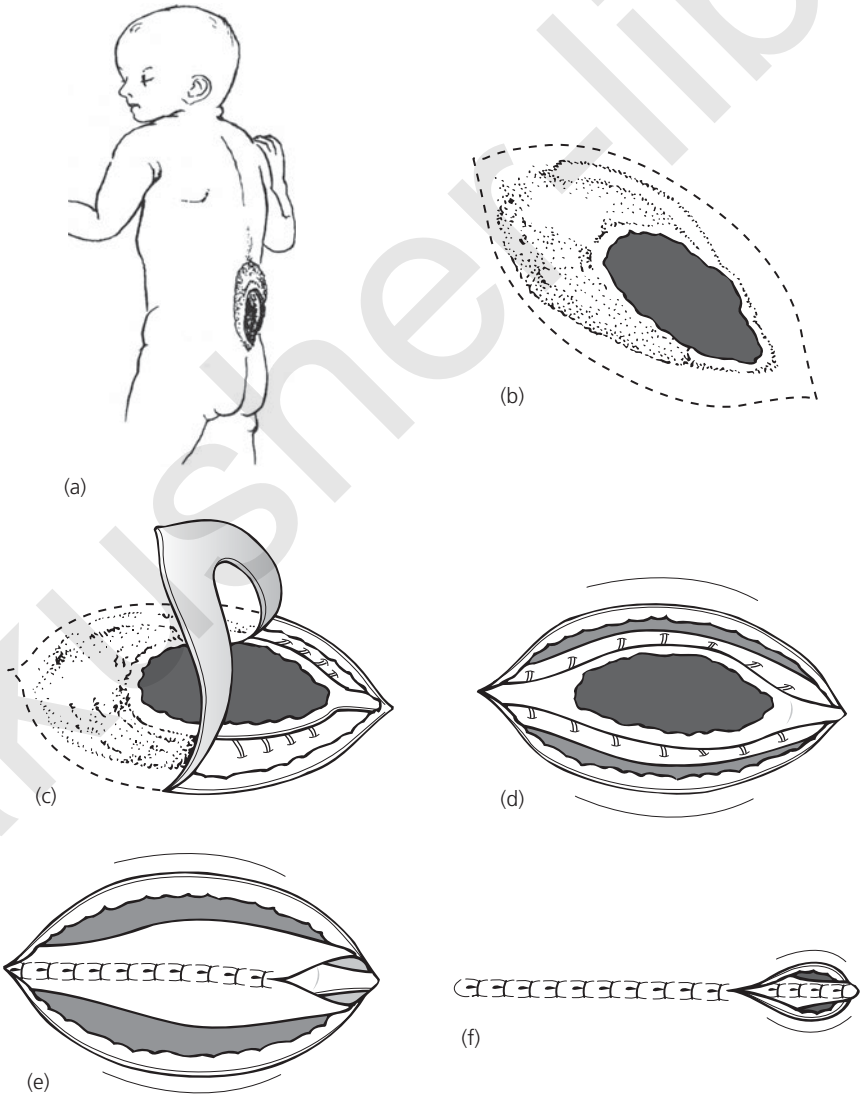

Figure 89.5 Closure of myelomeningocele. (a) Position of the patient on the operating table; (b) an elliptical incision at the junction of the arachnoid membrane and the skin; (c) membrane is excised and neural plaque freed; (d) the dura is dissected laterally from the underlying muscle; (e) dura is closed with an interrupted or continuous 5-0 monofilament absorbable sutures; (f) skin is closed with interrupted 5-0 nylon sutures.

CSF dynamics. From a practical point of view, after neurosurgical closure and shunt placement if indicated, referral and management is continued by pediatric orthopedic surgeons, urologists, and physiotherapists, thus encompassing a multidisciplinary team approach.

CLINICAL OUTCOME AND LONG-TERM MANAGEMENT

The results of myelomeningocele operations vary considerably because of differences in approach to management. Historically, in the units where a highly selective approach was taken, all 100% conservatively managed patients died, while only 14.3% of actively managed patients died.[75] In centers where patients were managed unselectively, a 41% mortality rate has been reported.[69] In the modern era, we await the results of cohort studies of patients treated from the 1990s onwards, as these will likely reflect reduced early mortality and less severe disability.

Medical problems

URINARY INCONTINENCE

Only 10% of myelomeningocele patients have a normal bladder, the remainder have a neurogenic bladder. The introduction of clean intermittent self-catheterization, pharmacological agents (e.g. anticholinergics), external devices, biofeedback, and innovative surgical procedures for the neurogenic bladder have enabled patients to develop social relationships while preserving renal function – up to 75% of these patients can be socially continent of urine.[76] Urodynamic studies in the newborn period are useful in identifying 'at-risk' children with high bladder pressure and detrusor instability.[77,78]

CHIARI II MALFORMATION AND HINDBRAIN DYSFUNCTION

Older children and young adults with Chiari II malformation may complain of symptoms related to foramen magnum impaction, such as headache, neck pain, and upper limb sensory disturbance. Brainstem dysfunction and lower cranial nerve palsies may also be present. Surgical treatment may be indicated in symptomatic patients, once adequate CSF diversion by either shunting or endoscopic third ventriculostomy has been established.[79] In our own series of 21 patients with myelomeningocele surviving into adulthood, eight patients underwent foramen magnum decompression for late deterioration, which stabilized symptom progression.[80]

HYDROCEPHALUS

Shunt placement has a significant impact for the future life of the child and parents. Shunt malfunction and complications (e.g. infection, hemorrhage) in myelomeningocele patients has a cognitive impact,[81] as well as being related to long-term survival.[70,82,83] If shunt malfunction occurs in later childhood, then ETV has a 89% success rate and should be considered before shunt revision.[79]

Lifestyle issues

Whether patients are managed conservatively or actively, the quality of life is an important factor in those who survive. In the long-term follow-up study by Oakshott and Hunt[69,70] of 117 patients treated unselectively, who were followed up for 16–20 years, it was found that 41% of patients had died before 16 years of age. Of the survivors, almost 31% were educationally subnormal and 48% were unable to live without help or supervision, while only about one-quarter of the survivors were capable of competitive employment.[69,70]

INTELLIGENCE

Patients who have associated hydrocephalus and episodes of shunt malfunction (blockage and infection) have lower intelligence than those who only have myelomeningocele.[81] Two recent studies have demonstrated significant cognitive impairment in myelomeningocele patients in the pediatric population that have been attributed to the structural defects associated with the Chiari II malformation, rather than repeated episodes of hydrocephalus.[84,85] Fiber tract anomalies in the limbic system were correlated with memory deficits.[84] In a small adult cohort undergoing in-depth neuropsychological testing at our own center, visuospatial construction and memory were impaired in all myelomeningocele patients.[80] Nevertheless, patients, although severely physically disabled, but who have relatively mild cognitive impairment, can be self-supporting and in competitive employment.

AMBULATION

Ambulatory potential and capacity are related to intelligence, orthopedic deformity, level of lesion, obesity, and motivation. Most of the patients with lesions below L5 are ambulators, those with lesions at L4 are functional ambulators, and those with lesions above L3 are wheelchair-bound.[86,87] The proportion of those patients who retain ambulant status into adulthood gradually decreases due to combinatorial factors including increasing weight, spinal and foot deformity, and respiratory compromise. Long-term follow-up studies have reported that only 30% of patients remain ambulated at 30 years of age.[88] A wheelchair is certainly a more energy efficient means of mobility.[89]

PSYCHOSOCIAL PROBLEMS

Educational mainstreaming, special counseling, improved understanding of the patient's potential and increased public awareness of spina bifida contribute to a reduction in stress through psychosocial problems originating within themselves, their families, and society.

ENCEPHALOCELE

Encephalocele constitutes 10–20% of all NTDs and has a prevalence of between 1 in 2000 and 1 in 5000 live births.[1,90] Encephaloceles have a higher incidence in Asia than in Western countries.

Pathology

With this anomaly, there is a defect in the cranial vault which is either oval or circular in shape, with variable degrees of abnormality, ranging from skin-covered meningocele to gross herniation of abnormal brain. These abnormalities are classified according to location as occipital, parietal, frontal, nasopharyngeal, nasal, frontoethmoid, and basal encephalocele. Occipital encephalocele is the most common type in the Western world, while the frontal lesion predominates in Asia.[56] The contents of the encephalocele vary according to its location and size. Brain tissue has been described in 25–80% of cases, usually in occipital encephalocele. In addition to the brain tissue in the sac, the rest of the brain, especially the optic pathway, is distorted and may be associated with microgyria, holoprosencephaly, heterotopia, agenesis, hydrocephalus, cerebellar aplasia, pyramidal tract aplasia (causing spasticity), and spinal cord distortion. Encephaloceles are also commonly associated with other congenital anomalies, including spina bifida, Klippel–Feil syndrome, facial cleft, and renal, cardiac, and pulmonary anomalies.

Clinical features

Most encephaloceles are obvious at birth and some may have been diagnosed prenatally. The size, content, and location are variable, occipital encephalocele being the most common (Fig. 89.6), and there may be an overlying hamartomatous lesion. Anterior lesions may cause airway obstruction. Occasionally, the diagnosis may be delayed and only becomes evident when a CSF leak occurs and the child presents with episodes of recurrent meningitis. A full neurological examination is necessary to determine any spasticity, focal motor weakness, or visual impairment. Physical examination will reveal any associated anomalies.

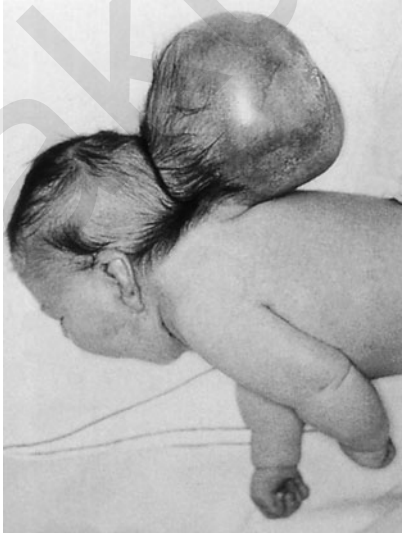

Figure 89.6 Occipital encephalocele.

Differential diagnosis

The anterior lesion can be difficult to diagnose and may need to be differentiated from the nasal polyp, glioma, dermoid cyst, teratoma, neurofibroma, meningioma, and hamartoma. A pulsatile mass that increases in size with crying is the classical sign of an encephalocele.

Investigations

Craniospinal MRI should be performed on all patients with encephalocele to determine the severity and extent of the abnormality, as well as screening for associated congenital malformations (Fig. 89.7). Visual evoked response will establish the presence of the occipital cortex within the sac, which may be helpful in surgical planning.

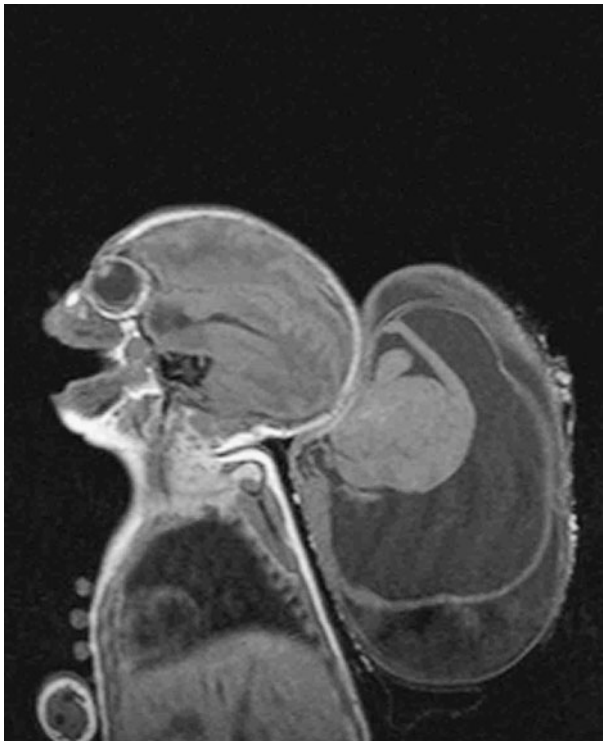

Figure 89.7 Encephalocele. Sagittal T_1-weighted MRI shows a large mass arising from the occipital region.

Treatment

Conservative treatment may be justified for patients with microcephaly and large amounts of brain within the encephalocele, where death is inevitable. Most of the patients are treated by surgical repair of the encephalocele. The aims of the surgery are excision of the extracranial non-functioning brain tissue, closure of the dura at the level of the cranium, and restoration of cranial contour with good skin coverage. Taking these steps to treatment also helps to prevent infection and preserve function.

OPERATIVE TREATMENT AND TECHNIQUE

Under general anesthesia, the patient is positioned with the encephalocele uppermost (e.g. prone for an occipital lesion). The lesion is prepped and draped, while ensuring adequate support for the encephalocele. Large lesions may be aspirated to facilitate handling and dissection. A sample of CSF is sent for microbiological examination and cultures. Usually a transverse ellipse incision is made near the base of the lesion, planned so as to enable closing it without causing undue tension (Fig. 89.8). The incision is then deepened until the dura is seen, which is traced up to the bony defect. The sac is opened where the cerebral tissue is not adhered. If the cerebral tissue is too large, necrotic, and if no visual evoked potentials are demonstrated, it is excised. Every effort should be made to preserve brain tissue without causing an acute rise in intracranial pressure. Bony defects may sometimes need to be enlarged. While dissecting the dura and brain tissue, care must be taken to avoid abnormal venous sinuses and venous connections. The distal sac is then excised. The dura is closed with continuous monofilament absorbable sutures and a dural graft may be required (pericranium is ideal). Meticulous hemostasis is achieved with the closure of all layers. A small suction drain is occasionally used. Subcutaneous tissue is approximated with fine, absorbable interrupted sutures, and the skin is closed with interrupted nylon or continuous absorbable subcuticular stitches (Fig. 89.3). A dressing and bandage is applied.

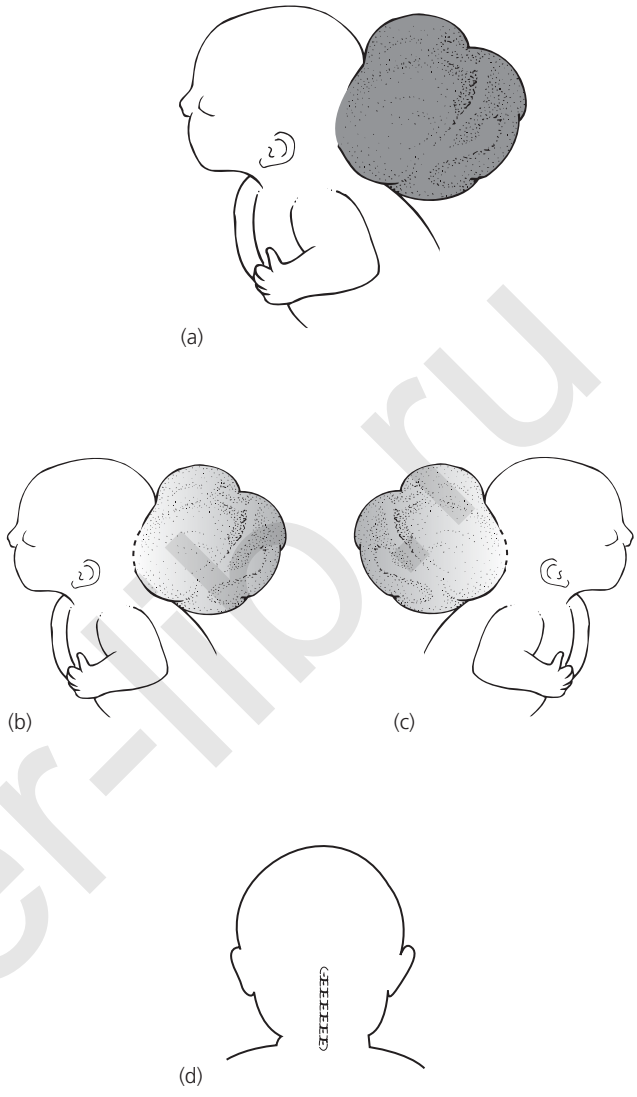

Figure 89.8 Closure of encephalocele. (a) Diagrammatic representation of occipital encephalocele; (b,c) incision around the base of the encephalocele; (d) skin closure.

POSTOPERATIVE CARE AND COMPLICATION

The infant is nursed opposite to the site to minimize pressure in the wound and closely observed for signs of increasing intracranial pressure or development of hydrocephalus. Meningitis is common with anterior encephalocele repair, where contamination is more likely because of the proximity to the nose, mouth, and air sinuses. An intracranial approach may help to avoid this. A CSF leak can occur despite meticulous dural closure. Once hydrocephalus has been excluded with a CT scan, CSF leaks are managed with additional skin sutures and a lumbar drain. If a CSF leak persists, then wound revision may be indicated. Most infants with encephalocele repair develop hydrocephalus which should be treated with a CSF shunt.

RESULTS

Encephalocele carries a high rate of mortality (up to 50%).[35] These deaths may be due to cerebral anomalies, associated congenital abnormalities, an acute rise in intracranial pressure and shunt malfunction and complications.

PROGNOSIS

Simple isolated encephalocele, without associated abnormalities, has a good prognosis. However, the prognosis is worse with larger lesions, those associated with microcephaly and hydrocephalus, and those forming part of other syndromes (e.g. trisomy 18, Meckel syndrome).[91,92] Anterior encephalocele has a poorer prognosis than posterior lesions.

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Hydrocephalus

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INTRODUCTION

The term 'hydrocephalus' relates to the presence of an excessive amount of cerebrospinal fluid (CSF), which may cause an increase in intracranial pressure (ICP) with or without associated abnormal enlargement of the cerebral ventricles. Rather than being a single pathological disease, hydrocephalus can result from a variety of pathological processes or insults that end with an imbalance between the production and absorption of CSF. Numerous classifications and categories exist with two widely used functional subdivisions being obstructive (where there is an anatomical obstruction to flow of CSF within the ventricles) and communicating hydrocephalus (where there is either presumed blockage with the circulation of CSF in the subarachnoid space or failure to absorb CSF).

The estimated prevalence of congenital and infantile hydrocephalus is between 0.5 and 0.8 per 1000 births (live and still).[1–3] Until the advent of shunts (over 55 years ago), hydrocephalus was usually fatal. The mainstay of treatment of hydrocephalus in the infant remains CSF diversion procedures with shunting; however, the evolving role for neuroendoscopy has proven successful for specific pathological entities. Technological advances in neuro-imaging, neuro-navigation and shunt hardware, and with a better understanding of CSF dynamics and hydrocephalus pathophysiology, are leading to a more 'tailored' patient-specific approach to this complex and multifactorial pathological entity. Hydrocephalus may cause pathological changes to brain morphology, microstructure, circulation, biochemistry, metabolism and maturation. Although treatment does not always reverse the damage, the timing of therapy is crucial in determining the reversibility of the lesions and the subsequent outcome for the patient. In essence, once the diagnosis is confirmed a definitive treatment should not be unduly delayed.

CSF CIRCULATION

The three components influencing CSF dynamics are production, circulation and drainage. CSF is derived by adenosine triphosphate (ATP)-dependent active secretion from cerebral arterial blood across epithelial walls. The global average rate of CSF production is constant under normal and stable conditions at 0.35 mL/min.[4,5] The current widely accepted view is that CSF circulation is via bulk flow.[6] It is produced mainly in the choroid plexus of the lateral and third ventricles and flows along the aqueduct of Sylvius to reach the fourth ventricle. CSF flows out of the fourth ventricle through the midline foramen of Magendie and the lateral foramina of Luschka into the subarachnoid space comprised of an interconnecting network of basal CSF cisterns. CSF flows around the tentorium upwards to the superior sagittal sinus. Some CSF flows downwards towards the lumbar subarachnoid space. Drainage of CSF into the venous compartment is predominantly a pressure-dependent one-way pathway through the arachnoid villi granulations that penetrate the walls of the superior sagittal sinus.[4,6]

Although our understanding of CSF dynamics is still incomplete, the distinction between communicating and obstructive hydrocephalus remains important (albeit sometimes knowingly inaccurate) as it affects treatment options. Obstruction of CSF flow between the third and fourth ventricles results in accumulation of CSF in the lateral and third ventricles. This is described as obstructive (non-communicating) hydrocephalus and may be the result of a congenital or acquired stenosis of the aqueduct. Endoscopic fenestration of the floor of the third ventricle (ventriculostomy) has been shown to be effective in this category of hydrocephalus. Impaired CSF flow and absorption in the subarachnoid space and arachnoid granulations, respectively, may arise as part of a post-meningitic or post-hemorrhagic complication and result in communicating hydrocephalus. Third ventriculostomy is less likely to be effective in this category and shunting may be the treatment of choice.

CAUSES OF HYDROCEPHALUS

The numerous causes of hydrocephalus are outside the scope of this chapter. Only those most relevant to the newborn

are outlined and divided into the following causative categories: (1) obstructive hydrocephalus (radiologically visible obstructive lesion), (2) communicating hydrocephalus (non-obstructive/no radiologically visible obstructive lesion), (3) external hydrocephalus, and rarely, (4) overproduction of CSF.

Obstructive hydrocephalus

AQUEDUCT STENOSIS

This accounts for about 6–66% of cases of hydrocephalus in children. In the vast majority of cases, aqueduct stenosis cases are sporadic, however rare X-linked syndromic cases have been described.[7] Aqueductal obstruction may be caused by gliosis secondary to infection or hemorrhage or acquired stenosis due to compression from neoplastic (e.g. tectal tumors), vascular (e.g. vein of Galen aneurysms), or congenital central nervous system (CNS) malformations (Dandy–Walker, Chiari, spina bifida). Magnetic resonance imaging (MRI) is mandatory to confirm the status of the aqueduct which cannot be visualized on computed tomography (CT).

SPINA BIFIDA AND CHIARI MALFORMATION

Approximately 95% of patients with spinal myelomeningocele involvement have some degree of hydrocephalus, which is almost invariably associated with the Chiari II malformation.[8] The major craniocervical features of a Chiari II lesion include: caudal displacement of the fourth ventricle into the upper cervical canal, elongation and thinning of the upper medulla and lower pons, caudal displacement of the medulla and lower cerebellum through the foramen magnum, and various bony defects of the upper cervical vertebrae and occiput (see Chapter 089, Spina bifida and encephalocele).[9]

DANDY–WALKER COMPLEX AND POSTERIOR FOSSA CYSTS

The 'Dandy–Walker complex' is a term encompassing a rare group of varying malformations in which abnormal posterior fossa CSF collections show clear communication with the fourth ventricle. Dandy–Walker malformation is included in this category and typically involves cystic dilatation of the fourth ventricle, partial or complete agenesis of the cerebellar vermis, and hydrocephalus in up to 90% of cases.[10] It can be associated with other nervous or systemic abnormalities. Posterior fossa arachnoid cysts do not communicate directly with the fourth ventricle. Both third ventriculostomy and shunting are valid surgical options and overall morbidity appears to be related to early and adequate treatment of the associated hydrocephalus.[11,12]

NEOPLASTIC LESIONS

Fortunately, brain tumors in newborns are very rare. The most common types in newborns are often of neuroectodermal origin and are more commonly supratentorial. Hydrocephalus can result from obstruction at various points of the CSF pathway by any neoplastic lesion.

Communicating (non-obstructive) hydrocephalus

POST-HEMORRHAGIC HYDROCEPHALUS

Hemorrhage in the neonatal period is a common cause of hydrocephalus.[13,14] The premature infant born before 32 weeks' gestation is especially vulnerable and the hemorrhage most commonly originates in the highly vascularized germinal matrix. Most studies agree that the incidence is highest in infants weighing less than 1.5 kg at birth and up to 50% of hemorrhages occur within 8 hours of birth.[13,14] In the term neonate, the most common site of hemorrhage is from the choroid plexus, but this accounts for only a small percentage of neonatal hemorrhages. Post-hemorrhagic hydrocephalus (PHH) can be defined as progressive dilatation of the ventricular system that develops as a complication of neonatal intraventricular hemorrhage (IVH). The hemorrhage is postulated to provoke an inflammatory response leading to thickening of arachnoid in the basal cisterns and temporary or permanent occlusion of the arachnoid villi.[15] Although historically classified under communicating/non-obstructive hydrocephalus – the obstruction at the level of the basal cisterns demonstrates the flaw in the simple classifications of hydrocephalus. PHH may contain elements of both communicating and obstructive hydrocephalus at varying stages. The incidence of PHH after IVH of prematurity ranges from 25 to 74% and is proportionately linked to the degree of blood load within the ventricular system.[14] The continuous improvement in perinatal care has led to an increased survival rate in preterm infants, and thus the greater risk of these infants developing IVH. Fernall *et al.*[16] reported that an infant born very preterm has a 60 times higher risk of developing infantile hydrocephalus than an infant born at term. Ultrasonography has been shown to be sensitive and specific in diagnosing IVH and some advocate routine ultrasonography in any infant born before 34 weeks' gestation and/or for those infants weighing less than 1.5 kg at birth.[17–19] Most IVHs are small and resolve spontaneously, but the more severe hemorrhages are associated with an increased risk of developing PHH, and higher risk of mortality and neurodevelopmental outcome.

The risk of IVH in the preterm infant has been significantly reduced by measures that may indirectly ameliorate fluctuations in cerebral blood flow, such as surfactant to reduce pulmonary hypertension and antenatal steroid administration.[16,20] Some also advocate that premature infants should be maintained on paralytics and sedation for the first 72 hours following birth to reduce the risk of IVH.[20] Once PHH has been diagnosed radiologically, temporizing interventional methods may be employed, as some patients may either be too unstable for surgery or their hydrocephalus resolves with degradation of the IVH without obvious lasting imbalance to the CSF dynamics. Most cases of PHH occur 3–4 weeks after IVH, but it is important to note that many of these cases are clinically silent and early detection requires a high index of suspicion and serial radiological monitoring. Of those who develop PHH, over 50% become shunt-dependent with a high rate of neurodevelopmental disabilities. Medical

and surgical management options will be discussed in the following sections of this chapter.

Post-infective hydrocephalus

Intrauterine infection by cytomegalic inclusion disease, mumps, toxoplasmosis, and syphilis may cause congenital hydrocephalus. Also, in the postnatal period following meningitis and/or ventriculitis, hydrocephalus may form from either adhesions in the subarachnoid space or internal obstruction affecting the basal cisterns. Meningitis in the newborn may result from amniotic infection where the membranes have been ruptured for a prolonged period. In the first 2 weeks of life, the organism is usually that of *Escherichia coli* and other Gram-negative enteric bacilli. In the second 2-week period, the pathogens are more likely to be Gram-positive cocci, *Listeria* and *Pseudomonas*.[21–23] Post-infective hydrocephalus (PIH) typically occurs 2–3 weeks following diagnosis of bacterial meningitis and studies have shown that associated complications include abscess formation, ventriculitis, and subsequent CSF loculations and intraventricular septations.[23,24] The management is difficult and frequently requires multiple shunt placements and revisions with associated poor developmental outcome and high morbidity and mortality rates.

External hydrocephalus

This controversial pathological entity is also linked to or referred to as 'pseudohydrocephalus', 'benign subdural effusion', 'benign enlargement of the subarachnoid spaces', and 'benign pericerbral effusion'. Its etiology and pathophysiology in relation to CSF dynamics is uncertain, but include abnormal collections of fluid in the subarachnoid or subdural space overlying the cerebral convexity. The condition occurs while the cranial sutures are open. Although most cases do not require intervention and maintain a benign course, some patients present with features related to mass effect and raised intracranial pressure and in rare cases may require management with a subdural peritoneal shunt.

Overproduction of CSF

Choroid plexus papillomas are intraventricular tumors that may cause overproduction of CSF resulting in massive ventricular enlargement. They are most often found in the lateral ventricle and appear as homogenously enhancing lesions on MRI. They are vascular lesions and resection of the tumor may be curative if the tumor is benign.

CLINICAL FEATURES OF HYDROCEPHALUS IN THE NEWBORN

Despite the vast variation in etiology, the clinical presentation of hydrocephalus is remarkably similar in all pathological processes and is mainly related to signs and symptoms of localized or generalized raised intracranial pressure.

An increase in head size is the major feature of hydrocephalus in the neonate, with an increasing deviation of head circumference from the normal centiles for age. Incremental plotting of head circumference is essential in this regard, using a centile chart, such as that produced by Gairdner and Pearson, allowing for gestational age at birth.[25] It should be noted that there are causes for head enlargement other than hydrocephalus (e.g. a familial tendency for a large head, osteofibromatosis, macrocephaly, or intracranial cysts). The head shape may also be abnormal.

Bulging of the anterior fontanelle with a variably open posterior fontanelle, separation of the suture lines and dilatation of superficial scalp veins (due to venous reflux from cerebral sinuses) are classical features of raised intracranial pressure in hydrocephalus. 'Setting sun sign', an upward gaze palsy may be seen with the superior sclera visible. The component parts of this phenomenon consist of downward rotation of the eyeballs and retraction of the upper eyelids and may be accompanied by brow raising. It may be intermittent, disappearing when ICP is reduced. However, this sign can also be seen and elicited, although rarely in normal infants. Sixth nerve palsy can be seen as this nerve is most sensitive to pressure due to its long intracranial course. Papilledema, decreased level of consciousness, and other focal neurological deficits can also be presenting signs. Opisthotonic posturing, bradycardic and apneic episodes are critical signs of raised intracranial pressure suggesting brainstem compromise and require emergent neurosurgical assessment and treatment.

Other important presenting symptoms of hydrocephalus in the infant are related to raised intracranial pressure, such as irritability, lethargy, poor feeding, vomiting, failure to thrive, and delayed motor development. The clinical presentation may also include features specifically related to the associated causative pathology.

CURRENT IMAGING AND INVESTIGATIVE TECHNIQUES FOR HYDROCEPHALUS IN THE NEWBORN

Skull x-rays are largely obsolete in the management of hydrocephalus in the newborn. Historically, widening of the sutures beyond 3 mm can be seen with associated lacunar skull defects. Ultrasonography is exceptionally useful as a non-invasive technique (Fig. 90.1).[17–19] Antenatal sonography can detect hydrocephalus *in utero* and is the screening procedure of choice in patients under the age of 18 months. In the newborn, the anterior fontanelle provides a window. Measurements of both the ventricle size and the cortical mantle are possible. Serial ultrasonography has not only improved the ability to detect hydrocephalus, but has also resulted in more prompt treatment of this condition and has proved extremely useful in detecting IVH and hydrocephalus in premature infants. It is considered the initial investigation of choice for neonates with hydrocephalus (Fig. 90.1) and can be performed at the bedside.[17–19] It is worth noting that

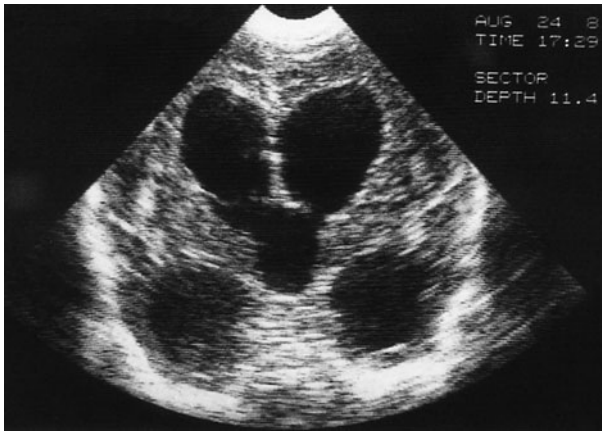

Figure 90.1 Aqueduct stenosis. Coronal section on sonography showing dilated lateral ventricles and foramina of Monro passing into a dilated third ventricle.

although sensitive and specific for the diagnosis of hydrocephalus, clarification of its pathology usually necessitates subsequent CT or MRI.

CT is used where greater detail is required (Fig. 90.2). A complete high resolution CT can be obtained within 2 minutes of the patient being on the CT table. MRI is the gold standard for diagnosing hydrocephalus-related causative pathology and demonstrates the ventricular and CSF anatomy in exquisite detail. Pathological entities, such as aqueductal stenosis, Chiari malformation, and neoplastic lesions, are readily identifiable. MRI also allows for detailed surgical planning when considering the options of endoscopic third ventriculostomy, shunting, posterior fossa surgery, etc. MRI T_1- and T_2-weighted dynamic flow sequences can highlight the relevant ventricular, periventricular, and CSF flow with remarkable clarity.[26] This is particularly useful when assessing the anatomy of the third ventricle and aqueduct in relation to determining the surgical procedure of choice. Volume datasets for both CT and MRI

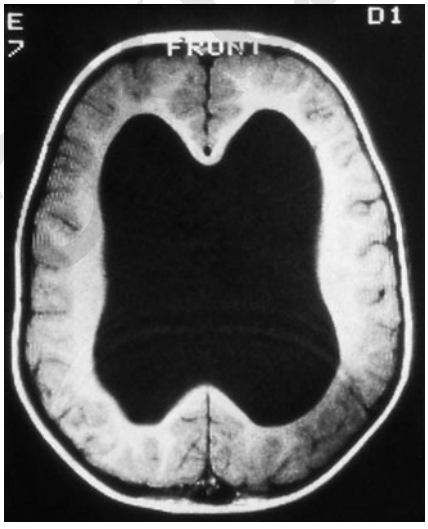

Figure 90.2 Computed tomographic scan of head showing dilated lateral ventricles.

are now readily obtainable which are compatible to bespoke three-dimensional neuronavigation workstations for shunting and neuroendoscopic procedures. MRI is increasingly used for antenatal investigation and is valuable in both outlining congenital malformations and hemorrhage.[27]

Postoperative imaging to assess ventricular size after shunting or neuroendoscopy can be performed with both CT and MRI. However, after a third ventriculostomy, phase contrast dynamic MRI sequences are required to identify CSF flow through the ventriculostomy and is best visualized on sagittal images.[26,28] Invasive pressure measurements, such as fontonometry, are less often justified as they are unreliable when compared with modern methods of imaging.

An antibody screen should be carried out if an intrauterine infection is considered. CSF analysis is indicated where infection or hemorrhage is suspected, as these factors may influence the subsequent clinical management. A raised protein level, or indeed blood-stained CSF, is not necessarily a contraindication to shunting, but is taken into consideration when determining the timing of shunt placement. It may be appropriate to delay surgery until the protein count and/or the blood in the CSF clears to an acceptable degree. If active infection is suspected then a temporizing external ventricular drain would be preferred before a permanent shunt can be implanted once the infection has been treated and confirmed with sterile CSF samples.

TREATMENT OPTIONS FOR HYDROCEPHALUS IN THE NEWBORN

Non-surgical/medical management

The complications associated with surgery in the low birth weight neonate or neonates with coexisting unstable medical conditions raises the need to explore non-surgical means of managing hydrocephalus. The additional possibility of occasionally self-limiting conditions such as PHH may only require temporizing management options. However, pharmacotherapeutic agents, such as acetozolomide, frusemide, and steroids, have not been shown to be effective in reducing the rate of shunting and cannot be recommended.[29,30] Although historically a common practice, serial lumbar punctures should probably no longer be used. A published meta-analysis concluded that no evidence of benefit was demonstrated with a significant risk of secondary infection.[31] Similarly, serial multiple percutaneous ventricular taps have been abandoned by most large tertiary neurosurgical centers due to the numerous associated complications such as 'puncture porencephaly', infection, and encephalomalacia.[32,33]

Surgical management

Surgery remains the overwhelming mainstay of treatment for hydrocephalus in the newborn, shunting converted hydrocephalus from what was an almost exclusively terminal disease to a frequently curable condition. The first permanent CSF diversion for hydrocephalus was performed in Mikulicz

in 1893 in the form of a ventriculo-subarachnoid-subgaleal shunt.[34] This procedure was also simultaneously the first intrathecal ventriculostomy. Since then, virtually every anatomical cavity has been utilized as a potential reservoir or conduit for CSF drainage with varying degrees of success, which included subcutaneous tissues of the scalp, atria, pleura, ureters, gallbladder, and thoracic duct. Most of these are no longer considered in standard first-line practice in newborn hydrocephalus. This section outlines the most common surgical techniques in newborn hydrocephalus surgery.

EXTERNAL VENTRICULAR DRAINAGE

External ventricular drainage (EVD) has been in wide use in the temporary treatment of hydrocephalus for several decades. The frontal and occipital horns of the lateral ventricles are the site of choice via a single burr-hole and the CSF is drained into a sterile closed circuit system which can be continuously controlled by a simple gravity-based outflow valve. It is of particular use in the presence of active infection whereby a permanent shunt system cannot be placed until the infection has been successfully treated and also until a high related CSF protein level (as seen in some peri- and post-infectious settings) normalizes to allow shunt placement. It also allows for the direct administration of intrathecal antibiotics into the infected CSF space. EVD is also potentially useful in IVH or PHH as a temporizing measure before either persistent hydrocephalus has been confirmed or the blood load has reduced. In the emergent setting arising from tumor-related obstructive hydrocephalus, EVD may provide necessary control until such time as to allow definitive tumor resection or reduction of related high CSF protein levels that may cause occlusion of a permanent shunt system. Despite the introduction of antibiotic impregnated EVD systems, they are still prone to significant infection rates and catheter dislodgement. Several studies have assessed the efficacy of intraventricular fibrinolytic therapies and CSF irrigation; however, these have not translated to proven clinical practice and remain experimental.[33,35]

SUBCUTANEOUS RESERVOIR VENTRICULAR CATHETER SYSTEM

This device may be indicated in the newborn infant whose low birth weight and/or the potential for spontaneous arrest of the hydrocephalus preclude the immediate need for a permanent shunt. It is a viable option in PHH. The reservoir allows easy CSF tapping, lower infection rates compared to EVD, and access for intraventricular antibiotic. Complications and limitations include skin erosion and only intermittent pressure control.

VENTRICULO-PERITONEAL SHUNT

The majority of hydrocephalic newborns undergoing CSF diversion surgery will have a ventriculo-peritoneal shunt (VPS). The principle of VPS remains unchanged since first described in 1908 and was initially less favored than the ventricle-atrial (VA) or ventriculopleural shunt.[34] The peritoneum has since become the choice of drainage site when complications with VA shunts, such as sudden death from pulmonary embolism, endocarditis, and nephritis, were noted. Another recognized problem in many VA shunts in the neonate is the need to lengthen the lower end as the child grows and the catheter pulls up out of the atrium. This can be obviated with VPS in the neonate with a longer intraperitoneal catheter. The hardware required for a VPS includes a ventricular catheter, CSF reservoir, shunt valve, and distal peritoneal catheter. Recently introduced antibiotic-impregnated shunt tubing with *in vivo* antibacterial activity is gaining popularity and may confer a protective benefit against infection, particularly in the neonatal setting.[36] Further randomized studies are required to confirm this and the effect of other potential antimicrobial shunt tubing materials on the market, such as those with silver coating.

The choice of valve type remains a regular source of debate within the neurosurgical community. Valve types include differential-pressure, flow-regulating, gravity-actuated, and programmable valves. All the valve types only allow unidirectional flow of the CSF. An anti-siphon device may be included in the system to prevent overdrainage. There are no studies that conclusively prove one valve type to be superior.[37,38] In practice, some factors that may influence decision-making include valve size and profile in relation to newborn/premature neonate scalp skin, cortical mantle thickness, cost, and individual surgeon experience. Some authors advocate a flow control valve for shunts in the newborn to avoid the later complication of slit ventricle syndrome. This is related to chronic overdrainage and is seen most commonly in patients who have a shunt implanted in the first two years of life.[39] Overdrainage and development of subdural hematomas in newborns with large ventricles and thin cortical mantle may be avoided with high-resistance valves.[40]

Both frameless and frame-based neuronavigation systems have been utilized to reduce the incidence of poorly sited ventricular catheters and recent studies have shown benefit in catheter placement accuracy, but it remains to be seen if this relates to a significant reduction in shunt revision rates in the long term.[41] With the bespoke electromagnetic (EM), frameless neuronavigation system, no rigid head fixation, pins, or screws are required and this confers a significant advantage for neonatal shunt surgery. Previous studies on endoscopic versus non-endoscopic catheter placement did not demonstrate any difference in shunt revision rates.[42]

Complications of VPS most commonly includes infection, malposition of the ventricular catheter, mechanical failure leading to suboptimal drainage or blockage, overdrainage, shunt migration/disconnection, and less commonly intra-abdominal sequelae, such as bowel perforation, hernias, hydroceles, appendicitis, and peritonitis. Shunt complication rates are significantly higher in the newborn, and studies have shown low birth weight to be linked to a higher incidence of shunt infection and revision rates.[43] If the CSF is sterile on insertion, the usual organisms causing postoperative shunt infection are skin commensals, such as

Staphylococcus epidermidis (*albus*). Where infection has been proven, the removal of the entire system and temporary CSF diversion via an EVD and concomitant intrathecal antibiotic administration is usually necessary. The treatment of shunt infections has been reviewed extensively by Bayston.[44]

Unfortunately, despite advances in neuronavigation and shunt tubing material, shunt failure remains a considerable source of morbidity for hydrocephalus patients with up to 40% of shunts failing in the first year.[45] Indeed, shunt failure remains an almost inevitable consequence during a patient's life, up to 80% of shunts requiring revision after 12 years.[46]

NEURO-ENDOSCOPY AND ENDOSCOPIC THIRD VENTRICULOSTOMY

Advances in fiberoptic camera technology combined with high-resolution MRI have seen renewed widespread enthusiasm for neuroendoscopy as a therapeutic option in hydrocephalus. Endoscopic third ventriculostomy (ETV) was first performed as an open procedure in 1922 by Dandy, and subsequently as an endoscopic procedure by Mixter in 1923.[33]

Endoscopic third ventriculostomy is a minimally invasive procedure most commonly performed via a single paramedian coronal burr hole to gain access into the lateral ventricle. The ventricle is cannulated with a 10- or 12-Fr cannula which then serves as a conduit for the rigid or flexible endoscope. The endoscope is then introduced and advanced towards and into the enlarged foramen of Munro and then into the third ventricle. A midline fenestration and dilatation is performed in the thinned third ventricle floor avoiding critical structures, such as the mammillary bodies and the basilar artery. The endoscope is then advanced through the fenestration to ensure that effective communication into the interpeduncular and pre-pontine subarachnoid space has been achieved by further opening any thickened membranes that may be present deep to the fenestration. At completion, the endoscope and cannula is removed and no hardware is left *in situ*.

The obvious advantages of shunt independence have made this an attractive surgical option; however, current evidence suggests that patient selection is crucial to outcome success rates. ETV in obstructive hydrocephalus with maintained CSF absorption, such as in congenital aqueduct stenosis, is associated with the highest success rates. While in older children, the indications for endoscopic treatment have been relatively well defined, much debate continues on the value of this treatment in the first few months of life.[47–49] While various studies have reported differing success rates, there remains a lack of consensus on the value of third ventriculostomy in infants and neonates.

The ongoing International Infant Hydrocephalus Study (IIHS) is an international multicenter prospective randomized, controlled trial of endoscopic third ventriculostomy versus shunting in children presenting under the age of two years with pure aqueduct stenosis and aims to provide more evidence in this area.[50,51] The role of ETV as a secondary treatment option after initial or multiple shunt failures is gaining popularity with encouraging success rates.[52] This is relevant to the newborn with PHH or PIH who may benefit from a primary shunt (where primary ETV is ineffective) and then be considered for a secondary ETV when presenting with a future shunt failure.

ETV may also have an important role in the treatment of hydrocephalus in developing countries.[53] The lack of a follow-up service for children in developing countries having permanent shunt implants reinforces the obvious advantage of a shunt-free therapeutic option – ETV. PIH accounts for up to 60% of hydrocephalus cases in certain developing countries.[53] In keeping with published results for infants in developed countries, success rates in a relatively large series of patients treated in a developing country in the under one year group was lower than in the older child. Nevertheless, up to a 60% shunt avoidance rate has been reported in infants in developing countries presenting with PIH aqeuduct stenosis undergoing ETV.[53] The challenge posed by the lack of a shunt follow-up service in developing countries and the consequent impetus for ETV as a treatment modality had also potentially led to a clinical situation in which ETV may be performed on a patient whose CSF absorption capability has not recovered sufficiently, whereas these patients would probably have been treated with a shunt in a developed country. The combination of ETV and choroid plexus cauterization (CPC) may be a viable option in temporarily reducing the rate of CSF production until the absorptive function potentially returns. Results from a study employing this management technique on patients in the developing world reported a success rate of over 70% in infants under one year with PIH and an open aqueduct.[54]

Other applications of neuroendoscopy include aqueductal stenting for isolated fourth ventricle enlargement, multiloculated hydrocephalus requiring communication of CSF spaces via septum pellucidotomies, cyst fenestrations, and as an adjunct to shunt surgery by aiding shunt placement under direct endoscopic vision.

Although a safe procedure in well-trained and experienced hands, the complications of neuroendoscopy can be devastating. Severe hemorrhage, cardiac arrest, cerebral infarction, diabetes insipidus, and damage to the fornices resulting in memory deficit have all been reported.[55] Also of importance is the rare but potential risk of sudden post-ETV death due to closure of the ventriculostomy.[55] Nevertheless, neuroendoscopy alone or in combination with permanent shunting, and the development of computerized neuronavigation for both, has an increasingly important role in the management of hydrocephalus.

FETAL SURGICAL THERAPY

Hydrocephalus is detectable *in utero* and the question of prenatal intervention arises. In spite of extensive experimental work and indeed some human intervention in countries where abortions are legally banned, the results in general, so far, have been poor and this method of management is not currently recommended.[56] The majority of patients who had undergone fetal surgery for hydrocephalus required VPS insertion after birth.

SHUNT OPERATION TECHNIQUE

Ventriculo-peritoneal shunts

Routine preoperative preparations, such as blood parameters, are a necessity.

The patient is positioned while under general endotracheal anesthesia. Antibiotic prophylaxis is recommended such as a cephalosporin, e.g. cefotaxime, at the time of induction. The head is rotated to the opposite side to the shunt with the neck extended to create a straight line between the scalp and abdominal incision. The site of the burr hole and abdominal incision should be marked prior to skin preparation and draping (Fig. 90.3). Occipital burr holes are usually 3–4 cm from the midline along the lambdoid suture. Frontal burr holes are 2–3 cm along the coronal suture from midline. It is vital to tailor the burr hole to the ventricular morphology on imaging so as to ensure optimal ventricular catheter placement. In infants with splayed sutures, access can be achieved via an opening of the sutures. The site of the burr hole is according to the surgeon's preference as there is little evidence showing advantages of one over the other. Occipital burr holes are traditionally used as they are more cosmetically acceptable (Fig. 90.4a). Durotomy is made and the brain pia is cauterized. Dural opening should be kept minimal to reduce the risk of CSF escape around the ventricular catheter, hence promoting CSF leak (Fig. 90.4b).

Figure 90.3 The dotted line represents the course of the ventricular catheter. The patient is positioned with a roll of gamgee under the shoulders to straighten out the neck and allow easier passage of the cannula. The skin is marked, predisinfection, with a pen, showing the curved incision site behind the posterior parietal eminence. The transverse abdominal incision site is also marked with a dark line.

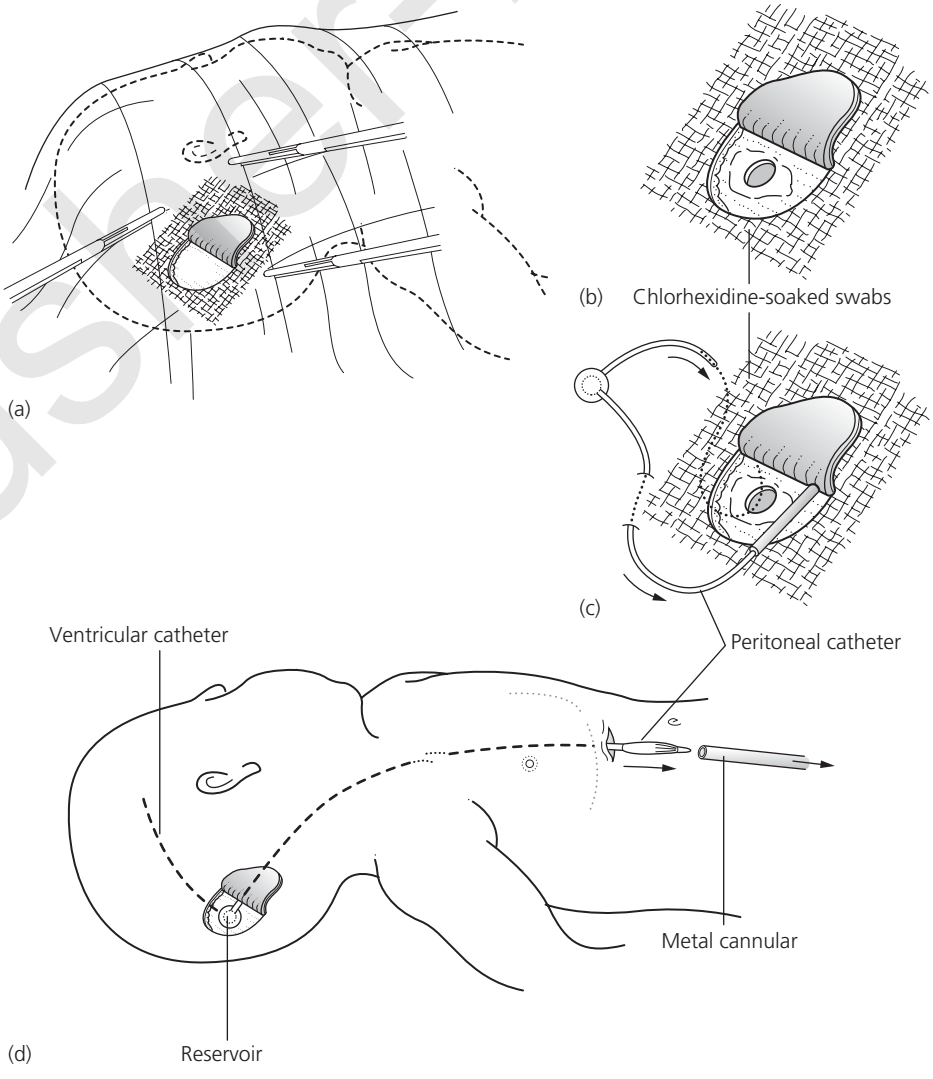

Figure 90.4 (a) Wound drapes surrounding the scalp incision. An upper incision to the pericranium is made. (b) The pericranium is diathermied and rasped peripherally and a burr hole made. (c) Following incision in the abdomen, a long trocar and cannula are passed percutaneously to exit at the lower incision. The long trocar is removed, allowing passage of the peritoneal catheter along the metal cannula. The trocars in some prepared shunt sets have a device for attaching the distal catheter and allowing it to be pulled through distally. (d) Having lightly diathermied the dura, a small hole is made in it and the ventricular catheter introduced and connected to a reservoir. With free flow from the distal end, the catheter is placed in the peritoneal cavity and the peritoneum closed snugly around it.

The abdominal incision is usually performed on the same side, either upper midline or paraumbilical site, however the site is unimportant. The most crucial part is to be sure that the peritoneum space is opened. An open technique, use of trocar,[57] and more recently laparoscopic assistance have been described.[58] The distal catheter is tunneled subcutaneously from the burr hole site to the abdominal opening, or vice versa. If a frontal burr hole is used, an intervening incision is made at the occiput.

The ventricular catheter is introduced mounted on a stylet. The trajectory is determined according to external landmarks. From the occipital burr hole, the target is at the midpoint of the forehead at the hairline so that the lateral frontal horn will be entered. From a frontal burr hole, aim for a target at the intersecting planes' midpupillary line and the external auditory meatus. Intraoperative ultrasonography or image-guided stereotaxy (for example, EM guidance)[41] can be used for more accurate positioning of the catheter. CSF pressure may be measured at this point and a sample of CSF taken for biochemical and microbiological examination. The proximal catheter is connected to the distal catheter via a reservoir and a valve system, depending on the type being used.

The distal end is examined to ensure that there is free-flowing CSF. The distal catheter is placed within the peritoneum. The peritoneum is closed using absorbable sutures, the muscle layers and skin are then closed (Fig. 90.4d).

Ventriculo-atrial shunts

These may be performed in a similar fashion to ventriculoperitoneal shunts, except for the lower incision which is over the right side of the neck. The objective is for the shunt tip to lie in the superior vena cava just rostral to the tricuspid valve. The two most common methods are open versus percutaneous insertion. Access to the jugular vein can be achieved by exposing the common facial vein, which is tied proximally and held with a stay suture at the venotomy site; the distal catheter is fed into the superior vena cava. Intraoperative fluoroscopy or x-rays are helpful in achieving the ideal position. Throughout the procedure, the anesthiologist should inform you of any cardiac alterations or rhythm changes. A purse-string suture is closed around the catheter sufficiently to prevent hemorrhage, but not so tight as to cause obstruction to the catheter. Percutaneous methods into the jugular or subclavian veins can be achieved with the aid of ultrasound guidance and fluoroscopy.[59–61] Complications include cor pulmonale and catheter emboli.

Ventriculopleural shunts

The proximal approach is identical to the ventriculoperitoneal shunt placement. The pleural space can be entered at a variety of sites, however along the anterior axillary line in the fifth intercostal space is both convenient and safe. Intercostal muscle layers are split on the upper border of the rib to avoid the neurovascular bundle to reveal the pleura. It is then opened, the distal catheter is gently introduced into the space to avoid entering the lung parenchyma. The muscle is closed to avoid further air entry into the pleural space. Distal catheter placement may be aided by thoracoscopy.[58] Contraindications for this technique include previous thoracic surgery, acute or chronic pulmonary disease, and poor pulmonary function. CSF will usually accumulate as benign pleural effusion, however if this is progressive it may lead to respiratory distress and therefore vigilance for this complication is important. This technique, however, is rarely applicable in newborns or indeed infants as the pleural cavity cannot cope with the CSF load at this age. The technique is thus usually reserved for very rare cases where few options for the distal catheter remain in older children.

Other sites for the distal catheter include the cerebral venous system, gallbladder, ureter, and bladder. These sites are used rarely in neonates because of their complexity and complications leading to increased morbidity and mortality.

POSTOPERATIVE CARE

Postoperative scans are obtained and act as a reference to future surgery and shunt positioning. Continual monitoring of head circumference is required.

OUTCOMES

The outcome of hydrocephalus will ultimately be determined by the underlying pathological entity that caused it, the treatment selected and complications thereof, the socioeconomic status of the child, and numerous other factors beyond the scope of this chapter. The important message to remember is that hydrocephalus is not a single disease entity, that the treatment must be tailored to the etiology and age of the patient. Avoidance of complications is of paramount importance as complications, such as infection, may dramatically alter the natural history and outcome of the disease.

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PART X

GENITOURINARY

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91

Urinary tract infections

MARTIN A KOYLE

INTRODUCTION

A urinary tract infection (UTI) is not an uncommon event early in life. This condition should be given strong consideration in the differential list when evaluating the febrile, ill neonate. The diagnosis of a UTI can lead to significant morbidity for the child, not only from the disease process itself, but also from the formidable diagnostic evaluation subsequent to their initial presentation. Given the premature immune system, infants and particularly neonates, are at risk for disseminated bacteremia which can lead to a more dangerous scenario than in older children and adults. Due to this associated danger, a thorough evaluation and prompt treatment when necessary are mandatory. In addition, the pediatric specialist needs to recognize that UTI may be a marker of a more serious, underlying urologic congenital and/or functional anomaly, which may be amenable to operative correction and cure.

Potential urological sequelae from a UTI include renal scarring and compromised renal function, although such severe morbidity may be less likely than formerly perceived. Indeed, with the popularity of maternal fetal ultrasound and antenatal detection of congenital anomalies it is now well documented that such scarring is more often due to dysplasia. This is most obvious in the neonate with congenital vesicoureteral reflux (VUR). Regardless, it is still known that acquired renal scarring can occur in the vulnerable child, even when febrile UTI occurs and VUR is absent on radiological imaging. Current investigations are attempting to identify those specific groups at risk for renal damage. However, serious compromise of function is uncommon nowadays, especially when prompt treatment is instituted. An accurate evaluation is paramount given the implications of delayed or incorrect diagnosis which negatively impacts the start of timely therapy. Diagnostic tests recommended after a urinary tract infection vary, and the usefulness of invasive testing is being questioned. Treatment, although benign and effective, has potential risks, in particular the generation of resistant bacterial strains. Needless to say, a urinary tract infection carries with it a significant emotional and economic burden for the family of the sick child.

INCIDENCE

Urinary tract infections account for 0.7% of all pediatric office encounters and 5–14% of pediatric emergency department visits in the United States.[1,2] In addition, UTI has consistently been the most commonly diagnosed serious bacterial infection in the first months of life with a prevalence varying from 1.8 to 7.5%. It is also the most consistently missed serious bacterial infection in studies attempting to define low risk criteria for the evaluation of fever in the neonatal age group.[3] This unquestionably translates into a significant number of physician visits annually and/or extended hospitalizations of neonates, which add significantly to already escalating healthcare costs. It must be acknowledged that estimated costs do not include charges for subsequent evaluations, including clinic visits, follow-up studies, and time missed from work by parents.

Neonates represent a special subgroup in regards to UTI with a male predominance of 2.5- to 6-fold, which is in striking opposition to the high prevalence rate of UTI among females in the over-six months age group.[2] Overall, the reported incidence of neonatal UTI varies between 0.1 and 1% in the general population of healthy newborns.[4] In preterm neonates, the incidence is much higher. Furthermore, this incidence is estimated at 10% in low-birth weight infants.[5]

Reported prevalence in the preterm neonate ranges between 4 and 25%.[6] A meta-analysis of studies looking at the prevalence of UTI in febrile children less than three months of age found that febrile female infants had a relatively high prevalence rate of UTI (5% in the first three months). Uncircumcised males under three months had the highest rate at 20.1%, whereas circumcised males had the lowest rate (2.4%).[7]

ETIOLOGY

Numerous factors seem to predispose the child's urinary tract to infection. Most pathogenic bacteria that cause UTIs arise from a reservoir in the intestinal tract (Fig. 91.1). *Escherichia coli* is by far the predominant bacteria to cause UTI because of the unique ability of certain serotypes to adhere to the urothelium. One way of differentiating strains of *E. coli* is based upon differences in the antigens they elaborate on their polysaccharide capsule, which surrounds the bacteria. These antigens are known as K antigens and it has been demonstrated that certain K antigenic *E. coli* have a much higher propensity for causing UTI than other strains.

Perhaps the most significant predictor of a bacteria's uropathic potential is its ability to adhere to the epithelial membrane where they cause infection – in the urinary tract, the urothelium. Pili or fimbrae are long filamentous appendages, composed of protein, that project from the bacterial surface and allow for this adhesion to take place. In *E. coli*, type 1 pili is highly associated with bacteria that cause UTI. Type 1 pili act to bind uroplakin, a protein cap that is elaborated by the umbrella cell or urothelial cell. Another form of pili, P pili, named for its ability to bind the P antigen of blood group antigens, is highly associated with strains of *E. coli* that cause pyelonephritis. Bacterial adherence, colonization, and subsequent UTI is a complex process that involves a balance between bacterial virulence factors and a host's immune response to invasive bacterial infection and colonization. Clearly, there are specific strains of enteric bacteria that cause UTI with a much higher virulence than many of the bacteria harbored in the gut. In addition, there are also individuals that are much more prone to UTI due to the complexity of the relationship between host and bacterial factors that allow adherence to first occur. Other uncommon organisms leading to newborn urinary tract infections include *Klebsiella*, *Proteus*, *Pseudomonas*, and *Enterobacter* (Table 91.1).

P fimbriae *E. coli* adhere to the urothelial cells and lead to a decrease in ureteral peristalsis. Bacterium secretes endotoxins that cross the ureteral mucosa and leads to paralysis of ureteral smooth muscle along with risk of ascent and reflux of bacteria. Consequently, this slows flow in the peripheral ureters, and adherent bacteria are not washed away.

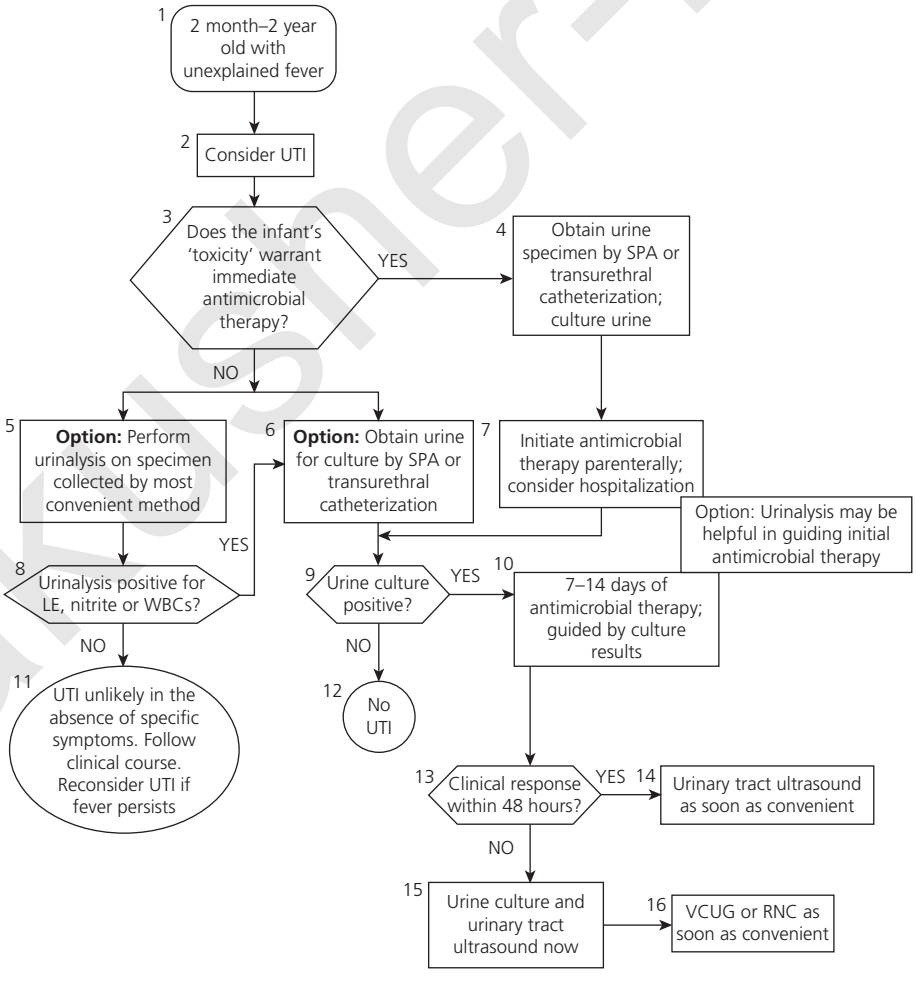

Figure 91.1 Algorithm of treating infants with unexplained fever. Reproduced with permission from American Academy of Pediatrics, Committee on Quality Improvement. Practice parameter: The diagnosis, treatment, and evaluation of the initial urinary tract infection in febrile infants and young children. *Pediatrics* 1999; **103**: 843–52.

Table 91.1 Common uropathogens.

Bacteria	Incidence (%)
Escherichia coli	77–93
Klebsiella	0–11
Enterococcus	2–9
Serratia	~1
Staphylococcus aureus	~1
Psuedomonus aeruginosa	~1
Enterobacter cloacae	~1
Streptococcus	~1
Proteus	~1

Compromise of host natural immune defenses that protect the urinary tract from infection, in particular immunologic immaturity, also predispose pediatric patients to the development of UTI. In addition, some children will have colonization of their feces by virulent bacteria.[8] This is especially true in those patients with slow stool transit times and severe constipation, a cofactor that is more common in older children in the potty training age group.

PRESENTATION

In neonates, the most common clinical presentation varies and is less classical than in older children and adults. Symptoms such as fever, irritability, food intolerance, respiratory distress, and jaundice are common; in premature infants, symptoms encountered may be even more nondescript or 'urinary tract specific', including feeding intolerance, apnea, bradycardia, lethargy, and abdominal distention.[9] Rarely will symptoms referable to the urinary tract, such as hematuria and foul smelling urine, be observed in the neonate. Given this diagnostic dilemma, many UTIs are either not diagnosed or are diagnosed late, some are undoubtedly missed or treated as another entity. Primary care providers must have a high index of suspicion for UTI in the neonatal period to achieve an accurate diagnosis and, of course, obtain a properly collected urine specimen.[10]

Additional concerns of the practitioner lie in the knowledge that not only is the risk of serious bacterial illness higher in young infants and neonates, but also the clinical clues that are often used to detect serious illness are not reliable. Clinical illness indicators, such as state variation and reaction to parental stimulation, are not reliable predictors of serious illness. As many as 65% of neonates with a febrile illness involving a serious bacterial infections appear well on initial examination.[11]

Clinical manifestations of neonatal UTI can be similar to clinical signs of neonatal sepsis, although digestive symptoms have been reported to be more frequent in newborn infants. Elevation of body temperature and poor feeding were the most frequent clinical symptoms, in particular in infants with community-acquired infections. Children younger than three months with a UTI are more likely than older children to have bacteremia, sepsis, and congenital genitourinary abnormalities.[1] Bacteremia associated with UTIs is mostly observed in patients less than six months of age, particularly those less than two months of age, whose risk of bacteremia is estimated to be between 4.0 and 22%.[12]

IMPACT OF CIRCUMCISION

As we debate the medical indications for circumcision in this country, it is well documented that newborn uncircumcised males are at higher risk for urinary tract infections. Uncircumcised boys have an overall 12-fold increased risk of UTI compared with circumcised boys during the first six months of life.[13] The benefit of circumcision in terms of UTI prevention is known to extend for six months after birth, and possibly for as long as one year. After one year of age, there is no evidence that circumcision affects the rate of UTI in males.

Uncircumcised boys less than six months have a greater quantity of both *E. coli* and Gram-negative uropathogens in their urethras as compared with circumcised cohorts. Voiding pressures in newborn males are higher on urodynamic evaluation. Higher voiding pressures, along with a higher risk for cystitis and colonization, amount to an increased propensity for illness in these children. Total costs for treating UTI are reported to be ten-fold higher in uncircumcised than in circumcised male infants, which reflect the greater number of UTI diagnosed in this patient group and possibly a higher number of hospital admissions.[14] Findings confirm the strong body of evidence of attesting to the protective effect of newborn circumcision against UTI in the first year of life, an age when infections are most severe and likely lead to hospital admission.[14] Still, there is morbidity to this procedure and it is estimated that the number needed to treat is approximately 111, that is, 111 boys need to undergo circumcision in order to prevent one UTI.[15]

BREASTFEEDING

Breastfeeding may have a protective role in preventing UTI in premature infants and should be encouraged.[9] Breastfeeding has been significantly associated with a lower risk of UTI. It has been reported to have a protective effect against many infections in the first year of life, including gastroenteritis, acute otitis media, pneumonia, bacteremia, and meningitis. The protective effect is attributed to its action on the intestinal flora, including its high concentration of IgA, which inhibits adherence of bacteria. In addition, lactoferrin prevents the growth of intestinal *E. coli*. Furthermore, the low pH of stool in breastfed babies allows for the growth and colonization with less virulent organisms such as bifidobacteria and lactobacilli.[9]

DIAGNOSIS

Unlike older children, neonates lack diurnal temperature variation and have less normal temperature variability

Table 91.2 Prominent symptoms in neonatal nonobstructive urinary tract infection.

Symptom	Prevalence (%)
Failure to thrive/weight loss	51
Fever	41
Jaundice	12
Cyanosis	30
Vomiting	35
Diarrhea	20

Modified from Phol *et al.*[21]

(Table 91.2). During an acute infection fever is commonly absent in neonates.[16] The general appearance and physical examination of the febrile neonate cannot be relied on to exclude a serious bacterial infection. Multicenter prospective studies of febrile infants who were 60 days of age or younger and evaluated in an emergency room for fever, circumcision status, and height of fever were associated with an increased likelihood of UTI.[3] Hyperbilirubinemia with prolonged jaundice (lasting more than 14 days) is commonly the main clinical feature at presentation that may be the only manifestation of UTI.[4] Jaundice can be an early sign in afebrile infants and was more common in those neonates with nosocomial UTI. Positive urinalysis findings have been reported in approximately 56% of cases.[6]

The most common current emergency department (ED) practice management of even a well appearing febrile neonate is a full sepsis evaluation, including a complete blood count (CBC), blood cultures, urinalysis and urine culture, evaluation of cerebrospinal fluid (CSF), and administration of antibiotics (ampicillin, cefotaxime, or gentamicin), with hospitalization pending culture results.[17] The initial evaluation must include a detailed history along with a thorough physical examination. Care must be taken when evaluating the newborn for abdominal masses. The back must be carefully examined for the presence of dimples or abnormalities suggestive of a spinal dysraphism. The degree of phimosis should be noted if the child is uncircumcised, and although rare, labial adhesions must be ruled out in female newborns. The presence of adhesions and recurrent UTI is an indication for intervention. In neonates, adhesions are treated surgically in order to avoid the utilization of estrogen or betamethasone ointments which are commonly recommended in older children (older than six months of age).

The definitive diagnostic test of a UTI is a positive urine culture. This can be obtained through suprapubic aspiration or urethral catheterization. A false-positive culture obtained via a bag specimen may lead to inappropriate treatment, misdiagnosis, and unnecessary testing. The urinalysis which is immediately available is suggestive but not diagnostic. Although the presence of leukocyte esterase has a high sensitivity it lacks specificity; the nitrate test behaves conversely. When combined with microscopic findings, the sensitivity approaches 100% when all three are positive, and the specificity is 100% when all three are negative.[18] The presence of any bacteria on Gram stain has a sensitivity of 93% and specificity of 95%, better than dipstick evaluation for leukocyte esterase and nitrates.[10] There are four ways that urine can be obtained: (1) a bagged specimen, where a bag is taped to the perineum and urine obtained after the child voids (useful in infants, but there is a high risk of obtaining a contaminated specimen); a midstream collection (unreliable in children, especially in young girls and uncircumcised boys in whom contamination is likely) is useful if negative, but if positive, it is hard to tell if the collection was contaminated; (3) a catheterized specimen (obviously traumatic in children and further, in the uncooperative girl it can easily be contaminated); and (4) suprapubic aspiration, clearly the least likely to be contaminated, but again traumatic in children and rarely practiced in the current litigious environment.[10]

In neonates less than three months old, a catheterized urinalysis or suprapubic bladder aspiration is part of the standard work up for fever. Suprapubic aspiration, although not usually necessary, is considered the gold standard method for obtaining urine. It is performed after cleaning the suprapubic area with antiseptic solution. A 21- to 25-gauge needle is inserted one finger breadth above the symphysis pubis perpendicularly, while aspirating until urine is obtained. Although suprapubic aspiration is popular in some emergency departments, it is both invasive and has variable success rates for obtaining urine because of the lack of urine in the bladder. Physical examination to palpate for a full bladder is sometimes limited if the child is very upset. Ultrasound, if available, may be useful to check bladder fullness before aspiration. For males with phimosis, tight foreskin, or stricture, and for girls with severe labial adhesions, suprapubic aspiration may be the only method for obtaining clean urine.[19] Although the probability of a true infection with a positive culture obtained via suprapubic aspiration is approximately 99%, this method is the most technically challenging and is associated with the lowest rate of success (23–99%).[20]

Recovery of any organism from a suprapubic specimen, at least 50 000 colony-forming units per milliliter (CFUs/mL) from a catheterized specimen, or at least 100 000 CFUs/mL from a clean-catch specimen is considered significant bacteriuria.[1] We should re-emphasize the importance of accurate diagnosis and the appropriate collection of specimen. Results affect the child's care, and can potentially subject them to invasive procedures, and parents to undue stress. The American Academy of Pediatrics (AAP) has published recommendation for the diagnosis, treatment, and evaluation of initial UTI in febrile infants and young children, however, no recommendations for neonates less than two months of age have been suggested.[6] Investigators have commented on the value of urine smell in the diagnosis of UTI. Struthers *et al.*'s study[21] demonstrated no association between reported abnormal or different urine smell and UTI.

CRP >20 mg/L, ESR >30 mm/hour, and WBC >15000/μL are key findings in various studies on febrile infants. The diagnostic value of these for predicting serious bacterial infection in febrile infants, however, is conflicting. Lin *et al.*[22] showed that febrile infants with CRP >20 mg/L and ESR >30 mm/hour were at risk for UTI, but that a WBC count >15000 was not significantly associated with UTI. Although the specificity of ESR and CRP was high, their sensitivity was relatively low, demonstrating that elevated CRP and ESR are poor predictors for identifying UTI in febrile illness.

VESICO-URETERAL REFLUX

Prenatal hydronephrosis is noted in 1–5% of pregnancies. The rate of prevalence of vesico-ureteral reflux in neonates varies from 11 to 12.5%. Considering fetal and postnatal dilation as a combined test and a value of less than 10 mm as a negative indication for voiding cystourethrogram (VCUG) results in increased sensitivity and diagnostic odds ratio for detecting clinically significant VUR.[23] The likelihood of significant renal abnormalities postnatally correlates with the severity of anterior posterior diameter (APD) dilation. A meta-analysis of 17 studies reported the risk of renal abnormalities for three classifications of antenatal hydronephrosis. The probability of ureteropelvic junction obstruction increased, but there was no association of VUR with APD measurement (Tables 91.3 and 91.4).[24]

Table 91.3 Degree of prenatal hydronephrosis and postnatal risk of renal abnormalities.

Degree of hydronephrosis	Postnatal risk (%)
Mild	
<7 mm in the second trimester <9 mm in the third	11
Moderate	
7–10 mm in the second 9–15 mm in the third	45
Severe	
>10 mm in the second >15 mm in the third	88.3

Table 91.4 Prenatal hydronephrosis and risk of postnatal VUR.[Hothi et al.]

Degree of hydronephrosis	Postnatal risk (%)
>12 mm at 20 weeks and >14 mm at 34 weeks	15
6–8 mm during second or third trimester	5

The incidence of VUR in children presenting with symptoms of a UTI is in the order of 30–50%. The incidence, however, is believed to be lower in neonates. Standard of care calls for antibiotic prophylaxis in a child presenting with a febrile UTI, or recurrent non-febrile UTIs, until VUR can be ruled out. Traditionally, recommended work-up has consisted of a renal and bladder ultrasound, as well as a voiding cystourethrogram, or a nuclear medicine cystogram, both of which are invasive studies. The false-negative rate of VCUG is estimated at 20%. A nuclear medicine cystogram involves a fraction (1%) of the radiation exposure experienced with a VCUG. Although its sensitivity is excellent, one major disadvantage is the lack of anatomic detail. It is difficult to identify Hutch diverticula, bladder trabeculation, or a dilated posterior urethra with a nuclear medicine study.

A DMSA scan at the time of presentation is the hallmark of the 'top-down' approach. Some authors advocate that 50% of children will have a positive DMSA during the acute phase. Of those children with a positive DMSA scan, 30–40% will demonstrate reflux. Conversely, 90% of children with VUR will have had a positive DMSA scan. If VCUG is deferred for those children with febrile UTI and a positive acute DMSA scan, presence of hydronephrosis, or a dilated ureter, one would miss 10% of children with VUR, most of these being children with low-grade and low risk for UTI and late renal scarring.[25] Small studies looking into early DMSA scanning in neonates, mainly females and uncircumcised males, agree that DMSA is helpful in ruling out later development of permanent renal damage, but was not predictive of the absence of dilating VUR. Therefore, if dilating VUR is to be ruled out a VCUG needs to be performed even in the presence of a normal DMSA scan.[26] Neonatal reflux, even high grade, is more likely to resolve than VUR detected after UTI at a later age. Prospective data on the follow up of infants with prenatal hydronephrosis diagnosed with grade III, IV, or V showed resolution rates of 53, 28, and 40%, respectively, at four years.

The goal of radiologic studies is to identify genitourinary malformations and defects that can predispose the newborn to recurrent urinary tract infection. Anatomic obstruction (posterior urethral valves, ureteropelvic junction obstruction, ureterovesical obstruction, and ureterocele) as an etiology for UTI is seen in 2–10%.[27] Urethral obstruction during fetal development secondary to anatomic reconfiguration of the bladder neck is suggested as the cause of high-grade bilateral reflux in male neonates.[28] Hoberman *et al.*[29] evaluated the value of renal ultrasound after first febrile UTI in children as young as one month. Their conclusion was that in less than 1% of their study, renal US after first febrile UTI will show findings significant enough to impact management, including additional imaging studies. In their conclusion, the authors did not recommend ultrasonography after a first febrile UTI in children with unremarkable prenatal ultrasound after 30–32 weeks of gestation. In a study of early DMSA scanning in neonates with febrile UTIs, Siomou *et al.*[26] found that the ability of DMSA to predict dilating VUR was low, since the majority of children with greater than grade III VUR had normal DMSA results. Moreover, they noted that none of these patients were noted to have normal renal US.

MANAGEMENT

Developmental considerations exist that must be taken into account when treating neonates with a UTI. Glomerular filtration rate is low at birth and develops with age. This must be taken into consideration when prescribing medication and calculating fluid requirements.[5] Treatment depends on the diagnosis of either cystitis or pyelonephritis, and whether the diagnosis is either simple or complicated. Simple cystitis requires a short course of oral antibiotics based on suseptibilities (3-day course). A complicated UTI will require a longer course and even parenteral antibiotic administration based on initial presentation. Pyelonephritis

requires a 10- to 14-day course of parenteral medication followed by oral administration based on initial presentation. It has been established that oral and i.v. antibiotics have been equally effective in treating young children with acute pyelonephritis. It was shown that time to defervescence and return to sterile urine within 24 hours was identical; also that the cost of a 10-day oral course was significantly lower, without clinical compromise, i.e. reinfection or renal scarring.[30] Studies evaluating the treatment of febrile UTIs in young children with oral versus i.v. antibiotics have demonstrated similar efficacy with the use of third-generation cephalosporins.[31]

The antibiotic repertoire available to the physician in the newborn period is significantly more limited than that available to older children. Aminoglycosides, penicillins and cephalosporins can be utilized in the newborn period, however, their use is not without risk. Potential complications associated with their use include diarrhea, intolerance, and allergic reactions including anaphylaxis, as well as nephrotoxicity if not carefully dosed and monitored. Nitrofurantoin has been linked to hemolytic anemia in the neonatal period, and should not be utilized in children with glucose-6-phosphate dehydrogenase deficiency because of the risk of hemolysis. Given low tissue levels attained during administration, nitrofurantoin is a poor choice for the treatment of pyelonephritis. Trimethoprim use should be avoided in patients with megaloblastic anemia with folate deficiency, or in children with sodium-wasting disease (i.e. posterior urethral valves or renal insufficiency) because of potential hyperkalemia by blocking the sodium channels present in the principal cells of cortical collecting ducts. It can also increase serum creatinine levels by blocking the proximal tubular secretion of creatinine. Trimethoprim/sulfamethoxazole should not be used in the newborn period because of concerns for hyperbilirubinemia and kernicterus. The metabolic acidosis seen in patients taking trimethoprim/sulfamethoxazole is attributed to bicarbonate loss induced by the sulfamethoxazole component through an acetazolamide-like effect on the proximal tubules.[28]

PROPHYLAXIS

The benefits from prophylactic antibiotic use have been debated (Table 91.5), including their use in those children with VUR and those without it. Some have published short follow-up studies demonstrating their inefficacy in the management of low and moderate VUR.[32] Recently, results from the PRIVENT trial were published demonstrating a modest reduction in the rate (7%) of recurrent symptomatic urinary tract infection in predisposed children, including those with VUR and those with a previous UTI with the use of prophylactic antibiotics.[33]

SURGERY

Surgical intervention in the newborn for recurrent UTI is rarely necessary. Indications for surgery include recurrent episodes of urinary tract infection, and/or deteriorating renal function noted on nuclear medicine studies (Table 91.6). Infection in the face of hydronephrosis from a ureteropelvic junction obstruction mandates consideration for surgical reconstruction. Surgery can also be considered for ectopic ureteral insertion, and distal ureteral obstruction with recurrent infection, with or without antibiotic prophylaxis. The size of the newborn bladder has to be taken into consideration during reconstruction, given that a ureteral reimplantation into a small newborn bladder can be a difficult task. Some authors advocate the utilization of proximal, or distal diversion in order to allow the bladder time to grow, and attain a larger capacity. Staged repairs can be considered, especially if there is the potential need for tapering of the distal ureter during reimplantation. The presence of a ureterocele and infection calls for prompt incision followed by antibiotic prophylaxis given the high likelihood of vesico-ureteral reflux. Ureterocele puncture or incision is usually followed by reconstruction of the bladder.

Since its approval by the Federal Drug Administration, dextranomer/hyaluronic acid (Dx/HA) copolymer has revolutionized the management of vesico-ureteral reflux. Its applicability to newborns has not been well documented. However, given the low morbidity associated with this procedure, injection therapy is a viable option in the face of recurrent UTIs and low-grade vesico-ureteral reflux. It should be noted, however, that injection into a newborn bladder can be challenging and long-term follow-up studies after injection in younger children are lacking.

Urinary tract infections in the myelodysplastic newborn warrant earlier urodynamic evaluation, the implementation

Table 91.5 Prophylactic antibiotic regimens for prevention of urinary tract infection.

Antibiotic	Dose
Trimethoprim	2 mg/kg daily
Trimethoprim-sulfamethoxazole (TMP-SMX)	2 mg/kg TMP, 10 mg/kg SMX daily
Nitrofurantoin	1–2 mg/kg daily
Amoxicillin	20 mg/kg daily
Cefexime	4 mg/kg daily

Table 91.6 Surgical conditions leading to febrile urinary tract infection.

	Condition
Anatomic	Vesico-ureteral reflux
	Ureterocele
	Ureteropelvic junction obstruction
	Posterior urethral valves
	Ureteral or renal calculi
	Obstructed megaureter/megacalicosis
Functional	Neurogenic bladder – myelomenigocele
	Dysfunctional voiding – Hinman's syndrome

of anticholinergic therapy, and clean intermittent catheterization, along with the use of prophylactic antibiotic therapy. Recurrent infections may require surgical intervention in the form of vesicostomy, and rarely more proximal diversions, such as ureterostomy/pyelostomy. Recurrent infections following ablation of posterior urethral valves (PUV), and persistent hydronephrosis can also lead to diversion, including the use of ureterostomy or pyelostomy to prevent recurrent infections. Prior to diversion in the PUV, patient imaging studies (VCUG) should be obtained confirming that the valves have been adequately ablated. A thorough urodynamic evaluation is also recommended. However, in the author's opinion, the use of diversion rarely affects the clinical course of the patient, and rarely seems to affect the recurrence rate.

CONCLUSION

Neonates are particularly susceptible to develop urinary tract infection which may be explained by the compound effect of immaturity of the local defense mechanisms (decreased uroepithelial bactericidal activity, low levels of local immunoglobulin A, decreased urinary acidification) and heavy periurethral colonization occurring in healthy neonates and gradually resolving after six months of age.[2] The benefit of circumcision in the prevention of early urinary tract infection is not questionable in the neonate. In the general population, the recurrence rate for UTI is very high. Within one year of a first infection, approximately 30% of boys and 40% of girls will develop a repeat infection. The rate will double for each subsequent episode.[27] Unfortunately, recurrence is not uncommon in the neonatal period. With the widespread use of prophylactic antibiotics, recurrence with multiresistant organisms is also a possibility. The need and extent of radiologic imaging required following a neonatal UTI is still under investigation. The usefulness of invasive, expensive studies continues to be questioned.

Pediatric UTIs constitute a significant health burden. Although the actual costs are not known, it is estimated to be in the order of US$180 million for inpatient costs in the United States. This fails to include the costs to society of parental productivity from lost wages, treatment, and follow up after the infection.[10] There are a number of complex host and bacterial virulence factors that play into the susceptibility of children to UTI. It is important that the clinician be familiar with the spectrum of UTI, and children at risk of UTI, so infants and children that need to be evaluated for anatomic or functional abnormalities of the urinary tract are correctly identified and managed.

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Imaging of the renal tract in the neonate

LORENZO BIASSONI AND MELANIE HIORNS

INTRODUCTION

The widespread use of antenatal ultrasound in the last 25–30 years has allowed the early identification of a number of congenital nephro-urological abnormalities, which are now assessed with imaging soon after birth. In addition, a congenital nephro-urological abnormality may declare itself postnatally, for example with a urinary tract infection, anomalies in urine stream, septicemia, metabolic upset due to renal failure, or simply vomiting. Occasionally, the neonate may have hematuria due to renal vein thrombosis, especially in the case of a prolonged labor with hypoxic events. A well neonate may present with an abdominal mass found on routine examination or with an apparently unrelated congenital abnormality, e.g. esophageal atresia.

Once the attention of the clinical team has been focused on the genitourinary tract, the role of the radiologist is to establish whether the child has been born with a normal urinary tract and whether he is therefore suffering from an acquired condition, or whether he suffers from a congenital anomaly.

Usually, the questions asked by the clinical team are the following: (1) how many kidneys are present and where are they within the abdomen; (2) is there dilatation of the renal collecting system and is the renal parenchyma normal or abnormal; (3) are the bladder and the urethra normal or is there a thick-walled bladder and/or an obstructed urethra; and (4) what is the renal function, both in absolute terms and in terms of the split function of each kidney.

The radiologist has three key imaging examinations available, which can provide an answer in the vast majority of cases: the abdominal ultrasound (US), the micturating cystogram (MCU), and the radioisotope examinations. Nowadays, there is no indication for i.v. urography (IVU) in the neonatal period (and almost no role in the older child). Computed tomography (CT) in the neonatal period would be confined exclusively to the assessment of a renal mass if the US had not been able to provide satisfactory information, and if magnetic resonance imaging (MRI) was not available. MRI has an important role to play in the work-up of renal tumors and in the assessment of the morphology of the urinary tract, again, if insufficient information has been obtained by US. In this instance, most babies can undergo a 'feed and wrap' technique and will not necessarily require sedation or a general anesthetic.

