SURGICAL CARE OF MAJOR NEWBORN MALFORMATIONS



Stephen E Dolgin • Chad E Hamner
editors

World Scientific

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INTRODUCTION

Caring for newborn patients with major malformations has been an essential feature of pediatric surgical training since its inception. The relative rarity of these cases partly explains why training centers are limited to places with significant volume of tertiary neonatal surgical challenges. These cases often represent conditions with which graduates of general surgical residencies have limited experience. One of the goals of pediatric surgical training is to produce surgeons able to help solve these problems. We offer this work as a tool for those managing these patients.

The historical context can serve as a springboard for future advancement since the status quo is never as good as can be. A fundamental part of the education process today is to make adaptable problem solvers. This applies particularly well to caring for newborn surgical malformations. Each individual patient has a unique specific combination of features that demands creative management. By sharing the evolution of our present methods, we hope to facilitate a creative and adaptable surgical approach.

The growth of our specialty has seen marked improvement in outcomes for patients born with major malformations. Some of the progress is related to improved methods in neonatal intensive care units, advances in technology including monitoring, ventilators, warming devices, and means to provide nutrients. It is a mark of pride that pediatric surgeons themselves, by focusing on these patients for many decades, have made large strides in improving the care of children born with major malformations.

Focusing on the surgical care of major newborn malformations, this book emphasizes clinical management and diagnosis, reviews operative techniques, and situates the present approach to these patients in its historical context.

We hope this book is a useful resource for clinicians caring for newborns victimized by malformations. The psychic rewards for all concerned are potentially enormous.

The editors owe a debt of gratitude to Mr. George Rodriguez for editorial guidance, for his heightened organizational skills and for his graceful help with this project. We appreciate the kind and skilled efforts of Meade Barlowe. We gratefully acknowledge the venerable Dan Dolgin and the redoubtable Ari Kahn.

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CHAPTER 1

PERIOPERATIVE MANAGEMENT OF THE NEONATAL PATIENT

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INTRODUCTION

Over the past several decades, advances in prenatal evaluation, neonatal care, diagnostic techniques, anesthesia, and clinical management have enhanced care of pediatric surgical patients. Neonates have their own physiologic characteristics that must govern their care. The most distinctive and rapidly changing functions occur during the neonatal period. This is due to the newborn infant's adaptation from complete placental support to the extrauterine environment, differences in physiologic maturity of individual neonates, small size of these patients, and demands of growth and development.[1] Advances in neonatal care have resulted in survival of increasing numbers of extremely low birth weight infants. However, pediatric surgeons and neonatologists are now faced with more complex diseases due to extreme prematurity. Derangements in temperature regulation, fluid and electrolyte homeostasis, glucose metabolism, hematologic indices, and immune function are magnified in this setting. Preterm infants are more vulnerable to specific problems such as intraventricular hemorrhage, hyaline membrane

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disease, and hyperbilirubinemia. This chapter will focus on principle considerations that distinguish the perioperative care of neonates.

GENERAL CONSIDERATIONS

Fetal Circulation and Implications of the Ductus Arteriosus

Fetal growth and development occur in a "hypoxic" environment and the placenta, rather than the lung, is the source of oxygen. Oxygen saturation of blood that flows through the umbilical vein is only 65%, corresponding to a partial pressure of oxygen of 35 mmHg. In the fetal right atrium, this blood mixes with even lower oxygen saturated blood that comes from the fetal liver, inferior and superior vena cava, and coronary sinus. This hypoxic environment is compensated by different mechanisms that help provide adequate oxygen to fetal tissues. First, in contrast to adult hemoglobin, fetal hemoglobin has a lower p50 which allows more efficient oxygen extraction from the placenta. Second, there are three physiologic shunts that allow preferential circulation of more saturated umbilical vein blood into the systemic circulation. These include the ductus venosus, which helps bypass unsaturated portal flow, foramen ovale, which allows flow into the left heart avoiding mixture with the superior vena cava and coronary sinus, and ductus arteriosus, which shunts blood from the pulmonary artery into the aorta for systemic oxygen delivery. Finally, fetal cardiac output is about three times greater than that of adults. This, coupled with low systemic resistance, allows better oxygen delivery. The two umbilical arteries that originate from the internal iliac arteries return blood with lower oxygen content from the systemic circulation back to the placenta.

Pulmonary vascular resistance in fetal life is suprasystemic and therefore the right ventricle performs twice the work as the left ventricle. Ninety-percent of right ventricular output goes into the aorta via the ductus arteriosus. Within hours to days after birth, there is physiologic closure of the ductus arteriosus as pulmonary vascular resistance decreases and systemic vascular resistance increases. These hemodynamic changes, together with an increase in arterial oxygen saturation, cause constriction of the ductus' vascular smooth muscle, which shortens and narrows its lumen. This functional closure is followed by an anatomical closure several weeks later, resulting in the fibrotic ligamentum arteriosus.[2] Postnatal failure of the ductus to close can result in a left-to-right shunt into the pulmonary artery with resultant pulmonary hypertension and high output congestive heart failure. If this problem persists, pulmonary hypertension can get so severe that the shunt reverses, resulting in systemic hypoxemia.

In preterm infants, clinical evidence of a patent ductus include a continuous murmur, bounding pulses with widened pulse pressure (greater than 20 mmHg), and respiratory failure. Diagnosis is confirmed by echocardiography. Initial treatment consists of relative fluid restriction and indomethacin, which inhibits cyclooxygenase activity and reduces local ductal tissue synthesis of prostaglandin E_2, the most potent dilator of the ductus arteriosus. Side effects of indomethacin include inhibition of platelet function and reduction of renal and splanchnic blood flow. Treatment of asymptomatic patent ductus arteriosus remains controversial due to these side effects. Surgical occlusion is reserved for patients who are refractory to medical treatment, have a contraindication to indomethacin therapy (e.g. intraventricular hemorrhage, established necrotizing enterocolitis), or have developed a complication of indomethacin treatment (e.g. ileal perforation).

Low Birth Weight Infants

Neonates may be classified (Tables 1 and 2) according to their level of maturation (gestational age) and development (weight). This classification is important because the physiology of neonates may vary significantly depending on these parameters.

Under this classification system, a term, appropriate for gestational age infant is born between 37- and 42-week gestation with a birth weight greater than

Table 1. Newborn classification by maturation (gestational age).

Classification	Age at birth
Preterm	Birth before 37-week gestation period
Term	Birth between 37- and 42-week gestation period
Post-term	Birth after 42-week gestation period

Table 2. Newborn classification by development (weight).

Classification	Birth weight
Small for gestational age	Birth weight below 10th percentile
Appropriate for gestational age	Birth weight between 10th and 98th percentile
Large for gestational age	Birth weight greater than 98th percentile

Table 3. Alternative newborn classification by weight.

Classification	Birth weight	% of preterm births	Mortality rate vs. term infants
• Moderately low birth weight	Birth weight between 2500 g and 1501 g	82%	40 times higher
• Very low birth weight	Birth weight between 1500 g and 1001 g	12%	200 times higher
• Extremely low birth weight	Birth weight < 1000 g	6%	600 times higher

2500 g. In the United States, approximately 7% of all babies do not meet these criteria. This may be due to prematurity or intrauterine growth retardation. From a clinical standpoint, neonates born under 2500 g are broadly classified as low birthweight (*LBW*) infants. Further subclassification into moderately low birth weight, very low birth weight, and extremely low birth weight infants have been used for epidemiologic and prognostic purposes (Table 3). Using this terminology, low birth weight infants may be preterm and appropriate for gestational age, term but small for gestational age, or both preterm and small for gestational age. This distinction is important in that overall prognosis and potential risks may be significantly different for the different populations.

Preterm infant

By definition, preterm infants are born before 37 weeks of gestation. They generally have body weights appropriate for their age, though they may also be small for gestational age. The rate of premature birth is the major contributor to infant mortality and has not changed significantly. The United States ranks between 20th and 30th among countries around the world in infant mortality and premature delivery rates.[3] If gestational age is not accurately known, the prematurity of an infant can be estimated by physical examination. Principle features of preterm infants are head circumference below 50th percentile, thin, semi-transparent skin with absence of plantar creases, soft and malleable ears with poorly developed cartilage, absence of breast tissue, undescended testes (testicular descent from the inguinal canal towards the scrotum begins in the 26th week of gestation) with a flat scrotum in boys, and relatively enlarged labia minora and small labia majora in girls.

In addition to these physical characteristics, several physiologic abnormalities exist in preterm infants. These abnormalities are often a result of unfinished

fetal developmental tasks that normally enable an infant to successfully transition from intrauterine to extrauterine life. These tasks, which include renal, skin, pulmonary, and vascular maturation, are usually completed during final weeks of gestation. The more premature the infant, the more fetal tasks are left unfinished and the more vulnerable the infant.

This physiologic and anatomic vulnerability sets the preterm infant up for several specific and clinically significant problems:

(1) Central nervous system immaturity leading to episodes of apnea and bradycardia, and a weak suck reflex;
(2) Pulmonary immaturity leading to surfactant deficiency which can result in hyaline membrane disease and respiratory distress at birth;
(3) Cerebrovascular immaturity leading to fragile cerebral vessels which lack the ability to autoregulate. This predisposes preterm infants to intraventricular hemorrhage, the most common acute brain injury of neonates;
(4) Skin immaturity leading to underdeveloped stratum corneum with significant transepithelial water loss. This complicates thermal regulation and fluid status management of infants;
(5) Gastrointestinal underdevelopment causing inadequate absorption and risk of necrotizing enterocolitis;
(6) Impaired bilirubin metabolism causing predominantly indirect hyperbilirubinemia;
(7) Cardiovascular immaturity leading to patent ductus arteriosus or patent foramen ovale. These retained elements of fetal circulation can cause persistent left-to-right shunting and cardiac failure;
(8) Fragile retinal vessels leading to retinopathy of prematurity.

From a practical standpoint, care of preterm infants must therefore be directed at preventing and/or treating these specific problems. Episodes of apnea and bradycardia are common and may occur spontaneously or as nonspecific signs of problems such as sepsis or hypothermia. Prolonged apnea with significant hypoxemia leads to bradycardia and ultimately to cardiac arrest. All preterm infants should therefore undergo apnea monitoring and electrocardiographic pulse monitoring, with the alarm set at a minimum pulse rate of 90 beats per minute. In neonates with respiratory difficulties, chest radiography will help detect hyaline membrane disease and cardiac failure. The lungs and retinas of preterm infants are very susceptible to high oxygen levels, and even relatively brief exposures may result in various degrees of pulmonary insult and retinopathy of prematurity. Infants receiving supplemental oxygen therefore require continuous

pulse oximetry monitoring, with the alarm set to trigger below 85% and above 92%. Preterm infants may also be unable to tolerate oral feeding because they have a weak suck reflex, necessitating intragastric tube feeding or total parenteral nutrition. Finally, impaired bilirubin metabolism may necessitate serum bilirubin monitoring for rising levels of unconjugated bilirubin; this may require phototherapy or exchange transfusion in order to prevent brain damage (i.e. kernicterus).

Small for gestational age infant

Infants whose birth weight is below the 10th percentile are considered to be small for gestational age (SGA). SGA newborns are thought to be a product of restricted intrauterine growth due to placental, maternal, and fetal abnormalities. Table 4 lists several conditions which may lead to intrauterine growth retardation. It should be noted that not all infants in this group are truly growth retarded. Some infants are simply born small as a result of a variety of factors including race, ethnicity, sex, and geography. It is important to differentiate these infants from those whose relatively low birth weight is a result of genetic or intrauterine abnormality.

SGA infants can be divided into two broad categories; symmetric SGA infants and asymmetric SGA infants. This distinction is primarily based on when in the gestational period fetal growth was actually restricted. If fetal growth is restricted during the first half of pregnancy, when cellular hyperplasia and differentiation lead to tissue and organ formation, the neonate is generally a symmetric SGA

Table 4. Common conditions associated with intrauterine growth retardation.

Age at delivery	Condition
Preterm	Placental insufficiency Discordant twin Chronic maternal hypertension Intrauterine infection Toxemia
Term	Congenital anomaly Microcephaly
Post-term	Placental insufficiency

infant. Fetal factors such as genetic dwarfism, chromosomal and congenital abnormalities, inborn errors of metabolism, and fetal infection, as well as maternal factors such as genetics, toxin ingestion, and substance abuse, are all causative etiologies. While only 30% of SGA infants fall into this group, they have the highest morbidity and mortality rate.

In contrast, asymmetric SGA infants experience intrauterine growth restriction during the last half of gestation, often during the third trimester. This is usually due to inadequate nutrient supply. An example of this is twin gestations. Though both infants may be full term at birth, they generally have low birth weight because placental mass/function is inadequate to meet growth demands of both fetuses. Other causes of asymmetric growth retardation include maternal conditions that reduce uteroplacental blood flow such as hypertension, toxemia, and cardiac and renovascular disorders.

In general, SGA infants have low body weight for their gestational age, though their body length and head circumference are appropriate. SGA infants are older and developmentally more mature than preterm infants of equivalent weight. They therefore face significantly different physiologic problems. The metabolic rate of SGA infants is much higher in proportion to body weight than preterm infants of similar weight because of the longer gestational period and resultant well-developed organ systems. Therefore, fluid and caloric requirements are increased. Intrauterine malnutrition results in a relative lack of body fat and decreased glycogen stores. In fact, body fat levels in SGA infants are often below 1% of their total body weight. This, coupled with their relatively large surface area, greatly predisposes these infants to hypothermia and hypoglycemia. Close monitoring of blood sugar level, therefore, is essential. In addition, polycythemia is common in SGA infants due to increased red blood cell volumes, occurring in 15–40% of asymmetric SGA babies. Polycythemia may lead to hyperviscosity syndrome characterized by respiratory distress, tachycardia, pleural effusions, and risk of venous thrombosis. This requires frequent monitoring of the infant's hematocrit level and possibly plasma exchange transfusions. Lastly, fetal asphyxia and distress due to inadequate placental support may lead to passage of meconium *in utero*, resulting in increased risk of meconium aspiration syndrome in SGA infants if the material is aspirated during labor and delivery. Perioperative management of these conditions will be detailed in following sections. While SGA infants are at significant risk for morbidity and mortality associated with these syndromes, their longer length of gestation reduces their risk for many conditions that affect preterm infants, such as retinopathy of prematurity, intraventricular hemorrhage, and hyaline membrane disease.

Physiologic Considerations in Perioperative Care of Neonates

Glucose homeostasis

The fetus receives glucose from its mother by facilitated placental diffusion; very little is derived from fetal gluconeogenesis. Limited liver glycogen stores accumulated during the later stages of gestation are rapidly depleted within 2 to 3 hours after birth. The neonate's blood glucose level then depends on its capacity for gluconeogenesis, adequacy of substrate stores, and total energy requirements. Of note, the neonate's ability to synthesize glucose from fat or protein substrates is severely limited, necessitating intake of exogenous carbohydrates to maintain adequate blood glucose levels.

The risk of developing hypoglycemia is high in low birth weight infants (especially SGA infants), those born to toxemic or diabetic mothers, and those requiring surgery that are unable to take oral nutrition and have additional metabolic stresses from their disease and surgical procedure. Clinical features of hypoglycemia are nonspecific and include a weak or high-pitched cry, cyanosis, apnea, jitteriness or trembling, and seizures. Differential diagnosis includes other metabolic disturbances or sepsis. Over 50% of infants with symptomatic hypoglycemia suffer significant neurologic damage. Neonatal hypoglycemia is defined as serum glucose level less than 30 mg/dl in full-term infants and less than 20 mg/dl in low birth weight infants. However, neurologic abnormalities have been reported with higher blood glucose levels.

Hyperglycemia is commonly a problem of very low birth weight infants on parenteral nutritional support since they have a lower insulin response to glucose. Hyperglycemia may lead to intraventricular hemorrhage and renal water and electrolyte loss from glycosuria. Prevention of hyperglycemia is by small and gradual incremental changes in glucose concentration and infusion rate.

Practical considerations

All pediatric surgical patients, particularly neonates, are monitored for hypoglycemia. To avoid delay, blood glucose levels can be rapidly determined in the neonatal unit using blood glucose reagent strips activated by blood from a heel stick. This may be correlated at intervals with serum glucose determinations, the frequency depending on patient stability. Any intravenous fluids administered should contain at least 10% dextrose. If non-dextrose–containing solutions such as blood or plasma are being administered, close monitoring of blood glucose levels is essential. Hypoglycemia should be treated urgently with intravenous

50% dextrose, 1–2 mL/kg, and maintenance intravenous 10% to 15% dextrose, 80–100 mL/kg every 24 hours.

Hematologic regulation

Total blood, plasma, and red cell volumes are higher during the first few hours after birth than any other time in an individual's life. Levels may be further increased if significant placental transfusion takes place at delivery (e.g. delayed cord clamping). Several hours after birth, plasma shifts out of circulation and total blood and plasma volumes decrease. High red blood cell volume persists, decreasing slowly to reach adult levels by the third postnatal month. The estimated blood volume in infants ranges between 85 and 100 mL/kg.[4]

Neonatal polycythemia may occur in SGA infants, infants of diabetic mothers, and of mothers with toxemia of pregnancy. In neonates, polycythemia is defined as central venous hematocrit greater than 65% or hemoglobin level greater than 22 g/dL. Values at or above this threshold may be associated with high blood viscosity which is further increased by a fall in body temperature. Partial exchange transfusion may be indicated since hyperviscosity is associated with central nervous system and gastrointestinal tract disorders.

Anemia

In neonates, anemia is generally due to hemolysis, blood loss, or decreased erythrocyte production. Hemolytic anemia in the newborn is most often caused by placental transfer of maternal antibodies that destroy the infant's erythrocytes. Significant hemolytic anemia is most commonly due to Rh incompatibility, producing jaundice, palor, hepatosplenomegaly, and in severe cases, hydrops fetalis. In addition, congenital infections, inherited hemoglobinopathies, and thalassemias may all manifest as hemolytic anemia in the newborn period. In severe cases, these conditions may require exchange transfusions. Severe anemia in neonates also may occur secondary to acute hemorrhage as a result of placental abruption or *in utero* internal bleeding into the intraventricular, intraabdominal, subgaleal, or mediastinal spaces. Twin–twin transfusion syndrome may produce severe anemia in the "donor" twin. Lastly, "anemia of prematurity" can occur in preterm infants born before 30 to 34 weeks gestational age due to decreased red blood cell production, resulting from a lack of erythropoietin synthesis in the neonate's kidneys.

Given an infant with normal blood volume, blood loss less than 10% of blood volume does not require transfusion. Transfusion of packed red blood cells at a

volume of 3 mL/kg or whole blood 6 mL/kg usually raises the hematocrit levels by 3–4%. Only warmed, fresh (<3 days old) whole blood or packed red cells should be transfused.

Hemoglobin

Erythopoiesis does not occur during the first 2 or 3 months of life. Until that time, fetal hemoglobin represents the vast majority of circulating hemoglobin in neonates. This is significant in that the high proportion of fetal to adult hemoglobin in neonates shifts the hemoglobin dissociation curve to the left. Since fetal hemoglobin has a higher affinity for retaining oxygen, lower peripheral oxygen levels are needed to release and deliver oxygen from fetal blood to the receiving tissues.

Coagulopathy

Levels of several clotting factors (II, VII, IX, X, XI, and XII) are significantly decreased in the neonatal period, mostly as a result of immature liver function. Levels in preterm infants are typically more severely decreased than in full term infants, and normal adult levels are only achieved by 6 months of age. This factor deficiency combined with rapid vitamin K depletion may produce hemorrhagic disease of the newborn, with localized (e.g. cephalohematoma) or diffuse bleeding classically developing in the first week of life. Routine administration of vitamin K to all neonates, therefore, is an established practice to prevent hemorrhagic disease. This may be overlooked during the activities attendant on major congenital anomalies or conditions requiring urgent surgical evaluation. When in doubt, 1.0 mg of vitamin K should be administered by intramuscular or subcutaneous injection. PT and especially PTT are typically elevated in the first months of life. This does not correlate with clinical bleeding and so these tests, that require a relatively large volume of blood, should not be done routinely in neonates.

Jaundice

Bilirubin is produced by catabolism of heme pigments, most notably hemoglobin, in the liver and spleen. Lipid-soluble, unconjugated (indirect) bilirubin in fetal circulation is bound to albumin and either is cleared across the placenta or taken up by the liver. Uridine diphosphate glucuronyl transferase in the liver conjugates bilirubin with glucuronic acid, forming a water-soluble substance excreted *via* the biliary system into the intestine. In the fetal intestine β-glucoronidase hydrolyzes

conjugated (direct) bilirubin back to its unconjugated state, which is then reabsorbed for enterohepatic circulation or transplacental clearance.

The neonate's capacity for conjugating bilirubin is not fully developed and may be exceeded by the bilirubin load. This imbalance results in transient physiologic jaundice which peaks at 4 days of age but typically resolves by the sixth day. Usually, the maximum bilirubin level does not exceed 10 mg/dL. Physiologic jaundice is particularly common in SGA and preterm infants in whom a higher and more prolonged hyperbilirubinemia may occur.

When serum levels are high, unconjugated bilirubin may cross the immature blood–brain barrier in the neonate and act as a neural poison leading to kernicterus. In its most severe form, kernicterus is characterized by athetoid cerebral palsy and sensorineural hearing loss. Predisposing factors are hypoalbuminemia, acidosis, cold stress, hypoglycemia, caloric deprivation, hypoxemia, and competition for bilirubin binding sites by drugs (e.g. furosemide, digoxin, and gentamicin) or free acids.

Practical considerations

Clinical jaundice is apparent at serum bilirubin levels of 7–8 mg/dL. A rapid bilirubin rise early in the neonatal period suggests hemolysis, either secondary to inherited enzyme defects or maternal–neonatal blood group incompatibilities. In otherwise healthy infants, jaundice associated with breast feeding commonly appears between 1 and 8 weeks of age and resolves rapidly with cessation of breast feeding. Prolonged hyperbilirubinemia associated with increased conjugated bilirubin often indicates biliary obstruction (e.g. biliary atresia) or hepatocellular dysfunction (e.g. hepatitis). Indirect hyperbilirubinemia may occur with pyloric stenosis and quickly disappears after pyloromyotomy. Intestinal obstruction can intensify jaundice by increasing enterohepatic circulation of bilirubin. Finally, jaundice is an early and important sign of septicemia. If hemolysis is suspected, serial hematocrit estimations, reticulocyte counts, peripheral blood smears, and a Coomb's test are appropriate. Evaluation of neonatal sepsis includes hematocrit, white blood cell count and differential, platelet count, chest radiography and cultures of blood, urine, and cerebrospinal fluid.