COMMONLY AVAILABLE IMAGING MODALITIES

Abdominal ultrasound

The first imaging examination of the urinary tract should always be an abdominal US. With modern US equipment and well-trained personnel, it is possible to obtain anatomical detail of the entire urinary tract. The equipment is mobile, and a comprehensive US examination can be undertaken even in the ill neonate in an incubator on intensive care. The results of the US examination set the framework of the anatomical state and frequently permit the nephro-urological team to begin therapy with either a shortlist of differential diagnoses or a presumed single diagnosis. In the majority of cases, the US examination will identify how many kidneys are present, the renal size, whether the kidneys are simplex or duplex, if the parenchyma is sonographically normal, and if there is dilation of the renal collecting systems. The bladder should be examined at the beginning of the US examination, as micturition may occur at any moment and a full bladder is useful when searching for dilated ureters behind the bladder (Fig. 92.1). Bladder wall thickness is easy to identify and measure; the proximal posterior urethra may be dilated in the male with posterior urethral valves, and this can be identified during micturition if looked for. The patient needs no preparation for an US examination. The examination should be performed with both the standard curvilinear probe and also with a high frequency (and thus high resolution) linear probe. Ideally, the infant should be scanned both supine and prone, although if a neonate is being ventilated it will not be possible to obtain prone images.

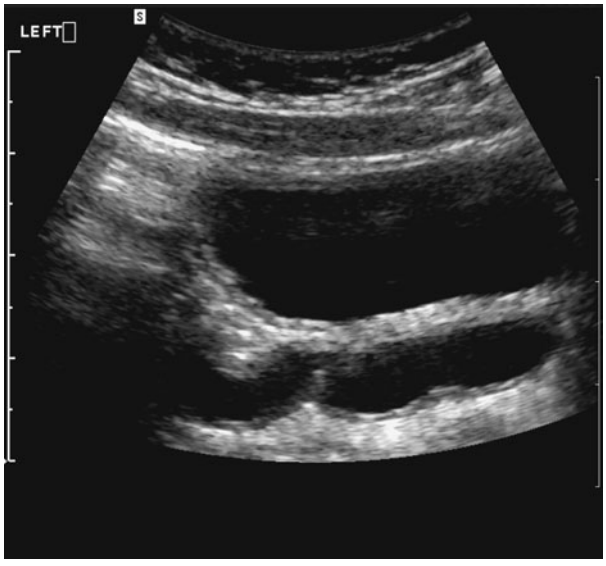


Figure 92.1 Ultrasound showing a dilated left ureter behind the bladder, in this patient this was secondary to a vesico-ureteric junction obstruction.

The normal US appearance of the kidney in a neonate is of a slightly echo bright cortex, when compared to the adjacent liver or spleen, with a slightly echo poor medulla (pyramids). The difference between the cortex and the medulla is termed corticomedullary differentiation. A small kidney with loss of corticomedullary differentiation indicates an abnormal parenchyma (Figs 92.2 and 92.3). This may be due to an acute insult, such as acute renal failure or renal vein thrombosis, or may represent an underlying intrinsic abnormality, such as renal dysplasia, which may be associated with cysts to varying degrees. The presence of dilatation of the collecting system must raise the possibility of obstruction, but does not necessarily infer this. If the dilatation is bilateral, then bladder outlet pathology must be excluded. However, vesico-ureteric reflux (VUR) may give a very similar appearance.

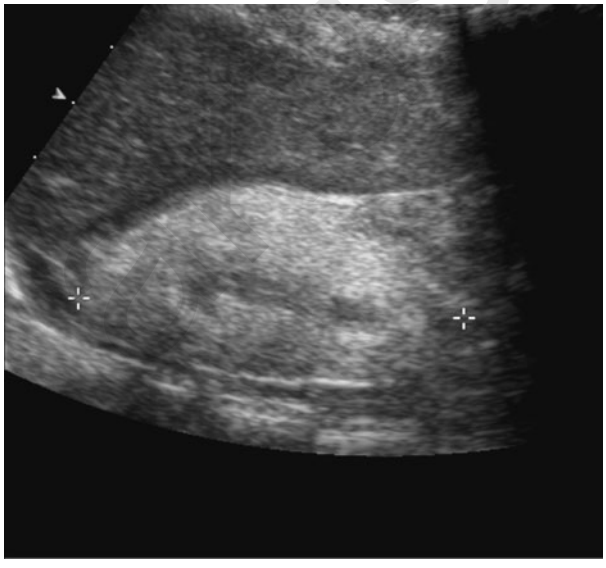


Figure 92.2 Ultrasound in a newborn male patient with primary hyperoxaluria. The kidney is echo bright compared to the adjacent liver and has lost its corticomedullary differentiation. In this condition, the brightness represents global nephrocalcinosis.

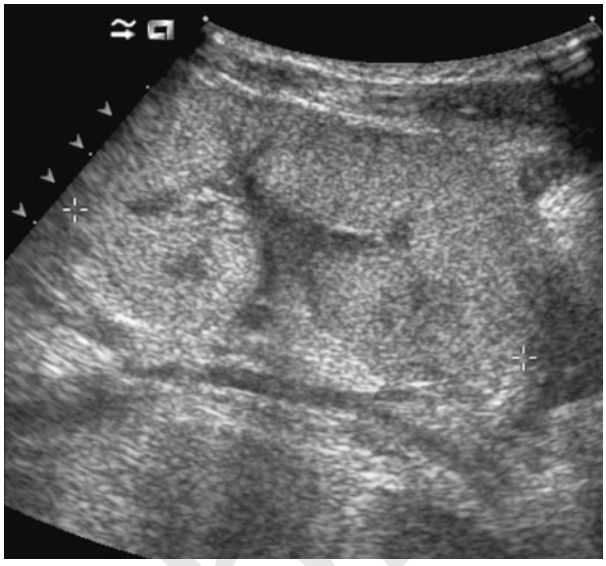


Figure 92.3 Ultrasound in a 4-week-old male patient with congenital nephritic syndrome. The kidney is bright and enlarged, but some of the normal architecture can still be recognized.

In the neonate, features on US of echogenic areas within the kidneys may suggest nephrocalcinosis (Fig. 92.2), and this is the most common cause of focally echo bright kidneys following furosemide diuretic therapy. Tamm Horsfall proteins may give a similar appearance, but are transitory.

There are two important pitfalls in the use of US that should be stressed. The first is in the presence of a sick neonate who is either anuric or oliguric, when US may not reveal any dilation, but an obstructive uropathy may still be present. In this clinical situation, a repeat US must be carried out once the infant starts to produce urine. The second pitfall is in the case of antenatally diagnosed unilateral hydronephrosis: here, the US may fail to show significant dilation during the first 48 hours of life due to physiological dehydration and the US should be done on the 3rd postnatal day or later.

Micturating cystourethrogram

An MCU gives invaluable anatomical information about the bladder, and the bladder outflow tract in the male, and if VUR is detected, then details of the ureters, pelvis, and calyces are well outlined (Fig. 92.4). Contrast showing calyceal detail may suggest renal dysplasia. The combination of US and MCU allows adequate evaluation of all kidneys and collecting systems shortly after birth and permits appropriate management to be instituted immediately in all cases, especially if an obstructive uropathy is present, e.g. posterior urethral valves (Fig. 92.5). The timing of the MCU will depend on clinical presentation and clinical state of the baby.

The baby will need to be catheterized and in most patients a 6-F feeding tube can be used. It is not necessary to use a catheter with a balloon as there is no indication to inflate the balloon for this study. The voiding views of the urethra in the male child should be obtained with both the tube still in and

with it removed to ensure that a tiny valve leaflet is not missed. Antibiotic cover should be given before and after the procedure, which should be done under sterile conditions.

An MCU is only rarely indicated in the immediate neonatal period, although there may be extended indications when the infant is slightly older. In the neonatal period it is most commonly indicated with the US finding of bilateral hydronephrosis. This raises the possibility of an obstructive uropathy either in the urethra (posterior urethral valve in the male infant), at the bladder base (ureterocele), at the vesicoureteric junction (VUJ) bilaterally, or a bilateral pelviureteric junction (PUJ) obstruction. Bilateral VUR may give identical images (Fig. 92.4). In this context, an MCU should be carried out as soon as the baby is in a good clinical state.

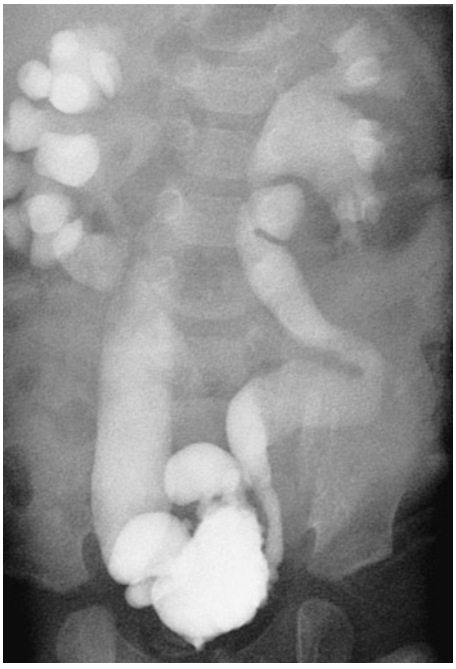
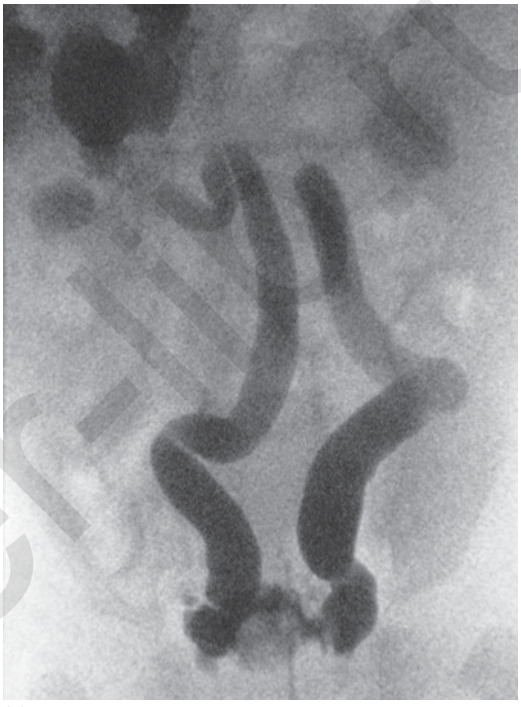


Figure 92.4 Micturating cystogram in a patient with gross reflux outlining the hydro-ureteronephrosis and the configuration of the collecting system. There was no outflow tract obstruction in this patient (no posterior urethral valve).



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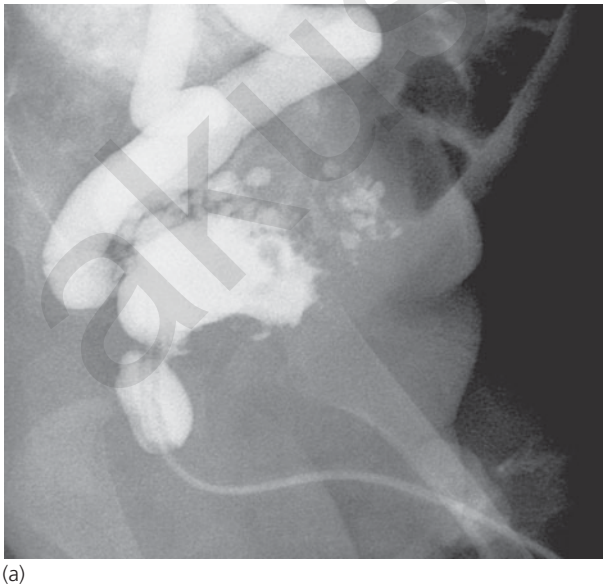

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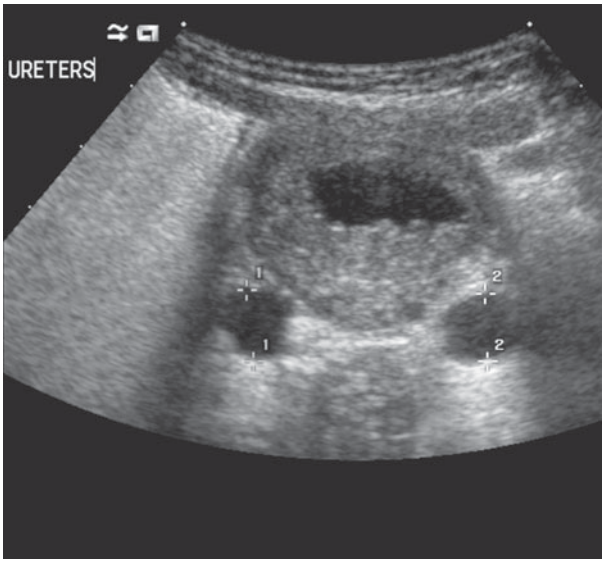


(c)

Figure 92.5 (a) Micturating cystourethrogram in a newborn male demonstrating a tight posterior urethral valve and a very trabeculated and thickened bladder wall; (b) a later view in the same patient showing gross reflux in both ureters to the level of the collecting systems; the bladder has preferentially refluxed contrast into the upper tracts as this presents less obstruction than overcoming the tight posterior urethral valve; (c) ultrasound in the same patient showing a very thick-walled bladder and bilateral dilated ureters behind the bladder.

If an MCU is being performed for possible posterior urethral valves and these are confirmed, then the catheter should not be removed; the diagnosis has been established and there is no additional information to be gained by a tube-out view, and there is a risk of a difficult recatheterization to re-establish continued bladder drainage.

The neonates with an antenatal diagnosis of hydronephrosis requiring an MCU include all those with postnatal US confirmation of either a dilated ureter, bilateral hydronephrosis, or an abnormal bladder. Unilateral hydronephrosis with a normal opposite kidney and bladder on US in a well neonate does not require an MCU.

If the clinical question is only about the presence of VUR, and the anatomy of the urethra in a male infant has already been assessed with a previous MCU, a radioisotope cystogram (direct isotope cystography, DIC) will answer the question, with a negligible radiation burden (less than a chest x-ray) to the infant. This test is obtained by positioning the child on the gamma camera head and catheterizing the bladder. A minimal amount of Tc-99m pertechnetate (20 MBq is sufficient) is then instilled in the bladder via the catheter. The catheter is connected to a bag with saline; the saline is run and the bladder is filled until the child feels the urge to void. The acquisition begins after instilling the tracer in the bladder and continues until the end of the emptying phase (or when VUR has been demonstrated). If there is VUR during the bladder-emptying phase, this will be detected with high sensitivity (Fig. 92.6).

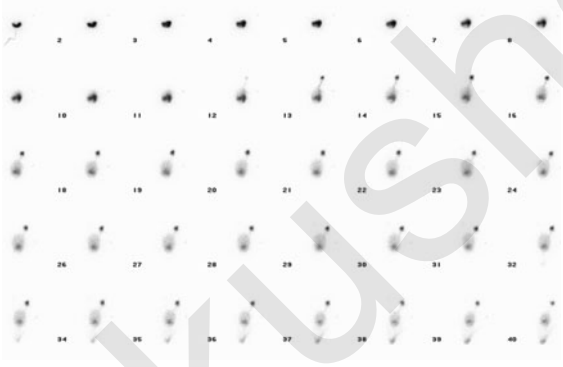


Figure 92.6 Direct isotope cystogram in a 16-month-old girl, showing clear evidence of right-sided VUR.

Functional imaging

Radioisotopes examinations provide an *in vivo* evaluation of the global and regional renal cortical function, with a precise estimate of the contribution of each kidney to the total renal function. Moreover, the dynamic radionuclide renography shows how each kidney drains, with identification of possible hold-ups.

TRACERS AVAILABLE

The main tracers available are the Tc-99m dimercapto-succinic acid (DMSA), the Tc-99m mercapto-acetyl-triglicine (MAG3) and the Tc-99m diethylenetriaminepentacetic acid (DTPA). Some centers use ^{123}I ortho-iodo-hippuran (OIH), but the labeling with ^{123}I (cyclotron produced) makes it an expensive and not readily available tracer. The DMSA is taken up by the proximal renal tubules and, once in the renal parenchyma, approximately 60% sticks within the tubules, while approximately 30–40% of the tracer leaves the kidney with the urine. The DMSA is the current gold standard for the evaluation of the differential renal function (DRF) and the evaluation of renal parenchymal integrity. The MAG3 and the OIH are secreted by the proximal tubules into the lumen and leave the kidney via the collecting ducts and the renal collecting system. The DTPA is filtered by the glomerulus and leaves the kidney via the collecting system. Tc-99m MAG3 has a higher extraction fraction than Tc-99m DTPA and therefore is a better tracer, especially in the neonate. The tracers used for dynamic renography can evaluate DRF almost as accurately as the DMSA. They can also provide an evaluation of renal parenchymal integrity (although small scars can be missed) and assess drainage.

PATIENT'S PREPARATION

The child should be appropriately hydrated. This allows normal flow of urine throughout the renal parenchyma and pelvi-calyceal system. If the child is suboptimally hydrated, the tracer will progress slowly through the renal parenchyma and collecting system, thus giving a false impression of obstruction. In some centers, i.v. fluids (saline 10–15 mL/kg) are given, starting 30 minutes prior to the tracer injection. In other centers, oral hydration is preferred. It is also essential that the child is immobile during the examination: this is achieved with sandbags at both sides of the neonate and velcro straps. If the neonate has been fed prior to the start of the examination, it is likely that he will fall asleep and keep still. Sedation/general anesthesia are not necessary and should not be used.

EVALUATION OF THE DIFFERENTIAL RENAL FUNCTION

This is achieved by drawing regions of interest (ROI) around each kidney at a time after tracer injection when the parenchyma-to-background ratio is optimal and no significant tracer has reached the collecting system (normally between the first and the second minute after tracer injection in the case of tracers used in dynamic renography). In the case of DMSA scintigraphy, the split function is usually calculated between 2 and 4 hours after tracer injection, when the tracer has been taken up by the renal parenchyma. ROI around each kidney to subtract background activity are also drawn. A precise estimate of the DRF can be challenging in the neonate, with immature kidneys and consequent reduced tracer uptake and relatively high background activity, even more so if there is also chronic renal failure (for example, due to posterior urethral valves), because the kidneys extract the tracer much less avidly. Another challenging clinical situation is when one of the kidneys is much bigger than the other, for example, in a neonate with prenatally diagnosed severe hydronephrosis.

In a neonate with antenatally diagnosed hydronephrosis, functionally imaging is normally deferred until the child is two or three month old, with better, even if not complete, renal maturation. Occasionally, a functional study may be requested in a younger infant: the clinical question then is whether a kidney shows any significant function at all, leading to the consideration of a possible nephrectomy versus more conservative treatments.

EVALUATION OF DRAINAGE

Drainage can be influenced by several different factors, especially in the neonate: the function of the kidney, the hydration status, the size of the renal pelvis, the bladder status, the effect of gravity (supine versus upright position). Therefore, an accurate evaluation of drainage has to take into account all these factors. Intravenous furosemide administration (5 mg in neonates and infants up to six months of age) can help to distinguish between an obstructed renal pelvis and a dilated non-obstructed one. It may happen that the neonate voids in the nappy during the dynamic renography, especially after administration of furosemide: this can be helpful as it shows the drainage pattern with an empty or almost empty bladder and it can even demonstrate the possible presence of VUR. An image after change of position (from supine to upright) at the end of the dynamic renography is essential to differentiate an obstructed pelvis from a dilated non-obstructed one.

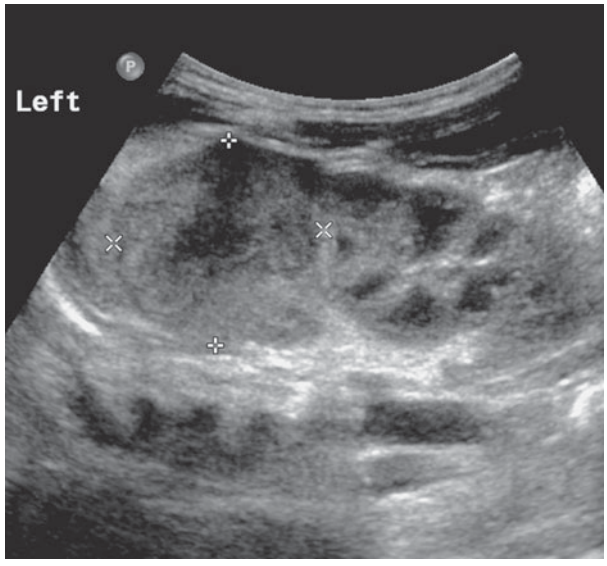
There are computerized methods to assess drainage. The half-time diuretic wash-out method calculates how long it takes to halve the counts within the renal pelvis following furosemide administration. This method is only reliable if it gives a normal value (<10 minutes half-time). If it is prolonged, it cannot differentiate between a dilated pelvis and an obstructed one, as it does not take into account the size of the renal pelvis, the bladder status, the gravity effect, and the hydration status and therefore in the context of antenatally diagnosed hydronephrosis it should not be relied upon. Methods such as the pelvic outflow excretion efficiency (PEE) or the normalized residual activity (NORA) evaluate how much tracer has left the kidney as a percentage of what has come into the kidney (PEE) or how much tracer has remained in the kidney as a percentage of the amount that has left the kidney.

DEFINITION OF OBSTRUCTION

It is important to bear in mind that slow drainage via a dilated collecting system on dynamic radionuclide renography does not necessarily mean obstruction in the context of an asymptomatic infant with an antenatally diagnosed hydronephrosis. A dilated pelvis and/or ureter in an asymptomatic infant can be due to a number of conditions: PUJ or VUJ obstruction, PUJ dilatation with no obstruction, VUR, hydro-ureteronephrosis, megaureter with or without VUJ dysfunction, a complex duplex system with a dilated upper moiety. All these conditions can give slow drainage on dynamic radionuclide renography. Urinary stasis within a dilated renal pelvis/ureter does not necessarily cause suffering of the renal parenchyma. Even a mild stenosis at the PUJ may not cause sufficient resistance to urinary outflow to cause suffering of the renal parenchyma. Therefore, the only definition of obstruction that has been accepted at present is 'a condition of resistance to urinary outflow that, left untreated, will cause deterioration of renal function'. As it can be seen, unfortunately this definition is a retrospective one. Therefore, on a single dynamic renography examination showing slow drainage and urinary stasis either at the PUJ or at the VUJ, obstruction cannot be reliably diagnosed, as it is not known whether this condition will cause a fall in function of that kidney or not.

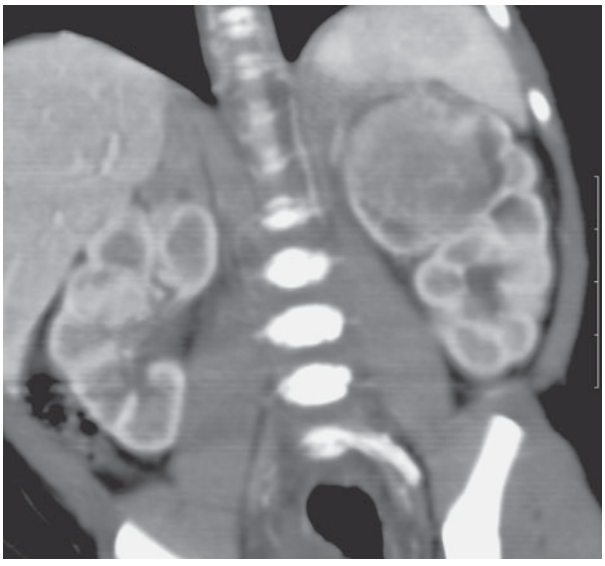
MRI and CT: cross-sectional imaging

In the presence of a transonic lesion on US, there is no indication for cross-sectional imaging as cystic lesions can be followed with US. Solid lesions will usually require further imaging after the initial US. The major differential diagnosis of renal tumors in the neonate is that of a mesoblastic nephroma (Fig. 92.7), as Wilms' tumors (Fig. 92.8) are rare in the neonatal period. Neuroblastoma (in the adrenal) can sometimes be confused with a renal mass lesion and should also be considered. MRI is the optimal technique to assess mass lesions as it does not use radiation and has better inherent tissue contrast resolution than CT. CT has good spatial resolution and is fast to acquire, but carries a heavy radiation dose penalty. Furthermore, the neonate has little fat



(a)

Figure 92.7 (a) Ultrasound in a 6-day-old male patient showing a mass at the upper pole of the left kidney. Histology subsequently confirmed mesoblastic nephroma; (b) computed tomographic scan in the same patient; (c) magnetic resonance image with T_2 weighting showing the displacement of the collection system around the mass and demonstrating the normal corticomedullary differentiation in the rest of the left kidney and in the right kidney.



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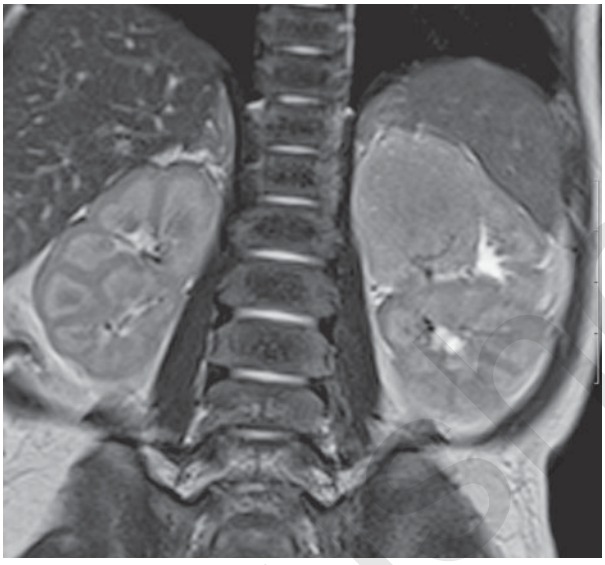


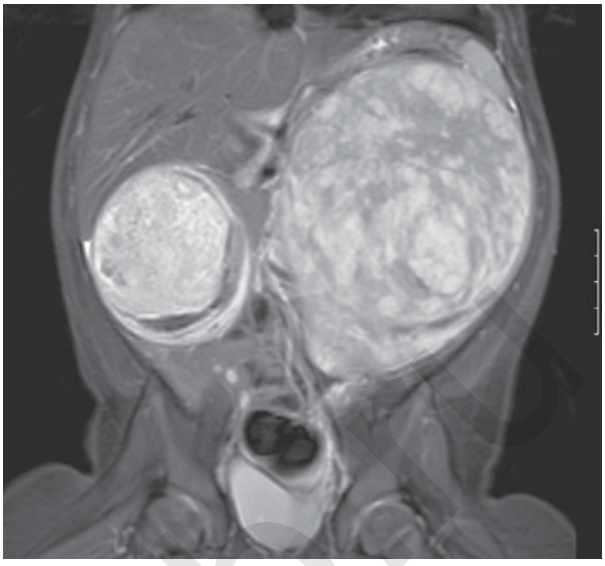
(c)

Figure 92.7 *Continued*

to provide contrast between tissues and thus CT images may be suboptimal.

MRI can also provide exquisite depiction of the urinary tract, especially if it is dilated, as specific sequences will show water, and hence urine-containing structures, in great detail. This examination is also termed magnetic resonance urography (MRU) (Fig. 92.9). It is therefore increasingly useful in supplementing the information obtained by US regarding dilatation, anatomy, and in some cases the function, of the renal tract.

The use of MRI in the neonatal age group was previously limited by the length of time to acquire various sequences (up to 10 minutes each) and therefore the risk of patient movement degrading the images, but the sequences are now much faster and techniques are available to counteract the effects of breathing and cardiac movement. MRI can be performed under general anesthetic if the 'feed and wrap' technique fails.



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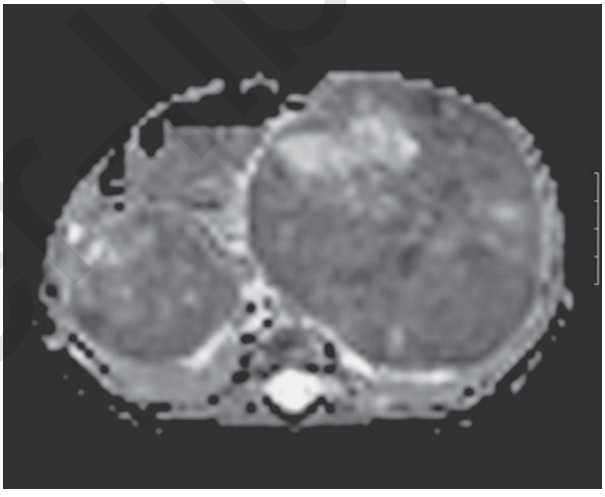


(b)

Figure 92.8 Magnetic resonance image in a three-month-old infant with bilateral Wilms' tumors: (a) STIR sequence in coronal plane showing the marked distortion of the normal anatomy due to the bulk of the tumors; (b) ADC sequence showing extensive areas of low signal (dark gray) within the tumors which represent densely packed tumor cells. The area of high signal (white) anteriorly in the larger left-sided tumor indicates an area of necrosis.

SPECIFIC CONDITIONS IN THE NEONATAL PERIOD

Hydronephrosis

Hydronephrosis in the neonatal period is most commonly imaged subsequent to an antenatal diagnosis of renal pelvic dilatation being made at a routine antenatal US scan. It is important to clarify if the dilatation is bilateral and how dilated the renal pelvis is. Imaging will always be by US. Bilateral pelvic dilatation (>7 mm) necessitates close inspection of the bladder (for bladder wall thickening and ureteroceles) and in boys will prompt MCU to exclude

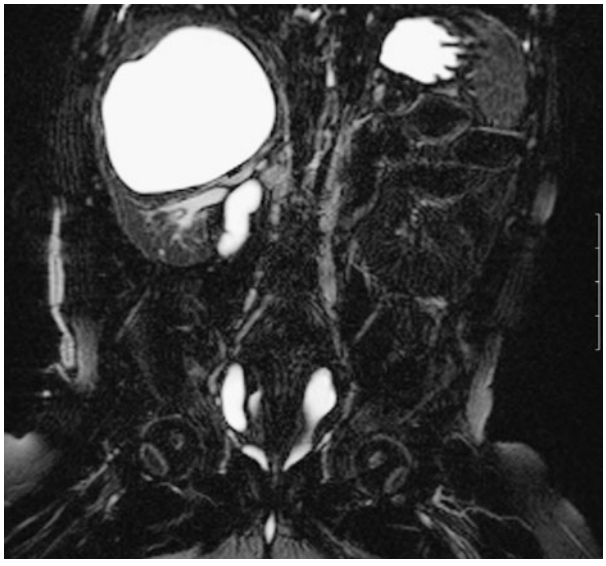
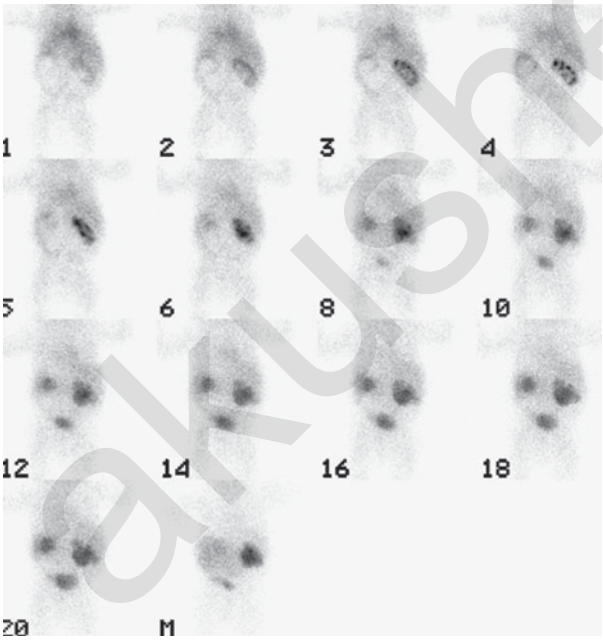


Figure 92.9 Magnetic resonance image in a six-month-old female patient in whom ultrasound had been unable to differentiate between a right-sided pelvi-ureteric junction obstruction and a dilated moiety of a duplex kidney. This heavily T_2-weighted sequence shows that the right kidney is in fact duplex with a very dilated upper moiety and a small and compressed lower moiety. Incidental note was also made of a didelphus uterus.

posterior urethral valves. A unilateral antenatally diagnosed hydronephrosis requires functional evaluation, normally with a MAG3 renography, to assess the split function of the hydronephrotic kidney and its drainage. It is important to realize that slow drainage does not necessarily mean obstruction. Follow up of a hydronephrotic kidney is normally performed with US, the frequency of which is controversial. Significant increase in renal pelvis dilatation on US will prompt a repeat functional study. A very significant unilateral dilatation at diagnosis may indicate an intrinsic severe PUJ obstruction, and a functional study (often with MAG3, but also DMSA can be used – especially if the kidney is very enlarged with a very stretched renal parenchyma) will be indicated to establish if the affected kidney has any useful function. A very enlarged and stretched kidney may still have function, or potentially recover its function if prompt intervention is instigated (Fig. 92.10).

'Bright' kidneys

In an unwell neonate, US may be requested by way of a baseline and to exclude any related renal cause for the infant's condition. On these occasions, the observation of 'bright' kidneys may sometimes be made. 'Bright' in this context implies that the parenchyma (both cortex and medulla) is



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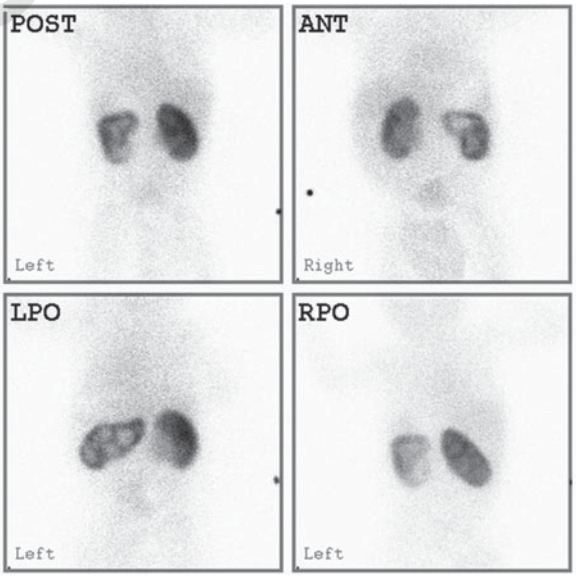


(b)

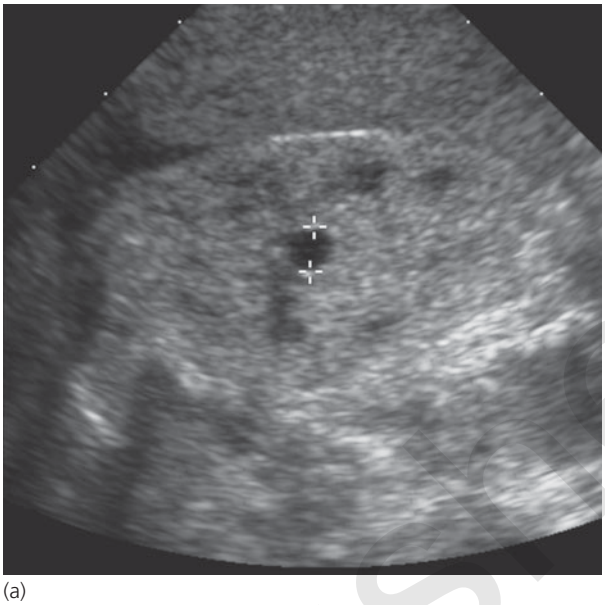
Figure 92.10 Two-month-old boy, presenting with massive left hydronephrosis. On ultrasound, the left kidney measured 11 cm in length, the left renal pelvis measured 8.4 cm, no left ureteric dilatation was seen. (a) Tc-99m MAG3 renogram. The split function of the left kidney is virtually impossible to measure accurately, as the kidney appears grossly enlarged and the region of interest around the left kidney together with the background region extends partially outside the body contour. However, there is tracer uptake within the left kidney suggesting some maintained function. Drainage from the left kidney is very slow, with urinary stasis in the very large renal pelvis seen even following change of posture and micturition. The child underwent an urgent left nephrostomy followed by a left pyeloplasty. (b) A DMSA scan performed a few days following pyeloplasty shows very good function in the left kidney (41% contribution to total renal function), with the kidney appearing much less stretched. On a follow-up MAG3 nine months later (not shown) the split function of the left kidney was unchanged. This case illustrates that prompt intervention on a massively enlarged kidney in an infant due to a PUJ obstruction can still restore good renal function.

more echo bright than the parenchyma of the adjacent liver or spleen. The kidneys may also be small, normal-sized, or large depending on the underlying cause (Figs 92.2 and 92.3).

The differential diagnosis of enlarged hyperechoic kidneys in the neonate includes acute tubular necrosis, renal vein thrombosis, polycystic kidney disease (autosomal dominant or autosomal recessive), autosomal dominant glomerulocystic kidneys, dysplastic kidneys (with or without an associated syndrome, Figs 92.11a and 92.12a) and, rarely, an underlying metabolic disorder (Fig. 92.2). In the case of renal vein thrombosis, a functional study can be useful once the acute episode has resolved to assess if the kidney drained by the thrombosed vein has lost significant function.

Cystic kidneys

Cystic kidneys will usually present in the neonate either because the infant is in renal failure, or because bilateral mass lesions can be felt in the flanks, or because the patient has an US scan for another reason. The main groups of cystic disease are listed above (see above under 'Bright' kidneys). A multicystic dysplastic kidney (MCDK) may be diagnosed antenatally, but may be picked up in the neonatal period or later (Fig. 92.13). Tuberous sclerosis may also give rise to multiple cysts in the kidneys, but it would be unusual for this to present in the neonatal period (Figs 92.12a and 92.14). US will always be the first examination and usually no other



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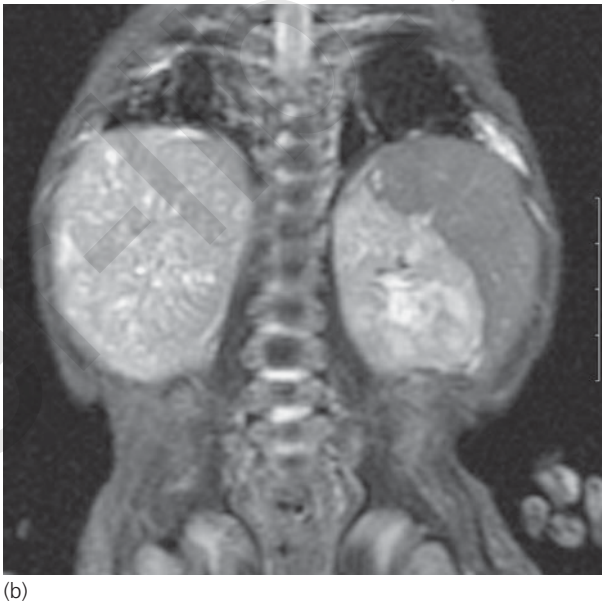

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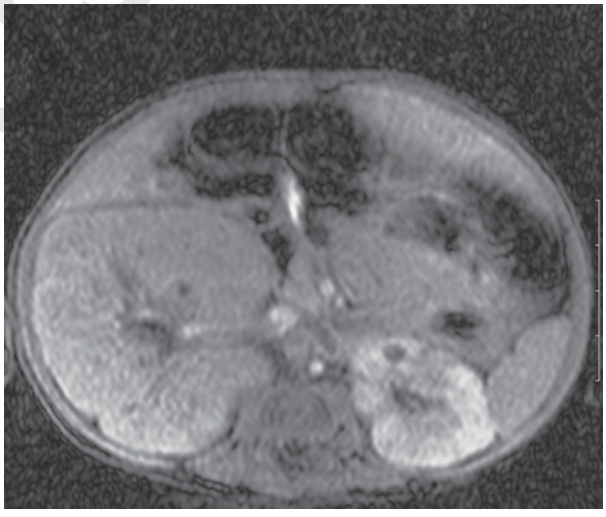
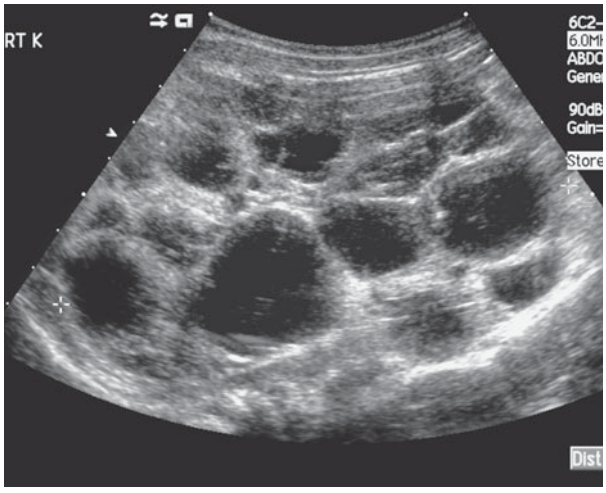


(c)

Figure 92.11 (a) Ultrasound in a one-month-old patient with dysplastic kidneys. Note the small cysts in an otherwise featureless parenchyma; (b) magnetic resonance image in the same patient at the same time: this coronal STIR sequence shows the enlargement of the kidneys and the very abnormal renal architecture, with a typical striated appearance; (c) axial T_1-weighted sequence following gadolinium demonstrating the small cysts seen on ultrasound and poor enhancement.



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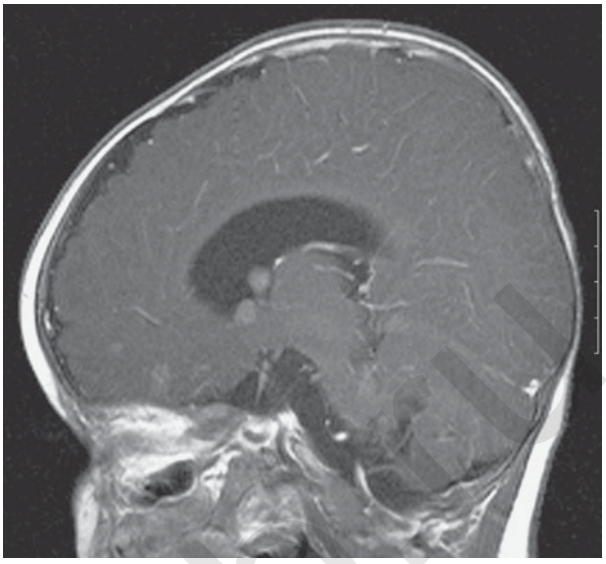


(b)

Figure 92.12 (a) Ultrasound in a two-month-old with large palpable kidneys showing multiple cysts; the differential diagnosis would lie between autosomal dominant polycystic kidney disease (ADPKD) and tuberous sclerosis. (b) Brain magnetic resonance image in the same patient demonstrates the presence of tubers (shown adjacent to the lateral ventricle), thus confirming the diagnosis of tuberous sclerosis.

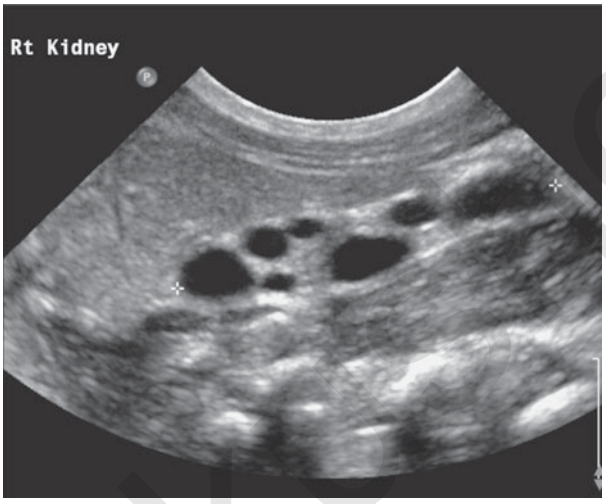


Figure 92.13 Right-sided multicystic dysplastic kidneys on ultrasound in a newborn patient. The cysts may vary in size, but are usually seen throughout the kidney(s) and the intervening parenchyma is echo bright. A true multicystic dysplastic kidney has no function on DMSA.

imaging would be necessary at the neonatal stage. Functional imaging may be performed later.

Tumors

Renal tumors in the neonatal period are rare, but the most likely type would be a mesoblastic nephroma. On US, this mass lesion would generally be mainly solid, if not entirely so (Fig. 92.7). Usually, no further imaging is required and surgery in the neonatal period is curative. Occasionally, the surgeon may wish for further cross-sectional imaging before operating and in this instance MRI would be the modality of choice if it is available. There is no indication for functional imaging for the affected side, but functional imaging may be indicated to assess the function of the contralateral kidney before surgery.

Renal anomalies

Duplex kidneys (Fig. 92.15), cross-fused ectopic kidneys (Fig. 92.16), horseshoe kidneys, and other anomalies are usually first detected by US. US will also be used for monitoring, and for searching for other related anomalies, for example spinal anomalies in patients with the VATER spectrum. Functional imaging is essential as it informs on the function of the upper and the lower moieties of the duplex kidney and on the drainage. Occasionally, it can also inform on the presence of VUR (Fig. 92.17). MRI may be very useful in the most complicated cases, being able to demonstrate the whole of the urinary tract in any desired plane, and giving some information about function and drainage. Unless there are specific complications requiring further intervention all of the secondary imaging may be delayed until the patient is older.

Infection

Infection in the neonatal period may be acquired at the time of delivery, or be secondary to an underlying urinary tract anomaly, or as a result of instrumentation/catheter placement. If imaging were required, then US would be the first modality. If the urinary tract is anatomically normal, US may not demonstrate any abnormal findings, however echogenic

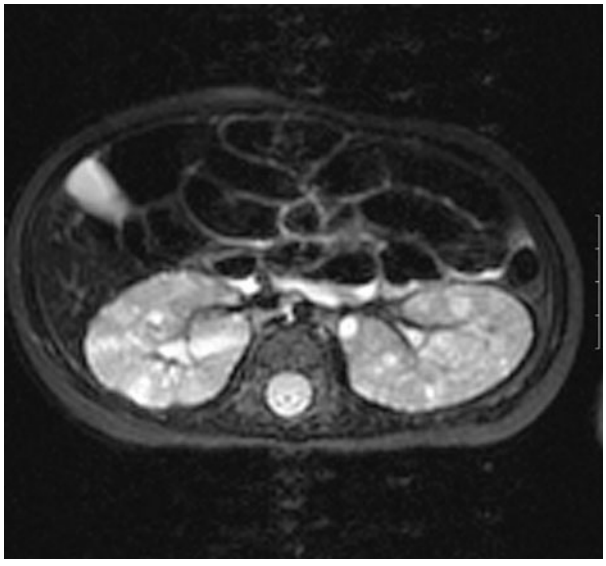


Figure 92.14 Magnetic resonance image in a five-month-old with tuberous sclerosis. This axial STIR sequence shows multiple cysts in both kidneys. These are easily demonstrated by ultrasound, but magnetic resonance imaging is also performed to exclude liver or pancreatic involvement.

debris may be seen throughout the urinary tract, and if the upper tracts are involved (pyelonephritis) it may be possible to demonstrate focal areas of low echogenicity, or the kidneys may simply be enlarged. If the patient has been systemically ill (eg. requiring i.v. antibiotics as an inpatient) functional imaging may be required. If the clinical question is to confirm whether the child has an acute pyelonephritis with renal parenchymal inflammatory involvement and how much of the renal parenchyma has been involved by the inflammatory process, then a DMSA performed during the infection will answer the question. If the question is whether

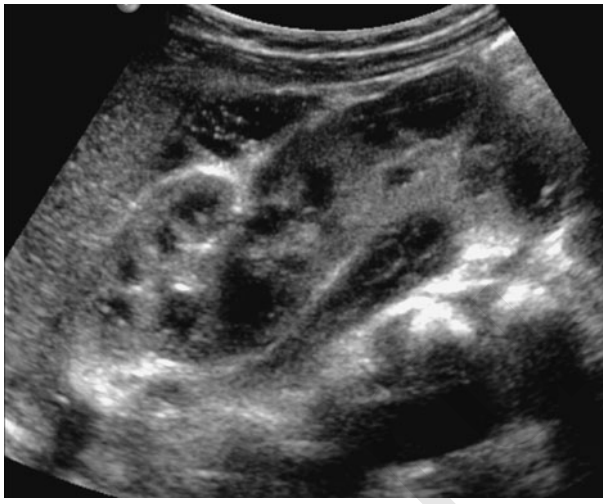
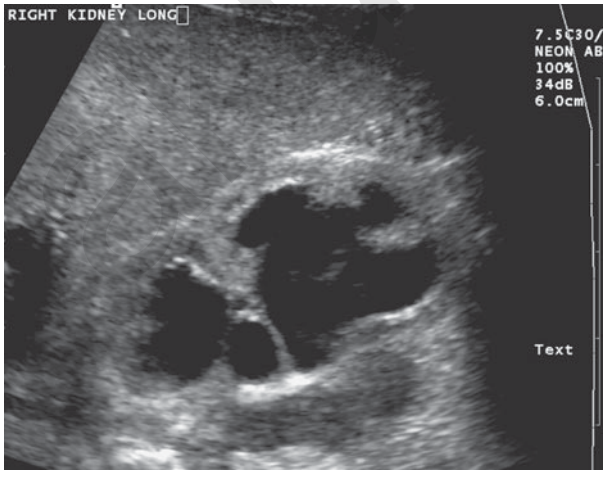


Figure 92.16 Ultrasound in a two-month-old male infant demonstrating a cross-fused ectopic kidney. The two kidneys lie in the right flank and are fused obliquely.

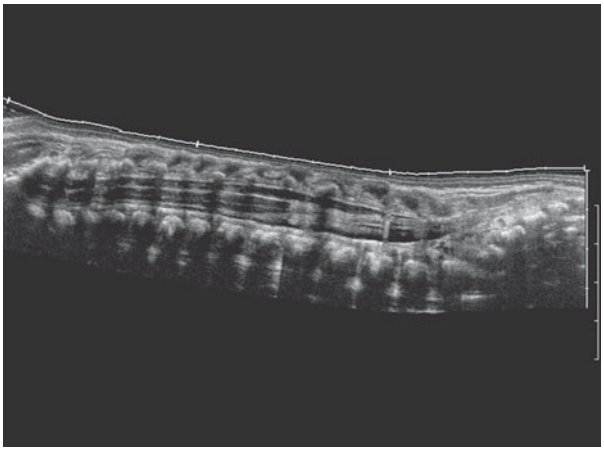
the infant has developed renal scarring as a consequence of the infection, then a DMSA scan will have to be performed between four and six months after the infection.

Renal calculi and nephrocalcinosis

Calculi are rare in the neonatal period but nephrocalcinosis may be seen in patients with an inherited underlying metabolic abnormality, such as primary hyperoxaluria (Fig. 92.2). It is most commonly asymptomatic. Nephrocalcinosis is well demonstrated on US and is described as medullary, cortical, or parenchymal. Initially, there is a mild increase in echogenicity and ringing of the pyramids, which may



(a)



(b)

Figure 92.15 (a) Ultrasound (US) of the kidney in a newborn male showing dilatation of both moieties in a duplex kidney; (b) US of the spine, also performed in the same patient (due to other anomalies in the VATER group), which shows a normal appearance. Spine US needs to be performed in the first few weeks of life before ossification of the spine becomes established.

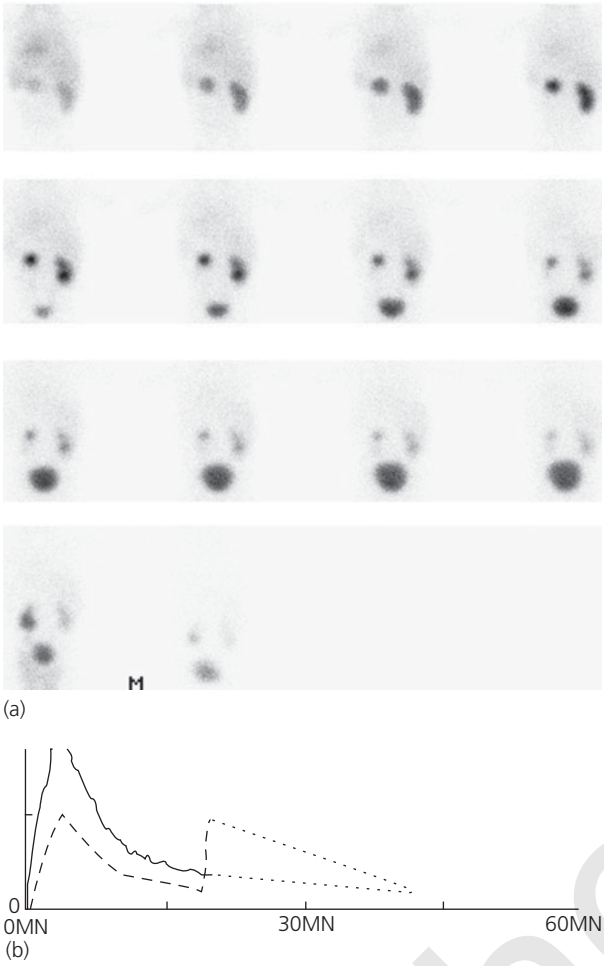


Figure 92.17 Four-month-old boy with an antenatal diagnosis of a left hydronephrosis. The upper moiety appears normal on ultrasound; the lower moiety shows a dilated pelvis of 11 mm and a thin rim of cortex surrounding it. (a) The MAG3 renogram shows good function in the left upper moiety and no function in the left lower moiety. The split function of the left kidney is 36% (right kidney, 64%). There is good drainage from the left upper moiety. The child partially voided in the nappy at the end of the study, with VUR clearly seen in the left lower moiety in the dynamic renography. The right kidney shows good function and drainage. The drainage pattern from the right suggests an uncomplicated duplex system. (b) The time activity curve clearly shows a spike corresponding to the episode of VUR in the left lower moiety. Following the functional study, which demonstrated no function in the left lower moiety, the child underwent a left lower pole heminephrectomy.

eventually progress to filling in of the medullae with acoustic shadowing.

Other causes of focal echogenicity mimicking nephrocalcinosis in the neonatal period include the use of furosemide (calcification seen at the tips of the pyramids, sometimes associated with stone formation), and Tamm Horsfall protein deposition in the medullae (which is a transitory event related to fluid regulation around the time of birth).

CONCLUSION

The US examination should always be the first imaging examination in the neonate. This may be supplemented by functional studies (DMSA or MAG3) or further anatomical studies (including MCU and MRI (or CT)) as determined by the underlying findings on US.

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93

Management of antenatal hydronephrosis

JACK S ELDER

INTRODUCTION

An abnormality involving the genitourinary tract is detected in one in 50 to one in 100 pregnancies, depending on the sonographic criteria.[1,2] The goal of management is to recognize and treat congenital anomalies that may adversely affect renal function or cause urinary tract infection (UTI) or sepsis. Many structural abnormalities of the urinary tract are characterized by hydronephrosis, which frequently is assumed to be obstructive. However, often antenatal hydronephrosis is not caused by obstruction; examples include vesico-ureteral reflux (VUR), multicystic kidney, and certain abnormalities of the ureteropelvic and ureterovesical junction.

DEVELOPMENT OF THE KIDNEY AND RENAL FUNCTION

The kidney is derived from the ureteral bud and the metanephric blastema. During the 5th week of gestation, the ureteral bud arises from the mesonephric (Wolffian) duct and penetrates the metanephric blastema, which is an area of undifferentiated mesenchyme on the nephrogenic ridge. The ureteral bud undergoes a series of approximately 15 generations of divisions, and by 20 weeks' gestation forms the entire collecting system, that is, the ureter, renal pelvis, calyces, papillary ducts, and collecting tubules. Under the inductive influence of the ureteral bud, nephron differentiation begins during the 7th week of gestation. By 20 weeks' gestation, when the collecting system is completely developed, approximately one-third of the nephrons are present. Nephrogenesis continues at a nearly exponential rate and is complete at 36 weeks' gestation.

Throughout gestation, the placenta functions as the fetal hemodialyzer, and the fetal kidneys play a minor role in the maintenance of fetal salt and water homeostasis. Formation of urine begins between the 5th and 9th weeks of gestation. The rate of urine production increases throughout gestation, and at term, volumes have been reported to be 51 mL/h.[3] The glomerular filtration rate (GFR) has been measured at 6 mL/min/1.73 m^2 at 28 weeks' gestation, increasing to 25 mL/min/1.73 m^2 at term, and thereafter triples by three months of age.[4] The main factors responsible for this increase in GFR after birth include an increase in the capillary surface area available for filtration, changes in intrarenal vascular resistance, and redistribution of renal blood flow to the cortical nephrons, which are much more numerous than the medullary nephrons. A congenital obstructive lesion of the urinary tract may have a deleterious effect on renal function. Severe early obstructive uropathy disrupts nephrogenesis and results in renal dysplasia.

MANAGEMENT OF THE FETUS WITH ANTENATAL HYDRONEPHROSIS

When a fetus is identified with a suspected urinary tract abnormality, the goals of management include determining the differential diagnosis, assessment of associated anomalies, and determining the fetal and postnatal risk of the anomaly.

Hydronephrosis is recognized by demonstrating a dilated renal pelvis and calyces. The ureter and bladder may be dilated also. The likelihood of having a significant urinary tract abnormality is directly proportional to the severity of hydronephrosis.[2,5,6] In general, if the renal pelvic diameter is more than 2 cm, 94% have a significant abnormality of the urinary tract requiring surgery or long-term urologic follow up. If the fetal renal pelvic diameter is between 1.0 and 1.5 cm, 50% have an abnormality, and if the dilated renal pelvis is less than 1 cm, only 3% have a significant abnormality.[2,7,8] Currently, a renal pelvic diameter of at least 4 mm before 33 weeks' gestation and at least 7 mm after 33 weeks' gestation is considered significant.[9] The later the sonogram is performed, the more likely an existing abnormality will be detected, because the obstructed renal pelvis gradually enlarges throughout gestation. In addition, *in utero* the fetus is usually upside down in the uterus and urine is draining uphill. For example, Fugelseth and colleagues[10] reported that only one-third of a series of women carrying babies with a urologic anomaly had an abnormal ultrasound study at 15–21 weeks' gestation.

The differential diagnosis of antenatal hydronephrosis is provided in Table 93.1. Virtually all of these conditions can cause bilateral hydronephrosis. A distended bladder and bilateral hydronephrosis is suggestive of bladder outlet obstruction, such as posterior urethral valves or a large ectopic ureterocele obstructing the bladder neck, but fetuses with non-obstructive conditions, such as high-grade VUR or prune belly syndrome, also may have bilateral hydroureteronephrosis and a distended bladder.[11]

In fetuses with a urologic anomaly, associated abnormalities are common. For example, in one series of fetuses with bilateral hydronephrosis and oligohydramnios, 16 of 31 (55%) had an associated structural or chromosomal abnormality.[12] Congenital heart disease and neurologic deformities can often be detected, if they are present. In contrast, large bowel abnormalities, such as imperforate anus, are more difficult to detect by prenatal sonography, whereas recognition of small bowel anomalies, such as atresia, are usually straightforward.

The main considerations in determining fetal management include overall fetal well-being, gestational age, whether the hydronephrosis is unilateral or bilateral, and the volume of amniotic fluid. There are no guidelines for determining how frequently to image the fetus or whether specific intervention is necessary. If hydronephrosis is unilateral, usually no specific fetal therapy is necessary. For example, if the hydronephrosis is secondary to a ureteropelvic junction

Table 93.1 Genitourinary anomalies detectable by prenatal ultrasonography.

Condition	Sex (ratio)	Frequency	Kidney(s)	Ureter(s)	Bladder	Amniotic fluid	Prognosis
Ureteropelvic junction obstruction (unilateral)	M/F (3–4:1)	1:2000	Hydronephrosis	Not seen	Normal	Normal	Good after surgical correction
Multicystic kidney (unilateral)	M/F (1:1)	1:3000	Large with cysts of variable size	Not seen	Normal	Normal	Normal
Primary obstructive megaureter	M/F (3:1)	1:10 000	Hydronephrosis	Dilated	Normal	Normal	Good after surgical correction
Ectopic ureterocele or ureter	M/F (1:6)	1:10 000	Large cyst; possible duplex kidney	Dilated	Normal or enlarged	Normal	Good after surgical correction
Posterior urethral valves	Male	1:8000	Bilateral hydronephrosis; possible cortical cysts	Dilated	Enlarged	Variable; diminished or absent in severe obstruction	Usually good after surgical correction or drainage; poor if oligo?hydramnios is present
Prune belly syndrome	Nearly always male	1:40 000	Bilateral hydronephrosis; possible cortical cysts	Dilated	Enlarged	Variable; diminished or absent if severely affected	Usually fair to good; may need surgical drainage; poor if oligo?hydramnios is present
Vesico-ureteral reflux	M/F (1:5)	1:100	Hydronephrosis if reflux high grade	Variable	Normal; dilated if reflux high grade	Normal	Good; may need surgical correction
Infantile polycystic kidney disease	M/F	1:6000–1:14 000	Large, echogenic	Not seen	Small or not seen	Usually absent or severely diminished	Poor
Renal agenesis	M/F (2.0–2.5:1)	1:4000 (bilateral)	Not seen	Not seen	Not seen	Severely diminished or absent	Stillbirth
		1:1500 (unilateral)	Not seen	Not seen	Normal	Normal	Normal
Hydrocolpos	Female		May have hydronephrosis	Not seen	Normal	Normal	Good after surgical correction
Ovarian cyst	Female		Normal (cyst may be confused with kidney or bladder)	Not seen	Normal	Normal	Good after surgical correction

(UPJ) obstruction, even if function is poor, the kidney has a significant capacity for improvement in function following neonatal pyeloplasty. Even with bilateral UPJ obstruction (characterized by bilateral hydronephrosis and a normal bladder), the amniotic fluid volume and pulmonary development typically are normal. Consequently, specific intervention, such as percutaneous drainage of the fetal kidney or early delivery to allow immediate urologic surgery, are unwarranted. These same principles apply to primary obstructive megaureter.[13]

The primary life-threatening congenital urologic anomalies include posterior urethral valves, urethral atresia, and prune belly syndrome, which are usually characterized by bilateral hydro-ureteronephrosis and a distended bladder that does not empty in a male fetus. Approximately one-third of infants with urethral valves eventually develop renal insufficiency or end-stage renal disease.[14,15] Although prune belly syndrome is considered non-obstructive, neonates with this condition frequently have renal insufficiency, in large part because of congenital renal insufficiency and also from renal deterioration in children with repeated episodes of pyelonephritis.[16] Urethral atresia is nearly always fatal, because the kidneys are usually dysplastic. A severe adverse prognostic factor is oligohydramnios, which prevents normal pulmonary development. In fetuses with severe obstructive uropathy and renal dysplasia, neonatal demise usually results from pulmonary hypoplasia rather than chronic renal failure.

Intuitively, it would seem that treatment of the obstructed fetal urinary tract by diverting the urine into the empty amniotic space might allow normal renal development to occur and restore amniotic fluid dynamics, stimulating lung development. Indeed, experimental procedures have been performed, including percutaneous placement of a vesico-amniotic shunt, creation of a fetal vesicostomy or pyelostomy, and even percutaneous urethral valve ablation through a miniscope.[17] Unfortunately, the complication rate is high, including shunt migration, urinary ascites, stimulation of preterm labor, and chorioamnionitis.[4,18] Furthermore, in most cases, irreversible renal dysplasia has already occurred, and although the procedure may be successful technically, often the baby is stillborn, dies of pulmonary hypoplasia, or is alive with end-stage renal disease.[18,19] Nevertheless, some fetuses may benefit from aggressive intervention if the kidneys do not have irreversible dysplasia. Unfavorable prognostic factors include:[4,13]

- prolonged oligohydramnios;
- renal cortical cysts;
- urinary Na >100 mEq/L, Cl >90 mEq/L, and osmolarity >210 mOsm/L;
- beta$_2$-microglobulin >6 mg/L;
- reduced lung area and thoracic or abdominal circumference.

Unfavorable urinary electrolytes may reflect stale urine in the fetal urinary tract. Consequently, many perinatal centers obtain two or three sequential samples, as subsequent samples yield fetal urine that is more reflective of true fetal renal function.[20,21]

MANAGEMENT OF THE NEWBORN WITH ANTENATAL HYDRONEPHROSIS

Management in the nursery

At birth, the abdomen is inspected to detect the presence of a mass, which most often is secondary to a multicystic dysplastic kidney or UPJ obstruction. In male newborns with posterior urethral valves, often a walnut-shaped mass, representing the bladder, is palpable just superior to the pubic symphysis. Newborns should also be evaluated for anomalies involving other organ systems. Renal function should be monitored with serial serum creatinine levels, particularly in infants with bilateral hydronephrosis. At birth, the serum creatinine level is identical to the mother's, but by 1 week of age, the creatinine should decrease to 0.4 mg/dL. The exception is premature infants, in whom the creatinine may not decrease until these children reach 34–35 weeks' conceptional age because of the immaturity of renal function before that age.

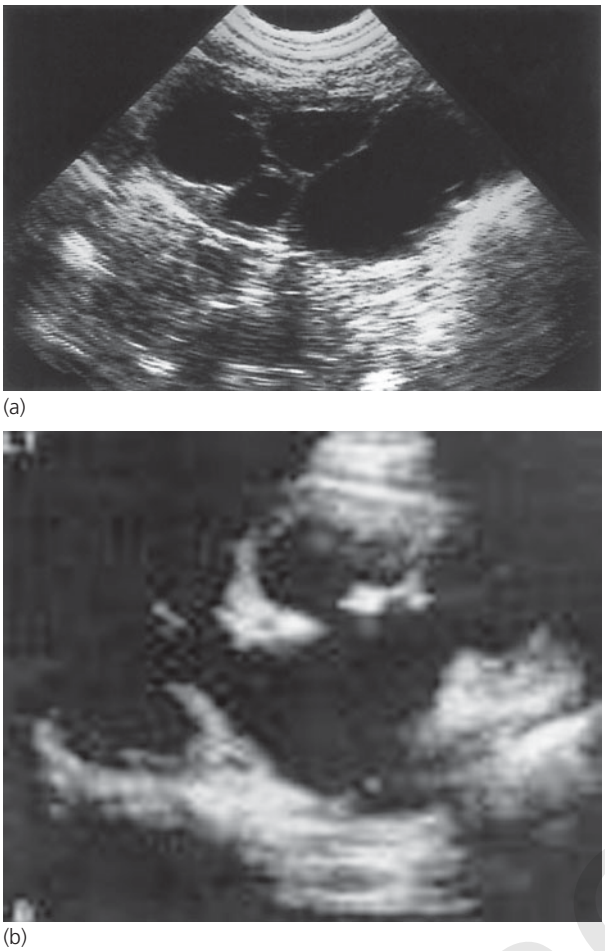
Neonates with hydronephrosis who are at risk for UTI should be placed on antibiotic prophylaxis with either amoxicillin 50 mg daily or cephalexin 50 mg daily.[22] There is evidence that children with vesico-ureteral reflux, ectopic ureter and ureterocele, and posterior urethral valves benefit from prophylaxis, but that those with hydronephrosis secondary to an abnormality of the ureteropelvic junction or ureterovesical junction are not at increased risk.[23] At two months beyond term, the prophylaxis is usually changed to trimethoprim-sulfamethoxazole. In addition, circumcision should be considered in male neonates to minimize the likelihood of urinary tract infection.

INITIAL RADIOLOGIC EVALUATION

Radiologic evaluation should be performed before infants are discharged to delineate the abnormality responsible for changes on prenatal sonography. Serial renal sonograms, a voiding cystourethrogram (VCUG), and a diuretic renogram usually provide the diagnostic information necessary to guide management, although all of these studies are unnecessary in many children.

Renal ultrasound

A renal and bladder sonogram should be obtained first. Typically, this study is obtained shortly after delivery or the following day. However, because neonates have transient oliguria, a dilated or obstructed collecting system may appear normal for the first 24–48 hours of life (Fig. 93.1). Ideally, if unilateral hydronephrosis was present prenatally, the renal sonogram should not be obtained until 72 hours to maximize its sensitivity, but with mothers being discharged within 24–48 hours of delivery, it seems impractical to have the baby brought back to the hospital after discharge for sonography. Inexperienced radiologists may misinterpret a normal neonatal kidney with hypoechoic pyramids for caliectasis.



(a)

(b)

Figure 93.1 Newborn with prenatal diagnosis of left hydronephrosis. (a) Ultrasound of left kidney taken shortly after birth. Normal study. Echolucent areas (arrow) in renal cortex are pyramids (normal finding). (b) Same patient. Ultrasound of left kidney at 6 weeks shows grade 4 hydronephrosis.

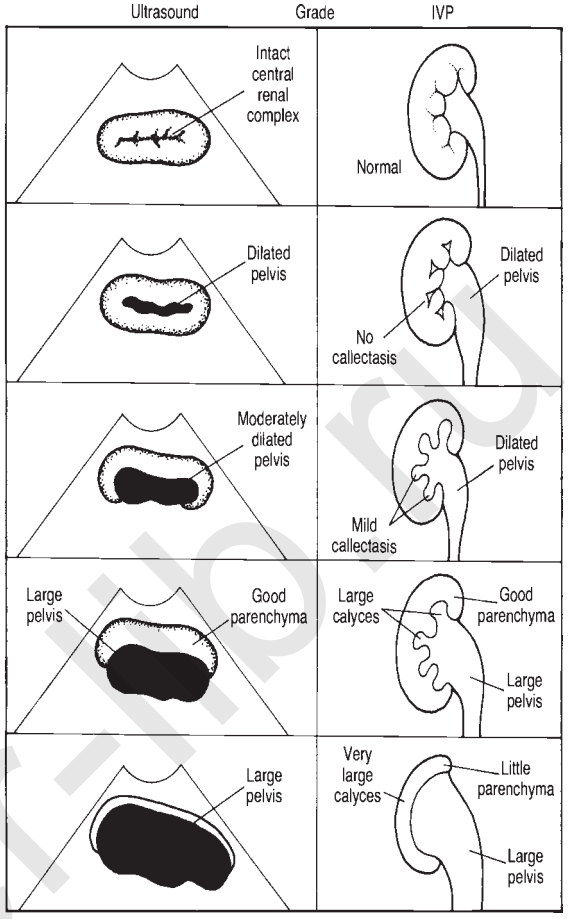


Figure 93.2 Grading system for hydronephrosis. Reproduced with permission from the Society for Fetal Urology.

Renal length, degree of caliectasis and parenchymal thickness, and presence or absence of ureteral dilation should be assessed. The severity of hydronephrosis can be graded from 1 to 4 using the Society for Fetal Urology (SFU) grading scale (Fig. 93.2).[24] Most significant urologic anomalies that require surgical correction or long-term urological follow up are associated with grade 3 or 4 hydronephrosis.[25] More sophisticated analyses, such as the renal resistive index, as well as urinary studies have been assessed, but efforts to demonstrate obstruction have been inconsistent.

The degree of pelvocaliectasis correlates closely with the likelihood that a significant urological condition is present. Lee *et al.*[26] performed a meta-analysis of reports of antenatal hydronephrosis and determined that the risk of finding postnatal pathology was 11.9% with mild antenatal hydronephrosis, 45.1% for moderate, and 88.3% for severe antenatal hydronephrosis. Their definitions of mild, moderate, and severe hydronephrosis depended on gestational age at the time of diagnosis. Similarly, Sidhu *et al.*[27] performed a meta-analysis and found that when postnatal hydronephrosis was SFU grade 1 or 2, there was stabilization or resolution of pelviectasis in 98%, whereas when there was SFU grade 3 or 4, there was stabilization or resolution in 51%.

The bladder should be imaged to detect a dilated posterior urethra (urethral valves), bladder wall thickening, ureteral dilation, inadequate bladder emptying, or a ureterocele. Perineal sonography may demonstrate a dilated prostatic urethra, which is consistent with posterior urethral valves.[28]

Voiding cystourethrogram

Next, a VCUG should be performed. This study may demonstrate VUR, posterior urethral valves, or a bladder diverticulum. A radiographic cystogram is preferred over a radionuclide cystogram because the latter does not provide sufficient delineation of bladder and urethral anatomy and because VUR, if present, cannot be graded.

In a recent analysis by the American Urological Association Pediatric Vesicoureteral Reflux Guidelines Committee, an overall VUR detection rate of 16.2% was found.[29] The mean incidence of VUR into a non-dilated kidney was 4.1%. In cases with antenatal hydronephrosis and a normal postnatal sonogram, the incidence of VUR was 17%. The prevalence of VUR was significantly higher in girls than boys with antenatal hydronephrosis. The likelihood is highest if there is SFU grade 3 or 4 hydronephrosis or if a dilated ureter

is identified. The chance of identifying VUR on a VCUG is less if there is only SFU grade 1 or 2.[30]

WHAT IF THE INITIAL SONOGRAM IS NORMAL?

A common dilemma is whether a full evaluation is necessary if the initial renal sonogram is normal. Assuming a significant degree of fetal renal pelvic dilatation (i.e. 4 mm anteroposterior pelvic diameter <33 weeks, 7 mm diameter after 33 weeks) was present, the child may have VUR. This issue is unresolved. For example, Blane and colleagues[31] reported that 12% of children with grade V, 31% with grade IV, and 80% with grade III VUR had a normal renal sonogram. However, the AUA Reflux Guidelines determined that the mean incidence of VUR into a non-dilated kidney was 4.1%.[29] Because VUR may cause intermittent renal pelvic dilation, theoretically babies with prenatal hydronephrosis and a normal postnatal sonogram may have VUR, and early diagnosis and medical treatment of VUR may reduce the likelihood of developing reflux nephropathy.[32] On the other hand, others have advocated performing a VCUG only if the postnatal sonogram were abnormal;[33] however, in these reports, neonates with a normal postnatal renal sonogram were not systematically evaluated to determine the real incidence of VUR in this group. This author generally recommends that VCUG not be performed unless the postnatal renal sonogram is abnormal.

Follow-up evaluation and treatment

If bilateral hydronephrosis or unilateral hydronephrosis in a solitary kidney is present, then close monitoring of the serum creatinine and electrolytes is necessary. If the hydronephrosis is caused by posterior urethral valves, then valve ablation should be performed before hospital discharge. If the hydronephrosis is secondary to VUR, the infant should be placed on prophylaxis and managed, as described later in this chapter. If the hydronephrosis is grade 3 to 4 and bilateral UPJ or ureterovesical junction obstruction is suspected, prompt evaluation with diuretic renography is indicated.

If unilateral hydronephrosis and a normal contralateral kidney are present, abnormalities in serum creatinine or electrolytes are uncommon. Nevertheless, these serum studies should be drawn to document that renal function is normal. Usually, follow-up functional radiographic studies can be delayed until 4–6 weeks of age, when renal function is more mature and studies of renal function and obstruction are more likely to be accurate.

If the sonogram and VCUG are normal, then only a follow-up sonogram in 6–8 weeks is necessary. In general, if hydronephrosis is discovered on the initial postnatal sonogram, pediatric urologic or nephrologic consultation is advisable to direct subsequent radiologic evaluation and plan therapy.

Diuretic renogram

The diuretic renogram is used to determine whether upper urinary tract obstruction is present. It is used to assess differential renal function and efficiency of drainage of the kidneys. Infants with grade 3 and 4, and occasionally grade 2, hydronephrosis should undergo this study. Mercaptoacetyl triglycine (MAG-3) is generally used, and is primarily secreted by the renal tubules. It provides excellent images with little background activity. Another option is diethylene triamine pentaacetic acid (DTPA), which is excreted by glomerular filtration, but there is much more background with this radiopharmaceutical.

During a diuretic renogram, a small dose of a radiopharmaceutical is injected intravenously. During the first 2–3 minutes, renal parenchymal uptake is analyzed and compared, allowing computation of differential renal function. Subsequently, excretion is evaluated. After 20–30 minutes, furosemide is injected intravenously, and the rapidity and pattern of drainage from the kidneys to the bladder are analyzed. If no upper urinary tract obstruction is present, then normally half of the radionuclide is cleared from the renal pelvis within 10–15 minutes, termed the $t_{½}$. In the presence of significant upper tract obstruction, the $t_{½}$ is greater than 20 minutes. A $t_{½}$ between 15 and 20 minutes is indeterminate. The images generated usually provide an accurate assessment of the site of obstruction.

The renal scan is considered superior to the i.v. pyelogram (IVP) in infants and children with hydronephrosis. The diuretic renogram may be unreliable, however, if certain important variables are not controlled.

Numerous variables affect the outcome of the diuretic renogram. For example, newborn kidneys are functionally immature, and in some cases even normal kidneys may not demonstrate normal drainage following diuretic administration. Dehydration prolongs parenchymal transit and can blunt the diuretic response. Giving an insufficient dose of furosemide may result in inadequate drainage. In addition, a full bladder may impede bladder drainage. Furthermore, if VUR is present, continuous catheter drainage is mandatory to prevent radionuclide from refluxing from the bladder into the dilated upper tract, prolonging the washout phase. Consequently, a urethral catheter should be inserted and bladder drainage measured.

Because of the limitations of the diuretic renogram in newborns with hydronephrosis, and because the methodology for performing diuretic renography varies substantially, the Society for Fetal Urology and the Pediatric Nuclear Medicine Club jointly developed a standardized methodology for performing diuretic renograms in infants.[34]

Magnetic resonance urography

The newest study used to evaluate suspected upper urinary tract pathology is magnetic resonance urography (MRU) (Fig. 93.3). The child is hydrated and given i.v. furosemide. Next, gadolinium-DTPA, which is filtered and excreted, is injected intravenously and routine T_1-weighted and fat-suppressed fast spin-echo T_2-weighted imaging is performed through the kidneys, ureters, and bladder. This study provides superb images of the pathology, and methodology is being developed to allow assessment of differential renal function and drainage.[35] There is no radiation exposure, but younger children need strong sedation or anesthesia. It is

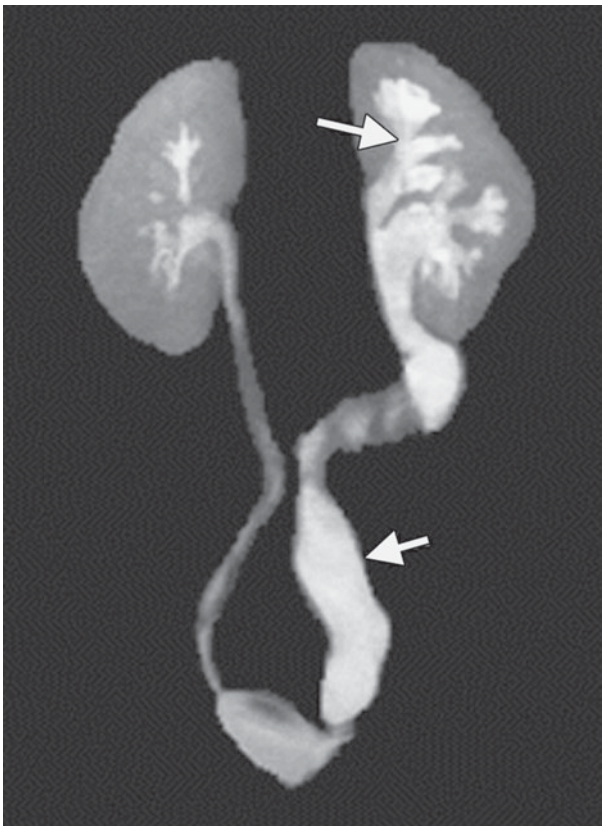


Figure 93.3 Magnetic resonance urogram in a one-year-old demonstrating left obstructive megaureter. The right kidney is normal.

used primarily when renal sonography and nuclear imaging fail to delineate complex pathology, and is the procedure of choice for complex genitourinary pathology.

Ancillary studies

In most cases, a renal sonogram, VCUG, and diuretic renogram provide sufficient information to establish a diagnosis and establish a plan of management. In particularly complicated cases, however, cystoscopy with retrograde pyelography, computed tomography (CT) scan, antegrade pyelography, or a Whitaker antegrade perfusion test is necessary.

CONGENITAL ANOMALIES CAUSING ANTENATAL HYDRONEPHROSIS

UPJ obstruction or anomalous UPJ

The most common cause of severe hydronephrosis without a dilated ureter or bladder in newborn infants is UPJ obstruction, which results from an intrinsic fibrotic narrowing at the junction between the ureter and renal pelvis (Fig. 93.4). At times, an accessory artery to the lower pole of the kidney also causes extrinsic obstruction, but this finding is rare in newborns with hydronephrosis. In kidneys with a UPJ obstruction, renal function may be significantly impaired from pressure atrophy. The anomaly is corrected by performing a pyeloplasty, in which the stenotic segment is excised and the normal ureter and renal pelvis are reattached. Success rates are 91–98%.

Lesser degrees of UPJ narrowing may cause mild hydronephrosis, which is usually non-obstructive, and typically these kidneys function normally. The spectrum of UPJ abnormalities has been referred to as 'anomalous UPJ'. Another cause of mild hydronephrosis is fetal folds of the upper ureter (Fig. 93.5), which also are non-obstructive.

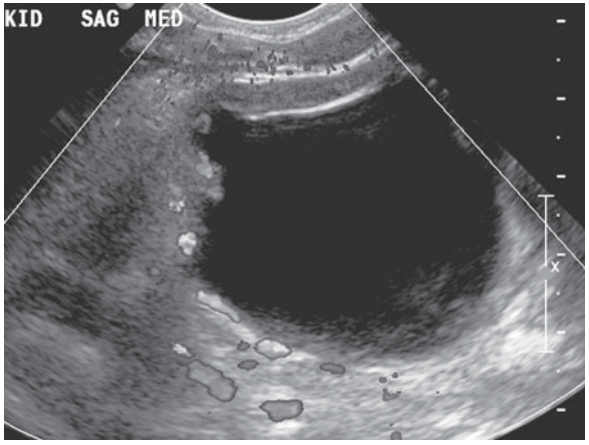
Hydronephrosis in many newborns gradually diminishes or resolves over months to years. The goal of early evaluation is to determine whether a true anatomic obstruction is present that should be corrected or whether it is safe to follow the infant non-operatively. Defining what constitutes obstructive and non-obstructive hydronephrosis is a constant source of debate in pediatric urology.

Cartwright and colleagues[36] studied 80 neonates with suspected UPJ obstruction. Of 39 with unilateral hydronephrosis and at least 35% differential renal function who were managed non-operatively, only six (15%) later underwent pyeloplasty, primarily because of deteriorating differential renal function on renal scintigraphy. Following pyeloplasty, the differential renal function returned to its initial level in these patients. One might question whether early pyeloplasty in these patients would have allowed renal function to improve to 50% (normal). The remaining patients managed non-operatively maintained differential function greater than 40%.

Koff and Campbell[37] reported 104 consecutive neonates with unilateral hydronephrosis managed non-operatively, with follow up as long as five years. In follow up, only seven (7%) underwent pyeloplasty because of reduction in differential renal function of more than 10% or progression of hydronephrosis. Pyeloplasty returned differential renal function to prepyeloplasty levels in all cases. Of 16 patients with significantly reduced renal function on initial scan and grade 4 hydronephrosis, rapid improvement was noted on follow-up diuretic renography in 15 and the washout curve became non-obstructive in six. In addition, hydronephrosis disappeared in six, improved in six, remained stable in three, and deteriorated in one. The physiology of the resolution or reduction in hydronephrosis and the improvement in differential renal function in these babies is unknown. In another more recent report from the same institution, of 19 newborns with bilateral grade 3 or 4 hydronephrosis, a total of 13 kidneys were subjected to pyeloplasty.[38] Of those managed non-operatively, 21 kidneys were grade 0 to 2 and grade 3 in two kidneys. The mean follow-up time to achieve maximum improvement in hydronephrosis was ten months.

Although these studies suggest that it is safe or appropriate to manage neonates with a suspected UPJ obstruction non-operatively, an infant's kidney has much greater capacity for improvement in differential renal function than an older child's. In addition, all of these studies base 'differential renal function' on the uptake during the first 2–3 minutes of the study, and there is substantial variability in the way this percentage is calculated.[39] Finally, these studies have not reported the pattern of washout on diuretic renography.

In a review of renal biopsies obtained at pyeloplasty at the author's institution, 63% showed minimal or no obstructive



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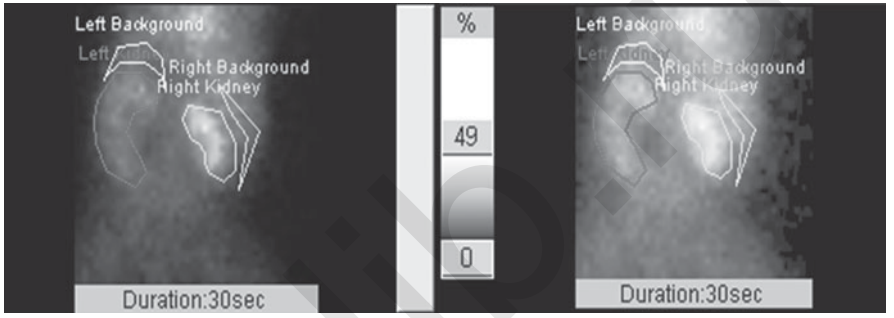

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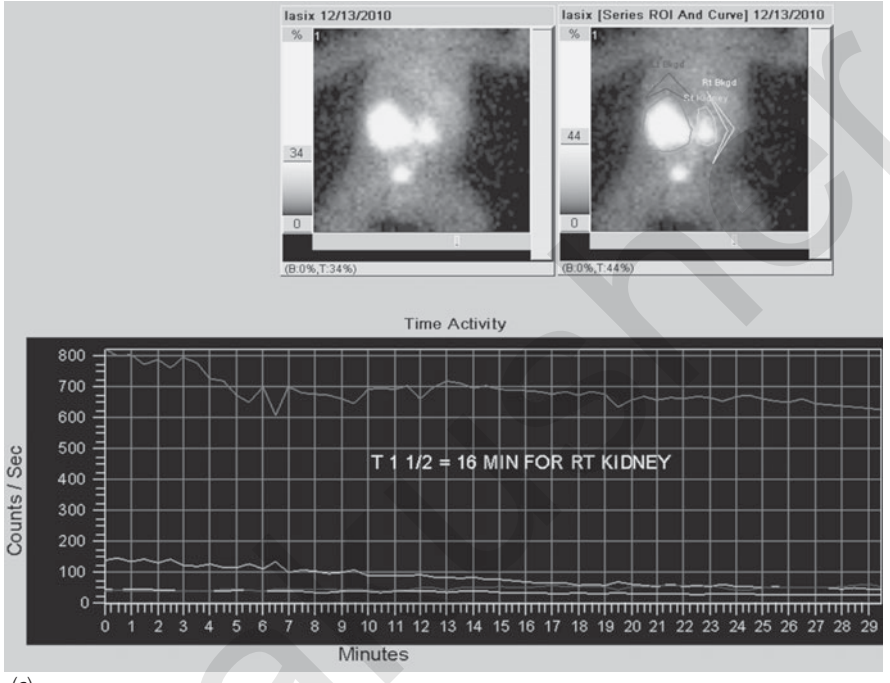

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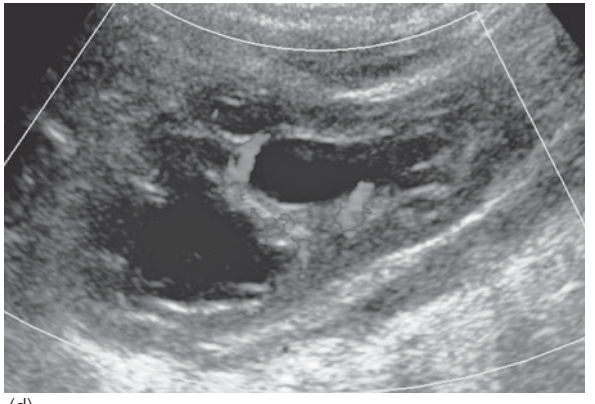


(d)

Figure 93.4 Newborn with prenatal diagnosis of left hydronephrosis. (a) Sonogram left kidney demonstrates grade 4 left hydronephrosis without a dilated ureter. The voiding cystourethrogram was normal. (b,c) MAG-3 diuretic renogram (left kidney on the left side of image) shows minimal drainage on the left side. The differential function left:right was 46:54%. Patient underwent left pyeloplasty at two months of age. (d) Follow-up sonogram of left kidney at five months of age demonstrates reduction in hydronephrosis.

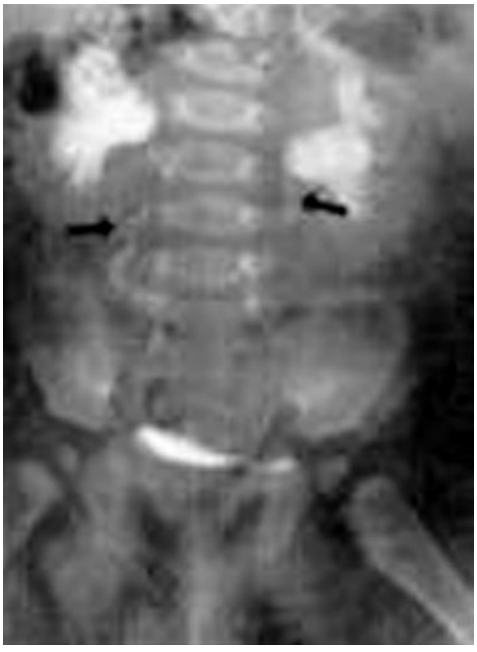


Figure 93.5 Excretory urogram in infant with bilateral grade 2 hydronephrosis shows bilateral fetal folds of upper ureters (arrows). Note sharp calyces (normal).

histologic changes; however, of those with differential function greater than 40%, 21% showed significant histopathologic changes, including reduced glomerular number, glomerular hyalinization, interstitial inflammation, and dysplastic glomeruli.[40] Of the kidneys with a low differential function (less than 40%), 33% showed minimal or no histologic changes. Overall, in 25% of the patients the findings on renal biopsy did not correlate with the computed differential renal function and reflect the need for more sensitive markers of obstruction.

The approach of most pediatric urologists to neonates with a suspected UPJ obstruction is as follows. The hydronephrosis is graded from 1 to 4 using the SFU grading scale and a VCUG is obtained. Nearly all infants requiring pyeloplasty have grade 3 or 4 hydronephrosis,[24] and those with grade 1 or 2 hydronephrosis do not seem to be at significant long-term risk.[41–43] If a neonate has an abdominal mass from a hydronephrotic kidney, bilateral severe hydronephrosis, or a solitary kidney, a prompt MAG-3 diuretic renogram is obtained. If signs of obstruction are apparent, prompt pyeloplasty is performed. Otherwise, the newborn is placed on amoxicillin 50 mg daily for prophylaxis, and the diuretic renogram is obtained at 6 weeks of age. The study is not obtained right away in these cases because renal function in the newborn is immature. If diuretic renography shows at least 35–40% differential renal function and there is some drainage on the diuretic renogram, the child is managed nonoperatively, regardless of the drainage pattern (Fig. 93.4). At two months, prophylaxis is changed to trimethoprim-sulfamethoxazole suspension 1.25 mL daily. A follow-up renal sonogram is performed three months later. If the hydronephrosis is unchanged from baseline, a repeat MAG-3 diuretic renogram is obtained. If there is deterioration in differential renal function or worsening of the diuretic washout curve, pyeloplasty is recommended. However, if these parameters remain stable or improved and the child does not develop a UTI, follow up three to six months later with another renal sonogram or MAG-3 diuretic renogram is performed, and management is individualized. It is incumbent on clinicians caring for these infants to have a good understanding of the vagaries of the diuretic renogram and to monitor infants with a suspected UPJ obstruction closely. In addition, review of the radiologic studies (not just the radiology report) by the pediatric urologist is strongly encouraged.

There has been significant progress in the development of minimally invasive techniques in pediatric pyeloplasty, even in infants. Although infant pyeloplasty is performed through a small incision (lumbotomy or flank muscle-splitting) in many centers,[44] an increasing number of pediatric urologists are performing the procedure with traditional laparoscopic techqniques,[45,46] or the daVinci robot.[47,48] Success rates are being compared to series of open surgical repair;[49] hospital stay and narcotic use are less with the minimally invasive approach. Generally, a transperitoneal approach has been used, with mobilization of the colon. However, on the left side, the pyeloplasty can be performed with a transmesenteric approach.

MULTICYSTIC DYSPLASTIC KIDNEY

A multicystic dysplastic kidney is composed of multiple noncommunicating cysts of varying sizes with a stromal component that is composed of dysplastic elements. These kidneys do not function. Although multicystic kidney is the most common cause of an abdominal mass in neonates, the vast majority of multicystic kidneys are detected by prenatal sonography. Some clinicians incorrectly assume that multicystic kidney and polycystic kidney are synonymous terms. Polycystic kidney disease is an inherited disorder and has an 'adult form' (autosomal dominant) and an 'infantile form' (autosomal recessive) and affects both kidneys. In contrast, a multicystic kidney is almost always unilateral and is usually not an inherited disorder.

Sonography of multicystic kidneys is often diagnostic, demonstrating multiple echolucent cysts of varying sizes with no discernible cortex (Fig. 93.6). Occasionally, the cysts may resemble a severe UPJ obstruction with minimal parenchyma, termed the 'hydronephrotic variant'. The contralateral kidney is abnormal in 5–10% of cases. Renal scintigraphy (MAG-3 or DMSA (dimercaptosuccinic acid) scan) shows nonfunction and generally should be performed to confirm the diagnosis. On occasion, there is a segmental multicystic kidney, in which there is a complete duplication anomaly of the upper urinary tract, with the upper pole being multicystic.[50] Many also recommend obtaining a VCUG, because as many as 15% have contralateral VUR,[51] although this recommendation is not universally accepted.

The management of a multicystic kidney is becoming less controversial. If an abdominal mass that is symptomatic is present, early nephrectomy is indicated. However, left untreated, most multicystic kidneys become smaller relative

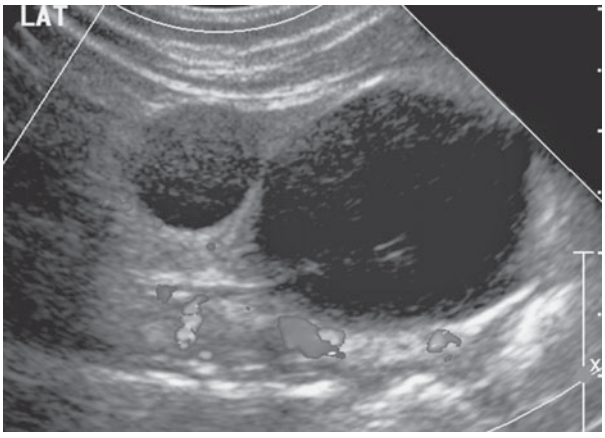


Figure 93.6 Left multicystic dysplastic kidney.

to total body size, and complete cyst regression is common. Potential complications include malignancy, and nodular renal blastema, which is a precursor to Wilms' tumor, and hypertension. In a review of 26 clinical series, no cases of Wilms' tumor were reported among 1041 children, and the maximum estimated risk was 3.5 per 1000 affected children.[52] Tumors arise from the stromal, not the cystic, component of multicystic kidneys. Consequently, even if the cysts regress completely, the likelihood that the kidney could develop a neoplasm is not altered. With regard to hypertension, in a review of 29 studies, six cases were reported among 1115 eligible children, and the mean probability was 5.4 per 1000 affected children (95% confidence interval (CI) 1.9 to 11.7 per 1000).[53]

Generally, a follow-up sonogram is recommended at six months of age. If the cysts enlarge, the stromal core increases in size, or hypertension develops, laparoscopic (or possibly open) simple nephrectomy is recommended. However, further follow-up sonography is unnecessary unless there is concern regarding the contralateral kidney, because finding a Wilms' tumor incidentally would be extremely rare. Because of the occult nature of hypertension, annual blood pressure measurement is recommended, and if hypertension occurs, nephrectomy should be considered.

Primary obstructive megaureter (non-refluxing)

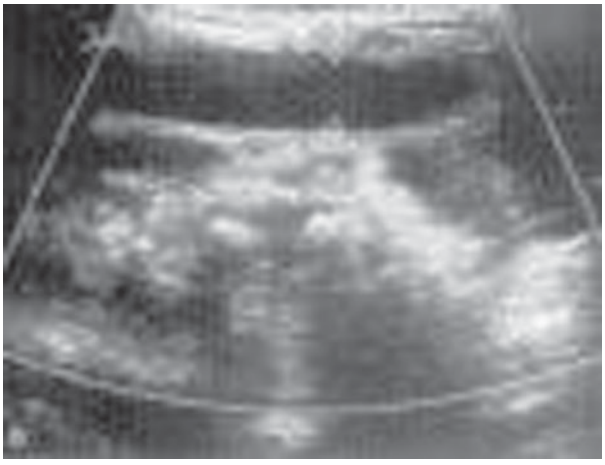
A megaureter refers to a wide ureter and may be (1) primary or secondary, (2) obstructive or non-obstructive, and (3) refluxing or non-refluxing. Non-refluxing megaureter results from an aperistaltic segment of the distal ureter that does not allow normal propulsion of urine (Fig. 93.3). In this condition, sonography shows a dilated ureter and renal pelvis with variable renal parenchymal atrophy. VCUG shows no VUR in most cases. Before the sonography era, most patients with this condition presented with flank pain, flank mass, pyelonephritis, hematuria, or stone disease. Surgical correction consists of excision of the aperistaltic segment, tailoring (also known as tapering) of the ureter, and reimplantation of the ureter into the bladder.

Although severe hydronephrosis may be present, there is often a tendency to gradual reduction in hydronephrosis over a period of several years (Fig. 93.7). For example, in one series of 40 neonates with 57 non-refluxing megaureters, only four underwent early repair because of diminished renal function.[54] With a mean follow up of 6.8 years, only one demonstrated late worsening of hydronephrosis at 14 years. Chertin *et al.*[55] reported on a series of 79 children with follow up as long as 18 years. Overall, 31% underwent surgical correction at a mean age of 14 months. Independent predictive factors for surgery included differential renal function $<30\%$, ureteral diameter >1.33 cm, and grade 3 or 4 hydronephrosis. Consequently, most of these patients may be followed non-operatively on antibiotic prophylaxis and serial monitoring of renal function and drainage.

In these neonates, a renal sonogram and VCUG should be obtained before discharge. Early management is identical to that of neonates with suspected UPJ obstruction. If an abdominal mass, solitary kidney, or bilateral hydro-ureteronephrosis is present, then a MAG-3 diuretic renogram should be obtained promptly. Otherwise, the study is deferred until 6–8 weeks of age. In some centers, the diuretic-stimulated drainage from the renal pelvis and ureter are measured separately. If the differential renal function is at least 40%, the child generally is managed non-operatively, even with grade 4 hydronephrosis, and a follow-up renal sonogram or diuretic renogram is obtained every three to six months.

Early repair of megaureter has a higher complication rate than in older children. For example, Peters and colleagues[56] reported on megaureter repair in 42 infants operated on at a mean age of 1.8 months. In that series, early complications occurred only in those less than 6 weeks of age and included transient apnea in three, UTI in one, hyponatremia in one, and meningitis in one. VUR occurred postoperatively in six infants, and none developed postoperative obstruction. The VUR resolved spontaneously between 18 and 36 months in three patients, and the remainder underwent secondary ureteroneocystostomy. Greenfield and colleagues[57] reported on repair of 11 megaureters in infants less than six months old. Of these children, two had transient ureteral obstruction immediately after stent removal and persistent grades 1 and 2 VUR in two children. In a series of older children who underwent tapered ureteral reimplantation, the success rate was 90% for obstructive megaureter.[58] The results were slightly better for intravesical compared with extravesical reimplantation.

There are two other reasonable treatment options if surgical repair seems necessary in the neonate or young infant. The first is to perform a temporary cutaneous ureterostomy, allowing the ureter to decompress over a period of 12–18 months. Subsequently, the ureterostomy can be taken down and ureteral reimplantation with or without tapering is performed. In a series of children who underwent this procedure, when undiversion and ureteral reimplantation was performed, only five of 23 ureters required tapering.[59] The other option is to insert a double J ureteral stent through the ureterovesical junction and leave it interposed between the bladder and the kidney. Castagnetti



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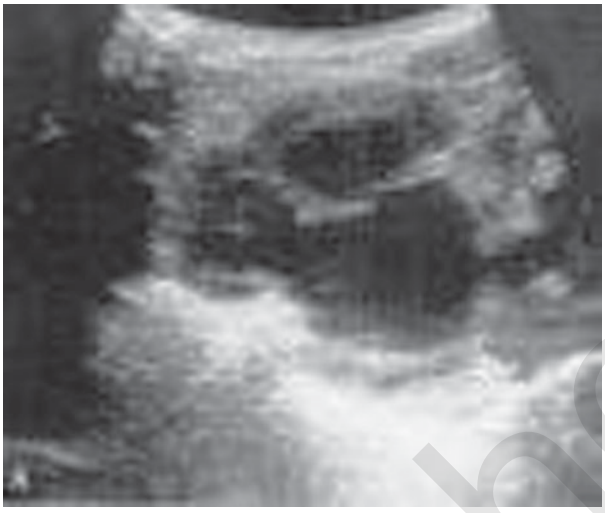

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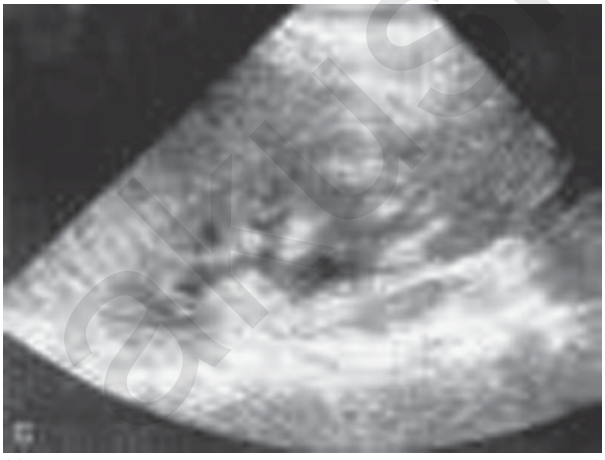


(c)

Figure 93.7 Female newborn with non-refluxing left megaureter discovered by prenatal ultrasound. (a,b) Newborn ultrasound shows grade 4 hydronephrosis and dilated ureter. Diuretic renogram, 8 weeks of age, showed 50% differential renal function in left kidney. Obstructive drainage pattern was noted following administration of furosemide. Patient managed non-operatively. (c) Ultrasound six months later shows grade 1 hydronephrosis. Diuretic renogram later showed normal drainage pattern.

et al.[60] reported ten infants, of whom five required open surgery for stent insertion. A total of seven had stent-related complications, including UTI in five and early stent removal was performed in two patients. Of the five who underwent subsequent surgical repair, none required ureteral tapering.

In summary, if differential renal function remains normal and the child is asymptomatic, it seems safe to follow these patients with renal sonograms and diuretic renography to monitor hydronephrosis, and renal function and drainage. If renal functional deterioration, slowing of upper urinary tract drainage, or UTI occurs, ureteral reimplantation is recommended. These infants should receive prophylactic antibiotics while stasis is present in the upper ureter and kidney.

URETEROCELE AND ECTOPIC URETER

A ureterocele is a cystic dilatation of the distal end of the ureter and is usually obstructive. In children, they usually extend through the bladder neck, termed 'ectopic', but may remain entirely within the bladder, termed 'intravesical' or 'orthotopic'. Ectopic ureteroceles and ectopic ureters occur more commonly in girls than in boys and usually are associated with the upper pole of a completely duplicated collecting system. In boys with a ureterocele, however, 40% drain a single collecting system. Prenatal sonography typically shows either hydro-ureteronephrosis or upper pole hydronephrosis with a dilated ureter. These conditions are bilateral in 10–15% of patients.

Early evaluation consists of:

- **Sonography** shows a hydronephrotic upper pole connected to a dilated ureter; the ureterocele typically is visualized in the bladder (Fig. 93.8a,b).
- **VCUG** often visualizes the ureterocele and demonstrates whether VUR is present, either into the lower pole moiety or contralateral collecting system (Fig. 93.8.c); an ectopic ureter that inserts into the bladder neck also typically refluxes into the upper pole obstructed ureter.
- **DMSA renal scan** shows whether the moiety drained by the ectopic system functions; this study may be done at 1–2 weeks of age because the result does not change with functional maturity. A DMSA renal scan is recommended rather than a diuretic renal scan, because there is not generally a question regarding 'obstruction' and the DMSA provides excellent cortical imaging. Alternatively, a CT or MRU demonstrates the anatomy adequately, although it may not provide functional information regarding the function of the obstructed upper pole (Fig. 93.8c).

The management of neonates with a ureterocele is highly individualized.[61] The least invasive initial form of therapy is transurethral incision (TUI), which can be performed either with a 3-F Bugbee electrode or the holmium:YAG laser (Fig. 93.8d,e). The ureterocele is punctured several times at its junction with the bladder mucosa. If the ureterocele is ectopic, it must be punctured both in the bladder and in the urethra.

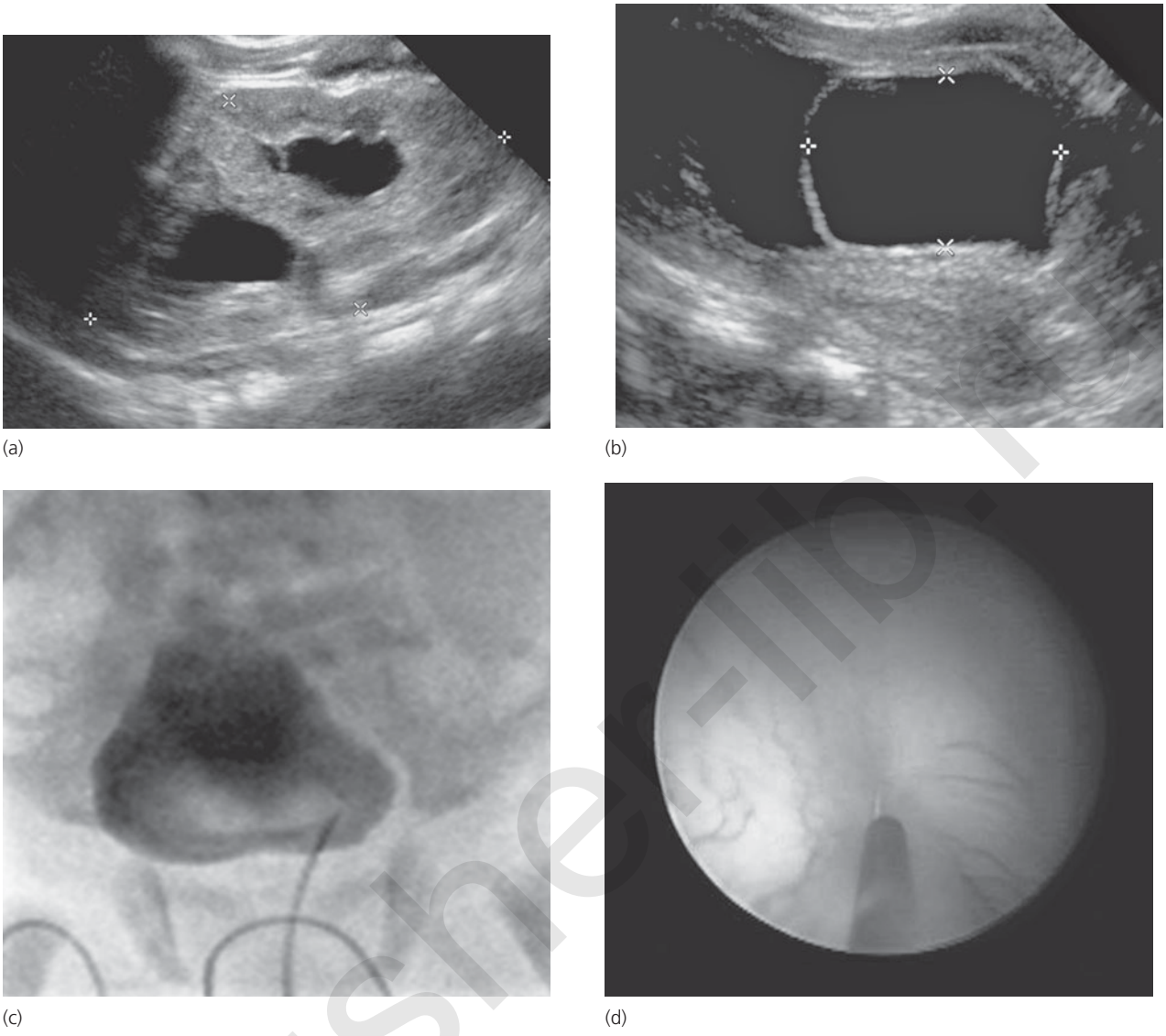
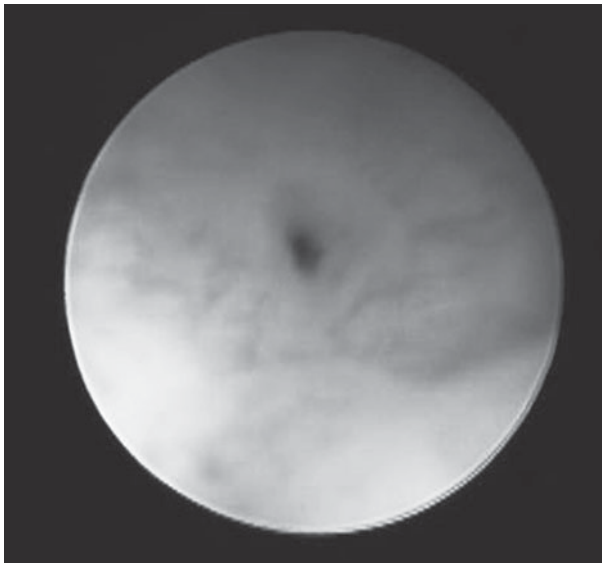


Figure 93.8 Infant with ureterocele and duplex collecting system, right side. (a) Sonogram of right kidney demonstrating echogenic right kidney with duplex collecting system and hydronephrosis involving both upper and lower pole. (b) Ureterocele in bladder. (c) Voiding cystourethrogram shows ureterocele in bladder, and no vesico-ureteral reflux. (d) Patient underwent transurethral incision; endoscopic view of ureterocele. (e) Appearance after transurethral incision. (f) Follow-up renal sonogram shows normal right kidney. (g) Bladder shows decompressed ureterocele.

TUI provides satisfactory upper tract decompression with a single procedure in >90% of cases. However, there is a significant risk of post-operative VUR through the ureterocele into the upper pole moiety, which may require subsequent definitive treatment. If the ureterocele is orthotopic, approximately 30% show VUR following TUI, whereas if it is ectopic, 75% have VUR following TUI.[62,63] TUI is often the only procedure necessary.[64]

TUI of a ureterocele draining a non-functioning moiety will not result in the development of any significant degree of function. Although the risk for subsequent VUR into the ureterocele is significant, TUI is an appropriate minimally invasive alternative to an open partial nephrectomy. However, in recent years many centers have been performing minimally invasive (laparoscopic) upper pole heminephrectomy. These procedures have been performed either with a retroperitoneal[65,66] or transperitoneal[67] approach. One recent series with a laparoscopic retroperitoneal approach reported an overall conversion rate to open surgery of 21%, although the authors stated that they had only one conversion in their most recent 20 cases.[68] Common complications include perirenal urinoma and, in some cases, devascularization of the lower pole moiety. The latter complication is most common in infants. Another option is to perform transperitoneal laparoscopic partial nephrectomy with robotic assistance.[69] Consequently, if the hydronephrotic upper pole does not function, this author maintains the infant on antibiotic prophylaxis and laparoscopic upper pole heminephrectomy (or nephrectomy, if the entire kidney does not function) with or without robotic assistance performed electively at six months of age, assuming the upper pole system remains hydronephrotic. If the DMSA scan shows significant



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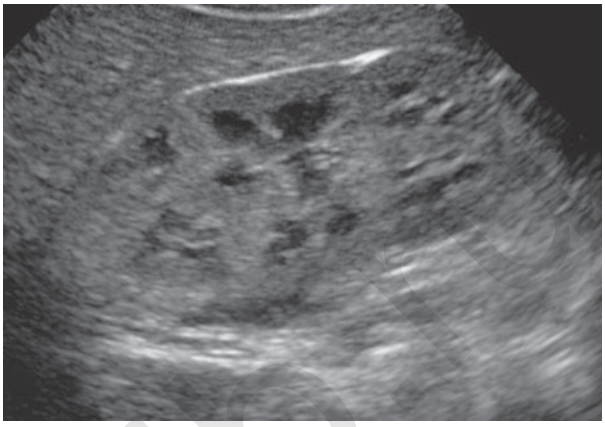

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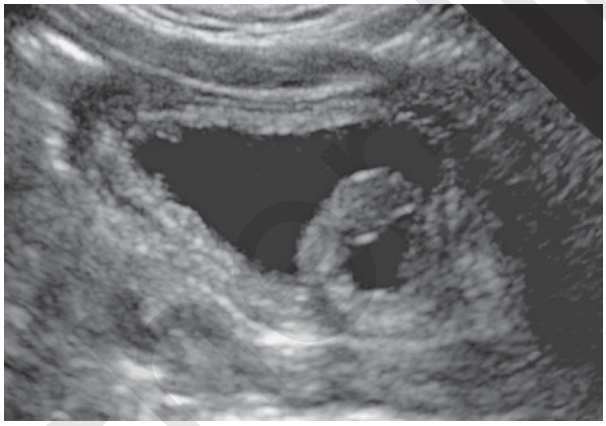


(g)

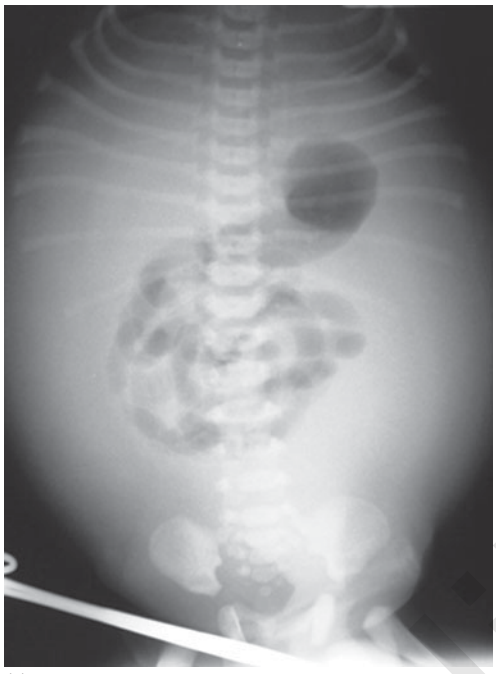
Figure 93.8 *Continued*

upper pole function, however, ureteropyelostomy or ureteroureterostomy, in which the upper pole ureter is anastomosed to the lower pole renal pelvis or ureter, is recommended. This procedure can be performed either at the level of the kidney, with removal of part of the redundant distal ureter,[70] or low, through an inguinal incision.[71] Total urinary tract reconstruction in neonates and infants is not recommended because of the high complication rate caused by the small size of the infant bladder.

POSTERIOR URETHRAL VALVES

The most common cause of severe obstructive uropathy in children is posterior urethral valves (PUV), which are tissue leaflets fanning distally from the prostatic urethra to the external urinary sphincter (Fig. 93.9). Typically, the leaflets are separated by a slit-like opening. Approximately one-third ultimately develop chronic renal failure or severe renal insufficiency. Prognosis is significantly better if the antenatal sonogram before 24 weeks' gestation was normal. In one study, nine of 17 patients with PUV whose hydronephrosis was discovered before 24 weeks' gestation developed renal failure, whereas only one of 14 recognized after 24 weeks' gestation developed end-stage renal disease.[72] Favorable prognostic factors include a serum creatinine level of less than 0.8–1.0 mg% after bladder decompression, unilateral VUR into a non-functioning kidney ('VURD syndrome'), ascites, and identification of the corticomedullary junction on renal sonography.

Early delivery of infants with an antenatal diagnosis of suspected PUV is not recommended, unless there is oligohydramnios. If severe bilateral renal dysplasia is present, pulmonary hypoplasia is often also present, and problems with ventilation may result. Initially, a small feeding tube should be passed into the bladder for urinary drainage until electrolyte imbalances can be corrected. A Foley catheter is not recommended because the balloon may cause significant bladder spasm and impede upper tract drainage. Care should be taken passing the catheter, as the prostatic urethra is dilated and there is bladder neck hypertrophy; the feeding tube may coil in the prostatic urethra and not drain the



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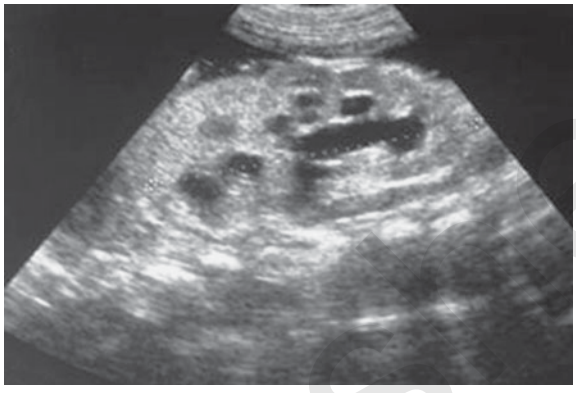

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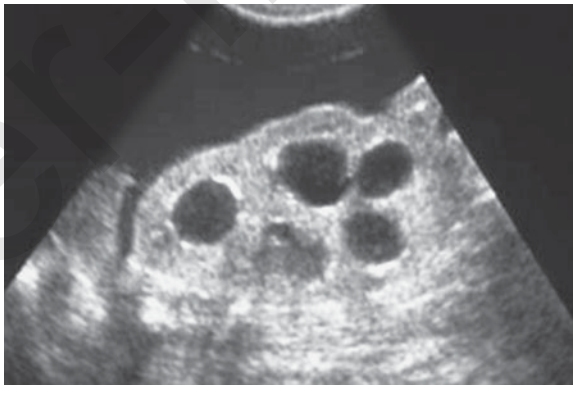


(c)

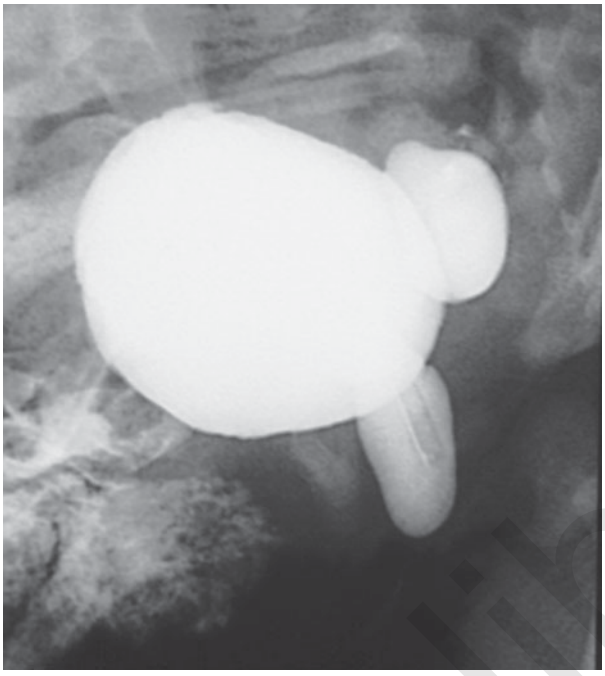
Figure 93.9 Newborn with posterior urethral valves and abdominal distension secondary to urinary ascites. (a) Plain film of abdomen showing ascites. (b,c) Renal sonogram showing bilateral hydronephrosis and urinary ascites. (d) Voiding cystourethrogram. Note dilated prostatic urethra proximal to the valve leaflets and bladder diverticulum on left side. Patient managed with upper tract drainage and transurethral incision of valve leaflets. (e,f) Renal sonogram, left and right kidneys at six months of age shows minimal hydronephrosis. At 17 years, patient had nearly normal renal appearance on ultrasound.

bladder. In this setting, catheter irrigation typically results in fluid coming out of the urethra next to the catheter. A VCUG should be obtained to confirm the diagnosis, and a DMSA renal scan should be performed to evaluate the upper tract differential renal function.[15]

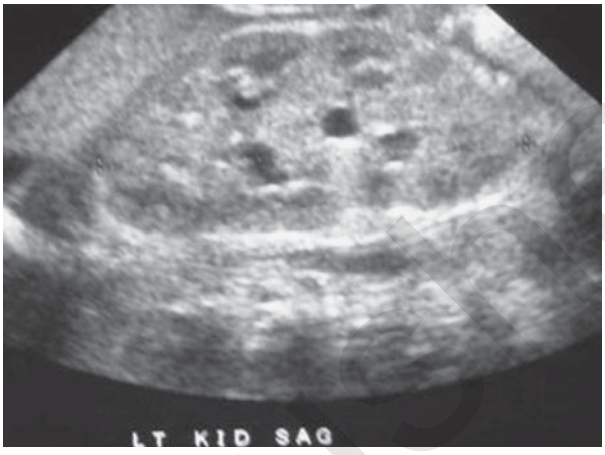
In newborns, alternative treatments include transurethral endoscopic ablation of PUV, cutaneous vesicostomy, and high diversion (cutaneous pyelostomy). The ideal initial treatment is valve ablation with a small Bugbee electrode, as is used with TUI, or the holmium:YAG laser. In small neonates, the 8 or 9 Fr resectoscope may be too large for the urethra, and a temporary vesicostomy may be necessary. A vesicostomy also should be considered for those with a serum creatinine level that remains significantly elevated after bladder decompression. Cutaneous pyelostomy rarely affords better drainage compared with cutaneous vesicostomy and diverts urine away from the bladder, which may prevent normal bladder growth.[73] However, in selected cases the Sober-en-T cutaneous ureterostomy is useful. In this procedure, the upper ureter is brought out to the abdomen and transected, and the distal segment is anastomosed to the renal pelvis; this option allows urine to drain both through the ureterostomy, as well as to the bladder.[74]

VESICO-URETERAL REFLUX

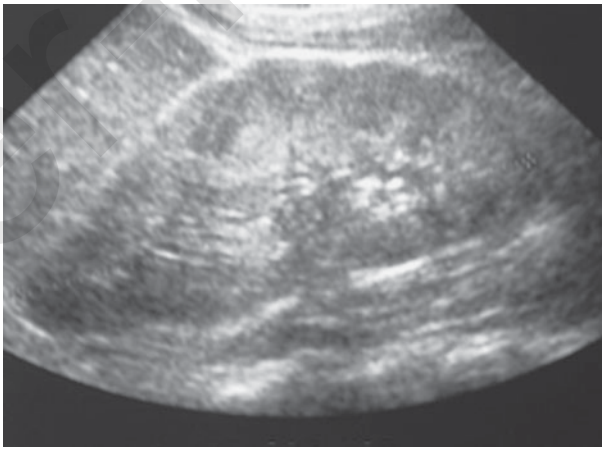
Some neonates with medium- and high-grade VUR are detected following the finding of antenatal hydronephrosis. Approximately 80% of such patients are boys. In the most severe cases of massive VUR, the bladder may also become distended from aberrant micturition into the upper



(d)



(e)



(f)

Figure 93.9 *Continued*

tracts, termed the 'megacystis-megaureter syndrome'. In the American Urological Association analysis, reflux-related renal scarring was present in 47.9% of those with grades IV–V VUR, but only 6.2% of those with grades I–II VUR. Consequently, in neonates with grades III–V VUR, a DMSA scan is recommended to determine whether reflux-related renal scarring is present.

Initially, neonates with prenatally diagnosed VUR are managed medically. Most are placed on amoxicillin prophylaxis for two months, followed by nitrofurantoin or trimethoprim-sulfamethoxazole prophylaxis, and circumcision is recommended for male neonates to decrease the risk for UTIs.

Neonates with VUR are more likely to show spontaneous resolution than are older children. Indeed, 20–35% of ureters with grade IV or V VUR have reflux resolution within two years; however, a significant proportion develop a breakthrough UTI, and antireflux surgery is recommended in these cases. The success rate for open surgical correction of VUR in infants can be as high as in older children.[57] Another option is subureteral injection of the ureterovesical junction with dextranomer microspheres, in which the success rate is 69% with a single injection.[75]

SUMMARY

Approximately 1–2% of newborns have an antenatal diagnosis of hydronephrosis or significant renal pelvic dilation. Hydronephrosis is often caused by non-obstructive conditions. The likelihood of significant urologic pathology is directly related to the size of the fetal renal pelvis, and 90% with an anteroposterior diameter more than 2 cm need surgery or long-term urologic follow up. Following delivery, antibiotic prophylaxis should be administered and a renal

sonogram and voiding cystourethrogram should be obtained. If there is grade 3 or 4 hydronephrosis, a diuretic renogram is usually also recommended. Pediatric urologic or pediatric nephrologic consultation is helpful in planning evaluation and treatment. Antenatal recognition of hydronephrosis allows postnatal diagnosis and treatment of urologic pathology, preventing complications of pyelonephritis and obstruction. In the past decade, significant progress has been made in the development of minimally invasive treatment options.

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94

Multicystic dysplastic kidney

DAVID FM THOMAS AND AZAD S NAJMALDIN

INTRODUCTION

Before the introduction of routine antenatal ultrasonography, multicystic dysplastic kidney (MCDK) was regarded as an uncommon anomaly which generally presented as an abdominal mass in the newborn period. Nephrectomy was the standard form of management.

It has become clear, however, that the prevalence of asymptomatic unilateral multicystic kidneys in the general population is far higher than was previously suspected, with an estimated incidence of around 1:3000 to 1:4000.[1,2] The majority of MCDKs are small, clinically undetectable and would have been destined to remain unrecognized in the neonatal period (and indeed throughout the individual's lifetime) if they had not been identified on antenatal ultrasonography.

ETIOLOGY

Although MCDK is almost invariably associated with atresia of the proximal ureter, it can rarely occur in conjunction with ureteral dilatation and a ureterocele. In both instances, however, the underlying mechanism is believed to be an obstructive insult to the developing metanephric mesenchyme at an early stage in gestation. Bilateral cases are invariably lethal and, when detected prenatally, usually lead to termination of pregnancy. Most cases of unilateral MCDK occur on a sporadic basis, although familial occurrence has been reported. MCDKs comprise an irregular collection of tense, non-communicating cysts of different sizes, lined by cuboidal or flattened tubular epithelium. Any renal parenchyma is limited to small islands or flattened plates of dysplastic tissue interposed between cysts.

It is important to note, however, that occasional variants of renal dysplasia which include a cystic component in addition to solid dysplastic tissue can create diagnostic confusion. Indeed, it is likely that some of the reports of hypertension and malignancy have been incorrectly attributed to MCDKs when they have, in fact, arisen in these variants.

PRESENTATION

Patterns of presentation include:

- Prenatal ultrasound detection (the majority).
- Clinical presentation, involving large multicystic kidneys, generally presenting as a firm, 'knobbly', abdominal mass which is apparent at birth or early in the neonatal period.
- Incidental finding during the investigation of some unrelated illness.
- Symptomatic complications (very rare).

INVESTIGATIONS

Ultrasound

The ultrasound features which characterize MCDK are now well defined in the radiological literature (Fig. 94.1).[3,4]

These important diagnostic criteria comprise:

- multiple oval or round cysts which do not communicate;
- presence of interfaces between the cysts;
- non-medial location of the largest cyst (a large fluid-filled component located medially is more likely to represent the dilated pelvis of a severely hydronephrotic kidney);
- absence of solid parenchymal tissue;
- complete absence of function (0% differential function) on ^{99m}Tc-DMSA (technetium-99m dimercaptosuccinic acid) scintigraphy.

Other causes of a renal mass in the neonatal period, such as mesoblastic nephroma or infantile polycystic kidney, can readily be excluded from the differential diagnosis. However,

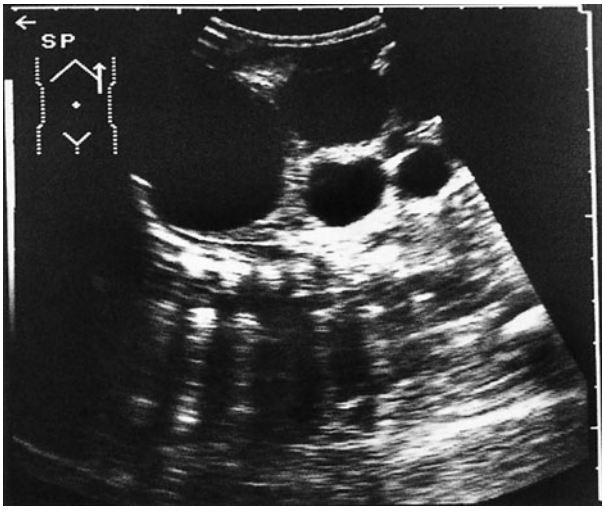


Figure 94.1 Typical ultrasonographic appearance of neonatal multicystic dysplastic kidney, i.e. non-communicating cysts of varying size, demonstrable septa between cysts, no visible rim or cortical tissue.

diagnostic difficulty can arise in distinguishing between MCDK and and gross hydronephroses due to pelvi-ureteric junction obstruction. Similarly, as already indicated above, other forms of renal dysplasia can be mistakenly diagnosed as MCDK by those unfamiliar with the diagnostic criteria. The bladder, ureters, and contralateral kidney should also be carefully evaluated by ultrasound for dilatation associated with vesico-ureteric reflux, contralateral pelvi-ureteric obstruction, or some other urological abnormality.

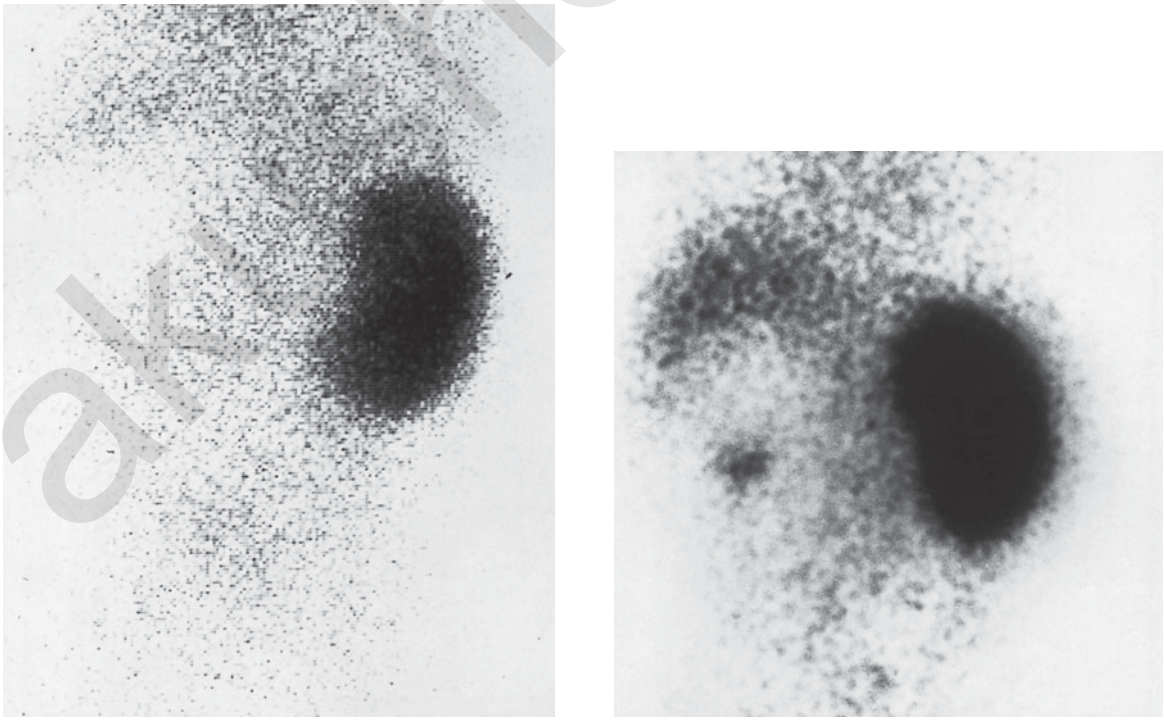
Isotope imaging

The main purpose of isotope imaging is to distinguish between MCDK and a grossly hydronephrotic kidney or a variant of renal dysplasia. MCDKs are entirely non-functioning, whereas even grossly hydronephrotic kidneys almost invariably demonstrate some degree of isotope uptake, corresponding to a small percentage of differential function. Similarly, some rare variants of cystic dysplasia have demonstrable function (although this is also usually apparent as an area of solid parenchymal tissue on ultrasound). In equivocal cases, nephrectomy is justified to establish a histological diagnosis and to obviate the possible risk of complications, notably hypertension.

^{99m}Tc-DMSA is the most reliable modality for demonstrating low levels of function (Fig. 94.2a,b). Nevertheless, ^{99m}Tc-MAG3 (technetium-99m mercapto-acetyl-triglycine) may be preferable if there is any suggestion of contralateral pelvi-ureteric junction obstruction (which is present in 5–10% of cases). Ideally, imaging should be deferred until after the fourth week of life.

Other investigations

Although voiding cystourethrography (VCUG) is undoubtedly indicated if postnatal ultrasonography reveals ipsilateral



(a) (b)

Figure 94.2 (a) ^{99m}Tc-DMSA scan demonstrating normal isotope uptake and renal morphology on the left, and no uptake or isotope in the right (multicystic) kidney. (b) A focus of poor, but discernible, uptake of ^{99m}Tc-DMSA in a grossly hydronephrotic right kidney. Ultrasound could not distinguish with certainty between gross hydronephrosis and multicystic kidney.

ureteric dilatation or contralateral upper tract dilatation, it is doubtful whether this invasive investigation is routinely necessary if the ultrasound appearances of the urinary tract are otherwise normal. In the absence of ureteric dilatation on ultrasound, any coexisting contralateral or ipsilateral vesicoureteric reflux (VUR) is invariably low grade, self-limiting, and rarely gives rise to infection. Miller and associates[5] studied the outcome of reflux into the contralateral kidney of 75 children with MCDK and found a high incidence of spontaneous resolution over a relatively short period. There was no difference in the growth between kidneys which were associated with VUR and those that were not. If a routine VCUG is not performed, it is nevertheless important that parents and general practitioners are aware that the occurrence of a documented or suspected urinary tract infection (UTI) or an unexplained febrile illness requires further investigation to look for possible VUR.

INDICATIONS FOR SURGERY

The following are widely accepted as definite indications for nephrectomy:

1. A large multicystic kidney giving rise to an obvious, visible, and readily palpable abdominal mass. In this situation, there is usually considerable parental anxiety. In addition, there may be apparent discomfort or other symptoms attributable to the size of the mass.
2. Diagnostic uncertainty. Despite the combination of ultrasound and isotope imaging, it may occasionally be impossible to distinguish with certainty between an MCDK, a poorly functioning hydronephrotic kidney or a rare cystic variant of renal dysplasia. The presence of demonstrable function in what otherwise appears to be an MCDK should be viewed with suspicion and represents a valid indication for nephrectomy. Isotope function equates with perfusion and it can be reasonably argued that perfused tissue imparts a greater risk of renal hypertension. Likewise, a cystic anomaly which is also seen to contain a solid parenchymal component or which does not fulfil the other diagnostic criteria listed above is not an MCDK and is, therefore, best removed.

Issues surrounding surgery for asymptomatic MCDKs

The overwhelming majority of prenatally detected MCDKs are asymptomatic and clinically undetectable. Nevertheless, some surgeons have advocated the 'prophylactic' removal of asymptomatic, prenatally detected MCDKs, justifying this policy on the basis of the perceived risk of complications – notably hypertension and malignant transformation. When MCDKs were first diagnosed prenatally, the extent of these perceived risks was, of necessity, based upon historical case reports. However, closer analysis of the historical literature sheds doubt on the accuracy of the diagnosis of MCDK in some of the reported cases. Fortunately, it is no longer necessary to resort to historical data since the last two decades have witnessed the publication of an extensive body of literature specifically devoted to prenatally detected MCDK. In addition, there have been a number of authoritative literature reviews. For example, Narchi[6,7] undertook a detailed review of 26 published series totaling 1041 children with conservatively managed MCDKs. Information on duration of follow up was available in 18 publications and was between 1.25 and 6.5 years, with a maximum of 23 years. No cases of Wilms' tumor were identified by Narchi's literature review.[7] Cambio and associates[8] reviewed data reported by 105 publications on prenatally detected MCDK, to which they added unpublished data from the MCDK Registry on approximately 900 MCDKs. From their extensive analysis of the literature, these authors identified three cases of Wilms' tumor arising in a prenatally detected MCDK – none of which occurred after four years of age. There were no cases of Wilms' tumor arising in involuted MCDKs. Seven cases of Wilms' tumor arising in a purported MCDK were identified from the historical literature, but Cambio and associates highlighted uncertainties regarding accuracy of the diagnosis of MCDK in historical case reports. The Trent and Anglia MCDK Study Group[1] systematically collected prospective data on 202 children with prenatally detected MCDK born between 1985 and 2004. The mean duration of follow up was 8.1 years (0.1–19.7 years), with 43 children being followed beyond ten years. No Wilms' tumors were encountered in these patients. Similarly, no Wilms' tumors occurred in 325 children with prenatally detected MCDKs managed conservatively at Great Ormond Street Hospital, London. Of these, 180 children with MCDKs had been followed prospectively for more than ten years (unpublished data, Dhillon HK, personal communication, 2009).

Using published data on the prevalence of MCDK, the risk of Wilms' tumor has been calculated to lie in the range 0.0001%[9] to 0.0005%.[10]

Anecdotally, there have been cases of malignancy arising in prenatally detected MCDKs which have not been reported in the literature. Although the accuracy of the diagnosis of MCDK in anecdotal cases has not been subject to scrutiny in the peer-review process, it could reasonably be argued that calculations based upon the number of published cases of malignancy understate the true magnitude of the risk. However, the risk of malignancy can also be approached from a different perspective by asking 'how frequently does MCDK feature in published series of Wilms' tumor?'

The respected pediatric pathologist, JB Beckwith,[10] addressed this question by studying data on 7500 Wilms' tumors reported to the National Wilms' Tumour Study Pathology Centre over an 18-year period. Of the 7500 Wilms' tumors, five had arisen in MCDKs. On the basis of these data, coupled with published data on the prevalence of MCDKs, Beckwith calculated the individual life-time risk of developing Wilms' tumor in an MCDK as approximately 1:2000 (0.0005%). If anything, this calculation probably overstates the risk because more recent published information indicates that overall prevalence of MCDK in the pediatric population is somewhat higher than the original figure on which Beckwith's calculation was based. Beckwith also questioned the diagnostic accuracy of historical reports, observing that

'the literature concerning renal tumors in multicystic dysplastic kidney is burdened with poorly documented or unconvincing cases'.

The risk of hypertension has also been cited by the proponents of 'prophylactic nephrectomy'. There is now a growing body of evidence with which to quantify the scale of this risk. No cases of hypertension were encountered in the 202 children with prenatally detected MCDK followed prospectively by the Trent and Anglia MCDK Study Group[1] and no instances of hypertension were recorded in 441 children with prenatally detected MCDKs enrolled on the MCDK registry.[9]

Narchi's literature review did, however, reveal a published incidence of hypertension of 0.5%.[6] However, it is important to recognize that confirming a reliable diagnosis of hypertension in this age group can be problematic because of the difficulties inherent in obtaining accurate, reproducible blood pressure readings in fractious infants and young children.

As with malignancy, the risk of hypertension can also be viewed from a different perspective. MCDK is now known to be a relatively common anomaly with a birth incidence in the range of 1:3000–1:4000.[1,2] By contrast, hypertension is a relatively rare condition in the pediatric population. If MCDKs were resulting in hypertension on any appreciable scale, it could be expected that they would account for a sizeable proportion of children with hypertension. This is not the case. For example, in a series of 21 children with renal hypertension managed by nephrectomy at Great Ormond Street Hospital between 1968 and 2003, there was only a single case of MCDK.[11]

Removing a MCDK may not entirely obviate the risk since there are well-documented cases of hypertension arising in the contralateral kidney.[12] Moreover, there is also some evidence that individuals with a solitary kidney are at an increased lifetime risk of developing hypertension.

It must also be acknowledged that information on the possible long-term risk of hypertension (i.e. beyond ten years) is still very limited and the risk of later-onset hypertension cannot be entirely discounted. Nevertheless, the evidence of the adult nephro-urological literature suggests this risk is very low.

A more extensive review of the large body of published information on prenatally detected MCDKs is beyond the scope of this chapter, but, in summary, the best evidence currently available puts the risk of developing hypertension associated with a prenatally detected MCDK at less than 1% (probably significantly less) and the risk of malignant transformation at 0.0001–0.0005%.

With regard to malignancy, the risk of mortality associated with general anesthesia in this age group is probably of the same order (or higher) than the risk of dying from Wilms' tumor arising in a prenatally detected MCDK. In summary, cystic renal anomalies which do not fulfill the diagnostic criteria set out above are not MCDKs, and nephrectomy is reasonable in such cases – particularly if there is evidence of solid dysplastic tissue on ultrasound or demonstrable function on renography. By contrast, there is now a substantial body of evidence that the risk of complications arising in genuine MCDKs (the overwhelming of prenatally detected cystic anomalies) is exceedingly small and the natural history is generally one of spontaneous involution.

Surgeons must assess the arguments for themselves, but those who advocate routine 'prophylactic' nephrectomy should be aware that this approach will inevitably expose large numbers of healthy asymptomatic infants to the risks inherent in unnecessary general anesthesia and surgery.

Timing of surgery

Large multicystic kidneys associated with a sizeable mass should be removed electively in the first few weeks of life. Smaller lesions for which surgery is nevertheless thought to be appropriate can safely be left until 6–12 months of age or later. It is important to obtain an ultrasound scan shortly before surgery to confirm that the MCDK is still visible and has not undergone involution in the period since the decision was taken to operate.

SURGICAL OPTIONS

Nephrectomy can be performed as a conventional open procedure or laparoscopically, depending on such factors as the surgeon's expertise in minimally invasive surgery, availability of suitable pediatric instrumentation, and the preference of the parents.

Open nephrectomy

Dorsal or posterior lumbotomy has the advantage of simplicity, good cosmesis, reduced postoperative pain, and shortened hospital stay. The major drawback is the more limited exposure of the kidney offered by this incision and difficulty in extending it if the surgeon is faced with an unforeseen problem. For a small MCDK, the dorsal lumbotomy incision is ideal and even for larger lesions nephrectomy should not pose problems, provided that the bulk of the multicystic kidney is reduced by cyst aspiration. For an account of operative technique and an assessment of the place of the dorsal lumbotomy in pediatric renal surgery, readers are referred to the articles of Orland *et al.*[13] and Wise and Snow.[14]

Those unacquainted with the dorsal lumbotomy incision are advised to employ the more familiar loin approach, described in detail below.

OPERATIVE DETAILS

Position of the patient

A full lateral position is employed (Fig. 94.3). Lateral flexion of the spine is best achieved in this age group by the use of a sandbag under the contralateral loin rather than by a bridge or 'break' in the table. Once the required position has been achieved, adhesive strapping is used to maintain it. The strapping is fixed first to one side of the operating table,

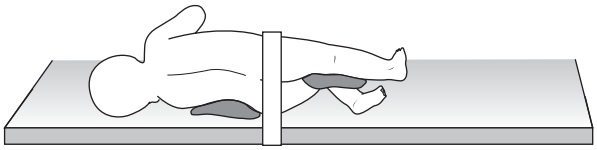


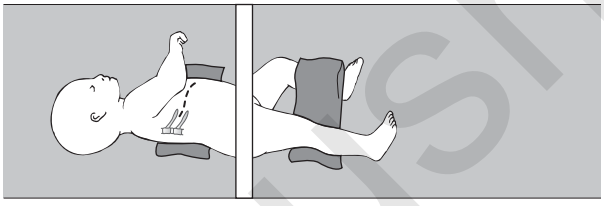
Figure 94.3 Lateral position of the patient.

taken across the abdomen at the level of the iliac crests and then is secured firmly on the other side of the table.

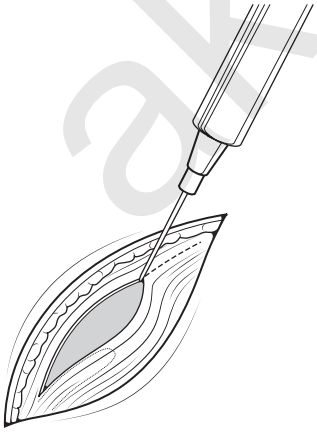
The incision

The 12th rib is identified by palpation. If available, a preoperative plain x-ray is helpful in determining the length of the 12th rib. An incision of modest length above the 12th rib nevertheless affords good access for nephrectomy if the procedure is combined with intraoperative cyst aspiration. Care should be taken to base the incision on the 12th rib (Fig. 94.4a), as an inadvertent incision above the 11th rib often results in the pleura being opened.

Once the skin and subcutaneous fat have been incised, cutting diathermy is used to deepen the incision to the tip of the 12th rib. The muscles attached to the superior border of the 12th rib (latissimus dorsi intercostal muscles) are incised along their insertion. The rib, thus mobilized, is deflected caudally to allow the surgeon to insert a finger which can be advanced anteriorly in the line of the rib to sweep the peritoneum medially and anteriorly from the overlying abdominal wall muscles. The incision can then be extended forwards in the line of the rib using the diathermy to divide the external oblique, internal oblique, and transversus abdominis muscles (Fig. 94.4b). Care is needed to avoid damaging the neurovascular bundle, as this can result in a visible obvious (but usually self-limiting) postoperative weakness of the relevant segmental abdominal musculature. When the incision has been completed, a self-retaining retractor can be inserted. A bent or 'offset' ring retractor is suitable for this purpose, but a conventional flat ring is not usually effective as it does not correspond to the marked curvature of the loin.



(a)



(b)

Figure 94.4 (a,b) The incision.

Mobilization of the kidney

Small MCDKs (particularly in older infants) are sometimes difficult to locate in the retroperitoneum. In this situation, it is necessary to dissect carefully through the retroperitoneal and perirenal fat, maintaining proximity to the posterior abdominal wall until the multicystic kidney is identified. More commonly, the MCDK is encountered without difficulty in the renal fossa. A combination of blunt and scissor dissection is commenced to develop a plane between the most superficial cysts and adjacent tissues (Fig. 94.5). It should be noted that the peritoneum is usually applied extensively over the anteromedial aspect of a large multicystic kidney. The phase of the dissection intended to identify and develop a plane around the multicystic kidney is best achieved with the cysts intact.

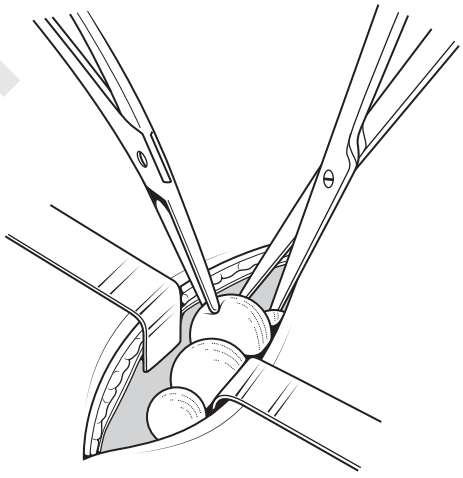


Figure 94.5 Mobilization of the kidney.

Aspiration of cysts

Once a portion of the kidney has been exposed and mobilized in this fashion, it is helpful to aspirate the visible cysts with a syringe and needle (Fig. 94.6). The decompressed cyst wall can then be grasped, e.g. with Allis tissue forceps, so that gentle traction can be applied to deliver the kidney out of the incision. By sequence of dissection around the intact cysts followed by aspiration and mobilization through the incision, it is possible to remove a MCDK through a much smaller incision than would have been required if the cysts were left intact.

Dissection of hilum

As the dissection is deepened, a malleable retractor is inserted to retract the peritoneum and expose the ureter and hilar

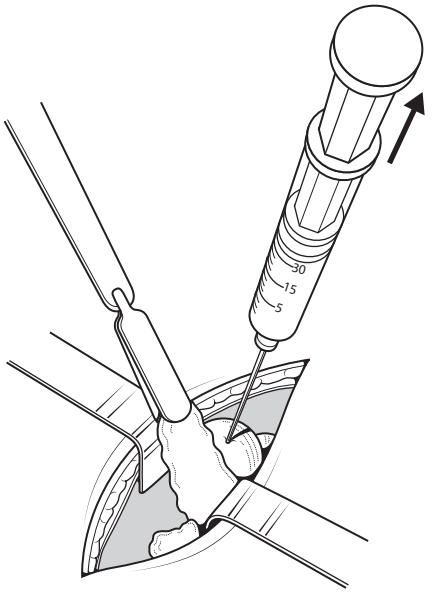


Figure 94.6 Aspiration of cysts.

vessels. A vascular sling or tape is placed around the ureter and gentle traction is applied to facilitate the final dissection of the hilum (Fig. 94.7). The ureter is then ligated with a 4-0 absorbable suture and divided. While it is good practice to ligate the renal arteries and veins individually (to prevent the risk of arteriovenous fistula formation), this may prove impossible in an MCDK since the vessels are usually small and frequently non-patent. Once identified, the vessels are ligated in continuity, then divided between ligatures. By this stage, mobilization of the decompressed multicystic kidney is usually complete and it can removed following division of any remaining attached tissue.

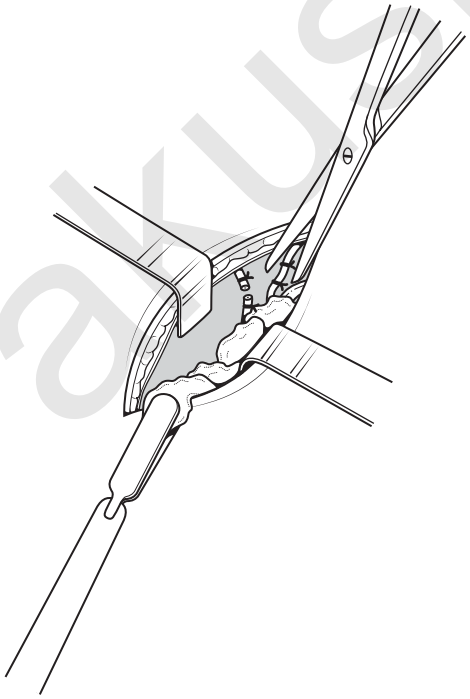


Figure 94.7 Dissection of the hilum.

The renal bed is inspected carefully and further diathermy hemostasis is performed, if required. Likewise, the peritoneum is inspected and any defect closed with a continuous suture of 4-0 absorbable suture. Drainage of the renal fossa is not necessary. This incision is closed either in two layers using continuous 3-0 PDS or vicryl, or alternatively by a series of interrupted mass sutures encompassing the rib. The skin is then closed with a subcuticular suture of 5-0 vicryl.

POSTOPERATIVE CARE

Postoperative recovery is usually rapid. Feeding is re-established within 24 hours and the child can generally leave hospital within 1–2 days.

Laparoscopic nephrectomy

Laparoscopic nephrectomy can be performed either transperitoneally[15–17] or extraperitoneally,[18] with the former being more widely practiced.

EQUIPMENT AND INSTRUMENTS

In addition to a set of instruments for open technique laparosocopy[19] and laparotomy in case of emergency or conversion to open surgery, the following equipment and instruments are required:

- Camera, light source, insufflator, and one or preferably two monitors with appropriate attachments.
- Diathermy unit (monopolar and bipolar) with appropriate cables and hand probes. Ultrasonic shears, ligasure, or plasma kinetic coagulation devices may be used as an alternative.
- Three or four, 2.5–12 mm cannulae and trocars with appropriate converters.
- A 30° or 45°, 2.5–10 mm, angled telescope (0° scope may be adequate).
- An appropriate retractor may prove helpful. Often, a simple instrument, such as an atraumatic grasper, may be used as a retractor.
- Two atraumatic, preferably insulated, relatively fine curved or angled double action jaw grasping forceps (an additional forceps with ratchet can be useful).
- One insulated, curved, double-action jaw scissors with appropriate diathermy lead.
- Suction/irrigation apparatus and probe.
- A single- or multi-load automatic clip applicator and clips (alternatively, suture ligatures may be used).
- One long needle to compress cysts, if necessary.
- Balloon dissector may be required for an extraperitoneal approach.

The size and length of instruments depend on the size of patient, surgeon's preference and availability of instruments.

PREPARATION AND POSITION OF THE PATIENT

General anesthesia with endotracheal intubation and full muscle relaxation are essential. A small nasogastric tube and a urinary catheter only if the bladder is palpable and cannot be expressed manually, may improve access. The infant is placed and strapped securely in the semilateral position with soft towels under the contralateral loin/lower chest to allow lateral flexion and the bowel to fall medially under gravity (Fig. 94.8).

TECHNIQUE FOR TRANSPERITONEAL NEPHRECTOMY

Theater layout, position of the surgeons, and the placement of the cannulae are illustrated in Figure 94.8. The primary cannula is place in the peri-umbilical region using an open technique laparoscopy.[19] A pneumoperitoneum is created with CO_2 insufflation through the primary cannula at a flow rate of 0.2–1 L/min and pressure of 8–10 mm mercury.[20] A telescope is then placed through the cannula and under direct vision, the working cannulae are placed in the direction of the kidney. The sites and sizes of the working 'secondary' cannulae are dependent on the size of the patient, the size of the instruments to be used, and the surgeon's preference.[21] Often, two (2.5–5 mm) working cannulae, in addition to the primary cannula provide adequate access to remove MCDKs. An additional cannula may be placed for retraction if necessary. A few centimeters long opening in the peritoneum, lateral to the upper border of the colon and directly over the lower part of the kidney allows adequate exposure.[15] A true mobilization of the colon is not necessary in pediatric patients. The kidney is then mobilized by blunt and sharp dissection and traction on the cysts may facilitate exposure (Fig. 94.9). The vessels, which are small and attenuated, are exposed usually close to the kidney and divided between clips or ligatures. Alternatively, diathermy, uni- or bipolar, ultrasound shears, ligasure or plasma kinetic may be used to secure hemostasis. A non-atretic ureter is clipped or ligated and divided at a convenient level. If necessary, the size of the specimen can be reduced by needle aspiration. The specimen is then removed via the largest cannula or site of a cannula with or without 1–2 cm extension. A retrieval bag is usually difficult to accommodate in infants and often not necessary. A change of telescope and/or instruments from one cannula to another may facilitate viewing and dissection during the procedure.[21] A drain is not necessary. In infants, cannula sites greater than 2.5 mm are closed with absorbable sutures. The peritoneal opening is covered by colon as the patient is returned to the supine position at the end of the procedure, thus leaving very little, if any, raw surface that might promote adhesion formation.

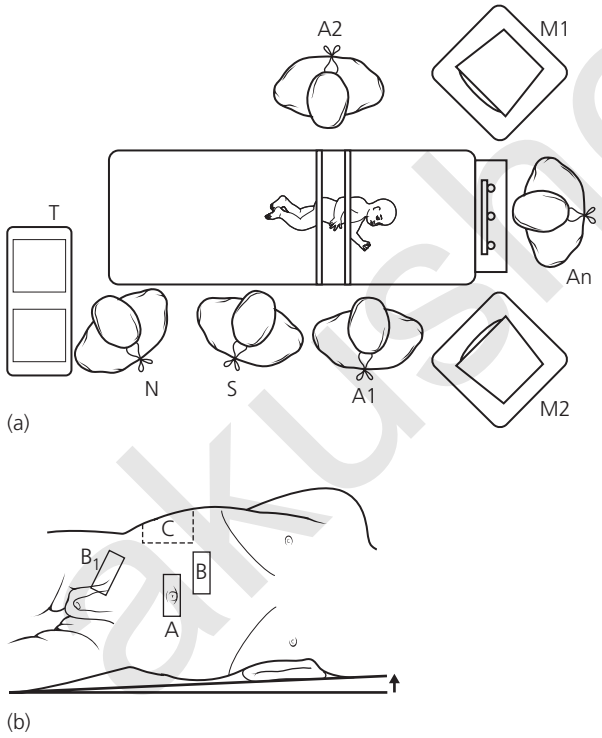


Figure 94.8 Laparoscopic transperitoneal right nephrectomy for multicystic dysplastic disease. (a) Theater layout. Note how the patient is fully supported and strapped in a semilateral position. S, surgeon; A1/A2, assistants; N, scrubbed nurse; An, anesthetic apparatus; M1/M2, monitors; T, instrument trolley. (b) Position of cannulae. A, peri-umbilical or lateral abdominal wall site for the primary cannula; B, working cannula 1; B1, working cannula 2 in the lower abdominal skin crease which may be extended to retrieve the specimen if necessary; C, an accessory cannula for hand instruments and/or retractor, if necessary.

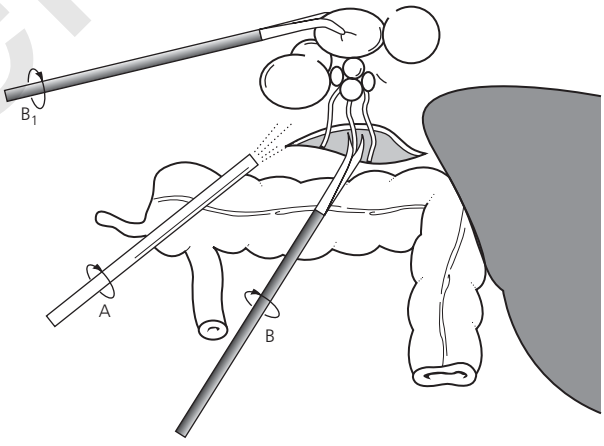


Figure 94.9 Laparoscopic transperitoneal nephrectomy. A, 2.5 to 10-mm angled or 0° telescope; B and B_1, two working instruments. Note how a few centimeter-long high paracolic peritoneal incision directly over the cystic kidney without colon mobilization allows full mobilization of the specimen and hemostasis.

POSTOPERATIVE CARE

At the end of the procedure, the nasogastric tube and/or urinary catheter are removed. Local infiltration of the cannula sites with an appropriate anesthetic agent provides adequate pain relief. Opiate analgesia is usually not required. However, i.v. paracetamol may be used for several hours postoperative, if thought to be necessary. The patient is usually ready to go home within 8–24 hours.

APPROACH FOR RETROPERITONEAL NEPHRECTOMY

In infants, extraperitoneal nephrectomy is a challenge but can be performed within a space created by breaking up the loose connective tissue binding the extraperitoneal space with either the tip of the telescope and direct CO_2 insufflation or a balloon dissector.[18,22]

This technique avoids the morbidity that may be associated with traversing the peritoneal cavity. However, its drawback is the more restricted exposure of the kidney offered by this approach and the possibility of peritoneal tear and extension pneumoperitoneum that makes extraperitoneal surgery difficult to achieve. Furthermore, published data indicate no significant difference between the two approaches in terms of clinical outcome.[23]

FOLLOW UP

Follow up is determined by the nature of any coexistent abnormalities. In an otherwise normal child who has undergone nephrectomy for a MCDK, follow up is limited to an occasional precautionary ultrasound scan of the solitary remaining kidney, until such age as the child could reasonably be relied upon to localize symptoms in the unlikely event of developing symptomatic pathology (e.g. pelvi-ureteric junction (PUJ) obstruction) in the remaining kidney. For reasons outlined above, lifelong annual blood pressure measurement may also be advisable for any individual with a solitary kidney.

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95

Upper urinary tract obstructions

PREM PURI AND BORIS CHERTIN

INTRODUCTION

With the widespread use of maternal ultrasound, the incidence of hydronephrosis has increased significantly, altering the practice of urology. A recent review of the trends in the prenatal sonography use and subsequent urological diagnoses in the United States demonstrated significant increase in the overall ultrasound use over the last two decades. Moreover, the mean number of ultrasounds per pregnancy also increased significantly from 2.7 in 1998 to 4.2 in 2005.[1] Pelvi-ureteric junction obstruction is the most common cause of hydronephrosis detected antenatally.[2,3] The next most common cause of prenatally detected hydronephrosis is obstruction at the uretero-vesical junction.[2] Management of these patients after birth remains controversial. The decision to intervene surgically has become more complex because spontaneous resolution of antenatal and neonatal upper urinary tract dilatations is being increasingly recognized.[2,4–6] The recognition and relief of significant obstruction is important to prevent irreversible damage to the kidneys.[7] Differentiating urinary tract dilatations that are significantly obstructive and require surgery from those that represent mere anatomical variants with no implications for renal function is not a simple task especially in newborns. It has been shown that the changes in the function of the involved kidney should be used as a measure of degree of obstruction and indication for surgical intervention.[4,5,7–10]

PELVI-URETERIC JUNCTION OBSTRUCTION

The overall incidence of pelvi-ureteric junction (PUJ) obstruction approximates 1 in 1500 births. The ratio of males to females is 2:1 in the neonatal period, with left-sided lesions occurring in 60%. In the newborn period, a unilateral process is most common, but bilateral PUJ obstruction was found in 10–49% of neonates in some reported series.[7] PUJ obstruction is classified as intrinsic, extrinsic, or secondary.

Intrinsic obstruction results from failure of transmission of the peristaltic waves across the PUJ, with failure of propulsion of the urine from the renal pelvis into the ureter, which results in multiple ineffective peristaltic waves, eventually causing hydronephrosis due to the incomplete emptying of the pelvic contents.[8–11] Tainio *et al.*[12] have shown the abnormalities of peptidergic innervation with dense innervation of neuropeptide Y (NPY) and vasoactive intestinal polypeptide (VIP) and proposed that these may have a role in intrinsic obstruction. Absence or reduction of smooth muscle with replacement by collagen fibers has been demonstrated histologically.[13,14] Some researchers proposed that downregulation of Cajal cells is responsible for the development of PUJ obstruction.[15] Extrinsic mechanical factors include aberrant renal vessels, bands, adventitial tissues, and adhesions that cause angulation, kinking, or compression of the PUJ. Extrinsic obstruction may occur alone, but usually coexists with intrinsic ureteropelvic junction pathology. Secondary PUJ obstruction may develop as a consequence of severe vesico-ureteric reflux (VUR) in which a tortuous ureter may kink proximately.[16] Previous reports have described VUR in 9–15% of children with PUJ obstruction, although the fractions that are secondary to reflux is difficult to determine.[9,16]

Prenatal diagnosis

The bladder is visualized by 14 weeks of gestation. The presence of a full bladder provides evidence of renal function. The ureters are usually not seen in the absence of distal obstruction or reflux. The fetal kidney may be visualized at the same time as the bladder. If not, they are always visualized by the 16th week of gestation. However, it is not until 20–24 weeks of gestation, when the fetal kidney is surrounded by fat, that the internal renal structures appear distinct.[16] Renal growth can then be assessed easily.[17] Beyond 20 weeks, fetal urine production is the main source of amniotic fluid. Therefore, major abnormalities of the urinary tract may result in oligohydramnios.

Because of the distinct urine–tissue interface, hydronephrosis can be detected as early as 16 weeks' gestation. An

obstructive anomaly is recognized by demonstrating dilated renal calyces and pelvis. A multitude of measurements and different gestational age cut-off points have been recommended in the assessment of fetal obstructive uropathy.[18–22] Routine estimation of the anteroposterior (AP) diameter of the renal pelvis in the fetus with hydronephrosis is considered as a useful marker for the classification of renal dilatation and possible obstruction. AP renal pelvis threshold values ranged between 2.3 and 10 mm. Positive predictive values for pathological dilatation confirmed in the neonate ranged between 2.3 and >40% for AP renal measurements of 2–3 and 10 mm, respectively. A study which included more than 46000 screening patients published the standards regarding renal pelvic measurement.[17] This study clearly demonstrated that only fetuses exhibiting third-trimester AP renal pelvis dilatations >10 mm would merit postnatal assessment. In order to standardize postnatal evolution of prenatal hydronephrosis, a grading system of postnatal hydronephrosis was implemented in 1993 by the Society for Fetal Urology (SFU).[23] Under SFU system, the status of calices is paramount, while the size of the pelvis is less important. Following the SFU grading of hydronephrosis, there is no hydronephrosis in grade 0. At grade 1, the renal pelvis is only visualized; grade 2 of hydronephrosis is diagnosed when a few (but not all) renal calices are identified, in addition to the renal pelvis; grade 3 hydronephrosis requires that virtually all calices are depicted; grade 4 hydronephrotic kidneys will exhibit a similar caliceal status with the involved kidney exhibiting parenchymal thinning. Often, this classification is also applied on prenatal hydronephrosis. We have recently published our data regarding prenatal findings with the special emphasis on the natural history of hydronephrosis during the postnatal period.[7] Our data show that SFU grade of prenatal hydronephrosis is not a significant predictive factor for surgery in unilateral hydronephrosis. However, SFU grade 3–4 prenatal bilateral hydronephrosis indicates that the majority of children will require surgical correction during the postnatal period.

In case of severe prenatal bilateral hydronephrosis, severe hydro-ureteronephrosis or severe impairment of the solitary kidney, fetal bladder aspiration for urinary proteins and electrolytes may be performed in order to predict the renal injury secondary to obstructive uropathy. Fetal urinary sodium level less than 100 mmol/L, chloride level of less than 90 mmol/L, and an osmolality of less than 210 mOsm/kg are considered as prognostic features for good renal function.

Clinical presentation

The clinical presentation of PUJ obstruction has dramatically changed since the advent of maternal ultrasonographic screening.[3–7] Before the routine fetal ultrasonography, the most common presentation was with abdominal flank mass. Fifty percent of abdominal masses in newborns are of renal origin with 40% being secondary to PUJ obstruction. Some patients present with urinary tract infection. Other clinical presentations include irritability, vomiting, and failure to thrive. Between 10 and 35% of PUJ obstructions are bilateral and associated abnormalities of urinary tract are seen in about 30%.[23] Pelvi-ureteric junction problems are often associated with other congenital anomalies, including imperforated anus, contralateral dysplastic kidney, congenital heart disease, VATER (vertebrae, anus, trachea, esophagus, and renal) syndrome, and esophageal atresia. In patients with such an established diagnosis, a renal ultrasound examination should be performed.[24] Although the majority of cases occur sporadically, familial cases have been reported. It has been suggested that hereditary pelvi-ureteric obstruction is an autosomal dominant trait with variable penetrance and Izquierdo *et al.*[25] proposed one of the loci to short arm of chromosome 6 as responsible for the development of PUJ obstruction. Moreover, the importance of angiotensin II and its type 2 receptor (AT2) in the development of congenital urinary tract abnormalities has begun to be appreciated.[24–26] Nishimura *et al.*[27] reported an association of a polymorphism of intron 1 of the AT2 gene (the A-1332G transition, which caused AT2 mRNA splicing) in patients with multicystic dysplastic kidneys and/or PUJ obstruction.

Diagnosis

With the increasing number of cases of antenatally diagnosed hydronephrosis, it is difficult to interpret the underlying pathology and its significance. Severe obstructive uropathies are detrimental to renal function. However, on the other hand, hydronephrosis without ureteral or lower tract anomaly is common. The important aspect of postnatal investigations is to identify the group of patients who will benefit from early intervention to those who need to be carefully followed up.

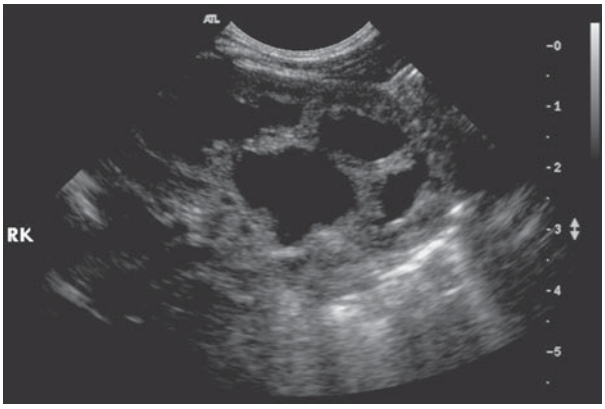
Ultrasound

Follow-up ultrasound examination is necessary in the postnatal period in antenatally detected hydronephrosis. If the bilateral hydronephrosis is diagnosed *in utero* in a male infant, postnatal evaluation should be carried out within 24 hours, primarily because of the possibility of posterior urethral valves. If the ultrasound scan is negative in the first 24–48 hours in any patient with unilateral or bilateral hydronephrosis, a repeat scan should be performed after 5–10 days, recognizing that neonatal physiological dehydration may mask a moderately obstructive lesion.

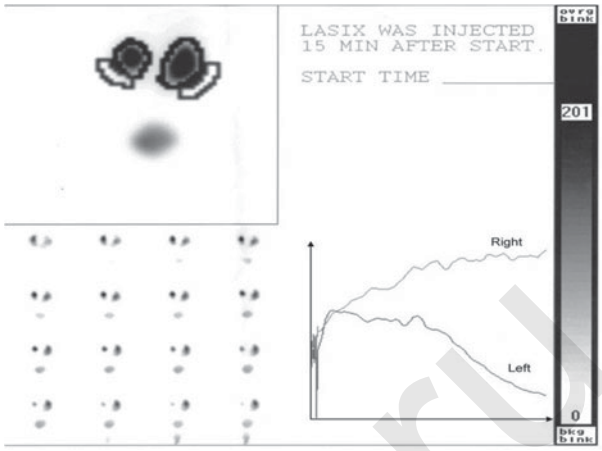
If hydronephrosis is confirmed on the postnatal scan, further careful scan of the kidney, ureter, bladder, and the posterior urethra in boys is essential. Ultrasonography depicts the dilated calyces as multiple intercommunicating cystic spaces of fairly uniform size that lead into a larger cystic structure at the hilum, representing the dilated renal pelvis (Fig. 95.1a). Peripheral to the dilated calyces, the renal parenchyma is usually thinned with normal or increased echogenicity.

In order to standardize the postnatal evolution of prenatal hydronephrosis, the SFU grading system of postnatal hydronephrosis mentioned above, is used.

Typically, the ureter is of normal caliber and not seen.[22] However, if it is dilated, the size of the ureter is also assessed ultrasonographically and graded 1–3 according to ureteral width <7, 7–10, >10 mm, respectively.



(a)



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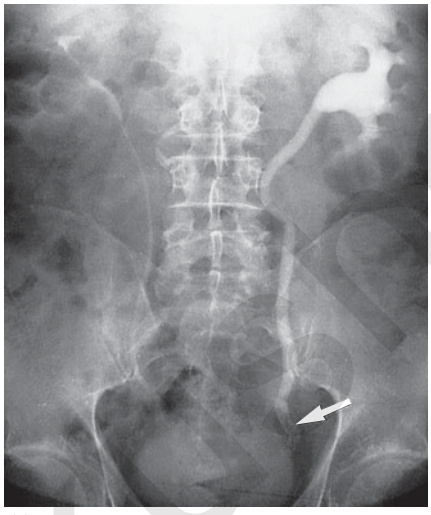

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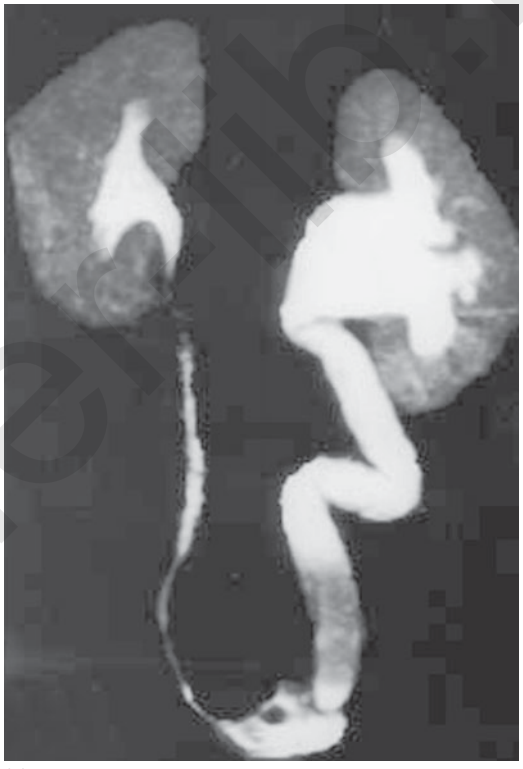

(d)

Figure 95.1 (a) A coronal plane scan through the obstructed left kidney confirms obstruction at the level of the pelvi-ureteric junction (PUJ); (b) ^{99Tc}-MAG3 scan in the above patient. Clearance curve for left kidney confirming the high-grade obstruction on this side; (c) 20 minute full-length film from an i.v. urogram (IVU) series showing left-sided high-grade PUJ obstruction in the same patient; (d) magnetic resonance urography (MRU) showing PUJ obstruction in the same patient (left arrow shows PUJ obstruction on the left side; right arrow shows normal urinary bladder with balloon of the Foley catheter).