Phototherapy is widely used prophylactically in high-risk neonates. This therapy decreases serum bilirubin levels by photodegradation of bilirubin in skin into water-soluble products. It is continued until total serum bilirubin level is less than 10 mg/dL and falling. Timing of phototherapy is based on the level of indirect bilirubin and patient weight. Exchange transfusion is indicated if the indirect bilirubin level exceeds 20 mg/dL, but precise indications vary according to the

individual patient. In very low birth weight infants, exchange transfusion is indicated at lower serum bilirubin levels. Factors increasing the risk of kernicterus also influence the indications for exchange transfusion.

Immune function

Neonates are particularly vulnerable to bacterial infections. This may be due to maternal factors as well as intrinsic deficiencies in their host defense system. Maternal factors independently associated with a higher incidence of neonatal sepsis include premature onset of labor, prolonged rupture of membranes (greater than 24 hours), chorioamnionitis, genital tract colonization with pathogenic bacteria such as group B streptococci, and urinary tract infection.[5] In general, these factors increase the risk of neonatal infection by exposing the neonate to bacterial pathogens during gestation as well as delivery. The neonatal immune system is immature, characterized by a diminished neutrophil storage pool, abnormal neutrophil and monocyte chemotaxis, decreased cytokine and complement production, and diminished levels of type-specific immunoglobulins including IgG, secretory IgA, and IgM.[5] Overall, these factors lead to a significantly impaired host defense mechanism in the neonate with compromised anatomical barriers. Furthermore, these deficiencies appear to be more severe in low birth weight infants.

Practical considerations

Impaired immune function and compromised anatomical barriers may contribute to postoperative infection rates in newborn surgical patients. Specifically, wound infections, as well as indwelling catheter-related sepsis, may complicate the perioperative course. For this reason, many surgeons advocate utilization of prophylactic, broad-spectrum antimicrobials in neonatal surgical patients. While this practice may be common, it should be noted that the specific antibiotics used as well as duration of therapy are very site- and surgeon-specific parameters. At this time, there are no conclusive studies supporting the use of any particular regimen. Therefore, use of prophylactic antibiotics in these patients is determined on a case-by-case and surgeon-by-surgeon basis.

Fluid and electrolyte homeostasis

Total body water

In the fetus, total body water (TBW) constitutes 94% of the body weight during early gestation. As the fetus grows, this percentage progressively diminishes to a

value of approximately 78% at term. During the first 5 days of life, TBW decreases by another 3–5%, and eventually reaches adult levels by 9 months to 1 year of age. Extracellular water (ECW) in the term infant is often 40% of birth weight at 5 days. Similar to TBW, ECW decreases over time and by 3 months of age is only 33%. ECW stabilizes at adult values of 20–25% by 1–3 years of age. Conversely, fetal intracellular water (ICW) slowly increases during gestation and the neonatal period. At the 20th week of gestation, ICW is around 25% and increases to 33% by birth. ICW finally reaches adult levels of approximately 44% by 3 months of age.

Under normal conditions, changes in fetal body water progress in an orderly fashion *in utero* and after birth. The neonate must complete these water redistribution tasks to effectively transition from the intrauterine to extrauterine environment. Premature birth or intrauterine growth retardation may interrupt this process leaving specific tasks unfinished and predisposing the infant to increased risk of serious complications such as necrotizing enterocolitis, patent ductus arteriosus, and congestive heart failure.

Renal function

Renal function is significantly limited in neonates. Compared to adults, the newborn has a relatively low renal blood flow and plasma flow and a high renovascular resistance. In fact, only 6% of the newborn's cardiac output is directed towards the kidneys. This is in contrast to 25% of cardiac output in adults. Overall, these factors lead to a relatively decreased glomerular filtration rate (GFR) in neonates. In term infants, the GFR rises rapidly during the first 3 months of life, nearing adult levels by 12 to 24 months of age. In premature infants, this process is delayed and GFR may lag behind that of the term infant. One should aim to achieve a urine output which will maintain urine osmolality of approximately 280 mOsm/ kg. In neonates, this usually results in a urine output of 2 mL/kg/h. For infants and older children, hydration is adequate if the urine output is 1–2 mL/kg/h with an osmolality of 280–300 mOsm/kg.

In addition to GFR, concentrating capacity of the neonatal kidney is significantly lower than that of the adult kidney. Specifically, while the adult kidney can concentrate urine up to 1200 mOsm/kg, the neonatal kidney is only able to achieve 500–600 mOsm/kg. Furthermore, newborn renal tubules are particularly insensitive to effects of antidiuretic hormone. Similarly, newborn tubules respond to a lesser degree to aldosterone. This blunted response is magnified in preterm infants. In addition, preterm infants are at significant risk for salt wasting. The fractional excretion of sodium, which is normally about 2%, can be as high as 5%

in normal preterm infants. This may lead to further growth retardation as sodium appears to be a permissive growth factor.

A rising blood urea nitrogen level and falling urine output may be due to acute renal failure or prerenal oliguria with azotemia resulting from hypovolemia. The distinction between these two states is important for appropriate treatment. Initially, response to a fluid challenge of 20 mL/kg of 5% dextrose and sodium chloride administered over 1 hour is monitored. If oliguria persists, blood and urine sodium, creatinine and osmolality levels are measured. Fractional excretion of sodium (FeNa) is calculated using the formula:

$$\text{FeNa} = (\text{Urine creatinine}/\text{Serum creatinine})/(\text{Urine Na}/\text{Serum Na}) \times 100.$$

A normal FeNa is 2–3%. In neonates, a value below 2% implies prerenal azotemia and a value above 3% implies renal failure.

Calculating maintenance needs

The neonate's basic maintenance requirement for water is the volume required to support growth and replace losses from renal excretion (renal water), skin, lungs, and stool. Stool water loss has been estimated at 5–10 mL per 420 Joules expended, the lower figure applying to those patients not being fed. In the surgical patient with postoperative ileus, stool water loss is usually insignificant. Growth is inhibited during periods of severe stress and is also not a major factor under these conditions. The basal fluid maintenance requirement is therefore renal water plus insensible loss. Requirements during the first day of life are unique because of the greatly expanded extracellular fluid volume in the neonate, which decreases after 24 hours. In addition, neonates with intestinal obstruction are not hypovolemic at birth because of intrauterine adjustments across the placenta. During these first 24 hours, basic maintenance fluid should not exceed 90 mL/kg in preterm infants weighing less than 1000 g or less than 32 weeks of gestation. In larger infants, maintenance fluid rates should not exceed 75 mL/kg.

Basic electrolyte and energy requirements are provided by NaCl (2–5 mEq/kg/day) in 5% or 10% dextrose with addition of potassium (2–3 mEq/kg/day) once urine production has been established. Calcium gluconate (1–2 g/L fluid) may be added, especially in preterm infants.

Insensible losses

Invisible continuing water loss occurs from the lungs (respiratory water loss) and skin (transepithelial water loss) and constitutes insensible water loss (IWL).

Respiratory water loss (RWL) accounts for approximately one-third of IWL in infants older than 32 weeks' gestation and is approximately 5 mL/kg body weight per 24 hours at a relative humidity of 50%. Transepithelial water loss (TEWL) for a full-term infant in a thermoneutral environment is approximately 7 mL/kg body weight. The insensible water loss for a full-term infant in a thermoneutral environment at 50% humidity is therefore 12 mL/kg per 24 hours.

The main factors that affect IWL are the gestational age of the infant and the relative humidity of the environment. For infants 25–27 weeks' gestation, TEWL has been estimated at 128 mL/kg per 24 hours at 50% relative humidity. Relative humidity has a marked inverse effect on TEWL, which decreases to almost zero as relative humidity approaches 100%. Plastic sheets may be used to increase the relative humidity around the infant and reduce TEWL by 50–70%. Conversely, radiant warmers and phototherapy increase IWL. This loss is magnified in preterm infants.

Management Program

The most commonly used method of calculating fluid requirements is based on body weight. After the first 24 to 48 hours of life, full-term appropriate-weight infants typically require approximately 100 mL/kg/day, but preterm or SGA infants typically need up to 180 mL/kg/day depending upon gestational age and total fluid losses (Table 5). However, because of many factors affecting maintenance requirements, there is no close or constant relationship between body weight and fluid and electrolyte needs. Thus, many surgeons advocate use of a dynamic approach to fluid management. Such approaches generally begin with administration of a safe fluid volume for the patient's status. This initial volume is essentially a "best guess" volume. The effects of this volume on the patient's physiology are then monitored and appropriate changes are made.

Calcium and magnesium homeostasis

In addition to fluid and sodium management, calcium and magnesium homeostasis are clinically significant challenges in the newborn surgical patient. The fetus receives calcium by active transport across the placenta, with 75% of the total requirement being transferred after the 18th week of gestation. Hypocalcemia, defined as a serum level of ionized calcium below 1 mg/100 mL, is most likely to occur 24 to 48 hours after birth. Causes include decreased calcium

Table 5. Maintenance fluid requirements of neonates (mL/kg/day).[6]

	Age (days)		
Birth weight (kg)	1–2	3–7	7–30
<750	100–250	150–300	120–180
750–1000	80–150	100–150	120–180
1000–1500	60–100	100–150	120–180
1500–2500	60–80	100–150	120–180
>2500	60–80	100–150	120–180

stores, decreased renal phosphate excretion, and relative hypoparathyroidism secondary to suppression by high fetal calcium levels. Low birth weight infants are at great risk (particularly if preterm) as are those born of a complicated pregnancy or delivery (e.g. diabetic mother) or those receiving bicarbonate infusions. Exchange transfusions or rapid administration of citrated blood may also lead to hypocalcemia. The symptoms of hypocalcemia are nonspecific and include jitteriness, high-pitched crying, cyanosis, vomiting, twitching, and seizures. Diagnosis is confirmed by determining the serum calcium level. However, evaluation of serum ionized calcium level is often useful as clinical hypocalcemia may result from low serum ionized calcium without a great reduction in total serum calcium.

Practical considerations

Most seizures that occur in the neonatal period have a central nervous system etiology and are not secondary to hypoglycemia or hypocalcemia. However, hypocalcemia should be suspected in high-risk infants, particularly after surgery. Immediate serum glucose and calcium measurements, therefore, should be performed in a "jittery" neonate. Treatment should be prompt with intravenous glucose when hypoglycemia is suspected, followed by intravenous calcium if symptoms persist.

PREOPERATIVE CARE

Goals of appropriate preoperative care include[1] identifying and optimizing potential coexisting diseases,[2] preparing the patient for the specific operation, and[3] preparing the family for the perioperative period.

Identifying and Managing Coexisting Diseases

Preoperative evaluations performed by the anesthesia team are extremely important in identifying potential perioperative complications. In a study including more than 90,000 pediatric noncardiac and cardiac anesthesia cases, the incidence of perioperative cardiac arrest attributable to anesthesia was 0.65 per 10,000 anesthetics, which represented 7.5% of all perioperative cardiac arrests, suggesting that the large majority of perioperative cardiac arrests in children are caused by factors not related to anesthetic management.[7] However, neonates and infants continue to have the highest risk for perioperative cardiac arrest and death during procedures requiring general anesthesia.

A full review of systems is very valuable during perioperative risk assessment. History of seizures, head trauma, hydrocephalus, brain tumors, or neuromuscular disease may result in increased intracranial pressure, adverse medication interactions or malignant hyperthermia. Murmurs, cyanosis, or hypertension can be indicative of congestive heart failure or congenital heart disease. History of prematurity, bronchopulmonary dysplasia, croup, asthma or cystic fibrosis usually mandates postoperative monitoring for apnea or subglottic stenosis, as well as institution of appropriate pulmonary toilette. Electrolyte abnormalities and aspiration pneumonia should be suspected in patients with gastrointestinal abnormalities, including gastroesophageal reflux disease, diarrhea, or bowel obstruction.

Preparing the Patient for the Specific Procedure

Informed consent

Informed consent has become a fundamental doctrine of modern medicine based on ethical and legal principles of respect for individual autonomy, beneficence, and justice.[8] Except in the rare case where surgical intervention is necessary to prevent imminent death, informed consent in infants requiring surgery mandates effective preoperative family education and counseling. Several critical elements must be included in the informed consent process: the physician provides adequate information with which to make a decision, a competent patient or legal representative who indicates full understanding of the intervention, including indications, risks, and possible alternatives, and voluntarily consents to the proposed intervention.[9]

All legal jurisdictions, either by statutory law, case law, or both, currently require informed consent be obtained before any medical intervention, whether performed for diagnostic, therapeutic, or research purposes.[10]

The American College of Surgeons has provided guidelines on the content of information provided to patients needed to meet informed consent requirements.[11] Although adequate for most adult patients, existing guidelines may not always satisfy the needs of pediatric patients since by definition they lack decision making capacity. Parents may give informed "permission" for the procedure, but it is very difficult to assess whether the child's best interest are being represented. Informed consent should disclose as a minimum information which includes:

(a) Surgeon's understanding of the problem;
(b) Further measures to be taken to clarify the diagnosis, if indicated;
(c) Indication for emergency operation;
(d) Brief description of the procedure;
(e) Alternatives to treatment, including the option to do nothing;
(f) Surgeon's recommendation as to the best alternative;
(g) Benefits and risks of the proposed operation, compared with alternatives;
(h) Anticipated outcome.[12]

It is very important for the pediatric surgeon to spend quality time providing informed consent because it helps gain parents' trust and promotes adequate communication and physician-to-patient relationships.

Preoperative fasting guidelines

Neonates and infants who are able to be fed enterally require a period of fasting before major surgery in an attempt to avoid regurgitation and possible aspiration of particulate matter or liquid from the child's stomach during anesthesia induction. Each institution has its own fasting guidelines. As an example, our institution's guidelines are outlined below:

Minimum fasting intervals for neonates and infants over 3 kg in weight:

(A) >6 hours for milk, formula, solids, barium contrast, citrus juice etc.;
(B) >4 hours for breast milk;
(C) >2 hours for clear liquids.

Minimum fasting interval for neonates and infants under 3 kg in weight:

(A) Greater than usual duration between feedings for formula, breast milk, barium contrast etc.

For example, if a former premature neonate weighing 2 kg is fed formula or breast milk every 3 hours, then the fasting period must be > 3 hours.

(B) Formula, breast milk and fluids administered to the jejunum continuously through a stoma may be continued until operation.

Antimicrobial prophylaxis

The immaturity of an immune system renders newborn infants vulnerable to major bacterial insults. Therefore, prophylactic antimicrobial therapy is advised for neonates undergoing major surgery, particularly of the gastrointestinal tract or genitourinary system. Adequate coverage is provided by combining a penicillin (e.g. ampicillin) or first-generation cephalosporin (e.g. cefazolin) with an aminoglycoside (e.g. gentamicin). Clindamicin or metronidazole is added when anaerobic coverage is deemed necessary. Alternatively, single-drug therapy using a broad-spectrum cephalosporin (e.g. cefoxitin) may be appropriate. Antibiotics are commenced prior to operation and may be discontinued postoperatively at the surgeon's discretion.

Preoperative bowel preparation

Varied opinion exists whether mechanical bowel preparation is needed for elective intestinal procedures. There is also lack of concensus as to the best regimen to accomplish bowel preparation and whether administration at home or in hospital is superior. An example of a regimen is shown in Table 6.

Diagnostic studies

Most laboratory tests pose an additional burden to already stressed neonates. Therefore, diagnostic studies should be restricted to those essential for diagnosis and disease management. The volume of blood drawn for laboratory tests should be documented as these small volumes can cumulatively represent significant loss in a small infant.

When the patient is transferred to other departments for investigational procedures, monitoring and resuscitation equipment should be available. All studies should be performed with minimal disturbance, taking steps to prevent heat loss. Before using hyperosmolar radio-opaque contrast materials, intravenous fluids must be administered and fluid deficits corrected, regardless of route of administration. To counteract osmotic effects of contrast medium, intravenous infusion

Table 6. Bowel preparation for elective pediatric surgery.

Inpatient preparation	• Begin preparation at noon or sooner, the day before surgery. • Place a small nasogastric (NG) feeding tube. • Administer Reglan® 0.1–0.2 mg/kg/dose (maximum of 0.8 mg/kg over 24 hours) per NG every 4 hours (unless contraindicated). • Begin Golytely 25 mL/kg/hour per NG tube for 4 hours or until effluent is clear. • Clears or Pedialyte® by mouth ad lib until fasting period.

of sodium chloride 34 mEq/L at twice the maintenance rate should be given during the radiographic study and for 2–4 hours afterwards. During this period, the patient should be carefully monitored.

OPERATIVE CARE

Operative Checklist: "The Time Out"

Even though there are scarce data in the pediatric literature, adult data suggest at least half of all surgical complications are avoidable.[13] In 2008, the World Health Organization published guidelines identifying multiple recommended practices to ensure safety of surgical patients worldwide.[14] Using these guidelines as reference, the Safe Surgery Saves Lives Study Group implemented a prospective 19-point checklist and showed the rate of any complication significantly decreased from 11% to 7%.[15] Overall rates of surgical-site infection and unplanned reoperation also declined significantly, and overall surgical outcomes were improved. At our hospital, the checklist verifies the patient's identity and surgical site mark, introduces all team members by name and role, reviews the need for preoperative antibiotics and/or blood products, highlights significant concerns or previous adverse reactions, reviews the need for any special equipment, and matches the operative procedure with the informed consent. Use of a preoperative checklist involves a radical change in behavior of surgical teams, since it introduces formal pauses in the usual flow as well as does implementation of briefings and postoperative debriefings. The idea of ensuring correct patient identity and surgical site through preoperative site marking, oral confirmation in the operating room, and postoperative debriefings sets a new bar in the care of surgical patients and has

potential to prevent a large number of disabling complications and deaths in the perioperative period.

Thermoregulation

Neonates are susceptible to heat loss because of their large surface area, low body fat-to-body weight ratio, and limited heat sink capacity due to their small size. In addition, neonates have a relatively high thermoneutral temperature zone. Optimal thermal environment (thermoneutrality) is defined as a range of ambient temperatures in which an infant, at a minimal metabolic rate, can maintain a constant normal body temperature by vasomotor control. Environmental temperature must be maintained near the appropriate thermoneutral zone for each individual. In adults, this critical temperature range is 26°C–28°C while in term infants it is 32°C to 34°C. In low birth weight infants, this critical range is even higher at 34°C to 35°C.

Mechanisms of heat loss

In neonates, heat loss may occur by evaporation, conduction, convection, and radiation. Evaporative heat loss occurs as result of transepithelial water loss and depends on gestational age of the infant, relative humidity, and other environmental conditions. In addition, the presence of liquid (e.g. prep solution) in contact with an infant's skin contributes to evaporative heat loss. Conductive heat loss occurs when an infant's skin is in contact with a solid object of lower temperature, causing heat to flow from the infant to the object at a rate dependent on the temperature difference between the two as well as the insulating properties of the baby and object. Similarly, convective heat loss occurs when ambient air temperature is less than the infant's skin temperature. Convective heat loss depends on the temperature gradient between the infant's skin and the air as well as the speed of the air current over the infant. Lastly, radiant heat loss occurs via passage of infrared rays from the infant's skin to a cooler surface, such as the incubator or nursery wall. This type of heat loss is often most difficult to control. Table 7 details the types of heat loss affecting neonates.

Thermogenesis in neonates

Neonates generate heat by increasing metabolic activity. This can occur via shivering, as in adults, or non-shivering thermogenesis using brown fat. This has

Table 7. Types of heat loss in the neonate.

Type of heat loss	Mechanism	Prevention
Evaporation	• Transepithelial water loss • Skin in contact with wet surface	• Humidity • Plastic sheets
Conduction	• Direct skin contact with a cooler object	• Insulating padding
Convection	• Air currents in contact with the infant	• Warming incubator air
Radiation	• Radiation of heat to a cooler surface not in direct contact with the infant	• Double-walled incubators

practical consequences because pressors, anesthetic and neuromuscular blocking agents may render brown fat inactive.[16] Brown fat stores may also be depleted due to poor nutritional intake, such as in an SGA infant. When an infant is exposed to the cold, metabolic work increases above basal levels and calories are consumed to maintain body temperature. If prolonged, this depletes the neonate's limited energy reserves and predisposes them to hypothermia and increased mortality.

Practical considerations

The neonate's environmental temperature is best controlled in an incubator where ambient temperature can be monitored and thermoneutrality maintained. Clothing the infant can increase insulation, reducing radiant and convective heat loss inside the incubator. In particular, covering the head with an insulated hat can reduce heat loss and total metabolic activity during cold stress by up to 15%. Similarly, conductive heat loss is minimized by the use of insulating padding. Incubators themselves are plastic-walled containers that warm the infant by convection. Air in the incubator is heated by a heating element and then circulated by a fan. A servo system regulates incubator temperature according to the patient's skin temperature monitored by a skin probe. In this manner, the infant's skin temperature is maintained at a relatively constant value. Double-walled incubators minimize radiant heat loss by maintaining the inner wall of the incubator at the same temperature as the air temperature inside the incubator. Finally, humidity can be provided to the incubator environment, thereby reducing evaporative heat loss.

Optimal air temperature for individual infants varies with gestational age and condition of the infant as well as specific environmental factors such as humidity and air-flow. Standard nomograms are available that aid in determining appropriate incubator temperature necessary to achieve thermoneutrality.[17] Term infants usually require incubator air temperature to be 32°C to 34°C. Low birth weight infants may require temperatures at or above 35°C.

In contrast to fully enclosed incubators, radiant warmers provide open access to and visibility of infants. Their use has become common for ill neonates who require frequent manipulation. Radiant warmers generate heat by means of an overhead panel that produces infrared radiation. However, these warmers do not prevent heat loss by convection and often lead to higher evaporative water and heat losses. This evaporative heat loss may be reduced by plastic sheets.

Feedback mechanisms of both incubators and radiant warmers are used to maintain an infant's skin temperature in the normal range. Normal skin temperature for term infants is 36.2°C and for low birth weight infants is 36.5°C. Increased metabolic activity can be detected by comparing skin and rectal temperatures which normally differ by 1.5°C. Decreasing skin temperature with constant rectal temperature suggests metabolic rate has increased to maintain core temperature.

In a cold environment, such as the operating room or radiology suite, heat loss may be reduced by wrapping the head, extremities, and as much of the trunk as possible in clothing, plastic sheets, or aluminum foil. A plastic sheet placed beneath the infant decreases humidity of the microenvironment between it and the sheet. Any exposed intestine (e.g. gastroschisis) should be wrapped in plastic. An overhead infrared heating lamp should be focused on the infant during induction of anesthesia, preparation for operation, and at the termination of the operation. Solutions used for skin cleansing as well as intracorporeal irrigation should be warmed.

A major advance in the intraoperative care of neonates has helped curtail episodes of hypothermia and made operating rooms much more pleasant since the room no longer has to approach the uncomfortable temperatures of the neonate's thermal neutral environment. Forced air devices circulate warm air into disposable soft blankets in which the patient rests while on the operating table.