Radionuclide scans

Diuretic renograms using ^{99m}Tc-DTPA augmented with furesemide were useful in the diagnosis of urinary tract obstructions over a long period.[28,29] DTPA is completely filtered by the kidneys, with a maximum concentration of 5% being reached in 5 minutes, falling to 2% at 15 minutes. However, in the last decade, it has been reported that use of the tracers that rely on tubular extraction such as ^{123}I-Hippuran and ^{99Tc}-MAG3 (Fig. 95.1b) may improve diagnostic accuracy.[30–32] The kidney of the young infant is immature; renal clearance, even when corrected for body surface, progressively increases until approximately two years of age. Therefore, renal uptake of the tracer is particularly low in infants, and there is a high background activity. Thus, traces such as ^{123}I-Hippuran and ^{99Tc}-MAG3 with a high extraction rate provide reasonable images, enabling estimation of differential kidney function during the first few weeks of life. It is also helpful in assessing the size, shape, location, and function of the kidney. Diuretic augmented renogram is a provocative test and is intended to demonstrate or exclude obstructive hydronephrosis by stressing an

upper urinary tract with a high urine flow. Obstruction is usually defined as a failure of tracer washout after diuretic stimulation. If unequivocal, it eliminates the need for further investigations. In equivocal cases, F15, in which furosemide is given 15 minutes after injection of the radionuclide trace, provides a better assessment of the drainage of the upper urinary tract. Forced hydration prior to scan increases the predictive value of non-obstructed pattern up to 94%.[31] Since glomerular filtration and glomerular blood flow are still low in the newborn, the handling of the isotype is unpredictable and can be misleading. Koff *et al.*,[32] therefore, feel that the risk of making a misdiagnosis of obstruction in this age group far outweighs the potential damage to renal function that might result from delaying surgery for a few weeks until the diagnosis can be made more accurately. Therefore, the timing of radionuclide studies is of crucial importance.

In those cases where DTPA is used as an isotype, radionuclide study should be postponed until 6–8 weeks after birth allowing the kidney to multiply the number of the functioning glomeruli. When ^{99Tc}-MAG3 is utilized in the diagnosis of the obstruction, the radionuclide study may be performed as early as 2 weeks of age in those cases where prompt diagnosis is required.

Diagnosis of pelvi-ureteric junction obstruction can be made by i.v. urography. Although this investigation can show a dilated renal pelvis with clubbed calyces, it is often not helpful as the concentration of contrast is unreliable and, nowadays, it has no place in the in the diagnostic armamentarium (Fig. 95.1c).

Recently, the value of magnetic resonance urography (MRU) has begun to be appreciated in the diagnosis of upper tract obstructions.[33,34] The advent has facilitated the assessment of both function and morphology of the urinary tract, thereby increasing the accuracy of diagnostic work-up. The advantages of this relatively new modality reside not only in not using ionizing radiation, but especially in the acquisition of images with higher contrast and spatial resolution in any orthogonal plane, compared with conventional techniques. Certain pathological conditions, such as neoplasms, infections, parenchymal ischemias, and hemorrhage, as well as obstructions and anomalies, can be accurately identified. The addition of new rapid magnetic resonance imaging (MRI) techniques with high temporal resolution has allowed quantification of cortico-medullary perfusion along with the renal excretory function (Fig. 95.1d).[34]

PRESSURE-FLOW STUDY

In ambiguous cases and in the presence of impaired function, the pressure flow study (Whitaker test) and antegrade pyelography may be necessary to confirm or exclude obstruction.[35] Whitaker test is based on the hypothesis that if the dilated upper urinary tract can transport 10 mL/min without an inordinate increase in pressure, the hydrostatic pressure under physiological conditions should not cause impairment of renal function and the degree of obstruction, if present, is insignificant. However, it is an invasive test and is seldom required. Antegrade pyelography may be performed with ultrasound guidance in patients where diagnosis is difficult.[36] Retrograde pyelography is seldom required to determine the status of ureters. The disadvantages include difficulty in ureteral catheterization in neonates, and trauma and edema may change partial to complete obstruction. In patients where diagnosis is equivocal, serial examinations may be necessary.

Treatment

Considerable controversy exists regarding the management of newborn urinary tract obstructions. Some authors advocate early surgical intervention to prevent damage to maturing nephrons,[37] while others feel that early surgery carries no specific benefit.[4–7] During late prenatal and early postnatal life, there is a progressive increase in the glomerular filtration rate.[5] Additionally, this transition is associated with an abrupt decline in urine output from what appears to be a quite high *in utero* output to a rather low early neonatal level of urine production.[38] These physiological observations may explain the common observation of hydronephrosis detected antenatally, which on postnatal follow up reverts to an unobstructed pattern.[1,5,10] In 1990, in a pioneering manuscript, Ransley *et al.* reported the results of non-operative treatment in newborns with non-refluxing hydronephrosis and differential renal function $>40\%$.[4] At six-year follow up, only 23% needed surgical correction. The most common indication for surgery in this group of children was deterioration of renal function. Subsequently, Koff and Cambell[5] reported that out of 104 neonates with prenatally diagnosed unilateral hydronephrosis who had been followed conservatively, only 7% required pyeloplasty on long-term follow up. Furthermore, the same group reported results of initial conservative management of children with severe unilateral hydronephrosis due to PUJ obstruction.[39] Only 22% of these children required pyeloplasty. All children who required surgery were younger than 18 months and had progressive hydronephrosis and/or reduction in renal function. Therefore, immediate postnatal surgical intervention is unnecessary in the majority of newborn children with pelvi-ureteric junction obstruction. These babies should be followed up with serial examinations to observe anatomical and functional improvement. Surgery is undertaken in infants with deteriorating renal function.[3–57,39,40] We have recently reported over a 16-year period (1988–2003) experience with 343 children (260 males and 83 females) with antenatal diagnosis of hydronephrosis, which led to postnatal diagnosis of PUJ obstruction, who were followed conservatively. Of these, 110 had right-sided hydronephrosis and 233 had left-sided hydronephrosis. According to the Society for Fetal Urology classification, none had grade 0 postnatal hydronephrosis, 20 had grade 1, 118 grade 2, 147 grade 3, and the remaining 58 children grade 4 postnatal hydronephrosis. Relative renal function (RRF) on radionuclide scans revealed 235 children with RRF of more than 40%, 68 with RRF between 30 and 40%, and 40 patients with RRF less than 30%. Renal function deterioration of greater than 5% served

as a main indication for surgery.[7] We have found that 179 (52.2%) children required surgical correction in the course of conservative management. Average age at surgery was 10.6 months (range, 1 month–7 years). Of those, 50% underwent surgery during the first two years of life and the majority of the remaining patients underwent surgery between the second and fourth years of age; only two patients required surgery later than this. Univariate analysis revealed that child sex, side of hydronephrosis, and SFU grade of prenatal hydronephrosis are not significant predictive factors for surgery. However, SFU grade 3–4 of postnatal hydronephrosis and RRF less than 40% were significant independent risk factors which led to the surgical correction.

Pyeloplasty

Pathological variations in PUJ obstruction necessitate the surgeon to be conversant with the various techniques of the pyeloplasty.[41–47] The objective of the pyeloplasty is to achieve a dependent, adequately calibered, watertight PUJ. There are different approaches for open pyeloplasty. The classical traditional approach is an extraperitoneal approach via a lateral flank incision. The infant is placed on the operating table in a supine position with the affected side elevated on a roll (Fig. 95.2a). Muscles are either cut or split (Fig. 95.2b–d) and Gerota's fascia is opened (Fig. 95.2e). In the past, it was recommended that an appropriate size silicone tube be passed from the opened PUJ down the ureter to the bladder, in order to check for distal obstruction. However, we have abandoned this approach due to the possibility of the development of subsequent ureterovesical junction (UVJ) obstruction as a result of the injury to the fragile UVJ area from the passing catheter. The current diagnostic modalities almost certainly exclude existence of any double pathology. In those cases where suspicion to the distal to PUJ area has arisen, antegrade or retrograde study of the ureter upon or during surgery is recommended.

In some cases, the posterior lumbotomy may be applied.[41,42] The use of muscle splitting, rather than muscle cutting, makes it an almost minimally invasive procedure. The location of the incision just under and parallel to the 12th rib has a cosmetic advantage. The bilateral procedure is possible, if indicated, under the same anesthesia without changing position. This approach should not be used in older children or those who are significantly obese.

The various techniques of pyeloplasty are divided into dismembered and non-dismembered pyeloplasty.

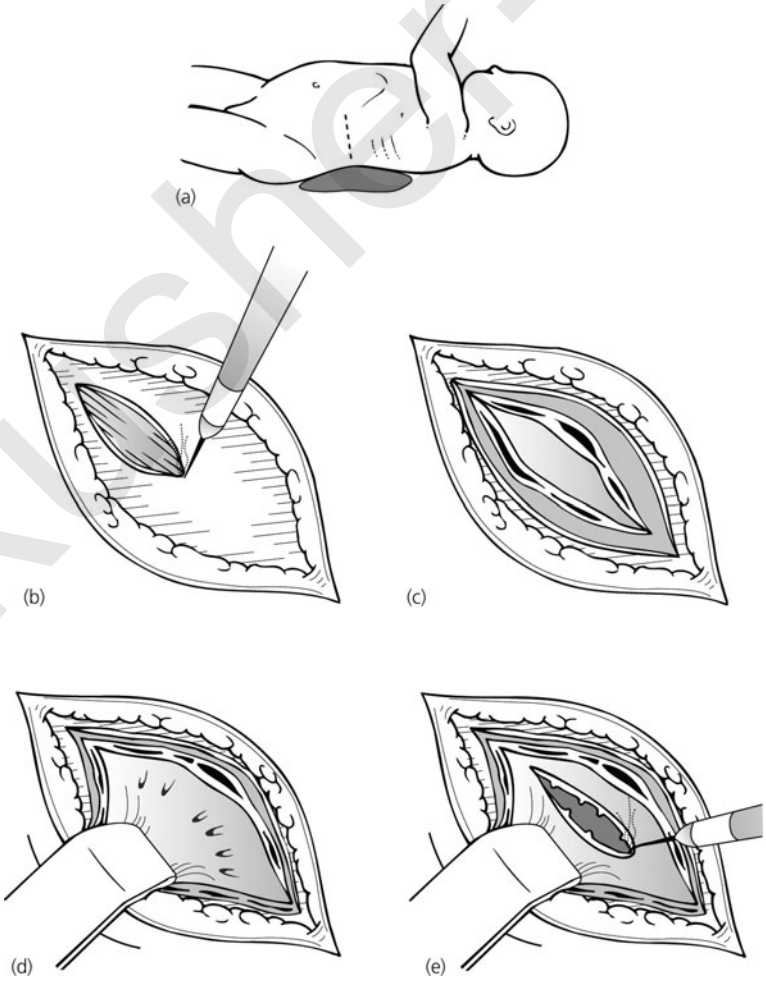

Figure 95.2 (a) Position of the infant on the operating table, showing line of skin incision; (b) incision through skin and subcutaneous tissue; (c) incision through external and internal oblique muscles; (d) renal facia exposed; (e) the renal fascia opened.

DISMEMBERED PYELOPLASTY

Anderson–Hynes pyeloplasty

The renal pelvis, pelvi-ureteric junction, and proximal ureter are freed of perirenal fat. Three stay sutures are placed: (1) at the superomedial aspect of the pelvis, (2) at the inferolateral aspect of the pelvis, and (3) on the ureter about 5 mm below the pelvi-ureteric junction. The ureter is divided obliquely above the ureteric stitch and the redundant pelvis trimmed (Fig. 95.3a). The superior two-thirds of the pelvis is closed by using continuous 6/0 maxon stitch (Fig. 95.3b). An oval-shaped anastomosis between the ureter and lower part of the pelvis is carried out from the posterior to the anterior layer over a silastic stent using 6/0 maxon continuous stitch (Fig. 95.3c,d). After the anastomosis is completed, a radivac drain is inserted. Gerota's fascia is closed with interrupted 3/0 chromic catgut sutures. Muscles are approximated in layers using subcuticular 5/0 dexon. We have used a Pippi-Salle stent nephrostomy tube (Cook, Bloomington, IN, USA) for dismembered pyeloplasty. In order to avoid passing of the distal end of the Pippi-Salle stent nephrostomy through the UVJ in small children, we cut the distal tail of the tube and leave a distal end in the ureter below the anastomosis. The proximal end of the stent is positioned in the renal pelvis. The nephrostomy end is opened for drainage for the next 48–72 hours after surgery. Then the nephrostomy is closed and the patient is discharged home following removal of the drain. The tube is usually removed in the office 4 weeks after surgery.

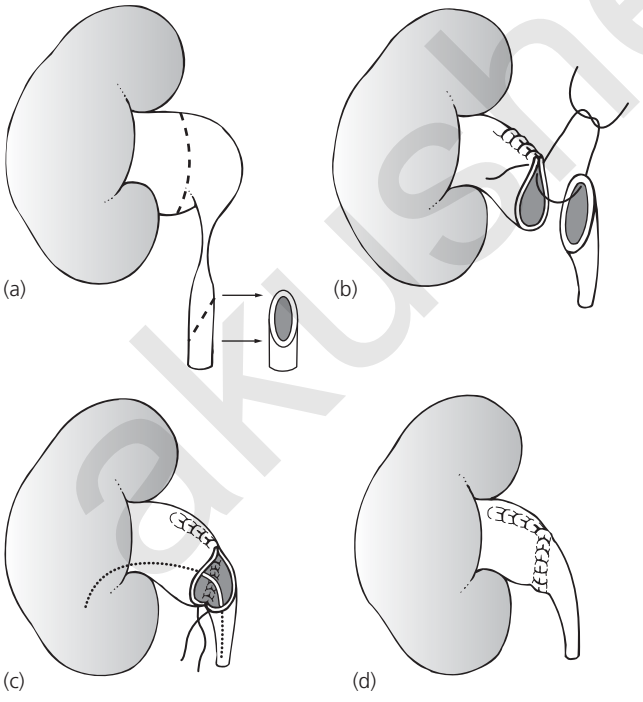

Figure 95.3 Anderson–Hynes pyeloplasty. (a) Vertical *en bloc* resection of the pelvis, pelvi-ureteric junction, with oblique division of the ureter; (b) superior part of the pelvis is closed and start of the posterior layer anastomosis between ureter and pelvis; (c) posterior layer anastomosis completed and anterior layer anastomosis commenced over a stent; (d) an oval-shaped anastomosis completed between ureter and renal pelvis.

NON-DISMEMBERED PYELOPLASTY

The Y plasty (Foley)

This is based on the principle of a Y–V flap. This operation is suitable when the ureter inserts high on the pelvis. A V-shaped incision is made on the pelvis on the anterior and posterior surface. The tail of the incision is on the lateral surface of the ureter well below the obstruction. The pelvic flap is brought down, and posterior and anterior anastomosis of the flap and ureter performed using 6/0 maxon.

The spiral flap (Culp)

The spiral flap (Culp) is suitable for long, dependent, stenotic ureteropelvic obstruction. The incision on the ureter must be adequate covering the stenotic area. A flap of equal length is based on a broad base (Fig. 95.4a). The posterior layer of the ureter and flap is sutured using 6/0 maxon (Fig. 95.4b). The anterior layer is crossed over the stent and anastomosed using 6/0 maxon (Fig. 95.4c).

The endoscopic technique has gained some popularity in the surgical treatment of PUJ obstruction.

Endopyelotomy

Endopyelotomy can be performed using either the percutaneous antegrade approach or endoscopic retrograde procedure.[43] Even experienced surgeons do not recommend this procedure in neonates, infants, or young children.[44] Percutaneous endopyelotomy is performed by making an incision

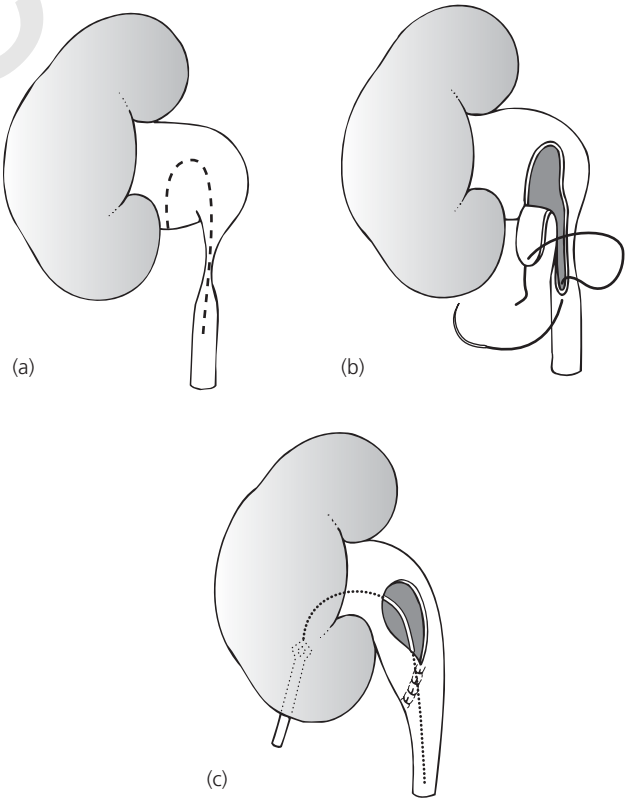

Figure 95.4 The spiral flap (Culp) pyeloplasty. (a) Spiral fashioning of the flap; (b) the flap brought down and the first suture positions the rounded tip of the flap distally to the ureter; (c) anterior layer closed over a stent.

on the posterolateral wall using a smaller endoscope and using a 3F or 5F electrocautery probe and followed by separating the cut edges using a balloon. A ureteral stent is placed for drainage for 6 weeks and nephrostomy tube for between 3 days to 6 weeks. Kavoussi *et al.*[45] have shown that this procedure is also safe and effective in treating secondary PUJ obstruction.

Figenshau and Clayman[46] used a retrograde technique for older children and combined antegrade-retrograde for young children. The incision in the PUJ segment was performed using an Accucise balloon under fluoroscopic control. They concluded that the technique has an 86% success rate and should be offered to pediatric patients with PUJ obstruction. Balloon dilatation of PUJ has also been reported in infants and young children. This consists of dilatation of the PUJ segment using a dilating balloon catheter (12–24 Fr), which is positioned, confirmed, and inflated for 3 minutes under fluoroscopic control. The success rate has been reported as 63% with a follow up to 23 months.

LAPAROSCOPIC PYELOPLASTY

Laparoscopic Anderson–Hynes dismembered pyeloplasty has recently gained wide popularity in the pediatric population.[47–49] A decade ago, Yeung *et al.*[48] reported the results of initial experience with retroperitoneal dismembered pyeloplasty in 13 infants and children. The authors concluded that laparoscopic Anderson–Hynes dismembered pyeloplasty is feasible and safe in infants, but stressed that the long-term results are awaited in order to prove that this method is durable in the long term in children. Since then, the visibility of the laparoscopic approach has found support in numerous publications.[49] Surgery may be performed through either retroperitoneal or transperitoneal approaches. The retroperitoneal approach is safe, but technically more demanding due to the smaller operating space and additional difficulties in facilitating intracorporal suturing. Moreover, it is more difficult to teach residents to perform laparoscopic surgery, while using the retroperitoneal approach. In order to facilitate a laparoscopic pyeloplasty, some technical steps may be employed. Taking a transperitoneal approach allows the operative space to be increased especially in small children. Laparoscopic pyeloplasty on the left side may be performed through the transmesenteric approach. The placement of the stay suture on the renal pelvis prior to suturing the anastomosis between the renal pelvis and the ureter stabilizes the suture line and allows precise placement of the sutures, therefore eliminating the risk of reobstruction.

The final development in laparoscopic reconstructive surgery in children was the employment of robot-assisted surgery. The currently available system (DaVinci, Intuitive Surgical, Sunnyvale, CA, USA) is a robotic manipulative device which permits the surgeon to have better control over the instruments. The impression with robot-assisted surgery is that suturing is easier and less operating time is required to perform laparoscopic pyeloplasty. Furthermore, it is much easier to teach a surgeon without prior laparoscopic experience to perform laparoscopic pyeloplasty while using a robot-assisted suturing technique. However, the high initial cost of robotic equipment and expensive maintenance of the working system cannot be ignored.

NEPHRECTOMY

Because the recovery potential of the kidney is greater in neonates, extreme conservation is justified. Salvage pyeloplasty should be considered, as renal function as shown on renal scintigraphy can recover.[50] At operation, an assessment should be made of the renal cortex after emptying the pelvis. Severe cystic dysplasia is an indication for nephrectomy, otherwise every effort should be made to salvage the kidney.

BILATERAL PELVI-URETERIC OBSTRUCTION

Surgical correction of the symptomatic side (or the side with better function) should take precedence. If a nephrectomy is considered on one side, the pyeloplasty should precede this.

Postoperative complications

Postoperative complications include infection, adhesive obstruction (transperitoneal approach), temporary obstruction at the anastomosis resulting in excessive urine leakage and failure due to postoperative stricture at anastomotic sites. An overall reoperation rate of 8.2% was reported in the early series.[44] However, when temporary double-J stents or stent nephrostomy tubes were used, the reoperation rate was negligible.

Follow up and results

Follow up ultrasound may be performed three to six months after operation when maximum improvement can be seen.[7] Radionuclide scans are useful to monitor the postpyeloplasty function and drainage. Pyeloplasty in the neonatal period, when indicated, gives excellent results.

MEGAURETER

Megaureter is a ureter, which is dilated out of all proportion to the rest of the urinary tract and above the norms. Cussen[51] and later Hellstrom et al.[52] have established the normal measurement of the ureteral diameter in infants and children from 30 weeks of gestation to 12 years of age. Normal ureteral diameter in children is rarely greater than 5 mm, and ureters large than 7 mm can be considered megaureters.

Classification

In 1976, the Paediatric Urology Society[53] adopted a standard nomenclature for categorizing megaureters, which is a useful guide for management. There are three types described:

1. **Refluxing ureter**, which may be primary or secondary to distal obstruction or pathology
2. **Obstructive ureter**, which may be primary and include intrinsic obstruction, or secondary due to distal obstruction or extrinsic causes

3. **Non-refluxing, non-obstructed ureter**, which may be primary, idiopathic type or secondary to diabetes insipidus or infection.

In 1980, King[54] subsequently modified this classification by adding a fourth group consisting of the refluxing, obstructed megaureters.

URETERO-VESICAL JUNCTION OBSTRUCTION

The presence of an adynamic distal ureteral segment is the most common cause of primary obstructive megaureter. The presence of a narrowed terminal portion of ureter will not convey the peristaltic wave or dilate enough to permit free passage of urine. This results in excess boluses of urine which coalesce and cause ureteral dilatation. The contraction waves become smaller and are unable to coapt the walls of dilated ureters. This along with infection could damage the renal parenchyma. The proposed etiologies include:

- **Alteration in muscular orientation**: Tanagho *et al.*[55,56] noted in the fetal lamb that the muscle coats of the distal ureter develops last and that late arrest in development results in absence of longitudinally oriented musculature that conducts the peristaltic wave. This results in hypertrophy of the circular fibers causing obstruction.
- **Muscular hypoplasia with fibrosis**: McLaughlin *et al.*[57] found that 69% of narrowed terminal ureteric segments showed muscular hypoplasia which were separated by fibrotic sheets thus affecting the transmission of peristalsis. This fibrotic ring prevents expansion and free urinary drainage.
- **Excessive collagen deposition**, resulting in a discontinuity of muscular coordination is another hypothesis.[58] Lee *et al.*[59] examined the histology of ureteric smooth muscle and collagen in obstruction employing computer-assisted color image analysis. They found that the tissue matrix collagen ratios (collagen–smooth muscle) were significantly higher in patients with megaureters compared to the control.
- **Disturbance in the electric syncytium**, along with the nexus injury, has been suggested to precede pathological innervation.[60] Dixon *et al.*[61] showed dense non-adrenergic innervation in a smooth muscle collar surrounding the terminal ureter in cases of obstructed megaureter associated with ectopic ureteric insertion. Recently, it was reported that the myocyte apoptosis and decrease of the interstitial Cajal cells in the longitudinal muscular layer of the intravesical part of the ureter may lead to the development of the aperistaltic segment and subsequently to the UVJ obstruction.[62,63]

Prenatal diagnosis

Usually, the ureter is not seen in fetal scans. Visualization of the dilated ureter to the level of the vesico-ureteric junction without an abnormal bladder may suggest obstruction or reflux. However, this may be a transient phenomenon. Fetal urine flow is four to six times greater before birth than after and is due to differences in renal vascular resistance, glomerular filtration, and concentrating ability. This high outflow contributes to ureteral dilatation. Another contributing factor is increased compliance of the fetal ureter.[64]

Clinical features

The widespread use of maternal ultrasound has changed the age of presentation of congenital uropathies, including megaureter. Currently, about half of the cases are asymptomatic and discovered on prenatal ultrasound. The most common mode of clinical presentation is urinary tract infection.[65,66] Microscopic hematuria is frequent and may occur in the absence of infection. This is presumably caused by the disruption of mucosal vessels of the ureter secondary to ureteric distension. Primary obstructive megaureter is more common in males than females and the left ureter is more likely to be involved than the right. Between 17 and 34% patients have bilateral megaureters. Contralateral renal agenesis is found in 10% of the patients.[64–69]

Diagnosis

Antenatally diagnosed ureteral dilatation needs further evaluation to confirm or exclude obstruction, reflux or both. Clinicians are confronted with the two basic problems in assessing the dilated ureter in a neonate.[6,65,66,70–72] First, it is a real challenge to differentiate between obstructive and non-obstructive urinary tract dilatations. Second, there is no study that can determine accurately the potential of the kidney to recover after relief of obstruction.

Ultrasound

In antenatally detected cases, ultrasonography should be performed between 3 and 5 days after birth. If no dilatation is seen, repeat ultrasound should be performed after a few weeks as neonatal oliguria can mask dilatation. If dilatation persists on a repeat ultrasound, further work-up can be postponed for a few weeks unless bilateral disease or a serious abnormality, such as obstruction in a solitary kidney or urethral valves, is suspected. Such an approach allows for the expected changes of transitional renal function in the newborn period that might otherwise cause inaccuracies with many diagnostic studies. Ultrasonography classically shows hydroureter and variable hydronephrosis, with hyperperistalsis of a lower ureter that terminates shortly above the bladder in a narrow, adynamic segment (Fig. 95.5a).[73] However, the narrow segment may not always be visualized and therefore micturating cystourethrogram is necessary to exclude vesico-ureteric reflux.

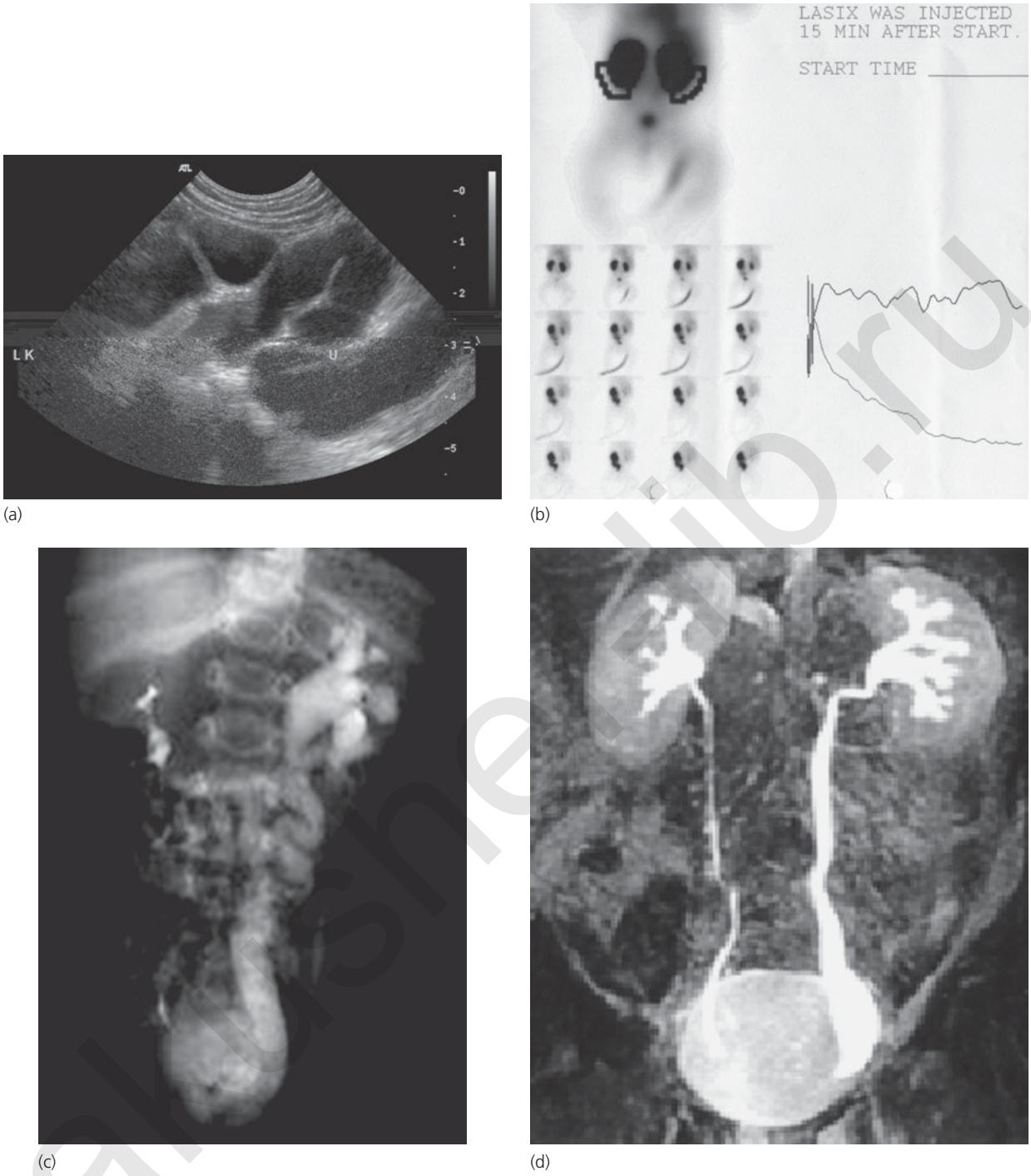

Figure 95.5 (a) Longitudinal scan to the left of the midline through the bladder demonstrates dilatation of the left lower ureter to the level of the vesico-ureteric junction; (b) MAG3 renal scan showing clearance curve for left kidney demonstrating obstructive pattern; (c) 30-minute full-length film from the i.v. urogram series shows obstructed megaureter of the same patient; (d) magnetic resonance urography image showing obstructive left megaureter.

Renal scintigraphy

A radionuclide scan is required to assess the urinary flow and stasis along with determination of the differential function and glomerular filtration rate. For the evaluation of neonatal hydronephrosis and hydroureter, MAG3 is the most frequently used (Fig. 95.5b).

Intravenous urography

Intravenous urography may be necessary in equivocal cases to establish the diagnosis. It delineates the anatomy showing dilated, obstructed ureter (Fig. 95.5c). However, it is better to wait for a few weeks for renal maturation to allow concentration of contrast reliability. Occasionally, Whitaker

test and antegrade pyelography may be required to establish the diagnosis.

Fung *et al.*[74] explored ureteral opening pressure as a novel parameter for evaluating pediatric ureterohydronephrosis. Renal pelvic pressure is assessed while simultaneously documenting the passage of contrast material from the distal ureter into the bladder. A pressure increase of 14 cmH_2O within the renal pelvis is consistent with distal ureter obstruction.

As in the diagnosis of PUJ obstruction, MRU has gained wide popularity in the diagnosis of UVJ obstruction (Fig. 95.5d).

Management

It is being increasingly recognized that many antenatal and neonatal ureteral dilatations improve over time.[5,65,66,72] Surgery is indicated in patients with progressive ureteral dilatation and deterioration in renal function. We have recently published our experience of over 18 years in 79 children (64 boys and 15 girls) with antenatal diagnosis of hydronephrosis, which led to postnatal diagnosis of megaureter, and tried to determine criteria for those who are at risk for surgery.[72] According to the SFU classification of hydronephrosis, eight renal units (RU) were grade 1, 57 were grade 2, 29 were grade 3, and 11 were grade 4 of postnatal hydronephrosis. Mean ureteral diameter was 1.2 cm. Relative renal function (RRF) was more than 40% in 82 RU, between 30 and 40% in 18, and less than 30% in 5 RU. Only a combination of renal function deterioration of the hydronephrotic kidney greater than 5% and worsening of hydronephrosis (considered as upgrade of SFU) served as main indications for surgery. Twenty-five (31%) children required surgical correction. Mean age at surgery was 14.3 months (range, 3–60 months). Univariate analysis revealed SFU grade 3–4 of postnatal hydronephrosis, RRF less than 30%, and ureteral diameter more than 1.33 cm were significant independent risk factors leading to reimplantation.

Operation

There are various techniques for reimplanting the ureter in a non-refluxing manner after excision of adynamic, narrow segment. The initial approach to the ureter can be either intravesical, extravesical, or combined.[75] The most commonly used techniques for intravesical approach are Cohen's transtrigonal reimplantation and the Politano–Leadbetter operation.

INTRAVESICAL APPROACH

Position

The patient is anesthetized and placed in supine position (Fig. 95.6a).

Incision

A low transverse suprapubic skin crease incision is made (Fig. 95.6a).

Exposure

The skin flaps are raised by diathermy dissection (Fig. 95.6b). The rectus sheath is cut and two recti are separated in the midline. The peritoneum is pushed upwards. The bladder is opened vertically between two stay sutures. A Denis-Brown retractor is placed over the gauze inside the bladder to improve exposure. The ureter openings are inspected. A 3 or 5 Fr infant feeding tube is passed into the ureter and a stay suture is placed around the tube. This facilitates the handling of the ureter during dissection. An incision is made circumferentially along the ureter opening and the distal ureter is dissected from mucosa and trigonal muscle. The ureter is freed keeping away from the adventitia and mesentery to avoid damage to the blood supply (Fig. 95.6c). Bladder opening is narrowed with interrupted absorbable sutures.

COHEN'S METHOD

This method is simpler and easier to perform, and an especially useful technique in infants in whom the bladder is small. An incision is made in the mucosa above and a little lateral to the opposite ureteric orifice. A submucous tunnel is made by inserting the closed blades of scissors and performing an opening and cutting movement. The ureter is threaded through the tunnel (Fig. 95.6d). The tunnel should be adequately wide for the ureter and two to three times the ureteric diameter in length to prevent reflux. The terminal narrow portion of the ureter is excised and sent for histology. If the ureter is very dilated, remodeling is necessary, which may be performed by one of the following methods:

- A non-excisional tapering technique has the advantage of avoiding a suture line with potential urinary leakage. However, it is inappropriate for very dilated ureters as it reduces the diameter by only 50% and in neonates it can become too bulky for the tunnel.
  - Folding (Kalikinski) where a 10–12 Fr catheter is placed into the ureter and a running mattress suture placed proximally and continued distally. The lateral excluded segment is folded posteriorly and its edge fixed to the medial wall with another running suture.
  - Plication (Starrr) of the ureteral wall is achieved by multiple mattress sutures in the anti-mesenteric border.
- Excisional tapering technique, where part of ureteral wall is excised by using a knife and scissors, or Hendren clamps. The remaining ureteral strip is tubularized over 8 Fr double-J stent or feeding tube utilizing a running absorbable suture. The distal end of the ureter is closed with interrupted absorbed sutures to allow for any shortening that might be necessary. The proximal segment of the tailored ureter should stay outside the bladder after completion of the reimplantation, in order to avoid a dilated obstruction of the tailored segment. The cuff of the ureter is then sutured into position. First, a 4/0 dexon suture is inserted laterally through the full thickness of the ureter and also through the full thickness of the bladder muscle, so as to prevent the ureter retracting. Next, bladder and ureteral mucosa are approximated using

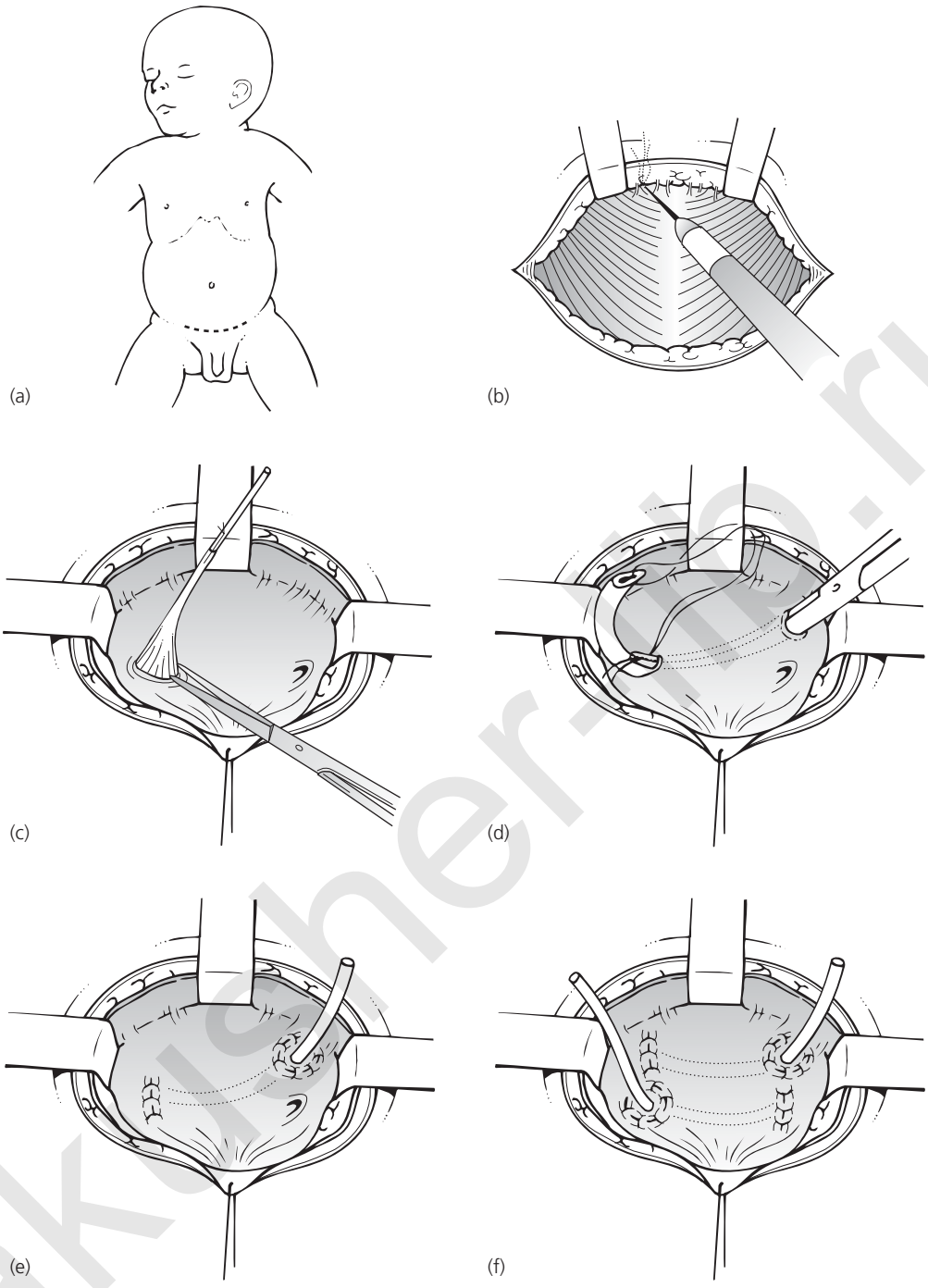

Figure 95.6 Reimplantation of ureter. (a) Position of patient on the operating table and line of incision; (b) skin flaps being raised; (c) opened bladder is retracted by Denis-Browne retractor and the stented ureter is dissected free; (d) the tunnel is commenced just above and lateral to the opposite ureteric orifice and continued to the original orifice. The ureter is threaded through the tunnel; (e) cuff of the ureter is sutured in position, while the original orifice in the bladder is closed; (f) in bilateral reimplantation, the second separate tunnel is parallel to the first and ends in the opposite orifice.

interrupted 5/0 dexon. The stents are placed into the ureter (Fig. 95.6e). In bilateral reimplantation, the second ureter has its tunnel below and parallel to the first ending in the orifice of the opposite side (Fig. 95.6b).

- Politano–Leadbetter technique: The ureter is further freed up to the dome of the bladder. The new opening for the entrance of the ureter is made on the posterolateral aspect of the bladder. The new submucosal tunnel is formed from there to the old ureteric orifice. Then, the stay suture of the ureter is passed and gently threaded through the new tunnel. The narrow terminal portion of ureter is excised and the ureter narrowed by one of the above techniques if needed and the neo-ureter opening fixed at the old opening with 5/0 dexon. Stents are put in place. A suprapubic catheter is left in the bladder and the bladder is closed in two layers, the mucosa with 4/0 plain catgut

and the muscles with 4/0 dexon. A retropubic drain is brought out through a separate incision and the muscles approximated with 3/0 dexon. The rectus sheath is sutured with 3/0 dexon and the skin approximated with a 5/0 dexon subcuticular stitch.

ENDOSCOPIC REPAIR OF THE URETER

Recent progress in endoscopic tools (such as miniscopes, balloons, and guide wires) has led to widespread use of endoscopy for ureteral repair.[76,77] Some suggest that a simple insertion of the double-J stent into the obstructive ureter for six months may solve the problem.[78] Barat *et al.*[79] recently reported preliminary results with endo-ureterotomy for congenital megaureter. The technique consists of incision of the obstructive segment of the ureter which is inserted into the ureteral orifice ureteroscope. All of the layers of the ureter are incised in the long axis through the entire obstructive segment, to expose the peri-ureteral areolar tissue. A double-J stent is inserted for 3 weeks after the procedure. The risk of secondary reflux, which is a main concern after this type of procedure has not been systematically checked. The role of endo-ureterotomy in the treatment of megaureters in children has not been widely established.

In some small children with severe obstructive megaureter, refluxing ureteric reimplantation was suggested as a novel method to temporize an obstruction.[80] The treatment consists of anastomosing the ureter proximal to the obstruction to the dome of the bladder in a freely high-grade refluxing fashion. This technique allows time for the child to mature, while accurately establishing renal function and preparing for a definitive surgical solution.

LAPAROSCOPIC REIMPLANTATION

In recent years, laparoscopic reimplantation has gained popularity in some medical centres.[81–83] Use of robot-assisted laparoscopic techniques in pediatric urology led to even wider application of laparoscopic reimplantation to the surgical armamentarium. Three procedures have been attempted laparoscopically: extravesical reimplantation, Gil-Vernet procedure, and the Cohen crosstrigonal reimplantation. Some difficulties were noticed with this approach: long operative time, steep learning curve, and the technical challenges in the creation of a submucosal channel without injury to the intact bladder mucosa, and suturing aspects of the procedure. Use of the robot-assisted technique is supposed to overcome these difficulties. However, the current port size is not suitable for small children.

POSTOPERATIVE COURSE

Patients are fasted for 24 hours in case of development of ileus. In the intravesical approach, the drain is removed after 24–48 hours. Stents are removed after 7–10 days followed by the suprapubic catheter. Ureteral reimplantation using the extravesical approach can be performed without stenting.[84,85] An indwelling urethral catheter is put in place usually for 3–5 days to avoid urinary retention.

Complications

Complications include wound infection, vesico-ureteral reflux due to short tunnel with no effective flap valve mechanism, or obstruction due to a fibrotic distal end secondary to ischemia.

FOLLOW UP AND RESULTS

Radiologic studies are used to assess the initial and long-term surgical results and to monitor renal growth. These include ultrasound, i.v. urography, or radionuclide scans. The success is measured by normal urinary drainage with no reflux and control of urinary infections.

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96

Ureteral duplication anomalies

PREM PURI AND HIDESHI MIYAKITA

INTRODUCTION

Duplication of the ureter and renal pelvis is the most common upper urinary tract anomaly with a reported incidence of 0.8 in the population and in 1.8–4.2% of pyelograms.[1–5] The vast majority of these anomalies have normally developed renal moieties and cause no functional problems. However, they can challenge the diagnostic acumen with a wide variety of manifestations. Vesico-ureteral reflux (VUR) is the most frequently associated anomaly found in duplex systems. A small proportion of ureteral duplications is associated with ureteroceles, ectopic ureter, and pelvi-ureteric junction obstruction.

EMBRYOLOGY

The ureteric bud appears at 5 weeks' gestation from the point where the Wolffian duct bends centrally and medially to the cloaca and pushes into the pelvic metanephrogenic mass and eventually forms the ureter and renal pelvis. Premature division of the ureteral bud gives rise to incomplete duplication. If two ureteral buds arise from the Wolffian duct and if both are incorporated into the urogenital sinus, then complete duplication occurs. The upper pole ureter is more closely associated with the Wolffian duct, while the lower pole ureteric bud is closest to the urogenital sinus and incorporated first. The upper pole ureter is carried medially and caudally along with the Wolffian duct. Therefore, the upper pole ureter opens more medially and inferiorly than the lower pole ureter, according to the Weigert–Mayer law.[6–8] Sometimes, this upper pole ureter has an abnormally prolonged or close attachment to the Wolffian duct which will migrate into the segment of urogenital sinus that is destined to become the urethra.

Occasionally in males, a separate opening into the urogenital sinus is not established and the bud continues to be linked to the Wolffian duct much longer and the ureter inserts into the male genital tract, for example in the seminal vesicles, vas deferens, or even epididymis.

Stephens[9] proposed that, in females, the fused Müllerian ducts after penetrating the urogenital sinus undergo significant epithelial activity and incorporate any Wolffian duct remnants, and thus the ureteral bud along with the Wolffian duct may be carried along as part of caudal Müllerian migration and this in turn would lead to drainage sites into the vestibule, vagina, cervix, and uterus.

CLASSIFICATION

A standard set of definitions used to describe ureteral duplication anomalies now exists. These definitions were established by the Urologic Section of the American Academy of Pediatrics Committee on Terminology, Nomenclature and Classification.[10] The following are the different types of ureteropelvic duplications, the recognition of which is important in understanding the pathophysiology, clinical manifestations, and management.

- Incomplete ureteral duplication, where two ureters unite and enter the bladder through a common orifice.
- Complete ureteral duplication:
  - Intravesical: Two ureters drain separately into the bladder. The upper pole opens caudal and medial to the lower pole ureter and has a longer ureterovesical course and therefore less risk of reflux.
  - Extravesical: where the ureter opens into the urethra or genital tract.
- Inverted Y ureteral duplication. Two distal ureters fuse to drain a single kidney; one of the limbs may be ectopic, blind-ending, or atretic.
- Blind bifid ureter. One branch ends blindly and this is thought to be because one ureteral bud does not join the metanephrogenic mass.

- Ureteral triplication and even quadruplication has been reported and is due to formation and/or division into three or four buds.[11–13]

CLINICAL MANIFESTATION

Most often, ureteral duplication anomalies are discovered incidentally unassociated with any symptoms. Infants may come to medical attention because of the complications of obstruction of the upper moiety or infection. VUR is common, occurring much more frequently in the lower segment and is present in 70% of children with duplex systems who present with urinary tract infections.[5,14]

Duplication affects both sides equally, while 15% of patients have bilateral duplications. It is more common in females, who are more likely to exhibit pathological complications. There is a familial tendency with the risk of duplication in a sibling up to one in eight and is suggestive of autosomal dominant inheritance with incomplete penetration.[3,15] A recent study reported prevalence of duplex systems in familial VUR.[16] Duplex systems were present in 39 (7.6%) of the 513 siblings with VUR. Families with exclusively boys affected with VUR had a significantly higher rate (15%) of duplex systems than in families with mixed affected siblings and girls.

Ureterocele, a cystic dilatation of the terminal intramural segment of the distal ureter, is classified as either simple or ectopic.[10] The ectopic variety is symptomatic in infants far more commonly than simple ureterocele and is nearly always with an obstructed upper segment of a duplex kidney. The bulging ureterocele protrudes into the intravesical space and terminates ectopically at the bladder neck or in the urethra. Whether associated with single or duplex systems, the problems of ureterocele are much more common in girls than boys.

Ureteral duplication can present with diverse clinical manifestations and include:

- Urinary tract infection, which may be due to reflux or obstruction. This can vary from overwhelming sepsis to asymptomatic bacteria.
- Epididymo-orchitis as a result of an ectopic ureter opening into the male genital tract or
- Incontinence, which is due to an ectopic ureter opening beyond the sphincter and is thus more common in females or because of infection causing urge incontinence.
- Urinary retention. A ureterocele occupying the bladder neck can cause urinary retention and overflow incontinence. Rarely, it may prolapse through the urethra (Fig. 96.1).
- Abdominal mass. Hydronephrosis secondary to obstruction may present with abdominal mass.
- Failure to thrive, because of chronic persistent urinary infection.

Prenatal diagnosis

The kidneys can be imaged at the 12th gestational week by abdominal ultrasound. With the increased availability and use of maternal ultrasonography, the incidence of urinary tract disorders diagnosed *in utero* has increased considerably. Oligohydramnios or anhydramnios in the mother is usually due to diminished amniotic fluid. Because amniotic fluid after 18 weeks of gestation is voided urine, it suggests bilateral renal agenesis or outflow obstruction. In order to be certain that renal development is normal, ultrasound at or beyond 20 weeks of gestation is necessary. An obstruction anomaly is recognized by demonstrating a dilated renal pelvis, calyces, or ureter. However, it is not possible to detect an uncomplicated duplex anomaly prenatally.[17]

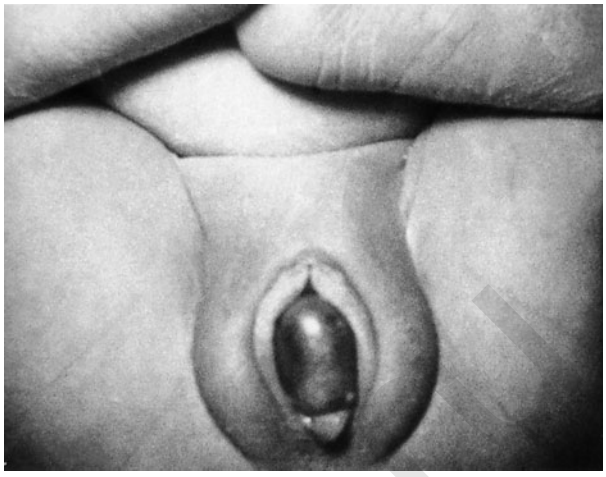


Figure 96.1 Ureterocele prolapsing through the urethra in a newborn.

Postnatal diagnosis

Ultrasonography, which does not visualize the excretory pathway, may be unable to differentiate between kidneys with and without pyeloureteral duplication, but is able to recognize thick transverse intermediate cortical mass (1 cm) in the latter group and also on the basis of the ratio between the longitudinal and transverse diameter which is greater than in kidneys without duplication.[18] An obstructed or refluxing system and ureteroceles can be visualized on the ultrasound scans (Fig. 96.2).

Micturating cystograms will delineate reflux and ureteroceles. Despite its declining role in the routine evaluation of infants with urinary tract infections (UTIs), intravenous urography is a useful and easily available modality of investigation.[19] It accurately defines the anatomy, while in the non-functioning segment the remaining pole will exhibit the 'drooping lily' sign (Fig. 96.3). Radionuclide scans are useful in determining the differential function.[20] Computed tomography and magnetic resonance imaging (MRI) may help to define the anatomy of kidneys and MRI is particularly useful in cases where conventional imaging fails to delineate occult dysplate renal moieties, ectopic ureters,

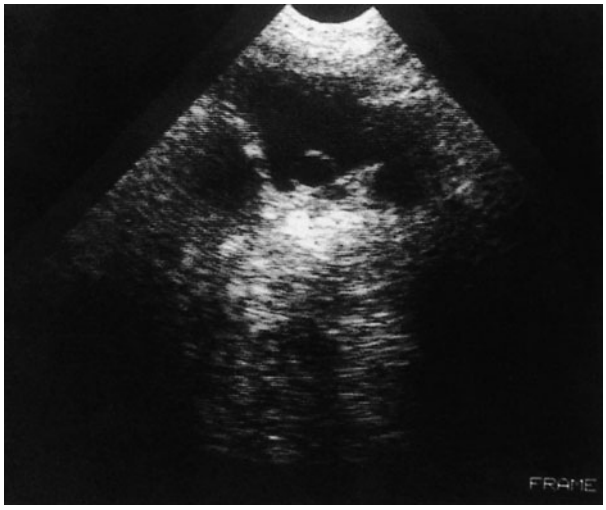


Figure 96.2 Sonographic appearance of a ureterocele within the bladder.

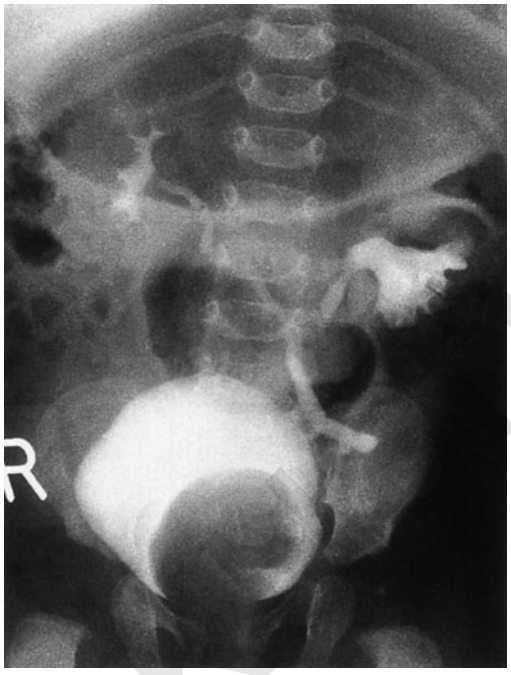


Figure 96.3 Twenty-minute film from urogram showing 'drooping lily' sign on the left as a consequence of an obstructed non-functioning upper moiety on this side due to a large ureterocele.

and ureteroceles. Diagnosis is usually confirmed by cystoscopy and endoscopic visualization of the ureteric orifices. It also helps to assess the extent of ureterocele.

MANAGEMENT

Asymptomatic uncomplicated ureteral duplications do not require active clinical management.

Vesico-ureteric reflux

VUR is the most common problem associated with ureteral duplication and is more common in lower poles than in upper poles. Most of the recent reports suggest that there is no difference in the rate of spontaneous resolution of minor grades of reflux into single ureters or lower pole ureters in duplex systems.[20–23] Medical surveillance should be continued in these patients to prevent renal scarring. High-grade VUR in duplex systems is unlikely to resolve and generally considered an indication for surgical treatment.[14,21] Afshar *et al.*[14] compared the outcome of VUR in duplex systems with VUR in single system and found that only 7% of refluxing units with grade III and none of those with grades IV and V resolved at a median follow up of 33 months. The reported rates of spontaneous resolution of grades I and II reflux in duplex systems vary from 22 to 85%.[21–23]

In the newborn period, conservative antimicrobial treatment combined with full urological investigation is the management of choice. Infants with grades I–III reflux should continue on chemoprophylaxis. High grades of reflux in infants associated with ureteral duplication, breakthrough infections in spite of prophylaxis and progressive renal scarring and poor function constitute indications for antireflux operation[24,25] or endoscopic correction.[26]

Polar nephro-ureterectomy is performed in patients who have one pole ureter reflux with poorly functioning segment of kidney, while nephro-uterectomy may be necessary if both poles are involved. Recently, the role of laparoscopic heminephrectomy in pediatric patients has begun to be appreciated.[27–30] Both transperitoneal and retroperitoneal laparoscopic techniques have been used for heminephrectomy in infants and children. The transperitoneal approach for moiety excision is technically simple and offers the added advantage of complete ureterectomy. The retroperitoneal approach, although technically more challenging, offers the advantages of a direct access to the kidney, minimal mobilization of kidney and surrounding structures, and a decreased risk of intraperitoneal organ injury and postoperative adhesions.

In patients with lower pole reflux only in complete ureter duplication, Ahmed and Boucout[25] and Bivens and Palken[31] recommend ipsilateral uretero-ureterostomy when there is no abnormality on the contralateral side, or there is history of bladder operation or abnormality-thickened bladders. They propose that this operation has fewer complications, requires shorter hospitalization, no postoperative bladder catheters are required and, as the non-refluxing ureteral orifice and submucosal tunnel are not disturbed, there is no risk of creating reflux. This can be undertaken either by suprapubic incision or extraperitoneal iliac fossa incision. Lashley *et al.*[32] reported excellent results of uretero-ureterostomy in 94 children with complete ureteral duplication associated with VUR, obstructing ureterocele, and ectopic ureters. The significant discrepancy in ureteral size did not preclude uretero-ureterostomy.

Another surgical option is reimplantation of ureters. Only a refluxing ureter may be undertaken if it can be safely separated. In patients with reflux into both ureters and those where the refluxing ureter cannot be safely separated, common

sheath ureteric reimplantation is undertaken. Ellsworth *et al.*[33] reported ten-year experience with common sheath reimplantation in 54 refluxing units. Common sheath reimplantation yields a 98% success rate with minimal morbidity. Recently, Lopez and colleagues[34] described their experience with laparoscopic extravesical transperitoneal approach following the Lich–Gregoin procedure in 60 refluxing duplicated collecting systems. All procedures were successfully completed laparoscopically and reflux was corrected in all children.

In incompletely duplicated ureters, surgical options include reimplantation of the common distal ureter if the junction is proximal or when junction is close to bladder excision of the common segment, with reimplantation of both ureters in the bladder or uretero-ureterostomy with reimplantation of one ureter. However, if the function is poor, nephro-ureterectomy is necessary to avoid a diverticulum-like defect.

Minimally invasive endoscopic technique for the correction of VUR has become an established alternative to long-term antibiotic prophylaxis and surgical treatment. Endoscopic subureteric Deflux® injection is effective in treating duplex reflux of higher grades in complete and incomplete systems.[24,35,36] The technique of endoscopic injection of Deflux is simple and straighforward. With an incomplete duplex system, the technique is the same as in a single system. All cystoscopes available for infants and children can be used for this procedure. The disposable Puri flexible catheter (Storz, Tuttlingen, Germany) or a rigid metallic catheter can be used for injection. A 1-mL syringe filled with Deflux is attached to the injection catheter. Under direct vision through the cystoscope, the needle is introduced under the bladder mucosa 2–3 mm below the affected ureteral orifice at the 6 o'clock position. In children with grade IV and V reflux with wide ureteral orifices, the needle should be inserted not below but directly into the affected ureteral orifice. The needle is advanced about 4–5 mm under the mucosa and the injection started slowly. As the Deflux is injected, a bulge appears in the floor of the submucosal ureter. A correctly placed injection creates the appearance of a nipple on the top which is a slit-like or inverted crescent orifice (Figs 96.4 and 96.5).

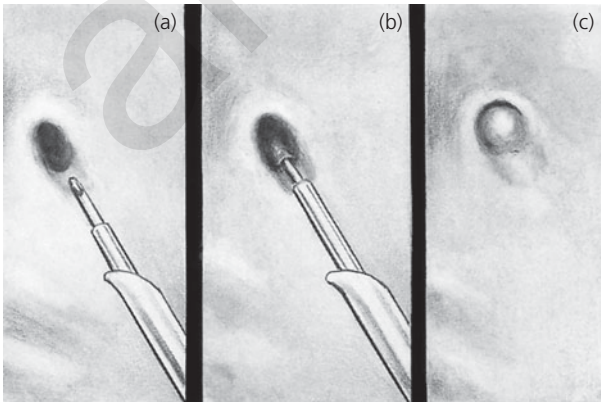


Figure 96.4 Technique of subureteric injection in an incomplete duplex system.

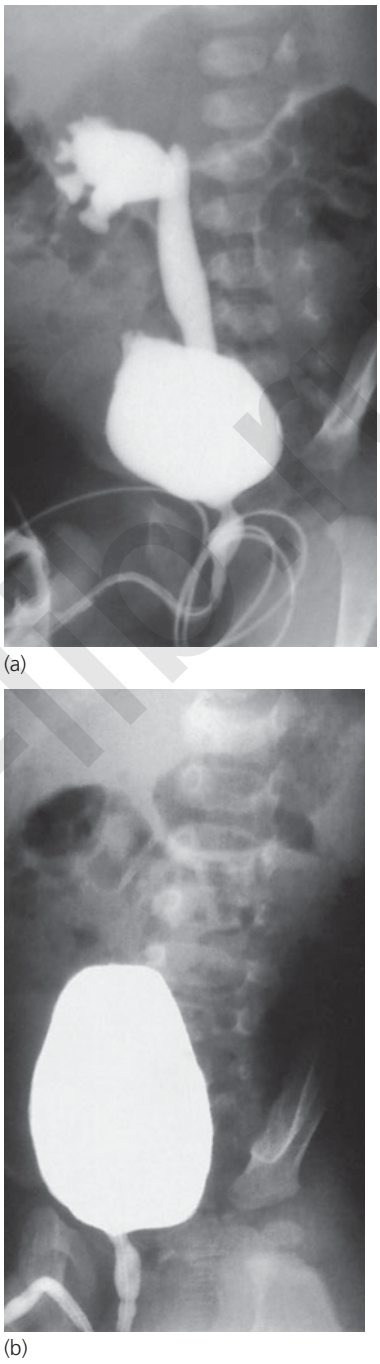


Figure 96.5 (a) Micturating cystogram in an 8-week-old boy shows grade IV vesico-ureteric reflux into the lower moiety of the right duplex system. (b) Micturating cystogram in the same boy following endoscopic correction of reflux.

In the case of a complete ureteral duplication, the needle is introduced 2–3 mm below the lower ureteric orifice at the 6 o'clock position, but the entire length of the needle (8 mm) is advanced behind the two ureters. During injection, the needle is slowly withdrawn until a 'volcanic' bulge of paste is seen and the two ureteric orifices look slit-like (Fig. 96.6). Patients are treated as day cases and a voiding

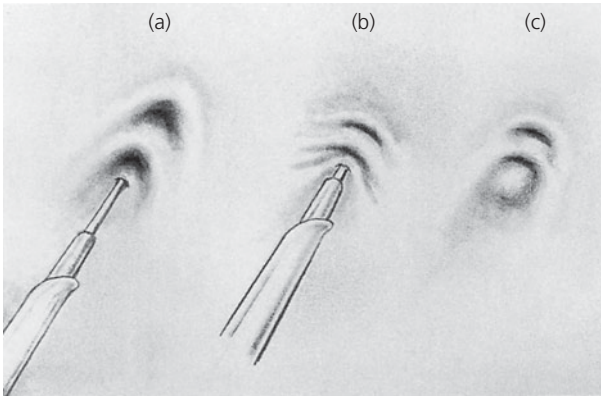


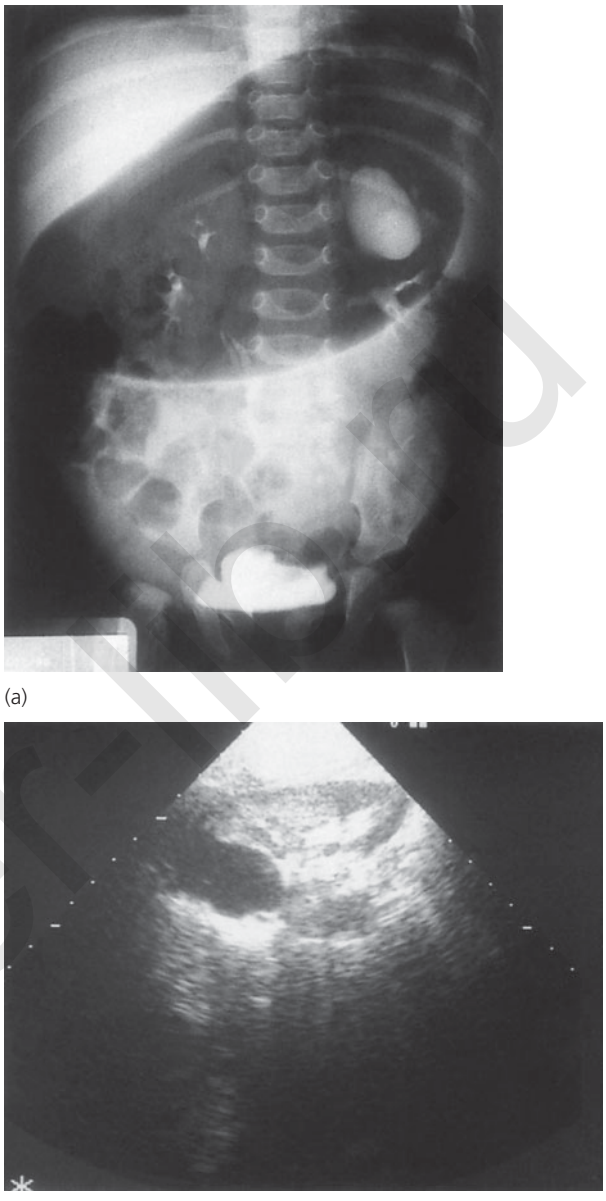
Figure 96.6 Technique of subureteric injection in a complete duplex system.

cysto-urethrogram and ultrasound are performed 6–12 weeks after discharge.

Ureteropelvic obstruction

In the bifid system, obstruction commonly involves the lower pole.[30–33] Upper pole ureteropelvic junction obstruction is uncommon (Fig. 96.7a,b). In patients with low bifurcations and who have long ureteral segments, a standard pyeloplasty can safely be performed. If the lower pole ureteral segment is short, an end-to-end anastomosis of the lower pole pelvis to the upper pole ureter, eliminating the short lower pole ureter, may be necessary. Alternatively, the short lower pole ureter is retained and incorporated into a wider anastomosis. In patients with incomplete duplications, it is possible to widen the narrowed junction of the lower pole segment to the upper pole ureter by making a vertical incision in the anterior wall and suturing it transversely.[37] If there is nonfunction of the obstructed segment, a heminephro-ureterectomy to the level of the bifurcation is necessary to avoid leaving a ureteral stump into which uretero-ureteral reflux can occur.[37]

The management of ureterocele is complex.[38–40] Consideration of ureterocele as intravesical or extravesical is important because the technique of surgical reconstruction can be different. If the function is good, endoscopic incision of the ureterocele may be tried. The advantages of this procedure are that this is straightforward management, especially in septic babies. The obstruction can be solved by simple puncture of ureterocele rather than endoscopic incision. The reflux rate to the ureterocele moiety following endoscopic puncture is negligible. In all our patients, we have used a stylet of the 3-Fr ureteral catheter for endoscopic puncture. The puncture hole is made high enough and lateral on the ureterocele in order to avoid reobstruction and to create postpuncture flap sufficient to preserve the flap-valve antireflux mechanism. If the reflux developed after endoscopic puncture, it is usually a low grade and does not require any treatment. If the child develops breakthrough infections or high-grade reflux, endoscopic correction of reflux can be easily performed.[26]



(a)

(b)

Figure 96.7 (a) Bilateral duplex system. Urogram showing obstructed upper moiety on the left due to pelvic-ureteric junction obstruction. (b) Longitudinal sonographic scan through the left kidney in the coronal plane in the same patient, demonstrating pelvi-ureteric junction obstruction to upper moiety and normal lower moiety.

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Vesico-ureteral reflux

PREM PURI

INTRODUCTION

Primary vesico-ureteral reflux (VUR) is the most common urological anomaly in children. It occurs in 1–2% of the pediatric population and in 30–50% of children who present with urinary tract infection.[1,2] The association of vesico-ureteral reflux, urinary tract infection, and renal damage is well known. Marra *et al.*[3] reviewed data on children with chronic renal failure who had high-grade VUR in the Italkid project, a database of Italian children with chronic renal failure and found that those with VUR accounted for 26% of all children with chronic renal failure. Parenchymal injury in vesico-ureteral reflux occurs early, in most patients before the age of three years. Kidneys of young infants are more vulnerable to renal damage. Most renal scars are present when reflux is discovered at initial evaluation for urinary tract infection.

The hereditary and familial nature of vesico-ureteral reflux is now well recognized and several studies have shown that siblings of children with vesico-ureteral reflux have a much higher incidence of reflux than the general pediatric population. Prevalence rates of 27–51% in siblings of children with VUR and a 66% rate of VUR in offspring of parents with previously diagnosed reflux have been reported.[4–8]

ETIOLOGY

The uretero-vesical junction (UVJ) acts as a valve and closes during micturition or when the bladder contracts. The UVJ is structurally and functionally adapted to allow the intermittent passage of urine and prevent the reflux of urine in the bladder. The main defect in patients with VUR is believed to involve the malformation of the UVJ, in part due to shortening of the submucosal ureteric segment due to congenital lateral ectopia of the ureteric orifice. Since VUR primarily involves abnormalities of the ureter and ureteric orifice, it has been suggested that the timing and positioning of branching of the ureteric bud from the Wolffian duct may be related to VUR. The underlying abnormality could be due to mutations in one or more developmental genes that control these processes.

Mechanism of renal scarring

The association between VUR and renal scarring is now widely recognized. Scarring is directly related to the severity of reflux. Belman and Skoog[9] assessed renal scarring in 804 refluxing units and found renal scars in 5% of those with grade I reflux, 6% of those with grade II reflux, 17% of those with grade III reflux, 25% of those with grade IV reflux, and 50% of those with grade V reflux.

The mechanism by which reflux produces renal scars is still not clear. It is essential to distinguish between the commonly acquired segmental scarring associated with VUR and infection, and the primary scarring seen congenitally, in which the etiology is very different and linked to abnormal metanephric development. There is no doubt that bacterial pyelonephritis produces renal scars experimentally and clinically. Dimercaptosuccinic acid (DMSA) scans have allowed us to follow sequentially the evolution of a scar from an area of decreased blood flow during the acute inflammatory phase to a parenchymal defect indicative of a mature scar. Yet only half of patients with acute pyelonephritis will have such a scar. What converts an acute inflammatory process into a scar in some patients and not in others is not clearly understood. Factors implicated in the formation of a mature scar include magnitude of the pressure driving the organisms into the tissues, the intrinsic virulence of the organism itself, and the host defense mechanisms. Furthermore, some of the worst examples of renal injury associated with VUR are those that are present at birth. As renal damage at that time cannot be the consequence of infection, such injury is assumed to be developmental in origin, but the pathophysiology of this is not entirely clear.

The three mechanisms considered potential etiologies for renal scar formation are (1) reflux of infected urine with interstitial inflammation and damage, (2) sterie, usually

high-grade reflux, which may damage the kidney through a mechanical or immunological mechanism, and (3) abnormal embryological development with subsequent renal dysplasia. Patients in the latter group may also have urinary tract infection in the postnatal period, resulting in extensive parenchymal damage. It is well recognized that in the first two groups of renal parenchymal damage, it is essential to discover reflux early before damage can be initiated. In the third group, it is clear that congenital damage currently cannot be prevented. However, in these patients, it is mandatory to discover reflux at the early stages to prevent exposure to urinary tract infection and avoid the possible progression of renal parenchymal damage.

DIAGNOSIS

Antenatally diagnosed reflux

Prenatal ultrasonography has resulted in a dramatic increase in the number of infants detected with significant asymptomatic uropathology, allowing treatment before the potential devastating consequences of UTI occur.[10] An incidental anomaly is detected by antenatal ultrasonography in about 1% of studies and 20–30% involving the urinary tract.[11] By far the most common abnormal finding is hydronephrosis, comprising over 90% of the urological abnormalities detected. Underlying diagnoses include pelvic-ureteric junction obstruction, vesico-ureteric junction obstruction, posterior urethral valves, and VUR.

Although antenatal hydronephrosis is generally considered to represent an obstructive lesion, VUR is not an uncommon cause. Najamaldin and colleagues[12] performed micturating cystography in the first six months of life in 97 of 102 patients with renal abnormalities detected *in utero* and found that 18 males and 12 females had VUR. In the series of Gordon and associates,[13] of 25 cases of primary VUR suspected *in utero* and confirmed in the neonatal period, 21 (84%) were males. In another series, prenatal hydronephrosis was due to VUR in 34 of 309 cases (11%).[14]

Natural history of prenatally diagnosed VUR

The vast majority of infants found to have VUR following detection of antenatal hydronephrosis are males. The male preponderance is reported to range from 2:1 to 5:1 in various series.[15–17] This is in total contrast to the female preponderance that has been consistently reported in later childhood. In approximately two-thirds of the cases, the reflux is bilateral. VUR diagnosed prenatally tends to be of high grade.[15–17]

It has also been reported that boys are more vulnerable to UTI, especially in the first six months of life, where different factors play a significant role.[18] Host factors, such as the inner non-keratinized epithelium of the foreskin, create a moist reservoir for uropathogens and contribute to the first contact between the host and the bacteria. Once the prepuce has been colonized, the bacteria can ascend the urinary tract, causing cystitis or pyelonephritis. Rushton and Majd[18] showed a clear predominance of males among infants less than six months old with febrile UTI, and a disproportionately high frequency of uncircumcised male infants. Cascio *et al.*[19] showed a pure growth of a uropathogen in 48% of uncircumcised infants with VUR despite the use of prophylactic antibiotics.

At birth, between one-third and a half of refluxing kidneys may have reduced renal function on DMSA scintigraphy, even in the absence of UTI.[20,21] In the series of Anderson and Rickwood,[14] 75% of the kidneys with grade V reflux, 80% with grade IV reflux, 46% with grade III reflux, and 0% with grade I or II reflux exhibited reduced isotope uptake with an overall 18% of renal function.

Yeung *et al.*[20] studied 155 infants with prenatal hydronephrosis and postnatally diagnosed VUR. They observed renal parenchymal damage in 42% of the 135 infants (101 males and 34 females) without history of UTI.[20] Furthermore, Nguyen *et al.*[21] reported renal parenchymal abnormalities in 65% of predominantly male infants with sterile high-grade reflux. The resolution rate of antenatally diagnosed high-grade VUR (grade IV or V) is approximately 20% by the age of two years.[10,11] However, in approximately 25% of boys followed non-operatively, UTIs developed by the age of two years, despite antimicrobial chemoprophylaxis.[11]

CLINICAL PRESENTATION

It is obviously important to diagnose VUR at the earliest possible age, preferably in infancy. There are a number of clinical presentations, which should raise the suspicion of VUR in an infant. As antenatal ultrasound becomes increasingly routine, many cases will be suspected before birth and should be investigated within the first month of life. Infants with a poor urinary stream as in posterior urethral valves or infants with spina bifida have a high incidence of VUR, while early investigations are indicated in the first-degree relatives of patients with high-grade VUR.

In most cases, VUR is discovered clinically after investigations for urinary tract infection. The incidence of VUR in infants with febrile UTI is 30–50% with even higher incidence in male infants. Cascio *et al.*[22] found VUR in 33% of the 57 neonates investigated for first hospitalized UTI. Sixteen had bilateral VUR and three unilateral with 91% having high-grade VUR. Another study evaluated the incidence of renal damage by DMSA in 141 consecutive male infants with grade III–V VUR.[23] Renal parenchymal damage was detected in 44% of infants.

RADIOLOGICAL INVESTIGATIONS

Ultrasound

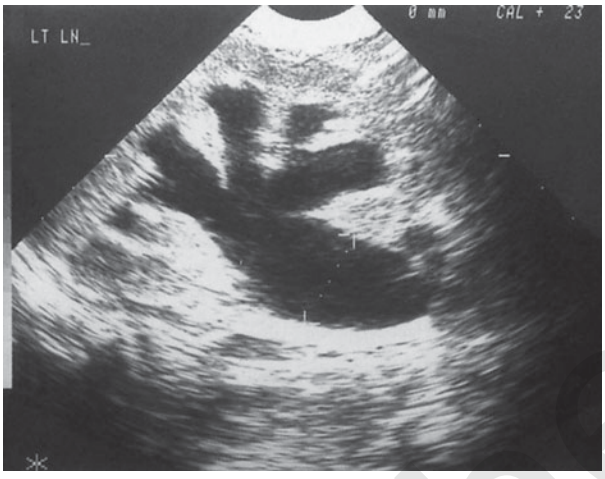
Sonography should be performed in any infant with suspicion of VUR. The kidneys and upper ureters should be examined both in B-mode and real time. The bladder and lower ureters are assessed by real-time examination at each uretero-vesical junction for dilatation, configuration, peristalsis, and continuity with the bladder base. VUR is

suspected in the presence of a dilated pelvicaliceal system, upper or lower ureter, unequal renal size, or cortical loss and increased echogenicity (Fig. 97.1a–d). Sonography is not sufficiently sensitive or specific for diagnosing VUR.[17,24,25] The intermittent and dynamic nature of VUR probably contributes to the insensitivity of routine renal sonography in the detection of even higher grades of reflux.

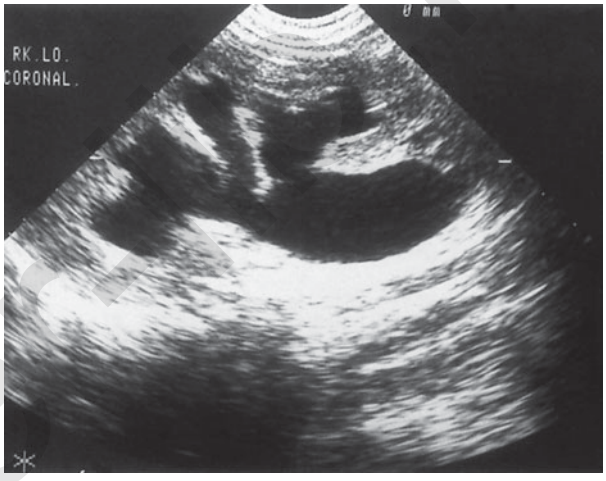
Micturating cystography

VUR is a dynamic process. Bladder filling and voiding are necessary for its elucidation which requires catheterization for adequate documentation. Micturating cystogram remains the gold standard for detecting VUR (Fig. 97.2). Despite the unpleasant nature of the procedure, it has a low false-negative rate and provides accurate anatomical detail, allowing grading of the VUR (Fig. 97.3a–c). It is commonly performed as a first-line investigation, together with ultrasound.

Some investigators employ nuclear cystography for diagnosing VUR. This can be either direct or indirect using technetium-labeled diaminotetra-ethyl-pentaacetic acid (DTPA). In direct nuclear cystography, DTPA is instilled into the bladder by urethral catheter or suprapubic injection and the ureters and kidneys are observed on camera during bladder filling and voiding. In indirect nuclear cystography, DTPA is injected intravenously. After the bladder is filled, the



(a)



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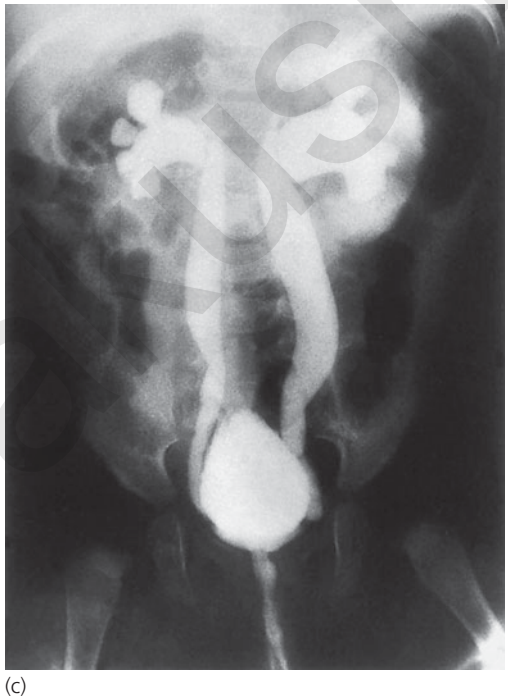
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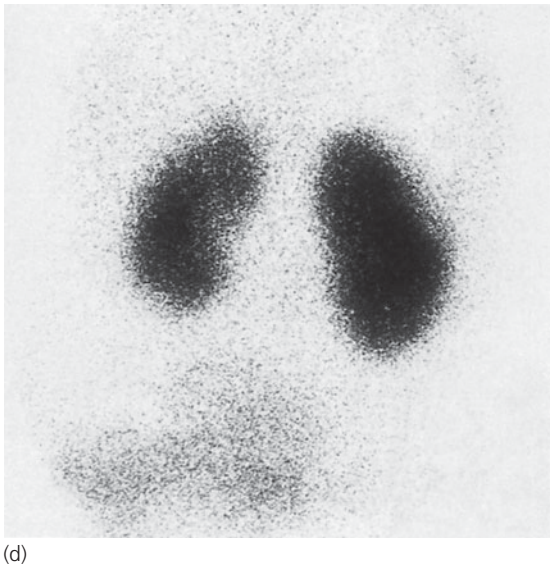
(d)

Figure 97.1 (a,b) Ultrasound showing bilateral hydronephrosis in a 6-week-old infant; (c) micturating cystography in the same infant shows bilateral high-grade vesico-ureteric reflux (note intrarenal reflux on the left side); (d) DMSA scan demonstrates significant left renal scarring, particularly in upper and lower poles.

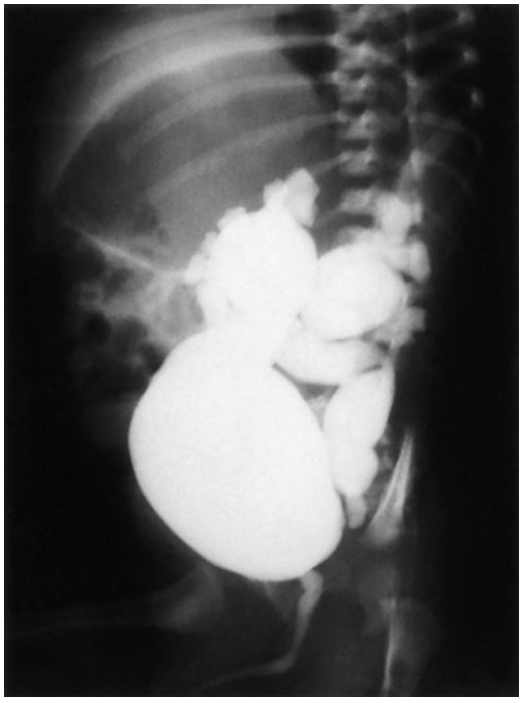

Figure 97.2 Four-week-old male infant with bilateral grade V vesico-ureteric reflux (note normal urethra and bladder wall).

patient is instructed to void and the counts taken over the ureters and kidneys are used to assess the presence of VUR. Indirect nuclear cystography requires a cooperative patient and therefore is of no value in infants. The main disadvantage of nuclear cystography is that it does not give anatomical detail and VUR cannot be graded according to international classification.

According to the international classification of reflux, there are five grades of reflux:

1. grade I, ureter only
2. grade II, ureter, pelvis, and calices – no dilatation, normal caliceal fornices
3. grade III, mild dilatation and/or tortuosity of the ureter and mild dilatation of the renal pelvis – minor blunting of the fornices
4. grade IV, moderate, dilatation and/or tortuosity of the ureter and moderate dilatation of the renal pelvis and calices – complete obliteration of the sharp angle of fornices but maintenance of the papillary impressions in the majority of calices
5. grade V, gross dilatation of the renal pelvis and calices (Fig. 97.4).

DMSA scan

DMSA is the most sensitive technique for detecting renal scarring. When performed in the course of acute urinary tract infection, the DMSA scan is currently the most reliable test for the diagnosis of acute pyelonephritis. Several reports have suggested that a normal[26–28] acute DMSA scan rules out the possibility of high-grade VUR. However, others have reported that acute DMSA scintigraphy has limited overall ability in revealing VUR after first febrile UTI in infants.[25,29] This was true even when the findings of the acute DMSA scan were combined with those of renal ultrasonography.

MANAGEMENT

Management of VUR has been controversial. The various treatment options currently available in the management of VUR are: (1) long-term antibiotic prophylaxis, (2) intermittent antibiotic therapy for UTI, (3) antibiotic prophylaxis and anticholinergics, (4) open or laparoscopic reimplantation of ureters, and (5) minimally invasive endoscopic treatment.

Medical management

This strategy is based on three important assumptions: (1) Sterile VUR in most cases is not harmful to the kidneys and has no relevant affect on kidney function. (2) Children can outgrow VUR, at least the lower grades. (3) Continuous low-dose antibiotic prophylaxis can prevent infection for many years while VUR is still present.

The patient is required to take low-dose daily antibiotics and annual ultrasound and VCUG are performed to assess whether the reflux has resolved. The European arm of the International Reflux Study Group, in children at ten-year follow up showed that half of the children with grade III and IV reflux randomly allocated to medical treatment still had reflux after ten years.[30] In those with bilateral reflux, 61% had persistence of reflux after ten years. In a long-term study, Schwab *et al.*[31] reported spontaneous resolution rates of 13% yearly for grade I to III reflux and only 5% for grade IV to V reflux. Additionally, long-term antibiotic prophylaxis has the risk of bacterial resistance accompanied by potential breakthrough UTIs.

Surgical treatment

OPEN ANTIREFLUX PROCEDURES

Open surgical treatment of reflux has been the gold standard. However, surgery is not without risk, and in infants it is technically more challenging. The majority of the open antireflux procedures entail opening the bladder and performing a variety of procedures on the ureters, such as transvesical reimplantation (Politano–Leadbetter technique) and transtrigonal advancement of the ureters (Cohen technique). These procedures, although effective, involve open surgery, prolonged in-hospital stay, and are not free of complications, even in the best hands. Although open surgery achieves a success rate of 92–98% in grade II–IV VUR, the American Urological Association report on VUR reported persistence of VUR in 19.3% of ureters after reimplantation of ureters for grade V reflux.[32] The rate of obstruction after ureteral reimplantation needing reoperation reported by the American Urological Association in 33 studies was 0.3 to 9.1%.