Gastrointestinal Decompression

The importance of gastric decompression in neonates undergoing surgery cannot be overemphasized. Gastric distension carries the risk of regurgitation, aspiration

and pneumonia, and it may impair diaphragmatic excursion, resulting in respiratory distress. With congenital diaphragmatic hernia, ventilation is progressively impaired as herniated intestine becomes distended with air and fluid. With gastroschisis, omphalocele and diaphragmatic hernia intestinal distension impedes reduction of herniated intestine into the abdominal cavity. This may be alleviated by adequate orogastric decompression. A double-lumen sump tube is preferred, utilizing low continuous suction. If a single-lumen tube is used, intermittent aspiration is required. Correct tube position in the stomach is confirmed by carefully measuring the tube before insertion, noting the nature of the aspirate, and radiography. The tube should be carefully taped to avoid displacement. Use of gastrostomy tubes for postoperative gastric decompression is decreasing in popularity but should be considered when prolonged postoperative gastric or intestinal stasis is anticipated.

Invasive Monitoring

The dynamic physiology of the neonatal period requires newborn surgical patients to be monitored continuously in the neonatal unit. As described above, transcutaneous pulse oximetry is useful to monitor for episodes of apnea and bradycardia which can be common in preterm infants. In addition, accurate monitoring of fluid status often requires an indwelling urinary catheter and frequent laboratory evaluations.

Invasive blood pressure monitoring and intravenous access in newborns can be achieved through the umbilical vessels as they are relatively accessible in this population. Umbilical venous catheters can provide central venous access.

Umbilical artery catheter placement

A 3.5 French catheter is required for infants less than 1500 g while 1500- to 3500-g infants can accommodate a 5 French catheter. Umbilical artery catheters may be indicated in infants with significant respiratory distress or who may require frequent blood sampling. These catheters usually enter the aorta through the internal iliac arteries. The umbilical cord base is tied with an umbilical tape tightly enough to prevent blood loss but loosely enough to allow passage of the catheter. The umbilical cord above the tie is divided sharply leaving a 1-cm stump. Usually two arteries and one vein are identified. The arteries are smaller and located at the 4 and 7 o'clock position. The artery is gently dilated with a hemostat and the catheter is advanced. A practical formula to calculate an appropriate catheter length in centimeters is:

$$(\text{Weight kg} \times 3) + 9 + \text{length of umbilical cord stump.}$$

Appropriate positioning is either below L3 (where the renal artery orifices lie) or between T6 and T9 (below the ductus arteriosis orifice). The tip of the umbilical artery catheter is a site of thrombogenesis an it should not be near the orifice of the major visceral vessels. Catheter position is confirmed by a post-insertion chest/abdomen radiograph ("babygram").

Umbilical vein catheter placement

The umbilical vein can usually accommodate a 5 French catheter. Placement technique is very similar to the umbilical artery catheter. Appropriate length is calculated by using the following formula:

$$1/2\ [(\text{Weight kg} \times 3) + 9] + 1.$$

A babygram is obtained to confirm positioning, and the catheter tip should be about 1 cm above the diaphragm. If the catheter enters the portal vein, it should be repositioned by either flushing and advancing the catheter simultaneously or by placing a second smaller catheter into the umbilical vein so one passes through the ductus venosus while the other enters the portal vein. The catheter in the portal vein can then be removed.

POSTOPERATIVE CARE

Nutrition

In neonatal surgical patients, proper nutrition must be delivered to meet their relatively large energy requirements. Specifically, neonates require a large energy intake because of their high basal metabolic rate, requirements for growth and development, energy needs to maintain body heat, and limited energy reserves. On average, neonates require between 90 and 120 kcal/kg/day, with 30–35% of this total energy need expended for growth. SGA infants may use up to 50% of their total energy expenditure for growth. Hepatic glycogen stores make up most of the neonate's major energy reserve and are usually consumed in the first 3 hours of life. These limited reserves are even more restricted in preterm and SGA infants. Young infants can tolerate up to 4 or 5 days without nutrition before signs of starvation develop. Premature infants, however, may develop signs of starvation in as little of 2 days without nutrition.

In older children and adults, energy requirements are significantly increased by cold stress, surgical procedures, infections, and injuries. On the contrary, a neonate's energy requirements actually decrease significantly during periods of metabolic stress, including surgery and critical illness. Cessation of growth during catabolic stress likely accounts for much of this reduced energy need; however, close thermoregulation in the humidified environment of the incubator, mechanical ventilation, and chemical sedation and paralysis also contribute to reduced energy expenditure. In one study of critically ill infants undergoing major surgery, mean energy expenditure (MEE) was only 43 kcal/kg/day immediately following operation, approximately 54% of predicted values.[18] In a follow-up study comparing infants with high and low levels of metabolic stress, MEE was increased significantly in high stress infants, but still both groups were expending less than 60 kcal/kg/day. Also, infants with high metabolic stress took longer to recover while those with low stress returned to near baseline in 8 days.[19]

Energy needs of individual newborns, therefore, can be calculated according to the requirements for basal metabolism plus growth regardless of the degree of critical illness or metabolic stress. Using this approach more closely approximates actual MEE for most infants.[19] Failing to appropriately adjust postoperative predicted energy needs for stressed infants may lead to complications from overfeeding. The goal of nutritional support should be to achieve a normal weight gain of 10–15 g/kg/24-hr. Typically, this can be accomplished by providing protein at a rate of 2–3 g/kg/24-hr. Thirty to forty percent of total nonprotein calories are often provided as fat, although lowering and/or altering the lipid content in the diet is a strategy to limit cholestasis in patients dependent on parenteral nutrition for prolonged periods, such as those with short gut syndrome.

Enteral nutrition

The best means of providing calories is via the gastrointestinal tract either by mouth, nasogastric or nasojejunal feeding tube, or through a surgically placed gastrostomy or jejunostomy tube. Enteral nutrition has a direct trophic effect on bowel integrity and development. Furthermore, early enteral nutrition has been demonstrated to have a beneficial effect on intestinal tract maturity in very low birth weight and sick infants. It should be started right after birth unless otherwise contraindicated. Average neonates should gain between 20 and 30 g per day or 1–2% of total body weight per day.

Intragastric feeding is preferable because it allows for normal digestive processes and hormonal responses, greater tolerance for large osmotic loads, and low incidence of dumping. Breast or bottle feeding is preferable for infants greater than 32 to 34 weeks' gestation who have a coordinated suck and swallow mechanism. Gavage feeding is indicated for infants with an impaired suck and swallow mechanism, or for supplementing those infants with a high metabolic rate who cannot gain weight with oral feeding alone. This is performed by passing a number 5 French silastic or polyethylene feeding tube into the stomach. The use of nasoduodenal or nasojejunal tubes is reserved for infants who cannot tolerate intragastric feeding (e.g. delayed gastric emptying, gastroesophageal reflux, depressed gag reflex). A Silastic mercury-tipped feeding tube (length: tip of nose to knee) is passed through the nose into the stomach. Transpyloric tube placement can be accomplished by either placing a mercury-weighted tube into the stomach, positioning the patient right side down, and administering a prokinetic agent if gastric peristalsis does not propel the tube into the duodenum, or by fluoroscopic guidance. It is mandatory to confirm proper tube placement by aspirating bilious fluid and obtaining a radiograph.

Common contraindications for establishing enteral nutrition include hemodynamic instability, respiratory distress, sepsis, abdominal distention, and necrotizing enterocolitis or intestinal obstruction. Prolonged delay or inability to initiate oral feeding mandates placement of a gastrostomy or jejunostomy tube. These can be placed during open surgery, laparoscopic surgery, or by percutaneous approach aided by gastroscopy or fluoroscopy.

Formula selection

Mother's breast milk

Every effort should be made before and after delivery to encourage maternal pumping. Breast milk contains an average of 20 kcal/oz and has several advantages compared to commercial formula feeds including:

(a) Lactoferrin, which limits availability of iron to pathogenic bacteria;
(b) Secretory IgA antibodies against specific pathogens;
(c) Numerous hormones and growth factors such as epidermal growth factor;
(d) Lysosome, a protective factor thought to influence flora in the intestinal tract through cell wall lysis;
(e) Ability to meet growth needs for preterm infants with addition of human milk fortifier.

Infant formulas

Iron-fortified formulas are an appropriate substitute for infants who are not breast fed. Standard infant formulas all contain a similar distribution of macronutrients with 40–45% of calories from carbohydrate, 8–12% of calories from protein, and 45–50% of calories from fat. These formulas usually contain 20 kcal/oz, but can be concentrated to 24 kcal/oz. Infant formulas are classified into the following categories based on source and/or type of protein: cow's milk, soy, protein hydrolysate, and amino acid[20] (Table 8).

(1) Cow's milk-based formulas

Cow's milk formulas are the most commonly used formulas in infants who are not breastfed and can meet nutritional needs during the first 6 months of life. Lactose is the carbohydrate source in standard cow's milk-based formulas; however, there is a lactose-free version. Whey and casein are the main protein sources,

Table 8. Infant formulas.

Formula type	Product names	Protein source	Fat source	Carbohydrate source
Cow's milk (term)	Enfamil, LIPIL, Similac Advance	Casein, whey	Vegetable oils	Lactose
Cow's milk (preterm)	Premature Enfamil, Similac Special Care	Casein, whey	MCT oil, soy, coconut or sunflower, DHA, ARA	Corn syrup solids, lactose
Soy	Prosobee, Isomil, Good Start Essential	Soy protein	Soy and coconut oils	Glucose polymers, sucrose, lactose free
Hydrolyzed protein	Nutramigen, Pregestimil, Alimentum	Hydrolized casein, added amino acids	55% MCT, 45% vegetable oil	Glucose polymers, lactose free
Free amino acid	Neocate, Elecare	L-amino acids	Soy, safflower, coconut and MCT oils	Corn syrup solids

ARA: arachidonic acid, DHA: long-chain polyunsaturated fats docosahexaenoic acid, MCT: medium chain triglycerides.

and fat content comes from vegetable oil. Cow's milk formulas can be used in both term and preterm infants.

(2) Soy-based formulas

Soy formulas contain soy protein and are lactose-free. They are indicated for infants with lactose intolerance and galactosemia, and are a safe alternative for term infants. However, studies in preterm infants show slower gains in weight and length, as well as decreased bone mineralization.[21]

(3) Hydrolyzed protein formulas

Hydrolyzed protein formulas contain casein and/or whey which have been enzymatically hydrolyzed into peptide chains and free amino acids. These formulas are recommended for infants intolerant to cow's milk and soy proteins. They contain a higher concentration of medium chain triglycerides which can be absorbed by intestinal venules and bypass the lymphatic system, thus requiring less pancreatic and biliary secretions for absorption. Indications for a formula high in medium-chain triglycerides include liver disease, cystic fibrosis, lymphangiectasia, and chylothorax.

(4) Amino acid-based formulas

Amino acid formulas contain 100% free amino acids and are designed for infants with extreme protein hypersensitivity. These formulas are nutritionally complete but are the most expensive of all infant formulas. Amino acid-based formulas are often used in patients with short bowel syndrome.

Parenteral nutrition

Indications for parenteral nutrition include the following: extremely low birth weight infant, surgical gastrointestinal tract abnormalities with prolonged postoperative ileus (e.g. gastroschisis, necrotizing enterocolitis), short gut syndrome following extensive bowel resection, chronic diarrhea (e.g. malabsorption syndrome), chylothorax, and intestinal fistulae.[22]

Short-term or supplemental, relatively low calorie, parenteral nutrition may be administered via peripheral vein. However, the glucose concentration in peripheral parenteral nutrition is limited to 12.5% dextrose solution, because more concentrated solutions can thrombose peripheral veins. In contrast, central venous administration allows higher dextrose loads as greater blood flow immediately dilutes the

Table 9. Total parenteral nutrition requirements.

Component	Neonate	6 m–10 yr
Calories (kcal/kg/d)	90–120	60–105
Fluid (cc/kg/d)	120–180	120–150
Dextrose (mg/kg/min)	4–6	7–8
Protein (gm/kg/d)	2–3	1.5–2.5
Fat (gm/kg/d)	0.5–3	1–4
Sodium (mEq/kg/d)	3–4	3–4
Potassium (mEq/kg/d)	2–3	2–3
Calcium (mg/kg/d)	80–120	40–80
Phosphate (mg/kg/d)	25–40	25–40
Magnesium (mEq/kg/d)	0.25–1	0.5
Zinc (mcg/kg/d)	300	100
Copper (mcg/kg/d)	20	20
Chromium (mcg/kg/d)	0.2	0.2
Manganese (mcg/kg/d)	6	6
Selenium (mcg/kg/d)	2	2

solution. Central venous access can be obtained percutaneously or via cutdown. Catheter tip position should be at the superior vena cava/right atrial junction as judged by fluoroscopy. A post-procedure chest radiograph is recommended to rule out pneumothorax following percutaneous central catheter placement through a subclavian vein. Daily total parenteral nutrition (TPN) component requirements for neonates with comparison values for older children are detailed in Table 9.

Initiating total parenteral nutrition

(1) Carbohydrates

Begin neonates at 4–6 mg/kg/min of dextrose and infants at 7–8 mg/kg/min. Increase by 2 mg/kg/min every day until the goal of 10–12 mg/kg/min is reached. Do not exceed 12.5% dextrose in peripheral veins. Central veins can tolerate up to 30% dextrose.

(2) Protein

Begin neonates and infants at 0.5 gm/kg/day and advance by 0.5–1 gm/kg/day up to a maximum of 3 gm/kg/day. Do not exceed 10–12% of total daily caloric intake. Protein intake should be restricted in patients who cannot tolerate a large nitrogen load (e.g. patients with renal insufficiency).

(3) Fat

Begin neonates at 0.5 gm/kg/day, infants at 1.0 gm/kg/day and advance 0.5–1.0 gm/kg/day as a continuous infusion up to a goal of 3.0 gm/kg/day. Contraindications to lipid infusion include allergy to egg yolk phospholipids and fat metabolism abnormalities (e.g. hyperlipidemia, lipoid nephrosis). Thrombocytopenia is a relative contraindication to lipids as intralipid may interfere with platelet function. Do not exceed 1 gm/kg/day in premature infants with hyperbilirubinemia as free fatty acids can displace bilirubin from albumin. Intralipids must account for at least 2% of caloric requirements to prevent essential fatty acid deficiency. Omega 3 fatty acids are an alternative form of lipid that may help limit cholestasis.

Pain Management

Postoperative pain management in newborn surgical patients may be challenging. During the 1980s, the World Health Organization designed a three-step analgesic ladder using cancer pain as reference.[23] Step 1 includes nonsteroidal analgesics such as acetaminophen, ketorolac, ibuprofen etc. Step 2 includes mild opioids like codeine, oxycodone, and tramadol. Step 3 is reserved for stronger opioids like morphine, fentanyl, and methadone. Use of opioid analgesics in neonates must be monitored carefully. As a group, neonates have a narrower therapeutic window for postoperative morphine analgesia than older age groups. In addition, neonates treated with opioids exhibit variable pharmacokinetics and are at high risk for respiratory depression.[24] Despite these challenges, postoperative opiate analgesia can be effectively used to control pain in neonates.

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CHAPTER 2

MALROTATION

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INTRODUCTION

The care of children with anomalies of intestinal rotation requires an appreciation of anatomy and embryology, an ability to interpret a variety of radiographic studies, and a swiftness of appropriate action depending on the clinical scenario. The incidence of malrotation in the general population is estimated at 1 in 500 live births, but it is much more common in a number of genetic, chromosomal and congenital disorders.[1] The diagnosis is most often made in infancy or early childhood, when it becomes clinically evident. Occasionally the diagnosis is discovered incidentally in the asymptomatic patient. Regardless, malrotation and midgut volvulus with progression to bowel ischemia is potentially fatal. Early surgical intervention is necessary and is frequently life-saving. Symptomatic malrotation most frequently occurs in the first weeks of life.

History

The modern day understanding of normal human intestinal development is based on the work of Mall, first published in 1898,[2] and Frazer and Robbins in 1915.[3] Their initial descriptions of normal intestinal rotation and fixation were founded on the study of reconstructed embryos. Dott was the first to correlate embryology with the surgical aspects of malrotation in 1923. His assertions were based on encounters with only five patients, two of which were his own.[4] William Ladd reported his experience with surgical treatment of malrotation and volvulus in

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1932 and focused on the necessity of counterclockwise mesenteric detorsion in the surgical correction of midgut volvulus.[5] Four years later, he described the adhesive peritoneal bands found to the right of the duodenum.[6] He stressed the importance of releasing the duodenum and placing the cecum in the left upper quadrant. This remains the cornerstone of treatment in these patients today. While Ladd did not initially identify the more commonly found right upper quadrant cecal bands that entrap the duodenum, they would eventually bear his name.

Embryology

The primitive intestinal tract is a straight tube from mouth to rectum at 4 weeks of gestation.[7] Further differentiation is related to vascular anatomy. The gut tube is served by three arteries: celiac trunk, which supplies the abdominal foregut (esophagus, stomach, superior half of the duodenum and its derivatives); superior mesenteric artery (SMA), which supplies the midgut (distal duodenum, small intestine, ascending and proximal transverse colon); and inferior mesenteric artery, which supplies the hindgut (distal transverse colon, descending colon, sigmoid colon, and rectum).[8] During the 6th week of gestation, the midgut disproportionately lengthens to the extent that it can no longer be accommodated within the abdominal cavity. Room is found instead within the umbilical cord, producing a hernia of the midgut.[9] Normal rotation begins within the hernia, which normally persists until the 12th week of gestation. At week 12, the peritoneal capacity has increased enough to accommodate the intestine's return to the abdomen.

Normal rotation

As it enters the umbilical cord, so-called physiologic herniation, the midgut begins to twist on itself. The axis of rotation is provided by the SMA, which runs to the apex of the loop (Figure 1a). The intestinal tube first rotates 90 degrees counterclockwise. This rotation leaves the duodenojejunal segment to the right of the SMA, and the cecocolic segment to the left (Figure 1b). Next, independent rotation of these two segments will determine their final destination. Complete intestinal rotation requires each segment to turn 270 degrees around the vascular axis.

Duodenojejunal rotation

Within the 8th gestational week, the duodenojejunal segment begins a counterclockwise rotation. As the duodenum elongates, it leaves the starting

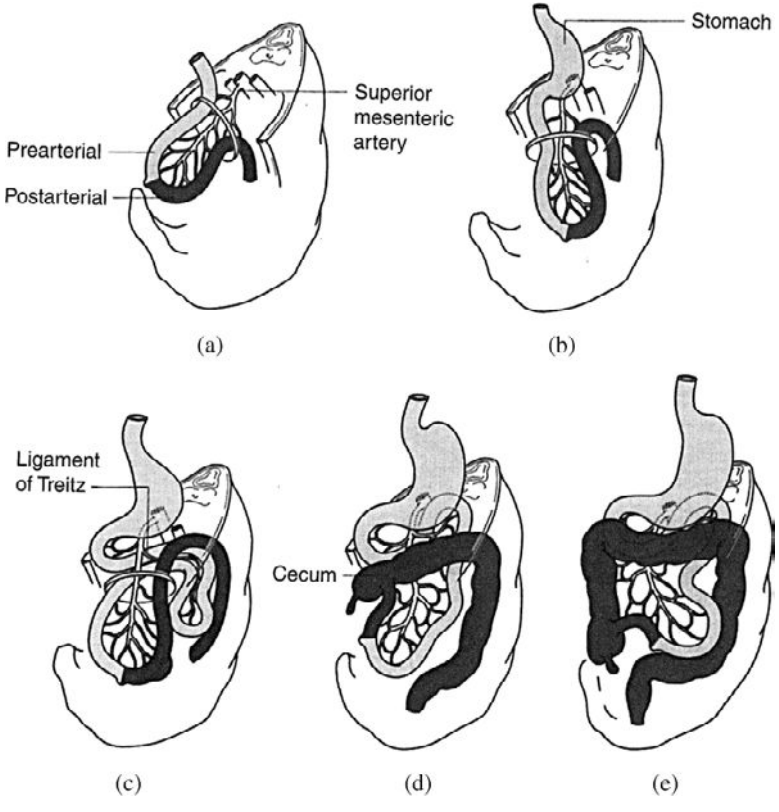


Figure 1. Normal midgut rotation is shown (a) beginning in gestational week 5 (e) through completion of the process in week 12 (see text). Duodenojejunal segment = light, Cecocolic segment = dark. (Adapted from Oldham KT: Pediatric abdomen. In Greenfield LJ, Mulholland M, Oldham KT, *et al.* [eds]: *Surgery: Scientific Principles and Practice.* Philadelphia, Lippincott-Raven, 1997. Illustration by Holly R. Fischer.)

position and begins to turn behind the SMA. The duodenum and the small intestine are the first to return to the peritoneal cavity. The leading edge of this return is the duodenojejunal junction, which ascends high into the left upper quadrant, behind and to the left of the SMA (Figure 1c). Here it becomes invested in the retroperitoneum. Meanwhile, the small intestine continues to lengthen forming a number of coiled loops of jejunum and ileum in the process.[10]

The ligament of Treitz represents this most cranial aspect of duodenojejunal migration and fixation. When midgut rotation is complete, the broad mesenteric

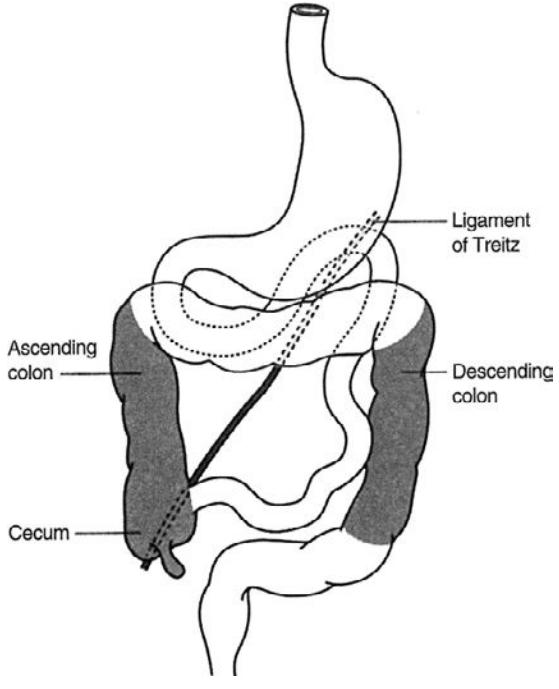


Figure 2. Normal oblique fixation of the midgut extends from the ligament of Treitz to the cecum in the right iliac fossa. The shaded portions of the ascending and descending colon are fixed in the retroperitoneum as well. (Adapted from Oldham KT: Pediatric abdomen. In Greenfield LJ, Mulholland M, Oldham KT, *et al.* [eds]: *Surgery: Scientific Principles and Practice.* Philadelphia, Lippincott-Raven, 1997. Illustration by Holly R. Fischer.)

root extends from the left upper quadrant to right lower quadrant where the cecocolic loop begins (Figure 2). Absence of a broad mesenteric fixation is the principle risk factor for midgut volvulus associated with malrotation.

Cecocolic rotation

The cecocolic loop initially lies caudal to the rotational axis of the SMA. Like the duodenojejunal loop, the cecocolic loop first rotates counterclockwise during the 8th week of gestation. The initial 90 degree twist places the cecocolic loop to the left side of the artery (Figure 1b). Next, the loop moves cephalad and then to the right of the SMA, through a total arc of 270 degrees (Figure 1d). The cecum is suspended from the dorsal body by a shortened mesentery soon after it returns

to the right lower quadrant. There, it becomes fixed and invested in the retroperitoneum finally. The colon lengthens, differentiates and returns to the abdomen. The colon always maintains a position anterior to the mesenteric vessels. In this manner, the loop achieves its normal adult position.[11] After the large intestine returns to the abdominal cavity, the dorsal mesenteries of the ascending and descending colon shorten and fold, bringing these organs into contact with the dorsal body wall, where they adhere and become secondarily retroperitoneal.

Normal rotation dictates that the two midgut structures most deeply buried in the retroperitoneum are the third portion of the duodenum and the cecum. Several factors at play are still poorly understood, but this natural propensity for peritoneal investment may explain the formation of Ladd's bands. Ladd's bands refer to intermesenteric adhesions which involve the third portion of the duodenum and constrictive bands which extend from the cecum towards the right upper quadrant. It is certainly plausible that in the absence of normal rotation (malrotation or nonrotation), the duodenum and cecum find themselves following a developmental program of retroperitonealization even though they are abnormally positioned.

CLASSIFICATION OF ANOMALIES

Anomalies of intestinal rotation are classified as either "classic" malrotation, nonrotation, duodenojejunal malrotation, or cecocolic malrotation. Duodenojejunal and cecocolic types are often referred to as pre-arterial and post-arterial malrotation, respectively, based on their embryologic position in relation to the SMA.

Classic malrotation is most common. Both duodenojejunal and cecocolic loops rotate incompletely. The ligament of Treitz is found to the right of midline, and the cecum is found in the upper abdomen. The mesenteric base is most narrow with this arrangement, which puts the patient at risk for volvulus. Ladd's bands or kinking of the duodenum are additional causes of bowel obstruction (Figure 3).

Nonrotation is the failure of rotation of both limbs of the primary intestinal loop. In a state of nonrotation, the small bowel lies on the right side of the abdomen and the colon on the left. The mesenteric base is usually wide enough to prevent midgut volvulus; however, this can be variable. This is the position of the intestine following a Ladd's procedure (Figure 4).[12]

Duodenojejunal or pre-arterial malrotation occurs in the presence of normal cecal rotation and fixation. The ligament of Treitz is not normally positioned and peritoneal bands are sometimes present in the right upper quadrant. The base of the midgut mesentery is usually broad, making volvulus unlikely.

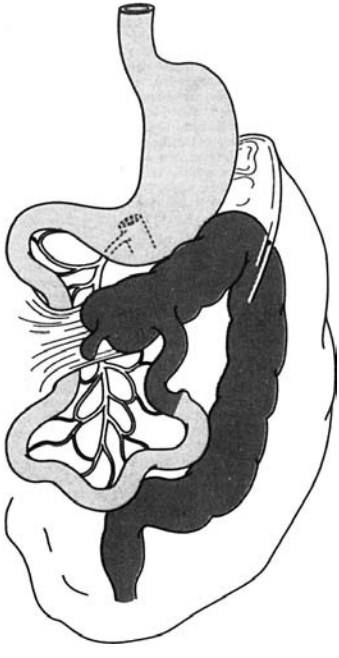


Figure 3. Malrotation. The pre-arterial midgut segment (lightly shaded) has failed to undergo 270-degree rotation and resides largely to the patient's right. The postarterial segment has rotated to reside anterior to the duodenum. Note that Ladd's bands fix the cecum to the posterior body wall and may compress and obstruct the duodenum. (Adapted from Oldham KT: Pediatric abdomen. In Greenfield LJ, Mulholland M, Oldham KT, *et al.* [eds]: *Surgery: Scientific Principles and Practice.* Philadelphia, Lippincott-Raven, 1997. Illustration by Holly R. Fischer.)

Incomplete cecocolic or post-arterial malrotation is the rarest condition. A lack of colonic fixation does in fact lead to a narrow mesenteric stalk. In addition to a risk of midgut volvulus, this anatomic variant is a predisposition for isolated cecal volvulus.

CLINICAL MANIFESTATIONS

Clinical manifestations of malrotation are variable and include acute ischemic crisis from midgut volvulus, partial duodenal obstruction from Ladd's bands, and in older patients, nonspecific chronic abdominal complaints from intermittent volvulus. Fifty to seventy-five percent of patients with malrotation develop

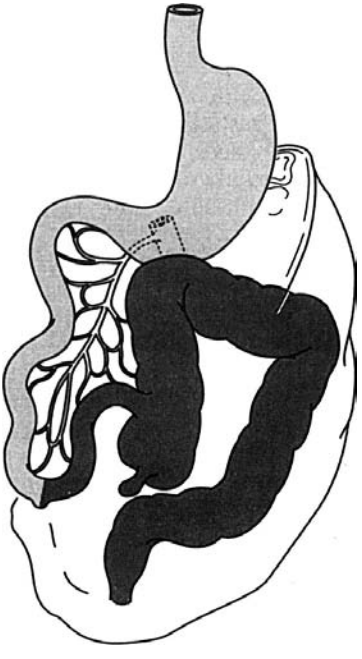


Figure 4. Nonrotation. The pre-arterial midgut (lightly shaded) resides on the patient's right and the post-arterial segment (darkly shaded) is on the left. Neither segment of the midgut has undergone rotation. (Adapted from Oldham KT: Pediatric abdomen. In Greenfield LJ, Mulholland M, Oldham KT, *et al.* [eds]: *Surgery: Scientific Principles and Practice*. Philadelphia, Lippincott-Raven, 1997. Illustration by Holly R. Fischer.)

symptoms during the first month of life. Robert Gross reported that over 80% of his patients developed symptoms before they reached 1 year of age.[13] Rare cases are detected during radiologic evaluation or abdominal surgery for unrelated complaints. The most common and classic acute presentation of malrotation is bilious emesis in an otherwise healthy infant. Many of these infants already have midgut volvulus, which is an absolute surgical emergency. Once the bowel has twisted around the mesentery, the strangulation process has begun. Signs of bowel ischemia, including abdominal wall erythema, peritonitis, respiratory failure, thrombocytopenia, hematemesis and melena, usually do not manifest until the process is advanced at which time intervention may be too late to save the midgut. Mortality rate is at least 65% when more than 75% of the bowel is necrotic.[14] Therefore, every infant with bilious vomiting should be presumed to have midgut volvulus until proven otherwise and undergo immediate evaluation

for bowel obstruction. Of course, several other congenital gastrointestinal anomalies may cause newborn bilious emesis, including duodenal atresia, annular pancreas, Hirschprung's disease, intestinal atresia etc. However, unless the diagnosis of volvulus can be refuted, the patient requires abdominal exploration. Unnecessary delays before abdominal exploration and detorsion are unacceptable.

A subacute presentation may involve partial obstruction at the second portion of the duodenum from adhesive Ladd's bands or intermittent transient volvulus. Evaluation of these patients typically proceeds rapidly and involves plain films followed by a contrast study.

Chronic abdominal symptoms associated with malrotation are more cryptic. Older children or adults with malrotation may describe vague intermittent abdominal pain. A history of reflux or vomiting is common. Failure to thrive, feeding intolerance, diarrhea, constipation irritability, lethargy, pancreatitis, fever, and bloody stools have all been described.[15] Symptoms often can be correlated with each patient's unique anatomy intraoperatively, but this does not necessarily lead to a swift preoperative diagnosis.

Occasionally an older, asymptomatic patient is diagnosed when malrotation is discovered in the operating room or incidentally during a radiologic work-up. While the risk of volvulus may be lower in this patient population,[16] treatment still is indicated to avoid a potential abdominal catastrophe in children given the low morbidity of surgical intervention. Surgical intervention in the asymptomatic adult is more controversial but certainly acceptable in at-risk individuals.[17]

Diagnosis

Radiographic evaluation should never delay surgical intervention in the patient with bilious emesis in the presence of peritonitis, acidosis, or shock. If the presentation is less dramatic and the patient is stable, then it is reasonable to proceed with a speedy work-up. Careful attention should be paid to patient temperature and intravenous hydration status throughout this interval. Radiographic diagnosis of a patient with malrotation/midgut volvulus focuses on the presence of a number of anatomic findings depending on the chosen modality. Position of the duodenojejunal junction, distance between the ligament of Treitz and ileocecal junction, position of the cecum, presence and level of bowel obstruction, and position/relationship of the superior mesenteric vessels are all relevant to confirm a "positive" radiographic diagnosis.

Plain films

Plain films of the abdomen are often the most expedient study available in the work-up of the vomiting child, but they generally are nonspecific for malrotation. A "double bubble" is suggestive of duodenal obstruction. While most often associated with duodenal atresia or annular pancreas, a "double bubble" may be a sign of midgut volvulus or congenital right upper quadrant bands, especially if there is air distally consistent with partial duodenal obstruction (Figure 5a). This diagnosis is rarely secured by plain films alone, but a patient with acute duodenal obstruction may benefit more from expeditious surgical exploration rather than further radiographic evaluation. Volvulus is often associated with a "gasless abdomen" (Figure 5b), but again this is not always the case.[18] Retained gas in small and large bowel loops on plain films does not exclude the diagnosis. In the case of volvulus, which has progressed to intestinal ischemia, pneumatosis intestinalis or hepatic portal venous gas may be present on plain film, and the picture may be indistinguishable from necrotizing enterocolitis.

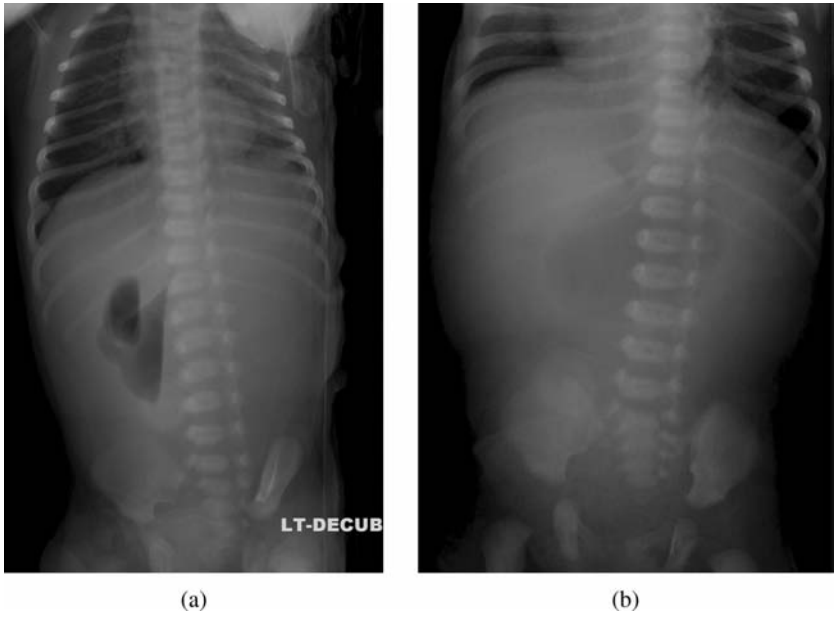


Figure 5. (a) This plain abdominal radiograph demonstrates the "double bubble" sign of duodenal obstruction. This finding is consistent with duodenal atresia, obstructive right upper quadrant bands and midgut volvulus. (b) A gasless abdomen also suggests high grade proximal bowel obstruction and is consistent with midgut volvulus.

Upper gastrointestinal tract

Upper gastrointestinal series (UGI) is the gold standard for evaluation of a pediatric patient with bilious emesis. Water-soluble contrast should be administered through a nasogastric tube if the patient has been vomiting. A normal duodenal contour outlined with contrast can be described as follows: the duodenal bulb fills first in the right upper quadrant on AP projection. Next, a lateral view with fluoroscopy demonstrates the second portion of the duodenum as contrast courses posteriorly into a retroperitoneal location. Switching back to the AP projection, contrast should traverse the patient's vertebral column from right to left within the third portion of the duodenum. In the same view, a normal duodenojejunal junction is located lateral to the patient's left transverse process near the height of the pylorus. Any disparity from this normal duodenal anatomy on UGI deserves attention (Figure 6).

A duodenojejunal junction to the right of midline is diagnostic of malrotation on UGI. Other findings coincident with malrotation include displacement of jejunal loops into the right side of the abdomen and a cecum positioned in the right upper quadrant or midline. The finding of a "corkscrew" of contrast flowing into the duodenum and proximal jejunum on the patient's right side is most

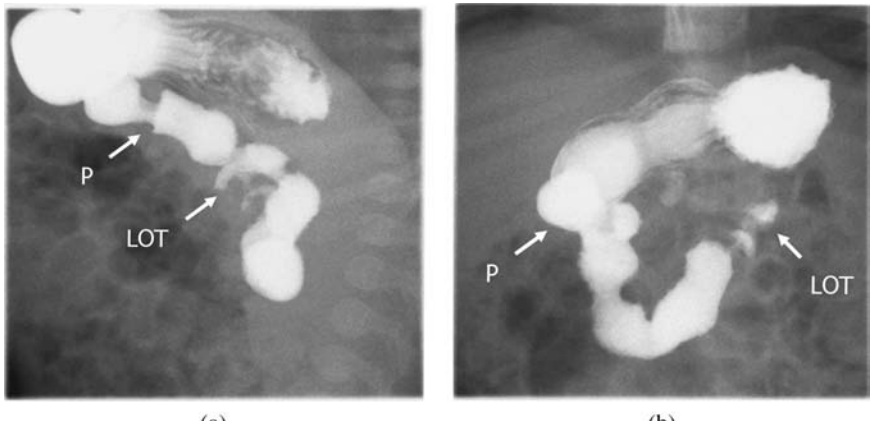


Figure 6. (a) Normal anatomy as seen on lateral projection during an upper gastrointestinal (UGI) series: Contrast exits the pylorus (P) and courses posterior (towards the spine) in the second portion of the duodenum. Contrast leaves the retroperitoneum as it exits the third portion of the duodenum at the Ligament of Treitz (LOT). (b) Normal UGI as seen from anteroposterior view. The ligament of Treitz is to the patient's left of the midline, and at the height of the pylorus.

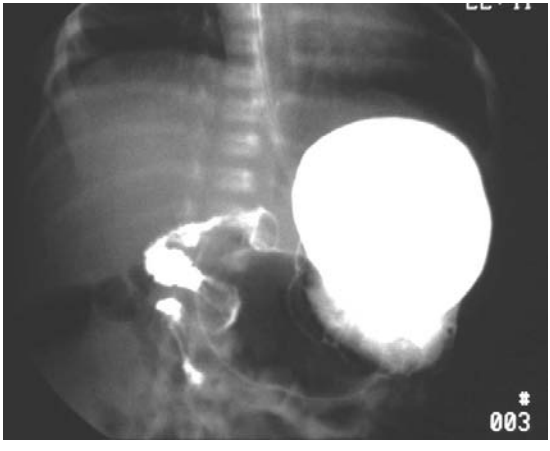


Figure 7. Absent duodenal sweep with a corkscrew of UGI contrast diagnostic of malrotation.

classic for malrotation without volvulus[19] (Figure 7). Conversely, a "bird's beak" of contrast which abruptly stops in the second portion of the duodenum is pathognomic of malrotation with volvulus. While UGI series is an effective way to diagnose malrotation it can not consistently establish the presence of volvulus.

Contrast enema

An unusually high position of the cecum on contrast enema should raise the index of suspicion for malrotation (Figure 8).[20] However, an abnormally high-riding cecum does not always correlate with complete duodenal malrotation with the risk of volvulus. Likewise, a normally positioned cecum does not confirm normal duodenal anatomy, nor does it rule out a narrow-based mesentery and its associated risk of volvulus. With a false negative rate as high as 40%,[21] contrast enema is not a reliable test to rule out malrotation.

Ultrasound

Ultrasound has become increasingly popular in the evaluation of several intestinal abnormalities in recent years. In expert hands, it is an excellent imaging modality to detect malrotation. The main role of ultrasound imaging in this setting is to determine the relationship of the mesenteric vessels to one another as



Figure 8. Abnormal cecal position seen on contrast enema confirms an abnormality of post-arterial rotation. Duodenal anatomy cannot be defined by this study.

they exit the retroperitoneum inferior to the pancreatic substance. Normally, the SMA lies posterior and to the left of the superior mesenteric vein (SMV). The classic finding in malrotation is a reversal of this orientation, i.e. the SMA sits to the right of SMV (Figure 9). This finding is diagnostic of malrotation. Midgut volvulus may also be detected on Doppler ultrasound with the presence of the "whirlpool sign," which describes the swirling of the SMA and SMV around the torsed mesentery.

Recently radiologists have directed focus away from the vessels and towards the retroperitoneum.[22] The third portion of the duodenum can be followed with a transducer as it crosses the spine within the retroperitoneum. Confirmation that the duodenum lays retromesenteric in this location excludes malrotation. A duodenum which is not retromesenteric has not completed the embryologic journey, and has thus remained intraperitoneal. While ultrasound may eventually supplant UGI as the modality of choice for evaluation of malrotation, it has not yet gained wide acceptance. This likely represents a combination of factors; ultrasound is the

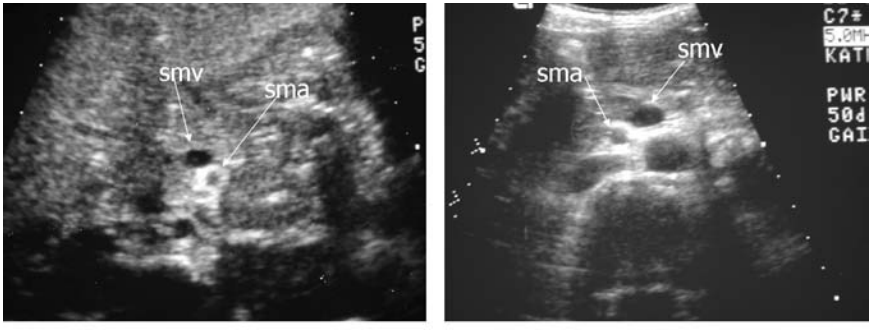


Figure 9. (a) Normal anatomy. The superior mesenteric vein (SMV) is anterior and to the patient's right of the superior mesenteric artery (SMA). (b) A reversal of the normal mesenteric vascular orientation is diagnostic of malrotation.

most user-dependent imaging modality, expertise varies widely, and surgeons are reluctant to abandon more traditional modalities (UGI).

Computed tomography scan

Although computed tomography (CT) scans are being used earlier in the evaluation of children with acute abdominal pain, they are less commonly done on neonates. On occasion malrotation can be found serendipitously.[23] Although CT scan is not the recommended study when suspicion of malrotation or midgut volvulus is high, it has become necessary for us to familiarize ourselves with the common patterns of malrotation as seen with this modality. Reversal of the SMA and SMV relationship can be identified quite easily if intravenous contrast has been given. The ligament of Treitz will be absent, and proximal small intestinal loops can be followed into the right abdomen in the patient with malrotation.

The findings of midgut volvulus on CT can best be described as a central mass of mesentery with vessels and bowel twisting around the SMA axis in a whirlpool pattern. Edema of the mesentery secondary to venous and lymphatic obstruction, closed loop obstruction, and dilatation of the proximal bowel (usually the stomach and duodenum) also may be seen.[18,24] Signs of bowel ischemia or infarction, such as bowel wall thickening from submucosal edema and hemorrhage, are late findings. Occlusion of the volvulized SMA may lead to absence of bowel wall enhancement by vascular contrast in the small intestine and proximal large intestine, sparing the bowel which is supplied by the inferior mesenteric artery.[25–27]

Treatment

Preoperative care

If the index of suspicion for midgut volvulus is high, then time is of the essence. Any delay in abdominal exploration and detorsion may contribute to significant loss of bowel. Immediate preoperative interventions should include placement of a nasogastric tube to suction and intravenous access. Aggressive infusion of isotonic crystalloid solution should include at least one bolus of 20 mL/kg of body weight. This is important to counteract the hypovolemia caused by vomiting and third space losses. Hypothermia should be avoided with resuscitation and during transport to the operating room. Broad-spectrum antibiotics are administered preoperatively.

Ladd procedure

The Ladd procedure corrects anomalies of intestinal rotation and involves five important steps: (1) counterclockwise detorsion of volvulus, (2) lysis of cecal bands and intermesenteric adhesions to allow straightening of the duodenum, (3) broadening of the mesentery, (4) appendectomy, and (5) placement of the small bowel on the right and the colon on the left side of the abdomen (Figure 10).

Traditionally, this operation begins with a generous transverse right upper abdominal incision. The primary benefit of this exposure is that it allows quick evisceration and early inspection of the bowel and mesenteric root for torsion (Figure 10b). The obliterated umbilical vein within the falciform ligament should be identified and divided. Yellow or milky chylous fluid is often encountered upon peritoneal entry and is indicative of underlying bowel obstruction. Foul smelling or bloody fluid is worrisome for intestinal necrosis. The small bowel is eviscerated and the surgeon looks at the root of the mesentery. One or more transverse loops of intestine crossing the root of the mesentery confirm midgut volvulus.

Midgut volvulus occurs in a clockwise fashion. Detorsion requires gentle counterclockwise rotation of the entire midgut around the SMA pedicle. Some find it helpful to remember the phrase “turning back the hands of time” to describe the counterclockwise direction of detorsion. Complete detorsion may require more than 360 degrees of counterclockwise rotation (Figure 10c), and should proceed until the colon comes into view. Because of the malrotation, the colon is likely to be obscured by small bowel loops.