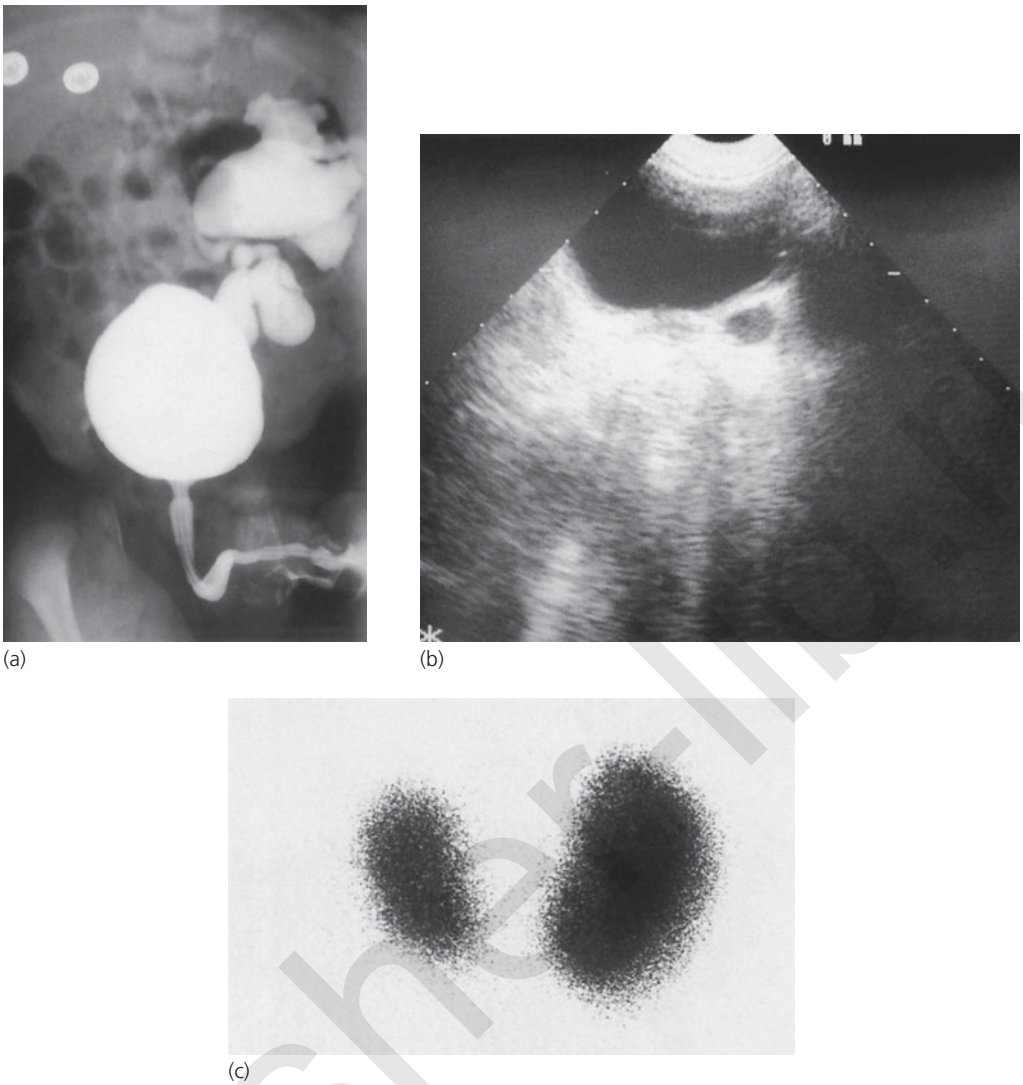

Figure 97.3 (a) Male infant showing grade V left vesico-ureteric reflux; (b) ultrasound in the same patient. Transverse scan through the full bladder demonstrates dilated left ureter. (c) DMSA scan in the same patient demonstrates small left kidney.

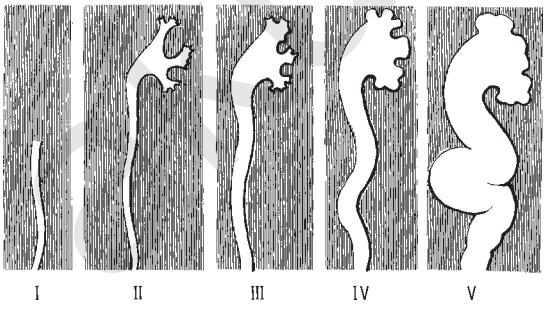

Figure 97.4 International classification of vesico-ureteric reflux (grades I–V).

LAPAROSCOPIC URETERAL REIMPLANTATION

In recent years, several authors have reported their experience of ureteral reimplantation with laparoscopic extravesical transperitoneal approach, as well as pneumovesical approach.[33–35] This technique results in a shorter hospital stay and less postoperative discomfort compared to open operation.

ENDOSCOPIC TREATMENT OF VUR

Minimally invasive endoscopic technique for the correction of VUR has become an established alternative to long-term antibiotic prophylaxis and open surgical treatment. Endoscopic treatment has several advantages over the two other options. In contrast to long-term antibiotic prophylaxis, it offers immediate cure of reflux with a high success rate, its success does not rely on patient or parent compliance and the procedure is virtually free of adverse side effects. Long-term administration of antibiotics implies the danger of bacterial resistance with promotion of breakthrough UTIs and antibiotics are usually needed for years. In 2001, Deflux was approved by the Food and Drug Administration (FDA) as an acceptable tissue augmenting substance for subureteral injection therapy for VUR. Since then, endoscopic treatment has become increasing popular worldwide for managing

VUR and Deflux is the most widely used tissue augmenting substance.

During the last two decades, the author has performed endoscopic correction of high-grade VUR in infants as the first line of treatment because it provides early resolution of reflux at a time when infants are at a higher risk for renal scarring.[36–38]

The technique of endoscopic injection of Deflux is simple and straightforward.[37,38] All cystoscopes available for infants and children can be used for this procedure. The disposable Puri flexible catheter (Storz, Tuttlingen, Germany) or a rigid metallic catheter can be used for injection. A 1-mL syringe filled with Deflux is attached to the injection catheter. Under direct vision through the cystoscope, the needle is introduced under the bladder mucosa 2–3 mm below the affected ureteral orifice at the 6 o'clock position (Fig. 97.5). In children with grade IV and V reflux with wide ureteral orifices, the needle should be inserted not below but directly into the affected ureteral orifice. The needle is advanced about 4–5 mm under the mucosa and the injection started slowly. As the Deflux is injected, a bulge appears in the floor of the submucosal ureter. A correctly placed injection creates the appearance of a nipple on the top which is slit-like or inverted crescent orifice. Patients are treated as day cases and a voiding cysto-urethrogram and ultrasound are performed 6–12 weeks after discharge.

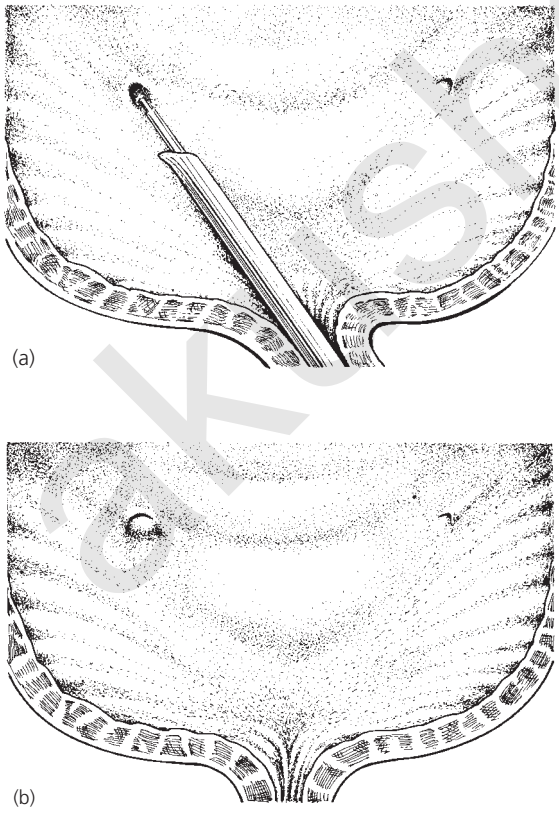

Figure 97.5 Technique of endoscopic subureteric injection: (a) the site of insertion of the needle; (b) appearance of ureteric orifice at completion of injection.

Endoscopic subureteral injection of Deflux is excellent first-line treatment in children with 87% success in high-grade vesico-ureteral reflux after one injection. This 15-minute outpatient procedure is safe and simple to perform, and it can be easily repeated in failed cases.

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98

Ureteroceles in the newborn

JONATHAN F KALISVAART AND ANDREW J KIRSCH

INTRODUCTION

Ureteroceles are congenital, cystic dilations of the terminal, intravesical portion of the ureter. The associated ureteral orifice, often extremely difficult to visualize, may be partially or totally obstructed, resulting in variability in size from small to very large. They can also vary in location from intravesical to ectopic. The use of fetal ultrasonography has improved the diagnosis of ureteroceles, however, they often remain difficult to diagnose and require complete postnatal evaluation when suspected.

PATHOGENESIS

The pathogenesis of the ureterocele remains unclear, although several theories have attempted to explain it. Chwalla[1] and Ericsson[2] attributed the ureterocele formation to the persistence of an epithelial sheet (Chwalla's membrane) separating the lumen of the distal portion of the Wolffian duct and the urogenital sinus. Chwalla's membrane is a normal embryologic structure that disappears spontaneously approximately two months after conception. If it persists, it can balloon out and form the ureterocele. Stephens,[3] on the other hand, postulates that the terminal ureter becomes involved in the growth of the bladder and undergoes extensive enlargement, resulting in the formation of the ureterocele. Tanagho[4] suggests that the ureterocele forms secondary to local dilatation of the ureteral bud prior to its migration from the Wolffian duct. Tokunaka and colleagues[5] demonstrated poor muscle development in the dome of the ureterocele and suggest that ureterocele formation is based on a segmental embryonic arrest of the development of the most distal portion of the ureter. These theories regarding the pathogenesis of ureteroceles are still only speculation.

Pathological anatomy and associated pathology

Ureteroceles can be associated with the ureter draining of the upper moiety of a duplex collecting system or with the ureter of a single system. Duplex system ureteroceles occur in approximately 85% of diagnosed cases and can vary in size and position. The upper renal moiety is non-functional and dysplastic in over 80% of cases.[6,7] Occasionally, ureteroceles are small and well demarcated from the bladder wall, but often they present as very large subtrigonal masses. The ureterocele may also protrude towards the contralateral ureteral orifice or the bladder neck causing contralateral ureteral or bladder outlet obstruction. More commonly, the ipsilateral orifice of the ureter draining the lower pole is pushed upwards by the distended ectopic ureterocele, shortening the intratrigonal tunnel, leading to reflux and hydronephrosis. On the contralateral side, reflux and secondary hydronephrosis can be seen, likely due to the disruption of the normal trigonal anatomy. Less commonly, reflux can be seen to occur into the ureterocele itself.

Ureteroceles are attached to single collecting systems in approximately 15% of cases, often in males.[6,7] The cystic swelling tends to be asymmetric with the ureteral orifice located in an eccentric position. The single system ureterocele is usually smaller in size than the ectopic ureterocele and the size of the ureterocele is generally related to the degree of obstruction caused by the pinpoint orifice.[8]

Single-system ureteroceles rarely prolapse and cause bladder neck obstruction, and reflux is extremely uncommon. Although the ureter and pelvicalyceal structures are hydronephrotic to varying degrees, function of the renal unit is often preserved.

CLASSIFICATION

In 1954, Ericsson[2] classified ureteroceles into orthotopic or simple ureteroceles if the ureter forming the ureterocele ends in a normal site in the bladder or ectopic ureteroceles if the ureter ends in an ectopic location. However, confusingly, a simple ureterocele can also mean a ureterocele involving a single system and an ectopic ureterocele can describe a ureterocele associated with a duplicated system. Stephens[3] classified ureteroceles based on the anatomic location and appearance of the orifice into stenotic (narrowed opening

found in the bladder), sphincteric (an orifice distal to the bladder neck), sphincterostenotic (a narrowed opening distal to the bladder neck), and a cecoureterocele (intravesical orifice with a submucosal extension into the urethra). These traditional classifications, based on the location of the ureteral orifices or on the anatomical description, can be quite confusing. The modern classification system is based on the report of the Committee on Terminology, Nomenclature and Classification of the Urology Section of the American Academy of Pediatrics.[9] It subdivides ureteroceles based on:

1. Number of ureters that drain the kidney ipsilateral to the ureterocele
2. Location and extent of the ureterocele
3. Any additional anatomic distortions of the ureterocele resulting from eversion, prolapse, or secondary incompetence or obstruction of the other ureteral orifice or the bladder neck.

Thus, a duplex-system ureterocele is when the ureterocele is attached to the upper pole ureter of a completely duplicated collecting system, and a single-system ureterocele is when the ureterocele is attached to a single ureter draining the kidney. If the ureterocele and its orifice are located entirely within the bladder, the term 'intravesical' is used and if the ureterocele and its orifice extend beyond the trigone to the bladder neck or outside the bladder to involve the urethra, the term 'ectopic' is applied. Single-system ureteroceles are generally intravesical and ectopic ureteroceles are usually associated with the upper pole ureter of a duplex-system (Fig. 98.1).[10]

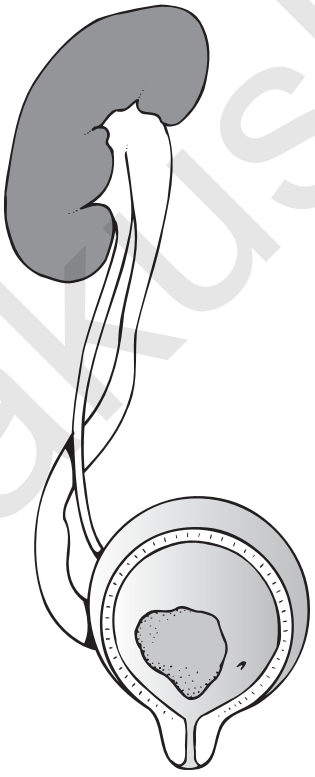


Figure 98.1 Ectopic ureterocele in relation to the upper moiety of a duplex collecting system.

INCIDENCE

The incidence of ureteroceles varies between 1:1500 and 1:12 000 pediatric admissions, depending on the study[11,12] and in 1:4000 autopsies.[13] Ureteroceles occur most frequently in females with a 4:1 ratio and are more common in Caucasians.[14] Duplex-system ureteroceles are four to seven times more common in females than in males,[15] and single-system ureteroceles appear to have a slightly male predilection.[10]

There does not appear to be a predilection towards laterality as both kidneys are equally affected[16] and bilateral ureteroceles are found in approximately 10% of cases.[8]

CLINICAL PRESENTATION

The clinical presentation of ureteroceles in infants and children is a febrile urinary tract infection in 39–73.5% of cases.[7,17–19] Sepsis, hematuria, urinary incontinence, and/or flank pain can be present. Non-specific symptoms, such as failure to thrive, irritability, urinary retention or recurrent vomiting, should also lead to further investigation of the urinary tract. In cases of severe obstruction and consequent gross megaureter and hydronephrosis, a palpable mass may be present in the abdomen or in the pelvis. Severe electrolyte disturbances, such as hyperkalemia may occur, and in very rare cases of hyponatremia and hyperkalemia, pseudohypoaldosteronism should be suspected.[20]

In baby girls, the ureterocele may prolapse through the urethra and can be seen as an apparent vaginal or vulvar mass (Fig. 98.2).

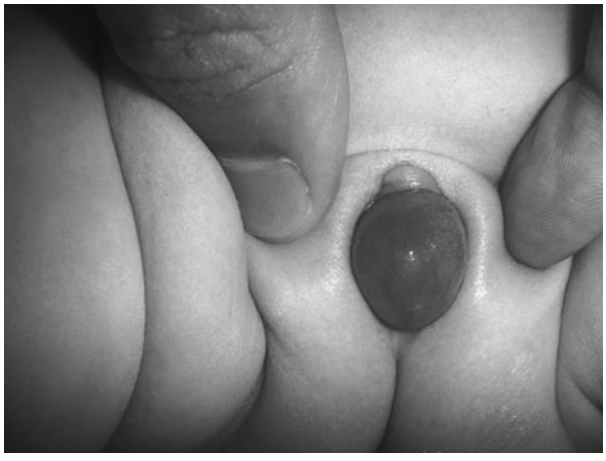


Figure 98.2 Prolapsing ureterocele in a female newborn.

DIAGNOSIS

Ureteroceles can be diagnosed in the antenatal period as part of a screening ultrasound. After the 30th week of pregnancy, the ureterocele may be demonstrated in the fetal bladder (Fig. 98.3). More often, however, the antenatal ultrasound

Figure 98.3 Antenatal ultrasonography. Ureterocele in the fetal bladder as seen in the 30th gestational week.

performed after the 16th gestational week shows only hydronephrosis. The causative pathology of this hydronephrosis can generally only be established by immediate postnatal investigations. These investigations have traditionally consisted of ultrasonography, voiding cysto-urethrogram (VCUG), and cystoscopy. In addition, DMSA, DTPA, MAG3 renal scintigraphy, or magnetic resonance urography (MRU) should be used to detect renal cortical defects, evaluate renal function and the degree of ureteral obstruction (Fig. 98.4).

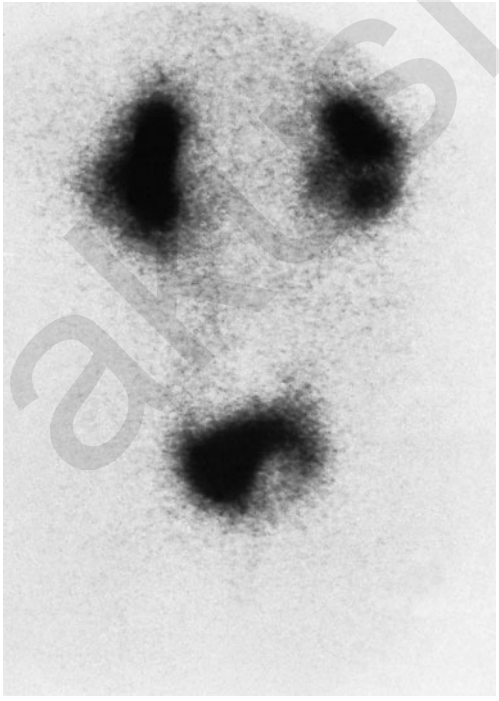


Figure 98.4 Isotope scan (DMSA) demonstrating the ureterocele (uptake defect in the bladder) and the non-function of the upper renal moiety.

Although inferior in many ways, i.v. urogram (IVU) may be used in cases where other imaging modalities are unavailable.

Ultrasonographic findings are of a cystic mass within the bladder, often with dilatation of the associated ureter and pelvicalyceal structures (Fig. 98.5). VCUG shows a filling defect within the bladder varying in size and position. The ectopic ureterocele is seen as a filling defect placed eccentrically along the bladder wall extending into the bladder neck or into the posterior urethra. The intravesical ureterocele is generally surrounded by contrast medium demonstrating most of its circumference. If the images are taken when the bladder is full, the ureterocele may evert, mimicking a bladder diverticulum (Fig. 98.6).

With the VCUG, reflux into all renal units can also be assessed. Studies have estimated that 50% will have reflux into the ipsilateral lower pole, 25% into the contralateral ureter, and 10% into the ureterocele-bearing ureter.[21]

MRU has also been used to diagnose ureteroceles in both fetal life and in infants with a sensitivity of 89–100%.[22,23] The advantages of MRU include anatomic images of both the upper and lower tracts, and with the correct sequences, functional data of the upper tract can also be delineated.[24] This information can be useful both in decision-making and in surgical planning (Fig. 98.7).

Once the diagnosis is suspected based on imaging, cystoscopy can confirm the diagnosis and help with surgical planning.

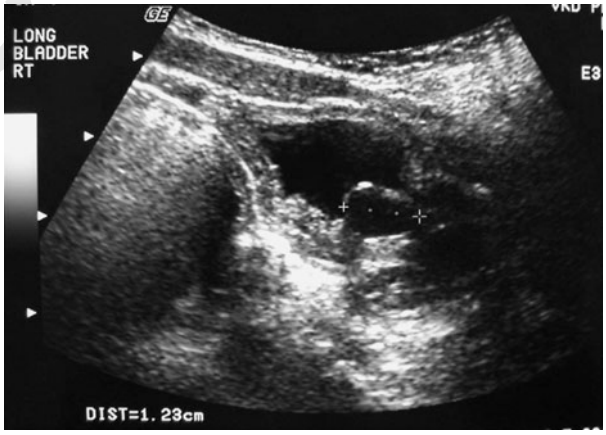
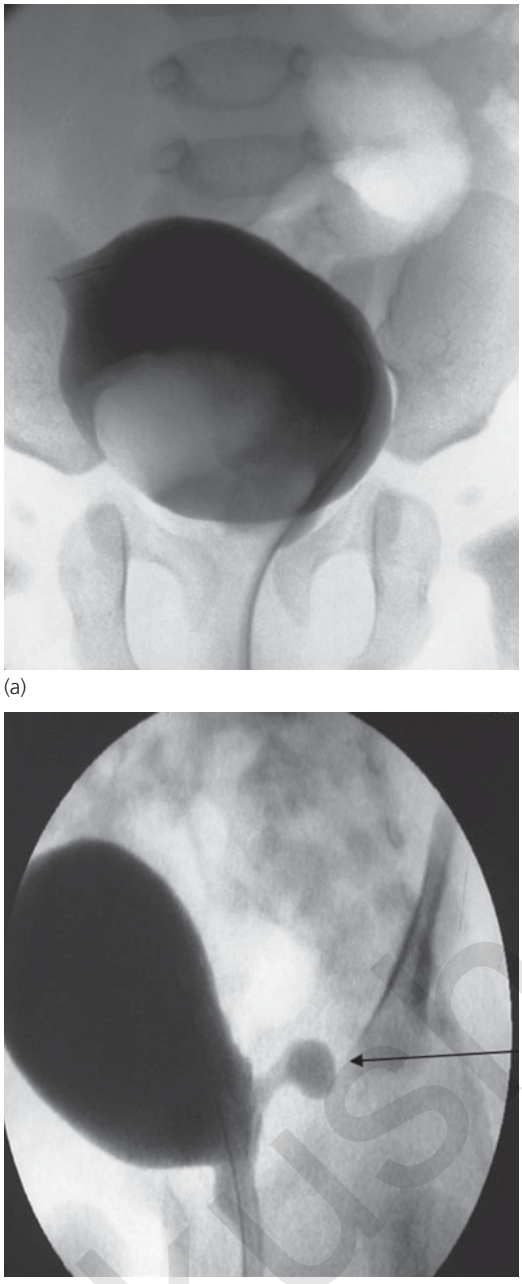


Figure 98.5 Postnatal ultrasonography. Ureterocele within the bladder.

TREATMENT

Ureteroceles are often complex anomalies. Although considerable controversy still exists regarding the best treatment, the final aims of the surgical management of the ureterocele are to relieve obstruction, prevent urinary infection, prevent or correct vesico-ureteral reflux, and preserve renal function. The latter goal may be considered secondary as the upper pole moiety serving the ureterocele is often dysplastic with marginal function.

As a result of these goals, four aspects have to be taken into account in the planning of the correct surgical treatment:[25]



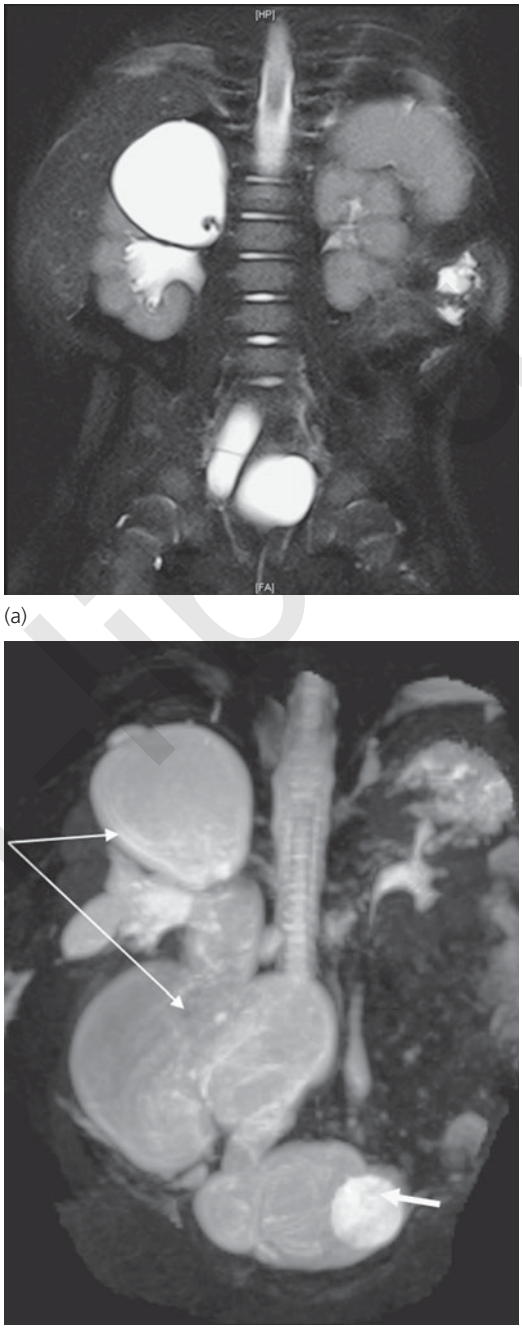
(a)

(b)

Figure 98.6 Voiding cysto-urethrogram (VCUG) showing (a) ureterocele in the bladder and (b) eversion of the ureterocele with filling of the bladder (arrow).

1. Degree of renal dysplasia and its resulting loss of renal function
2. Presence of reflux into the ureterocele-bearing ureter, the ipsilateral ureter, and/or the contralateral ureter
3. Altered trigonal anatomy, as well as the weakness of the detrusor muscle backing the ureterocele
4. Degree of obstruction caused by the prolapsing or ballooning ureterocele.

A standardized approach is probably impossible and it seems reasonable to individualize the management according to the aspect of each particular case.



(a)

(b)

Figure 98.7 T_2-weighted magnetic resonance urography (MRU) showing (a) the dilated upper pole associated with the ectopic ureterocele and (b) the characteristic appearance of the ureterocele (thick, white arrow) with the associated dilated renal upper pole and ureter (thin, white arrows).

Conservative management

Patients meeting specific criteria have been successfully managed with prophylactic antibiotics only. These criteria are:

- either a well-functioning renal moiety associated with the ureterocele or a completely non-functioning renal unit associated with the ureterocele;

- no evidence of obstruction on functional renal imaging;
- no other pathology (i.e. bladder outlet obstruction).

Between 60 and 70% of these highly selected patients managed conservatively had resolution of reflux and hydronephrosis[26,27] showing that, in this highly selected group, surgery may be avoided. However, the long-term potential sequelae of small persistent ureteroceles, such as urolithiasis and infection, have not been evaluated.

Endoscopic puncture or incision

With improvements in urologic endoscopic technology, a more conservative approach in the surgical management of the ureterocele is feasible. Several authors have demonstrated the advantages of the endoscopic incision or puncture of ureteroceles in the preservation of renal tissue,[28–31] and in the case of the septic or acutely ill child with an obstructing ureterocele, endoscopic puncture should be considered to be the first-line treatment. This procedure can be performed with the patient under general or regional anesthesia, on a same-day surgery or outpatient basis.[32] Satisfactory postoperative urinary tract decompression has been reported in 85–100% of cases of endoscopic decompression,[32–34] and recovery of renal function following endoscopic puncture or incision has been reported.[32,33]

Several techniques of endoscopic puncture or incision of ureteroceles exist, but the most common technique consists of a small 2–3-mm incision or puncture made just above the distal junction of the ureterocele with the bladder using a Bugbee electrode[35] or a sharp electrode[28] through a pediatric cystoscope (Fig. 98.8). This avoids leaving a flap of ureterocele that might obstruct the bladder outlet and works to preserve a flap valve of the collapsed ureterocele. All these techniques bear the risk of interfering with the structures of the lower pole orifice and an attempt to visualize the lower pole orifice should be made to prevent such damage. Postincision imaging should be performed to detect reflux in all renal segments and to determine the need for further surgery. A second puncture should be considered in cases where a large ureterocele persists postoperatively and the degree of hydroureteronephrosis on ultrasound remains unchanged or worsened.

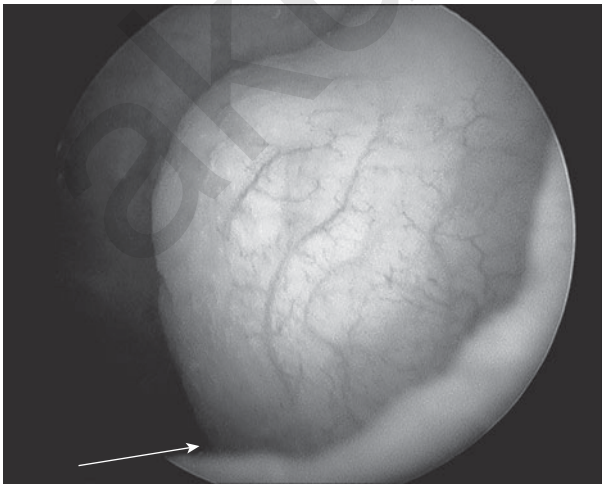


Figure 98.8 Cystoscopic view of a ureterocele. The arrow indicates the target for endoscopic puncture. Image courtesy of Dr Edwin Smith.

Controversy still exists regarding the advantages of the endoscopic puncture or incision of ureteroceles as a 'first-stage' treatment, principally due to the high association of postoperative reflux and secondary operations.[21,36–38] Surgeons in favor of the endoscopic puncture or incision 'first-stage' treatment in neonates with ureteroceles, suggest that:

- Approximately one-third of these patients will be definitively treated by this technique.
- Early renal and ureteral decompression will allow improvement or stabilization of renal function, as well as a decreased risk of pyelonephritis.
- It allows for a delay in definitive surgical correction, if necessary, and a technically easier operation after the neonatal period due to bladder growth, and decreased distention of the affected ureter.[21,28,29,36,37,39,40]

A recent meta-analysis found that, among patients undergoing endoscopic puncture of their ureterocele, risk factors for repeat surgery included an ectopic versus an intravesical ureterocele (RR, 2.78), ureteroceles draining the upper pole of a duplex system versus those draining a single system (RR, 3.93), and patients with preoperative reflux versus those without reflux (RR, 1.56).[41,42] Thus, the anatomy of each individual patient needs to be taken into account prior to any attempt at endoscopic puncture as a primary treatment.

Duplex system ureteroceles

For the treatment of duplex system ureteroceles, three definitive surgical options are available:

1. Heminephrectomy with partial or total ureterectomy, allowing the ureterocele to collapse ('upper-tract approach').
2. Excision or marsupialization of the ureterocele, reconstruction of the bladder, and reimplantation of the ureter(s) ('lower tract approach').
3. Combination of heminephrectomy and excision or marsupialization of the ureterocele ('combined upper and lower tract approach').

Ureterocele excision or marsupialization

The traditional open surgical approach involves the complete excision of the ureterocele with reconstruction of the bladder and bladder neck to create a functional bladder neck mechanism. Potential problems with this approach involve injury to adjacent structures, primarily the bladder neck, sphincteric mechanism, or creation of a vesicovaginal fistula. An alternative involves the marsupialization of the ureterocele which leaves the floor of the ureterocele intact and adhered to the bladder mucosa. This prevents the potential

injury to the surrounding structures due to the decreased dissection needed. One study has found no statistical difference between these two techniques.[43]

Procedure

Using a modified Pfannenstiel incision, the skin and the anterior rectus sheath are opened transversally. The recti are bluntly separated in the midline and the bladder is well mobilized laterally. Over the bladder dome the peritoneal covering has to be carefully stripped off, avoiding entry into the peritoneal cavity.

The previously filled bladder is incised longitudinally, taking care to avoid injury to the bladder neck. The lower end of the incision can be secured with a holding stitch to prevent tearing into the bladder neck or urethral sphincter and to make for easy identification when closing. The edges of the incised bladder are suspended and held open with holding sutures over the Denis-Browne ring retractor. Several sponges are placed into the superior bladder (the exact number varies depending on the size of the bladder) and the cranial blade is positioned inside the bladder dome over the sponges, pulling it upwards and forwards, exposing the trigonal area. The ureterocele, the orifice of the lower renal pole ureter and the contralateral ureter are visualized (Fig. 98.9). Each ureter is catheterized with an infant feeding tube or a ureteral catheter. Stay sutures are placed in the dome of the ureterocele and the urothelium is incised in an elliptical fashion (Fig. 98.10a,b).

If the ureterocele is to be completely excised, a dissection plane between the wall of the ureterocele and the urothelium and the detrusor muscle is found and the ureterocele is dissected off the urothelium (Fig. 98.10c). Once the ureterocele is freed completely, the remaining intramural ureter is mobilized as with a standard intravesical ureteral reimplantation (Fig. 98.10d). If the ureterocele reaches into the bladder neck or the posterior urethra, this procedure can be extremely difficult to perform and care has to be taken not to damage the urethral sphincter or its nerve supply. Once the ureterocele is resected, its backing detrusor muscle must be carefully reconstructed using resorbable monofilament sutures (Fig. 98.10e). This is to minimize diverticulum formation.[44] In girls, damage to the underlying vagina, and in boys, damage to the ipsilateral vas deferens, has to be avoided during this procedure.

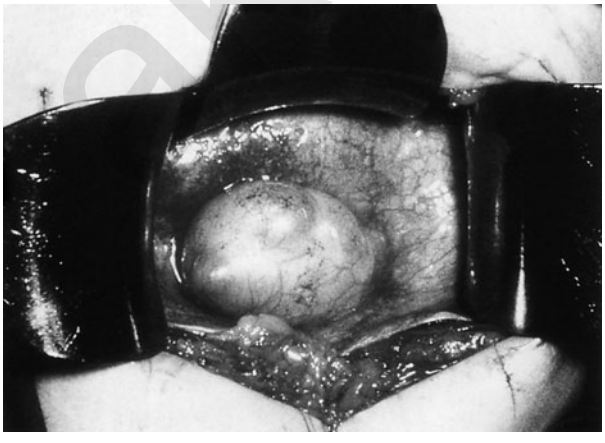


Figure 98.9 Operative treatment: intraoperative findings of a duplex system ectopic ureterocele.

Alternatively, the ureterocele can be marsupialized by excision of the anterior and lateral walls of the ureterocele using cautery. This leaves the posterior wall in continuity with the detrusor muscle behind it. The edges of the ureterocele are then reapproximated to the surrounding mucosa using absorbable sutures.

At this stage, the ureters are reimplanted according to Cohen's technique,[45] creating a cross-trigonal submucosal tunnel. Stenting of the reimplanted ureter can be performed according to the surgeon's preference. We generally do not stent the ureter, unless there is a specific reason, i.e. a solitary kidney, an abnormally small ureter, etc.

The bladder is then closed in a standard two-layer technique using resorbable sutures. The bladder is drained with a transurethral catheter. The urethral catheter is generally removed between 1 and 7 days after surgery depending on the surgeon's preference. Prophylactic antibiotics are administered perioperatively and are continued until absence of reflux is confirmed with postoperative imaging.

Heminephro-ureterectomy

This procedure can be performed either in the traditional open technique, or laparoscopically. The laparoscopic partial (or polar) nephrectomy has had good results reported, but is widely considered to be one of the hardest laparoscopic procedures to perform.[46] As a result, it is generally reserved for the skilled laparoscopist. It is less technically demanding in older, larger children, although it has been done successfully in infants.[47,48] The open surgical approach will be covered here.

Procedure

The upper pole nephrectomy is performed through a flank incision just off the tip of the 12th rib. The incision is extended to a length of 3–4 cm.

The muscle layers are incised using cautery down to the level of the retroperitoneum. The retroperitoneum is entered and the peritoneum is gently dissected anteriorly. The wound is held open with a retractor. Gerota's fascia is exposed and opened posteriorly. The upper pole ureter can then be identified, generally quite easily due to its size. The upper pole ureter is dissected free from the surrounding tissue. The lower pole ureter needs to be identified and dissected free, being careful to leave a sufficient amount of peri-ureteral tissue in place to avoid devascularization. The dilated upper pole ureter is then followed up towards the renal hilum. It is brought under the renal vessels being careful not to injure them. Once this is accomplished, the ureter can be followed to the upper pole segment which can be dissected free from the remainder of the renal parenchyma. There is generally a renal groove between the upper and lower pole segments which can assist in the dissection. The different color and

consistency of the dysplastic upper renal pole can be of additional help in the anatomical definition of the two segments (Fig. 98.11). Alternatively, the upper pole system can be entered and can be dissected away from the lower pole from the inside of the collecting system. Extreme care must be taken to preserve the lower renal vasculature.

It is important to remove the entire pelvicocalyceal structures of the upper renal pole and to carefully inspect the remaining kidney for opened lower pole calyces, which need to be closed meticulously with absorbable sutures.

Once hemostasis is achieved, the renal capsule is approximated and sutured with absorbable sutures (Fig. 98.11b). Hemostatic agents, such as Floseal®, Tisseel®, or Surgicel® can be of additional help to control hemostasis.

Heminephrectomy is now accomplished without having interrupted the circulation to the lower moiety.

Following this procedure, the upper pole ureter is dissected towards its distal portion as far as possible. The dissection line is kept close to the diseased ureter in order not to disturb the lower pole ureter blood supply. If the ureter

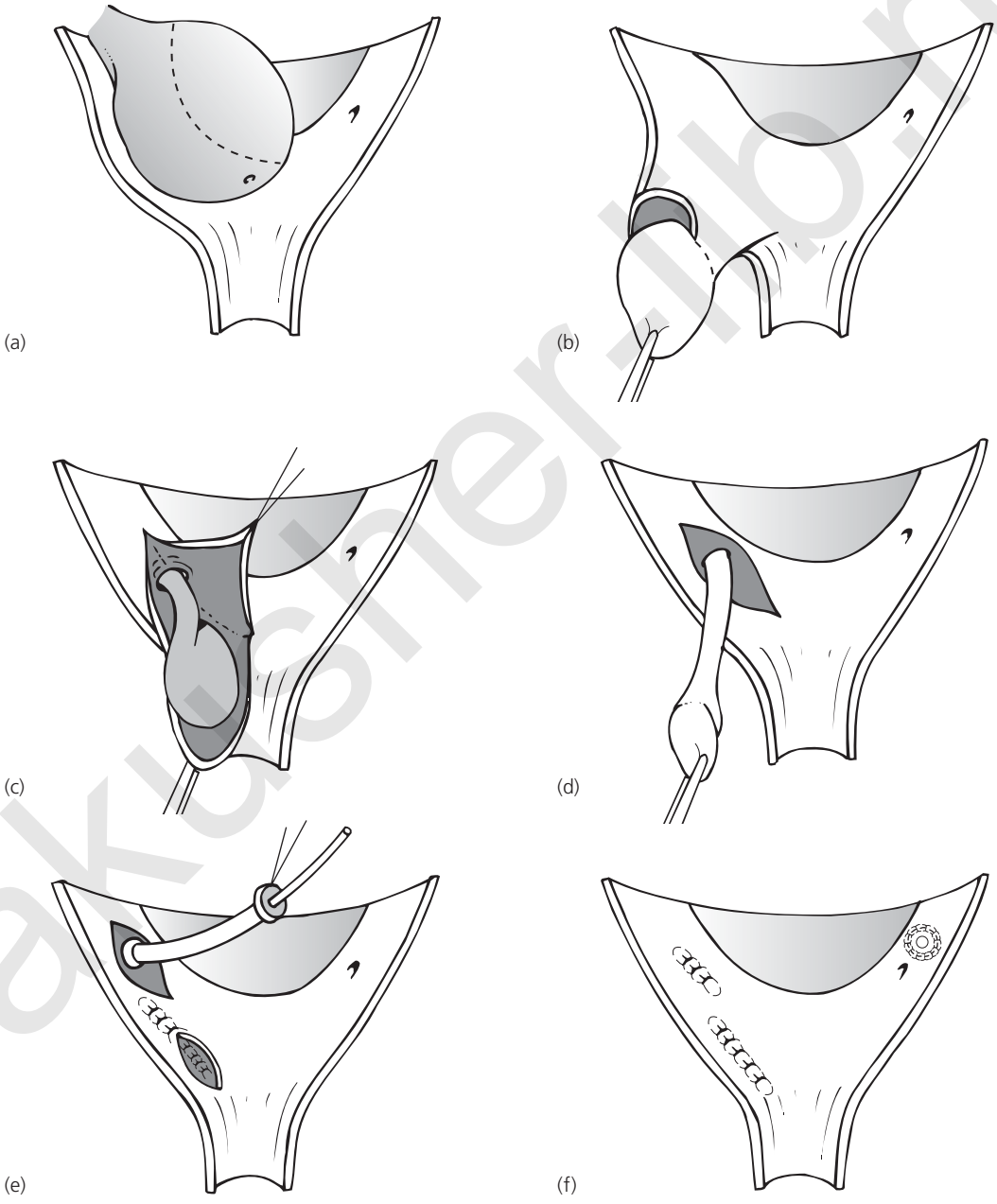


Figure 98.10 Operative treatment: ureterocele enucleation. (a) Planned elliptical incision on the dome of the ureterocele. (b) The ureterocele is held with stay sutures and the elliptical incision is performed. (c) A plane between the wall of the ureterocele and the urothelium or the detrusor muscle is dissected. (d) The intramural ureter of the upper moiety is mobilized, taking care not to damage the lower moiety ureter. (e) Reconstruction of the detrusor muscle backing the ureterocele and the urothelial defect. (f) The lower moiety ureter is reimplanted according to Cohen's technique, creating a transverse suburothelial tunnel.

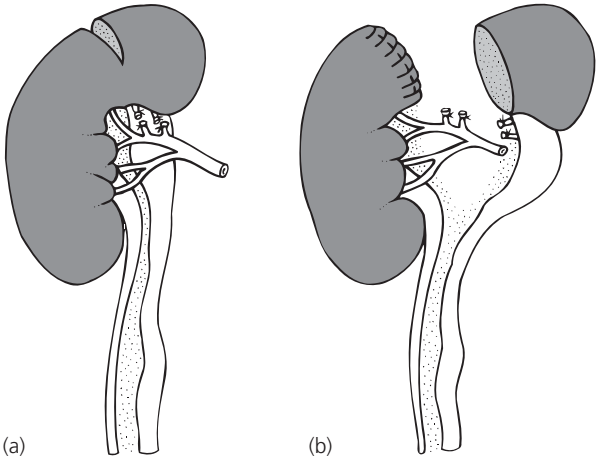


Figure 98.11 Operative treatment: heminephrectomy. (a) Transverse resection of the affected upper renal moiety of a duplex system; (b) after hemostasis, the renal parenchyma and the renal capsule are closed, often over a bolster of hemostatic material.

refluxes, it is ligated and transacted, but if it is obstructed it is transacted without ligation to prevent infection.

Once the heminephro-ureterectomy is completed, a drain can be placed according to the surgeon's preference and the muscular layers are approximated using continuous 3-0 or 4-0 resorbable sutures. The subcutaneous tissues are approximated and the skin closed with a subcuticular suture.

Percutaneous drainage

Percutaneous drainage of systems with ureteroceles is generally only indicated in cases in which the patient is acutely ill and endoscopic puncture is not an option due to small urethral size or the inability to undergo anesthesia.

SUMMARY

Ureteroceles are a fairly common urologic finding. The management of the ureterocele can be quite complex and needs to be individualized for the patient and their condition, as well as the findings of imaging and functional studies.

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99

Posterior urethral valves

PAOLO CAIONE AND VALENTINA DE PASQUALE

INTRODUCTION

The main cause of urethral obstruction in neonates and infants is related to posterior urethral valves (PUV) and these continue to be a significant cause of morbidity and mortality in the pediatric age patients.[1,2] In males, children born with bladder obstructive uropathy and renal dysplasia represent the single largest group undergoing renal dialysis and transplantation under five years of age. End-stage renal disease develops in a significant proportion, varying from 30 to 42%.[1–3] In 2003, the Italkid Project, consisting of a prospective population-based registry assessing the epidemiology of chronic renal failure (CRF) in 1197 children recruited over ten years, showed that renal hypodysplasia, with identified congenital uropathy, was the most common cause of CRF (43.6%): in this group, PUV was second only to vesico-ureteral reflux (VUR), accounting for 23.8%.[4]

HISTORICAL NOTES

Congenital obstruction of the posterior urethra has been recognized for almost 200 years, and the earliest description of this condition in infants was by an Italian anatomist in 1717, Giovanni Battista Morgagni.[5] At the beginning of the nineteenth century, Langenbeck described infravesical urethral obstruction in 1802 in his monograph on stone disease,[6] and a few years later, in 1832, Velpeau coined the term 'valves'.[7] Subsequently, many reports of posterior urethral obstruction can be found in the literature. The most important contribution to define the anatomical aspects of the valves was made by Hugh Hampton Young in 1919[8] and 1929.[9] Young was the first to clearly describe the features of PUV. The description included the first classification of this entity based on his initial report of 12 patients, and a review of the literature.[8] The Young classification distinguished congenital obstruction of the posterior urethra on three types of valves (types I, II, and III), and which he described in detail (Fig. 99.1). In more recent years, some criticism arose from the analysis of Young's original work, revealing disagreement with his original conclusions.[10–15] In fact, recent post-mortem dissection studies from different authors have suggested that congenital obstruction of the posterior urethra is due to a membrane with a posterior defect and paramedian reinforcements.[16–18] Contribution to a better anatomical definition of PUV and urethra diaphragm was given more recently by Dewan *et al.*,[19,20] who identified the morphological evidence of the congenital membrane obstructing the male posterior urethra (see below under Classification). However, Young's classification, although not anatomically precise, is known worldwide and is still in current use.

EPIDEMIOLOGICAL DATA

Epidemiology of PUV is difficult to define, as most authors believe that only those with typical appearance on voiding cystourethrograms (VCUG) should be included. The incidence of PUV is often reported as 1:5000–8000 infant males.[18,19,21] A multicenter review in the United Kingdom between 1970 and 1980 estimated the incidence to be approximately one in 25000 live births,[22] but this value seems to be an underestimate. The point is that the true incidence of congenital posterior urethral obstruction is difficult to ascertain.

The lesion could be more common than previously thought: this is due to the fact that the widespread use of prenatal and postnatal ultrasonography and of VCUG during the recent decades led to recognition of a higher number of congenital valves, diaphragms, or strictures on the male posterior urethra, not always recognized as classic 'valves'.

Moreover, the frequent observation at endoscopy or at VCUG of 'mild' or 'minor' forms of inframontanal 'plicae' or mucosal folds, responsible for partial or little urinary outflow impairment, is nowadays a more common observation in male children and infants, as a consequence of the increasing use of cysto-urethroscopy. Thus, the full spectrum of congenital posterior obstruction is probably twice as frequent than previously thought.[21]

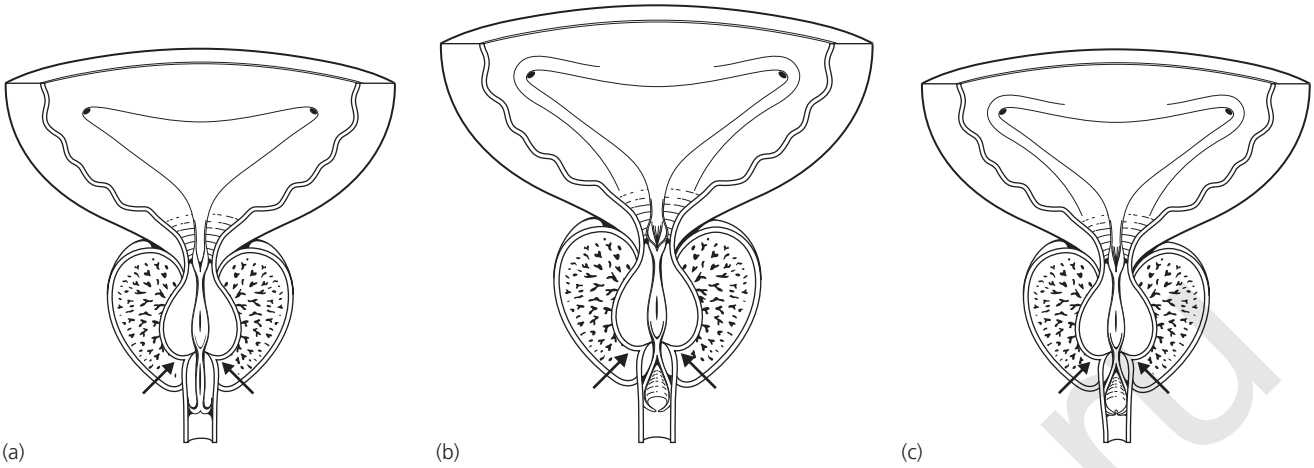


Figure 99.1 Posterior urethral valves: the original classification proposed by Young in 1919 as three types.[8,9] Reproduced with permission from Macpherson RI, Leithiser RE, Gordon L, Turner WR. Posterior urethral valves: an update and review. *Radiographics* 1986; **6**: 753–91.

EMBRYOLOGY

Obstruction of the male posterior urethra is a congenital abnormality, which is considered to have no genetic basis and no pattern of inheritance. There is no agreement as regards the true embryogenesis. It has been argued that posterior valves could originate from an abnormality of development during formation of the urogenital sinus.[23] Livne *et al.*[24] proposed that the embryogenesis of the valves arise from the plicae colliculi diverging from the distal end of the verumontanum appearing at 11 weeks' gestation (mesonephric Wolffian duct). Field and Stephens[25] believed that valves could be vestiges of the receding Wolffian ducts, which migrated posterolaterally to converge on the posterior wall of the urethra, creating the inferior urethral crests. Fusion of these folds anteriorly would explain the formation of a membranous obstruction with a posterior deficit, as described by Dewan.[20] A detailed review of the literature has been recently undertaken by Krishnan *et al.*,[26] better elucidating the precise origins regarding the anatomy, classification and embryology of PUV. Anyway, the embryological development of the congenital posterior urethra obstruction in male fetuses and infants remains uncertain. With the advent of more accurate imaging techniques, such as ultrasonography, VCUG, and fetal/infant magnetic resonance imaging (MRI), the obstructive membranes of posterior male urethra are now better defined. It has been hypothesed that the severity of the congenital diaphragm obstructing the urethra is variable, consistent with the differential clinical presentation of PUV. In some cases, the membrane only partial obstructs, whereas in other situations it may totally obstruct, as in infants with severe renal sequelae.[26] When a feeding tube or catheter is passed into the newborn urethra, the oblique membrane could be ruptured ventrally, modifying the appearance into the Young's classic valves.[26]

CLASSIFICATION

Classically, Young and colleagues in 1919 divided PUV into types I, II, and III, based primarily on autopsy findings.[8] Young described type I valves as sails or strong plicae colliculi, which extend distally from either side of the verumontanum to attach to the anterolateral walls of the urethra; type II valves are folds that arise from the verumontanum and pass proximally towards the bladder neck where they divide into fin-like membranes; type III valves are diaphragms with a central perforation located distal or proximal to the verumontanum, but not attached to it (Fig. 99.1).

Most authors agree that Young's classification is incorrect. In particular, the existence of type II valves has been questioned, as these plicae should be considered as normal mucosal folds.[13–18]

The type I valves are the most commonly recognized. The clinical description of a valve with two separate leaflets is derived from autopsy specimens in which the urethra is laid open by cutting through the anterior wall. However, when viewed endoscopically, it is seen to be a single structure originating from the inferior margin of the verumontanum, the lateral folds fusing anteriorly to form a slit-like aperture. Dewan and colleagues, in accurate endoscopic studies, demonstrated that the commonly defined PUV are represented by a single membrane with a posterior defect, distal to the verumontanum, but connected to it by mucosal folds. Dewan proposed the term 'congenital obstructive posterior urethral membrane' (COPUM) to define this lesion.[19,20,27,28]

Type III valves are considered very uncommon and represent a severe form of urethral obstruction.[16] In a review of cysto-endoscopies of boys with urethral obstruction, Dewan described a fibrous membrane without attachment to the verumontanum, with a central defect below the verumontanum in the bulbar urethra.[19,20] These lesions are known as a Cobb's collar,[29] Moormann's ring,[30] or congenital

bulbar urethra stricture, but should be distinguished from the COPUM or misnamed type III valves, that have a posterior defect at the level of the lower aspect of the prostatic urethra.[27,28]

In conclusion, nowadays we consider PUV as a spectrum of anatomical and pathological entities, presenting different severity of urinary outflow obstruction and having probably only two structural features:

1. a membrane at the level of the posterior urethra distal to the verumontanum, with connecting folds and a posterior defect (COPUM);
2. a fibrous membrane in the bulbar urethra with a central defect (Cobb's collar).

PATHOPHYSIOLOGY AND SECONDARY CONSEQUENCES

Congenital posterior urethral obstruction interferes with all the lower and upper urinary tract, causing significant anatomical and functional changes. In pediatric urology, PUV could represent a severe congenital uropathy, with lifelong consequence.

Urethral pathology

Valves of the posterior urethra represent a spectrum of lesions within the male urethra, grouped under the more extensive term of congenital obstructive posterior urethral membrane.[20,28] The macroscopic appearance has been described above under Classification. The severity of the obstruction varies from small folds without obstruction to unyielding and hard membranes with a small deficit, causing a high degree of outlet obstruction.[31] The valves cause a mechanical and functional obstruction in the urethral conduit, leading to sequential secondary pathological changes. The heaviness of the secondary pathological changes on the upper urinary tract will depend on the degree and timing of the primary obstruction.

Proximally to the obstructive valves, high back-pressure prenatally determined, is responsible for significant changes on the anatomical appearance. The prostatic urethra is enlarged and elongated and the verumontanum is much more evident; the posterior aspect of the bladder neck is very pronounced, as a consequence of muscular hypertrophy, and it could also cause impaired bladder emptying after removal of the urethral obstruction.

The severity of the pathological changes on the urethral and bladder structures and on the upper tract, depends on the degree and timing of the primary urethral obstruction that is considered to have an early onset during the embryological life (16–18 weeks of gestion).[26]

Secondary pathology on bladder and upper urinary tract

Not only does the posterior urethra dilate and elongate secondarily to the congenital urethral obstruction, but also the bladder, the ureter, and the kidneys will present significant structural and functional consequences.

Bladder secondary changes

The congenital urethral obstruction is responsible for significant changes on the bladder reservoir, with consequences on the upper urinary tract and on the renal parenchyma. These changes may persist, although the primary urethral obstruction could be fully solved. As the valves are formed very early in fetal life, the abnormal condition of high endoluminal pressure and overdistension of the urinary structures leads to a pathological development and dysfunctional activity of the entire urinary tract and of the renal parenchyma.[29] Experimental studies on fetal lambs demonstrated the induction of renal parenchyma dysplasia and significant histological and functional bladder changes.[32] Bladder dysfunction may present a variety of forms, changing over the years, before and after puberty.[33]

Macroscopically, the bladder wall presents trabeculations as a consequence of hypertrophy of the muscular components and of the high-pressure regimen. Histologic studies of the bladder wall have shown increased collagen and connective tissue elements within the muscular cells. The collagen/muscular ratio could be increased with reduced muscular components of the bladder wall. The overall structural and functional changes of the bladder, that persist after urethral obstruction release, was named 'valve bladder syndrome'.[34]

Ureteral pathology

Dilatation of one or both ureters is often seen in newborns or infants presenting with PUV. Ureteric dilatation may be due to vesico-ureteric reflux, vesico-ureteric junction obstruction, or inefficient ureteric drainage secondary to high vesical pressures. These changes may persist following valve removal[35] and the ureters may remain enlarged and tortuous, with thickened and rigid walls (Fig. 99.2).

Vesico-ureteric reflux

Reflux is frequently associated with PUV. It has been reported in 19–78% of children[36–40] and is thought to be due to the high-pressure regimen in the prenatally obstructed bladder (Fig. 99.3). Once the urethral obstruction has been resolved, a significant proportion of patients is expected to have resolution of their reflux.[41] Thus, a conservative approach to VUR in children with previous valves or diaphragm on posterior urethra is strongly recommended in infancy and early childhood. The incidence of bilateral and unilateral reflux is almost equal; however, bilateral reflux and posterior urethral obstruction denotes a more severe disease with a higher grade of renal parenchymal involvement and risk of CRF.[41]

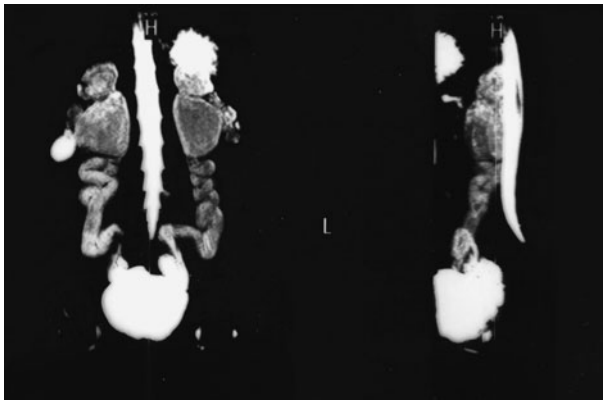


Figure 99.2 Magnetic resonance image of urinary tract in a five-year-old boy, born with posterior urethral valves ablated shortly after birth: the pyelocaliceal system remains bilaterally dilated, with ureters enlarged and tortuous.

'VURD' syndrome

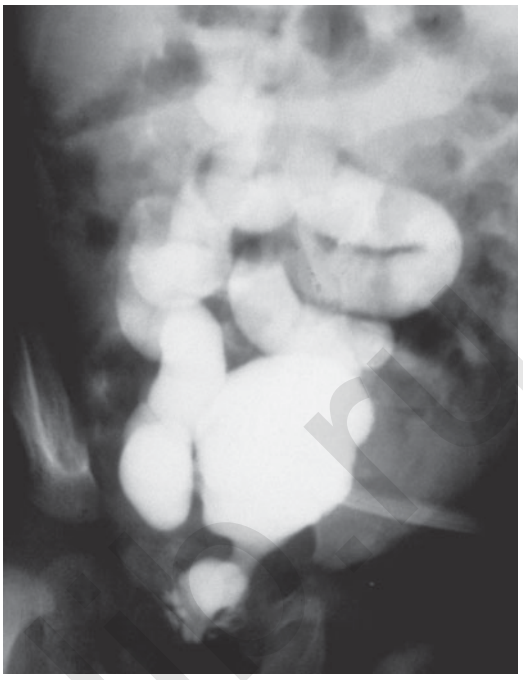
John Duckett and others focused on the protective factors in PUV, stating that unilateral reflux denotes less severe disease, although the VUR is usually high grade and ipsilateral renal parenchyma is very damaged and dysplastic.[38,42] In fact, in such cases, the contralateral side is protected by the 'pop off' mechanism which keeps bladder pressures low.[42,43] The kidney on the side affected with reflux is usually non-functioning as a result of dysplasia (Fig. 99.4). VUR and renal dysplasia in posterior urethral obstruction could be a primary event due to abnormal location of the ureteric bud arising from the Wolffian duct. More probably, the pathogenesis of unilateral renal dysplasia in the VURD (vesico-ureteral reflux and dysplasia) syndrome is due to the high-pressure regimen of the upper urinary tract, which starts very early during the fetal life, with consequent impairment of the renal parenchymal maturation.[43]

Renal dysplasia and hydronephrosis

Renal damage is very frequent in PUV and it can be attributed to a variety of reasons:

- primary renal dysplasia;
- renal dysplasia induced by early intrauterine bladder outlet obstruction;
- VUR or uretero-vesical obstruction;
- postnatal urinary tract infection;
- persistent bladder dysfunction.

Association between renal dysplasia and hydronephrosis can be seen as a consequence of severe obstructive posterior valves or urethral diaphragm. Renal dysplasia is typically associated with abnormal histology and is not reversible. Hydronephrosis and stasis secondary to obstructive uropathy has normal renal histology and is reversible with treatment. Whether renal dysplasia is a primary event, or is secondary to urinary obstruction, has not been established. Using a fetal lamb model, Beck[44] has given experimental evidence that



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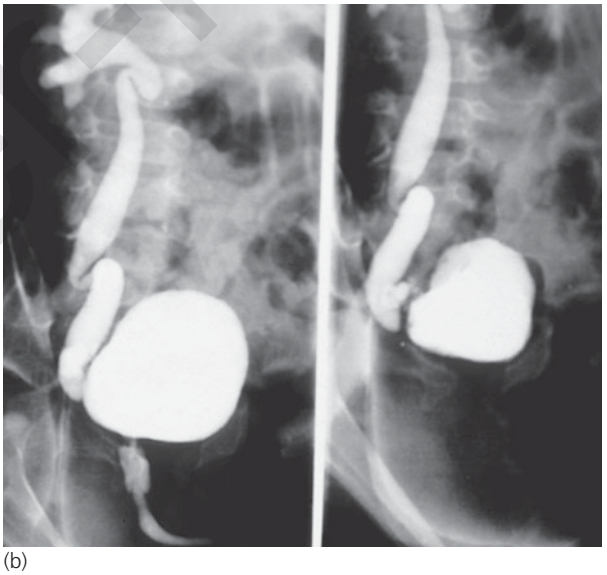
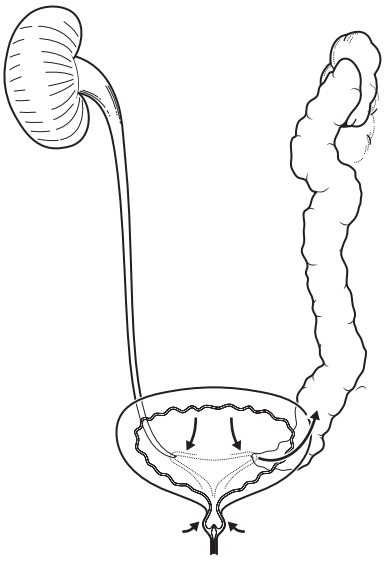


(b)

Figure 99.3 (a) Micturating cystogram at birth: gross bilateral posterior urethral valves with enlarged trabeculated bladder presenting with congenital posterior urethra obstruction, before valve ablation. (b) Micturating cystogram of the same patient at four years of age: normalization of the bladder and urethra outline, with persisting right posterior urethral valve.

early obstruction of the developing kidney results in dysplastic changes, while obstruction in the latter half of embryogenesis results in hydronephrosis.

On the other hand, Hoover and Duckett[43] described that frequent association of posterior urethral obstruction, reflux, and renal dysplasia suggested a common embryological error. Henneberry and Stephens[45] proposed that renal dysplasia associated with posterior urethral obstruction is not secondary to reflux or high pressures, but a primary embryologic malformation that is the result of an abnormal position of the



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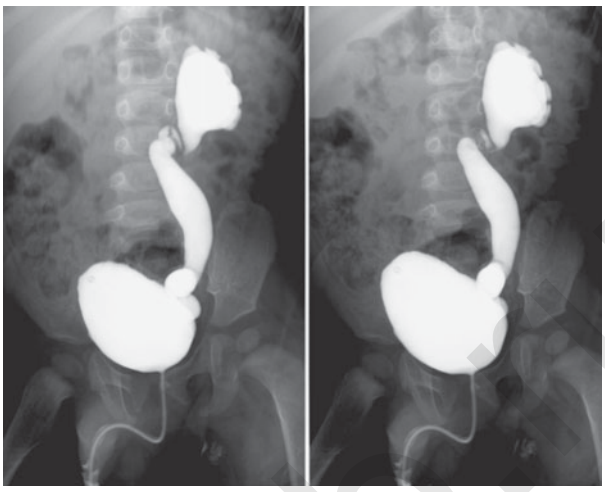

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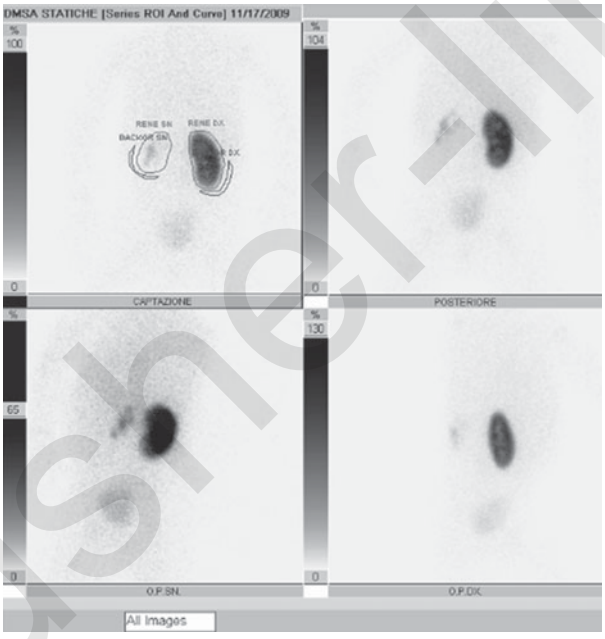


(c)

Figure 99.4 (a) The VURD syndrome (valve, unilateral reflux, dysplasia) as a protective factor for the contralateral kidney and bladder activity.[43] (b) Left severe posterior urethral valves in a six-month-old infant with previously ablated posterior urethral valves: normal light kidney. (c) Poor functioning left kidney at DMSA scan.

primitive urethral bud. This pathogenetic theory may be the reason why the long-term outcome does not depend on management but on congenital embryological status.[2,3,36]

Early bladder outlet obstruction, as in PUV, can also produce impaired tubular function. Pediatric nephrologists and urologists from the Great Ormond Street Children's Hospital in London observed that defective urine concentration occurs in as many as 60% of boys with urethral obstruction, and is severe in 15%.[46] The resultant concentrating defect causes high urinary output and sodium loss and the severe polyuria carries a risk of dehydration and electrolyte imbalance. Furthermore, high urine output may increase the overload of work of lower tract and enhance the bladder dysfunction, causing incontinence and further renal damage in an attempt to obtain dryness in toilet-trained boys and adolescents.[35] This clinical picture was named 'valve bladder' syndrome.[47]

These secondary consequences on pathophysiology of kidneys and lower urinary tract in boys with previous valves have a significant role in the management of these patients after obstruction removal.[47]

Pulmonary hypoplasia

During the pregnancy, oligohydramnios secondary to decreased fetal urine output produces an abnormally small

uterine cavity. This compresses the fetus and interferes with the normal growth and expansion of the fetal thorax, resulting in pulmonary hypoplasia. The kidneys themselves have an important role in early lung growth, while the presence of amniotic fluid contributes to growth later in gestation. The amniotic fluid index (AFI) is an important marker of renal physiology during pregnancy. If severe oligohydramnios is present in early fetal life (19–26 weeks' gestation), repeated maternal amnioinfusions or fetal bladder shunting may be considered, in an attempt to prevent lung maldevelopment. Preliminary hypoplasia represents the main cause of postnatal death in newborns with severe PUV or other congenital obstructions of the urethra.

CLINICAL FEATURES

Over the last three decades, advances in antenatal diagnosis have resulted in an increase in the number of babies with urinary tract obstruction being diagnosed either *in utero* or within the first few days of life, some of whom have posterior urethral obstruction. The ultrasonographic features of bilateral hydronephrosis in a male newborn with dilated and winding ureters, associated with enlarged and poor emptying bladder with thickened walls is very suspicious for PUV or urethral diaphragm (Fig. 99.5).

Nowadays, the picture of a very sick newborn, who is admitted as an emergency into the neonatal intensive care unit, is uncommon, as urethral obstruction is usually suspected by the pre- and postnatal ultrasonographic screenings which are offered in the more developed countries.[18,23] Classically, in the neonatal period, the baby may present with urinary tract infection, septicemia, uremia, and metabolic acidosis. Urinary symptoms may include a poor urinary stream, which can be an unreliable sign as some infants with severe obstruction have developed detrusor hypertrophy, enabling them to have a good stream. Quite often, the bladder and/or kidneys are palpable in infants with bladder outlet obstruction.

More commonly, infants with PUV can present with chronic urinary stasis and upper tract changes, vomiting, failure to thrive, and loss of weight. Rarely, they may present

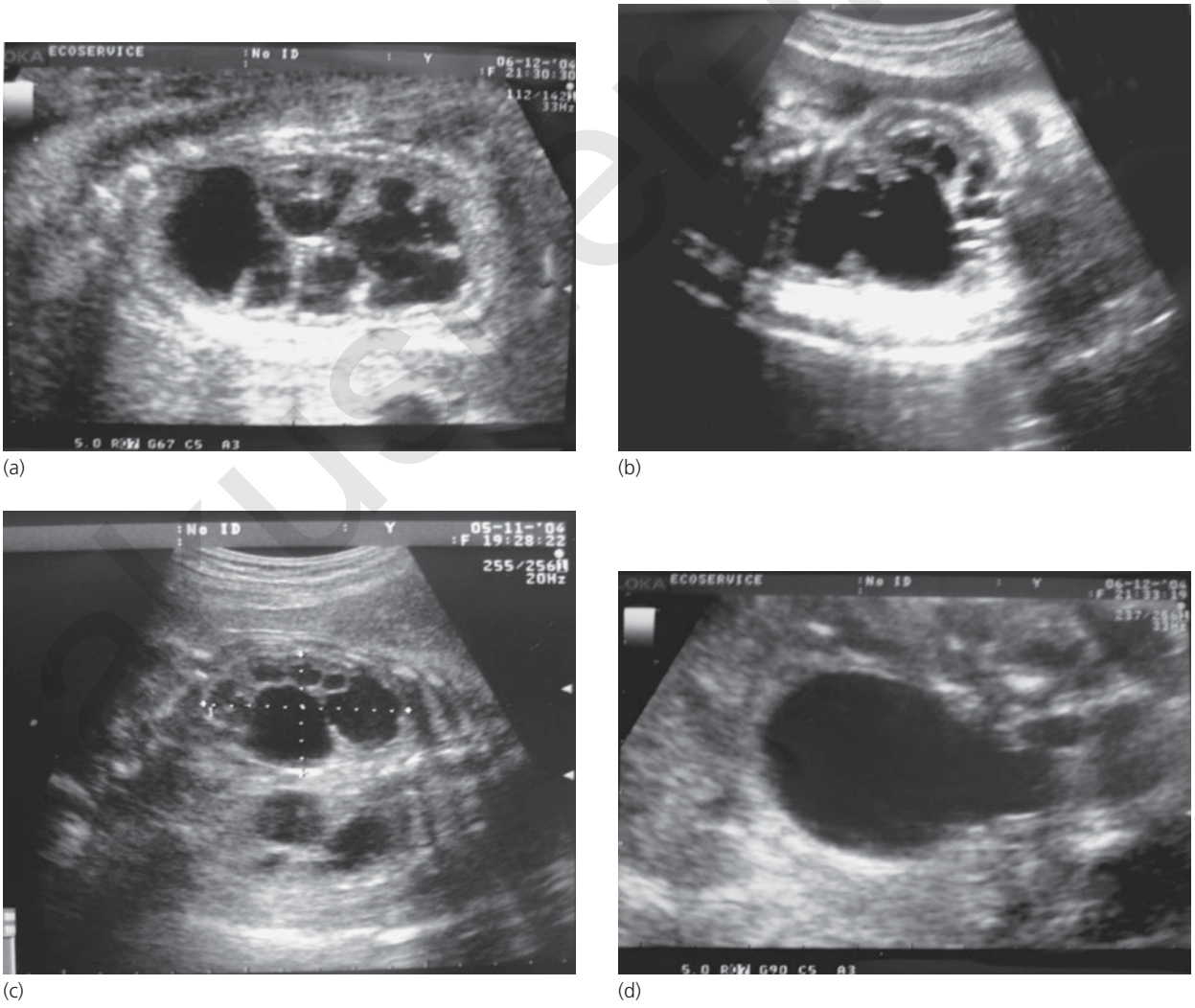


Figure 99.5 Prenatal ultrasonographic pictures of fetal urethra obstruction. (a,b,c) Bilateral hydronephrosis in a male newborn, with dilated ureters. (d) Enlarged and poorly emptying bladder, presenting thickened walls and wide bladder neck.

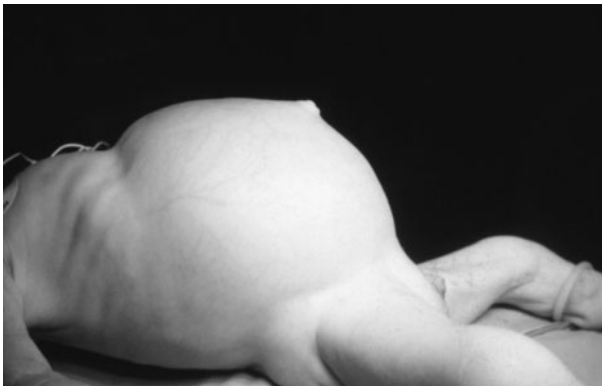


Figure 99.6 Picture of a very sick newborn, with severe abdominal distension due to urinary ascitis from congenital posterior urethral obstruction.

with abdominal distension due to urinary ascites or perirenal urine collection. Urinary ascites is usually a result of perforation of the kidney and in many instances the site of actual leak is not obvious radiologically. The newborn may present with severe abdominal distension, due to urinary tract dilatation and/or urinary ascitis (Fig. 99.6). A dyspneic or polypneic breathing is often observed, as a consequence of pulmonary dysplasia, metabolic acidosis, and abdominal distension.

INVESTIGATIONS

Ultrasound scan is the first diagnostic step, that is often suggested by the prenatal sonographic studies during pregnancy. The ultrasound should be perfomed at the earliest opportunity. The kidneys are scanned to determine the severity of hydronephrosis and to identify any perineal collections of urine. The dilated ureters can be traced down to the bladder. In an uncatheterized patient, a dilated posterior urethra can be demonstrated by a perineal sagittal scan. The bladder is thick-walled and with irregular edges, caused by the presence of pseudodiverticula (Fig. 99.7).

After birth, once the infection has been brought under control, the diagnosis can be confirmed by a **micturating cystogram** that is the gold standard for the diagnosis of posterior urethral obstruction. The examination should be performed to record the micturition in the lateral oblique position. The following features can usually be demonstrated (Fig. 99.8): trabeculated bladder walls, poorly emptying, and dilatation and elongation of the posterior urethra, with prominence of the bladder neck, particularly the posterior lip. VUR may be present in many infants (Figs 99.3 and 99.4).

Intravenous pyelogram is no longer performed in infants and young children, as it has been replaced by ultrasound and radionuclide studies. Useful anatomical information on ureters for boys requiring upper tract surgery or bladder enlargement can be obtained by **magnetic resonance imaging** studies (Fig. 99.2).

Radionuclide studies should not be performed in the neonatal period, but are very useful to assess the later functional status of both kidneys and to guide the urologist's

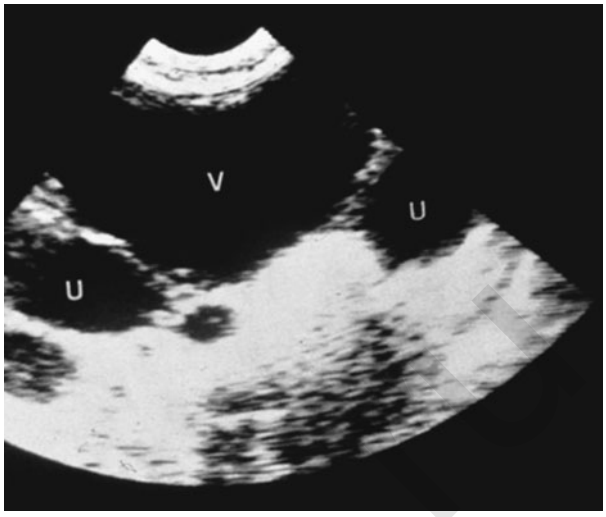


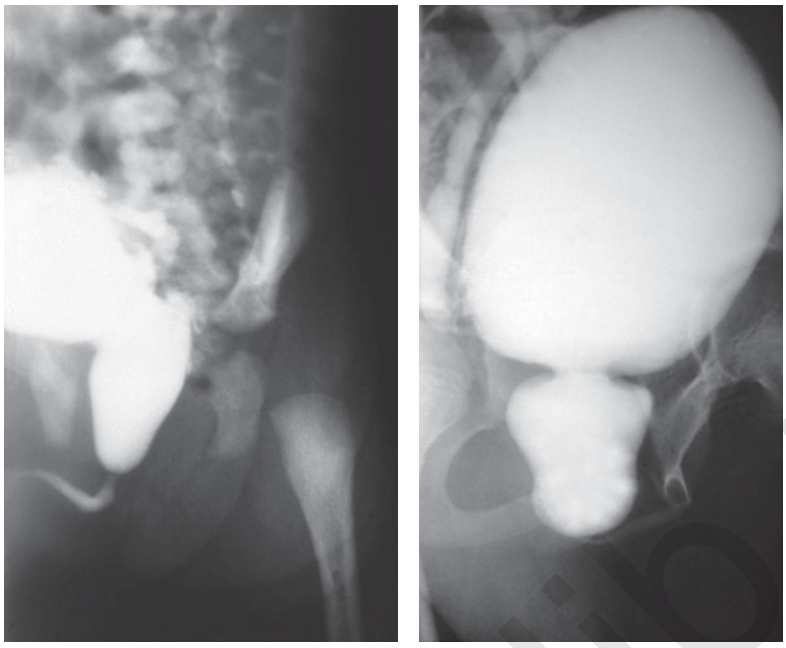
Figure 99.7 Ultrasonographic findings in an infant with posterior urethral valves: bilateral hydronephrosis, enlarged ureters with distended bladder.

decision on upper tract repair and on the decision for nephrectomy (VURD syndrome). In infants in whom a postoperative ultrasound scan shows no improvement, a MAG3 scan may help to distinguish between persistent obstruction and cystic dysplasia. The uptake is negligible in dysplasia. A renogram should be performed to assess the differential glomerular filtration rate, and the uretero-vesical or pyelo-ureteral junction obstruction.

Urodynamic investigations are not usually performed in the neonatal age or before valve ablation, but are essential for the outcome evaluation of bladder changes over time.[48] Urodynamic studies are necessary to investigate the functional manifestation of the valve bladder syndrome and their relationship with urinary incontinence, voiding dysfunction and upper tract persisting dilatation. From initial patterns of hypercontractility in infancy and early childhood, bladder activity may gradually change to hypocontractility in many boys, expecially after puberty (Fig. 99.9).[49] The overdistended bladder in adolescence may lead to decompensation and increasing post-micturition residual and maximum bladder capacity. Upper tract persisting dilatation is a possible severe consequence, necessitating drug manipulation and/or intermittent catheterization.[35]

PRENATAL DIAGNOSIS AND MANAGEMENT

The prenatal suspicion of urethral obstruction in a male fetus has enabled evaluation and treatment to begin before the onset of infection, electrolyte abnormalities, and renal failure in the newborn. With the introduction of screening ultrasonography and improvement of technology, an increased level of expertise in detecting fetal urological abnormalities has been reached. A more frequent *in utero* diagnosis of PUV is now feasible.[50] Classic sonographic findings of PUV include a combination of megacystis, thickened bladder wall, dilated posterior urethra with the 'keyhole sign', and bilateral hydronephrosis in a male fetus (Fig. 99.10). Oligohydramnios may be associated in more severe forms.[51]



(a) (b)

Figure 99.8 Micturating cystogram imaging in posterior urethral valves. (a) Trabeculated bladder walls, dilatation and elongation of the posterior urethra, and sharp-cut reduced lumen of the urethra distally to the obstructing membrane. (b) Late presentation of posterior urethral valves, with prominence of the bladder neck and wide prostatic urethra. Right vesico-ureteral reflux is present.

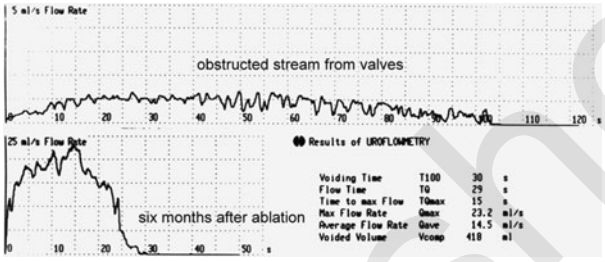


Figure 99.9 Uroflowmetry in a four-year-old child with posterior urethral valves. Reduced flow-rate at presentation and normal pattern at six months after ablation.

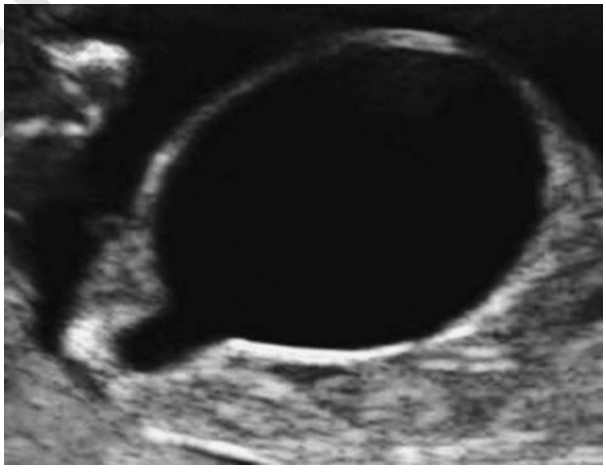


Figure 99.10 The 'key-hole sign' of the fetal bladder at prenatal ultrasonography: poorly emptying megacystis, with thickened bladder wall and dilated posterior urethra in a male fetus.

Even in the absence of these signs, antenatal diagnosis of urethral obstruction can be considered, especially in the presence of a constellation of findings including oligohydramnios and evidence of spontaneous urinary tract decompression (ascites, perirenal urinoma) (Fig. 99.11).

Urethral obstruction *in utero* produces a wide variety of clinically significant effects in addition to obvious obstructive uropathy. Fetal urine is produced by the 13th gestational week, a decreased production of which results in an abnormally small uterine cavity. This compresses the fetus and interferes with normal growth and expansion of the fetal thorax, resulting in pulmonary hypoplasia. Bladder distension and urinary ascites expand the fetal abdomen and compromise the development of the abdominal wall muscle, resulting in the prune belly appearance. In conclusion, prenatal ultrasound can accurately detect fetal lower urinary tract obstruction, with a sensitivity of 95% and a specificity of 80%.[52,53] MRI may be increasingly used in the diagnosis and assessment of fetuses with lower urinary tract obstruction, enhancing the ultrasound findings.

Pulmonary and renal consequences vary in severity with the degree of urethral obstruction *in utero*; where high-grade oligohydramnios and pulmonary hypoplasia develop this leads to postnatal respiratory insufficiency and death. In less severe cases, enough urine passes to give a sufficient amniotic fluid volume to allow adequate pulmonary growth.

The advantage of prenatal diagnosis is considerable. The maternal and fetal management can be planned early, which usually results in maternal transport to a tertiary

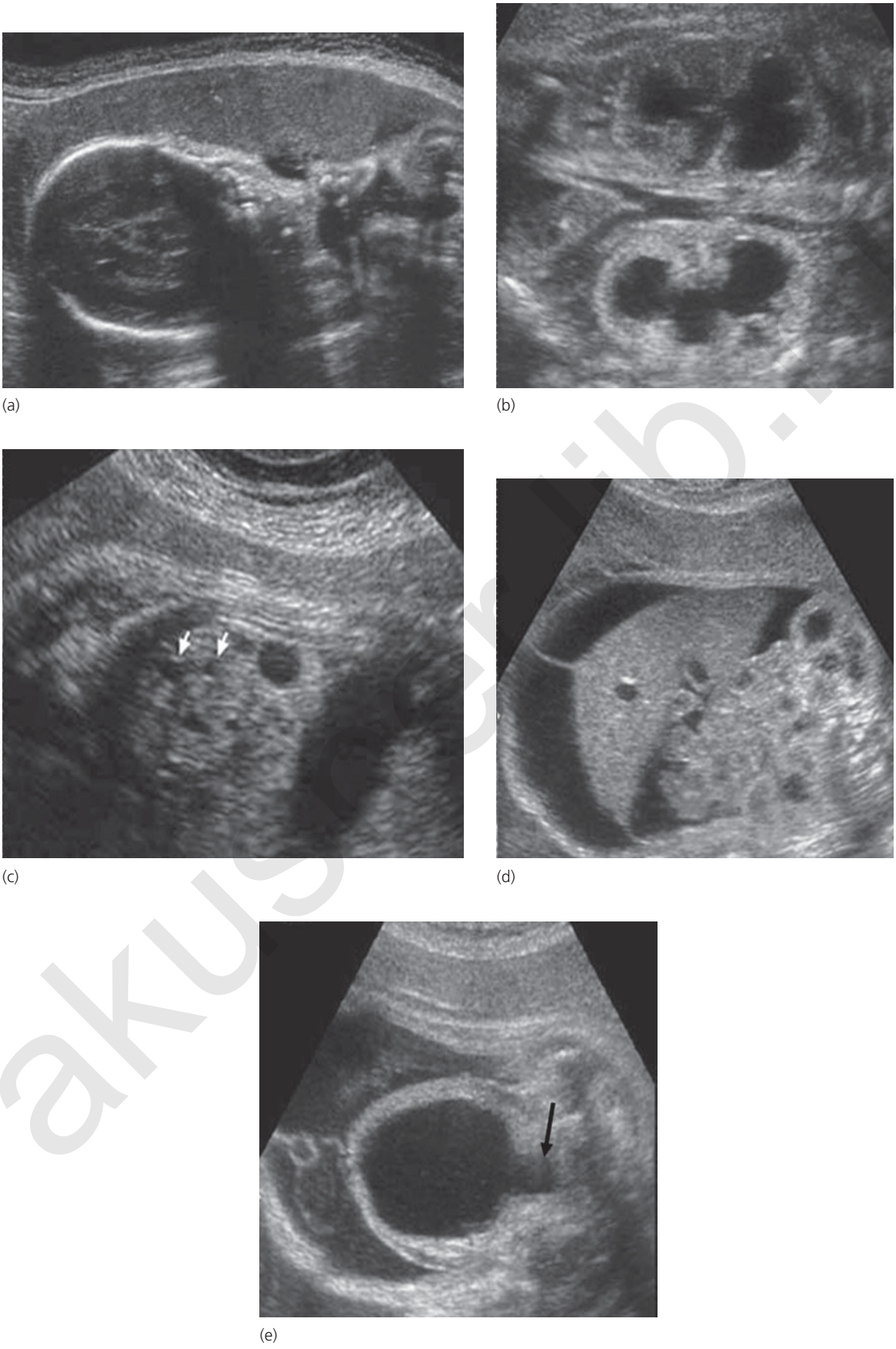


Figure 99.11 Prenatal ultrasonographic pictures. (a) Severe oligohydramnios; (b) bilateral hydronephrosis; (c) dysplastic kidneys; (d,e) fetal urinary ascites with enlarged thickened bladder.

center where the newborn can receive optimal treatment immediately after birth. A flow chart on the prenatal management of PUV is presented in Fig. 99.12.

Fetal lower urinary tract obstruction is a condition of high mortality and morbidity, associated with progressive renal dysfunction, oligohydramnios, and secondary pulmonary hypoplasia. Intrauterine intervention is now possible and was developed from the pioneering research of Harrison and co-workers.[46–48] The most difficult problem has been the selection of the fetus with obstructive uropathy, who might benefit from *in utero* treatment. Studies of the natural history of untreated congenital hydronephrosis have shown that the fetus with mild bilateral hydronephrosis and normal amniotic fluid volume requires no *in utero* intervention. Also, the fetus who presents with severe oligohydramnios and severely dysplastic kidneys sonographically is unlikely to benefit from antenatal intervention. Between the two groups, cases with obstructive uropathy can be observed, where potentially fatal renal and pulmonary damage may be averted by intervention. Prognostic criteria have been developed by Glick *et al.*[54] (Table 99.1). Fetal urine analysis may provide improvement in prenatal determination of renal prognosis. However, precise criteria to guide prenatal management remain uncertain.[55] Further predictors of renal dysplasia have been examined in fetal obstructive uropathy, as bladder pressure and beta$_2$-microglobulin assessment, to achieve prenatal evaluation of fetal renal function.[55,56]

Table 99.1 Favorable prognostic criteria of prenatally detected posterior urethral valves.