Once the volvulus has been relieved, intestinal viability must be assessed. Moderately ischemic bowel, which appears congested and dusky, will rapidly resume a normal pinkish color after reduction of the volvulus and release of vascular

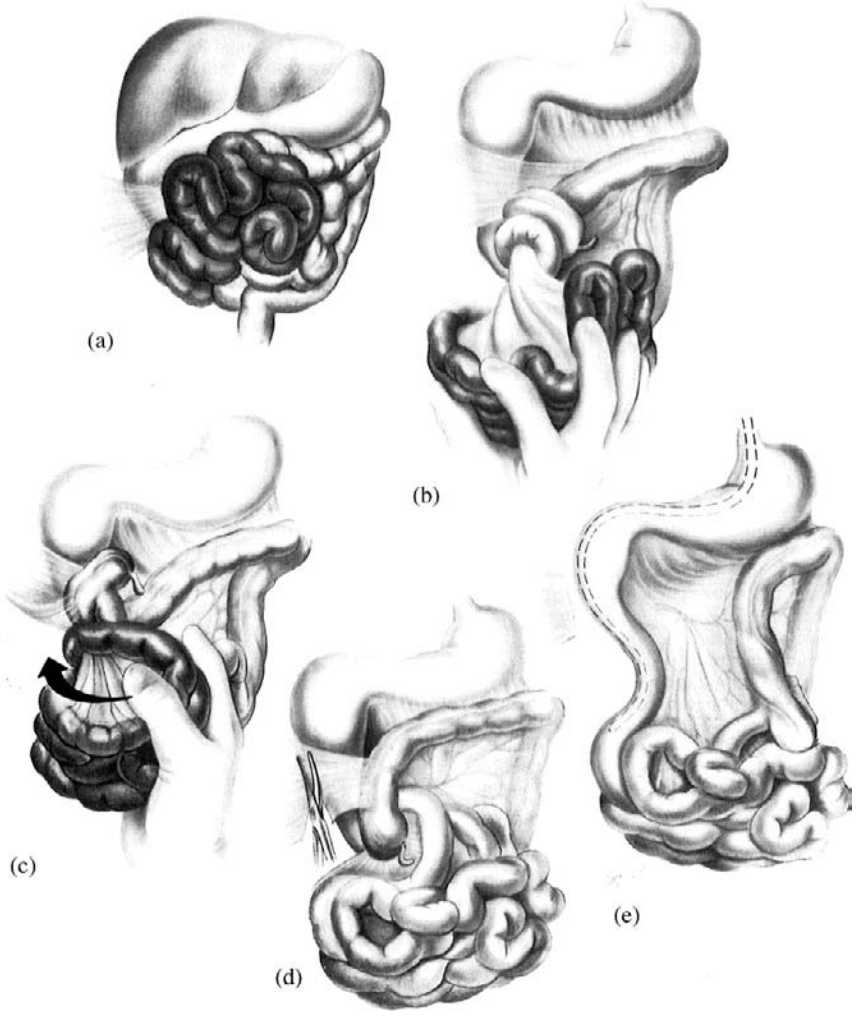


Figure 10. The Ladd procedure: surgical correction of malrotation with midgut volvulus. (a) Findings at laparotomy. (b) Inspection of the mesenteric root. (c) Counterclockwise detrosion. (d) Lysis of Ladd's cecal bands. (e) Nasoduodenal tube passage to ensure patency. (Adapted from Ladd WE, Gross RE: *Abdominal Surgery of Infancy and Childhood.* Philadelphia, WB Saunders, 1941.)

constriction. Bowel of questionable viability should be covered with warm moist sponges and left undisturbed for several minutes before assessing the extent of ischemic damage. In patients with extensive intestinal gangrene, only frankly necrotic bowel should be resected. Bowel ends should either be tied off or fashioned into stomas with a plan to perform second-look laparotomy in 12–24 hours when clearer lines of demarcation will be evident. At the second-look procedure, an end-to-end anastomosis may be feasible.[28] It may be better to preserve all borderline viable intestine at the time of initial operation since extensive resection may lead to severe short bowel syndrome. In the intervening period, the patient is electively ventilated and resuscitative measures are continued.

Folds of peritoneum extending from the cecum towards the right paracolic gutter, liver and gallbladder, so called Ladd's bands, are divided (Figure 10d). Ladd's bands are avascular, but great care must be taken throughout the dissection to avoid injuring the underlying mesentery. These bands cause mechanical duodenal obstruction unrelated to volvulus. This maneuver will free the ileocolic loop laterally. Further dissection between the duodenum and colon is usually necessary to allow a full medial colonic rotation. The root of the mesentery is then exposed, and avascular connections between the duodenum and ascending colon are carefully dissected with Metzenbaum scissors. Cautery should be kept to a minimum as mesenteric injury is a real risk.[1]

The duodenum is gently drawn towards the patient's right side until it follows a straight course towards the right lower quadrant. This is probably the best time to ensure proximal duodenal patency. If a nasogastric tube can be passed forward through the straightened duodenum, then a concomitant duodenal web can be excluded as a cause of bilious emesis (Figure 10e).

Once the superior mesenteric vessels with their proximal branches are exposed, separation of the duodenocolic bands is complete. The purpose of this maneuver is to widen the mesenteric base. A broad mesentery, which can be splayed out between the duodenum and cecum, is not prone to twist (Figure 11). It is for exactly this reason that patients with congenital diaphragmatic hernia and abdominal wall defects (omphalocele, gastroschisis) do not have a high incidence of volvulus despite the fact they all have malrotation. The developing mesentery of these patients is often stretched widely as the viscera develop in ectopic locations. Additionally, adhesions which develop after abdominal exploration are thought to help prevent volvulus. Therefore, a formal Ladd procedure is rarely performed during laparotomy for the correction of these conditions. There is some debate as to whether laparoscopy affords the same protection given a decrease in the number of postoperative adhesions. Regardless of the approach, duodenopexy and cecopexy are unnecessary and have not been shown to prevent

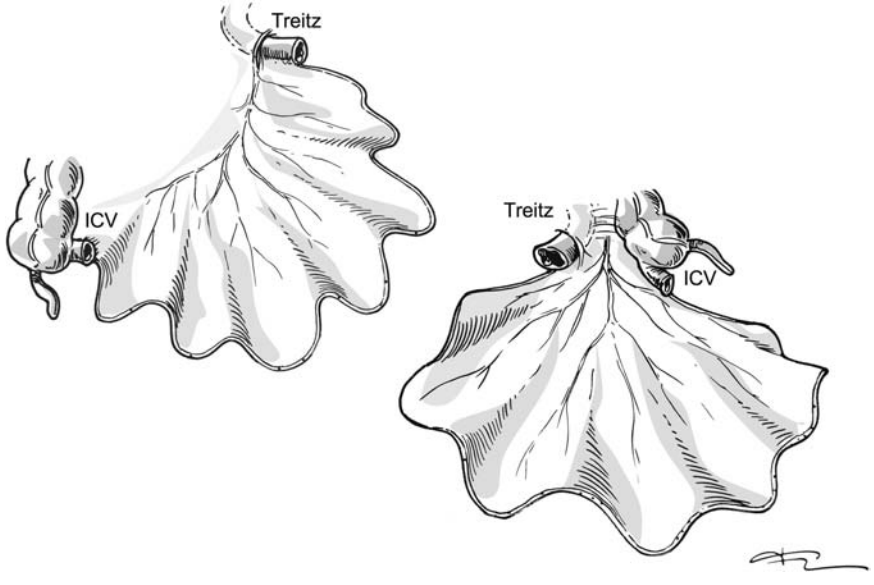


Figure 11. Cutout view of the mesentery in normal rotation (left) and nonrotation (right). Normally, the posterior attachment of the mesentery stretches from the ligament of Treitz to the ileocecal valve (ICV), preventing torsion of the mesenteric vessels. In nonrotation, the posterior mesenteric attachment (between duodenum and ICV) is narrow, placing it at risk of volvulus around the superior mesenteric artery. (Adapted from Luks FI. Malrotation. In *Fundamentals of Pediatric Surgery*. Mattei [ed]. Second Edition. Springer 2010: With kind permission of Springer Science+Business Media.)

volvulus after Ladd procedure. Inadvertent mesenteric defects created during dissection should be reapproximated with careful avoidance of small vessels.

At the conclusion of a Ladd procedure, the intestines are left in a position of nonrotation, with the small intestines on the right side of the abdomen and the colon on the left. This will exaggerate the breadth of the mesenteric arrangement. Cecal position is now left sided, which could potentially confuse or delay the diagnosis of appendicitis in the future. Consequently, the appendix is routinely removed at this time. An inversion appendectomy is favored by many, but regardless of technique, the added morbidity from this procedure is minimal.

Postoperative care

Postoperative ileus should be expected whenever extensive duodenal mobilization is necessary, but especially when significant bowel ischemia has been encountered.

A nasogastric or orogastric sump tube is routinely left in place for decompression and for precise fluid management. Excessive fluid losses should be replaced with 0.45% normal saline with 20 mEq/L of KCl to avoid electrolyte imbalance. Parenteral nutrition may be necessary in the case of prolonged ileus, or when a lengthy segment of intestine has been resected. Urine output is monitored closely and should be brisk reflecting adequate resuscitation.

COMPLICATIONS

An early postoperative complication is bleeding from mesenteric vessels damaged during the operative dissection. Reperfusion injury to the volvulized intestine may also occur after detorsion and lead to a significant systemic inflammatory response (SIRS) from the massive infusion of cytokines, bacteria, and other toxins into the circulation. This phenomena may contribute to hemodynamic instability during the intraoperative or postoperative period.[29]

Recurrent bilious emesis in the postoperative patient should prompt immediate evaluation for recurrent midgut volvulus, which occurs after Ladd's procedure in 2% to 10% of cases. It is unclear why recurrent volvulus arises, be it insufficient adhesion formation or incomplete widening of the mesentery. Regardless of the mechanism, failure to act upon recurrence can lead to significant morbidity or mortality from loss of intestine. Radiographic studies may be difficult to interpret in this scenario, and abdominal exploration is sometimes necessary if the clinical picture is not clear. Adhesive small bowel obstruction is another cause of postoperative bilious emesis. Lifetime risk for adhesive small bowel obstruction approaches 15%, which is similar to rates cited for laparotomy performed for other indications.

Mortality rate for correction of malrotation ranges from 3% to 9%. Poor results are associated with volvulus, intestinal necrosis, prematurity, and the presence of other abnormalities. Survival has improved along with the refinement of pediatric surgical intensive care and parenteral nutritional support. Furthermore, early diagnosis, heightened awareness of the significance of rotational anomalies, and urgency in management are the most important factors contributing to favorable outcomes. Still, midgut volvulus accounts for 18% of cases of short gut syndrome in the pediatric population. Urgent recognition and management is the most important factor in preventing this complication.[29]

LAPAROSCOPY

Laparoscopic correction of malrotation was first reported in 1995. Since that time, minimal access techniques have been employed with increasing frequency for

correction of rotational anomalies, although many reports have included older children and adults.[12,30–32] Proponents of this method cite several benefits of a minimally invasive approach including shorter hospital stay, less postoperative pain, rapid return of bowel function, fewer postoperative adhesions, and better cosmesis. Detractors argue that lengthy operating room times and technical difficulty make this strategy impractical and that fewer adhesions may allow recurrent volvulus. These claims are not yet supported or refuted by statistics, however, as the overall number of cases is far too small and there is a paucity of comparative data.[33] Regardless, as more pediatric surgeons become comfortable with the laparoscopic approach, there has been an accumulation of preliminary data to suggest that laparoscopic surgery is at least as safe and effective as the traditional open technique for the treatment of malrotation.[12]

While there have been a few reports of successful laparoscopic detorsion of midgut volvulus,[30,34] this practice is not widely endorsed. Laparoscopy is not suitable for an unstable patient or one with presumed intestinal necrosis. Friable and edematous intestine is easily injured by laparoscopic graspers. When time is of the essence to restore perfusion to compromised bowel, a speedy laparotomy is recommended.

The technical maneuvers one makes laparoscopically for treatment of malrotation parallel the open approach. They include detorsion of volvulus (if present), lysis of peritoneal adhesive bands, straightening of the duodenum, broadening of the mesentery, and appendectomy.

Trocar placement and instrumentation are patient and surgeon dependent. We prefer 3-mm instruments for neonates and 5-mm equipment for older children. Umbilical access is obtained using an open approach. Surgical focus is in the upper abdomen, which can make the choice of supplementary working sites a bit awkward. Our standard practice has been placement of additional trocars in both lower quadrants. This particular trocar configuration does not allow a classic diamond-shaped approach to the area of interest. To achieve adequate triangulation, we use a 30-degree telescope which is frequently repositioned at one of the lower quadrant sites. Occasionally, a fourth trocar is placed near the epigastrium for traction during duodenal mobilization. This is most often necessary in older children.

If volvulus is discovered and laparoscopic detorsion is to be attempted then visualization should be perfect. The second portion of the duodenum must be positively identified and followed distally. Traction on the duodenum and jejunum to a location underneath the right lobe of the liver will reduce the volvulus and place the bowel in the desired position of nonrotation. It will be necessary to divide adhesive peritoneal bands during detorsion (Figure 12). Duodenal mobilization continues until it follows a straight course towards the right lower quadrant. Next, the mesentery is broadened using a combination of gentle traction and

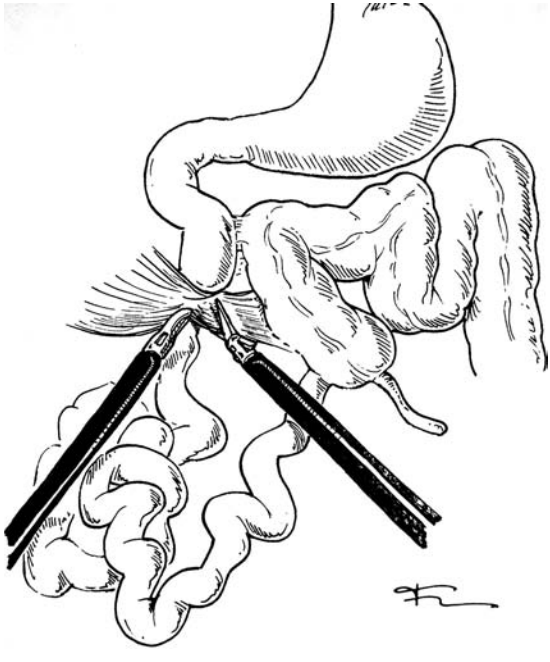


Figure 12. Laparoscopic take-down of Ladd's bands between cecum and right abdominal wall. (From Lessin MS and Luks FI. Laparoscopic appendectomy and duodenocolic disscociation (Ladd) procedure for malrotation. *Pediatr Surg Int* 1998, Springer Verlag: With kind permission of Springer Science+Business Media.)

sharp dissection. Again, sharp dissection is favored over cautery to avoid inadvertent injury to the bowel or mesentery. At the conclusion of this procedure, the small bowel should rest comfortably in the right side of the abdomen, and the colon on the left (Figure 13). The appendix is identified and mobilized laparoscopically. Small mesoappendiceal vessels can be cauterized using an intracorporeal technique. This allows easy delivery of the appendix through one of the trocar sites for extracorporeal ligation and excision.

When the anatomy is unclear based on radiographic findings, laparoscopic exploration has been used to separate asymptomatic patients into a group that is prone to volvulus and a group that is not.[32,35] Since the main goal of intervention in these patients is to prevent midgut volvulus, "overtreatment" can potentially be avoided if a broad based mesentery is found. In the absence of adhesive bands, if the cecum and ligament of Treitz are located in their normal position, then exploration can be safely concluded. However, if the patient has obstructive bands or a

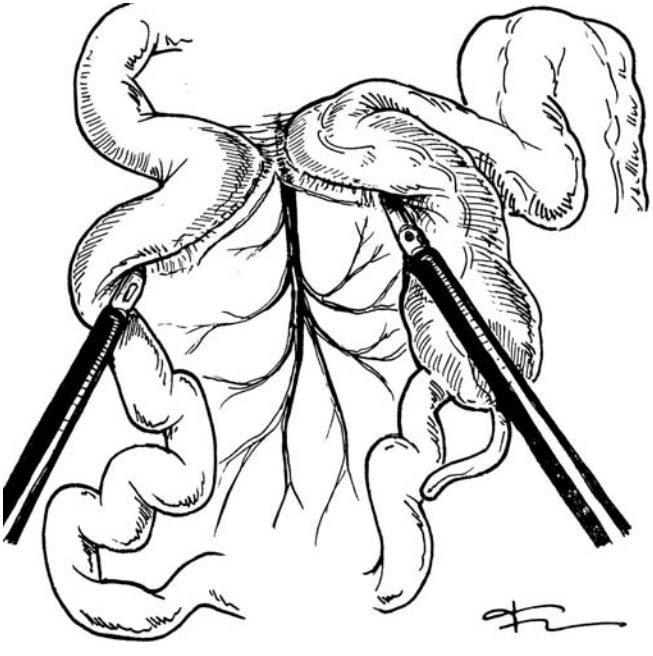


Figure 13. Laparoscopic division of duodenocolic bands to expose the root of the superior mesenteric artery and widen the posterior attachment of the mesentery. (From Lessin MS and Luks FI. Laparoscopic appendectomy and duodenocolic disscociation (Ladd) procedure for malrotation. *Pediatr Surg Int* 1998, Springer Verlag: With kind permission of Springer Science+Business Media.)

narrow mesenteric pedicle, then a formal Ladd procedure should be performed. Appropriate mesenteric width to justify (or not) a Ladd procedure is debatable.[33] While somewhat intuitive, long-term comparative data are not yet available to support this practice.

Heterotaxia

Heterotaxia syndromes include a range of abnormalities of the spleen (from asplenia to polysplenia) and abnormal situs that is indeterminate (neither normal nor situs inversus). Heterotaxia is associated with congenital heart disease. Cardiologists at times request upper GI series for asymptomatic patients with heterotaxia to rule out malrotation since errors in midgut rotation are common. Abnormalities found on UGI series may include subtle aberrations in rotation,

such as a low lying ligament of Trietz that may appear a bit anterior on lateral view. Risk of volvulus in this setting is unclear.

When pediatric surgeons are referred such patients, some advocate the Ladd procedure.[36] Others do not and suggest that screening for malrotation in the asymptomatic child with heterotaxia can be avoided.[37] One option for the pediatric surgeon facing an asymptomatic child with heterotaxia and a somewhat abnormal ligament of Treitz is to obtain a contrast enema. If the cecum is in the right lower quadrant, it may be sensible to conclude that the risk of volvulus is not high. Another option is laparoscopic exploration to clarify intestinal anatomy, proceeding on to a Ladd procedure if warranted.

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CHAPTER 3

CONGENITAL DUODENAL OBSTRUCTION

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INTRODUCTION

The duodenum is the most common site of congenital intestinal obstruction. Although duodenal obstruction may develop from a variety of congenital anomalies, duodenal atresia or stenosis is by far the most frequent cause of obstruction identified in the neonatal period.[1–14] In large population studies, duodenal atresia and stenosis develop in approximately 1 out of every 10,000 live births and are responsible for nearly 45% of all cases of congenital intestinal obstruction.[1,2,8,15,16] The earliest record of duodenal atresia dates back to the early 18th century; however, the first successful repair was not accomplished until almost 200 years later at the beginning of the 20th century. Advances in surgical techniques and perioperative management during the last forty years have improved contemporary survival rates to nearly 90% even in the presence of potentially severe associated congenital anomalies.[1–14,17,18]

EMBRYOLOGY

Embryonic folding during the 4th week of gestation incorporates part of the endoderm-lined yolk sac forming the primitive gut tube. At this stage, the primitive gut already is demarcated into three distinct regions: foregut, midgut, and

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hindgut. The foregut and hindgut develop enclosed within the craniad and caudad embryonic folds, respectively. Derivatives of the foregut include the pharynx, tracheobronchial tree, esophagus, stomach, and proximal duodenum, while the hindgut gives rise to the distal colon, rectum, and portions of the genitourinary system. The midgut remains in open communication with the yolk sac, and by the 5th week of gestation, the communication narrows to become the vitilline or omphalomesenteric duct. At this point, the midgut dilates just caudal to the vitilline duct to give rise to distinct small and large intestinal loops. The small intestinal loops develop into the distal duodenum, jejunum, and ileum, while the large intestinal loops become the cecum, appendix, and proximal 2/3 of the colon.[19,20]

As development of the primitive gut tube progresses, epithelial proliferation obliterates portions of its lumen. This phenomenon has been observed during the 5th to 8th week of gestation. Nothing approaching the solid phase seen in the duodenum occurs in the rest of the developing intestines. By 10 weeks' gestation, the lumen is recanalized and the epithelium becomes single layered.[19]

Rapid elongation of the midgut begins during the 6th week of gestation. Small intestinal loops cephalad to the vitilline duct experience the greatest increase in length. As a consequence of slower embryonic somatic growth and simultaneous liver expansion, the embryonic abdominal cavity becomes too small to contain the intestinal loops. The midgut herniates into the extraembryonic coelom and begins a 270-degree counterclockwise rotation around the axis of the superior mesenteric artery. Between the 10th and 12th weeks of gestation, the intestinal loops return to the abdominal cavity and become fixed to the retroperitoneum. The jejunum enters first into the left upper abdomen, and as more intestinal loops return, they move progressively caudal and to the right. The cecum returns to the abdomen last, initially lying in the right upper abdomen adjacent to the liver prior to its descent to the right lower abdomen. Complete midgut rotation and fixation continues throughout fetal development and after birth.[19,20]

Pancreatic development begins in the 4th week of gestation. Two endodermal buds arise from the ventral duodenum adjacent to the developing bile duct and within the dorsal duodenal mesentery. As the duodenum rotates towards the right and takes on its characteristic C-loop orientation, the smaller ventral pancreatic bud migrates dorsally in association with the orifice of the bile duct and fuses with the larger dorsal pancreatic bud around the 8th week of gestation. The two pancreatic ducts also fuse to form the main pancreatic duct of Wirsung, which empties into the duodenum at the major papilla, and the accessory duct of Santorini. In 10% of cases, the ducts partially or completely fail to fuse producing a dual

pancreatic ductal system with separate duodenal papilla. If ventral pancreatic bud migration is incomplete, a ring of pancreatic tissue, annular pancreas, develops encircling the duodenum.[19,20]

ETIOLOGY

Extrinsic duodenal obstruction can arise from annular pancreas, a pre-duodenal portal vein, intestinal duplication, or peritoneal bands found in midgut malrotation that partially or completely occlude the duodenum by compressing its lumen.[1–11,14,17,21,22,26] Often, these abnormalities are non-obstructive and found incidentally to underlie duodenal atresia or stenosis. Little is known about the genetic, molecular or environmental factors that play a role in the development of these various abnormalities.

In 1902, Tandler first suggested duodenal atresia and stenosis may develop from epithelial proliferation and failure of complete recanalization of the duodenum after observing epithelial occlusion of the duodenum in 11 embryos.[23] Today, his theory remains widely accepted as the basis for duodenal atresia although other theories have assumed prominence for intestinal atresias distal to the duodenum especially a vascular accident *in utero* as from intussusception, entrapment in the umbilical ring or volvulus.[19,24] Alternate theories for the cause of duodenal atresia have been largely dismissed; however, vascular thrombosis is felt to cause jejunoilial atresia, as demonstrated by Barnard's classic animal studies.[24]

The genetic, molecular, and developmental errors responsible for epithelial proliferation, failure of recanalization, and ultimately duodenal atresia and stenosis have yet to be fully understood since Tandler's observation 100 years ago. Familial inheritance patterns, high prevalence rates among twins, and the large frequency of associated defects strongly support a genetic basis.[1–15,17,18,21,22,25–34] Recently, altered intercellular signaling pathways involving fibroblast growth factor (FGF) and fibroblast growth factor receptors (FGFR) have been implicated in the development of duodenal and other intestinal atresias.[35,36] Fibroblast growth factor signaling pathways regulate mesenchymal–epithelial interactions via tyrosine kinase activation, and loss of function produces an imbalance in cellular proliferation and apoptosis, favoring apoptosis of both epithelial and, to a lesser degree, mesenchymal cells.[36] Kanard *et al.* produced both complete duodenal atresia and duodenal webs in mice with homozygous deletion of FGF-10 and FGFR-2b, achieving 38% and 35% penetrance, respectively.[35,36] Both phenotypes display a constellation of critical developmental defects, making it unlikely that human embryos would survive these germ-line mutations. However,

alterations in less critical downstream intracellular signaling proteins, variable tissue-specific transcription, or genetic mosaicism arising from point mutations or early somatic mutations involving FGF and receptor genes may produce a less extreme, viable phenotype.

Associated Anomalies

Other congenital anomalies are identified in approximately 60% of infants with duodenal atresia or stenosis (Table 1).[1–12,14,15,17,18,26,30–34,37] Nearly 30% of infants will have more than one anomaly and 12% will have more than two. Down syndrome, trisomy 21, is the most common of all anomalies and by far the most common chromosomal abnormality encountered. Other chromosomal abnormalities and syndromes have been reported including 47 XXY, 47 XXX, translocation t,[7,21]

Table 1. Associated anomalies*.

Anomaly	Percentage (%)
Down syndrome (trisomy 21)	30
Annular pancreas	26
Congenital heart defects	25
Malrotation	19
Esophageal atresia/ tracheoesophageal fistula	7
Renal	6
Anorectal malformation	5
Skeletal	4
Second intestinal atresia	3
Meckel's diverticulum	3
Preduodenal portal vein	3
Situs inversus	2
Central nervous system	2
Other	11
Greater than 1 anomaly	29
Greater than 2 anomalies	12
None	41

*Average reported events.[1–12,15,17,18,26]

interstitial deletion of chromosome 13q, Cornelia De Lange syndrome, Goldenhar syndrome, Martinez-Frias syndrome, and arthrogryposis multiplex congenita.[4,5,7,11]

Congenital heart defects occur in a little more than a quarter of cases and are a major source of morbidity and mortality.[1–12,14,15,17,18,26,30–34,37] Infants with duodenal atresia or stenosis and Down syndrome carry a significantly higher risk for concomitant congenital heart defects compared to those with a normal karyotype.[26] The spectrum of cardiac defects includes a wide variety of pathologic variants: atrial septal defects, ventricular septal defects, atrio-ventricular canal defects, patent ductus arteriosis, tetrology of Fallot, double outlet right ventricle, hypoplastic left heart, anomalous pulmonary venous return, and coarctation of the aorta.[5,7,12,26] Nearly half of cardiac defects require operative repair.[26] The relative risk for open heart surgery is higher in infants with Down syndrome.[26]

A wide variety of associated gastrointestinal anomalies may be discovered and are of particular interest to pediatric surgeons since many need to be addressed during the operation for the duodenal atresia or stenosis or at a subsequent procedure.[1–12,14,15,17,18,26,30–34,37] Annular pancreas and malrotation are by far the most common anomalies, and like the preduodenal portal vein, they may produce extrinsic duodenal obstruction. When malrotation is present, a Ladd procedure is indicated to reduce the risk of midgut volvulus. Esophageal atresia with or without tracheoesophageal fistula and anorectal malformations occur in conjunction with duodenal atresia or stenosis in 7% and 5% of infants, respectively. Single-stage versus delayed repair of esophageal atresia and placement of a decompressive gastrostomy tube at the time of the duodenal repair remains controversial.[38] Because the tracheoesophageal fistula threatens the patient, its division, usually with repair of the esophageal atresia, and placement of a draining gastrostomy tube and staged, subsequent repair of the duodenal atresia may be safest in some patients. The presence of anorectal malformations typically warrants a colostomy to prevent distal intestinal obstruction, with subsequent anorectoplasty at a later operation. A second intestinal atresia may be identified in 5% of cases and can occur anywhere along the intestinal tract. Jejunoileal atresias occur most frequently but second duodenal atresias or stenoses as well as colonic atresia have been reported.[1–5,8,9,11,12,14,15,17,18,26,30–34] In some cases, these additional atresias were not identified at the initial procedure and led to continued intestinal obstruction requiring a second operation.[2,4,12] This underscores the importance of closely investigating the integrity of the entire bowel during the initial duodenal repair. Hirschsprung's disease, intestinal duplication, pyloric atresia, gastroschisis, omphalocele, choledochal cyst, and biliary atresia are rarely encountered with duodenal atresia or stenosis.[1,2,4,6,7,12]

PRENATAL DIAGNOSIS

Fetal ultrasound has been used to detect duodenal obstruction since the early 1970s. Currently, approximately half of cases are detected on routine antenatal ultrasound including complete or partial obstruction by intrinsic or extrinsic abnormalities.[1,6,8,9–12,16–18,39] The classic sonographic image is a "double-bubble" characterizing the fluid-filled, dilated stomach and duodenum. Maternal polyhydramnios may also be detected on antenatal ultrasound in approximately a third of all cases of duodenal obstruction[9,14,40] and up to 80% of cases diagnosed in the immediate prenatal period.[1,3,4,6–11,14,39] Frequently, prenatal diagnosis is delayed until after 24 weeks' gestation, likely due to the fact that only small amounts of amniotic fluid are swallowed by the fetus during the first half of pregnancy.[9–11,14,16,39,40] Earlier detection often signifies the presence of associated anomalies.[9,16,17,39]

A timely prenatal diagnosis may be beneficial in permitting appropriate parental counseling regarding additional karyotyping and obstetric management, including prompt referral to high-risk maternal-fetal specialists in order to reduce perinatal complications.[11] Early in pregnancy, parents also have the option for elective termination in cases with severe associated anomalies. However, as many as 25% of associated congenital defects are not discovered until after birth,[9] and false-positive ultrasound results can occur in up to 12% of cases.[17] Benefits of prenatal diagnosis for the infants with duodenal obstruction are still debated. Limited reports comparing pre- and postnatal diagnosis have shown earlier diagnostic confirmation of duodenal obstruction, reduced morbidity associated with metabolic derangements, and shorter time to surgical repair and transition to enteral feedings.[10,40,41] Yet other similar series refute these findings and most have not demonstrated any improvement in neonatal mortality with prenatal diagnosis.[9,11,14,17,42] If chromosomes are normal and other anomalies not evident, the family whose fetus has duodenal obstruction can be given optimistic support for a likely good long term outcome. It is, however, worth a gentle warning that multiple atresias distal to the duodenum cannot be recognized until the operation and will of course complicate the outcome.

CLINICAL PRESENTATION

Duodenal obstruction affects males and females almost equally (1.07:1).[1–8,10,12–14,17,26] Although most infants are born full term, approximately 40% will be premature[1–3,5,6,8,9,12,18] and 15% will be small for gestational age.[7,9,11,12] The cause of prematurity is unclear, but maternal polyhydramnios and anxiety related to

high-risk pregnancy have been associated with an increased risk of spontaneous preterm birth.[9]

Repeated emesis with feeding intolerance or high volume aspirates with gastric suctioning is the characteristic presentation in approximately 90% of neonates with duodenal obstruction.[1,4,6–8] Emesis is typically bilious since duodenal obstruction most often occurs distal to the ampulla of Vater. However, approximately 20% of infants will have nonbilious emesis, either from a more proximal or incomplete obstruction.[1,4,6,7] Infants lacking prenatal diagnosis occasionally may be misdiagnosed with meconium aspiration in the delivery room if bile-stained amniotic fluid is observed or endotrachael suctioning is performed inadvertently down the esophagus. Since duodenal obstruction is very proximal in the intestinal tract, neonates typically do not have abdominal distension, but subtle upper abdominal distension has been reported in approximately 20% of cases.[1,4,6,7]

DIAGNOSIS

An antenatal ultrasound suspicious for duodenal obstruction facilitates early postnatal diagnosis in many cases, often before signs of intestinal obstruction have time to develop.[40,41] In unsuspected cases of complete or high-grade duodenal obstruction, clinical features typically develop within hours of birth. If an orogastric tube is placed, aspirates greater than 30 mL suggest intestinal obstruction in a newborn. The presence of bile in the stomach also raises concern. A plain radiograph of the abdomen showing the characteristic "double bubble" appearance with two large upper abdominal air filled spaces and of the absence of distal intestinal gas confirm the diagnosis of complete duodenal obstruction in the majority of cases (Figure 1).[1,3,4,7–10] If suspicion is high and the "double bubble" is not readily apparent on plain radiograph, injection of 30–60 mL of air into the stomach as contrast often clarifies the imaging diagnosis.[45] This has to be done with caution and diligent emptying of the stomach immediately after the film to limit the risk of vomiting and aspiration. Further imaging studies of the gastrointestinal tract prior to operative intervention are unnecessary given the proper clinical scenario and characteristic radiographic findings. Still, contrast enema has been used by some authors to rule out colonic atresia or malrotation prior to operation. The extreme rarity of colonic atresia and unreliability of contrast enema to confirm normal intestinal rotation does not justify this practice as routine.[43]

Partial duodenal obstruction often is diagnosed much later in the newborn period with progressive feeding intolerance or can go undetected into



Figure 1. Plain radiograph demonstrating the "double bubble" sign and absence of distal bowel gas identified in duodenal atresia.

childhood, rarely even adulthood, until worsening duodenal dysmotility or food impaction increases symptoms.[5,6,12,14] Plain radiographs in partial obstruction may show the "double bubble" sign. Classically, the plain film shows two distended upper abdominal air-filled loops with a paucity of air distally. The plain film may be nondiagnostic. Upper gastrointestinal contrast series is beneficial in this scenario if the presence of partial duodenal obstruction is uncertain or if exploration is to be delayed in order to differentiate the infant with duodenal stenosis from that with malrotation and midgut volvulus who requires urgent operation to correct volvulus and prevent intestinal infarction. Upper gastrointestinal series will usually demonstrate a dilated proximal duodenum with a smooth blind-ending duodenal pouch in duodenal atresia (Figure 2), whereas contrast may be seen to pass towards the jejunum in cases of incomplete obstruction. In comparison, midgut volvulus typically demonstrates a distal "bird beak" appearance.[43] It is not necessary to clarify the cause of partial duodenal obstruction preoperatively when clinical signs of intestinal ischemia or peritonitis warrant urgent abdominal exploration. If complete duodenal obstruction is diagnosed by plain film, contrast study is not indicated since the constrast will spread out across the upper abdomen, be less clear than the air contrast of the plain film and increase the danger of aspiration of gastric contents.



Figure 2. Upper gastrointestinal series demonstrating dilated proximal duodenum and abrupt cutoff in duodenal atresia.

TREATMENT

Preoperative

Initial management of duodenal obstruction is aimed at correcting fluid and electrolyte disturbances while appropriate diagnostic studies are obtained to exclude associated congenital anomalies. These infants routinely require long-term central venous access for hydration and nutritional support as normal enteral feeding is generally delayed several weeks following operative repair. Central venous access should be obtained preoperatively without delay either by peripherally inserted or tunneled central catheters depending upon the size of the neonate and skill set of the neonatology and surgical teams. An orogastric tube should be placed to decompress the dilated stomach and proximal duodenum. This maneuver offers the added benefit of effectively identifying esophageal atresia in the subset of patients with both anomalies. Echocardiography is essential in the preoperative period to identify severe congenital cardiac defects that are a major source of infant morbidity and mortality and may require surgical correction prior to repair of duodenal obstruction. Renal ultrasonography and chromosomal studies are routinely recommended, but the timing of these investigations is less critical. Repair of duodenal obstruction is not urgent and should only be

performed once the infant's hemodynamic status and severe associated anomalies have been optimally addressed.

Operative

Traditionally, duodenal obstruction has been repaired through an upper transverse right sided abdominal incision placed midway between the liver edge and umbilicus; however, laparoscopic techniques are rapidly gaining popularity among contemporary pediatric surgeons with comparable short-term results in experienced centers.[13,18,44] Abdominal exploration is undertaken paying close attention for a synchronous atresia in the remaining bowel and noting the presence of a normal gallbladder. Approximately 20% of cases have associated malrotation evident by the absence of the ligament of Treitz.[1–10,12,14,17,30–34] In these patients, a Ladd procedure should be performed in addition to the duodenal repair to reduce the risk of midgut volvulus. Others are found to have a medially displaced ascending colon and hepatic flexure due to proximal duodenal dilatation, but on careful inspection actually have normal rotation.[45] Mobilization of the hepatic flexure and transverse colon and Kocherization of the duodenum from the retroperitoneum facilitate examination of the entire duodenum to identify the type and location of obstruction.

With complete or severe partial obstruction, the proximal duodenum typically appears thick walled and dilated, while the distal segment is thin walled, gasless and collapsed. Duodenal atresia is the underlying anomaly in approximately 78% of cases of complete obstruction.[1,2,6–8] Three variants of duodenal atresia may be recognized that differ by the extent of separation in the duodenal wall and mesentery.[19] With type I duodenal atresia, the duodenal muscular wall is continuous whereas the lumen is disrupted by a thin mucosal and submucosal septum or "web" which often arises adjacent to the ampulla within the second portion of the duodenum. In a subset of type I atresia, the web becomes elongated and billows into the distal duodenum creating a "windsock deformity" (Figure 3). The billowing web creating the windsock usually has an opening, resulting in partial duodenal obstruction. This malformation often presents well after the neonatal period. The obstruction is usually alleviated by duodenotomy with partial excision of the web. Locating the ampulla of vater and protecting it is critical at the time of repair. The ampulla can have variable locations but often ends near the opening in the web. With this variety, the duodenum may appear dilated much more distal to the level of actual obstruction. Type I accounts for 70% of atresias.[1,2,6–8] Type II and III are characterized by complete discontinuity of the duodenal wall and account for 13% and 17%

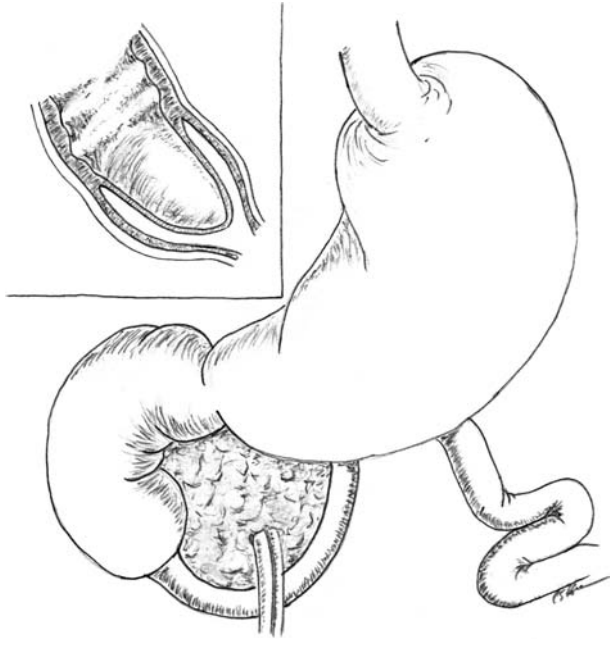


Figure 3. Type I duodenal atresia and "windsock" duodenal web. Note the continuity of the bowel wall at the level of obstruction.

of duodenal atresias, respectively.[1,2,6–8] In type II, the atretic segments of the duodenum are joined by a thin fibrous cord (Figure 4), whereas absence of an intervening cord and addition of a V-shaped mesenteric defect characterize type III atresia (Figure 5).

In most remaining cases, duodenal stenosis from a perforated duodenal web creates varying degrees of incomplete obstruction.[1–4,6,9–14] A duodenal web is strongly suspected when, in cases of partial duodenal obstruction, the duodenal muscular wall appears intact at the level of obstruction. The severity of proximal duodenal distension and the appearance of the distal intestine vary with the size of the orifice in the web. Other potential sources of duodenal stenosis, including annular pancreas and preduodenal portal vein, should also be identified as these may influence the type of operative repair. However, when one of these anomalies exists further careful scrutiny of the duodenum often uncovers an underlying atresia or web. Whenever uncertainty exists, manipulation of the orogastric tube into the duodenum with the assistance of anesthesia may clarify the presence and level of an underlying intrinsic obstruction.

The major goals of operative repair are reconstitution of bowel continuity and preservation of unobstructed biliopancreatic drainage. Regardless of the

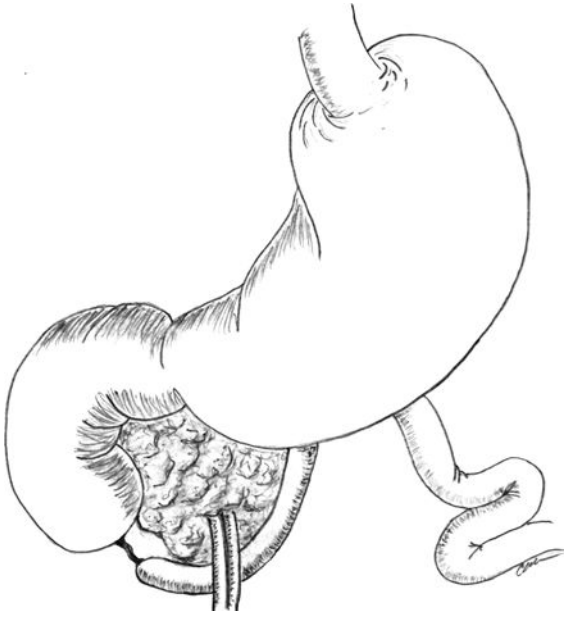


Figure 4. Type II duodenal atresia with fibrous cord connecting the two atretic ends of the duodenum.

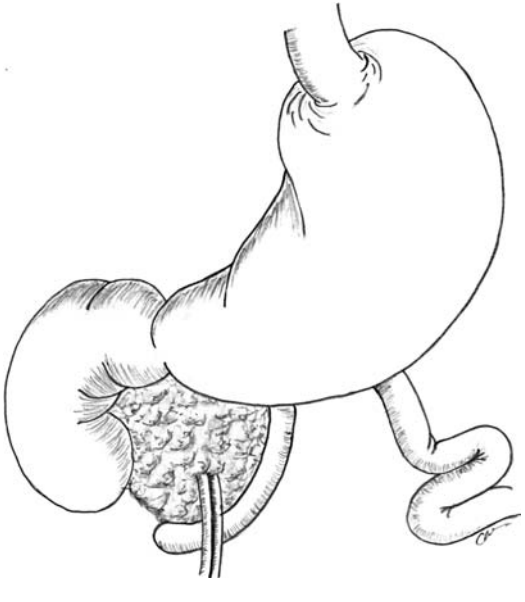


Figure 5. Type III duodenal atresia with complete separation of the two atretic ends of the duodenum.

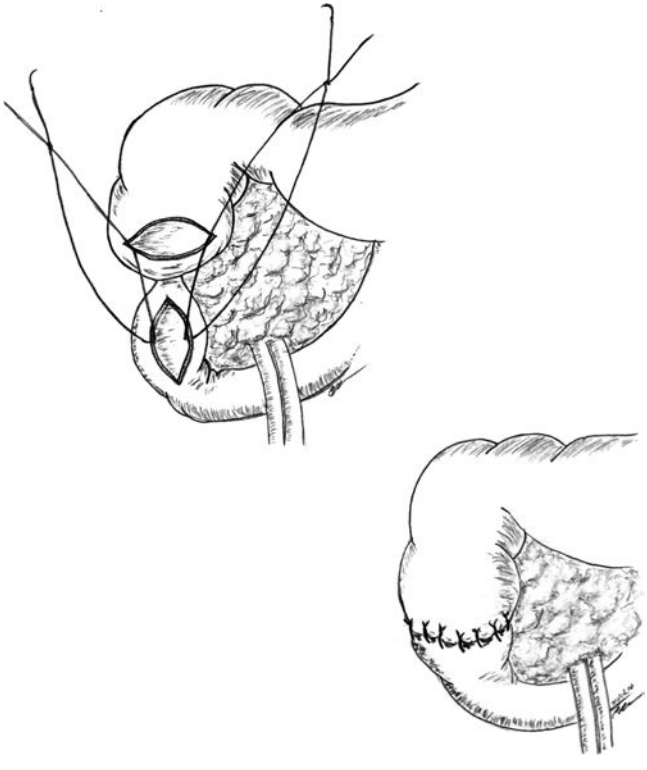


Figure 6. Kimura "diamond-shaped" duodenoduodenostomy. Note proximal transverse and distal longitudinal duodenotomies in upper diagram.

cause of obstruction, in most cases, these goals are best achieved with a duodenoduodenostomy approximating the duodenal segments proximal and distal to the point of obstruction. The asymmetric Kimura "diamond-shaped" anastomosis is the preferred technique over a simple anastomosis in most published series (Figure 6).[1–10,12–14,46] A transverse duodenotomy is performed at the most dependent portion of the dilated proximal atretic segment, and a longitudinal antimesenteric duodenotomy is created along the distal segment in a position to allow apposition without tension. Both incisions need to be sufficient length, usually 1–2 cm depending on the patient's size, to ensure patency of the repair.[45] Prior to anastomosis, a soft rubber or silastic catheter should be passed from proximally through the stomach and distally into the jejunum to exclude the presence of another obstructing intrinsic duodenal lesion. Also, distending the distal segment slightly by injecting saline while manually occluding the downstream

bowel lumen may facilitate a technically easier repair. Directing saline down to the cecum will help exclude other distal sites of obstruction.

The diamond anastomosis is created by joining the corners of one duodenotomy to the midpoints of the other in a single layer with absorbable suture (Figure 6). Proper orientation is best achieved by placing the first sutures from the corners of the proximal duodenotomy to the midpoints of the distal longitudinal duodenotomy. Remaining sutures are placed along the posterior edge using a bisecting technique to ensure even distribution with the knots tied inside the lumen. The anterior row is completed in a similar fashion with the knots positioned to the outside of the duodenum. Patency can be tested by carefully manipulating the orogastric tube through the anastomosis or by having the anesthesiologist instill saline through the tube while gently occluding both ends of the duodenum.

When a duodenal web is present, a longitudinal duodenotomy and partial web excision is a viable alternative to duodenoduodenostomy.[1–14] The duodenotomy should be created overlying the point of obstruction to allow visualization of the mucosal septum and position of the ampulla. If the ampulla lies along the medial wall of the septum, the lateral segment of the web may be removed without jeopardizing the repair. A gentle squeeze of the gall bladder can help identify the papilla. The duodenotomy should be closed transversely to prevent stenosis. Duodenoduodenostomy remains a better option when the web is especially thick or the position of the ampulla is not well visualized.

With type II or III duodenal atresia, a long gap or variations in anatomy occasionally exist, making it technically impossible to anastomose the atretic ends directly without kinking the bowel or creating tension in the repair. In this scenario, a duodenojejunostomy is a reasonable alternative with nearly equivalent results.[1–9,11,12,14] The duodenojejunostomy is created using a loop of proximal jejunum that reaches the proximal duodenum through a right-sided mesecolic window without tension. Gastrojejunostomy has been used in this scenario as well but is not recommended due to potential complications from marginal ulceration and blind loop syndrome.[14]

When annular pancreas or preduodenal portal vein is present with or without an underlying intrinsic anomaly, duodenoduodenostomy still provides the best option to bypass the obstruction.[21,22] Both duodenotomies should be about 1 cm from the pancreatic annulus in cases of annular pancreas for optimal approximation without tension.[21] The pancreatic annulus should not be divided as the pancreatic ductal anatomy is often aberrant and portions of the ductal system may be injured leading to pancreatitis or pancreatic leak.