Urinary electrolytes	$Na^+ < 100$ mmol/L $Cl^- < 90$ mmol/L
Fetal osmolarity	< 2/0 mOsm/L
Beta$_2$-microglobulin	< 5 mg/L
Renal parenchyma ultrasound	Preserved appearance or mild hyperechogenicity. No cortical cysts
Amniotic fluid (AFI)	Normal or slightly reduced
Diuresis	> 2 mL/h

Modified from Ref.[54]

It is now possible to decompress the obstruction *in utero*, through percutaneous vesico-amniotic shunting or cystoscopic techniques.[57] Quintero and colleagues[58] focused technique and results on the insertion of a vesico-amniotic shunt passed either percutaneously using ultrasound or via a fetoscope, allowing the bladder to decompress into the amniotic cavity. The International Fetal Surgery Register of

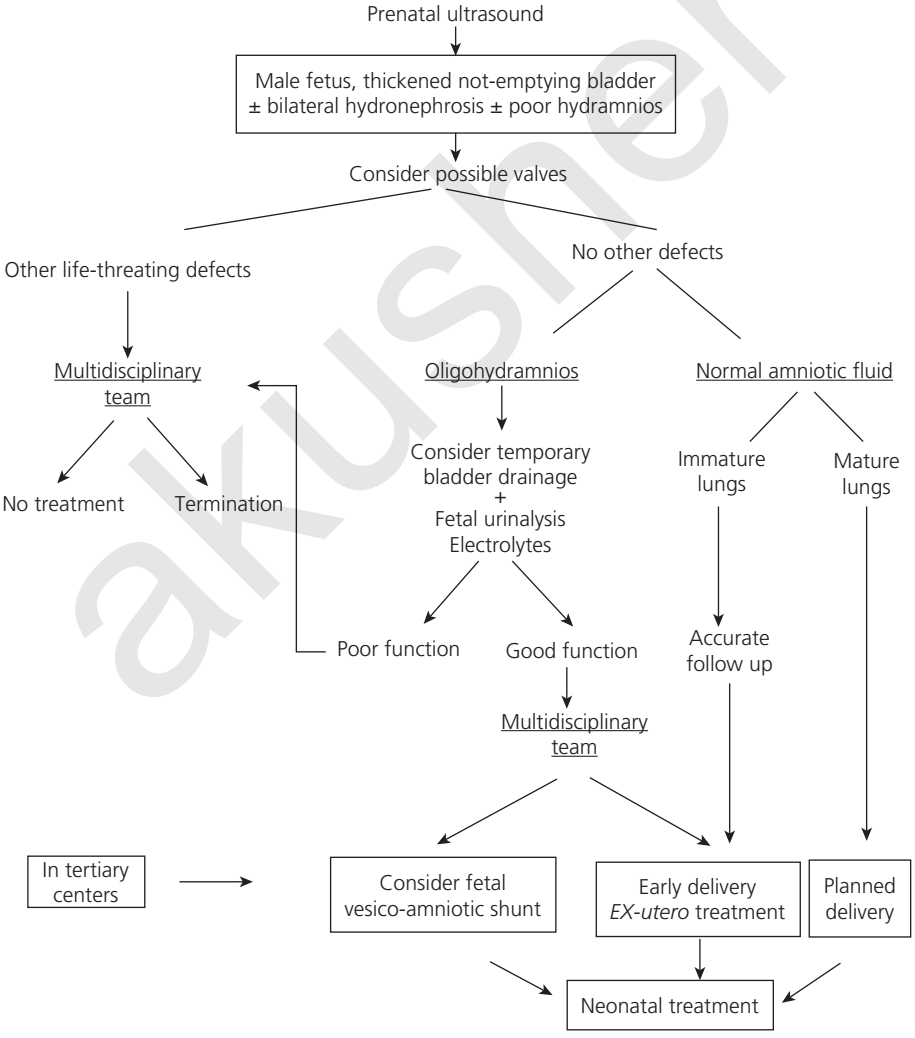


Figure 99.12 Posterior urethral valves: prenatal diagnosis and management.

1985 reported 73 cases of fetal obstructive uropathy treated by *in utero* placement of a vesico-amniotic shunt. The shunts are not satisfactory for long-term fetal urinary tract decompression due to the high incidence of catheter obstruction, displacement, and risk of chorio-amnionitis.[59] Today, it has been demonstrated to be possible to perform endoscopic ablation of PUV *in utero*.[60]

In conclusion, in appropriately selected fetuses, prenatal intervention may improve perinatal survival, but long-term renal damage remains mostly unsolved. Randomized multicentric studies are warranted.[61] Currently, the initial enthusiasm has been reduced by the poor ability to modify the long-term outcome for the severely affected newborns. Open decompression for fetal obstructive uropathy is still in the experimental stage, awaiting further control trials to establish its efficacy.[59,61]

POSTNATAL MANAGEMENT OF NEONATES WITH POSTERIOR URETHRAL VALVES

Infants born with posterior urethral obstruction may often have upper tract dilatation and renal damage that varies with the severity and duration of obstruction *in utero*. Most neonates with PUV when first seen are acutely ill with electrolyte abnormalities, metabolic acidosis, renal insufficiency, and septicemia (Fig. 99.6). They may have respiratory distress, the severity of which will depend on the degree of associated pulmonary hypoplasia. Improved management of these neonates has resulted in a better outcome for the treatment of posterior urethral obstruction in the last two decades.

The treatment strategy in neonates with PUV can be divided into three stages:

1. Immediate management and confirmation of diagnosis
2. Surgical treatment of the obstructing valves
3. Long-term follow up and treatment of associated pathology and complications.

Immediate management

The initial resuscitation of the sick neonate and confirmation of clinical impression by ultrasound and micturating cystogram is mandatory. Almost all neonates presenting with posterior urethral obstruction will need i.v. rehydration and electrolyte replacement. At the same time, blood samples can be obtained for:

- full blood count, including platelet count that may be low or high in septicemic babies;
- urea, creatinine, and electrolytes which should be estimated as baseline values;
- blood and urine should be sent for culture and sensitivity tests prior to starting antibiotic therapy;
- arterial blood samples to determine the degree of acidosis, to treat by sodium bicarbonate infusion.

Temporary vesical drainage can be achieved by passing a fine feeding tube (size 5 or 6 Fr gauge) transurethrally. Balloon catheters are not suitable for vesical drainage in posterior urethral obstruction. If the bladder is not emptying, a suprapubic catheter can decompress the urinary tract without interfering with the congenital urethra obstruction and its radiological study. A sample of urine obtained on catheterization should be sent for microscopy and culture.[62]

Once urine and blood samples are obtained for culture and sensitivity tests, the baby should be treated by antibiotic therapy. An aminoglycoside or cephalosporin is suitable initially and changes can be made once the urine and blood culture results are available. Respiratory insufficiency should be considered, and information on the respiratory states is given by means of a chest x-ray and blood gas estimation, and treated aggressively as and when necessary. A multidisciplinary team in the neonatal intensive care unit is often needed.

The confirmation of diagnosis usually involves a micturating cystogram, performed when the general condition of the patient is improved and the infection is brought under control (Fig. 99.8). However, an ultrasound scan can be done even in a sick neonate, by a sagittal perineal scan. The 'keyhole sign', although specific, cannot always be observed.[63]

Surgical treatment of congenital posterior urethral valves

To release the congenital obstruction in a male newborn with PUV should be considered as early as possible, because the indwelling transurethral catheter is only very transient, due to the risk of serious urinary tract infections and of defunctionalized bladder retraction. There is no consensus as regards the optimum method of treatment of posterior urethral obstruction, and its management constitutes an ongoing challenge in pediatric urology practice. The range of opinion varies from primary ablation alone to upper renal tract drainage, followed by delayed ablation. Ideally, the treatment option should be individualized, depending on the condition of the baby, the state of the upper renal tracts, and the size of the baby's genitalia.

PRIMARY TRANSURETHRAL RETROGRADE ABLATION

It can be performed under endoscopic view or blindly, depending on the preference of the surgeons and the available instrumentation.

Retrograde endoscopic ablation

It is the treatment most widely utilized, thanks to appropriate neonatal cystoscopes and resectoscopes now available, that may reduce the risk of secondary urethral damage and strictures in the newborn.[64,65] Fulguration can be undertaken once the infant's overall condition and renal function have stabilized. The development of smaller endoscopic equipment, as well as improved fiberoptics, has permitted transurethral endoscopic incision or fulguration of posterior urethral obstruction in virtually all but the most premature

patients. In most cases, primary ablation is sufficient to decompress the bladder and upper renal tracts.

Bugbee electrodes, available for use with the 8 Fr cystoscope, can be used for fulguration of PUV. One satisfactory alternative is to use a 3 Fr ureteric catheter with a metal stylet that can be used to coagulate. This can be passed through the side channel of an 8 Fr cystoscope. The obstructing membrane is incised at the 5, 7, and 12 o'clock positions. The neonatal resectoscope is commonly used in term newborns, as the caliber is 8 Fr (Fig. 99.13). This instrument allows the valve leaflets to be hooked and cut with more precision than the Bugbee catheter. It must be stressed that the valves or the congenital obstructive membrane should not be resected, but a full section of the leaflets should be undertaken at 5, 7, and 12 hours (Fig. 99.14). The section is enough to release the bladder outlet obstruction and avoiding the main severe complication that is postoperative urethral stricture. The reported incidence of strictures following endoscopic ablation is between 3.6 and 25%,[65] but an incidence of 0% has been reported with improved delicate maneuvers.[66]

Blind transurethral ablation

Particularly in very small newborns or premature babies, the transurethral endoscopy cannot be accomplished without the risk of urethral injury. Blind ablation of valves and urethral diaphragm can be performed, utilizing different instrumentation and techniques:

- **Fogarty balloon catheter**. The baby is anesthetized and a 6 Fr urethral catheter is passed transurethrally. The bladder is filled with contrast material until the posterior urethra is filled and an obstructing membrane identified. The catheter is then removed and, under fluoroscopic control, a No. 4 Fr Fogarty balloon catheter is placed into the bladder and inflated with approximately 0.75 mL of saline. With gentle withdrawal, the operator visualizes engagement at the level of the balloon. Sharp withdrawal of the catheter ruptures the valves or the membrane without injuring the sphincter.[67,68] Postoperative catheter drainage is recommended for 48–72 hours.
- **Mohan's valvotome**. This simple instrumentation may solve the problem of valve ablation in small infants. The advantages of the technique are its suitability in small neonates and the fact that it can be performed in areas of the world where pediatric endoscopic equipment is not easily available. However, a significant number of children have shown urethrorrhagia and periurethral extravasation of contrast in a post-ablation cystourethrogram.[69]
- **Whitaker–Sherwood diathermy hook**. Innes Williams successfully used a diathermy hook to ablate posterior urethral obstruction.[11] Whitaker and Sherwood[70] have modified the hook to its present form, which is fully insulated, except for the inside of the hook itself where the metal is bare for application of the diathermy. The advantages are its small caliber, 6–7 Fr, and applicability without the need for a general anesthetic. However, the proximal end of external stricture is above the obstruction, putting the sphincter at risk.[67] The sterile lubricated hook is passed up the urethra, pointing to the 12 o'clock position, with the bladder full of contrast medium. The obstructive membrane is immediately engaged by rotating it to either side and often it will not disengage until the diathermy is applied. The obstructing membrane is destroyed with the smallest effective diathermy current at the 3 and 9 o'clock positions, and elsewhere if it can be re-engaged.

With the advances in small cystoscopes, all these relatively blinded techniques are less favored over recent years.

Primary antegrade ablation

A percutaneous antegrade ablation technique was proposed by Zaontz and Firlit,[71] combining the techniques of antegrade urethral obstruction ablation and percutaneous endoscopy. The disadvantages of urethral instrumentation are avoided and the technique is applicable even in small premature infants.

Antegrade laser ablation in newborns has been proposed by some authors.[72,73] The Nd:YAG laser can be used via antegrade or retrograde access. The main advantage should be the limited inflammatory response of the injured tissue, with a reduced risk of bleeding and of secondary stenosis.

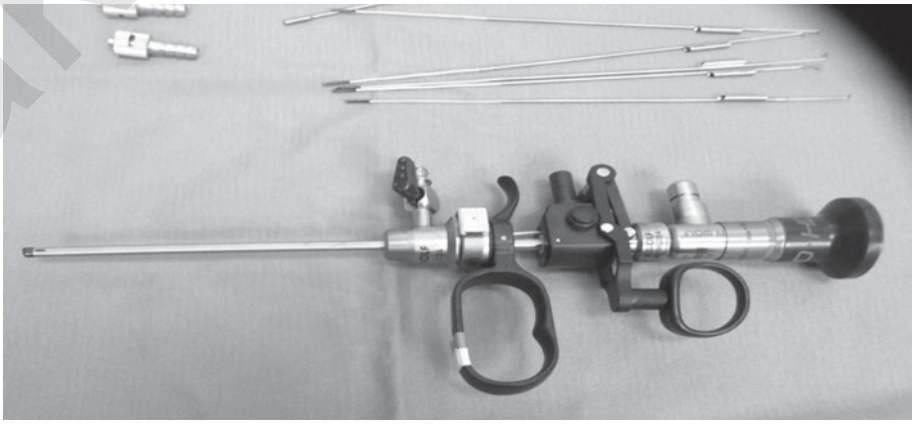


Figure 99.13 Neonatal resectoscope, suitable in newborns presenting with congenital obstructing membrane or valves on posterior urethra.

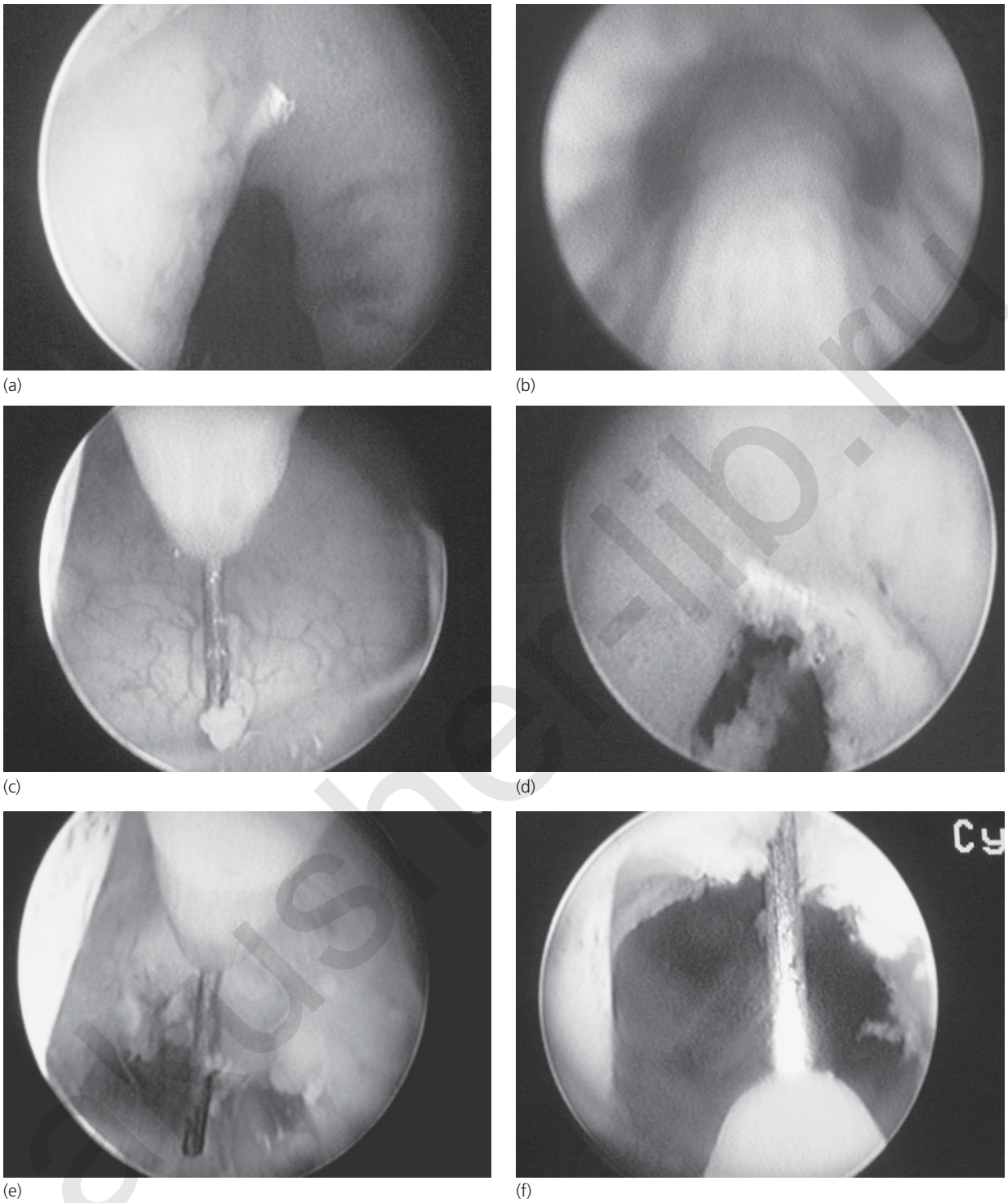


Figure 99.14 Endoscopic pictures of the section of the valve leaflets; a male newborn with posterior urethral valves. (a) The obstructing membrane; (b) dilated prostatic urethra; (c) diathermic hook; (d,e) the valve flaps are hooked at 12, 5, and 7 o'clock; (f) final appearance after posterior urethral valves fulguration.

INITIAL URINARY DIVERSION FOLLOWED BY SECONDARY TRANSURETHRAL ABLATION

There is general agreement on some indications for temporary diversion in neonates, including prematurity, small body size, and/or small urethral caliber with massive VUR.

Vesicostomy

In 1974, Duckett described the use of cutaneous vesicostomy as an alternative to primary ablation in a neonate.[74] By creating a vesicostomy, urethral instrumentation is avoided, high voiding pressures causing persistent high-grade reflux are managed, and hydroureteronephrosis due to poor

ureterovesical drainage is relieved. The bladder should be closed at the time of the subsequent diathermy of the urethral obstruction. However, vesico-ureteric junction obstruction and shrinkage of a defunctionalized hypertrophied bladder may occur, if it is proposed that the vesicostomy is long term.

Upper tract diversion

Upper tract diversion in posterior urethral obstruction is practiced in some limited indications. Primary ablation or temporary vesicostomy will be enough for hydroureteronephrosis to resolve in most cases. However, for severe or late presentation cases, and if significant dilatation of upper tract persists, in spite of lower tract drainage and ablation, non-intubated upper tract drainage may be beneficial. However, we know that dilatation does not mean obstruction and that temporary nephrostomy diversion on the use of double J catheters may ameliorate the hydronephrosis. In work by Krueger *et al.*,[75] infants treated with high-loop cutaneous ureterostomy ultimately had better outcome with regard to renal function and growth than the group managed by primary transurethral ablation of the valves. In 79% of patients who were treated initially with high diversion, Reinberg *et al.*[2] demonstrated that mild to severe renal failure developed versus 47% with primary ablation. Although no controlled study has been conducted, unilateral low ureterocutaneostomy could be useful in case of VURD syndrome with refluxing ureter and non-functioning kidney, allowing urinary tract decompression without interfering with bladder cycling and maturation in the small infant (Ransley, personal communication, 2009).

Temporary nephrostomy diversion on insertion of double J stents

Temporary nephrostomy with an insertion of double J stents may be useful in patients with vesico-ureteric junction obstruction or severe dilated upper tract. The insertion of double J stents prevents dry bladder and maintains bladder cycle, which is needed for normal bladder development.

EARLY POSTOPERATIVE MANAGEMENT

After valve ablation, the urethral catheter is left *in situ* for 48–72 hours, to allow the edema to subside and the urinary output to be measured. Accurate hydro-electrolytic balance is monitored by i.v. fluids and electrolyte solutions. Serial serum creatinine, electrolytes, and urinalysis are monitored after the patient is discharged with antibiotic prophylaxis. Post-void residual urine volume is frequently checked by ultrasound, and sonographic appearance of kidneys and upper tract is observed at four to six months intervals. If the post-void residual urine volume is significant (greater than 10% of expected bladder capacity), alpha-1 adrenergic blocker drug treatment can be started (terazosin 0.04–0.4 mg/kg per day), after obtaining informed consent.[76] Blood pressure must be routinely monitored.

The first micturating cystogram is usually performed at three months from valve ablation, and a 'second-look' cystoscopy is indicated if residual valves or leaflets are suspected, to guarantee complete removal of the urethral obstruction. A simple measurement that allows quantitative assessment of valve ablation is the 'urethral ratio' on micturating cystogram.[77] A post-fulguration urethral ratio of 2.5–3.0 represents positive results postoperatively. Renal radionuclide scan (MAG3 or DMSA) is suggested at 6–12 months from valve ablation to check parenchymal function.

FOLLOW UP AND TREATMENT OF LONG-TERM SEQUELAE AND COMPLICATIONS

Urethral stricture

It can be a significant complication following the transurethral approach for the treatment of PUV, as a consequence of mechanical trauma on posterior urethral wall. The stricture can happen where the lesion on the urethral wall is deeper and the corpus spongiosum could be injured. The incidence of urethral strictures following PUV ablation is reducing from 25 to almost 0%, but it can be avoided, utilizing small endoscopes and delicate maneuvers.[65,66,78]

Dysfunctional voiding and urinary incontinence

THE 'VALVE BLADDER' SYNDROME

At least 30% of children with previous PUV have different degrees of dysfunctional bladder. It often presents with daytime and night-time urinary incontinence at the toilet-trained age. Initially, it was thought to be secondary to external sphincter incompetence, depending on the primary maldevelopment of the sphincteric urethra, rather than iatrogenic injuring of this structure during endoscopic manipulations. Further urodynamic studies showed the presence of vesical dysfunction which does not resolve after complete urethral obstruction removal.[48]

A number of different voiding dysfunction pictures may be present after primary valve ablation in children born with PUV. The incidence of voiding dysfunction in posterior urethral obstruction has been reported to occur in 13–38% of all patients treated, of which incontinence is the most common problem.

The main bladder anomalies causing incontinence are detrusor overactivity, reduced compliance, and myogenic failure. Detrusor overactivity and reduced compliance are treatable with anticholinergic pharmacotherapy, but bladder augmentation may be necessary in selected cases. Myogenic failure may be most effectively treated with clean intermittent catheterization and nocturnal bladder emptying.[47]

Early valve ablation allows the bladder to fill and empty with normal cycling, starting shortly after birth. The restored bladder cycling is crucial for regaining normal bladder function and dynamics.[79,80] Mitchell[35] suggested the term 'valve bladder syndrome' to denote the association of a non-compliant bladder and upper tract dilatation in boys with a history of previous PUV.

The evolution along the years of this severe bladder dysfunction may result in upper tract dilatation and renal

function deterioration.[34,35,47] Serial urodynamic studies, with pressure-flow analysis and evaluation of post-voiding residual urine are necessary. Bladder activity may change over time from hyperactive, low-compliant, and reduced functional volume bladder to hypocontractile, high capacity, and poorly emptying behaviour (decompensated bladder with myogenic failure).[48,49,81]

Early valve ablation, even in patients with severe bladder changes, could provide better bladder function results, with a higher resolution rate of VUR and hydronephrosis.[80] Bladder neck incision, performed simultaneously to valvulotomy or later in infancy or childhood, has been advocated to increase low-pressure bladder outlet if pharmacological treatment by α-1 adrenergic blocker drugs has not been efficacious.[78,82]

VESICO-URETERAL REFLUX AND HYDRONEPHROSIS

The incidence of VUR in boys with PUV ranges from 26 to 72%.[83] More recently, bilateral VUR was observed in 37% and unilateral VUR in 27% of patients.[84] Children born with bilateral high-grade VUR are at greater risk for CRF than those with unilateral or no VUR. Unilateral VUR may confer a protective pop-off effect in the contralateral kidney.[43,85]

A high rate of reflux resolution is expected after valve ablation, even in the presence of vesical diverticuli, with a consistent follow up. VUR resolution is correlated with bladder dysfunction normalization. In a recent series of Heikkila *et al.*,[84] VUR resolved spontaneously in 62%, was corrected by antireflux surgery in 21%, and required nephrectomy in 17% of boys with previous PUV. Indications for ureteral reimplantation remain undefined today, but the recent experience tends to support a less aggressive surgical approach than in the past.

Pyelo-ureteral dilatation persisting after treatment of an obstructing membrane is either due to vesico-ureteric junction obstruction or ureteral atony. Diuretic renograms may be helpful in the differentiation between the two conditions, although temporary drainage of the upper tract may be necessary to make the diagnosis. A conservative approach, with care to bladder dysfunction treatment, is often recommended today.

Renal dysplasia

Unilateral renal dysplasia with a nonfunctioning kidney should be treated by nephro-ureterectomy, if there is a risk of blood hypertension or urinary tract infections. Bilateral renal dysplasia will go on to develop end-stage renal disease and will require dialysis and renal transplantation.

PROGNOSTIC FACTORS IN PUV

Congenital lower urinary tract obstruction is a disease of high mortality and morbidity in newborns. With the widespread use of prenatal ultrasound, most children with PUV are now recognized prenatally and confirmed at birth. Several prognostic factors have been underlined to better define the long-term outcome of an infant born with PUV.

- Prenatal prognostic factors for better postnatal outcome have been presented and discussed above under Prenatal diagnosis and management. Poor prognosis is related to reduced amniotic fluid volume, presence of cortical renal cystis, and other congenital or structural anomalies of the fetus.[57]
- Ultrasound findings of reduced parenchymal thinness, increased renal echogenicity, and cystic changes in infancy are usually correlated with severe renal damage and dysplasia, evolving into CRF.[50,52]
- Urinary extravasation with or without ascites in the prenatal or neonatal age, large bladder diverticula, and VURD syndrome are all factors decompressing the urinary tract and related to a better renal function outcome.[42,43]
- Delayed presentation of patients with PUV (after two years of age) are at higher risk of developing CRF on long-term follow up.[86] Early vesicostomy or other urinary diversion is not confirmed to give better outcome.[87]
- Early primary valve ablation of PUV seems to lead to better outcome than urinary diversion, reducing bladder dysfunction.[79,80]
- Unilateral gross VUR, associated with poor functioning ipsilateral kidney, may give a protective effect in the contralateral kidney ('pop-off' valve syndrome).[43,85]
- Patients with bilateral high-grade VUR are at greater risk for renal insufficiency, although this is not always confirmed.[84]
- Severe bladder dysfunction ('valve bladder' syndrome) may jeopardize the upper tract and renal function at long-term follow up.[47–49]
- Proteinuria, blood arterial hypertension, and febrile urinary tract infections do not correlate significantly with the ultimate functional outcome.[88] The nadir creatinine values of 0.8 mg/dL or higher within the first year of life is reported as the most significant prognostic factor correlated with poor renal function over the long term.[89,90]
- Renal transplantation can be offered to children with a history of previous PUV or congenital obstruction of posterior urethra, with the same good results as other pediatric candidates, with pre-emptive urological repair of the lower urinary tract.[91]

CONCLUSIONS

Congenital obstruction of male posterior urethra represents a spectrum of lesions, of which PUV is the most common. PUV often remains a severe structural cause of urinary outflow obstruction in newborn age and in infancy. It still represents one of the most significant causes of end-stage renal failure before the age of two years.[4,89] The prognosis of children born with PUV has improved significantly over the past two decades, but until now a large number of patients enter CRF and progress to end-stage renal insufficiency by adolescence, with the need for the dialysis and/or progression

to the renal transplant program.[90,91] A precise multidisciplinary approach may further increase the outcome of these children, providing a more pathogenetic and appropriate treatment at long-term follow up, until adulthood.

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Neurogenic bladder in the neonate

YVES AIGRAIN AND ALAA EL GHONEIMI

INTRODUCTION

The prevalence of neonates with neurogenic bladder dysfunction has decreased due to the wide prenatal ultrasonographic screening and the prophylactic use of folic acid during pregnancy. Nevertheless, there are still newborns presenting with spina bifida or other forms of spinal dysraphism or sacral agenesis.

Although the management of these children has been significantly modified over the last few decades, the main goal of the treatment has not changed, i.e. preventing urinary tract deterioration, which concerns the upper urinary tract as well as the bladder.

PRENATAL DIAGNOSIS AND COUNSELING

Despite the progress of the ultrasonographic evaluation and the information provided by fetal magnetic resonance imaging (MRI), it is almost impossible to predict prenatally the precise degree of bladder dysfunction. Urinary and anal incontinence are among the main disturbances in the life of these children, particularly in those with a low lesion without or with minor motor involvement. The treatment of the urinary tract involvment has to be started early in life,[1] which is why the participation of the pediatric surgeon (or urologist) is of utmost importance in the counseling of parents before the birth. It will help the parents to be prepared for the need for immediate neonatal management of bladder emptying by clean intermittent catheterization (CIC).

ANATOMY AND MICTURATION PHYSIOLOGY

The autonomic and somatic nervous systems are involved in the innervations of the bladder and sphincter. The parasympathetic component of the autonomic innervations is derived from the sacral segments of the spinal cord. These fibers emerge as preganglionic fibers within the pelvic nerve, which then joins the hypogastric nerve to form the bladder's plexus. The post-ganglionic fibers emerge from synapses close to the bladder and urethra, where they have the overall effect of producing sustained bladder contraction. Acetylcholine is the neurotransmitter for both the pre- and post-ganglionic fibers, although there is certainly more than one principal neurotransmitter. Within the bladder, the parasympathetic cholinergic receptors are largely muscarinic (M_2). Other neurotransmitters documented to be present in the bladder include vasoactive intestinal peptide, neuropeptide Y, substance P, somatostatin, calcitonin gene-related peptide, cholecystokinin, dopamine, serotonin, histamine, and tyrosine hydroxylase. The exact roles of these neurotransmitters, as well as their complex interactions, remain unclear.

The sympathetic component of the autonomic innervation arises from spinal cord segments T11–L2 with preganglionic fibers traveling to the hypogastric and inferior mesenteric ganglia, where they synapse with the noradrenergic, post-ganglionic fibers, which in turn travel to the bladder and urethra via the hypogastric nerve. Sympathetic input is mediated by both α- and β-adrenoreceptors. The α-adrenoreceptors are more densely represented at the bladder base and produce contraction, while the β-adrenoreceptors, which are more common in the bladder body, produce relaxation. Thus α-activity promotes outlet resistance, while β-activity promotes urine storage and opposes cholinergic tone.

Somatic motor innervations arise from the S2–S4 segments and pass via the pudendal nerve to the striated muscle of the external sphincter. While the external sphincter is voluntary muscle, in infancy external sphincter tone is mediated via spinal cord reflex. It is only as the child matures that cortical inhibitory influences develop that allow voluntary relaxation and contraction, which contribute to the development of continence.

Normal bladder sensation is relayed via pelvic and hypogastric nerves, with parasympathetic visceral afferent fibers transmitting information from pain, temperature, and stretch receptors.

In the newborn and infant, voiding occurs as a result of a spinal reflex secondary to bladder distension, which stimulates the efferent limb of the reflex arc, resulting in spontaneous detrusor contraction. Initially, as the bladder fills, the peri-urethral striated muscles make the external urinary sphincter contract to prevent urine loss. The act of micturition occurs with subsequent relaxation of the external sphincter, resulting in the bladder emptying at low pressure. During the first year of life, the number of voiding episodes per day remains constant at about 20, occurring during both sleep and while awake; with increased age, there is a reduction in the voiding frequency that relates to the relative increase in bladder volume and decreasing proportion of the caloric intake associated with fluid.

CLASSIFICATION

There are many classifications describing neurogenic bladder dysfunction. Most of these classifications depend on the site of the neurological lesions, well adapted to adult pathology, but not to congenital spinal lesions. In fact, in children, there is poor correlation between the spinal level of lesion and the clinical impact. For this reason, classification based on clinical disorders and urodynamic findings are more practical for use in children. The main dysfunctions are due either to detrusor or to urethral sphincter dysfunction.[2] The four main anomalies are defined as: overactive bladder, underactive detrusor, overactive sphincter, or underactive sphincter. Many patterns may be the result of combinations of these four anomalies.[3] The most common is the detrusor sphincter dyssynergia (DSD), which is often associated with both overactive bladder and overactive sphincter. DSD is the main characteristic of neurogenic bladder in children.

URODYNAMIC INVESTIGATION

Urodynamic investigation has become an integrated part of any discussion of the management of neurogenic bladder even in neonates. It is mandatory to understand the definition and specificity of urodynamic findings as they relate to children. The International Children's Continence Society has established the standardization of the terminology to be used in children's bladder dysfunction.

Performing a urodynamic evaluation in a neonate should be undertaken under optimal conditions, including treatment of the associated constipation and emptying of the rectum on the day of examination.[4] The common basic principles specific to children are the following: smaller catheter, rectal pressure measurement, and measurement of urethral profile (even if its interpretation needs caution). Most importantly, the rate of bladder filling should be adapted to the expected bladder capacity (usually divided by 10/min). Surface patches measure the electrical activity of the external sphincter. Video urodynamometry has gained popularity over the last decade. Visualization of the bladder and the bladder neck during filling, and the urethra during voiding, add more accuracy in the determination of voiding dysfunction. In case of associated reflux, its visualization allows a proper interpretation of the bladder pressure and compliance.

DIAGNOSIS OF NEUROGENIC BLADDER IN THE NEONATE

The most common cause for neuropathic bladder dysfunction in the neonate is the congenital spinal anomalies. Prenatal occurrence of a tumor with intracanal expansion is another rare cause of paraplegia and neurogenic bladder dysfunction in the neonate. The expected findings and the modalities of follow up of the most common of these pathologies during the first months of life are discussed below.

Myelodysplasic patient

In the event of myelomeningocele (MMC), the workup is performed in the neonatal period, usually after the surgical closure of the defect. The initial workup will serve as the baseline information for the follow up of the child. It will include renal and bladder ultrasound (US), urodynamic study, voiding cystourethrogram (VCUG) (or a video urodynamic study). These initial studies will help to identify children at risk for urinary tract deterioration: poor compliant or overactive bladder, or outflow obstruction as a part of DSD. The identification of such risk factors will justify initiating the prophylactic measures before deterioration of the upper urinary tract. It is not enough to look at the radiological appearance of the upper urinary tract. Detailed functional screening of the lower urinary tract is necessary to allow an early preventive therapy, before the later appearance of upper tract deterioration. It will also help to preserve bladder compliance, and to avoid or delay as far as possible bladder augmentation procedures.

The neurological lesion produced by MMC can be variable. The bony vertebral level provides little or no clue to the exact neurological level or lesion produced.

Three categories of lower urinary tract dynamics may be detected: (1) synergic (26%), (2) dyssynergic with and without detrusor compliance (37%), and (3) complete denervation. Bauer reports that 15% of neonates have abnormal urinary tract that developed *in utero*.[5]

Within the first three months of life, 71% of newborns with DSD have deterioration of bladder compliance or upper tract, by comparison to the initial evaluation, whereas 17% of synergic children and 23% of those completely denervated developed similar changes. Outlet obstruction is a major contributor to the development of urinary tract deterioration in MMC children. The leak point pressure is not the only pejorative prognostic factor; so is the filling pressure, which should remain lower than 30 cm H_2O, while voiding pressure should not exceed 100 cm H_2O. If this is not the case, CIC and anticholinergic medications are mandatory.

Anal incontinence is unpredictable and is not correlated with urinary incontinence. Anal incontinence is not a problem during the first year of life, but treatment of constipation should be undertaken as soon as needed.

Other spinal dysraphisms

This group of congenital defects affects the formation of the spinal column, but does not result in an open vertebral canal. In young infants, the vertebral bones have not ossified, thus a window exists for ultrasound to screen spinal cord lesions. Many of these lesions are now detected by an accurate prenatal US screening, raising the question of a prophylactic surgical treatment before the onset of symptoms.

Occult spinal dysraphism

Lipomeningocele, intradural lipoma[6,7] and other rare anomalies of filum terminale are increasingly being diagnosed by prenatal ultrasound screening. The majority of these children have a normal neurological examination, but Keating reports that the urodynamic evaluation reveals anomalies in one-third of infants younger than 18 months. These anomalies produce different neurologic findings. Satar *et al.*[6] report that lipomas invariably cause upper motor neuron either alone or in combination with lower motor neuron defect. Neonates and infants with various occult dysraphism may have skin lesions, varying from a small dimple or a skin tag to a hair's tuft, a dermal vascular malformation, subcutaneous lipoma, or an asymmetrical curving gluteal cleft.

SACRAL AGENESIS

Sacral agenesis is defined as the absence of part or all of two or more lower vertebral bodies. Curarino syndrome associates in complete forms: sacral agenesis, a presacral mass, and an anorectal malformation. This is a familial disease with dominant inheritance, due to a deletion in chromosome 7 in the *HLXB9* gene.

In 1999, Wilmhurst *et al.*[8] reported that more than three-quarters of the cases were detected either prenatally or in early infancy. Most of these children have normal skin sensation and no abnormalities in the lower extremities. On clinical examination, palpation of flat buttocks and absence of vertebrae in the sacrococcygeal area may be observed. A plain x-ray will confirm the diagnosis of sacral agenesis, while the spinal cord-associated anomalies are explored by US and MRI. One typical finding is the sharp cut-off of the cone at T12 as shown by Diel *et al.* (2001).[23]

The urodynamic findings may be either an overactive bladder, with exaggerated sacral reflex and DSD, with a thick and trabeculated bladder on the VCUG with a closed bladder neck or an acontractile detrusor with open bladder neck and a small, thin-walled bladder. These neurological findings are stable and rarely progress with time. Urodynamic evaluation and VCUG are mandatory to tailor the management of these neonates and infants.[9]

NEUROLOGIC BLADDER ASSOCIATED WITH ANORECTAL MALFORMATION

Spinal cord anomalies (tethered cord, filum terminale anomalies, or lipomas) may be found in up to 50% of cases, especially in the high type of anorectal malformation (ARM). Intraspinal imaging at least by US is mandatory since not all patients with spinal cord anomalies and ARM have a vertebral body defect. The timing of the urodynamic evaluation in ARM infants is discussed. To perform these investigations in ARM children with proven spinal cord anomalies before the definitive pull-through procedure will help to distinguish between the congenital and acquired anomalies, secondary to the surgical procedure. Most of these infants with spinal cord anomalies have upper motor lesions with DSD and are at high risk of upper urinary tract deterioration.

CEREBRAL PALSY

Cerebral palsy is a non-progressive injury of the brain occurring in the perinatal period. Most children with cerebral palsy will develop total urinary control. As Karaman *et al.* reported in 2005,[10] when they explored the urodynamic anomalies in every child with cerebral palsy, urinary symptoms were not the major concern of these neonates and no screening is recommended in this group of patients.

MANAGEMENT OF NEUROGENIC BLADDER

The first goal of the treatment of a neonate with a neurogenic bladder is the preservation of a normal upper urinary tract. The second goal will be to improve the urinary and fecal continence of these children to improve their social life and their quality of life. These objectives would ideally need a reservoir, the bladder, with adequate capacity and a low storage pressure, able to empty itself with a normal micturition profile. In a child with a neurogenic bladder, none of these characteristics is present. As mentioned above, the urodynamic evaluation done in the neonatal period will help to tailor the treatment to each individual child. Later, the motor and intellectual capacities of the children will also influence the choice of treatment.

Clean intermittent catheterization

Lapides introduced CIC in 1971.[11] CIC is the most important tool in the management of a child with neurogenic bladder. It is a clean, but not sterile procedure. It allows the emptying of the complete bladder, lowering the risk of urinary tract infection and protecting both the upper urinary tract against high bladder pressure and the deterioration of the bladder wall and compliance in relation to DSD and obstruction. CIC may be sufficient to induce dryness of the child if the bladder capacity and the sphincter pressure are correct, but this is not the main objective in the newborn. CIC is enhanced by the availability of single use lubricated catheters, but it may be realized with classical Nelaton catheter kept in an antiseptic solution in less developed countries.

Everyone agrees that there is no longer a role for Crédé and Valsalva maneuvers in children with congenital neurogenic bladder since these may induce reflux, worsened the high bladder pressure and the upper urinary tract deterioration.[1] We advocate the introduction of CIC as early as

possible in the neonatal period. This is mandatory in infants with overactive or low compliant bladder and DSD. In neonates with low sphincter pressure and no risk of deterioration of the upper urinary tract and bladder compliance, the age at which CIC should be started may be discussed, taking into account the burden of CIC to the parents of the handicapped child and the ease of starting CIC in a neonate by comparison to a two- or three-year-old child.

The authors do not have experience of urethral dilation for lowering the leak pressure as published by Kiddo *et al.*[12] These authors report a favorable outcome in 19 infants with upper tract deterioration (dilation or reflux) and urinary tract infection. When CIC is not applicable due to the familial condition or to associated anomalies, the authors would rather consider the construction of a tubeless vesicostomy to decompress the bladder and avoid deterioration of the upper urinary tract.[13] The surgical technique of vesicostomy should be precise to allow a correct decompression of the urinary tract. The incision should be done halfway between the umbilicus and the pubis exposing the rectus fascia, which is incised transversally. The rectus muscles are retracted and the inferior fascial edge is incised vertically. The peritoneum is reflected superiorly from the bladder (this may be helped by filling the bladder with a catheter). The urachus is identified and excising the urachus opens the bladder. The detrusor edge is anchored to the fascia to avoid the opening being too wide with the risk of bladder prolapse, or too small with resulting poor decompression. Suturing the full thickness of the detrusor to the skin and subcuticular layer creates the cutaneous stoma. A catheter is left in place for 2 or 3 days.

In selected cases, where despite CIC urinary tract deterioration occurs, the overnight catheter drainage of the bladder may be successfully attempted as shown by Koff *et al.*[14] and Nguyen *et al.*[15] These authors have shown that overnight drainage may increase bladder compliance and capacity, avoiding augmentation in some children.

CIC will have to be done for the full extent of the life of the child. Later in childhood, when CIC is difficult through the urethra, a Mitrofanoff[16] channel may be constructed, allowing catheterization through a continent abdominal stoma. The location of this stoma will be either at the umbilical site or in the lower abdominal wall depending on the child's motor disability. The continent channel is either realized as a specific procedure or together with a bladder augmentation or outlet procedure. Many variations of the original procedure described by Mitrofanoff, using the appendix as the channel have been reported. Use of one ureter, a refashioned ileal conduit (Monthy), or a flap from the bladder wall have to be known.

BLADDER CAPACITY AND COMPLIANCE

When CIC and sometimes overnight drainage fail to maintain normal bladder capacity and compliance, the preservation of the reservoir and the upper tract may need either pharmacological manipulation or surgery.

During the first year of life, a bladder augmentation procedure is very seldom, if ever, indicated.

Pharmacologic treatment of neurogenic bladder overactivity

Oxybutinin, an anticholinergic agent, is the reference treatment of bladder overactivity. Even if it has not been approved for use in children younger than five years, oxybutinin is in most cases well tolerated and may be introduced after the initiation of CIC, at an early stage, if the urodynamic evaluation shows bladder overactivity. The use of an oxybutinin solution helps the administration in infants. Oxybutinin should be administered at regular intervals during the nyctemer, starting with minimal dose increases according to the child's tolerance and the effects upon the overactivity. In older children, side effects of oxybutinin include mouth dryness, constipation, and headaches or eye trouble. These side effects may be reduced or suppressed by direct instillation of the oxybutinin within the bladder during CIC, but the sterile solution is not universally available. There is no report on the use of other anticholinergic agents during the neonatal period or in infancy.

Botulinum toxin A has been shown by many authors to be very effective in reducing the bladder overactivity, enhancing the bladder capacity and compliance.[17,18] Botulinum toxin A is injected in the detrusor muscle under cystoscopic guidance at 5–10 IU/kg body weight with a maximum dose of 300 IU. The site of injections are spread through the detrusor, respecting the trigone so as not to induce a vesico-ureteric reflux. The effects of Botulinum toxin A last for six to nine months, but the procedure is minimally invasive and may be repeated on an outpatient basis after ruling out any allergologic reaction. Most authors now consider Botulinum toxin A as an alternative to bladder augmentation procedure in children.

Alpha-blocking agents have a very limited place in the management of neurogenic bladder.

Guys *et al.*[19] introduced sacral neuromodulation in the treatment of neurogenic bladder dysfunction in children from five years of age. These authors showed a significant improvement in bladder compliance and capacity at six and nine months of treatment. These results have to be confirmed in a larger group of patients. Interestingly, the intestinal transit improved in many of these patients.

As already mentioned, bladder augmentation is rarely if ever indicated in neonates and infants. In older ones, the surgical increase in bladder capacity and compliance in order to preserve both the upper urinary tract and to allow a social continence between catheterizations may be done by bladder autoaugmentation or detrusorectomy,[20,24] or by intestinal augmentation, in most cases using the ileum. In some instances, the stomach (El Ghoneimi et al 1998) and the sigmoid may be an alternative to the use of ileum. These augmentation procedures may be associated with a reinforcement of the outlet resistance and/or with a continent cystostomy using Mitrofanoff's principle. The augmentation per se causes many complications, some being preventable, and others having to be identified during the life-long follow up of these patients. They are mainly infections, stone formation, and metabolic complications, including acidosis or vitamin B_{12} deficiency,[29] perforation,[28] and cancer. They explain why bladder augmentation should be avoided or delayed as much as possible. The neonatal

introduction of CIC and oxybutinin is in the event of severe dyssynergia, which is mandatory to prevent fast bladder deterioration.[22]

OUTLET RESISTANCE

There is obviously no need to increase the outlet resistance in a neonate or an infant where dryness is not relevant for the child and his parents. Nevertheless, the child's family will need information and the various possibilities should be known in order to provide the complete picture.

Increasing the outlet resistance may be obtained by the periurethral or pericervical injection of bulking agents, an open cervicoplasty, a sling suspension of the bladder neck, an artificial urinary sphincter, or closure of the bladder neck.

The injection of bulking agents has the advantage of being a non-invasive technique. Various agents have been tested including dextranomer (Deflux®) or silastic particles.[21] We have recently published our experience with dextranomer injections in 61 patients. The incidence of dryness or improvement at six months was 51% and this result was maintained during long-term follow up.[20] Similar results have been published with silastic particles by Guys *et al.*[19] They suggested the combined injections of Botulin toxin A and pericervical injection of silastic particles, combining in a non-invasive procedure the treatment of bladder overactivity and the increase of outlet resistance. These techniques are the only ones to be used in a young child. The neonatal management of neurogenic bladder and other possibilities that are reserved for older children will not be discussed in this chapter. This is obvious given the complications of the surgical procedures used to increase the outlet resistance. Any of these, including to some extent the injection of bulking agents, may induce bladder and upper urinary tract deterioration. The main goal of the neonatal management should be preservation of these structures.

URINARY DIVERSION

Despite the widespread acceptance of CIC, there are families with social conditions which make them unable to comply or simply to have access to any form of bladder catheter. As already discussed, in the neonatal period, urinary diversion is realized by a tubeless cystotomy. Later in life, quadriplegia, limited dexterity, devastating cognitive impairment, or lack of ancillary support are the main factors leading to the decision of urinary diversion. The urinary diversion is most often realized by an ileal conduit (Bricker's procedure).[25]

BOWEL MANAGEMENT

Constipation is a usual feature of babies with neurogenic bladder. It should be managed both to improve the infant's comfort and to reduce the risk of urinary tract infection. Later in life, the quality of life of a child born with a neurogenic bladder is even more altered by feces incontinence as by the leak of urine. It is then important to consider bowel management, including either retrograde enemas or antegrade colonic washing as described by Malone.

CONCLUSION

The management of a neonate with neurogenic bladder requires a multidisciplinary team and has to be tailored to each particular child and family. CIC is the most important part of the treatment and should be started as early as possible after birth and repair of the spinal defect. It will not always be sufficient to achieve continence, but is mandatory to protect the upper urinary tract, which is the main goal of the treatment.

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Hydrometrocolpos

DEVENDRA K GUPTA AND SHILPA SHARMA

HISTORICAL BACKGROUND

Although the historical literature on hydrometrocolpos is sparse, there are records of hydrometrocolpos dating back to the mid-nineteenth century. Godefroy in 1856 first described a case of a two-month-old infant with 5 mL of viscid mucoid fluid imprisoned behind a 2.0 mm thick, vascular hymen.[1] In 1899, Von Winckel found an atretic vagina containing 180 cc of fluid at autopsy in a stillborn infant.[2] In some instances, the baby with hydrometrocolpos was associated with such urogenital and hindgut grotesque abnormalities that the specimens were considered to be embryologic curiosities. These findings emphasize that hydrometrocolpos, when associated with other congenital anomalies, has a poor prognosis. A major undertaking, such as panhysterectomy, even in infants, was reported as long ago as the mid-twentieth century, even before the diagnosis could be established.[3,4] This kind of aggressive treatment for a simple benign vaginal obstruction in an infant is now obsolete and unethical. The diagnosis and treatment of hydrometrocolpos has now been revolutionized completely.[5]

DEFINITION

Hydrometrocolpos is a condition in which the uterus and vagina are grossly distended with retained fluid other than blood, usually in the presence of distal vaginal outflow obstruction.

INCIDENCE

The incidence of hydrometrocolpos is reported as 1 in 10000–30000 live births.[5,6] The condition is now being increasingly diagnosed prenatally, with the use of ultrasound and fetal magnetic resonance imaging.[7] The incidence is reported higher in communities with consanguinity.[8] The rarity of this anomaly was probably due to high mortality resulting from infections and associated anomalies.[9] Many of those affected are stillbirths due to serious associated anomalies and obstructive uropathy.

EMBRYOLOGY

The Müllerian ducts develop as tubular invaginations of the coelomic mesothelium parallel to the mesonephric ducts during the second month of gestation. The caudal ends (which form the uterus and vagina) fuse in the midline and join the urogenital sinus. The distal portion of the fused Müllerian ducts is temporarily completely occluded by a solid cord of cells, the Müllerian tubercle, the caudal end of which becomes the hymen. Failure of degeneration of the epithelial plate in the Müllerian tubercle results in imperforate hymen, and persistence of a portion of the solid cord of cells in the fused Müllerian ducts above this level results in atresia of the vagina. A transverse septum of the vagina might result from incomplete coalescence of the vacuoles that develop as the epithelial cord begins to degenerate.

ETIOPATHOGENESIS

The condition occurs at the two extremes of childhood – in the neonatal period, when there is a high level of maternal hormones, and in early puberty, when the patient herself begins to produce estrogenic hormones. The reason being that for hydrometrocolpos to develop there should be both an accumulation of excessive fluid in the female genital tract due to estrogenic stimulation, as well as vaginal obstruction. Thus, if there is a low level of maternal hormones in the presence of vaginal obstruction, the obstruction remains unnoticed until puberty and presents as hematocolpos at the time of the menarche. The common causes of distal vaginal obstruction are imperforate hymen, transverse vaginal septum, and vaginal atresia with or without persistence of a urogenital sinus or cloaca. The distal vaginal outflow obstruction is usually imperforate hymen (60–70%) that forms a thin translucent membrane bulging between the

labia. Atresia of the vagina is the next common cause. These anomalies may result from either a local error of development or as an inherited disorder, e.g. McKusick–Kaufman syndrome.

TYPES

Secretory

This is the most common type, consisting of mucoid material secreted mainly by the cervical part of uterine glands in response to maternal estrogenic hormones, mainly due to prenatal stimulation. The fluid is viscid, pearly gray in color, and may accumulate even up to one liter in volume. The retained fluid is usually acidic and serous or mucoid with large numbers of desquamated epithelial cells and leukocytes.

Urinary

In urinary hydrometrocolpos, urine collects in the vagina as a backwash during the act of micturition, although there is no complete distal vaginal mechanical obstruction. This is usually in association with urogenital sinus or cloaca. The size of the communication varies. It is usually valvular, allowing only one way flow of urine to the vagina.

The terms 'hematometrocolpos' and 'pyometrocolpos' are used for presence of blood or pus.[10] The collected fluid in the vagina often become infected very soon, resulting in pyometrocolpos. As the obstruction gets established, there is pyosalpinx and even peritonitis.

CLASSIFICATION

On the basis of the level of obstruction and the association with urogenital sinus (UGS) or cloaca, hydrometrocolpos has been classified into five types (Fig. 101.1).[5]

- I Low hymenal obstruction
- II Mid-plane transverse membrane or septum at the level of lower one-third and upper two-thirds of the vagina
- III IIIa, high obstruction with distal vaginal atresia; at the level of upper one-third and lower two-thirds of the vagina
  IIIb, high obstruction with distal vaginal atresia and gluteal swelling
- IV Vaginal atresia with persistence of the UGS
- V Vaginal atresia with cloacal anomaly

ASSOCIATED ANOMALIES

Almost 50% of newborns with hydrometrocolpos have associated anomalies. A large number of these are delivered as stillborns. Rare variants may be seen with fused labia or ipsilateral hydrometrocolpos in patients with uterus didelphys and septate vagina.[11] It may be associated with congenital heart disease, genitourinary and gastrointestinal anomalies.

Associated gastrointestinal anomalies include anorectal malformation, esophageal atresia, duodenal atresia, paraesophageal hiatus hernia, and congenital intestinal aganglionosis.[12] Associated genitourinary anomalies are most common and most serious. These include bicornate uterus and double

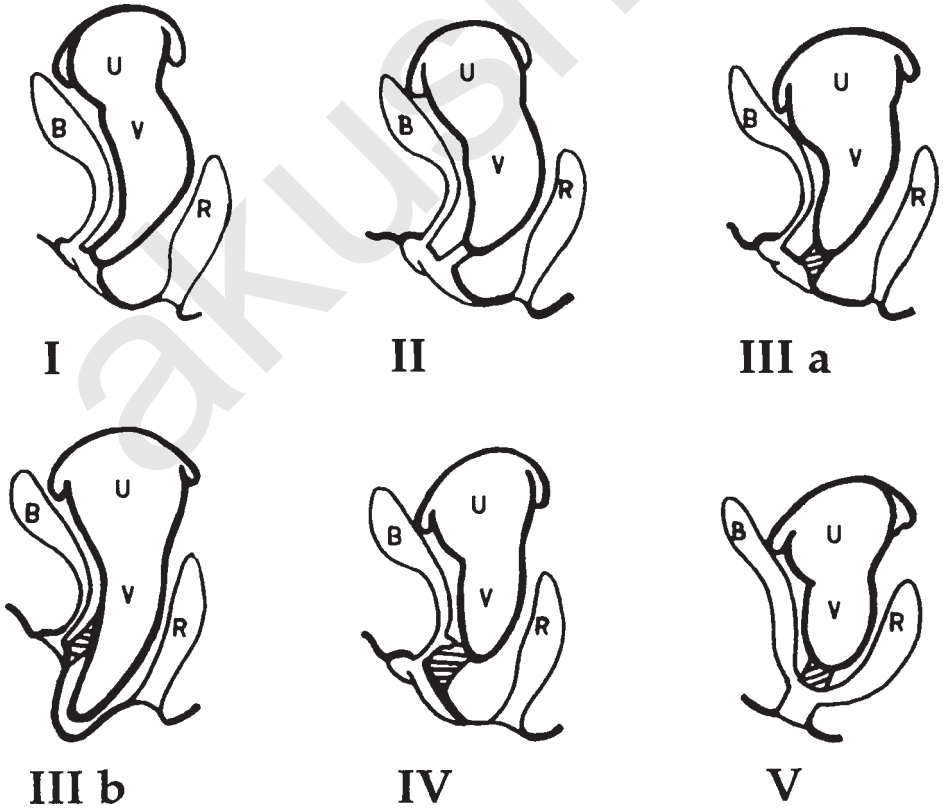


Figure 101.1 Classification of hydrometrocolpos.

vagina, duplication of the uterus and vagina, bifid clitoris, congenital urethral membrane, double ureter, ureteral stenosis, urethral atresia, absence of vulva, renal agenesis, and ambiguous genitalia.[13] Rare associations include Müllerian dysgenesis syndrome, staphyloma of the left eye, and severe hydrops.[14–16] Other additional findings include vertebral segmentation anomalies, lung hypoplasia, corpus callosum hypoplasia, and single umbilical artery.[17]

Patients with multiple congenital anomalies have a bad prognosis, thus awareness about associated anomalies is necessary for proper diagnosis and treatment.[18]

SYNDROMIC ASSOCIATIONS

Hydrometrocolpos may be associated with inherited disorders, such as McKusick–Kaufman syndrome (MKKS) and Bardet–Biedl syndrome (BBS).[19,20]

McKusick–Kaufman syndrome

This is a rare, autosomal recessive disorder characterized by dysmorphic features, hydrometrocolpos, post-axial polydactyly, and congenital heart disease and less often urinary and gastrointestinal anomalies. Fewer than 100 cases had been reported in the English literature until 2005, mainly in the Amish population.[21] McKusick–Kaufman syndrome is difficult to diagnose prenatally and requires postnatal phenotyping and molecular studies before a definitive diagnosis can be established.[22]

Bardet–Biedl syndrome

This is an autosomal recessive multisystemic disorder characterized by a combination of primary and secondary clinical features that include retinal dystrophy or retinitis pigmentosa (appearing usually between 10 and 20 years of age), post-axial polydactyly, obesity, nephropathy, and mental disturbances, or, occasionally, mental retardation. The phenotypic overlap of Bardet–Biedl syndrome and McKusick–Kaufman syndrome, both autosomal recessive syndromes, including hydrometrocolpos and post-axial polydactyly in the neonatal stage and this may cause diagnostic confusion initially.[23]

The presentation of Bardet–Biedl syndrome in an adolescent, 13-year-old girl with retinitis pigmentosa, obesity, polydactyly, learning disabilities, precocious puberty, hypertension, renal cysts, and Hirschprung's disease has been reported.[24] Based on the frequent association of Bardet–Biedl syndrome with hydrometrocolpos and also the recent findings in some mouse models of BBS, it has been suggested that hydrometrocolpos may be considered as an additional diagnostic criterion for BBS to be used in females in parallel with the criterion of hypogonadism in males, thereby improving diagnostic sensitivity.[24]

Typically, MKKS is diagnosed in very young children, whereas the diagnosis of BBS is often delayed to the teenage years. A series of nine patients diagnosed in infancy with MKKS because of the presence of vaginal atresia and post-axial polydactyly, who later developed obesity and retinal dystrophy, thus turning out to be instances of BBS has been reported.[20] Thus, some authors recommended that all children seen in infancy with a diagnosis of MKKS be re-evaluated for other signs of BBS, including mental retardation, obesity, and retinitis pigmentosa.[20,23] MKKS may be considered as a variant of BBS.[23] It has been postulated that mutations in MKKS cause Bardet–Biedl syndrome.[25]

In the inherited type of hydrometrocolpos, obstruction is mainly due to transverse vaginal septum or vaginal atresia, without a urogenital sinus.

ANTENATAL DIAGNOSIS

In recent years, prenatal diagnosis has been made possible by routine antenatal ultrasound scan.[26,27] Antenatal hydrometrocolpos may be associated with oligohydramnios. It may be initially misdiagnosed as a large bladder, representing the dilated proximal vagina.[17] Ultrasonographic findings include a large retrovesical septate hypoechogenic mass in the fetal abdomen. Fetal female urogenital anomalies are often difficult to evaluate by ultrasonography, especially in late gestation. However, when sonographic findings are inconclusive, magnetic resonance imaging (MRI) is a useful complementary tool for assessing fetal urogenital anomalies. It has been useful to diagnose a hydrometrocolpos with septate vagina and uterus didelphys.[7]

CLINICAL FEATURES

The condition has two peaks: during the neonatal period and around puberty.

Neonatal period

About 80% of the cases present at less than three months age. The newborn female infant under the effect of maternal hormones, in addition to having enlargement of the breasts, usually displays swollen vulva and a slight mucoid leukorrhea with a low pH and many Doederlein's bacilli. The vagina has thick, stratified squamous epithelium consisting of an active basal layer and 20–30 layers of large vacuolated cells containing abundant glycogen. By the age of one month, the vaginal secretion becomes scanty and alkaline. The epithelium is thin, the individual cells are small and devoid of glycogen, and the basal layer comparatively inactive.

Rarely, hematocolpos will develop in the newborn infant with estrogen-withdrawal bleeding from the uterus. Secondary infection of the vaginal fluid, usually with colonic organisms like *Escherichia coli* is not uncommon.

The typical presentation in a neonate is as a surgical emergency with lower midline mass, associated with abdominal distension. The female baby is usually sick due to the

gross distension. The upper vagina becomes enormously distended, usually producing a palpable abdominal mass arising from the pelvis. The uterus, with its less distensible and thick muscular wall, is involved to a lesser degree, but is always larger than normal. Examination of the abdomen reveals a tensely cystic, rounded mass arising from the pelvis and occasionally reaching as high as the costal margin. The tumor may seem lobulated because of the distended bladder anteriorly and the moderately enlarged uterus surmounting the vagina. The Fallopian tubes are usually normal, although occasionally they may be distended, even allowing escape of fluid into the peritoneum. Quite often, the fluid gets infected very soon with life-threatening generalized sepsis.

Compression of adjacent structures may cause acute respiratory distress that becomes life threatening. The patient may also have respiratory infection, neonatal sepsis, and fever.

Extensive squamous cell peritonitis has been described to result from vaginal atresia with hydrometrocolpos and squamous cell reflux through the genital system.[17]

Associated features include urinary retention with obstructive uropathy causing scanty and infrequent urination. The upward pull of the enlarging vagina elongates and angulates the urethra, producing dysuria and acute urinary retention. Pressure of the vagina on the ureters crossing the pelvic brim results in hydronephrosis and hydroureter, usually on both sides. Even low lesions may present with urinary retention and bilateral hydronephrosis. However, bilateral hydrosalpinx is extremely rare in the neonatal period.[28]

Besides abdominal distension and sepsis, renal failure is also a common presentation in hydrometrocolpos.[18,29] In addition, there may be presence of abdominal ascites.[29] Compression of the vena cava and iliac vessels will cause cyanosis, edema, and ecchymosis of the perineum, lower extremities and abdominal wall.

The rectum is less commonly involved, but constipation, ribbon stools, and intestinal obstruction may complicate hydrometrocolpos. The perineal examination in lithotomy position under adequate illumination may help to identify a bulging hymenal membrane. Rectal examination reveals the pelvic component of the mass. The translucent bulge of an imperforate hymen will be seen to increase in size when the infant cries or when pressure is exerted on the abdominal mass. In vaginal atresia, the upward pull of the enlarging vagina rising out of the pelvis may retract the atretic lower portion of the vagina up into the pelvis and make the examination difficult. If a major portion of the vagina is absent, the external genitalia may seem quite normal, and the diagnosis will be missed unless the vaginal orifice is deliberately looked for.

In some cases, a transverse septum higher in the vagina will be seen to protrude through a normally perforated hymen, apparently representing a congenital diaphragm. In the absence of clearly demonstrable patency of the vagina, the mass should be considered to be vagina until proven otherwise.[9]

In atresia of the vagina, the appearance of the external genitalia differs markedly from that seen with imperforate hymen. Instead of a bulging membrane protruding from the labia, with unusual prominence of the vulva and perineum, the area normally occupied by the vaginal orifice may be retracted upward into the pelvis, as a result of the enlarging upper vagina escaping from the small pelvis into the more capacious abdominal cavity. Rarely, the abdominal mass may be quite large and associated with gluteal swellings or acute abdomen with paralytic ileus.

In McKusick–Kaufman syndrome, hydrometrocolpos is always associated with post-axial polydactyly and less often congenital heart disease, and urinary and gastrointestinal anomalies.

For obstruction at a higher level, identification and probing of perineal orifices, endoscopy, and radiological studies are essential. When three perineal orifices are present, it is a type II anomaly; with two orifices it is type III or IV; and with one orifice it is type V. Type IIIb will have cystic gluteal bulge. In type II anomaly, there is mild depression at the vaginal site with a small orifice, which can be dilated. Types III and IV can be differentiated by endoscopy and radiological studies.

Around puberty

Rare cases presenting in the prepubertal group from 12 to 15 years may present with complications like leukorrhea through a pinpoint opening in the hymen. In asymptomatic hydrometrocolpos, the diagnosis is made only after accidental discovery of a bulging membrane. The early symptoms attributed to this condition are non-specific indications of discomfort followed by urinary, venous, or intestinal obstruction, respiratory distress, or superimposed infection of the urinary tract or of the fluid retained in the vagina.

Adolescent patients may present with abdominal pain, voiding dysfunctions, and backache.[30] Adults may present with the inability to consummate and infertility.[30]

DIFFERENTIAL DIAGNOSIS

These include congenital, inflammatory, or neoplastic cyst. The mass has also been confused with a presacral mass, such as a sacrococcygeal teratoma, rectosigmoid duplications, or an abdominal mass, such as ovarian cyst or teratoma. When the diagnosis is in doubt, exploratory laparotomy gives the definitive diagnosis.

INVESTIGATIONS

In addition to routine investigations, special preoperative investigations are necessary to differentiate hydrometrocolpos from other neonatal pelvic masses and also to confirm the type of hydrometrocolpos and plan surgery.

These include:

1. Plain skiagram abdomen – anteroposterior view and lateral view to identify the location and size of mass. The small intestinal loops will be displaced into the epigastrium by a rounded homogenous mass in the lower abdomen. Neonatal peritoneal calcifications along with the ascites have also been described in cases of hydrometrocolpos secondary to imperforate hymen, without evidence of gastrointestinal tract obstruction.[31]

2. Abdominal ultrasonography to identify dilated vagina and upper urinary tract anomalies, especially ipsilateral renal agenesis. Transperineal ultrasonography can help to measure a caudally placed obstructive septum in vaginal atresia and thereby help in planning reconstructive surgery. Ultrasonography after drainage of the bladder with a catheter may help in the diagnosis of hydrometrocolpos.
3. Retrograde genitourethrogram (RGU) to identify the urogenital sinus and its communication with the vagina (Fig. 101.2). This may be combined with a hysterovaginogram to delineate the site of vaginal obstruction. When a bulging membrane can be visualized clearly, aspiration of some of the contained fluid and injection of a water-soluble radioopaque material will outline the distended vagina and uterus.
4. Endoscopic evaluation of vaginal, urethral (type III, IV) and rectal orifices (in type V) is needed in addition to radiological procedures to give a composite and accurate picture. Endoscopic catheterization of vaginal and urethral orifices in urogenital sinus and vaginal, urethral, and rectal orifices in cloacal anomaly is indicated in order to establish the internal anatomy by contrast studies. An invertogram may be of help to identify a rectovaginal fistula in cloacal anomaly.
5. Skiagram spine to assess vertebral anomalies and digital skiagrams in the presence of digital or syndromal anomalies.
6. Echocardiogram to rule out cardiac anomalies.
7. Chromosomal anomalies may be needed rarely in cases of ambiguous genitalia to establish the genotype.
8. Intravenous urography (IVU) and computed tomography help to delineate the anatomical details to assess the anatomy while planning corrective surgery. The urogram will demonstrate anterior and superior displacement of the bladder and, possibly, hydronephrosis and hydroureter.
9. Renogram studies confirm the function of each kidney and its clearance.

Urinary hydrometrocolpos is rarely diagnosed and is most often attributed to a persistent urogenital sinus or a cloaca.

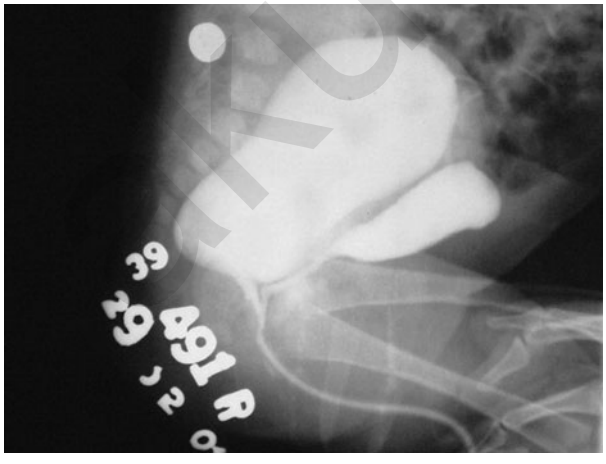


Figure 101.2 Retrograde genitourethrogram of a baby with hydrometrocolpos and anorectal malformation (pouch colon). A faint shadow of pouch colon opening in the vaginal septum (bifid vagina) can be seen. The outline of the urinary bladder with urethra anteriorly and hydrometrocolpos with bifid vagina posteriorly along with the urogenital sinus with 3 cm common channel can be appreciated.

Dynamic MRI has also been reported to accurately diagnose urinary hydrometrocolpos secondary to ectopic drainage of a small left pelvic kidney, associated with a bicornuate uterus.[32]

MANAGEMENT

The treatment of hydrometrocolpos is surgery. The kind of operative procedure and the timing of surgical intervention needed depends upon the severity of the condition and the age at presentation. Early surgery may be indicated in the neonatal period when a grossly distended hydrometrocolpos presents with bulging hymen or is associated with complications. Laparotomy is indicated for high vaginal obstruction, treatment of abdominal complications, or associated anomalies.

Timing of surgery

The management depends on the age at presentation, severity of the symptoms, and the type of the anomaly. The timing of the definitive surgery is a controversial issue.

In the authors' experience, during an acute stage with fluid infection, the baby needs resuscitation and stabilization. A temporizing procedure, such as aspiration of the turbid infected fluid or a vaginostomy in the neonatal period, will help tide over the crisis, enable definitive diagnosis with appropriate investigations, and plan the definitive management in future. Also, it is not feasible to proceed with a raft of investigations in a sick child in order to define the anatomy and withhold the urgent decompression needed. A percutaneous nephrostomy may be needed in patients with bilateral hydroureteronephrosis and uremia.

A definite protocol, awareness, and appropriate investigations with urgency before surgery are necessary and can avoid fatal complications (Fig. 101.3).

Some authors have suggested postponing the definite procedure to the age of menarche, when hematocolpos (accumulation of blood in the vagina) will develop, but before the further development of hematometra (accumulation of blood in the uterine cavity).[33] This will cause stretching of the obstructed segment, will enable correct diagnosis, facilitate the procedure, and eventually minimize the complications. However, they have suggested that if the vaginal obstruction in neonates or in childhood is symptomatic, aspiration of the fluid and temporary release of the symptoms should be the optimal choice, followed by a final surgical correction latter in life.[33]

PREOPERATIVE RESUSCITATION

Patients presenting with complications should be given incubator care with head-end elevated, systemic antibiotics, and i.v. fluid. In the case of respiratory distress, prompt decompression of the gastrointestinal tract by nasogastric aspiration and administration of oxygen and humidity is indicated. If vomiting is present with or without constipation, in addition to nasogastric decompression, fluid and electrolyte imbalance should be assessed and corrected. When

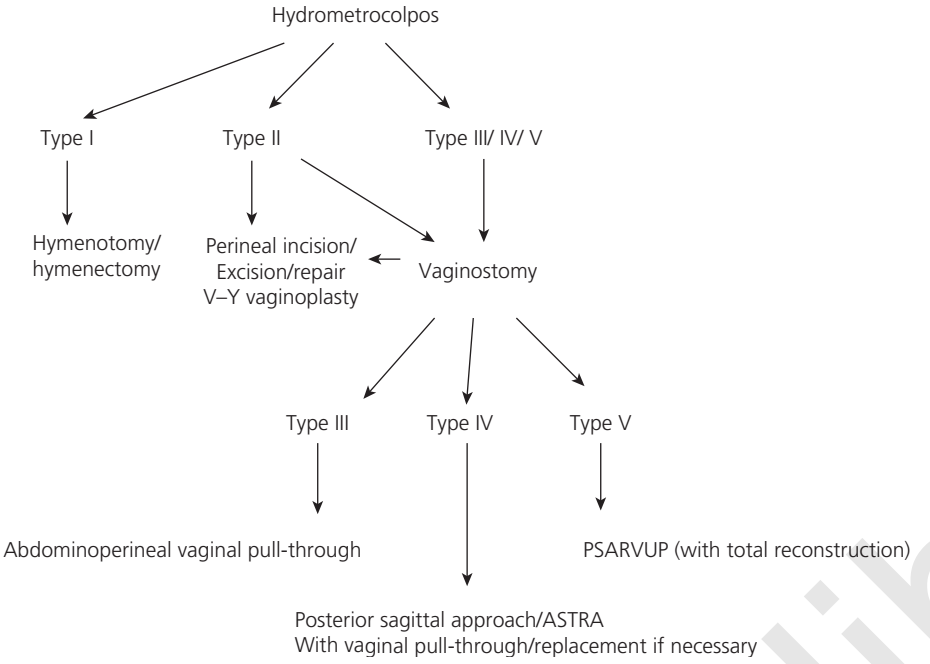


Figure 101.3 Algorithm for management of hydrometrocolpos. Vaginostomy is indicated for all cases with pyometrocolpos to drain out the pus (from the perineal or abdominal route) and improve the general condition of the baby.

dribbling or retention of urine is present, a Foley catheter should be inserted into the bladder for better drainage of urine. When huge distended abdominal mass is present in the actually ill neonate, a preliminary drainage by puncturing the vagina under ultrasonographic guidance may be performed for 24–28 hours prior to corrective surgery. Where experience is available, vaginal septum (type II anomaly) can be incised safely under ultrasonic guidance and x-ray imaging.

SURGICAL MANAGEMENT

The management options may be divided into emergency management and definitive management.

Emergency management

The management is simple with low anomalies (type I and II). However, the patients with type III, IV, and V are usually obstructed and infected. In complicated cases, the attempt should be to drain the infected material through the suprapubic vaginostomy and allow the dilated vagina to shrink. This is followed by a definitive procedure years later (staged procedure). All previous attempts to drain and simultaneously reconstruct the vaginal tract in the newborn stage carried very high mortality and it is not currently recommended.

In the presence of fused labia or adhesion, separation of adhesion followed by vaginal drainage is adequate. In others, it is a temporizing procedure and can be achieved by drainage into the perineum.

DRAINAGE PROCEDURE

Indications for early drainage in neonates

- To drain the infected material and reduce the chance of sepsis;
- To disconnect the communication and retrograde flow of urine to the vagina;
- To allow the inflamed vagina and uterus to shrink and occupy near normal anatomical positions and size to allow planning of definitive surgery.

Indications for early drainage in prepubertal age

- To allow natural passage for menstrual flow;
- To allow creation of passage for future sexual activity and fertility;
- Psychosocial reasons.

The drainage procedure through the perineum may be the only definitive treatment required in type I and II, while drainage provided through the abdominal route (extraperitoneal) will be a temporizing procedure in the other types. The majority of type I and II patients may be managed by vaginal drainage on to the perineum. Sometimes, however, in type II anomaly, due to secondary infection or complex anomalies, a perineal procedure may be deferred and these babies may need suprapubic drainage by catheter or a vaginostomy. The proximal diversion stoma helps not only in decompressing the vagina, but also provides a portal for detailed radiographic studies to delineate the anatomy. If the atretic lower portion of the vagina has been retracted up into the pelvis, it may be desirable to open the vagina through a laparotomy incision to avoid damage to the urethra, bladder, and rectum.

HYMENOTOMY/HYMENECTOMY

A bulging membrane in an infant with imperforate hymen or transverse septum of the vagina may be incised without anesthesia. If the hymen is thickened, the obstruction recurrent, or the patient an adolescent, excision is probably preferable. Hymenotomy may resolve the laboratory and

clinical abnormalities of a patient with hydrometrocolpos due to imperforate hymen presenting as acute renal failure.[34] In all cases, it is desirable to maintain patency of the opening by use of a drain and/or repeated dilatation.

In the lithotomy position, the bulging hymen becomes visible as a grayish membrane. If necessary, the abdomen may be compressed to make the hymen more prominent. A No. 8 Foley catheter is inserted into the bladder to decompress it, as well as for the identification of the urethra during surgery. A stay suture is placed at the center of the hymen and, with a No. 18 needle, an amount of fluid is aspirated and sent for microscopic examination and culture. A circular hymenal segment is excised using a No. 11 blade (Fig. 101.4). The cut margin is oversewn with vertical mattress sutures, and a soft silastic catheter is inserted into the vagina. A skiagram is taken while injecting contrast in order to delineate the internal anatomy. The vagina should be drained for a couple of days. This procedure is simple and can be performed at the bedside in a sick baby in the intensive care unit after assessing the depth with a needle puncture and ultrasonography. In case of doubt, the procedure may be safely performed in the operating room through the abdominal route after performing a dye study. A finger may be put through the vaginostomy as a guide to remove a disk of the septum which may be thick. The edges are then oversewn and a drain placed. In the postoperative period, suitable parenteral antibiotics should be given for 1 week to 10 days.

Vaginostomy

A vaginostomy may serve as a temporizing drainage procedure for cases with infected fluid:

- **Perineal vaginostomy** may be done through the perineal route in type II after needle aspiration. When a low transverse, vaginal septum is present, it presents as a bulging membrane allowing excision and drainage by the perineal route (Fig. 101.5a).
- **Abdominal vaginostomy**. In some patients with type II anomaly, the patients may have a minute opening at the site of the vaginal orifice in the septum (Fig. 101.5b). In a case with well-formed septum, it may be prudent to drain the vagina by a laparotomy approach. If the septum is 1 cm thick, it is wiser to drain the vagina from above by laparotomy and then incise the septum under direct vision after defining the anatomy, in order to prevent injury to the urethra and rectum during dissection.

For the high types (type III, IV, and V), an abdominal route is used for the vaginostomy. Abdominal vaginostomy may be of two types:

1. **Vaginostomy with indwelling catheter**: It is easy to perform. However, the disadvantages include infection, encrustation, need to keep the tube *in situ* causing social nuisance, inconvenience, and requiring frequent changings.

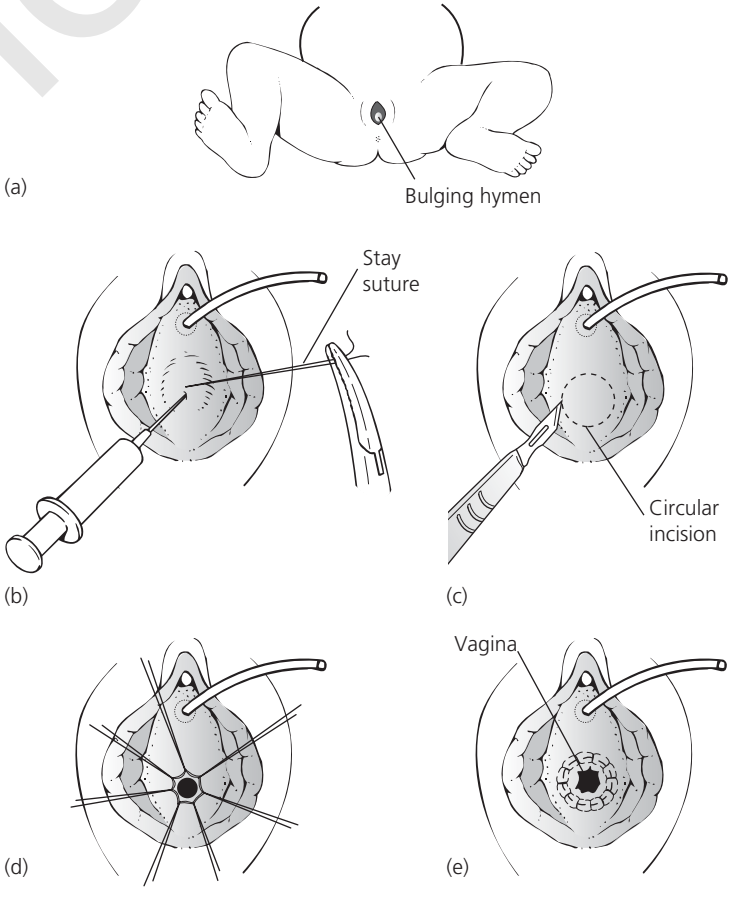


Figure 101.4 Hymenectomy. (a) Lithotomy position showing bulging hymen; (b) aspiration of vaginal fluid; (c) circular hymenal incision; (d) cut margin retracted by vertical mattress sutures; (e) sutures tied exposing the vaginal cavity.

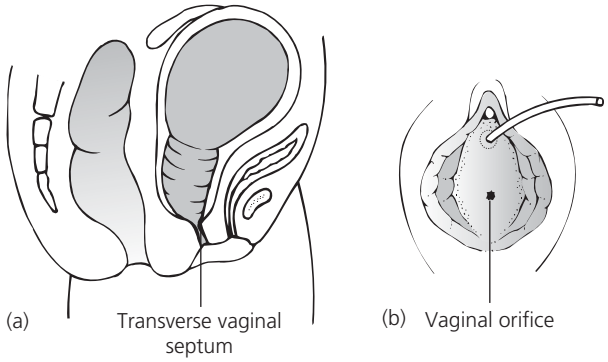


Figure 101.5 Type II hydrometrocolpos. (a) Transverse vaginal septum; (b) minute vaginal orifice.

2. **Tubed vaginostomy**: In this procedure, a U-shaped flap of the vagina is used to make a tube that provides a natural tract for effective drainage for long as necessary, until the time of definitive surgery (Fig. 101.6). A tubed vaginostomy avoids the use of any indwelling catheter and, at the same time, provides easy access for performing dye studies to outline the pathological anatomy of the cavity.[35]

COLOSTOMY

Cases of type V with associated common cloaca always require a diverting 'transverse' colostomy in the newborn stage. This is to be performed in a manner so as to preserve the sigmoid bowel for future use for vaginal replacement. Thus, a transverse colostomy is recommended in babies born with common cloaca.

Definitive management

In types III, IV, and V, the initial vaginostomy is followed by the definitive procedure. An early definitive surgery, around

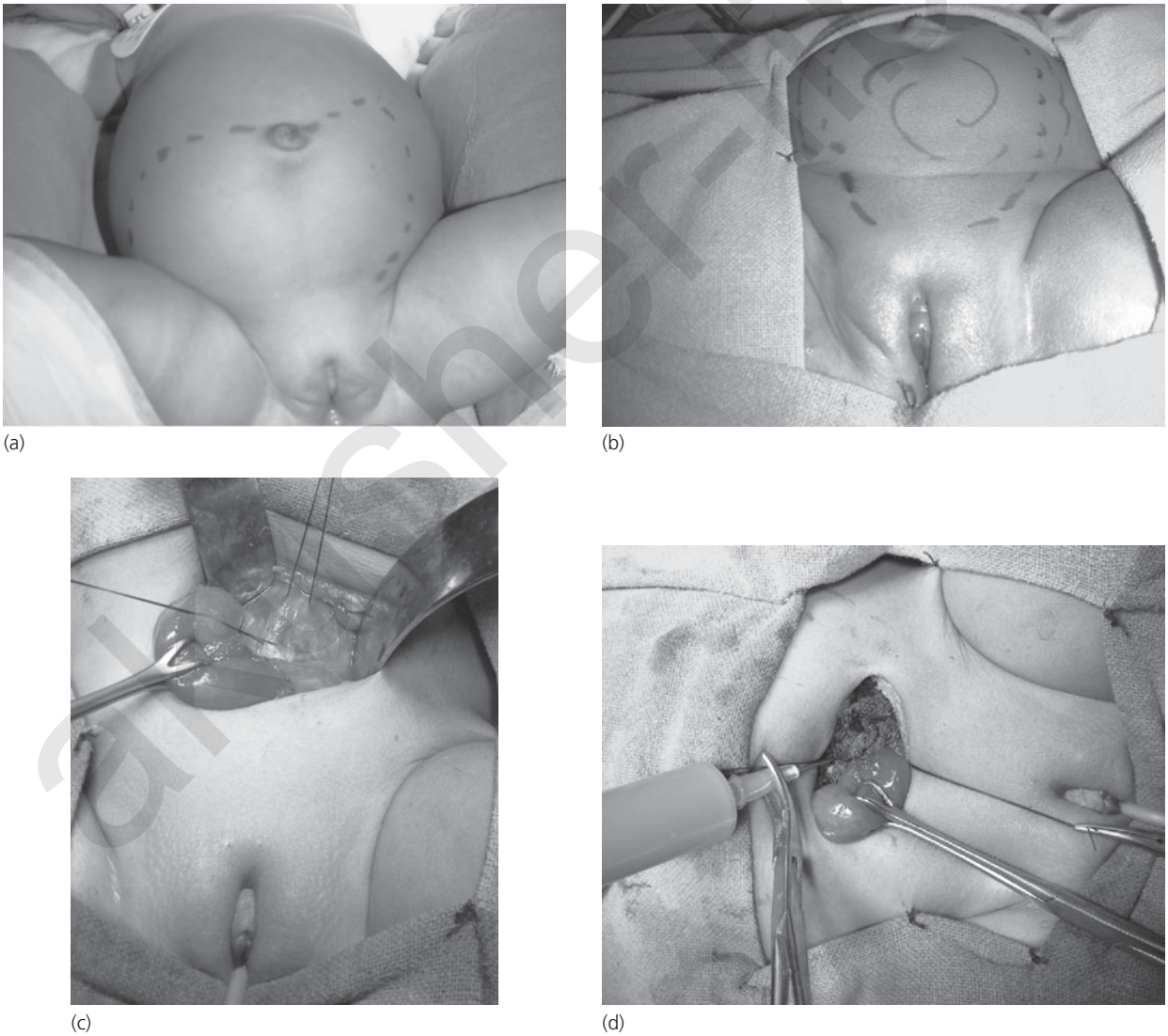
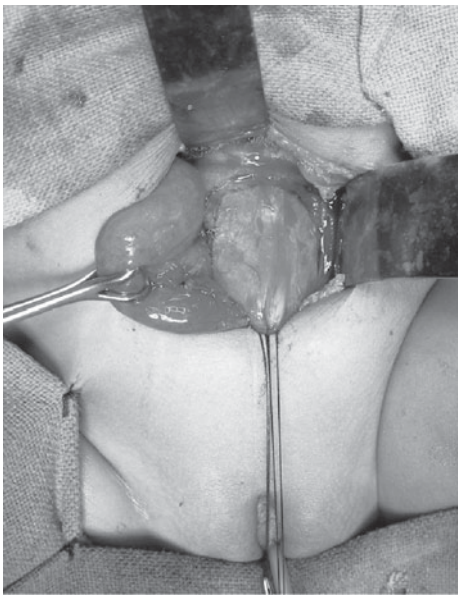


Figure 101.6 Case of hydrometrocolpos in a two-month-old baby. (a) Distended lower abdomen; (b) urogenital sinus with no bulge in perineum; (c) hydrometrocolpos pulled up in stay sutures and the bladder retracted anteriorly; (d) aspiration of pus around a betadine gauze piece; (e) inflamed cavity pulled down; (f) 'U' flap raised from the anterior wall of the vagina opening up the inflamed huge cavity; (g) tube vaginostomy completed.