Excessive dilation of the obstructed duodenum can lead to weak, ineffective peristalsis and chronic dysmotility. When this is encountered, duodenal tapering may facilitate earlier return of duodenal function.[47,48] Duodenal tapering is performed by resecting the antimesenteric surface along the longitudinal axis of the distended segment back towards the pyloris. Folding the duodenal wall over a large pool suction or silastic catheter and employing a linear stapler greatly facilitates this procedure as compared to suture plication. Routine tapering is controversial as exactly what degree of distension is excessive and which infants will benefit from tapering remains unclear.

A number of adjunctive procedures often are required at the time of duodenal repair. A tunneled central venous line should be obtained if not done so preoperatively for postoperative hydration and nutrition. Infants with malrotation should undergo a Ladd procedure to reduce risk of midgut volvulus.[1–4,6–12,14,17,18,30–34,37] Traditionally, infants with associated esophageal atresia have undergone decompressive gastrostomy and delayed esophageal repair since early duodenal dysmotility following duodenal repair is thought to increase the likelihood of gastroesophageal reflux and possible stricture of the esophageal anastomosis.[1,2,4–7,9–12,14,17,27] A safer option might be repair of the esophageal atresia and tracheoesophageal fistula with placement of the gastrostomy, and subsequent repair of the duodenal obstruction. Few reports have documented excellent outcomes with simultaneous repair without gastrostomy.[29,49] Most infants with anorectal malformations benefit from initial diverting colostomy and staged colonic pullthrough, although consideration may be given for simultaneous repair of perineal fistulas in selected cases.[1,2,4–9,11,12,14,17] Routine placement of a gastrostomy tube or postpyloric feeding tube has largely been abandoned due to increased morbidity, delays in initiation of enteral feeding and longer hospitalization associated with these procedures.[7]

Laparoscopic Technique

Highly skilled laparoscopic surgeons have safely performed duodenoduodenostomy and duodenotomy with web excision for almost a decade with equivalent short-term results compared to open repair.[13,18,44] Long-term results are yet unknown. The infant is positioned supine at the very foot of the operating table and two high definition monitors are placed along each side at the head of the bed. Proper positioning is critical such that the surgeon may stand at the patient's feet and have an in-line oriented view with the working field. A 5-mm umbilical port provides access for a 45° laparoscope. A 3-mm port is placed in the right lower quadrant and a 5-mm port is placed in the left upper quadrant positioned at about

a 90° angle from one another in reference with the duodenum to simplify intracaporeal knot tying. The larger left upper quadrant port is needed to introduce the suture needles into the abdominal cavity. Insufflating the peritoneal cavity to 10-mm mercury pressure provides excellent visualization of the relevant anatomy without impeding central venous return. On occasion, especially in smaller infants, a fourth port may be needed in the right upper quadrant to retract the liver edge.

The remainder of the conduct of the operation remains similar to the open procedure with few variations. The diamond-shaped duodenoduodenostomy is set up with stay sutures placed between the midpoints of the proximal transverse and corners of the distal longitudinal duodenotomies. These stay sutures are passed through the abdominal wall to allow traction and proper alignment along the apposing edges of the duodenal incisions. Both rows of the anastomosis are formed with a single layer of either interrupted or running sutures. Intracaporeal or extracaporeal knot tying are used at the discretion of the surgeon. Self-locking clips also have been employed to simplify anastomosis and reduce leaks, but outcome data for these devices are limited.[44] The remaining bowel is inspected for synchronous atresias and malrotation. If a second atresia is suspected, saline can be injected into the bowel lumen using a small spinal needle passed through the abdominal wall. Adjunctive procedures including Ladd's procedure, esophageal atresia repair or repair of imperforate anus may be performed safely at the same setting as laparoscopic repair.[18,49] However, the infant, often small, with complex associated malformations, tests the ingenuity and safety of the pediatric surgeon: and first correcting the most threatening physiology and staging other steps might avoid some poor outcomes.

Postoperative

Most near-term infants with isolated duodenal obstruction or with minor associated anomalies may be rapidly and safely removed from ventilatory assistance in the immediate postoperative period. Orogastric drainage, total parenteral nutrition, and electrolyte replacement is continued until duodenal motility returns, which is expected on average in about 10 days regardless of the type of repair.[5,7,9,10,12,14,18] Feedings may be initiated once gastric aspirates decrease in volume and the character of the drainage becomes less bilious. Because the pylorus can be dysfunctional from chronic *in utero* obstruction, waiting for bile to disappear from the aspirate may be futile. Conversion to full enteral nutrition is usually rapid and dismissal from the hospital can be anticipated within 3 weeks following operation.[5,7,9,10,13] Time to full enteral nutrition and length of hospitalization may be reduced in infants selected for laparoscopic repair.[13] Infants born extremely prematurely or with severe associated anomalies often have complicated postoperative courses, including delays in intestinal function and transition to enteral feeds.

OUTCOME

Early Complications

Early postoperative complications occur in up to 15% of cases of duodenal obstruction.[1,2,4–8,10–12,14] As expected, premature infants and those with associated cardiopulmonary anomalies suffer more nonsurgical complications including sepsis, congestive heart failure, pneumonia, ventilatory failure and renal failure than those with isolated duodenal obstruction. Technical complications such as anastomotic leak, dehiscence, or stricture occur in less than 3% of cases in contemporary, large series and have not been influenced as yet by laparoscopic techniques.[1,2,4,6,12,13,18] Wound infection and dehiscence have been reported in 5% and 2% of cases, respectively, and are almost nonexistent with laparoscopic surgery.[1,2,4,6–8,10,13,14,18] However, to date, no clinical trials comparing open to laparoscopic procedures for duodenal obstruction have demonstrated any benefit in terms of wound complications. A missed synchronous atresia or stenosis should almost never occur if adequate inspection of the intestine is performed at operation.

Late Complications

Persistent feeding intolerance is the most common late complication after repair of duodenal obstruction, and there is little evidence the choice of repair has any significant influence on its rate of occurrence.[1,2,6,11] Generally, this problem should only be suspected if normal bowel function has not returned within 3 weeks unless technical problems were encountered at operation. An upper gastrointestinal series performed at that time may delineate poor peristalsis from a persistent obstruction due to anastomotic stricture, incompletely excised web or previously unrecognized second atresia or stenosis. Most often the problem is functional and not anatomic.[45] A persistently dilated proximal duodenum may be identified on imaging for months despite an adequate anastomosis, but if discovered in the face of persistent duodenal dysmotility, then duodenal tapering is recommended to promote functional recovery.[47,48] Certainly, duodenal tapering at the time of initial repair may prevent this complication; however, most infants will regain duodenal function even in the face of a markedly dilated proximal duodenum and it is impossible to predict which infants will develop this problem long term. Functional impairment from anastomotic stricture or overlooked stenosis may worsen slowly over time and only present later in childhood when intake of solid food leads to a complete obstruction or duodenal dysfunction becomes severe enough to cause symptoms.[5,6,12,14] Upper endoscopy may assist in diagnosis as well as be therapeutic for these older children by means of balloon dilatation of a stricture or excision of a web.[50]

Other long-term problems including gastroesophageal reflux, duodenogastric reflux, peptic ulcer disease, adhesive small bowel obstruction and blind loop syndrome uncommonly occur.[1,2,4,57,12] Most of these can be managed without surgical intervention, but occasionally gastroesophageal reflux unresponsive to pharmacologic therapy requires fundoplication.[1,2,4,7] When duodenojejunostomy is performed for a very distal type III atresia, the intervening duodenum may develop blind loop syndrome with overgrowth of intestinal flora. In rare instances, this situation may only be resolved by resecting the stagnant intervening duodenal segment and reconstructing a duodenojejunostomy.[2,45] Delayed presentation of biliary atresia or choledochal cyst has rarely been reported but underscores the need for close long-term follow-up for infants with duodenal obstruction.[1,2,4,7] Since cholestasis occurs in many neonates who require intravenous alimentation, the possibility of extrahepatic biliary atresia can arise in these patients post-operatively. This apprehension is reduced if, at the time of the repair of the duodenal obstruction, the surgeon looks for and documents a completely normal gallbladder.

Survival

For infants with isolated duodenal obstruction, nearly 100% survival with complete recovery is expected. Almost all deaths are related to severe associated anomalies, most of which are cardiopulmonary in origin. Overall survival for infants with duodenal obstruction with or without associated anomalies is about 90% in major series published over the last twenty years.[1–14,17,18] This has improved remarkably from a survival rate of about 65% reported in the previous 20-year period.[30–34,37] Advances in perioperative management likely are responsible for the dramatic improvement. Although elective pregnancy termination in cases with severe associated anomalies may play a role, in studies of early prenatal detection, the rate of elective termination is low and all of these studies have failed to show a significant reduction in mortality with early detection.[9–11,14,16,17,39–42]

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CHAPTER 4

JEJUNOILEAL ATRESIA AND STENOSIS

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INTRODUCTION

Through the first half of the 20th century, death was the usual outcome for patients born with atresia of the small intestine. A survey of 1353 papers published in 1951 "complete to 1950" found 1141 deaths from 1498 cases (76.2% mortality) of intestinal atresia "without or with operation, during the first month of life"… "The highest mortality rate was found in cases of jejunoileal atresia".[1] "Only 5 infants with an atresia of the small intestine (jejunum or ileum) have successfully been treated by primary resection and anastomosis"…

The survival rate for jejunoileal atresia is now about 90%.[2] The turnaround over the past half century from very low to high survival overlaps with the evolution of pediatric surgery as a specialty. The first volume of The Journal of Pediatric Surgery (1966) included two key papers on this subject. The first scientific paper in the first issue reviews the experimental and clinical observations by pediatric surgeons on what had been a highly morbid malformation and announces major improvements in outcomes.[3] Experiments by surgeons on fetal dogs strongly supported the observation that the cause of jejunoileal atresia was a vascular accident *in utero*. In the 5th issue of that first volume, Moutsouris gives experimental embryologic observations that nothing approaching a "solid phase" occurs in the developing jejunum and ileum, as

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opposed to the developing duodenum, where epithelial hyperplasia nearly fills the lumen during the 6th and 7th week.[4] This report further lent doubt to the previously held theory that intestinal atresia was a failure of vacuolization of a solid phase during intestinal development. The observation that a solid phase does not occur in the jejunum and ileum was evidence strongly against the notion that intestinal atresias distal to the duodenum was due to a failure or recanalization.

PATHOPHYSIOLOGY

Christian Barnard, under the leadership of Jannie Louw in South Africa, famously demonstrated that by interrupting the mesenteric vessels of fetal puppies, assorted forms of congenital jejunoileal atresia could be reproduced.[5] This direct experimental evidence supported clinical observations by surgeons that also suggested a vascular accident *in utero* as the cause of jejunoileal atresia. These clinical observations include frequent concomitant findings in patients with jejunoilieal atresias that would cause vascular accidents *in utero* such as volvulus, kinking, intussusception, meconium ileus, and gastroschisis. In addition, surgeons observed evidence of ischemic inflammation affecting the intestine at both ends of small bowel atresias when exploring the abdomens of neonates.[6] The likelihood of a relatively late *in utero* causative event was supported by the presence of lanugo hair, squamous cells, and bile pigments in the meconium of neonates with small intestinal atresias (distal to the complete obstruction).[7] This finding implies there had been a formed functioning gastrointestinal tract that had allowed passage of material from proximal to distal before a vascular accident occurred that obstructed the intestine. A third clinical observation used to support this theory is the relative rarity of associated malformations. Several conditions, already mentioned, that are associated with jejunoileal atresia such as midgut malrotation, gastroschisis, and cystic fibrosis (when associated with meconium ileus) are contributing causes of the *in utero* vascular accidents rather than associated malformations. These represent factors in a causative sequence rather than associated programmed missteps in formation of the organism. The lack of associated malformations, not linked in a causative sequence, is in opposition to the circumstances applying to duodenal atresia, where associated malformations are common. The duodenum does go through a solid phase. Duodenal atresia presumably has a different pathogenesis than jejunoileal atresia.

DIAGNOSIS

Although distended intestinal loops are expected on a late fetal ultrasound if the intestines have an atresia, these prenatal studies are not reliable in establishing the diagnosis of jejunoileal atresia. The additional presence of calcifications on the late fetal ultrasound suggest that meconium peritonitis (*in utero* perforation) may be associated with atresia of the small intestine.

Soon after birth, a patient born with intestinal atresia develops abdominal distention and vomiting that is often bilious. Unlike in the patient with duodenal obstruction, multiple loops of intestine may be evident on examination and they do not decompress with gastric suction. Meconium may be pale but the presence of pigment occurs; thus supporting the theory that obstruction is due to a vascular accident relatively late *in utero* after bile entered the GI tract. Plain abdominal X-rays show dilated intestinal loops, some of which may be markedly distended, with air fluid levels and with no air in the pelvis, consistent with complete intestinal obstruction distal to the duodenum. If the abdominal radiograph shows complete intestinal obstruction and also reveals intraabdominal calcification, the patient has meconium peritonitis with atresia. If pneumoperitoneum does not evolve in such a patient and if there are no clinical signs of inflammation, this implies that the perforation sealed *in utero*, leaving intestinal atresia.

Contrast enema is often advocated when the clinical picture and plain X-rays suggest jejunoileal atresia. The contrast enema is expected to show a microcolon from disuse. The role for contrast enema in small intestinal atresia was emphasized years ago when cases of anastomotic leaks occurred after repairs of jejeunoileal atresia because of missed associated colonic atresias. A colonic obstruction would be unearthed preoperatively if a contrast enema is performed.[8] If a contrast enema is not done, the operating surgeon is obligated to milk saline down the intestine to the peritoneal reflection looking for colonic obstruction. Usually the patient with jejunoileal atresia will not benefit from upper GI series with small bowel follow through. The rare jejunoileal stenosis might be more difficult to diagnose by plain X-ray and could benefit from the contrast study. Multiple small bowel atresias can only be discovered at the time of surgical exploration, so excluding other sites of obstruction is an obligatory part of the operative procedure.

PREOPERATIVE MANAGEMENT

Orogastric drainage with a wide bore tube is initiated promptly. A 10 French, soft, double lumen, sump type catheter serves this purpose well. Intravenous fluid is

administered and the patient is kept warm. Prophylactic antibiotics are given before the incision. While an immediate operation may not be required, delay can eventuate in perforation.

EVOLUTION OF THE OPERATIVE APPROACH

A patient with intestinal atresia is born with chronic obstruction. The intestine proximal to the atresia is dilated. Louw and others emphasized that a vascular accident responsible for the atresia had an ischemic effect on the nearby intestine. deLorimier *et al.* used a canine model to demonstrate ineffective peristalsis in chronically dilated intestine.[9] He measured sequential pressures and correlated the findings with the motion of contrast seen by the fluoroscope showing to-and-fro–type motion without effective peristalsis in chronically dilated intestine. These observations buttressed the evolution of the current operative management that usually includes resection of the very dilated short bulbous end just proximal to the atresia, selective use of narrowing enteroplasty followed by an end-to-back (also called end-to-oblique) anastomosis.

Enteroplasty can be carried out to reduce the diameter of the dilated intestine proximal to the atresia. Because short gut syndrome is a dangerous consequence in cases where there is a paucity of viable intestine, resection must be limited. Neither resection or enteroplasty is likely to be applicable distal to the initial atresia in cases of multiple atretic sites since the intestine at those more distal sites is not dilated.

Several types of narrowing enteroplasty have been described. The first among these involves a long wedge-shaped resection of the anti-mesenteric side of the dilated small intestine. This is aided by the GIA staling device with a catheter in the lumen to help obtain a proper size (Figure 1).[10] A second option is to plicate the antimesentery, avoiding any further loss of mucosal surface (Figure 2).[11] Kimura *et al.* proposed an elliptical excision limited to the seromuscular layers with sutured approximation of the cut edges, avoiding entry into the lumen and preserving mucosal surface.[12] While it is helpful to have these techniques in our surgical armamentarium, it has yet to be proven if they should be utilized routinely. Some advocate it while others employ enteroplasties selectively as when short gut syndrome is expected.[2]

Despite resection of the extremely bulbous dilated piece, a significant size discrepancy presents a technical challenge to the surgeon and a functional challenge to the patient. A carefully sewn end-to-back, also called end-to-oblique, anastomosis has become standard. The wider proximal end is divided exactly perpendicular to the long axis to minimize the diameter. The narrower distal side

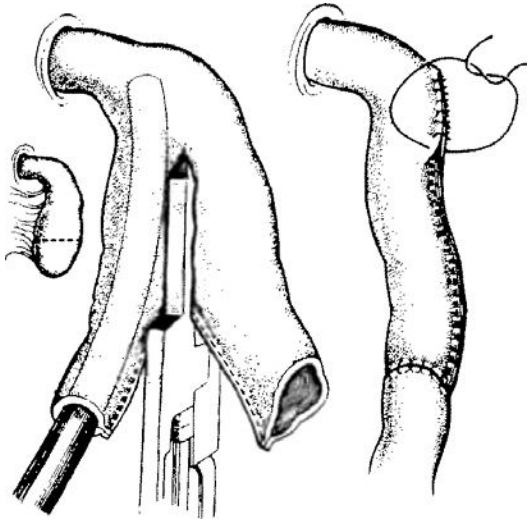


Figure 1. Tapering enteroplasty. Reprinted with permission from Grosfeld Jl, Ballantine VN, Shoemaker R (1979) Operative management of intestinal atresia and stenosis based on pathologic findings. *J Ped Surg* **14**: 368–375.

is cut at an angle to widen its diameter. This is angled acutely at the mesenteric side to avoid an ischemic tip on the antimesentery. An anti-mesenteric Cheatle incision, cut a short distance longitudinally, further reduces the size discrepancy and explains why the anastomosis is called end-to-back or end-to-oblique (Figure 3). If a tapering enteroplasty is done excising a wedge on the antimesenteric side of the dilated proximal end, special attention needs to be directed to the sutures near the staple line of the enteroplasty. An interrupted Connell type U stitch can be helpful at that site where the anastomosis meets the end of the staple line from the enteroplasty.

There is still an occasional role for a staged repair, initially diverting with an enterostomy and a mucus fistula. This may apply to a patient with a perforation and peritonitis who is not stable or to a child with an atresia complicating gastroschisis. In the latter case, the atresia is often left alone and repaired in a delayed fashion after 6 weeks or so, well after the abdominal defect has been closed and after the inflammation has resolved.

After repairing small bowel atresia, a prolonged period of intestinal dysfunction is possible, leaving the patient dependent on intravenous nutrition until it improves. The dysfunctional intestine not only represents the chronically dilated bowel proximal to the atresia but may include the intestine distal to it.[13] In

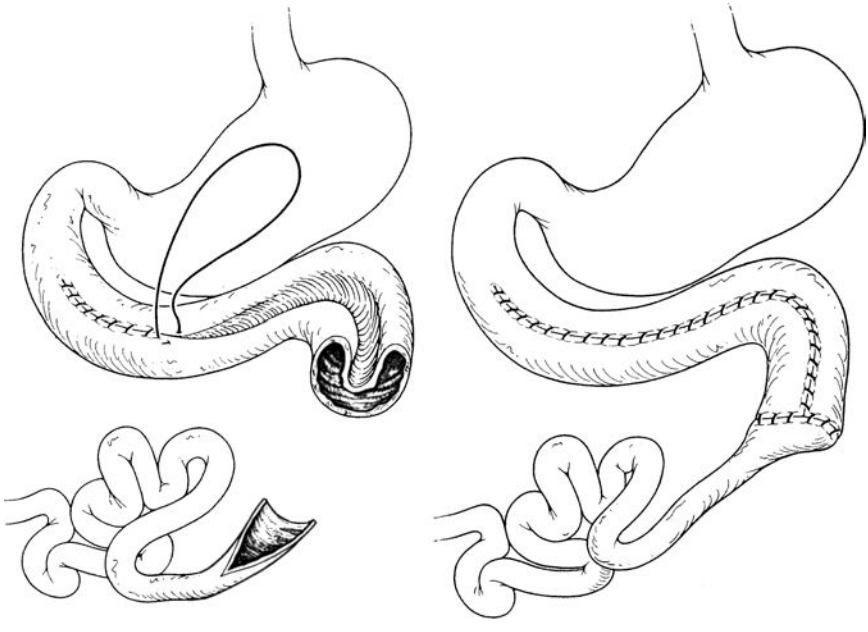


Figure 2. Tapering enteroplasty with imbrication without resection. Reprinted with permission from Raffensperger JG. (1990) Jejunoileal atresia and stenosis. JG Raffensperger (ed.), *Swenson's Pediatric Surgery*. 5th edition, pp. 523–531, Appleton & Lange, Norwalk.

addition, evidence of very late dysfunction can occur with proximal dilated intestine appearing decades later and causing blind loop-type physiology with bacteria overgrowth and symptoms of pain, vomiting, diarrhea and even anemia. At exploration, these older patients have large dilated intestines proximal to the anastomosis with inflamed mucosa but with a patent anastomosis. This has required resection of the hugely dilated dysfunctional intestine.[14] It is attributed to dysmotility.