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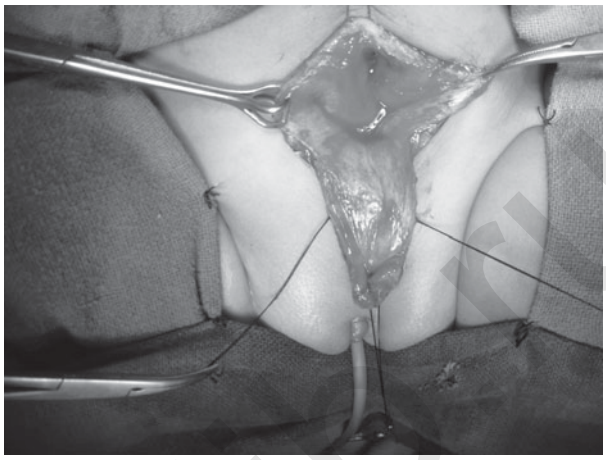

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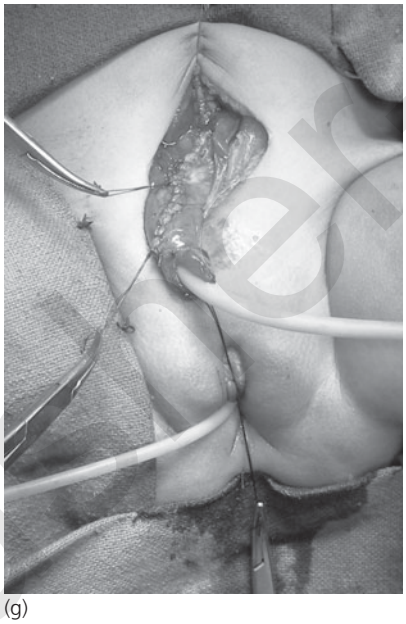

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Figure 101.6 *Continued*

one to two years of age, is indicated in cases with type IV and V as division of the fistulous communication is essential to decrease the morbidity associated with repeated infections. Cases of type III may be tackled at puberty.

After vaginostomy, the dilated vagina with infected material is flooded with urine making it very friable and adherent to the surrounding structures. Any attempt to mobilize and bring the vagina to the perineum may not be successful especially if the gap is >3 cm. Vaginal replacement will be the only option in such cases.

In type III, following initial vaginostomy and drainage, during the definitive procedure, the vagina is exteriorized on to the perineum by an abdominoperineal pull-through (Fig. 101.7).

In type IV, during the definitive procedure, the vagina is exteriorized on to the perineum and the urogenital sinus is left behind to function as the urethra. If the length of the common channel is less than 3 cm, posterior sagittal anorectovaginourethroplasty (PSARVUP) with disconnection of the fistula is performed, followed by mobilization and vaginal pull-through.

If the length of the urogenital sinus in type IV is more than 3 cm, then vaginal replacement would be required in most cases. The common channel in type V is usually more than 3 cm mandating a vaginal replacement.

An anterior sagittal transanorectal approach (ASTRA) in cases of neonatal urinary hydrometrocolpos associated with a persistent urogenital sinus (type IV) has also been described, although not widely practiced.[36]

In the cloacal anomaly (type V), the hydrometrocolpos may be secretory or urinary. In this condition, it is more

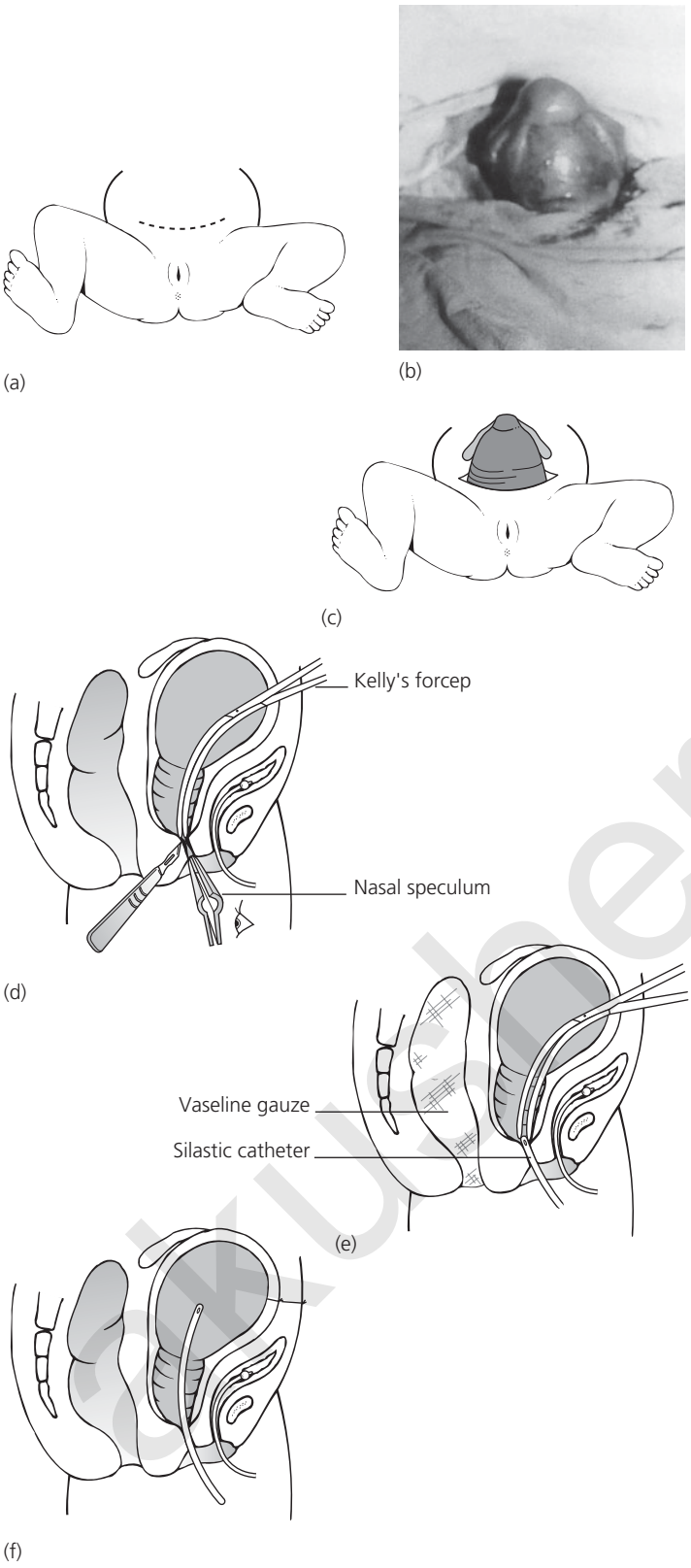

Figure 101.7 Abdominoperineal repair of type II hydrometrocolpos. (a) Low transverse abdominal incision; (b) hydrometrocolpos delivered from abdominal wound; (c) purse-string suture on vaginal wall; (d) Kelly's forcep introduced through the hysterotomy and tip advanced to the most dependent part of the dilated vagina; (e) vaginal septum is being incised while the vaginal orifice is spread open by the nasal speculum and the septum is pushed downwards by Kelly's forcep – the septum is incised and Kelly's forcep pushed down and out, grasping the tip of the Silastic catheter; (f) vagina being drained by an indwelling perineal catheter.

acceptable to perform a temporizing drainage procedure and then do the pull-through via the posterior sagittal route.[37] This route is also preferable for all cases with associated anorectal malformation, after the initial vaginostomy and colostomy (Fig. 101.2b). The vagina may occasionally open to the bladder with a small orifice.[38] Vaginal pull-through surgery and closure of the communication may be required for a vagina occasionally opening into the bladder.[38] The posterior sagittal route is the only option to reach the fistulous communication in such cases.

VAGINAL REPLACEMENT

In cases with type III, IV, and V especially with pyometrocolpos, due to severe inflammation, it may be difficult to separate it from the surrounding structures due to dense adhesions. Despite attempted mobilization, the vaginal length is just not achieved. In such situations, it would be better to replace the vagina using a segment of the bowel.

- **Bowel vaginoplasty**. A loop of sigmoid colon is usually used. Another option is an ileal loop.
- **Skin flap**. Flaps of perineal skin may be used to form the distal vaginal segment.
- **Prosthesis with skin graft**. A skin graft may be put on a prosthetic patch in a cylindrical form to form the vagina. Expertise is needed to perform such surgery. This kind of a replacement is better performed at puberty or before marriage as these are prone to shrinkage unless kept under reglar dilatation.
- **Buccal mucosa graft**. A buccal mucosa graft can be made in a mesh and used for vaginal replacement. However, it shrinks over the course of time and results in fibrosis in almost 60% of cases unless kept under regular dilatation.

MORTALITY

The main causes of mortality are associated anomalies and sepsis. As hydrometrocolpos is associated with serious anomalies, about 50% cases are stillborn. Associated genitourinary anomalies in more than half the cases with hydrometrocolpos are responsible for high morbidity and mortality in this entity. Other causes of mortality include inadequate drainage, urinary infection, spontaneous rupture, generalized peritonitis, and obstructive uropathy due to the large pelvic mass resulting in obstruction to ureters.

FOLLOW UP

If methods like skin flaps, skin grafts, or meshes have been used for vaginal replacement, vaginal calibration and dilatation is required as the chances of stenosis are high, especially if performed at an early age. On follow up (range 1–15 years; mean 7 years), more than 60% of patients have menstrual irregularity, endometriosis, and infertility. A comprehensive management is imperative to preserve the reproductive potentials, as a significant proportion of patients may experience sexual difficulties following vaginal reconstruction.[30]

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Intersex disorders

MARIA MARCELA BAILEZ AND ESTELA CUENCA

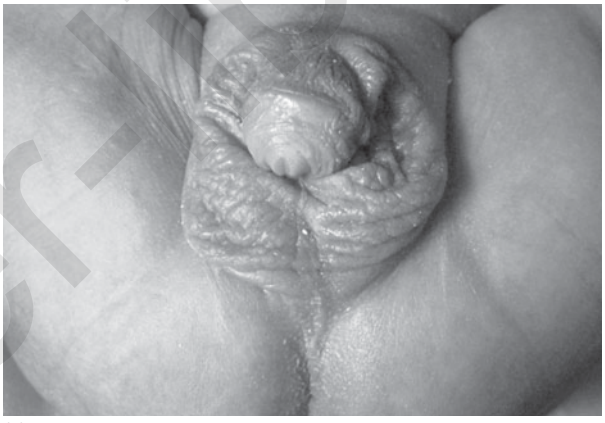
INTRODUCTION

Patients with ambiguous genitalia mostly present in the newborn period and require a multidisciplinary team, including a pediatric surgeon/urologist, to assign the sex of rearing as soon as possible after a thorough genetic, anatomic, functional, and socioeconomic workup.

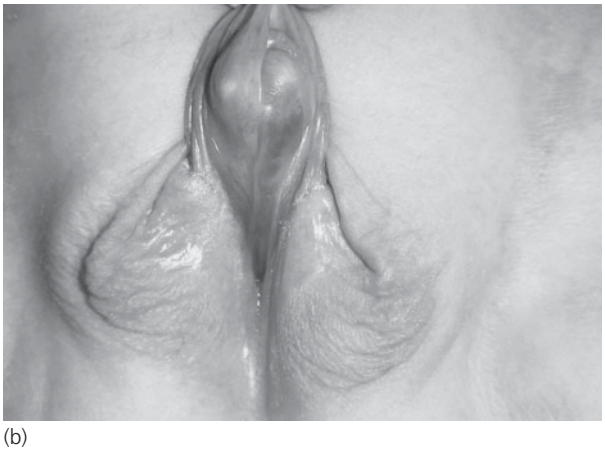
The diagnosis of 'ambiguous genitalia' is based on a meticulous perineal exam and gonadal palpation. Feminine phenotype presents a normal looking clitoris and no palpable gonads, while masculine phenotype presents a normal looking penis and two scrotal testicles.

Although exceptions to this pattern occur (for example, a female with an inguinal hernia or a male with a mild hypospadias or an undescended testicle), if a combined abnormal gonadal palpation and external genitalia appearance are detected, sexual ambiguity should be studied. Isolated severe defects, such as a perineal hypospadias or bilateral non-palpable gonads in a patient with a normal-looking phallus, should also be investigated (Fig. 102.1a, b and Fig. 102.2).

Occasionally, patients with previously unrecognized disorders of sex development (DSD) present later in infancy or puberty.



(a)



(b)

Figure 102.1 (a) A newborn with bilateral non-palpable gonads, but a normal looking phallus. Classic hyperpigmentation seen in congenital adrenal hyperplasia patients before treatment (b), with severe defects like a perineal hypospadias and bilateral non-palpable gonads.

ETIOLOGY

Sex differentiation refers to the anatomic development of the internal and external genitalia as male or female, dependent on the presence or absence of functioning androgens. Prenatally, genital development is constitutively female and non-dependent on estrogens. In contrast, male sex differentiation is androgen-dependent and requires optimal ligand activation of the androgen receptor.

Gonad development

Nineteen years have passed since the discovery of *Sry* as the primary testis-determining gene in Koopman *et al.*'s classic experiment showing that transgenic expression of *Sry* in XX mice results in testis development and male phenotype.[1] Studies in mice are continuing to provide exciting information about differential structural changes and gene expression

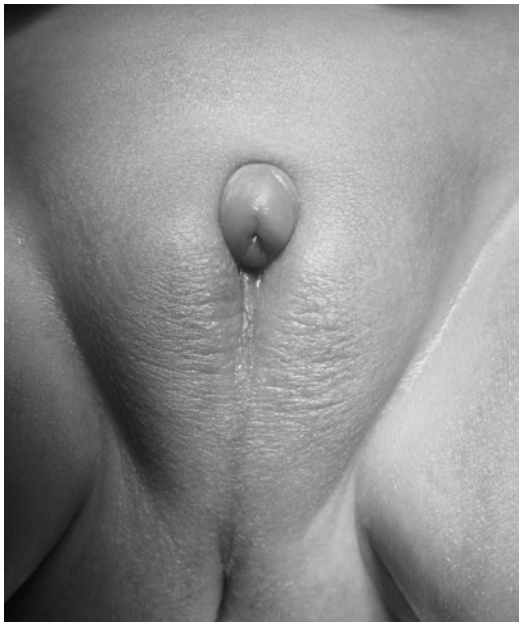


Figure 102.2 Sexual ambiguity should be studied in a patient with combined abnormal gonadal palpation and external genitalia appearance.

in normal gonad development (testis versus ovary), as well as the effect of targeted deletion of key genes involved in this process. WT1, SF1, SOX9, DHH, DMRT, SIDDT, and ARX are some of the genetic determinants of normal gonad development and gonadal dysgenesis.

Androgens

The production of androgens by fetal Leydig cells is initially gonadotrophin independent. During the first half of gestation, placental human chorionic gonadotropin (hCG) ensures that high concentrations of androgens stabilize Wolffian duct development and differentiation of the external genital anlage. Wolffian duct stabilization is dependent on high local concentrations of testosterone diffusing in a gradient along the duct from the adjacent ipsilateral gonad. This accounts for the asymmetric development of Wolffian ducts in some DSD.

The androgen receptor (AR) is a transcription factor that mediates male sexual differentiation *in utero* and is responsible for the development and maintenance of male sexual characteristics. The AR gene is located on the X-chromosome. Mutations in the AR gene may lead to diseases such as androgen insensitivity syndrome (AIS). In AIS, gonadal males had a spectrum of abnormalities ranging from individuals with a female phenotype (complete androgen insensitivity syndrome (CAIS)) through genital ambiguities in the partial form (partial androgen insensitivity syndrome (PAIS)) to men with fertility disturbances in minimal AIS (minimal androgen insensitivity syndrome (MAIS)). More than 500 mutations have now been documented in AIS.

In summary, circulating testosterone is responsible for virilization and is dependent upon 5-alpha-reductase (transforms testosterone into dihydrotestosterone) and the presence of appropriate receptors.

Anti-Müllerian hormone

The pre-Sertoli cells secrete a glycoprotein hormone – the anti-Müllerian hormone (AMH). It causes involution of the Müllerian ducts and stimulates the Leydig cells to produce testosterone. It is also responsible for the first stage of testicular descent. The AMH receptor is different from the AR. Persistent Müllerian structures in 46,XY DSD patients may be due to failure of the production of the hormone from the testes (50%) or to receptor deficiency.

Steroids

Problems in the early stages of steroid genesis can result in abnormalities of adrenal steroid synthesis, which may result in external virilization of a gonadal female-like congenital adrenal hyperplasia (CAH) or under-androgenization of the 46,XY fetus.

The 21-hydroxylase is encoded by a gene on chromosome 6. Its deficiency is inherited in an autosomal recessive fashion. Tremendous progress has been made in the past 15 years in understanding the role of mutation of factors involved in the steroid genesis process (e.g. STAR, CYP11A, HSD3B2, CYP17).

Considerably more research is needed to be able to translate this new knowledge into effective patient care and to understand the long-term outcome in specific conditions.

HISTORY

The term 'hermaphrodite' describes a person who has simultaneous male and female attributes. The term has its origin in Greek mythology: son of Hermes and Afrodita, *Hermafrodito*. The nymph Salmacis was rebuffed by him and she pleaded to the gods to unite him in one body. The gods complied, and from that time on Hermaphrodito had both male and female sex organs.

Oriental and Greek civilizations thought of hermaphrodites as superhuman and included them in much of their art. Plato, Aristotle, Galen, and Hippocrates were among many early physicians and philosophers whose hypotheses on the origin of the intersex child were based on natural phenomena**.** This is in marked contrast to the Romans, who saw the birth of such children as an evil omen, and promptly destroyed them by drowning or abandoning them in an open field to die.

Advances in identification of the molecular genetic causes of abnormal sex with a heightened awareness of ethical issues and patient advocacy concerns necessitate a re-examination of nomenclature. Terms such as 'intersex', 'pseudohermaphroditism', 'hermaphroditism', 'sex reversal', and gender-based diagnostic labels are particularly controversial. These terms are perceived as potentially pejorative by patients and can be confusing to practitioners and parents alike. The consensus

statement on management of intersex disorders proposes the term 'disorders of sex development', as defined by congenital conditions in which development of chromosomal, gonadal, or anatomic sex is atypical.

PHYSICAL EXAMINATION

External genitalia examination includes gonadal palpation and perineal exam; both are the key to choose the sequence of diagnostic procedures to reach an etiologic diagnosis. Visualization of both faces of the phallus is important, looking for the urethral orifice, defining its localization and aspect. The other diagnostic key is inguinal and perineal palpation looking for gonads. Each patient needs to be considered on an individual basis.

PRESENTATION

Traditionally, DSD patients were classified into three groups based on gonadal structure:

1. The presence of two well-defined ovaries with ambiguous or male external genitalia (female pseudohermaphroditism; now called overvirilized XX female). These patients have a 46,XX karyotype and virilization of the external genitalia which results from exposure to a high level of androgens *in utero*, while they have female internal genitalia. CAH is the most common disease in this group and accounts for 50–80% of all the cases of ambiguity, depending on the population analyzed. The most common enzymatic defect is 21-hydroxylase deficiency. The incidence of 21-hydroxylase deficiency is 1 in 15000 to 40000 newborns. Other defects are 11-hydroxylase (hypertension) and 3(β)-ol dehydrogenase or aromatase.
2. The presence of two well-defined testicles with ambiguous or female external genitalia (male pseudohermaphroditism, now called undervirilized XY male). These patients have a 46,XY karyotype and ambiguity of the external genitalia results from a failure of the masculinization androgenic action of the male fetus. This can be due to a failure in androgenic synthesis or in the biological response. This group includes rare defects of the biosynthesis of testosterone, defect of the 5-alpha-reductase (the enzyme that converts testosterone to dihydrotestosterone) and partial androgen insensitivity syndrome (partial defect of androgenic receptors). It is important to recognize that patients with a 46,XY karyotype and dysgenetic testicles are sometimes included in this group in the literature.
3. The presence of incomplete differentiated gonads or coexisting ovarian and testicular tissue with ambiguous or female external genitalia. This is a heterogeneous group with one common factor which is a structural defect in gonadal differentiation with or without a chromosome alteration. Patients with mixed gonadal dysgenesis, testicular dysgenesis, and true hermaphroditism (now called 'ovotesticular disorder of sexual development') are included in this group.

For the purpose of investigation they are divided into:

1. Disorders of chromosomes (chromosomal DSD)
2. Disorders of gonad development (gonadal DSD, sex determination)
3. Disorders of sex steroid synthesis and action (phenotypic/anatomic DSD, sex differentiation).

DIAGNOSIS

According to the Consensus Statement on Management of Intersex Disorders,[2] optimal clinical management of individuals with DSD should comprise the following:

1. Gender assignment must be avoided before expert evaluation in newborns.
2. Evaluation and long-term management must be performed at a center with an experienced multidisciplinary team.
3. All individuals should receive a gender assignment.
4. Open communication with patients and families is essential, and participation in decision-making is encouraged.
5. Patient and family concerns should be respected and addressed in strict confidence.

The initial contact with the parents of a child with a DSD is important, because first impressions from these encounters often persist. A key point to emphasize is that the child with a DSD has the potential to become a well-adjusted, functional member of society. Although privacy needs to be respected, a DSD is not shameful. It should be explained to the parents that the best course of action may not be clear initially, but the health-care team will work with the family to reach the best possible set of decisions in the circumstances. The health-care team should discuss with the parents what information to share in the early stages with family members and friends. Parents need to be informed about sexual development.

A detailed personal and familiar anamnesis can give important information. Some of these pathologies recognize a sex-linked transmission (X-link) and the mother will be able to transmit the defect to 50% of her sons (complete or partial androgen insensibility). Many have an autosomal recessive transmission (CAH, deficit of the testosterone synthesis, deficit of 5-alpha-reductase, deficit of the LH receptor). Neonatal death in the first days of life of male babies may be due to an unrecognized congenital adrenogenital syndrome. Diagnostic algorithms are useful as guidelines to simplify the study of these complex patients.[3]

Figure 102.3 resumes the sequence of investigations used in a newborn with a suspected DSD, according to gonadal palpation. A karyotype is mandatory, but this always requires several days to complete. In the absence of palpable gonads, the first blood tests are those to exclude problems that can

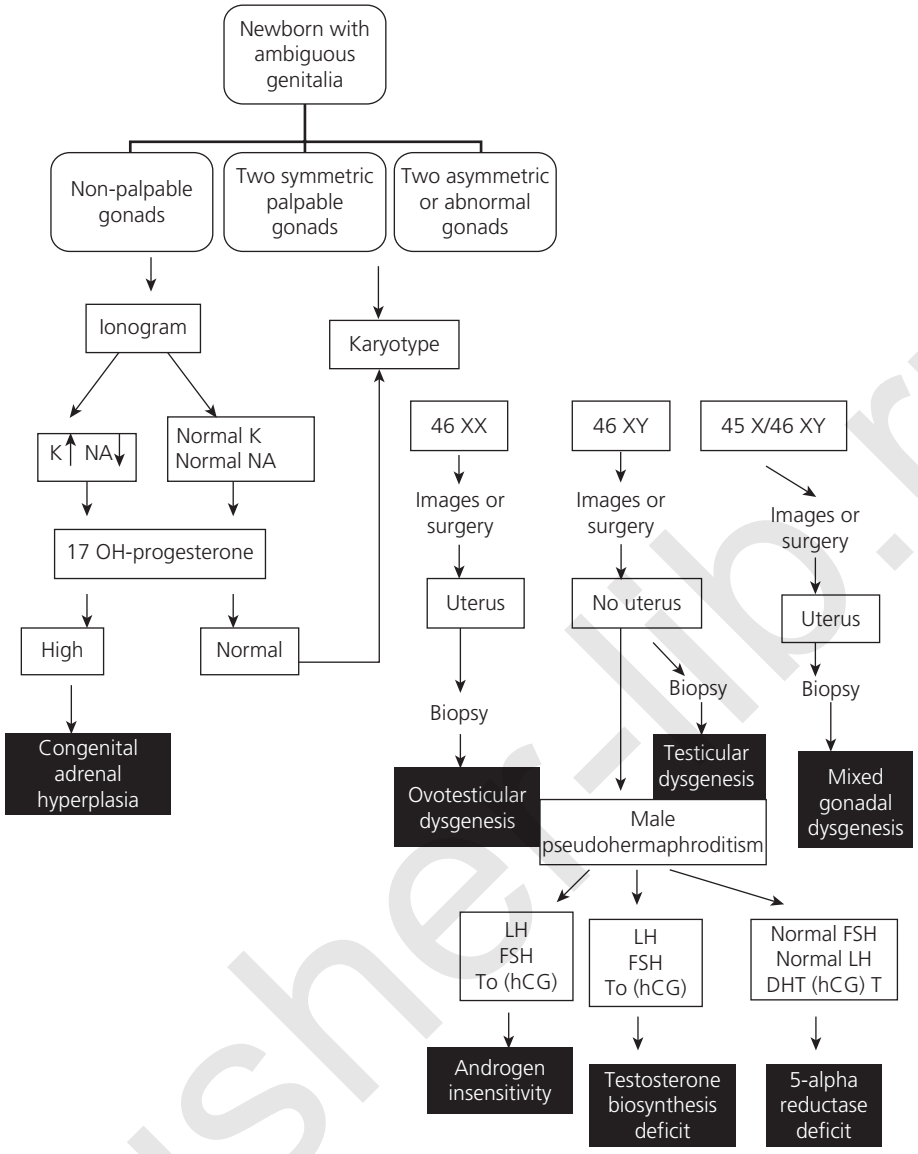


Figure 102.3 Sequence of investigations used in a newborn with a suspected disorder of sex development.

put the baby's life at risk (blood electrolytes) commonly found in the event of salt-losing CAH. The blood sexual steroids must be determined and among them the level of 17-OH-progesterone that, if elevated, will enable the diagnosis of the most common cause of DSD.[3]

The level of other steroids (testosterone, dihydrotestosterone, delta-4-androstenedione, DHEA, 17-OH-progesterone), ACTH, cortisol, and renin will allow a precise picture of the gonadal and adrenal steroidogenesis. For example, the ratio of testosterone to dihydrotestosterone (DHT) greater than 10 is suspicious of a deficit of 5-alpha-reductase enzyme.

The most valuable stimulation tests for evaluating steroid genesis are:

- hCG test for the study of testicular functionality.
- ACTH test for the study of adrenal steroid genesis.
- Low values of testosterone can be the sign of testicular dysgenesis if associated with low levels of all the other testicular steroids or of an enzyme defect of the steroid genesis path, if they are associated with high levels of their precursors.
- Normal or elevated levels of testosterone and dihydrotestosterone may be suggestive of receptor resistance to androgens.

The possibility of the ambiguous genitalia to virilize can be estimated after an hCG test or an appropriate stimulation trial with testosterone or topical DHT. This can be estimated by demonstrating the increment of the penile dimensions or indirectly by the dosage of androgen-sensitive circulating substances (SHBG). Its values are reduced if the patient tissues present sensitivity for the virilizing effect of androgens.[3]

Molecular biology techniques are more sensitive and specific tests for assessment of the tissue sensibility to androgens, but are not always available.

Histology is only required for diagnosis in patients with abnormal gonads (group 3).

Imaging tests

The primary objective of this test is the study of the internal genitalia anatomy. The pelvic ultrasound for the demonstration of the presence of Müllerian structures is an important diagnostic element.

Genitography is very useful for the study of vaginal morphology, dimension, and relation to the urethra (Fig. 102.4a–c). We look for the onset of the vaginal outlet in the urogenital sinus (UGS) with special attention to the proximal urethra to plan the urogenital reconstruction (see below under Management).

Sex of rearing

Factors that influence gender assignment include diagnosis, genital appearance, surgical options, need for lifelong replacement therapy, potential for fertility, views of the family, and, sometimes, circumstances relating to cultural practices.

More than 90% of patients with 46,XX CAH and all patients with 46,XY CAIS assigned female in infancy identify as females. Evidence supports the current recommendation to raise markedly virilized 46,XX infants with CAH as female.

Consistent penile development constitutes a basic element for the choice of male rearing, even though the criteria that must guide this choice are currently the object of debate. A good response in testosterone levels after the hCG test and an increase in penile length after administration of testosterone in the neonate will be useful to decide the choice in favor of a male.

In some patients, the possibility of future virilization at puberty has to be taken into account (deficit of 5-alpha-reductase and the defect of synthesis of testosterone from deficit of 17-βHSD). Nowadays, however, diagnosis is simpler due to the advent of molecular genetics.

Approximately 60% of 5-alpha-reductase-deficient patients assigned as female in infancy and virilizing at puberty (and all assigned male) live as males. In 5-alpha-reductase and possibly 17-hydroxysteroid dehydrogenase deficiencies, for which the diagnosis is made in infancy, the combination of a male gender identity in the majority and the potential for fertility (documented in 5-alpha-reductase-deficient patients, but unknown in 17-hydroxysteroid dehydrogenase deficiencies) should be discussed when providing evidence for gender assignment.

Among patients with partial androgen insensitivity syndrome, androgen biosynthetic defects, and incomplete gonadal dysgenesis, there is dissatisfaction with the sex of rearing in 25% of individuals, whether raised male or female.

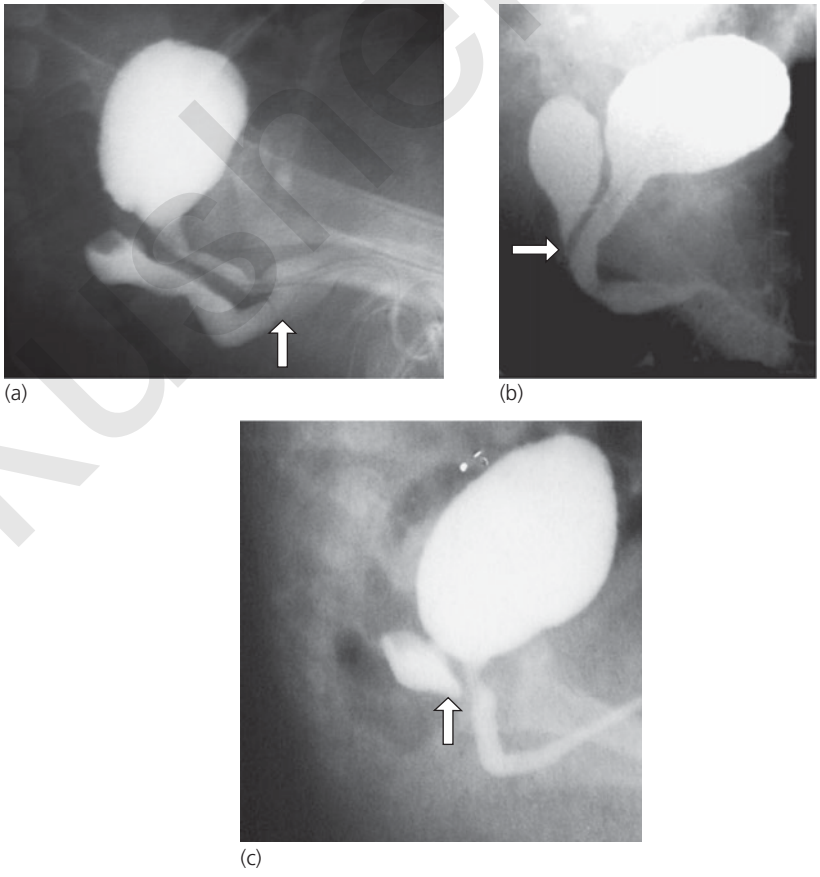


Figure 102.4 Genitography is very useful for the study of vaginal morphology, dimension, and relation to the urethra. Depending on vaginal confluence in the urogenital sinus, the vagina was classified as (a) low, (b) intermediate, and (c) high variant. The white arrows show the confluence of the vagina in the urogenital sinus.

Available data support male rearing in all patients with micropenis, taking into account equal satisfaction with assigned gender in those raised as male or female, but no need for surgery and the potential for fertility in patients reared as male.

Those making the decision on sex of rearing for those with ovotesticular DSD should consider the potential for fertility on the basis of gonadal differentiation and genital development, assuming that the genitalia are, or can be, made consistent with the chosen sex.

In the case of mixed gonadal dysgenesis (MGD), factors to consider include prenatal androgen exposure, testicular function at and after puberty, phallic development, and gonadal location.

MANAGEMENT

Except for gonadal biopsy or resection, no other surgery is performed in the neonatal period. Most of the reconstructive procedures, although performed early are not recommended in the first month of life.

However, the surgeon plays an important initial role in the interdisciplinary team that an institution is obliged to have in place to take care of these complex patients. He not only needs to take care of the best operative techniques for better functional results, but also manage the proper information (after consulting widely with the team) to be given to parents and family. The use of improper words and misinformation may result in irreversible sequela. In our opinion, the surgeon has to be fully informed and participate actively in the preoperative workup before making contact with the family.

Preoperative

A stable endocrine status, especially in CAH patients, is extremely important for a well-tolerated surgical procedure with the best postoperative results. A psychosocial analysis of the family is also recommended. Once again, the authors emphasize the interaction with clinical colleagues within the interdisciplinary team in charge of the case.

When reconstructing the urogenital sinus, a preoperative enema is indicated. Preoperative antibiotics are used according to the protocol of each institution.

Operative

The role of surgery consists of: (1) gonadal treatment, (2) feminizing genitoplasty, and (3) urethral/penile reconstruction in the undervirilized child.

GONADAL TREATMENT

Gonadal histology is required for diagnosis in intersex patients with abnormal gonadal development, such as mixed gonadal dysgenesis (MGD) and true hermaphroditism (TH), recently called ovotesticular DSD. Although sex may be assigned before the biopsy is taken, histology in these patients is required for a definitive diagnosis.

Gonadal biopsies must be taken along the longitudinal axis of the gonad as both ovarian and testicular tissue may be found at the polar ends of the gonad (Fig. 102.5). Depending on the result of the frozen section biopsy and the previous investigations, the gonad is removed. Patients with TH may have an ovary (O) and testicle (T), bilateral ovotestes (OT), and an ovary and ovotestes.[4]

Surgical management in DSD should also consider options that will facilitate the chances of fertility. The ovarian component of an ovotestes may be separated and the testicular tissue removed, using a zoom lens, although it must be borne in mind that these gonads need to be followed closely.

If a streak gonad is recognized as in most patients with MGD, it is removed without prior biopsy together with the surrounding peritoneum and the ipsilateral gonaduct (Fig. 102.6). This gonad has to be removed, avoiding previous biopsy, as it has a 25–50% chance of developing a gonadoblastoma and/or dysgerminoma and as there is the possibility of an *in situ* tumor at the time of the procedure. It is usually associated with an intra-abdominal or inguinal dysgenetic testicle, which is removed at the same time in patients with female sex assignment. Although there is the same risk of malignancy in the contralateral gonad (dysgenetic testicle), it may be biopsied and preserved in the scrotum of patients with male sex assignment because this gonad is functional.

The highest tumor risk is found in TSPY (testis-specific protein Y encoded)-positive gonadal dysgenesis and partial androgen insensitivity with intra-abdominal gonads, whereas the lowest risk (5%) is found in ovotestis and complete androgen insensitivity.

Better laparoscopic visualization and quicker access to intraperitoneal gonads encouraged the scheduling of simultaneous gonadal and genitalia procedures with good results. Nowadays, following a preoperative workup by an experienced multidisciplinary team, laparoscopic biopsies are performed followed by gonadal resection if required at the

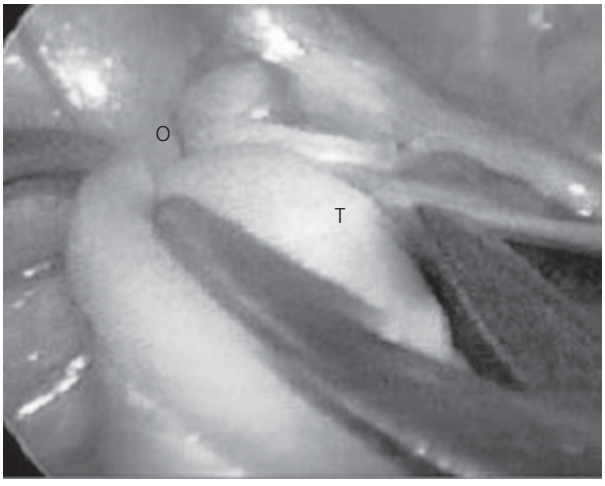


Figure 102.5 A laparoscopic view of ovotestes. This is the technique for gonadal biopsy along the longitudinal axis of the gonad. O, ovarian portion; T, testicular component.

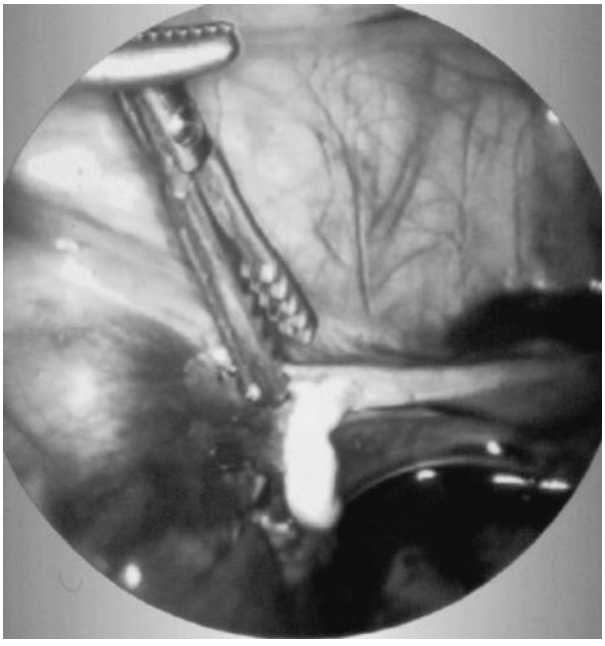


Figure 102.6 A laparoscopic view of streak gonad. Bipolar coagulation of the gonadal pedicle. These gonads are resected in block with the surrounding peritoneum.

same time of feminizing genitoplasty in female sex reassignment patients in a single stage initial approach.[4]

Sex may be assigned prior to laparoscopy in patients with 45,XO/46,XY gonadal dysgenesis. This is based on a functional and psychosocial basis in combination with the results of the karyotyping, hCG testing, and interview with the parents.

The authors have never found functional ovarian tissue in these patients, but always await the result of frozen section biopsy before removing any other gonad than a classical streak.

True hermaphroditism patients do not have such a classical pattern and definitive histology is often necessary for sex assignment. Although the most common karyotype is 46,XX and the most common gonadal combination is ovary/ovotestes, each case is unique and should be treated on an individual basis. Sometimes, the macroscopic aspect of the gonad and gonaduct, as well as the result of a frozen section biopsy strongly favors gonadectomy in patients with previous sex assignment. There is an advantage of a laparoscopic approach in these patients requiring secondary pelvic exploration, especially because many of them are potentially fertile.

An additional role of laparoscopy is excision of Müllerian structures, prostatic utricle, and orchidopexy in patients raised as males. In patients with a symptomatic utriculus, removal is best performed laparoscopically to increase the chance of preserving continuity of the vas deferens.[4]

An inguinal approach may be indicated in patients with palpable gonads (Fig. 102.7). However, a laparoscopic approach is preferred in most of them as it enables not only better visualization of potential Müllerian structures, but also allows for treatment of a patent peritoneal sac, when removing the gonads, with better cosmetic results. In addition, most of these patients have asymmetric gonads

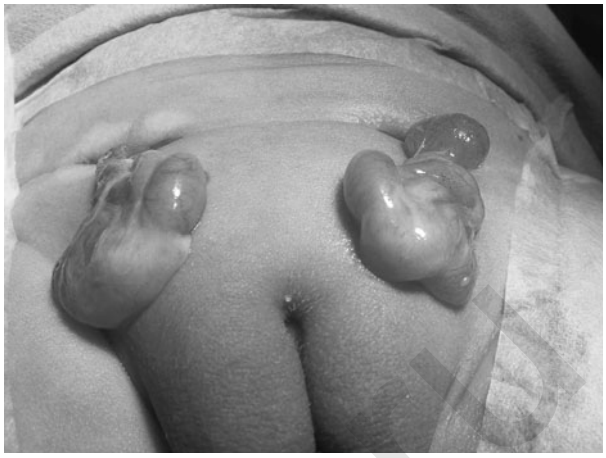


Figure 102.7 An inguinal approach for gonadectomy in a CAIS patient with palpable gonads.

with one of them being intra-abdominal. The inguinal approach is reserved for XY patients with symmetric palpable gonads introducing the telescope through the associated hernia sac in order to rule out the presence of Müllerian structures.[5]

FEMINIZING GENITOPLASTY

Fortunately, there have been many advances in ambiguous genitalia reconstruction with many surgeons contributing. Cosmetically, a near-normal appearance can now be achieved, but long-term functional results with newer techniques are still unknown.

Timing for this type of surgery is controversial. It is now the general belief that one-stage total reconstruction can be performed in most patients in the early months of life. Regardless of the timing or the procedure elected, the surgery must be performed meticulously with a clear understanding of the anatomy and only be undertaken in centers with great experience and after all aspects of controversy have been explained in detail to the parents. Surgery consists of: (1) management of clitoral enlargement, (2) reconstruction of the urogenital sinus, and (3) labioplasty.

Management of clitoral enlargement

Management of clitoral enlargement remains controversial because of the ablative nature of the structure so vital to psychological body image and gender. Initial techniques consist of total clitorectomy based on the belief that it was necessary to prevent gender dysphoria. However, new understanding that an intact clitoris plays a crucial role in the development of female sexuality has stimulated a more conservative surgical approach, but recession of the clitoris, keeping the corpora, may lead to painful erections during sexual arousal. The most used technique has been that based on Kogan's reduction clitoroplasty, including removal of the corporal erectile tissue with preservation of the neurovascular bundle to the glans (Fig. 102.8a–c). Glans reduction is accomplished by superficial excise of the epithelium of the glandular groove, avoiding a scar in the glans tissue which is fixed to the pubis attachment.

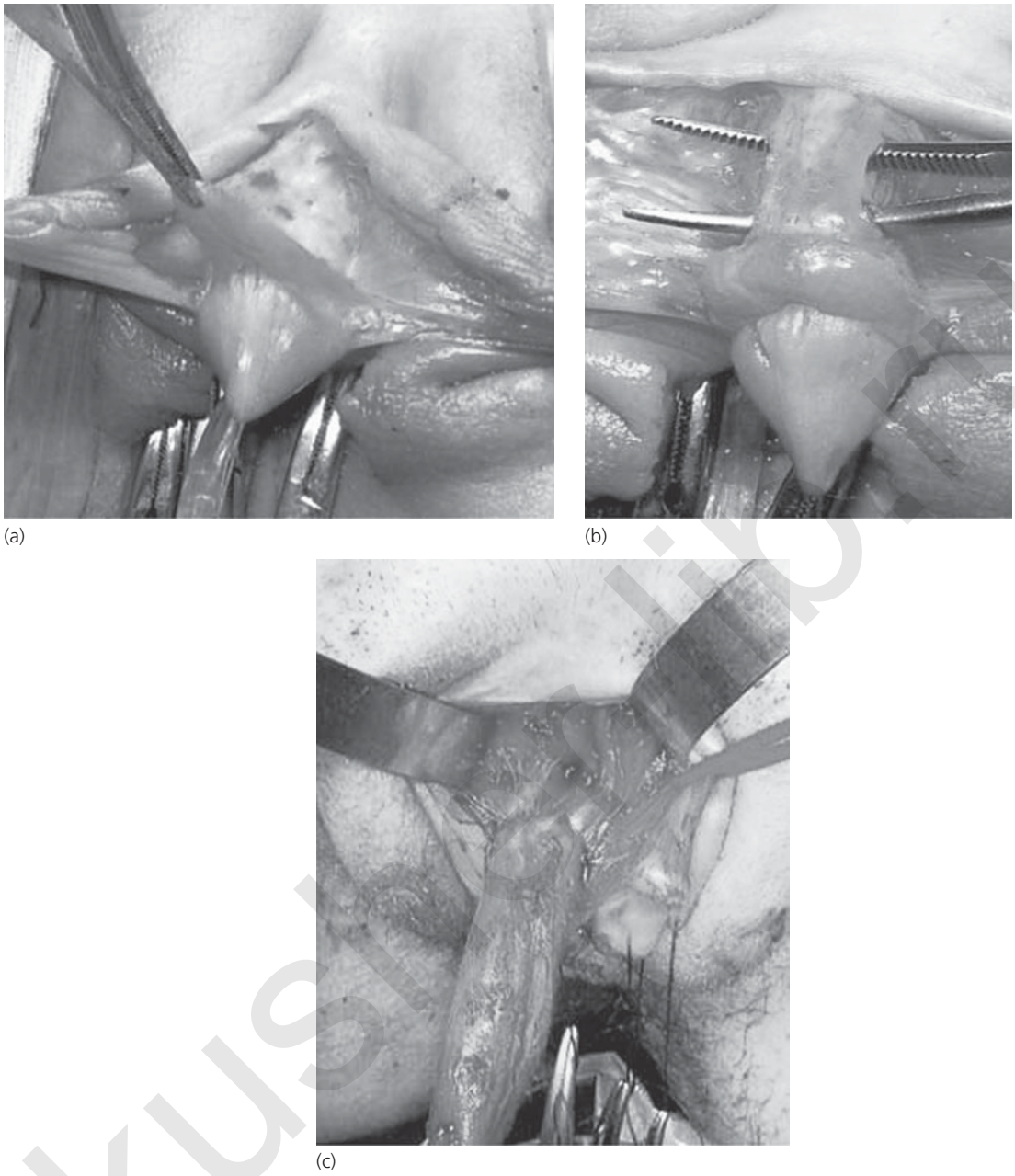


Figure 102.8 Reduction clitoridoplasty. (a) Dorsal incision of skin; (b) isolated neurovascular bundles; (c) corporal erectile tissue is ready to resect.

There is evidence that innervation of the glans comes from the surrounding skin and plays an important role in sexual arousal. Recently, surgeons have been careful in preserving most of the glands, trying to avoid its unnecessary section. The dorsal pedicle, as well as the ventral skin and mucosal surface, should be kept and it is preferable not to excise the glans in any surface, but rather hide it.

Recently, a non-ablative and potentially reversible technique that dismembers the corporal bodies keeping them in the labia major has been described by Pippi Salle *et al.*[6] in response to new understandings that an intact clitoris plays a crucial role in the development of female sexuality, but no long-term follow up is available.

Reconstruction of the urogenital sinus

UGS abnormalities present as a spectrum that goes from a labial fusion to an absent vagina, depending on the location of the vaginal confluence in the UGS. Powell *et al.*[7] described four types: (1) labial fusion, (2) distal confluence, (3) proximal confluence, and (4) absent vagina. In 1969, Hendren and Donahoe[8] described different procedures required for reconstruction depending on the location of the vaginal confluence in the UGS related to the external sphincter (low when distal and high when proximal to the sphincter). This has been very helpful for reconstructive understanding, but the vagina is not always high or low and the sphincter not well seen. Vaginas have been found to be

located in a wide spectrum of position from a normal position, to the entrance of the bladder. The low confluence was classically repaired by a 'flap vaginoplasty' and the mid to high by a 'pull-through vaginoplasty'.

Even in the low type, a very aggressive dissection of the posterior vaginal wall, separating it from the rectal wall is recommended. The vagina is then cut in the midline well back into its normal caliber and at this point a wide cutaneous flap can be sewn using delicate sutures. A rectal finger is very useful to facilitate vaginal exposure (Fig. 102.9a, b). This maneuver of bringing the vagina out (rather than skin in) prevents the known complications of the Fortunoff flap (growing of hair and stenosis).

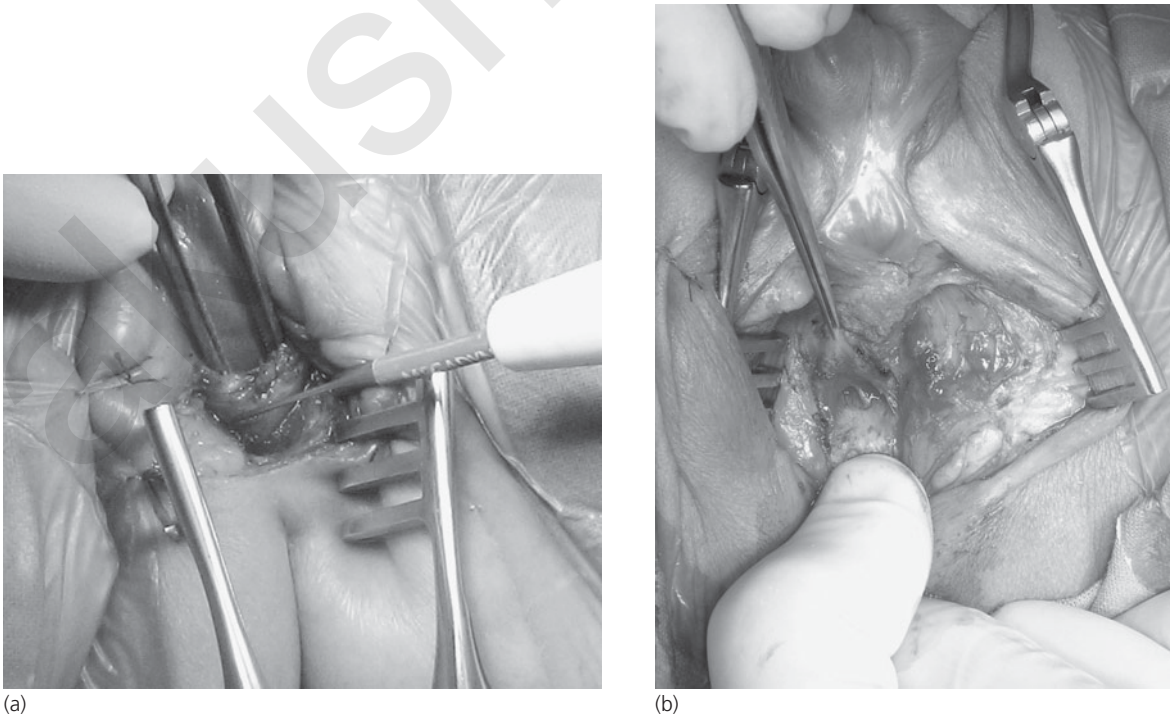
Exteriorization of the high vagina in the severely masculinized female is a surgical challenge. The vagina must be detached from the UGS and then connected to the perineum. The pull-through principle consists of placing a Fogarty balloon catheter into the vagina cystoscopically to locate it by palpation deep in the perineum later (Fig. 102.10a, b). The UGS is approached like a bulbous urethra. In severe cases, perineal anatomy is like that of a normal male. The vagina is incised over the balloon, detached from its entry point in the UGS and the anterior wall carefully dissected off the overlying urinary tract. The walls from the vagina to the perineum may be constructed using a combination of inverted U cutaneous flap (Fortunoff flap), prepucial flap (Gonzalez and Fernandez),[9] and redundant tissue from the UGS (Passerini flap). The anterior sagittal transrectal approach (ASTRA) in a prone position is another method of exposure using the perineal approach.[10]

In the middle of these two points, the authors found what is termed 'intermediate UGS'. Although the vaginal opening is distant from the UGS opening, there is enough proximal urethra to avoid urethra–vaginal dissection and separation. After Alberto Peña's description of 'total urogenital mobilization' (TUM) for the treatment of cloacas in 1997,[9] this maneuver was used to treat intermediate UGS abnormalities. The UGS is mobilized in block to the perineum (Fig. 102.11a, b). It is used in the lithotomy position, mobilized without previous opening to prevent bleeding and the sinus tissue is never amputated until the end, as it may be used in the repair. Each patient must be individualized and this technique can be combined with a pull-through if required.[11,12]

Recently, Rink *et al.*[13] has described a variant that he calls 'partial urogenital mobilization' (PUM), stopping dissection at the level of the pubo-urethral ligament. Currently, regardless of the level of the confluence, he starts with PUM, allowing a unified approach to all repairs.

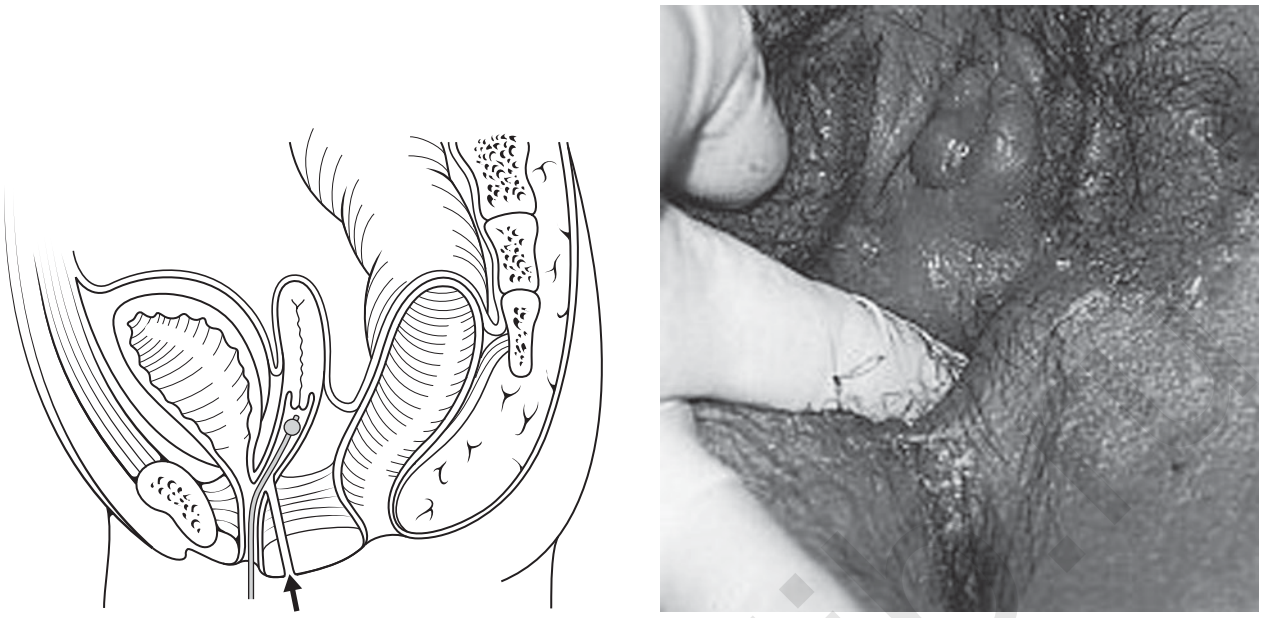
A posterior sagittal approach has also been described to correct intermediate and high UGS.[10]

In the authors' opinion, the best way to treat the high UGS is a combination of several techniques. A balloon catheter (most often a Foley one using a catheter as a guide) with a cystoscope is inserted. The UGS is mobilized in the lithotomy position without opening it (Fig. 102.12a). The patient is then turned to the prone position, the rectum retracted and sometimes the anterior wall opened (Fig. 102.12b). The vagina is opened over the balloon, the Foley catheter repositioned in the proximal urethra, and the uretrovaginal fistula closed, taking care not to denervate the bladder neck (Fig. 102.12c, d). The short vagina (which is usually the case in these patients) needs to be exteriorized.



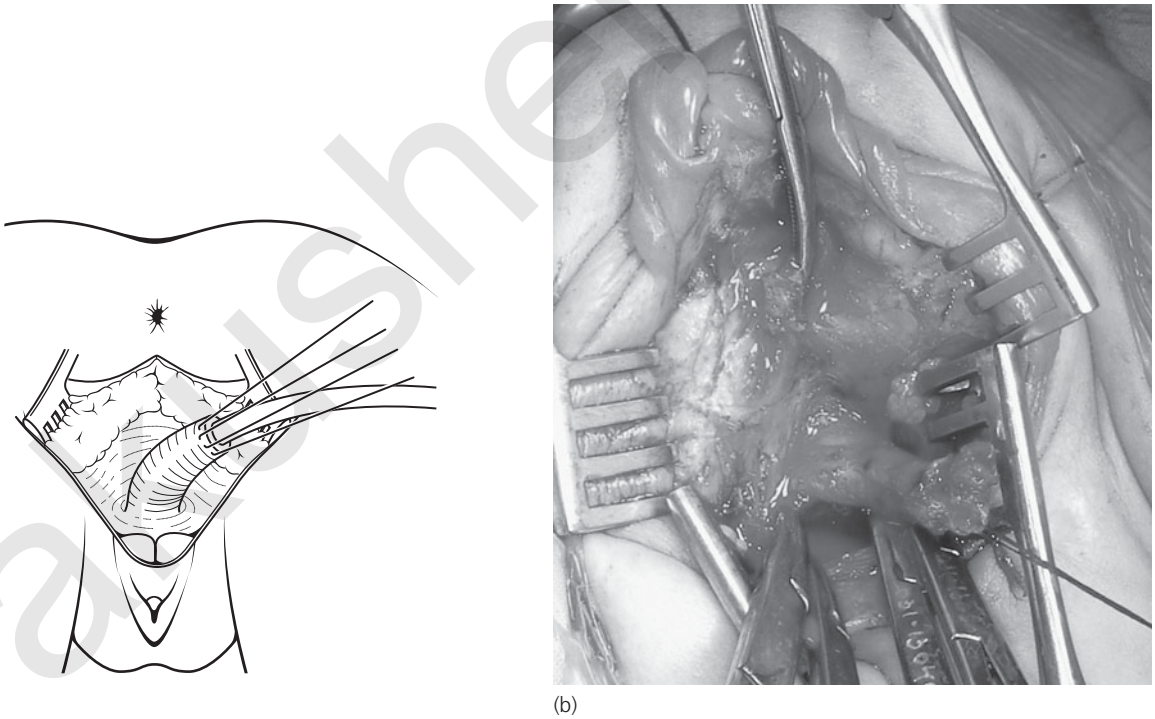
(a) (b)

Figure 102.9 (a) Dissection of the posterior vaginal wall, separating it from the rectal wall before sectioning the urogenital sinus. (b) A rectal finger is very useful to facilitate vaginal exposure.



(a) (b)

Figure 102.10 (a) Illustration showing the pull-through technique. The principle consists of placing a Fogarty balloon catheter into the vagina cystoscopically to locate it by palpation deep in the perineum later. (b) Cosmetic appearance after pull-through technique.



(a) (b)

Figure 102.11 Total urogenital mobilization (TUM). The urogenital sinus is mobilized in block to the perineum, after it is incised in the ventral wall. (a) Illustration of TUM. (b) Operative TUM technique.

The transected perineal skin between the vagina and rectum is used to reconstruct the dorsal wall and the previously dissected UGS is used for the ventral wall. For that purpose, it is transected ventrally and everted to reach the vagina and, in this way, the proximal part of it remains as the urethra (Fig. 102.13a–c). In this way, three principles were combined (pull-through, TUM, and ASTRA), not just a single technique.[14]

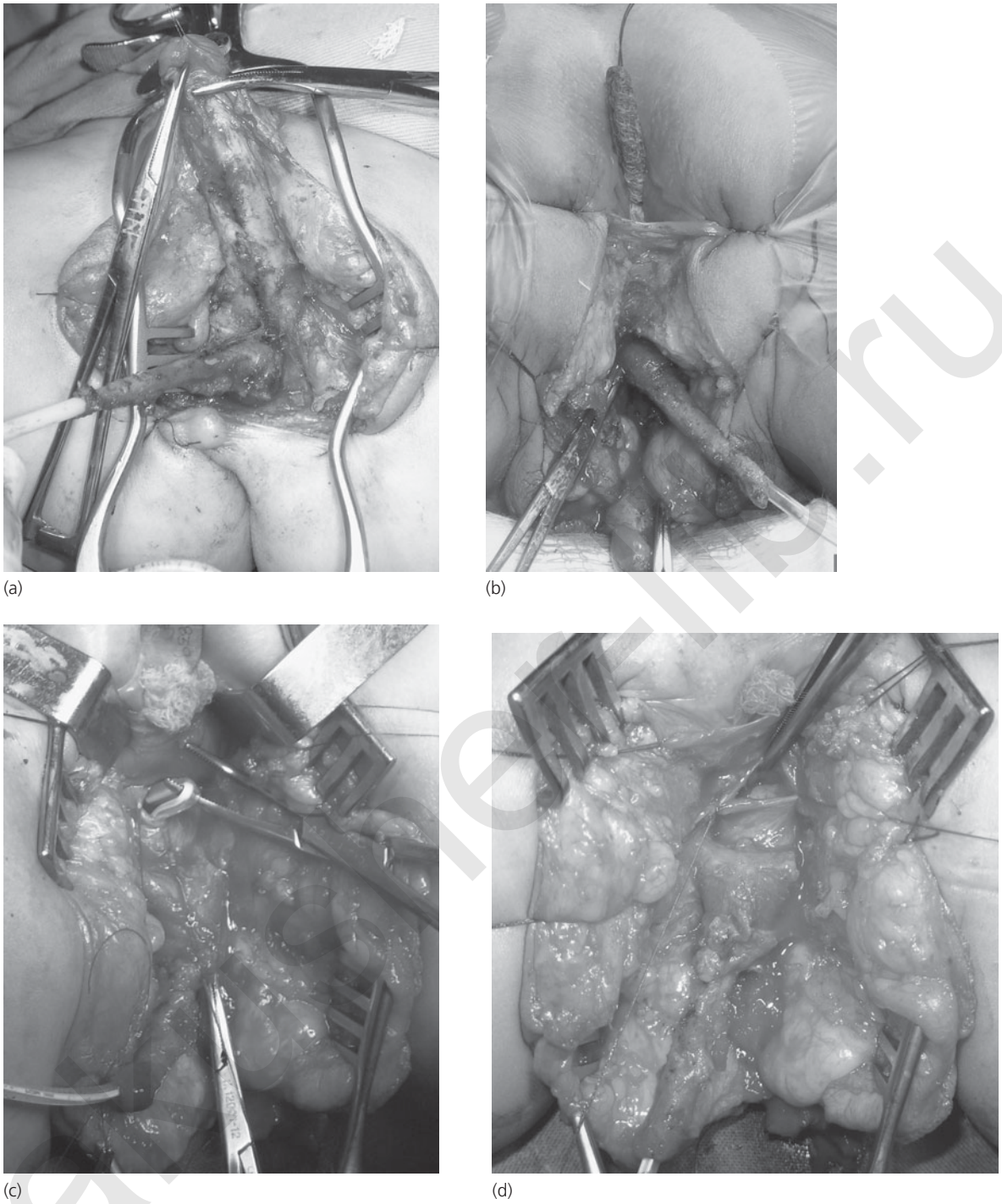


Figure 102.12 (a) Mobilization of the urogenital sinus in the lithotomy position without opening it. (b) The anterior sagittal transrectal approach. A midline sagittal incision was made through the anterior anorectal wall and provided an excellent view of the complete urethra and vagina without the need for complex preparation to gain exposure. In this patient, a previous placing of a balloon catheter in the vagina and a total urogenital mobilization were performed in the lithotomy position and the patient was then turned to prone. She had a very high urogenital sinus. (c) The vagina opened over the balloon, the Foley catheter repositioned in the proximal urethra. (d) The vagina is completed open.

Those patients with absent vagina (type IV) should undergo vaginal replacement. Most of these are undervirilized males and a bowel vagina (colon, if possible) is preferred. The authors have performed this laparoscopically since 1999 (Fig. 102.14).[15]

Labioplasty

Labioplasty is performed by dividing the clitoral hood skin in the midline (Byers flaps), sewing the flaps around the clitoris and along the central mucosal strip down to the lateral vaginal walls (Fig. 102.15a–c).

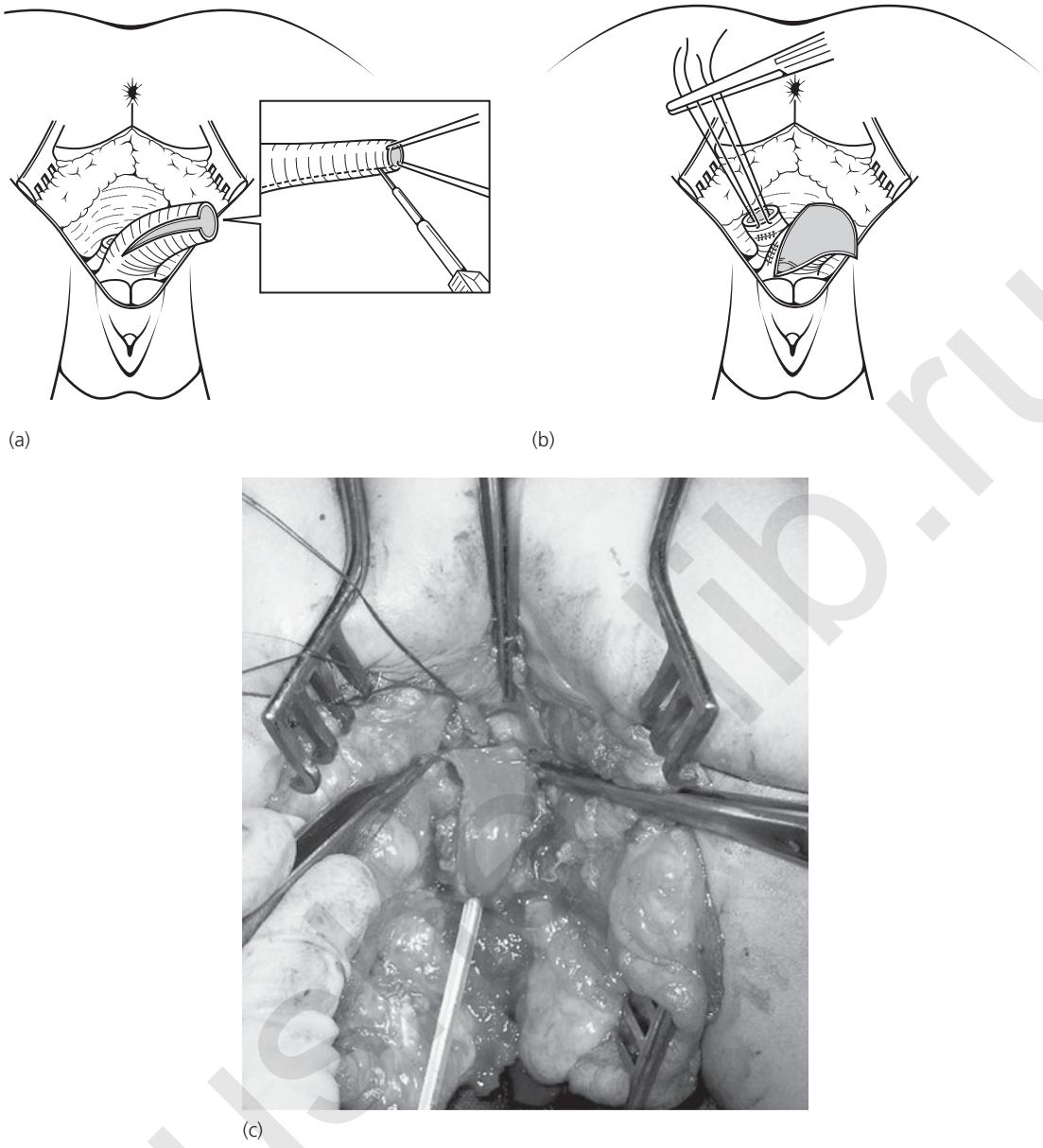


Figure 102.13 The UGS is transected dorsally (patient is in prone position) and everted to reach the anterior wall of the vagina. In this way the proximal part of it stays as urethra.

URETHRAL/PENILE RECONSTRUCTION

Urethral/penile reconstruction is addressed in Chapter 103, Male genital anomalies (hypospadias reconstruction chapter) and is not discussed here.

Postoperative

The perineum needs to be kept dry and clean for the first week to prevent dehiscence. The urethral catheter is left *in situ*, depending on the technique used. It is only left for the first postoperative day in the low or intermediate UGS and for at least 3 days in the high ones. Most of the patients only require non-steroidal anti-inflammatory drug (NSAID) for pain treatment.

COMPLICATIONS

Techniques for vaginoplasty carry the potential for scarring at the introitus, necessitating repeated modification before sexual function.

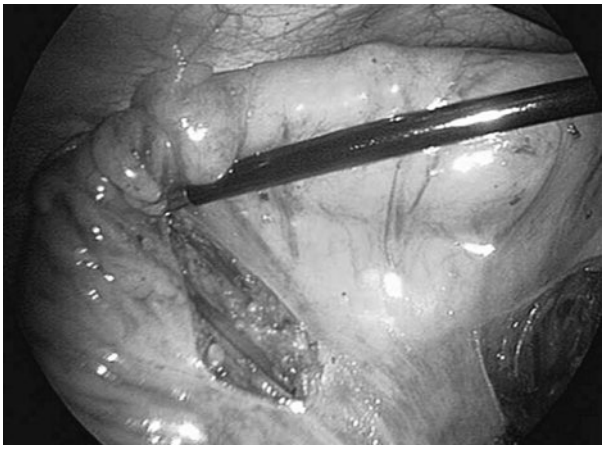


Figure 102.14 Laparoscopic aspect of an isolated piece of sigmoid colon to vaginal replacement.

The risks from vaginoplasty are different for high and low confluence of the urethra and vagina. The risk of urinary incontinence is decreased by recognizing the location of the vaginal confluence for the selection of the surgical approach and avoiding unnecessary mobilization or dissection in the urethrovaginal septum.

LONG-TERM RESULTS

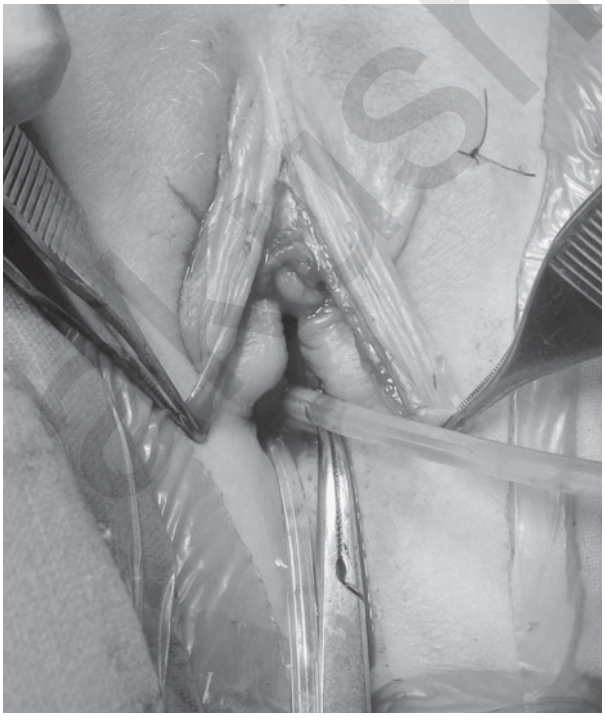
The pattern of surgical practice in DSD is changing with respect to the timing of surgery and the techniques used. It is essential to evaluate the effects of early versus later surgery in a holistic manner, recognizing the difficulties posed by an ever-evolving clinical practice.

Some studies suggest satisfactory outcomes from early surgery. Nevertheless, outcomes from clitoroplasty identify problems related to decreased sexual sensitivity, loss of clitoral tissue, and cosmetic issues.

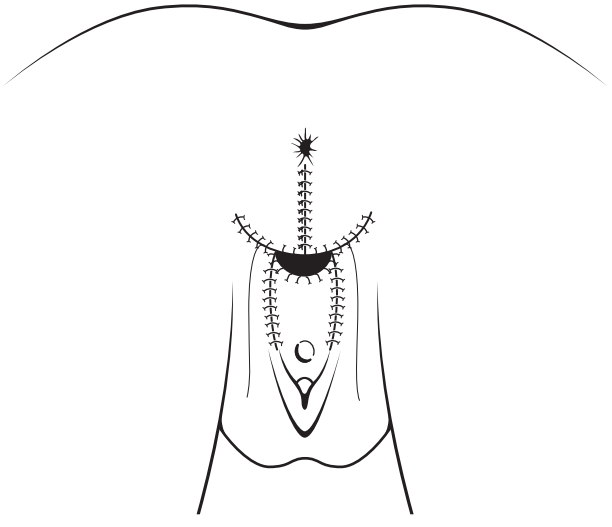
The analysis of long-term outcomes is complicated by a mixture of surgical techniques.

The outcome in undermasculinized males with a phallus depends on the degree of hypospadias and the amount of erectile tissue (Fig. 102.16). Feminizing genitoplasty as opposed to masculinizing genitoplasty requires less surgery to achieve an acceptable outcome and results in fewer urologic difficulties. Long-term data regarding sexual function and quality of life among those assigned female, as well as male, show great variability. There are no controlled clinical trials of the efficacy of early (12 months of age) versus late (in adolescence and adulthood) surgery or of the efficacy of different techniques.

Gender-role change occurs at different rates in different societies, suggesting that social factors may also be important modifiers of gender-role change.

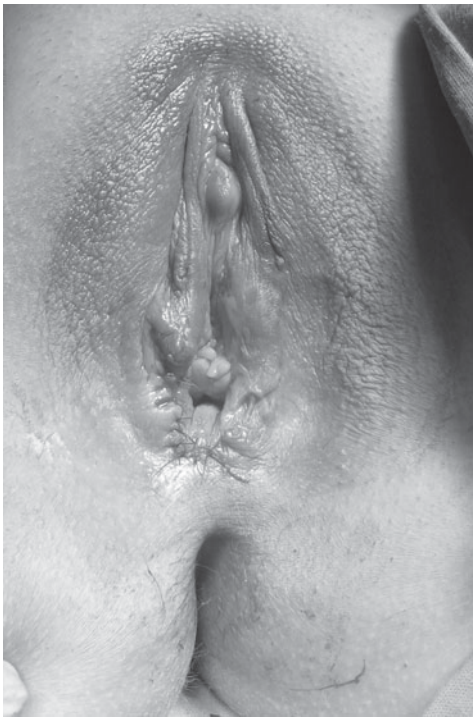


(a)



(b)

Figure 102.15 (a) Labioplasty is performed with flaps of Byers. (b) Illustration showing the finale aspect. (c) Two weeks postoperative perineal aspect of a patient who underwent feminizing genitoplasty.



(c)

Figure 102.15 *Continued*

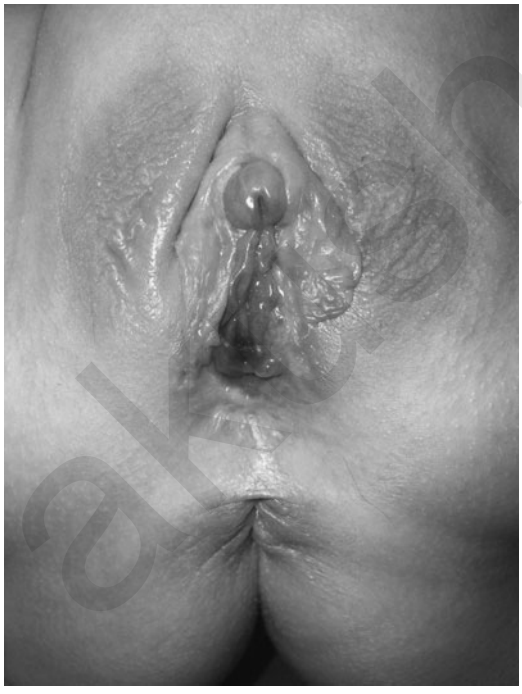


Figure 102.16 Long-term perineal aspect.

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103

Male genital anomalies

JOHN M HUTSON

INTRODUCTION

Development of the external genitalia is a complex process in the male, which predisposes to many congenital anomalies. Understanding these anomalies requires a detailed knowledge of the embryology, and particularly the central roles of androgens (in coordinating the masculinization of the anatomy) and the processus vaginalis (which allows descent of the intra-abdominal fetal testis into the scrotum).

EMBRYOLOGY

Masculinization of the external genitalia occurs in normal human embryos between 8 and 12 weeks of gestation. The inner genital folds fuse to create the male anterior urethra, while the outer genital folds fuse to make the scrotum. The genital tubercle enlarges to form the phallus. All these processes are mediated by secretion of testosterone from the embryonic testis. An enzyme in the target tissues, 5-alpha-reductase, converts the small amount of circulating testosterone into dihydrotestosterone, which binds five to ten times more tightly to the androgen receptor than testosterone itself. Although the genitalia appear 'male' by 12 weeks of gestation, the phallus is still tiny, but it continues to grow throughout pregnancy, in response to testosterone, to reach its newborn size (3–4 cm stretched length).

The normal process of testicular descent is multistaged. The first phase involves enlargement of the genitoinguinal ligament (or 'gubernaculum') and regression of the cranial suspensory ligament. The swollen distal gubernaculum anchors the embryonic testis near the groin during enlargement of the abdominal cavity. The hormonal regulation of this enlargement is by Leydig insulin-like hormone-3 (insulin-3, Insl3, or relaxin-like factor), as mutant mice with this gene deactivated have high intra-abdominal testes.[1,2]

The second phase involves development of a peritoneal diverticulum (processus vaginalis) inside the gubernaculum. Migration of the gubernaculum (with elongation of the processus) to the scrotum is likely to be controlled by the genitofemoral nerve releasing calcitonin gene-related peptide (CGRP), under stimulation of androgen.[3] During migration, the distal end of the gubernaculum is not anchored to the scrotum, which could predispose to extravaginal torsion in the perinatal period. After migration is complete, the gubernaculum involutes and the tunica vaginalis becomes adherent to the inside of the scrotum, preventing any further risk of extravaginal torsion.

Following testicular descent, the processus vaginalis obliterates between the internal inguinal ring and the top of the scrotum, leaving the testis within the tunica vaginalis. Failure of closure leads to inguinal hernia, hydrocele, or encysted hydrocele of the cord. In addition, failure of the fibrous tissue around the processus to disappear completely predisposes to acquired undescended testis (the 'ascending' testis) later in childhood.

PENIS

The penis of neonatal males is a focus of considerable parental anxiety and attention. The normal foreskin in a premature infant may appear relatively deficient, but by term it protrudes beyond the glans. The inner prepuce is attached to the glans and the distal opening is narrow, sometimes making catheterization difficult. Anomalies of the foreskin, such as phimosis or balanitis are rare in the neonatal period, although phimosis can occur secondary to neonatal cystoscopy in babies with urethral valves.

Circumcision

Neonatal circumcision is one of the most common operations in the United States and Israel, although in other Western countries the frequency is much lower.[4,5]

The procedure was known in the ancient societies of the Middle East and may have arisen as a way of preventing balanitis and phimosis in an arid, sandy region. Circumcision

is part of the ritual for such religions as Judaism, Christianity, and Islam, which all arose in the same geographic area.

In our own time, there is controversy over the advantages versus the risks of routine neonatal circumcision.[6–8] The American Academy of Pediatrics (AAP) first issued guidelines about neonatal circumcision in 1971, concluding that there was no absolute medical indication for routine circumcision.[9] By 1998, new evidence showed a potential benefit of circumcision in preventing neonatal urinary tract infection and sexually transmitted diseases, including HIV; this led to a revision of the guidelines to balance the risks against the advantages.[10] The current position of the AAP is to provide parents with an informed choice with accurate and unbiased information. Where circumcision is requested, the AAP now recommend procedural analgesia be provided.[9]

Circumcision should prevent phimosis, paraphimosis, and balanitis, although good clinical studies proving this at a population level are hard to find. Learman[5] concluded that the evidence supporting circumcision was too weak to recommend routine operation. Urinary tract infection in neonatal males can be reduced by circumcision from 7/1000 to 1.9/1000,[11] but whether improved penile hygiene would have the same effect is unknown. Sexually transmitted disease (STD) rates in circumcised men are 10% lower than without circumcision, when comparing men presenting to an STD clinic in a Western country.[12] In sub-Saharan Africa, the benefits of circumcision in reducing HIV risk may be much greater,[13] although meta-analysis has not confirmed a benefit.[14,15] Circumcision is linked with a three-fold reduction in penile cancer, although the low frequency of the condition does not justify routine neonatal operation. Learman[5] estimated that over 300 000 circumcisions were required to prevent one penile cancer per year. In Denmark, the incidence of penile cancer is falling, despite no increase in the number of circumcisions, suggesting that other factors, such as hygiene, are important.[16]

The complications of circumcision may be extreme, including amputation or diathermy necrosis,[17] although most complications are minor (e.g. minor bleeding or infection) and uncommon (<1%) (Fig. 103.1).[9] The Plastibell device or the Gomco clamp both have a low (0.2%) complication rate in neonates, and are equally safe techniques.[5]

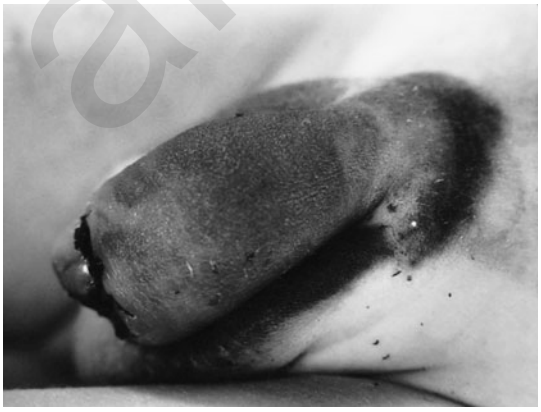


Figure 103.1 Postoperative penile hemorrhage after circumcision.

Neonatal circumcision should only be performed with adequate analgesia, using a ring penile block, local anesthetic cream, or a dorsal penile nerve block. If a Plastibell device is used, it is important to select the right size to avoid the ring slipping down the shaft and causing a form of paraphimosis.[18] The key to circumcision in the neonate is complete mobilization of the foreskin by separation from the glans with a lacrimal probe, and then inspection of the glans and urethral meatus to exclude hypospadias or other anomalies. Marking the level of the coronal groove through the base of the foreskin ensures that the skin of the shaft is not pulled up into the device.

Hypospadias

Failure of fusion of the urethral or inner genital folds leads to hypospadias (Greek for 'hole underneath'). Secondary anomalies include deficiency of the ventral prepuce (leading to a 'dorsal hood'), and relative deficiency in growth of the periurethral tissues compared with dorsal structures, such as the corpora cavernosa. The latter causes 'chordee', or relative curvature of the penis, particularly on erection.[19]

Depending on diagnostic criteria, the incidence of hypospadias is 1/100 to 1/300.[20] Siblings or the father are affected in about 10% of patients, suggesting polygenic inheritance. Hypospadias is an anomaly with a wide variation in severity, from a minor degree of meatal ectopia on the ventral glans to a severe abnormality with a perineal opening.

'Hypospadias' can be confused with more serious genital anomalies, and the most important initial aim is to exclude a disorder of sex development (DSD) (Fig. 103.2). Since hypospadias is an anatomical anomaly of anterior urethral development, the rest of the external (and internal) genitalia should be normal. By contrast, patients with DSD, have extensive genital abnormalities secondary to failure of all aspects of androgen-dependent development. A DSD can be

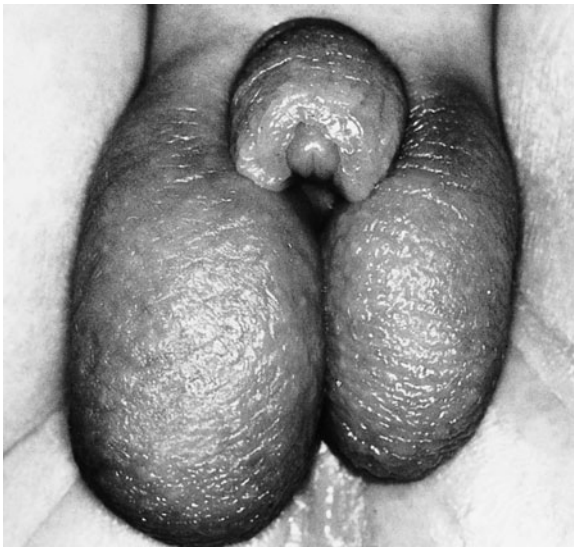


Figure 103.2 Apparent 'hypospadias and bifid scrotum', in a child with a severe genital anomaly. This child needs urgent investigation for disorder of sex development.

excluded if the scrotum is completely fused and both testes are descended. Babies with possible ambiguity need immediate referral, while those with hypospadias alone can be managed after the neonatal period.

Surgical treatment can be offered at three to six months of age, often as day surgery or overnight stay. Admission may be needed for urinary diversion, depending on severity of the anomaly and the surgeon's preference. A wide range of techniques are available,[21–24] which are not the main subject of this volume. Readers should consult the references for specific details.

Epispadias is a more severe and distantly related condition, which is more related to exstrophy of the bladder, and is included in Chapter 73, Bladder exstrophy: considerations and management of the newborn patient.

Micropenis/buried penis

A small penis may be caused by inadequate hormonal stimulation during pregnancy (hypothalmic, pituitary, or placental deficiency), although in some cases there is an anatomical deficiency. The buried penis occurs where the erectile tissue is adequate but the shaft skin is deficient.

Micropenis can be treated by androgen treatment, although whether postnatal hormone therapy is beneficial is controversial.[25,26] A number of operations have been proposed for buried penis, most of which use the foreskin.[27]

Penoscrotal web is a variant of buried penis where there is inadequate ventral shaft skin. This can be repaired later in infancy by Z-plasty.

Rare penile anomalies

Rare anomalies of the penis may be obvious at birth, including urethral duplication (Fig. 103.3) and megalourethra, which may be associated with prune belly syndrome[19,28] Partial duplication of the caudal embryo may lead to duplication of the penis, while penile 'agenesis' is usually a form of posterior ectopia, with the erectile tissue and urethra buried in the perineal body and the meatus on the anterior lip of the anal canal.[29,30] The latter anatomy is similar to the normal situation in marsupials, where the scrotum is inguinal in position and the phallus is in the perineum. Minor variants of penoscrotal transposition are common in DSD patients.[31,32]

Undescended testis

Any anomaly in the anatomical structures involved in testicular descent, or their hormonal regulation, will lead to congenital maldescent.[33] Failure of the transabdominal phase causes intra-abdominal testes that are truly 'cryptorchid' or hidden. Impalpable testes within the abdomen or canal are relatively uncommon (<5–10% of patients, depending on different authors).[34]

Intra-abdominal testes are associated with hypoplasia of the ipsilateral scrotum and often with absence of the external inguinal ring. The latter is a useful clinical feature to confirm absence of any inguinoscrotal migration. When the testis is inside the canal, the external ring may be open, consistent with intermittent emergence of the canalicular gonad.

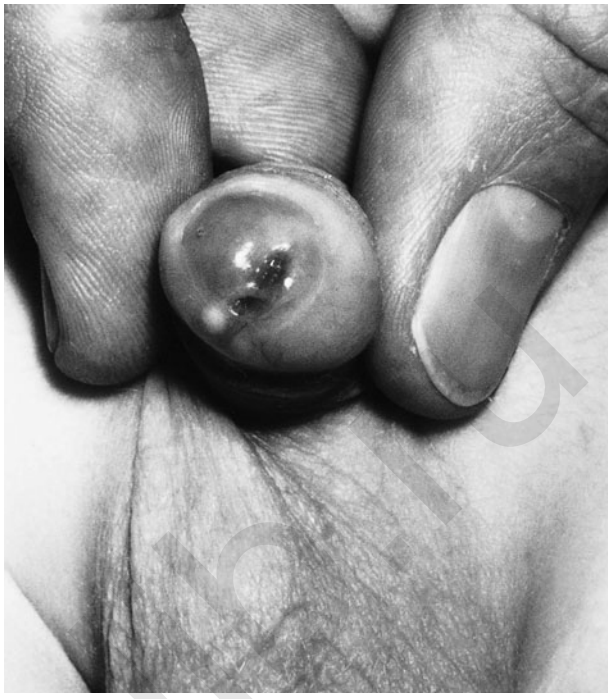


Figure 103.3 Urethral duplication in an infant.

The common site for undescended testes is just outside the external ring. Denis Browne described this as the 'superficial pouch', which is the name given to the tunica vaginalis when it is located in the groin, superficial to the abdominal wall, and deep to the superficial abdominal wall fascia (Scarpa).[35]

Maldescent is likely to have multiple causes, the most common being failure of gubernacular migration for various mechanical reasons.[34,36] Transient deficiency of gonadal androgens related to hypothalmic or pituitary anomalies or defects in placental function also may be important.[37] A number of less common and rare causes for cryptorchidism have been proposed (Box 103.1, Fig. 103.4).

In premature infants, as well as many term babies, cryptorchidism may be transitory, with further descent into the scrotum in the first 12 weeks postnatally.[38] These so-called 'late descenders' are at a high risk of developing acquired 'ascending' testes later in childhood.[39] The etiology of the latter is controversial, but has been proposed to be failure of the processus vaginalis to obliterate fully postnatally, leaving a fibrous remnant that prevents the normal elongation of the spermatic cord with growth.[40,41]

DIAGNOSIS

The aim of the physical examination is to locate the testis and determine its lowest position without undue tension. The latter corresponds with the caudal limit of the undescended tunica vaginalis.[42] In neonates, the examination may be hampered by vigorous leg movements, small size of all structures (including

Box 103.1 Proposed causes of cryptorchidism in rare cases

1. Aberrant location of genitofemoral nerve (perineal testis)
2. Persistent Müllerian duct syndrome (transverse ectopia with uterus and elongated gubernaculum)
3. Prune belly syndrome (massive bladder enlargement precluding entrance into inguinal canal)
4. Posterior urethral valves (same proposed mechanism as 3, above)
5. Anterior abdominal wall defects (ruptured gubernaculum)
6. Connective tissue disorders (deficient gubernacular migration)
7. Neural tube defects (genitofemoral nerve anomalies)

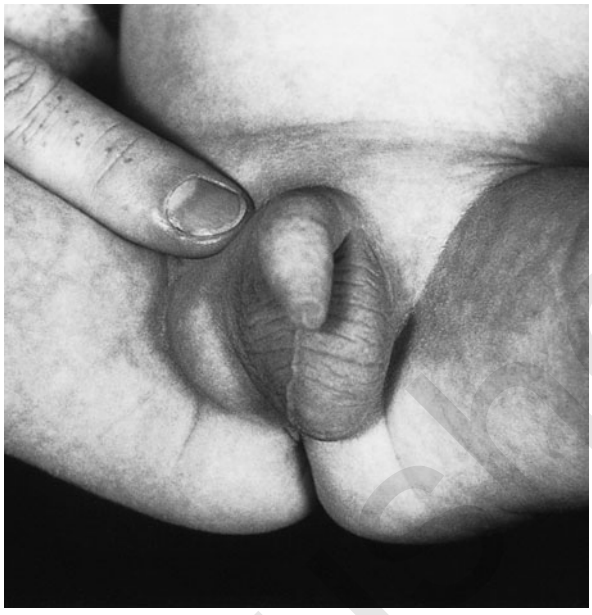


Figure 103.4 Ectopic undescended testis. In this case of perineal testis, it has been suggested that the cause is aberrant migration of the gubernaculum secondary to abnormal location of the genitofemoral nerve.

the testis, which is only 1–2 mL in volume), and motility of the testis within the tunica vaginalis. The scrotum is hypoplastic if the testis has never reached it, and the inguinal canal is shut in intra-abdominal testes. Palpation of a triangular defect at the pubic tubercle confirms the external ring is open and suggests that the testis is inside the canal. Conversely, hypertrophy of the contralateral testis (2–3 mL) suggests atrophy of the ipsilateral organ ('the vanishing testis').

TREATMENT

The aim of surgical treatment of undescended testis is to relocate the gonad into the scrotum before secondary dysfunction and degeneration occur (from high temperature). It is based on a premise, currently not proven in humans, that early placement of the testis in the scrotum will allow normal postnatal maturation of the germ cells to proceed. Careful study of testicular biopsies now suggests that the germ cells undergo transformation, from gonocytes to type A-spermatogonia, within 6–12 months after birth,[43] and that this maturation is deficient or arrested in cryptorchid testes. In addition, adult dark (AD) spermatogonia are now thought to be the stem cells for subsequent spermatogenesis. Animal models support the premise that early intervention can prevent germ cell loss[44] but this has not been confirmed in humans yet because of the inordinate lag time between treatment and end result (adult fertility).

The recommended age of orchidopexy has changed over the years, reflecting the accumulating knowledge about testicular function in infants. In our own department, orchidopexy is performed after about six months, as long as the anesthetic support is adequate. Since 4–5% of the males have undescended testes at birth, but about half of these show postnatal descent by 12 weeks, the baby should be re-examined then to confirm persisting cryptorchidism prior to referral for surgery. At this age, the operation is best performed by a trained pediatric surgeon, who is familiar with the handling of delicate tissues. Recent prospective trials confirm that surgery before one year (at approximately nine months) leads to better testicular growth (measured by ultrasonography) than when operation is delayed until three years of age.[45]

Rare anomalies of the testis

Tumors of the testis are rare at birth, but teratomas have been reported (Fig. 103.5). In a review of 68 patients with testicular

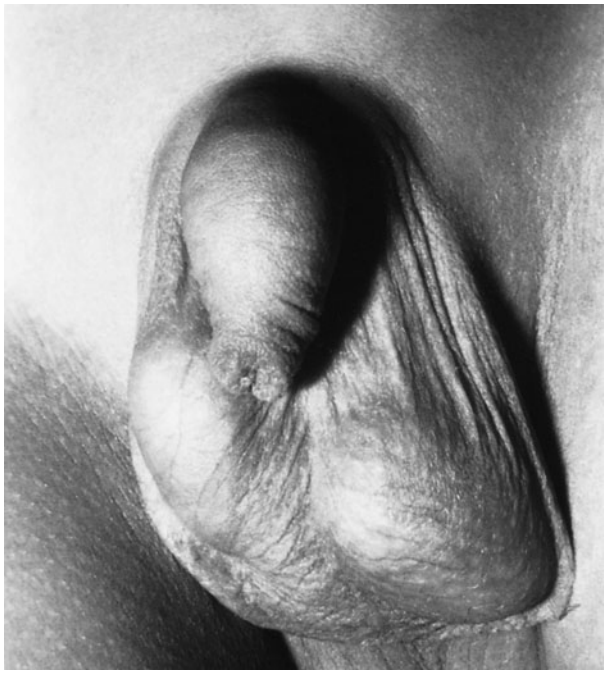
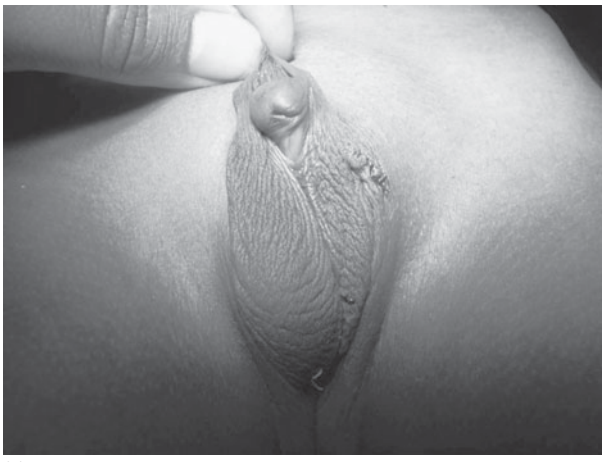
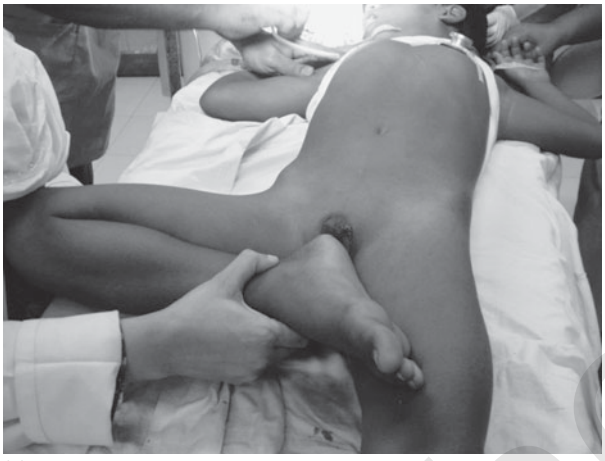


Figure 103.5 Neonate with a teratoma of the left testis.



(a)



(b)

Figure 103.6 Male with a congenital fistula of the anterior urethra caused by pressure of the heel during fetal development. (a) Close up of perineum (after left scrotal orchidopexy) showing normal terminal urethral meatus on glans as well as wide-open mid-shaft fistula. (b) Folding of legs confirmed that the right heel fitted exactly over the pressure area in the anterior urethra.

tumors over 30 years, one baby was found with a genital anomaly and a gonadoblastoma.[46] A neonatal teratoma may need to be distinguished from a hydrocele or testicular torsion. If the hydrocele is too tense to palpate a normal testis, an ultrasound examination would be useful. Most teratomas can be shelled out of the testis, thereby avoiding orchidectomy.

Exstrophy of the testis has been reported, presumed to be secondary to pressure necrosis of the scrotal skin from the baby's heel, and prolapse of the scrotal contents.[47] A similar defect has been reported in the proximal penile urethra from probable pressure atrophy, leading to a congenital urethral fistula (Fig. 103.6).[48]

Duplication of the gonadal primordium can cause polyorchidism. The presentation is of three scrotal masses, all of which feel like normal testis.[49] The differential diagnosis includes complete inguinoscrotal hernia, encysted hydrocele of the cord, and transverse testicular ectopia, where both testes are on the same side. In the latter situation, the contralateral hemiscrotum is empty. No treatment may be required, although one gonad can be removed if the vas deferens is deficient.

Transverse testicular ectopia is a rare anomaly, which may be associated with prenatal rupture of the ipsilateral gubernaculum, allowing the testis to prolapse into the contralateral processus vaginalis. In most cases, the ectopic testis has no gubernacular attachments; the diagnosis can be confirmed on scrotal ultrasound.[50] Transverse ectopia of the testis is also seen in a rare form of DSD known as persistent Müllerian duct syndrome.[51] Transverse ectopia is treated by trans-septal scrotal orchidopexy (i.e. both testes are brought through the same inguinal canal into the scrotum and one is placed in the contralateral hemiscrotum).

The vas deferens may be absent in the Rokitansky syndrome or in babies with cystic fibrosis. In the Rokitansky anomaly, the caudal growth of the distal Wolffian duct is arrested, leading to subsequent absence of the ipsilateral vas deferens, seminal vesicle, and ureteric bud (and hence ipsilateral renal agenesis)[52] The etiology of absent vas deferens is different in cystic fibrosis, where the Wolffian ducts undergo involution/atresia in mid-gestation. At birth, only the head of the epididymis is palpable, and the epididymal tail and vas deferens are absent bilaterally: this finding can be used to diagnose cystic fibrosis in neonates with possible meconium ileus.[53–55]

Apart from DSD anomalies with separate labioscrotal folds or bifid scrotum, scrotal anomalies are rare. There are case reports of ectopic hemiscrotum and duplication, which are a local manifestation of partial twinning of the caudal embryo or compression of the perineum by the feet of the fetus.[56]

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104

Neonatal testicular torsion

DAVID M BURGE

INTRODUCTION

Torsion of the neonatal testis is a well-recognized clinical entity which accounts for about 10% of all cases of testicular torsion admitted to pediatric surgical centers.[1] Torsion usually occurs extravaginally, i.e. in the spermatic cord above the insertion of the tunica vaginalis (Fig. 104.1), but both intravaginal and mesorchial torsion are reported.[2,3] Either testis may be involved. Bilateral torsion occurs and may be synchronous or metachronous.[4,5] Asynchronous torsion may occur in as many as 33% of cases.[6] Apparent primary infarction of the neonatal testis in the absence of torsion occurs less commonly,[7] and while it has been postulated that this represents previous torsion that has untwisted, good evidence exists to suggest that the initial event in neonatal torsion is a vascular one and that torsion may occur secondarily.[2] The neonatal testis may be prone to extravaginal torsion because of its extreme mobility within the scrotum.[8]

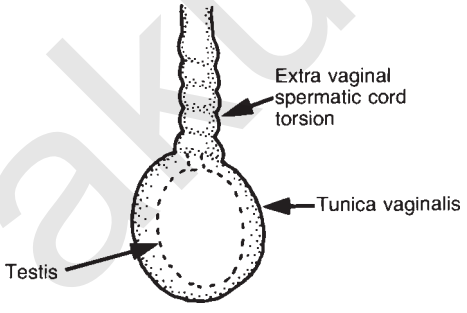

Figure 104.1 Anatomy of extravaginal torsion.

CLINICAL FEATURES

Neonatal torsion appears to be a condition of large term babies[2] and it rarely, if ever, affects the preterm infant. Previously, breech delivery was suspected as being a causative factor. Recent reports, however, fail to confirm this.[2] Affected babies are usually totally asymptomatic. The typical physical features are of a hard, edematous hemiscrotum with a noticeable blue or black discoloration.

The testis feels firmly adherent to the scrotal wall and is apparently non-tender. While there may be some enlargement of the hemiscrotum, this is not usually marked. These features are usually present from birth, supporting the contention that neonatal torsion is often an antenatal event. However, the clinical features are not always noted at delivery and in many cases are not detected until the second or third day of age. Occasionally, features consistent with acute torsion (sudden onset of swelling, erythema, and pain) may develop some days or weeks after delivery, and it appears that in these cases the torsion is more likely to be intravaginal. Torsion of an undescended testis may present in this way.[2]

Diagnosis can usually be made on the clinical features alone. The differential diagnosis includes hydrocele, testicular tumor, trauma, adrenal hemorrhage, and meconium peritonitis with tracking down a patent processus. Distinction from a simple hydrocele is usually easy by transillumination. Testicular neoplasia can be excluded by the presence of bluish discoloration and scrotal edema. Torsion can only be differentiated from spontaneous infarction at surgery. Some bruising of the scrotum may occur after breech delivery,[9] but this is usually in the presence of a testis that feels normal to palpation. Intraperitoneal injury from birth trauma may result in hematocele formation, but the fluctuation of this lesion will usually distinguish it from torsion. Adrenal hemorrhage may present with features indistinguishable for torsion, but adrenal ultrasound would be diagnostic.[10] While color Doppler studies of testicular artery flow and radionuclide scanning of the scrotum might support the diagnosis, they are not required.

A clinical diagnosis of neonatal torsion is sufficient indication for scrotal exploration. While it might seem mandatory that this be conducted urgently, reports of successful testicular salvage are rare.[3,11–13] The classical clinical features seem to be due to the presence of established testicular infarction and it can be argued that the only reason for surgery is to fix the contralateral testis. Because delayed

torsion of the contralateral testis does occur and may be at extravaginal, intravaginal, or mesorchial level, early surgery to assess the affected testis, excise it if necessary and securely fix the contralateral testis is recommended. No specific preoperative preparation is required.

OPERATIVE TECHNIQUE

Under general anesthesia, the scrotum is incised in the midline and dissection continued into the affected hemiscrotum (Fig. 104.2). Both testes are easily approached through this single incision (Fig. 104.3). In most cases, established infarction will have resulted in edema and fixation of the testis to the subcutaneous tissues. It is usual, however, to find a plane of cleavage outside the tunica vaginalis, resulting in a clear demonstration of the site of torsion. In some instances, necrosis is well established and the exact origin of the pathology cannot be identified. If, as is usually the case, the testis is clearly beyond salvage, it is wise to excise it, having transfixed the spermatic cord above the site of torsion. Retention of a necrotic testis is inadvisable as it invites sepsis which may put the contralateral testis at risk. While there is a theoretical possibility that retention of the infarcted testis may result in some hormonal production,[8] in the majority of cases in which the affected testis is not removed, involution occurs.[2] Following excision of the affected testis, the contralateral testis is exposed through the same excision. The tunica vaginalis is opened to allow accurate inspection of the anatomy and permit effective fixation. This may be performed by placement of the testis in a subdartos pouch, as used in orchidopexy, or by suture fixation, which is now described. The tunica vaginalis is sutured to the tunica albuginea of the testis at four points, using a fine non-absorbable monofilament material, thus preventing intravaginal torsion. It is wise to incorporate the scrotal septum in the two medial sutures, thus fixing the tunica vaginalis to the scrotum and preventing extravaginal torsion (Fig. 104.4). Care should be taken to site these two sutures fairly deep in the wound or else the testis will lie too superficially and skin closure made more difficult. The scrotal incision is then closed with a fine continuous absorbable suture. No specific postoperative care is required.

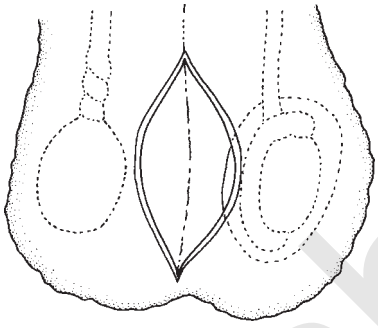

Figure 104.2 Midline scrotal incision.

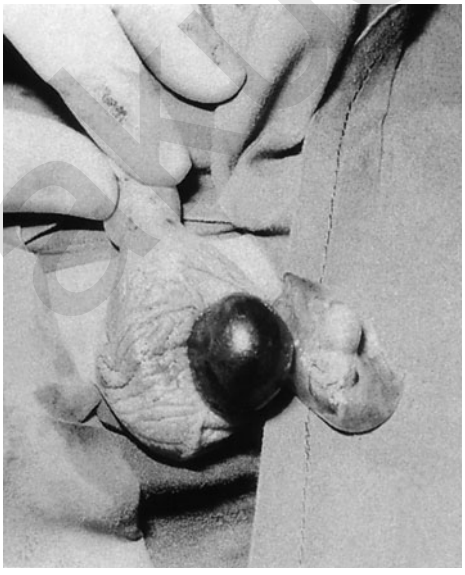

Figure 104.3 Midline exploration showing extravaginal torsion of right testis and normal left testis prior to fixation.

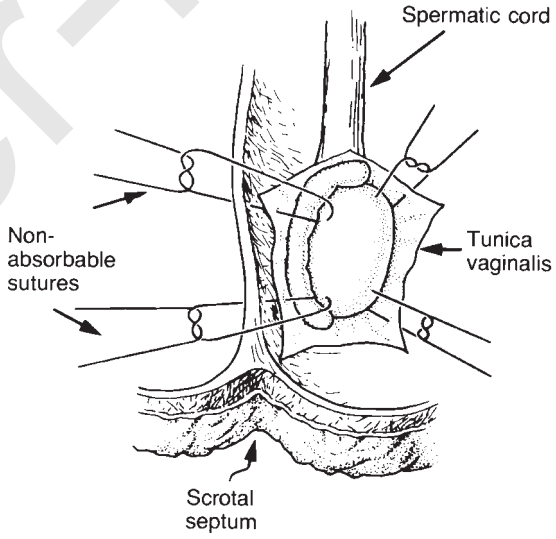

Figure 104.4 Technique of testicular fixation.

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PART XI

LONG-TERM OUTCOMES IN NEWBORN SURGERY

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Long-term outcomes in newborn surgery

CASEY M CALKINS AND KEITH T OLDHAM

INTRODUCTION

Ongoing advancements in the pre- and postoperative care of the neonate with a surgical condition have enabled the survival of an increasing number of infants with congenital malformations. For decades, surgeons have insisted on a regular self-examination of outcomes in order to ensure the optimal treatment of our patients. Outcome analysis traditionally relates to the rudimentary end result of an operation – utilizing variables such as mortality, operative time, specific complication rates (i.e. incidence of esophageal stricture following esophageal atresia repair), and hospital length of stay, to name a few. Recently, outcomes research has become a more complex endeavor. Measures of long-term outcomes, including 'functional outcome' and 'health-related quality of life' are equally important to the morbidity sustained as a result of a congenital malformation and its attendant surgical correction. The methods by which subjective assessments are expressed as a quantitative measure are therefore important for the surgeon to understand. These data serve as an important adjunct to prenatal counseling, offer information about future health expectations for families, assist the surgeon in identifying potential improvements in perioperative management, and will likely be utilized by public agencies charged with implementing health policy, especially in an era of diminishing resources. Therefore, long-term outcomes are of specific import to the neonates we care for, the families we answer to, and our colleagues charged with the continued efforts to improve the surgical care of our youngest patients. This chapter will begin by focusing on the specific language and methodology of modern long-term outcomes research as a prelude to the current status of long-term outcomes assessment in newborn surgical conditions commonly treated by the pediatric surgeon.

WHAT IS AN 'OUTCOME'?

In 1934, Ernest A Codman, an orthopedic surgeon, espoused the 'end result idea'. In his book *The shoulder*, Dr Codman introduced this 'common sense notion that every hospital should follow every patient it treats long enough to determine whether or not the treatment has been successful, and to inquire "if not, why not?"'.[1] Today, this 'end result idea' represents the very basis for conducting outcomes research, which examines how interventions delivered in the treatment of medical and surgical disease affect patient populations over time. It is one of many areas of investigation within the broad field of health services research.[2] Although, one can formally define a 'health service',[3] it seems intuitive to say that it is any organized effort to improve the health of a patient. The measurements and assessments utilized in outcomes research have changed considerably over the course of the last two decades. Regular assessment of our operative outcomes in the form of 'morbidity and mortality' conferences is, and continues to be an essential endeavor to ensure that we continue to improve the surgical care delivered to infants and children. It is an indispensable form of self-assessment and allows us to learn from one of the realities of human nature – error. However, assessment of individual and system failure represents only one part of how we improve the practice of pediatric surgery. Individual quality improvement depends on refining surgical technique, learning at regional and national society meetings, remaining knowledgeable by reading relevant peer-reviewed literature, and incorporating successful strategies and techniques into practice.

Assessment of patient outcomes (bad and good) helps us to understand what works and what does not. In this sense, an outcome can be any measure that affects the health, perceived health, physiologic function, financial status, or experience of a patient. Modern outcome measures have developed as a result of three general trends. First, traditional clinical outcomes are supplemented by measurements that take patient experience and concerns into account, particularly with regard to chronic illness, where the intent is typically to treat or offer palliation, rather than provide a definitive cure. Second, when making decisions regarding healthcare, patient preference is critically important, and information on health-related quality of life or functional results of one treatment versus another may ultimately influence decision-making in this regard. Finally,

health care policy-makers remain under pressure to effectively allocate resources. Benefits and quality of life perceived by patients and society as a whole may allow appropriate governmental bodies to do so with a sense of what is best for the collective good when resources may be limited. A common feature of health-related outcome measures today is measurement of well-being from the subjective viewpoint of the individual patient (or parent – the 'proxy') concerned. The three items crucial to understanding of modern-day outcomes research are: health-related quality of life, functional outcome, and utility (cost-effectiveness).

HEALTH-RELATED QUALITY OF LIFE

Where health and quality of life clearly intersect – the concept of health-related quality of life (HRQoL) assessment is born. In contrast to objective data obtained by laboratory, radiographic, or purely functional assessments, the measurement of HRQoL provides additional information about the subjective impact of a condition, or, for our purposes, the ramifications of an operation utilized to treat that condition. Transformation of qualitative assessments into quantitative data requires identification of measurable elements related to an individual's existence and assessment by way of an instrument.[4] Five general concepts define the scope of such an instrument: (1) impairment, (2) functional state, (3) health perception, (4) social opportunity, and (5) duration of life.[5] Distinct domains have been subsequently operationalized in order to translate these five concepts into quantifiable data. Although there is no consensus regarding a universal and inclusive set of domains, most researchers will agree that 'quality of life' differs greatly from person to person. A survey respondent may weigh various domains differently, and one must decide how to assess for these differences when interpreting the results from a cohort of respondents. The seven general domains of health in most HRQoL surveys include physical functioning, social functioning, emotional functioning, cognitive functioning, pain/discomfort, vitality, and overall well-being.

Instrument standards

A HRQoL instrument is developed utilizing psychometric testing principles and, once constructed, is reviewed against standards outlined by the Scientific Advisory Committee of the Medical Outcomes Trust.[6] Evaluation criteria include: appropriateness, validity, reliability, responsiveness, precision, acceptability, interpretability, and feasibility. **Appropriateness** is the first and most fundamental criterion to assess and asks whether the instrument measures what have been identified as the most important outcome(s) for the purposes of evaluation. Specifically, is the instrument relevant, and are the methods of evaluation and administration appropriate? **Validity** concerns whether an instrument measures what is intended. Face and content validity are matters of qualitative judgment – for instance, were the patient types targeted for assessment included in the creation of the instruments' content? Construct validation refers to comparisons with other instruments, relating the scores to sociodemographic variables, and comparing domain scores within the instrument itself. **Reliability** assesses whether or not an instrument is consistent in its measurements, both internally and over time. **Responsiveness** refers to the ability of an instrument to measure significant changes in health and is assessed by looking at changes in instrument scores for groups whose health is known to have changed. The **precision** of an instrument is measured by the range of response options and the existence of ceiling (maximum score) or floor (minimum score) effects. An instrument is likely to be **acceptable** to a patient or population group if it measures what they consider to be important aspects of quality of life. The optimal instrument is **interpretable** – and is able to translate a quantitative score into an external measure that has a familiar meaning. This aspect of an instrument is easily assessed when there are normative data from a representative sample of the general populous and/or patients with similar conditions for whom the instrument is intended. Finally, **feasibility** refers to the time and effort needed to complete the instrument, and whether such issues are prohibitive to completion of the instrument, or affect the manner in which it is completed. The United States Centers for Disease Control has established a comprehensive website that may aid the clinician when faced with the possibility of instrument evaluation or utilization (www.cdc.gov/hrqol).

Unique issues in health services research for the newborn population

As the goal of adult functioning is to be self-sufficient and economically productive, adult-based measures of functioning and quality of life are not likely to be relevant to children.[7] Furthermore, children often view health and illness as separate entities, whereas adults see these two items as part of a continuum.[8] Lack of a consensus upon a theoretical framework as to the nature of HRQoL in children means that there is lack of agreement regarding the optimal domains in a pediatric HRQoL assessment tool. Even within domains, there are often variations of emphasis. For example, within the physical functioning domain, an instrument may place varied emphasis on physical symptoms, self-care, participation in physical activities, or distress caused by limitations. As a result, different instruments may yield different results depending on the age of the child, the medical or surgical condition, the emphasis of the questions within a domain, and a variety of other factors unique to pediatric healthcare.

Although adult HRQoL measures suffer from some of the same issues of validity, the common feature of most adult instruments is that they measure health from the subjective viewpoint of the individual concerned. In children, this information is not always easily obtained from the subject. Although many children are able to provide self-reports of HRQoL if an instrument is chosen that is appropriate to his/her abilities, this assertion has not been well evaluated. Furthermore, different domains within an instrument may pose unique challenges to different age groups. Children as young as five years may be able to provide accurate

self-reports of pain, whereas subjective concepts such as behavior or self-esteem may not be able to be accurately assessed until ten years of age.[9] Several self-reporting biases are also more problematic in pediatric populations. Position bias (tendency to select the first answer), acquiescent response bias (tendency to agree with questions regardless of content), failure to accurately perceive time periods, boredom with having to answer written questions, and difficulty in understanding negatively worded items makes construction of pediatric outcome tools difficult. Given that self-reports suffer from such bias and many children are truly unable to fill out a self-assessment, other individuals – 'proxies' – have served to provide data on the child's behalf. Parents or caregivers who have a longstanding relationship with the patient commonly complete such proxy reports. However, the choice of proxy may add further bias to the instrument. For example, fathers generally rate children as having fewer behavioral and psychological problems than do their mothers.[10] In another study, children aged 8–11 years with a chronic health condition reported significantly lower HRQoL than their parent proxies.[11] In one review, nearly 90% of pediatric HRQoL assessments were completed by a proxy.[12] However, most modern pediatric-specific instruments can be utilized in a self-reporting mode, and proxy assessments may be applicable to only the youngest of children. When possible, self-reports should always be sought over proxy-generated data.

As the development of a child is not always linear, how does one separate development from outcome? This is one of several questions that remain unanswered regarding the instruments currently utilized for pediatric HRQoL. Outcome measures that not only are sensitive to changes in development and health, but also make allowances for different cognitive abilities of children at various ages with regard to reporting and valuing health status are required.[13] When selecting an instrument, the clinician should consider whether the concepts inherent in the tool are developmentally appropriate for age, gender, and culture. In addition, if one is interested in measuring longitudinal HRQoL in a patient cohort, selection of an instrument with items that are not overly age related may be optimal so that children of different ages may complete the same instrument.

To get around the problematic issue of 'child-friendly' tools and feasibility, some instruments have employed unique methods to entice children to complete the surveys. For example, the KINDL® instrument employs a computerized program to measure pediatric HRQoL by means of a touch-screen monitor or a mouse. It is a child-friendly (independent of reading and writing skills, in a playful format), economical, and developmentally appropriate program that is valid, reliable, and available in two languages (German and English). Other methods to entice and facilitate child participation include third-party interviewing and age-appropriate storybook formats.

Multidimensional generic measures of HRQoL

Generic quality-of-life measures are designed to assess physical, psychological, and social aspects of health without attention to a specific ailment or disability. These instruments emphasize breadth over specificity by focusing on the common elements of health that transcend all diseases. In practice, these instruments may also augment subjective and objective clinical data that focus on signs, symptoms, and effects of a specific disease.[14] The following list of instruments (Table 105.1) is not, by any means comprehensive, but serves to highlight the most common instruments available for the assessment of generic HRQoL in infants and children.

Table 105.1 Health-related quality of life instruments.

Instrument	Applicable age	Time to complete (mins)
PedsQL	5–18 years (self) 2–18 (proxy)	<5 (self or proxy)
CHIP	'CE' 6–11 years (proxy) 'AE' 6–18 years (self)	20 (self or proxy)
CHQ	5–15 years (proxy) 10–18 years (self)	7–30 (proxy) 15–30 (self)
KINDL	4–16 years (self) 4–16 years (proxy)	10–15 (self) 10 (parent)
KIDSCREEN	8–18 years (self) 8–18 years (proxy)	20 (52 items) 15 (27 items) 5 (10 items)
DISABKIDS	4–7 years (self or proxy) 8–16 (self or proxy)	20 (37 items)

CHQ, Child Health Questionnaire; PedsQL, Pediatric Quality of Life Inventory.

PEDIATRIC QUALITY OF LIFE

The Pediatric Quality of Life (PedsQL™) measurement model is a modular approach to measuring HRQoL in children and adolescents who are healthy, as well as those with acute and chronic health conditions. The model has the added ability to integrate both generic core scales and disease-specific modules into one measurement system. The PedsQL generic core scales include: brief (23 items), practical (less than 4 minutes to complete), and flexible (designed for use with community, school, and clinical pediatric populations). Its permutations are meant to be developmentally appropriate (different modules for ages – child self-report ages 5–7, 8–12, 13–18; parent proxy-report ages 2–4, 5–7, 8–12, 13–18). It is one of the most interpretable tools due to its widespread use. Additionally, it is translated into multiple languages including Spanish.[15–18] The 23-item PedsQL generic core scales were designed to measure the principal dimensions of health as delineated by the World Health Organization, as well as role (school) functioning. PedsQL condition-specific modules complement the generic core scales and are used in designated clinical populations. These are designed to provide greater measurement sensitivity for circumscribed populations (currently available for asthma, rheumatology, diabetes, cancer, and cardiac conditions, with additional modules in the development and planning stages). For the pediatric surgeon, the PedsQL is an attractive option as it is brief, practical, developmentally appropriate, multidimensional, reliable, valid,

and responsive. It has been cited in numerous peer-reviewed publications. The instrument has the ability to measure HRQoL over time with instruments that are age-appropriate and available in both patient and proxy forms.

CHILD HEALTH AND ILLNESS PROFILE

The Child Health and Illness Profile (CHIP) instruments were developed by Dr Starfield and colleagues at the Johns Hopkins School of Public Health.[19] Development of the child and adolescent editions occurred over 12 years and involved more than 5000 children and adolescents from ethnically and socioeconomically diverse families. The CHIP-CE (child evaluation, CE) instruments provide a comprehensive assessment of health status that can be completed by children 6–11 years old or by their parents. It describes aspects of health that can be influenced by health systems, school health systems, and health promotion efforts. The CHIP-AE (adolescent evaluation, AE) was developed to document the state of health in adolescent age populations, identify differences in the health of subpopulations, and assess the impact of medical and surgical interventions on health.

CHILD HEALTH QUESTIONNAIRE

Perhaps the most commonly used outcome assessment tool in contemporary health services research is the SF-36 ('short-form 36').[20] The Child Health Questionnaire (CHQ) is a byproduct of the SF-36 and a more appropriate choice for use in children and adolescents. A product of the RAND-sponsored Medical Outcomes Study (MOS), the SF-36 is a 36-item general health status assessment questionnaire. It has nine separate scales, although recent work has identified two dimensions that underlie the nine subscales: physical and mental health. There is substantial reliability and validity data for the SF-36 in a wide variety of adult populations.[21] However, the 28-item and 50-item CHQ short-forms (which cover the same 12 concepts as the full-length CHQ) are more efficient measures than the SF-36 and are valid for use in children aged 5–18 years.[22] In the United States, normative values and benchmarks for the parent-reported versions of the CHQ are available for some specific health conditions. The youth self-report version is 87 items, and was developed for use in individuals aged ten years and older. Authorized translations and internet-administered versions are also available.[23]

KINDL

Initially developed in Germany, the KINDL is a 24-item, methodologically suitable, psychometrically sound, and flexible instrument. The questionnaire can be completed by children and adolescents (aged 4–16), or by way of a parent proxy. The questionnaire is available for different age groups. The computer-assisted version (CAT-SCREEN) is a unique method of instrument administration that may be especially suitable for toddlers. Disease-specific modules exist for obesity, asthma, atopic dermatitis, cancer, and diabetes. The KINDL has been validated and is especially effective in the assessment of psychological well-being, social relationships, physical function, and everyday life activities.[24]

OTHER PEDIATRIC GENERIC INSTRUMENTS

The Infant Toddler Quality of Life Questionnaire™ (ITQOL) was developed for use in infants and toddlers from at least two months of age up to five years. The ITQOL adopts the World Health Organization's definition of health, as a state of complete physical, mental, and social well-being and not merely the absence of disease. The survey was developed following a thorough review of the infant health literature and a review of developmental guidelines used by pediatricians. Its child equivalent is the aforementioned CHQ. The Dartmouth COOP child-report charts were developed as a survey to evaluate treatment outcomes and as a tool for the detection of important health problems. It consists of six charts addressing physical fitness, emotional feelings, schoolwork, social support, family communications, and health habits.[25] The instrument was developed from literature review and a focus group of physicians and adolescents. The tool is completed by the subject and is reasonably feasible in that it contains only six items. The Exeter Quality Of Life Measure (Exqol) is another generic self-report HRQoL measure for children aged 6–12 years based on the authors' experience with chronically ill children. Like the KINDL CAT-SCREEN, it is computer administered and consists of 12 gender-specific pictures – each of which is rated twice: the first in terms of 'like me' and the second in terms of 'as I would like to be'. The DISABKIDS and KIDSSCREEN instruments were developed and validated in European countries to measure HRQoL in children from 4 to 18 years of age. These instruments are available in a variety of lengths and languages. Several disease-specific modules have been developed for both instruments (i.e. cerebral palsy, cystic fibrosis, and diabetes). Both instruments can be administered by a standard questionnaire or computer; and a child-friendly version of DISABKIDS is available for individuals from four to seven years of age.

CONDITION-SPECIFIC MEASURES OF HRQOL

Condition-specific measures aim to assess quality of life following a specific intervention or for individuals with a specific diagnosis. When condition-specific instruments are developed to assess quality of life following treatment of a specific anomaly, such measures are designed to be more sensitive to the detection of small treatment effects when compared to generic measures. In this regard, a condition-specific measure is designed to tap the domain(s) of greatest interest for the condition in question. At present, none of the generic HRQoL instruments have been specifically designed to evaluate patients who suffer from the conditions that are principally cared for by neonatal surgeons. However, a variety of studies have been performed with the intent of validating generic HRQoL instruments in patients with neonatal surgical disease. Furthermore, a select number of disease-specific outcome measures have been developed to assess quality of life after the treatment of pediatric surgical conditions. For example, in Europe, a proxy version of

EuroQOL (see below) was found to be feasible and valid in a population of children with anorectal malformations.[26] Similar studies have utilized generic quality-of-life measures in children with Hirschsprung's disease (HD),[27] anorectal malformations,[28] congenital diaphragmatic hernia,[29] and neurological impairment requiring gastrostomy or surgical treatment of gastro-esophageal reflux,[30,31] to name a few. Unvalidated questionnaires have also been utilized to assess health-related quality of life in many conditions treated by pediatric surgeons.[32,33] Condition-specific HRQoL measures have also been described for children with anorectal malformations and HD.[34] Ultimately, very few HRQoL measures to date have been specifically validated or developed for use in the neonatal surgical population.

FUNCTIONAL OUTCOMES

Functional outcomes can be measured in a variety of formats. It is a difficult area of health services research to clearly define. In one sense, these outcomes can be measured within the context of a specific disease state and the procedure that is designed to treat that disease. However, for neonatal surgery the impact of functional outcomes may be inherently distinct from adult conditions. Take, for example, a professional football (soccer in the United States) goalie who is able to consistently punt the ball to the opposite penalty box. He suffers a knee injury in the prime of his career and must undergo reconstructive knee surgery. A 'disease-specific' functional outcome measure following repair could be as simple as assessing his ability to kick the ball that same distance following surgery and physical rehabilitation. From the player's point of view, he is 100% functional if he is able to kick that same distance without any pain after treatment. However, how do we measure function in this case if he is only able to punt the same distance inconsistently? Also, what if he is able to punt the same distance, but suffers incredible pain in doing so – is this a issue of quality of life, function, or both? Thus, the assessment of 'functional outcome' is complex. However, since the sample of premier league goalies who consistently punt a soccer ball nearly the entire length of the football field is relatively small, most generic functional outcome instruments focus on the assessment of individuals with chronic health problems and their ability to 'function' in everyday life. These same issues confront the newborn surgeon attempting to study functional outcomes in populations where the congenital malformations are relatively rare. Furthermore, for such measures to have a meaningful individual and societal impact, they must be measured in adult life, where independent functioning is the expectation. The ability to function is distinct from the quality of function, or life. As it relates to health services research, functional outcomes are not necessarily meant to be condition specific, but are related to any of the general domains of functional health in a survey introduced earlier: physical, social, emotional, or cognitive functioning. The following instruments are the three most common tools utilized to measure general functional outcomes in children (Table 105.2).

Table 105.2 Functional outcomes tools.

Instrument	Applicable age	Time to complete (mins)
FIM[SM]/WeeFIMII[SM]	0–18 (proxy)	15–20 (18 items)
FSIIR	0–16 (proxy)	15 (short), 30 (long)
PEDI™	0–7 (proxy)	45–60 (237 items)

FIM[SM]/WeeFIMII[SM], Functional Independence Measure; FSIIR, Functional Status II; PEDI, Pediatric Evaluation of Disability Inventory.

Functional Status II

The Functional Status II (FSIIR) is able to distinguish between children with and without chronic health conditions, has acceptable internal consistency, reliability, and correlates with other indicators of illness, such as utilization of medical services and illness-related absenteeism.[35] The FSIIR is a 14-item instrument administered to parents to measure their child's capacity to perform age-appropriate roles and tasks in a variety of areas, such as communication, mobility, mood, energy, sleeping, and eating. Parents use a three-point categorical scale to indicate the observed frequency of specific behaviors. When impairment in child functioning is described, parents are asked to report whether each specific impairment is due to the child's illness. The **total** score is the sum of the scores, thus indicating the child's functional status without regard to whether or not observed impairment is due to the child's illness. The **illness** score is the sum of the scores indicating the child's functional status with deduction of points only for impairment related to the child's illness, thus often resulting in a score higher than the total score. The higher the score, the better the functional status.[36]

Pediatric Evaluation of Disability Inventory

The Pediatric Evaluation of Disability Inventory (PEDI) was developed to provide a comprehensive clinical assessment of key functional capabilities and performance in children between the ages of six months and seven years. The PEDI was designed primarily for the functional evaluation of young children; however, it can also be used for the evaluation of older children if their functional abilities fall below that expected of a seven-year-old child. The assessment is designed to serve as a descriptive measure of the child's current functional performance, as well as a method for tracking change over time. The PEDI measures both capability and performance of functional activities in three content domains: (1) self-care, (2) mobility, and (3) social function. It has been primarily utilized in the functional evaluation following neurologic insults (i.e. traumatic brain injury or stroke).[37–40]

Functional Independence Measure

The Functional Independence Measure (FIM[SM]) and its pediatric counterpart (WeeFIMII[SM]) are standardized instruments initially designed to allow clinicians to document

functional performance in children and adolescents with acquired or congenital disabilities.[41] These measures have been approved by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) to provide information for the ORYX initiative (a standardized initiative to allow JCAHO to measure performance standards across accredited organizations), as well as to meet accreditation standards for the Commission on Accreditation of Rehabilitation Facilities (CARF).[42]

Other assessments of functional outcome

The aforementioned scoring systems provide generic assessments of child functioning in daily life. However, a pediatric surgeon is often most interested in how a patient compares to his or her age-related peers following a specific intervention performed in the neonatal period. In this regard, disease-specific functional outcome measures have been utilized for a variety of different pediatric surgical conditions. However, 'function' can be measured by different instruments and/or objective assessments pertinent to the condition in question. The literature regarding the long-term functional results of congenital diaphragmatic hernia (CDH) illustrates this point.

The collaborative UK ECMO (Extracorporeal Membrane Oxygenation) trial concluded that a policy of ECMO support reduces the risk of death without a concomitant rise in severe disability, defined as an overall developmental quotient of <50 using the Griffiths Mental Development Scales.[43] In another study of infants with severe CDH (those who required ECMO support), survivors displayed mild neuromotor and cognitive delay in development at 24 months of age as measured by impairments in mean Bayley Mental Developmental Index and Psychomotor Developmental Index scores.[44] Both of these studies utilized cognitive functioning scores to report on the functional outcomes of infants with CDH.

Other assessments of functional outcome may be related to objective physiologic measurements. In a study of 23 adult survivors of CDH, pulmonary function tests, diffusion capacity, and a cardiopulmonary exercise test (CPET) were performed. The FEV_1 and FEF25–75% were found to be lower in CDH survivors. Despite these abnormalities, during CPET, percent predicted work load and percent predicted maximal oxygen uptake were normal in most of the patients.[45] In another study of functional respiratory outcomes of CDH patients treated in the perinatal period, 26 adolescent survivors and age- and gender-matched controls were subjected to pulmonary function testing. Significant differences were found in nearly every spirometric measurement.[46] Thus, as function relates to pulmonary mechanics in the CDH population, functional outcomes can be construed as favorable or unfavorable depending on the measure utilized.

In general, functional outcomes refer to things that are meaningful to the patient in the context of everyday living. However, for pediatric surgeons, function may be best related to how well the operation is able to recapitulate the 'normal'. In that regard, condition-specific functional outcomes are also worthy to gauge the 'success' of a neonatal operation. For example, it would be helpful for the pediatric surgeon to know what percentage of patients with a type C esophageal atresia are able to eat any food without dysphagia in adult life. Similarly, anorectal function (fecal continence) after the period where toilet training is typically achieved is an especially salient outcome measure for patients with anorectal malformations and HD. These types of disease-specific measures are helpful for patients and their families as they consider the long-term functional issues related to the congenital malformations we are charged with treating. In the final analysis, both disease-specific and generic functional outcomes have merit in the long-term assessment of patients with neonatal surgical conditions.

COST-EFFECTIVENESS AND UTILITY MEASURES

A panel convened in 1993 by the US Department of Health and Human Services suggested that standardized outcomes analyses be conducted to evaluate the cost-effectiveness of medical care.[47] One way to directly compare relative treatment effectiveness is to examine the impact of interventions on the utility gained. Cost-utility analysis fulfills this requirement.[48] In this type of analysis, health treatment effects are most commonly measured in terms of quality-adjusted life-years (QALYs) gained. Preference-based instruments allow one to compare interventions and treatment regimens for a given condition in this manner. Such analyses have become popular for examining the economic consequences of disease and the medical and surgical interventions aimed at treating such problems. A QALY takes into account both quantity and quality of life generated by health-care interventions. It is the arithmetic product of life expectancy and a measure of the quality of remaining life-years. A QALY places weight on time during different health states such that a year of perfect health is worth a score of 1, whereas death receives a score of 0. Health states considered to be worse than death receive a score below zero. The strength of QALY analysis is the fact that it provides a common currency to assess the extent of benefit gained from interventions to improve the quality of life. A cost-utility ratio can be calculated from a QALY assessment combined with the cost of treatment for the condition. For example, a disease that reduces the quality of life by one-half will take away 0.5 QALYs over the course of one year. If it affects two people, it will take away 1.0 QALY (equal to 2×0.5) over a one-year period. A medical treatment that improves the quality of life by 0.2 for each of five individuals will result in a score of 1 QALY if the benefit is maintained over a one-year period. Using this system, it is possible to express the benefits of various interventions by showing how many QALYs they produce versus the total economic cost of the intervention.[49]

Utility and cost ultimately are important components of health-care policy formulation (Table 105.3). Using the common metric of QALYs also allows one to introduce quality of life into the direct cost comparison of programs. This approach provides a framework within which to make policy decisions that require selection between competing

Table 105.3 Utility instruments.

Instrument	Applicable age	Time to complete (mins)
QWB	5–18 (self and proxy)	10
HUI:2	6–18 (self and proxy)	3–10
EQ-5D	5–18 (self and proxy)	1–2

EQ-5D, Euro Quality of Life; HUI:2: Health Utilities Index; QWB, Quality of Well-being scale.

alternatives. Importantly, these types of analyses are potentially influential in determining the extent of funding for particular pediatric interventions.[13] The Quality of Well-Being scale (QWB), the Health Utility Index (HUI), and the EQ-5D are three examples of utility-based measures developed for and validated in pediatric populations.

Quality of Well-Being Scale

Developed by researchers at The University of California, San Diego, the QWB assesses a patient's objective level of functioning in three areas: mobility, physical activity, and social activity.[50] An important distinction is made between 'functional ability' and 'functional performance' – whereby a patient is asked to report activity performed rather than what can possibly be performed. The scoring of the instrument utilizes population-derived preference weights. Current studies are addressing the validity of the QWB-SA translated into Spanish, German, Italian, Swedish, French-Canadian, and Dutch.

Health Utilities Index

The HUI (HUI2, version 2; HUI3, version 3) is a family of health status and preference-based health-related quality of life measures suitable for use in clinical and population studies.[51] Both HUI2 and HUI3 focus on capacity rather than performance. Each includes a health status classification system, a preference-based multi-attribute utility function, data collection questionnaires, and algorithms for deriving HUI variables from questionnaire responses. The attributes of health status included in HUI were chosen on the basis of their importance to people. HUI utility scores are based on the preferences of the community. HUI2 consists of seven attributes: sensation (vision, hearing, speech), mobility, emotion, cognition, self-care, pain, and fertility.[52] Similarly, HUI3 consists of eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain.

EQ-5D

Established in 1987, the EuroQOL Group initially comprised a network of international, multilingual, and multidisciplinary researchers from seven centers in Finland, the Netherlands, Norway, Sweden, and the UK. Currently, the group has expanded to researchers from Canada, Denmark, Germany, Greece, Japan, New Zealand, Slovenia, Spain, the United States, and Zimbabwe. The EQ-5D is a generic measure of health status that provides a simple descriptive profile and a single index value that can be used in the clinical and economic evaluation of healthcare and in population health surveys. The EQ-5D system consists of five dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension has three levels designated simply as no problem, some problem, or extreme problem, and subjects are asked to check the level most descriptive of their current level of function or experience in each dimension. These five dimensions, yield 243 possible distinct 'health states' comprising the classification system. The classification system has been assigned standardized scores derived through population-based samples of respondents asked to assign values to subsets of the 243 states. A set of valuation weights has been derived from a US sample.[53]

Although several measurement instruments have been developed to measure utility in children, measurement methods are seemingly fraught with inconsistencies and biases.[54] Indeed, a study of cost-utility analyses in the medical literature between 1976 and 1997, recommended the need for more consistency and clarity in reporting.[55] In response to such criticisms, the Paediatric Economic Database Evaluation (PEDE) project was conceived to promote research into pediatric health economic methods. In recent years, standard methods for the conduct of economic evaluations have evolved to improve allocation decisions that are unique to the pediatric population. The database contains over 1500 citations from January 1, 1980 to December 31, 2005 and continues to be updated. Consistent with use in allocation decision-making, only full economic evaluations are accepted for inclusion.[56]

Long-term outcomes in specific neonatal surgical disease

Assessment of outcome is an important part of the practice of neonatal surgery. The current tools available to quantify quality of life, function, and cost-utility have changed dramatically over the last decade. However, this area of health research remains in its infancy where patients with neonatal surgical conditions are concerned. Unfortunately, there are few studies in pediatric surgery that address long-term outcome. This offers an opportunity for further research, yet represents a host of difficulties. Information on long-term outcomes is difficult to obtain as studies require the meticulous collection of data over many years, are hampered by lack of long-term follow up (especially for those children who do well!), and attempts to corral a mobile patient population require efforts beyond the willingness or resources of most pediatric surgeons. Furthermore, relatively few clinical interventions and treatments in pediatric surgery are supported by adequately powered randomized controlled trials – which may undermine the subsequent analysis of long-term outcome. In many cases, the specific short- and long-term morbidities of each congenital malformation and its respective operative treatment have been previously addressed in the specific chapters of this text. However, we will cover some of the salient long-term standard and

modern outcome measures of the most common neonatal thoracic and abdominal surgical conditions and propose future opportunities to further our understanding of the ramifications of these malformations and the operations utilized to treat them.

LONG-TERM OUTCOMES FOR SURGERY IN THE NEWBORN PERIOD

General considerations: prematurity and low birth weight

The neonatal period is defined as the period after birth within the first 28 days of life. Indeed, no other patient demographic in medicine has achieved such a dramatic improvement in survival over the last 30 years as that of the premature neonate. Today, the survival for very low birth weight (VLBW) infants (birth weight less than 1500 g) has increased to over 80%. Furthermore, patients weighing less than 1 kg (extremely low birth weight, ELBW) have realized survival in as many as 70%. These increases have occurred as a result of many substantive improvements in perinatal care and the expertise and methods by which that care is delivered. However, as the number of deaths from sepsis and the sequelae of group B streptococcal infection and chorioamnioitis have declined, the proportion of mortality due to congenital anomalies has increased in both the United States and the United Kingdom. In 1998, some 28% of infant deaths in the United Kingdom were due to a congenital anomaly. In the most recent national vital statistics report released by the United States Centers for Disease Control in 2007, only 0.8% of infants died prior to 28 days of postnatal life, but the leading cause of death in this group is attributed to congenital malformations. In the United Kingdom, approximately 114 out of every 10 000 live births is complicated by a congenital malformation. In the United States, it is estimated that some 2–3% of infants are born with a major congenital malformation. For appropriately grown infants (not suffering from intrauterine growth restriction (IUGR)) between a birth weight of 1500 and 2500 g the mortality rate remains less than 10%. Below this weight, mortality rates incrementally increase and survival below 500 g is uncommon. Today, the gestational age at which there is a 50% chance of survival has declined to 25 weeks.[57]

Perhaps the most salient long-term outcome as it relates to prematurity and low birth weight is the incidence of impairment, disability, and handicap. According to the World Health Organization, 'long-term impairment' includes any loss or abnormality of psychological, physiological, anatomic structure, or function. 'Disability' is defined as any restriction of ability to perform an activity within the range considered normal for a human being. A disability reflects the consequence of an impairment in terms of functional performance and activity. Finally, a 'handicap' is a disadvantage for a given individual resulting from an impairment or disability that limits fulfillment of the role that is normal based on age, sex, and social and cultural factors.[58] The most significant major disability affecting premature infants is cerebral palsy (CP). CP is defined as a permanent impairment of voluntary movement or posture due to damage to the developing brain. It may involve one limb (monoplegia), both lower limbs (diplegia), or all four (quadriplegia). In patients weighing less than 2 kg at birth, the incidence of cerebral palsy at the age of two years was 8% in a geographical study of 1000 children.[59] Very and extremely low birth weight survivors are also at an increased risk for long-term visual impairment, such that approximately 5% of infants in this category are 'blind'. Retinopathy of prematurity is the most common cause of poor visual outcome, however cortical blindness can occur from damage to the occipital cortex due to periventricular leukomalacia or optic atrophy as a result of hydrocephalus. Cryotherapy for retinopathy of prematurity is an effective treatment, reducing the chance of severe visual loss by 50%, and this treatment has resulted in an improvement in long-term visual handicaps associated with prematurity.[60] Sensorineural hearing loss is also a problem in survivors of premature birth. This is most frequently seen in survivors with persistent pulmonary hypertension (PPHN) and high incidences are widely reported in survivors of extracorporeal life support (ECLS). In modern intensive care units, all infants are screened for hearing loss. Early diagnosis guides appropriate support and improves language development later in life. Whereas cerebral palsy is clearly one of the most devastating long-term consequences of prematurity, cognitive impairment is a more common adverse outcome.[61] The intelligence quotient (IQ) in long-term survivors of VLBW gestations is shifted one standard deviation lower when compared to normal birth weight controls, and a significant number of these children suffer from attention deficit or hyperactivity disorders when compared with controls. However, even with an IQ in a normal range, the VLBW survivor is more likely to require special educational provisions. In addition, small for gestational age infants suffer from a negative impact on school performance; 25% of such infants in 1985 were failing at school at age ten years compared to 14% of children who had been weight appropriate for gestational age.[62] Nevertheless, small for gestational age survivors report 'adequate' satisfaction with life, despite the fact that these individuals are less likely to secure professional or managerial employment.[63] Finally, poor motor coordination, altered manual dexterity and balance, short attention span and visual impairment are generally coexistent and together significantly impair the child's ability to function in school. The highest proportion of these adverse neurodevelopmental outcomes are seen in those treated with the highest acuity of care (i.e. ECLS).[64–67]

General considerations: psychological effects of neonatal surgery

In addition to the consequences of prematurity and low birth weight, the psychological consequences of surgery performed within the first 28 days of life should not be overlooked. Studies on the effects of hospitalization on young children show that between six months and four years of age, children will most likely demonstrate short-term emotional and

behavioral problems during that admission, and later psychological disturbances were associated with repeat hospital admission, as well as those hospitalizations lasting for more than a week. Based on these observations, Dr Loraine Ludman and colleagues at the Great Ormond Street Hospital for Children in London began a prospective longitudinal study to examine the psychological effects of major neonatal surgery on infants and their families. The infants studied were born at term and required major surgery within the first 28 days of life. These infants were compared to a carefully matched group of healthy newborns not requiring neonatal surgery. Interestingly, very early hospitalization and periods of separation did not differentiate between the case-control pairs at 12 months of age. However, by three years of age, the rate of behavioral disturbance was approximately 2.5 times greater among the patients undergoing surgery in the first 28 days of life compared to the control group (30% versus 11.5%). The two predominant factors associated with difficulty in the mother–child relationship were a lengthy first admission (more than 25 days) and/or repeat hospital admissions. In longer-term follow up between 11 and 13 years of age, emotional and behavioral problems were more frequent among the surgical group than among the controls based on parent and teacher reports. These data suggest that surgery and repeated admissions in early childhood have long-term effects on emotional behavior adjustment. However, although a third of children were affected by the chronic nature of their condition in their preschool years, at early adolescence only a small proportion of those included in the dataset were regarded as having a 'chronic condition'. In addition, the youngsters all rated themselves as 'well adjusted' and there were no differences between the two groups in terms of self-esteem and depression self-report scales. These data raise the need for long-term focused psychological support for children and their families who care for children with major congenital anomalies requiring surgery in the neonatal period.[68–70]

Thoracic surgery: general considerations

A number of conditions diagnosed within the first 28 days of life require access to the thoracic cavity by way of thoracotomy or thoracoscopy. Neonatal thoracotomy is typically well tolerated in the short term. The recovery and return to normal physiologic function following neonatal thoracotomy is in contrast with that observed in adults – in which long-term pain and disability is more often realized in older patients. However, rapid neonatal 'recovery' must be tempered by the potential for long-term chest wall growth abnormalities resulting from thoracotomy. Several types of orthopedic deformities have been described following neonatal thoracotomy, including scoliosis, rib deformities and synostosis, and shoulder deformities. Jaureguizar *et al.*[71] reported on 89 patients operated for esophageal atresia via standard right posterolateral thoracotomy with a follow up of 3–16 years. Of these, 32% had significant musculoskeletal deformities including 'winged scapula', marked asymmetry of the thoracic cage from atrophy of the serratus anterior, rib fusion, and severe thoracic scoliosis. Chetcuti and colleagues[72] reported on a similar experience in the study of 232 patients with esophageal congenital anomalies without pre-existent congenital vertebral anomalies who underwent neonatal thoracotomy. In this series, 33% of patients later developed chest wall deformities and 8% were reported to have scoliosis. One of the purported benefits of minimally invasive access to the chest (thoracoscopy) for lung resection and repair of esophageal atresia is the potential benefit of limiting this chest wall morbidity. The long-term outcome from minimally invasive access to the thorax requires assessment of this possible benefit. Because of the above concerns, many pediatric surgeons today utilize a muscle-sparing thoracotomy through the ausculatory triangle, while preserving the latissimus dorsi and serratus anterior musculature. The long-term benefits of this type of approach also have not been reliably compared to that of a standard muscle-splitting thoracotomy. Both of these newer approaches to thoracic access offer opportunities for the pediatric surgeon to assess the potential benefits of modern surgical technique to the long-term outcomes of neonatal thoracic surgery.

MALFORMATIONS OF THE TRACHEOBRONCHIAL TREE

Subglottic stenosis did not become an issue until prolonged endotracheal intubation and ventilation of neonates became commonplace in the mid-1960s. As survival of low birth weight infants increased, so too did the number of patients with acquired laryngotracheal stenosis. Today, advances in the equipment utilized for neonatal endotracheal intubation, tube stabilization, and the recognition of the deleterious effects of prolonged transglottic instrumentation have decreased the incidence of laryngotracheal stenosis to less than 10%. In patients suffering significant laryngotracheal stenosis, the surgical options largely depend on the grade of stenosis realized. The functional outcomes of laryngotracheal reconstructive (LTR) surgery are clearly critical in the determination of long-term success. Studies evaluating exercise tolerance, speech, swallowing, and voice are at this point limited, owing to the relatively recent advances in the surgical correction of these disorders. Early studies of voice function after LTR surgery were entirely subjective assessments; however, recent studies in children have paired subjective observations with objective measurements.[73]

PULMONARY RESECTION

Pulmonary resection in the neonatal period may be undertaken for a congenital pulmonary airway malformation (formerly 'CCAM'), pulmonary sequestration, or congenital lobar emphysema. The most significant long-term outcome facing patients undergoing neonatal pulmonary resection is that of respiratory function. Ayed and Owayed[74] reported on the safety of lung resection in the neonatal period for congenital malformations and found that none of the patients had physical limitations at a mean follow up of four years. In addition, Caussade and co-authors[75] reported normal spirometry values for vital capacity in 27 patients who underwent neonatal pulmonary lobectomy. Neonates

undergoing lung resection can expect to have normal vital capacity due to the compensatory growth of the remaining lung and most studies indicate that few children are functionally impaired by lung resection performed in the neonatal period. In addition, in patients who undergo pneumonectomy prior to the age of five years, ventilatory capacity is only minimally reduced when compared to that predicted for an individual with a complement of two normal lungs suggesting that 'lung growth' occurs well beyond the neonatal period as a result of compensatory pulmonary hyperplasia.[76] It appears that normal postnatal growth of lung parenchyma at the gas exchange (alveolar) level up to about seven to eight years of age contributes most of this additional reserve, as there is not regeneration of conducting airways. Whereas functional outcome studies have been limited in patients undergoing pulmonary resection in the neonatal period, reports of health-related quality of life are noticeably absent in this patient cohort. To date, there is no literature classifying the health-related quality of life of infants undergoing neonatal pulmonary resection.

MALFORMATIONS OF THE ESOPHAGUS

One of the most commonly performed operations undertaken by the pediatric surgeon in the neonatal period is the repair of esophageal atresia and/or tracheo-esophageal fistula. Mortality rates in patients with Waterson risk groups A and B esophageal atresia is well below 5% overall. Today, the nature of coexisting anomalies that determine survival is best described by a newer risk stratification taking into account birth weight and the presence of cyanotic congenital heart disease.[77] Early surgical complications, such as anastomotic leak, disruption, or stenosis, are often associated with a favorable short-term outcome when adequately treated. In the long term, dysphagia and food impaction are the most common foregut issues facing the child with repaired esophageal atresia. The motility of the esophagus is inherently abnormal to some degree in all patients despite 'adequately' repaired esophageal atresia.[78] Although symptoms of 'choking with feeding', odynophagia, and 'food impaction' are relatively common during childhood following esophageal atresia repair, these problems tend to decline with age. Those who have persistent difficulties with swallowing are more likely to have or have had an esophageal stricture or significant gastro-esophageal reflux. Today, radial balloon dilation of the esophagus under fluoroscopic control and medical and/or surgical control of reflux disease are useful adjuncts in the prevention of these long-term sequelae. Indeed, most adult survivors with repaired esophageal atresia have minor persistent gastrointestinal symptoms such that less than 10% report dysphagia that occurs once a day, and the majority report no symptoms of gastro-esophageal reflux.[79] While it is generally believed that persistent gastro-esophageal reflux in patients undergoing esophageal atresia repair contributes to dysphagia, there is little objective evidence of this. The majority of neonatal gastro-esophageal reflux disease (GERD) is a transient problem that abates by childhood. Although adults with repaired esophageal atresia may be at increased risk for developing esophageal malignancy, it is too early to tell whether or not the history of esophageal atresia affects the incidence of esophageal carcinoma later in life. Although there are sporadic reports of early development of esophageal adenocarcinoma following esophageal atresia repair, there is no clear-cut evidence that the anomaly itself or its correction contributes to the development of esophageal malignancy.[80] The concern is that esophageal dysmotility, poor esophageal clearance, and reduced lower esophageal sphincter pressure, even in the absence of symptoms may lead to the development of Barrett's esophagus, which is associated with an increased risk of adenocarcinoma of the distal esophagus. To date, there is no specific recommendation with regard to long-term surveillance for patients with esophageal atresia; however, as more survivors make their way into adult and elderly life, this certainly should be a consideration for pediatric and adult surgeons caring for patients who have undergone esophageal atresia repair. Follow up should be vigilant and lifelong until the risk of malignant degeneration in these patients is better delineated.

Few studies to date have examined the health-related quality of life in children and adolescents after repair of esophageal atresia. In a recent study by Peetsold and colleagues,[81] 24 patients with esophageal atresia (and their parents) completed a health-related quality of life instrument. In addition, functional outcome was assessed by a validated standardized gastro-esophageal reflux questionnaire and data compared to a healthy reference population. Parents, as well as patients themselves, scored significantly lower on the general health domain perception. In addition, patients reported that GERD symptoms reduced their general health perception. In another study examining psychosocial functioning in adolescents with neonatally repaired esophageal atresia, Faugli *et al.*[82] reported on a group of 21 adolescents with esophageal atresia and compared them to 36 adolescents from a general population. Overall, adolescents with esophageal atresia have normal mental health and psychosocial functioning compared to their peers. However, the need for postoperative dilatation of the esophagus and low birth weight were significant predictors of impaired mental health and psychosocial functioning. In another assessment of long-term, health-related quality of life in adult survivors following correction of esophageal atresia, Deurloo *et al.*[83] found no differences in overall physical and mental health compared to a control group. Interestingly, the presence of concomitant congenital anomalies did not negatively influence health-related quality of life. Only a third of the patients reported that esophageal atresia had negative effects on their daily lives and gastrointestinal (GI) symptoms, such as dysphagia, were the most often mentioned contributing to such.

There are fewer problems more technically challenging for the pediatric surgeon than the patient with long gap esophageal atresia. In the short term, the surgeon must decide on the appropriate management strategy for reconstruction of the esophageal conduit. The techniques by which this is accomplished are varied and each technique has its advantages and disadvantages. Although it is widely accepted that the optimal esophageal conduit is the native esophagus, a number of surgeons use either colon, native stomach, or jejunal grafts to bridge abbreviated esophageal segments. Techniques for

sequential and gradual elongation of the native esophagus, such as those popularized by Foker *et al.*[84] and Kimura *et al.*[85] appear to offer favorable short-term surgical outcomes in the institutions where they are employed. Nevertheless, the adverse long-term sequelae of either esophageal replacement or native esophageal lengthening are significant. In a recent study from the Great Ormond Street Hospital, the large majority of patients undergoing long gap esophageal atresia repair had long-term issues with gastro-esophageal reflux.[86] A report from the Children's Hospital of Los Angeles concluded that patients with a gastric conduit had a lower overall complication rate without evidence of conduit ischemia when compared to those with a colonic interposition; however, the incidence of long-term adverse physiologic sequelae were significant. In a review of published studies for esophageal replacement in children by Arul and Parikh,[87] there was no significant difference in either early or late complications associated with the different type of conduits utilized for interposition. However, the authors did note that larger series tended to have lower complication rates than those of small series likely reflecting the association between clinical expertise and experience and outcomes in larger surgical centers.

To date, the short- and long-term physiologic outcome of esophageal atresia and tracheo-esophageal fistula could be considered favorable. However few data exist with regard to health-related quality of life in this cohort of patients. Furthermore, the long-term follow up of patients with esophageal atresia and the impact of Barrett's esophagitis and later development of adenocarcinoma is yet to be fully realized and mandates vigilant postoperative follow up and a surveillance program that should be overseen by a practicing pediatric surgeon.

CONGENITAL DIAPHRAGMATIC HERNIA

Congenital diaphragmatic hernia has been widely studied. The mortality rate and adverse sequelae in survivors of CDH remain significant compared to the other commonly treated newborn surgical conditions addressed by the pediatric surgeon. Historically, the long-term follow up of patients with congenital diaphragmatic hernia was sporadic and uncoordinated. This likely led to an underestimation of the number and severity of problems affecting survivors of CDH repair. Data from long-term follow-up studies identifies several potential morbidities involving a number of different organ systems including pulmonary, cardiac, neurologic, gastrointestinal, urogenital, and musculoskeletal. Today, it is recognized that these patients are best cared for in a multidisciplinary setting where coordinated follow-up care involving multiple specialties is possible.[88,89] Although this is not a widespread practice among pediatric surgeons, large pediatric centers are encouraged to develop these types of outcome clinics to coordinate follow up and address ongoing physiologic concerns among survivors of CDH.[90] Indeed, the most remarkable accomplishment in caring for a patient with CDH is the improved survival to hospital discharge during the past decade.[91,92] However, while some authors have reported survival figures approaching 90%,[93] the current overall survival in the Unites States is 70% among 2676 live born infants from 50 tertiary centers.[94] For those patients who do survive to hospital discharge, long-term morbidity is a function of the severity and laterality of the defect, as well as the need for extracorporal life support (ECLS).[66,89,95]

Pulmonary morbidity is perhaps the most significant problem during early childhood in survivors of CDH.[96–100] Ventilatory barotrauma, bronchopulmonary dysplasia, and chronic lung disease play a larger role than previously suspected in both mortality and morbidity of those patients with CDH.[91,101,102] Nearly 60% of survivors require some form of medical therapy for reactive airway disease and long-term obstructive airway disease is demonstrable in approximately 25% of patients at five years of follow up.[103,104] The long-term sequelae of ventilation perfusion mismatch may also result in significant limitations in exercise tolerance in the adolescent years.[99] Mild airway obstruction and a slightly reduced diffusion capacity for carbon monoxide are observed in most survivors of CDH. Furthermore, pulmonary hypertension and subsequent right ventricular hypertrophy has been reported in as many as 50% of survivors of CDH treated with ECLS.[105] Nutritional morbidity and growth failure is also unfortunately common in patients surviving CDH. In a retrospective analysis of 121 survivors of CDH, over half of the patients were below the 25% for height and weight during the first year of life.[106] Approximately one-third of this population had issues severe enough to require a gastrostomy to provide adequate caloric intake. The need for ECLS and an oxygen requirement at discharge are predictive of growth failure within the first year of life. Others have reported similar trends in growth failure and nutritional morbidity.[107–110] Oral aversion, foregut dysmotility, and persistent GERD all contribute to the nutritional morbidity of CDH survivors.[99,111] Neurocognitive deficits play a significant role in the long-term functional outcome of CDH patients surviving to discharge. Mild-to-moderate development delay has been reported in more than one-third of CDH survivors followed in a multidisciplinary clinic.[90,112] Although the neurologic deficits in CDH survivors are the result of the critical nature of the postnatal disease process and its treatment, the contribution of ECLS on neurologic morbidity is of significant concern. The incidence of neurologic abnormalities among all neonatal survivors of ECLS ranges from 10 to 15% and includes cerebral palsy, hearing loss, seizure disorder, cognitive delay, and vision impairment. However, the use of ECLS in CDH patients confers an increased risk for long-term neurocognitive impairment such that up to 70% of survivors demonstrate some type of neurocognitive deficit. Furthermore, the incidence of sensorineural hearing loss in survivors of CDH ranges from 25 to 37% in reported studies.[99,102,113–116] The orthopedic deformities associated with CDH are also of significance in that CDH survivors are prone to scoliosis and chest wall deformities. Nobuhara *et al.*[90] reported a 21% incidence of pectus deformities and a 10% incidence of mild-to-moderate scoliosis in long-term follow up. These chest wall deformities are more common among patients with an initial severe ventilatory impairment and a diaphragmatic defect requiring the need for a prosthetic patch. It has been observed that these complex long-term issues appear more

prevalent as newer support strategies have allowed infants with severe disease to survive.

In terms of health-related quality of life of CDH survivors, Peetsold and co-authors have described a significant reduction and perception of general health in survivors of CDH compared to a reference population.[81] Lower functional status has also been described in CDH survivors in a recent study using the FSIIR tool.[117] Furthermore, in a study from the Children's Hospital of Boston, family impact was found to be profound and longstanding at a median of eight years after surgery for a subset of CDH survivors with comorbidities and current clinical problems.[118]

ABDOMINAL CONDITIONS

General considerations

Apart from the repair of inguinal hernia, abdominal conditions in the neonate comprise the majority of work performed by the practicing pediatric surgeon. The long-term outcome of a variety of these conditions is dependent on the method of peritoneal access. The two most important potential adverse outcomes of laparotomy include adhesive bowel obstruction and incisional hernia. In a study from the Great Ormond Street Hospital, the authors described only four documented cases of incisional hernia in 507 pediatric laparotomies.[119] More salient to the intra-abdominal conditions of the neonate is the potential for adhesive bowel obstruction following laparotomy or laparoscopy. In a study of 649 neonates undergoing laparotomy over ten years, 8.3% developed adhesive intestinal obstruction requiring surgical intervention.[120] In a similar study from the Netherlands of 304 neonates undergoing laparotomy, adhesive intestinal obstruction occurred in 3.3% of cases.[121] The indication for laparotomy clearly plays a role in the incidence of postoperative adhesive bowel obstruction. For example, in patients undergoing gastroschisis repair, up to 15% of patients may experience adhesive bowel obstruction, which can occur years following primary repair.[122,123] In patients undergoing a Ladd's procedure, 8–15% of patients experience one episode of postoperative adhesive bowel obstruction.[120] Techniques to prevent intestinal adhesions emphasize minimizing peritoneal trauma and the separation of potentially involved surfaces. Clearly, one of the benefits of minimal access surgery or laparoscopic surgery is in the potential decrease in the incidence of adhesive bowel obstruction, although persuasive long-term data are yet to be realized in supporting this contention. In addition, minimally invasive access to the abdominal cavity does result in a postoperative cosmetic result that is preferred by many patients after they grow into adulthood.[124] Indeed, a noticeable scar can have physical, esthetic, and psychologic consequences in children.[125] Cosmetic concerns with regards to abdominal wall scarring are likely to be more important for neonates as they grow into the teenage years. Minimizing these concerns is probably a unique benefit of minimal access neonatal surgery. Other purported benefits of minimal access laparoscopic surgery are that of a decreased inflammatory response, less postoperative pain with a subsequent decrease in the need for postoperative analgesia, and a shorter time to hospital discharge.[126–128]

Malformations of the midgut

The most profound sequela of neonatal surgical conditions involving the midgut involves massive small bowel resection or malabsorption and altered motility. Thankfully, the outcomes of intestinal failure due to short bowel syndrome have changed dramatically over the last 30 years. The development of total parenteral nutrition introduced a new era in the management of children with short bowel syndrome.[129] Although the functional impairment in short bowel patients typically results from an anatomic loss or deficiency of intestinal surface area, it may also occur in the setting of a normal intestinal mucosal surface with perturbations in intestinal absorption, motility, or both. The length of small bowel is clearly an important predictor of the development of short bowel syndrome, however the absolute length of 'viable' small intestine in the neonatal population may not be an adequate predictor of short bowel syndrome and intestinal failure. Today, the consensus definition for short bowel syndrome is 'intestinal failure as a result of surgical resection or congenital defect or disease which is associated and characterized by the inability to maintain protein energy fluid and electrolyte or micronutrient balances on a generally accepted normal diet'.[130] Although the amount of bowel that must be lost to produce malabsorption in short bowel syndrome is variable and depends on segments lost and whether the ileocecal valve is preserved, loss of greater than 80% of the small bowel is associated with an increased requirement for enteral nutritional support, decreased overall survival, and the need for further surgical intervention or small bowel transplantation. The neonatal surgical population at risk for developing short bowel syndrome includes patients with necrotizing enterocolitis, small intestinal atresia, malrotation and midgut volvulus, and gastroschisis. The complications encountered in short bowel syndrome are varied in complexity and dependent on a variety of factors. Survival rates reported for short bowel syndrome are influenced by the variable severity of the condition, underlying disorders and comorbidities. Potential complications are myriad and can include diarrhea and electrolyte disturbances, osteopenia, urinary oxalate stone formation, and total parenteral nutrition (TPN)-associated liver disease. In addition, the achievement of normal somatic growth is a challenge for the patient with short bowel syndrome. The most common causes of mortality following massive small intestinal resection in the neonate include liver failure and sepsis in patients requiring TPN for the majority of their nutritional support. In addition, the care of the patient with short bowel syndrome entails substantial economic expense. In 1992, the annual direct cost per home for patients requiring TPN averaged approximately US$100 000.[131] In addition, the complex medical needs and potential complications of short bowel syndrome have a clear and obvious impact on health-related quality of life. Although the development of home parenteral nutrition programs has

provided greater independence from the hospital for these patients, the responsibility has been shifted to caretakers, which has a profound impact on the family.[132] Unfortunately, there are few rigorous assessments of the obvious psychosocial impact of this chronic illness on both patients and their families. In adults requiring home TPN, social and emotional function as well as quality of life were lower in patients requiring home parenteral nutrition compared to those with short bowel syndrome not on TPN.[133] Although it is intuitive that the quality of life for both patients and their parents suffering from short bowel syndrome resulting from neonatal surgical conditions is likely to be low relative to normal, the real question is whether or not subsequent surgical interventions may improve the quality of life for these patients. Surgical treatment beyond the neonatal period (i.e. Bianchi procedure, longitudinal intestinal lengthening and tailoring, and the STEP procedure) may offer hope for improving the quality of life for these patients.[134] In addition, developing non-surgical enteral support strategies beyond the scope of this review offer some promise.

In those patients surviving to small intestinal transplantation, important outcome measures include graft and patient survival. In a study from the University of Pittsburgh, the overall patient survival at five years following small bowel and intestinal transplantation was 56%.[135] At the University of Miami, the two-year survival rate following small intestinal transplantation between 1997 and 2000 was 46%, although the current one-year survival is approximately 85% due to improvements in surgical technique and immunosuppressive care.[136] Furthermore, combined transplantation of the intestine and liver is associated with a 40% graft survival at five years,[137] although patient survival is best with isolated intestinal grafts. Both graft and patient survival will likely continue to improve with time. Also encouraging is that health-rated quality of life is improved with intestinal transplantation in patients with short bowel syndrome. Sudan and colleagues[138] obtained quality of life data from 29 successful pediatric transplant patients, and found that patients had comparable CHQ assessments to norms in physical function role, social limitation, general health, bodily pain, role limitations, self-esteem, health, and behavior. However, the parental assessment was generally lower than the child's in general health perception and role imitation. From a public health standpoint, the financial and emotional costs for caregivers must impact decisions regarding the allocation of medical resources. Long-term outcomes of the surgical treatment of intestinal failure including intestinal transplantation must include assessments of health-related quality of life, functional outcome, and utility, such that families can make appropriate decisions in the neonatal period when faced with the potential for short bowel syndrome.

Malformations of the hindgut

In patients with malformations of the hindgut, the importance of health-related quality of life and functional outcome cannot be ignored. As patients with anorectal malformations (ARM) and HD now frequently survive into adulthood, the quality of life, and functional outcomes related to these congenital malformations and their attendant surgeries must be examined with care. Perhaps one of the most salient contributions to the technical practice of pediatric surgery over the last several decades is that of the posterior sagittal approach to the repair of anorectal malformations popularized by Dr Alberto Pena.[139] However, as advances in surgical technique have allowed us to recreate the anatomic relationships in the perineum with greater short-term 'success', the long-term functional outcomes are less clear, and appear most dependent on the type of malformation encountered.[140] In addition, although few patients today die of Hirschsprung's-related enterocolitis in the neonatal period, the long-term functional results of the surgical treatment of HD are also variable as our patients proceed into childhood and adult life. The common relevant 'functional' outcome measure for both of these patient groups is that of bowel control. We are most interested in the ability for a child to defecate normally commensurate with his or her peers. However, the implications of constipation and incontinence also have significant impact on health-related quality of life.

In patients with anorectal malformations, associated anatomic malformations of the genitourinary tract and spinal cord not only affect the surgical complexity, but also impact the functional outcome and quality of life. Continued evaluation after the neonatal period must address the functional sequelae of anorectal malformations. Simply put, two parameters of bowel control are especially salient for the child with an anorectal malformation. The first is the capacity for voluntary bowel movements. The second is the incidence of soiling or defecation between bowel movements, that is uncontrolled and unwanted. The patient who can verbalize a desire to pass stool and uses the commode to pass voluntary bowel movements, has a significant advantage over the individual who has never had voluntary bowel movements following the repair of an anorectal malformation. The latter patients are physiologically incontinent, that is with either sensory or muscular failure (or both), and represent a specific category. In terms of soiling, Levitt and Pena[141] have categorized patients with soiling into two grades. Grade 1 patients soil once or twice a week where there is a spot or smear of stool in the underwear. The patient who soils every day is considered to have grade 2 soiling. Clinically, this is a simple and practical way to categorize patients in long-term follow up. However, for long-term functional outcome studies, disease-specific scores to assess and quantify bowel control in these patients may be useful for academic purposes. Brandt and colleagues[142] have developed and validated a continence scale in children with anorectal malformations termed the Baylor Continence Scale (BCS). This disease-specific functional outcome measure is administered by recording the responses to 23 questions using a psychometric response analog scale, and the higher the score the more significant the impact on continence. Higher scores were noted in their population of patients with ARM compared with both enuresis and normal control groups. This type of scoring system may allow pediatric surgeons and physicians to be able to quantitate qualitative data as they relate to the postoperative function following the repair of anorectal malformations. Overall, the most salient predictor of bowel control is related to the type of anorectal

malformation. The terms, 'low' or 'high' imperforate anus should be abandoned such that clinicians can adequately report and address the specific functional outcomes for each of the anatomic abnormalities.[143] Indeed, children with a perineal fistula are likely to be continent, but have a higher likelihood of constipation. Similarly, male patients with a recto-bladder neck fistula are more likely to be incontinent of stool compared to their anatomically normal peers.[140]

Assessment of generic health-related quality of life in patients with ARM has been undertaken in a number of studies. The EuroQOL score has been validated in children with a history of an anorectal malformation and repair.[26] In addition, disease-specific quality of life questionnaires have been developed.[34,144,145] In the Brandt study from 2007, patients with anorectal malformations in general had a lower HRQoL score (CHQ) compared to both enuresis patients and a normal control group. Utilizing a disease-specific quality of life questionnaire, Grano and colleagues[146] found that adults with previously repaired ARMs reported significantly lower emotional functioning and problems in the area of body image and physical symptoms when compared to those patients in the control group. In Hartman *et al.*'s study,[144] HRQoL is directly related to the nature and severity of the anorectal malformation. However, children and adolescents with anorectal malformations reported better quality of life over time. This could be attributed to coping mechanisms, utilization of a bowel management program, or more specific attention by the medical community to addressing the psychological and physiological needs of these patients in their societal context. Although psychological functioning is typically an attribute of HRQoL, specific psychological effects of anorectal malformations and their repair is also clinically important. A high proportion of children with previously repaired ARMs have clinically significant emotional problems based on psychiatric diagnostic interviews. Approximately 29% of children were found to have a psychiatric disorder with 19% having disorders severe enough to influence their daily lives.[147,148] This was significantly higher than the general child population in the United Kingdom where the rate of a significant psychiatric disorder is 10%. Other studies have delineated similar findings.[149,150]

For patients with HD, the recognition of enterocolitis and its prompt treatment have decreased the short-term morbidity and mortality associated with this disorder. Early recognition of the disease, improvements in neonatal and anesthetic care, and surgical technical advancement have allowed for successful and prompt surgical treatment in the neonatal period. Single stage laparoscopic or transanal pull-throughs are relatively new additions to the armamentarium that await long-term functional assessment. For long-term outcomes, the issues of bowel function and continence again become the most salient issues. All of the operations utilized in the treatment of HD carry some risk of constipation. In most series, the severity of constipation following repair improves with time or resolves. However, it is important to recognize and treat constipation in the postoperative period so as to prevent the long-term functional impairment of the pull-through segment. The occurrence of fecal soiling in patients who have undergone repair of HD can also affect quality of life. Indeed, the complete or partial loss of the rectal reservoir is an inevitable result of pull-through operations for HD owing to high amplitude peristaltic contractions. The incidence of true fecal incontinence is low regardless of the operative technique utilized to address HD. However, when postoperative fecal soiling is critically assessed in childhood, the proportion of patients with some degree of fecal incontinence or soiling is approximately 50%.[27,151–153] In a study by Mills and colleagues,[154] functional outcome and HRQoL were evaluated in 51 patients who had undergone surgical treatment for HD.[154] Overall, the mean continence score as assessed by this instrument was 3.34 and categorized as 'fair', however, there was statistically significant improvement in fecal continence scores with age, confirming the previous speculation of improvement of this particular entity with time. Only 7% reported poor fecal continence in the teenage years. Good fecal continence was reported in 80% of teenagers. Utilizing the PedsQL score for HRQoL assessment, these authors found that there was no statistically significant difference between patients with HD and healthy children, either by overall or age group. Interestingly, females had noticeably higher quality of life compared to their male cohorts, which also corroborates the long-held view that females with HD may fare better than their male counterparts. Despite the significant advances in the management of HD, the long-term functional outcome remains far from perfect for some patients. Furthermore, no individual surgical procedure is demonstrably superior with regard to long-term results, either as it relates to constipation or continence.

CONCLUSION

Today, the pediatric surgeon interested in the study of long-term outcomes must be cognizant of the tools available for outcome assessment and choose the instrument most appropriate for the patient population in question. Selection of the appropriate tool to measure an outcome is as important as the act of measuring it. Furthermore, although it is important to give emphasis to development and appropriate use of outcomes instruments, it is imperative that we think of ways in which to improve the quality of life or physical, cognitive, or social functioning of our patients. Interventions aimed at improving quality of life may play an important adjunct in positively affecting the health of infants and children as they make the transition into adult life (i.e. counseling to teach children better coping skills, support groups, or psychological therapy). Excellent instruments already exist in the realm of generic health-related quality of life and functional outcomes. Choosing the appropriate instrument is dependent on knowing what the instrument is capable of measuring. National and international organizations dedicated to the surgical care of infants and children would do well to recommend specific generic, or disease-specific instruments such that clinicians can utilize equalities of scale when comparing HRQoL or functional outcomes following the surgical correction of congenital or acquired disease. We owe it to our pediatric surgical patients to utilize these instruments, validate them in pediatric surgical populations, and employ strategies to ultimately improve outcomes.

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Note: Illustrations are comprehensively referred to from the text. Therefore, significant material in illustrations (figure and tables) have only been given a page reference in the absence of their concomitant mention in the text referring to the illustrations.