TYPES OF JEJUNOILEAL ATRESIA

The various types of small bowel atresia and stenosis have been subject to multiple classifications. The modification provided by Grosfeld is the standard (Figure 4). When the serosa is in continuity without a mesenteric defect, the atresia is Type I. Type II has a gap in the serosal surface. Type III includes a gap in the mesentery. Type IV is multiple atresias ("string of sausages"). Type IIIB, called apple

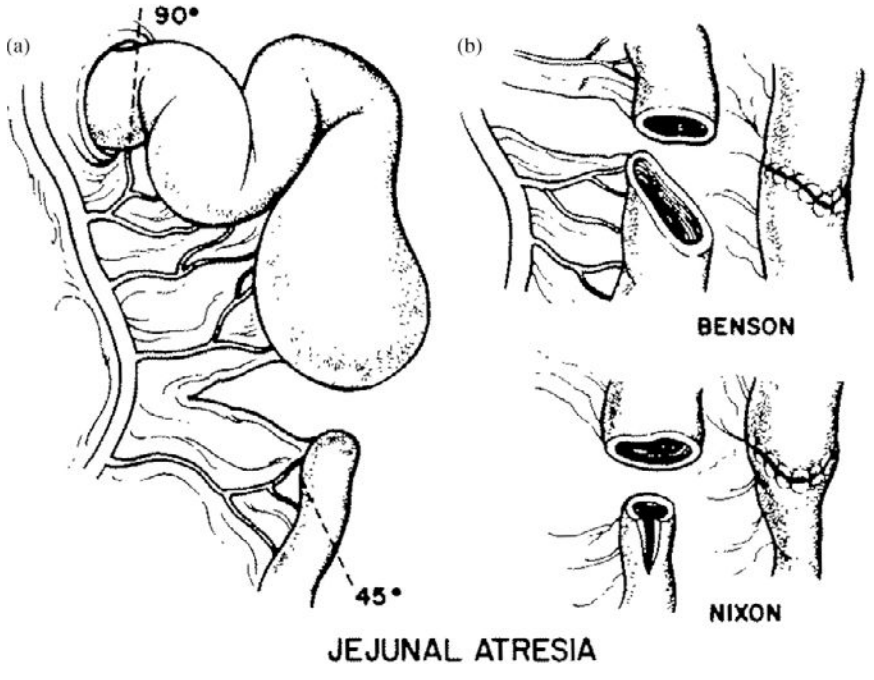


Figure 3. An anastomosis after cutting the dilated proximal end at right angles and after resecting the short very bulbous tip and angling the distal end acutely at the mesenteric side. Antimesenteric incision helps with the size discrepancy. Reprinted with permission from Grosfeld Jl, Ballantine VN, Shoemaker R. (1979) Operative management of intestinal atresia and stenosis based on pathologic findings. *J Ped Surg* **14**: 368–375.

peel or Christmas tree deformity, is a striking and frightening intestinal malformation (Figures 5 and 6). The atresia occurs proximally in the jejunum. The plain abdominal X-ray shows a dilated duodenum and a huge dilated loop of proximal jejunum with no air distally. The intestine distal to the atresia is of very small caliber without any fixation of its mesentery. Type IIIB is understood to arise from an *in utero* obstruction of the superior mesenteric artery. The intestine spirals around its blood supply that is retrograde from the ileocolic pedicle by way of the marginal artery and the inferior mesenteric. Surprisingly, these patients can do well although short gut syndrome occurs disproportionately in these patients compared to those with simpler forms of intestinal atresia.

Multiple atresias provide a large challenge. These patients may be at increased risk for short gut syndrome. Both apple peel deformities and multiple intestinal atresias have been seen in familial forms.[15,16]

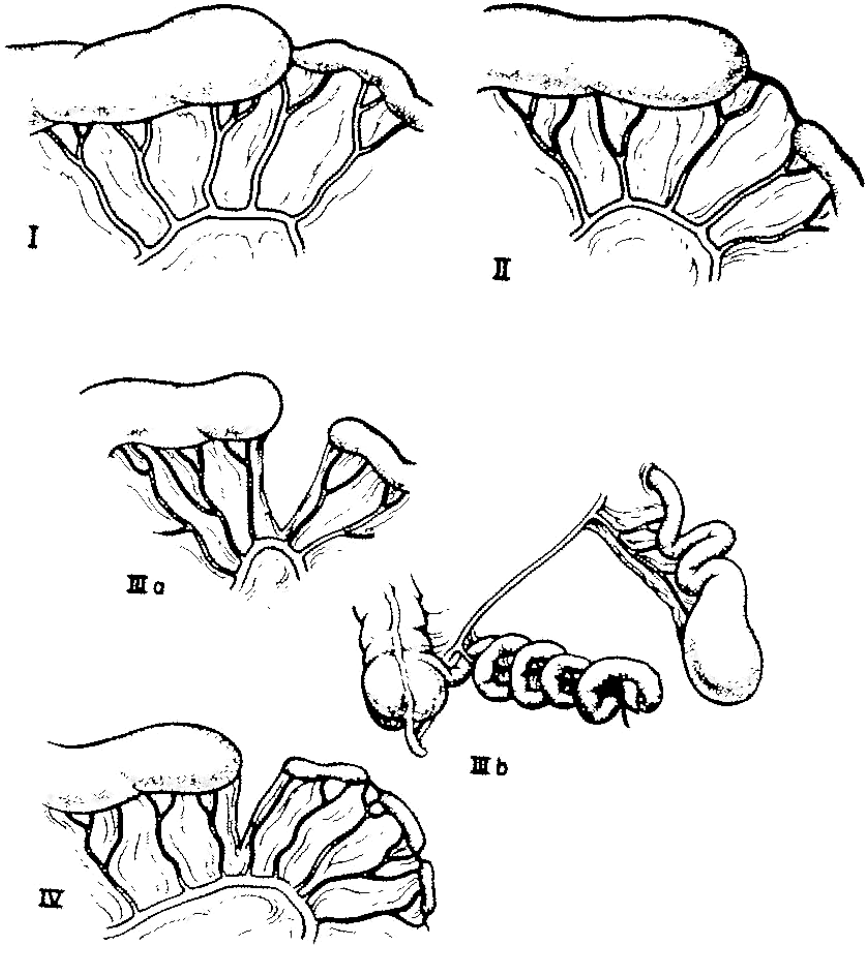


Figure 4. Classification of jejunoileal atresia. Reprinted with permission from Grosfeld Jl, Ballantine VN, Shoemaker R. (1979) Operative management of intestinal atresia and stenosis based on pathologic findings. *J Ped Surg* **14**: 368–375.

Jejunoileal stenosis, representing a web or membrane, causing partial obstruction of the small intestine, is quite rare. It occurred in 3 of 52 cases in one series.[17] Some have called such rare jejunoileal membranes or webs type 0 in their classification schemes.

Cystic fibrosis has been found in about 10% of children with jejunoileal atresia. This fact demands that these patients have a sweat test performed when they are large enough to produce adequate sweat for quantifying chloride



Figure 5. Type IIIb jejunal atresia.

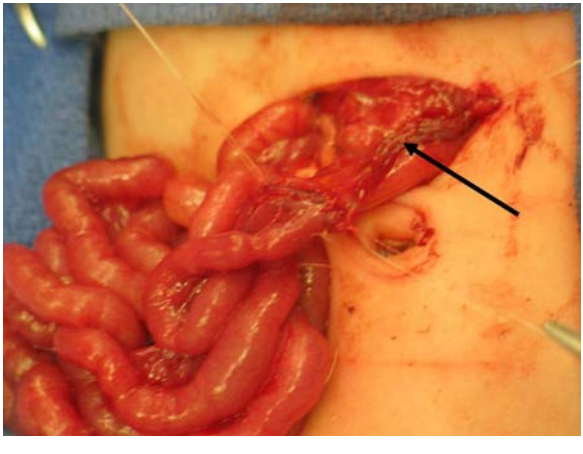


Figure 6. Type IIIb after anastomosis with tapering enteroplasty (arrow shows staple line from narrowing enteroplasty).

concentration. The association with cystic fibrosis may be largely because of meconium ileus as an underlying step in the sequence leading to the atresia but that is not clear from the literature, so presently all children with jejunoileal atresias deformities warrant testing for cystic fibrosis.[2]

COLONIC ATRESIA

Atresias of the duodenum, jejunum, and ileum are much more common than of the colon. Colonic atresia has been discovered occasionally in patients with small intestinal atresia. As mentioned, this association is one reason why some surgeons have advocated contrast enema when planning operations on patients with jejunoileal atresia. Colonic ateresia[8,18] does occur as an isolated malformation. This is diagnosed by contrast enema. It is managed either with colostomy and a subsequent repair or with primary colonic anastomosis in the neonate. That choice requires judgment by the surgeon and should be individualized based on the patient's clinical condition and the operative findings.

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CHAPTER 5

HIRSCHSPRUNG'S DISEASE

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INTRODUCTION

Hirschsprung's disease is a congenital condition of the distal gastrointestinal tract in which the affected segment acts as a functional obstruction due to the absence of ganglion cells and a failure of smooth muscle to relax. Affected children usually fail to pass meconium in the first 24 hours of life and develop distension. A contrast enema may suggest the diagnosis, which is confirmed with rectal biopsy. Definitive treatment depends on the child's condition, comorbidities, and the length of the segment lacking ganglion cells. Treatment options range from primary resection with pull-through reconstruction to diverting ostomy. Hirschsprung's disease is associated with a condition called enterocolitis, which results in distension and potentially life-threatening systemic illness, and can occur either before or after surgical correction. This chapter will provide a review of Hirschsprung's disease and then approach the problem in the same sequence that you would use in treating a patient with the disease.

History

The first widely accepted description of Hirschsprung's disease was in 1886 by the Danish pediatrician Dr. Harald Hirschsprung to the Pediatric Congress in Berlin.[1]

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He described two infants who died from recurrent bouts of enterocolitis with marked dilatation and hypertrophy of the colon but a normal appearing rectum seen at autopsy.[2] However, the disease may have been identified as early as 1691 by Frederick Ruysch in his work Observationum Anatomici-Chirurgicarum Centuria in which he described an autopsy on a 5-year-old girl in which "I could see (to my amazement) hardly any abdominal viscus except that part of the colon where the rectum begins. The other viscera were hidden under an enormous extension of that part".[3]

Following Hirschsprung's description and well into the 20th century, the disease's pathogenesis remained a mystery. Multiple theories were entertained but most were focused on the proximal dilated bowel as the site of the primary abnormality.[2,4] Tittel first observed aganglionosis of the distal colon in 1901,[4] but did not appreciate the significance of this finding. Some believed the absence of ganglion cells was a reaction to the disease, not the primary problem. It took an additional 40 years and the works of Robertson and Kernohan, Tiffen, Zeulzer and Wilson before the neurogenic basis of the disease started to be appreciated.[5,6] Ehrenpreis's doctoral thesis in 1946 concluded that the colon became secondarily dilated due to distal malfunction.[7]

The first successful reconstructive surgery for Hirschsprung's disease was performed by Treves in 1897 on a 6-year-old girl in which the rectum was removed and a new anus was constructed using descending colon.[2,8,9] Despite this isolated report, the major breakthrough came in 1947 when Swenson and Bill defined the pathophysiology as being caused by a functional obstruction from the distal most part of the gastrointestinal tract. They described a technique for resection of the aganglionated rectum[10,11] and creation of a neorectum using colon proximal to the obstructing segment.

Pathophysiology

The pathophysiology encountered in Hirschsprung's disease stems from a disorder of innervation caused by the absence of ganglion cells in the distal bowel wall. The enteric nervous system (ENS) controls the different physiologic features of the bowel such as absorption, blood flow, and motility and can allow adequate intestinal function without extrinsic control.[12] The extrinsic neural control of the alimentary tract serves to send excitatory or inhibitory signals to the gut.

In the normally innervated bowel, preganglionic cholinergic parasympathetic excitatory nerve fibers result in the contraction of smooth muscle. The postganglionic adrenergic sympathetic fibers are primarily inhibitory and

utilize norepinephrine as a neurotransmitter. In addition, the bowel contains nonadrenergic, noncholinergic (NANC) intrinsic nerve fibers which utilize nitric oxide (NO) and include both inhibitory and excitatory nerve fibers. The distal rectum has a motility reflex first described by Gowers[13] in which distention of the rectum causes both a proximal contraction above the bolus as well as relaxation of the internal anal sphincter. This reflex is mediated by the NANC nitrergic nerve fibers and, according to recent evidence, by the interstitial cells of Cajal.[14] The rectal relaxation reflex is absent in Hirschsprung's disease.

The precise mechanisms by which the aganglionated bowel in Hirschsprung's disease becomes spastically contracted are incompletely understood. It is clear that the excitatory parasympathetic cholinergic nerve fibers become characteristically hypertrophied. The ENS normally contains muscarinic acetylcholine receptors on the smooth muscle, particularly the m2 and m3 subclass. Recent data has shown a total lack of these receptors in the aganglionated bowel and, instead, nicotinic receptors that are normally found in the CNS and autonomic ganglia. When the aganglionated segment and transition zones were compared to normal bowel in the same patients as well as normal controls, the researchers found significantly greater numbers of aberrant nicotinic receptors in the aganglionated bowel and transition zone with normal expression in the ganglionated bowel.[15] The authors hypothesized that this aberrant presence of nicotinic receptors and absence of muscarinic receptors induces an "imbalance in conduction" that may be responsible for the tonic contraction of the distal bowel. In addition, there has been evidence for decades of increased adrenergic innervation to the aganglionated bowel,[16] and it has been speculated that the abnormal preganglionic parasympathetic and postganglionic sympathetic fibers contribute to this imbalance and lead to increased contraction of the muscle in the bowel wall.

Furthermore, the nitrergic neurons and nitric oxide synthase (NOS) are absent in the aganglionated segment,[17] also leading to increased smooth muscle tone. *In vitro* studies showed that smooth muscle from aganglionated bowel did not increase in contractility after nitrergic blockade and failed to relax after the administration of NO. The authors suggested that an intact nitrergic neural plexus is required for the bowel to adequately relax.[18] The same effect has been found regarding the internal anal sphincter.[19] The authors demonstrated that the internal anal sphincter was strongly innervated by cholinergic fibers and that the NANC NO-mediated fibers had no effect.

The overall result of these factors is an increased smooth muscle tone of the circular muscle of the bowel wall in the aganglionated segment. The result is an overall contraction and dysmotility of this segment causing functional obstruction in Hirschsprung's disease.

Embryogenesis

In the embryo, the enteric ganglion precursors derive from the neural crest, migrate from the upper alimentary tract and proceed in a craniocaudal direction. The neural precursors reach the esophagus by the 4th week, the midgut by the 7th week, and have completed their migration by the 12th week. The migration is preceded by certain proteins including fibronectin and hyaluronic acid providing a pathway for the neural crest cells with laminin and collagen type IV guiding the cells to their final destination. The migration occurs first into Auerbach's plexus (myenteric) and subsequently into the Meissner's (submucosal) plexus.[20]

Hirschsprung's disease is believed to result from the failure of neural crest cells to migrate craniocaudally and form the enteric nervous system, leaving a variable-length segment of distal aganglionosis. The cause for this failure is only partially understood. Neural precursors, after migrating along the developing gut, encounter a "hostile environment" and are unable to migrate through the intestinal wall to their final destination where they normally implant into the enteric plexuses in the bowel wall. Overexpressed levels of fibronectin and tenascin have been found within the extracellular matrix of the aganglionated portions of bowel in patients with Hirschsprung's disease with normal levels found in ganglionated bowel in the same patients.[21] High concentrations of fibronectin have an adverse effect on the motility of neural crest cells,[22] possibly secondary to varying integrin affinity of the migrating neural crest cells in response to the levels of fibronectin.[23]

A recent study has brought this migration theory into question. In a murine Hirschsprung's disease model, neural crest cells failed to form the enteric nervous system (ENS) due to nonapoptotic cell death rather than failed migration.[24] When this cell death was prevented, the mice developed a normal ENS.[25] These results draw the failed migration theory into question, although they do not propose an explanation for the variation in where the aganglionated segment starts.

WHEN TO SUSPECT HIRSCHSPRUNG'S DISEASE

The cardinal presenting symptom of Hirschsprung's disease in the neonate is delayed passage of meconium. Ninety percent of patients become symptomatic in the neonatal period.[26] That has become standard teaching, although some series, often of small numbers, suggest a lower percentage. Normal

neonates born after a full-term gestation are expected to pass meconium on the first day of life; and if they fail to do so, Hirschsprung's becomes a consideration. This does not apply to patients born after premature gestations who are not expected to have fully developed coordinated motility. Common initial symptoms are abdominal distention (76–100%), vomiting (69–72%) which can be bilious, as well as the delayed passage of meconium.[27,28] Hirschsprung's is a constipating disease, often characterized by poor feeding or failure to thrive. In some neonates and infants, diarrhea can be the initial complaint, which is a manifestation of enterocolitis.[14] In patients with any of these symptoms, the diagnosis should be entertained, especially when these symptoms develop in the first weeks of life.

On physical examination, infants may appear well. They will often have abdominal distention with a soft nontender abdomen. Rectal examination may be followed by passage of meconium or a vigorous release of gas. Infants who are distended and systemically ill, may be suffering from enterocolitis.

Making the Diagnosis

Rectal biopsy is the gold standard in diagnosing Hirschsprung's disease, but is rarely the first test obtained. Most patients will have an initial abdominal X-ray, which, when suggestive, is followed with a contrast enema. There are centers where anorectal manometry figures prominently prior to biopsy, but this is by no means universal. Each diagnostic modality will be reviewed for what information the study can provide you.

X-rays

Patients with feeding intolerance, obstipation, distension, and vomiting, usually have an abdominal X-ray as their first test. An X-ray film is neither sensitive enough to rule out Hirschsprung's nor specific enough to rule it in, but it can differentiate between proximal and distal intestinal obstructions. A film which shows multiple dilated loops of bowel, and a paucity or absence of rectal gas, would suggest Hirschsprung's disease. Differentiating on radiograph between dilated small bowel and dilated colon is unreliable in the neonate. If a film demonstrates multiple distended loops of gas-filled intestine, it suggests distal bowel obstruction. Hirschsprung's disease remains in the differential diagnosis, and the patient needs further testing.

Contrast enema

A water-soluble contrast enema is usually the next diagnostic step in the neonatal period. Traditionally, the test was performed with barium, which allowed for delayed films to show failure to pass the barium. Delayed films with water-soluble contrast are less useful because the contrast is both washed out and absorbed. Barium has fallen out of favor because it is more difficult to clean out following the test. Most centers have switched to water-soluble contrast which is equally sensitive in delineating a transition zone.

Classically, the contrast enema will show a narrow distal segment with dilated colon proximal to it. The segment of colon where the diameter changes is the transition zone and is the key diagnostic feature of the study (Figure 1).[29] The recto-sigmoid index has been used to augment the diagnostic value of the contrast enema since a clearly defined transition zone is less likely in the neonate than in the patient with a later presentation. It is calculated by dividing the measurements of the widest diameter of the rectum by the widest diameter of the sigmoid colon. A ratio less than one is consistent with Hirschsprung's disease, however this finding is not sufficient to make the diagnosis.[30]

Contrast enemas can be useful to suggest the diagnosis, or to get a rough idea of where the transition zone may be, but the test is not sensitive enough nor specific enough to establish the diagnosis of Hirschsprung's disease.[30,31] If the child has signs of Hirschsprung's-associated enterocolitis, a contrast enema is contraindicated due to the risk of perforation.

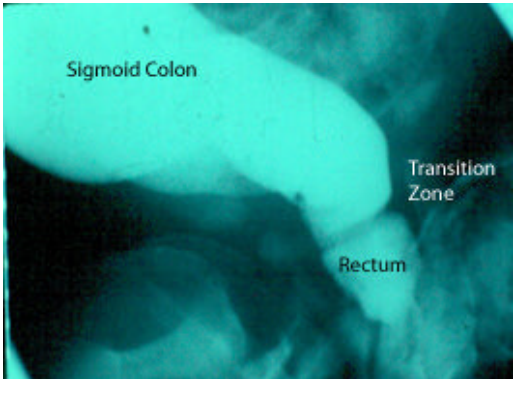


Figure 1. Lateral view of a contrast enema demonstrating a transition zone at the junction of sigmoid colon and rectum. Note the dilated colon proximal to the transition zone.

Manometry

Anorectal manometry can be used in the diagnosis of Hirschsprung's disease. This technique is based on the absence in Hirschsprung's disease of the recto-anal inhibitory reflex in which distention of the rectum stimulates inhibitory neurons (from the myenteric plexus) that cause relaxation of the internal anal sphincter. The failure of the internal anal sphincter to relax in response to distention of the rectum by a pressurized balloon catheter is characteristic of Hirschsprung's disease. Increased anal sphincter pressure is another positive finding in the disease.

Manometry does not require anesthesia. Manometry is limited by lack of standardization, technical difficulties, and artifacts created by crying or agitation, all of which can cause false positive and false negative results. Despite this, a recent meta-analysis found that in experienced hands, manometry can provide comparable accuracy to suction rectal biopsy.[32]

Biopsy — The gold standard

Hirschsprung's disease is confirmed and established via histology with a biopsy sample obtained via suction rectal biopsy or full thickness rectal biopsy. The absence of ganglion cells in the submucosal and myenteric plexuses, increased staining for acetylcholinesterase, hypertrophic nerve fibers, and a paucity of calretinin staining are consistent with Hirschsprung's disease.[33] With either biopsy technique, care must be taken not to sample the rectum too proximally as this causes false negative results. Likewise, a biopsy too distal in the anal canal, suggested by the presence of squamous epithelium, yields false positive findings because ganglion cells are normally absent in the distal most 1 or 2 cm.

Suction rectal biopsy

Suction rectal biopsy is the most common method used to confirm the diagnosis, and is safe and effective. It can be performed at the bedside without the need for anesthesia or formal bowel preparation, although preprocedure irrigation is often helpful. A specialized suction biopsy tool is required (Figure 2). Two specimens are usually obtained, commonly at 2–3 cm, and 4–5 cm from the anal verge.

The biopsy tool is inserted into the anus and the opening near the tip is directed posteriorly and positioned at the desired site. The operator's assistant applies the suction to the device with an attached syringe which pulls the rectal lining into the hole in the instrument, and the operator pulls the device trigger, cutting the small specimen that has been drawn inside the device. Suction

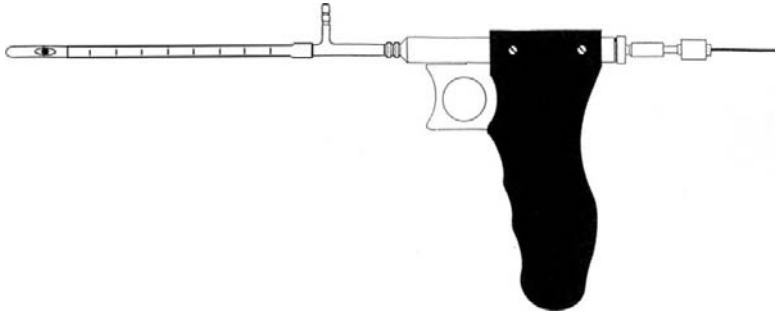


Figure 2. Suction rectal biopsy instrument. (Courtesy of Trewavis Surgical Instruments, Victoria, Australia.)

is released and the device removed. The small specimen is then retrieved and labeled in marked containers, so there is no confusion about the biopsy location. Biopsies are prepared by the pediatric pathologist who ensures that all the necessary studies can be performed. Complications include bleeding, perforation, and inadequate specimen.[34] If the specimen does not contain adequate submucosa for examination, it is inadequate for diagnosis. Specimens are optimally taken from the posterior wall to decrease the chance of perforation into the peritoneal cavity. Prophylactic antibiotics are not usually given for suction biopsy.

Full thickness rectal biopsy

The full thickness biopsy was once the primary means for diagnosis, but is now usually reserved for failure to obtain adequate suction rectal biopsy specimens, or for older children who require anesthesia for biopsy and in whom the intestinal wall may be too thick to yield adequate samples by the suction technique. If a child is undergoing general anesthesia for a biopsy, a full thickness biopsy increases the likelihood of obtaining a reliable specimen.[28]

No formal bowel prep is required, although on-table irrigation can be useful. The patient is positioned in the lithotomy position and a single dose of preoperative antibiotics is usually given. Retraction is obtained with a rectal speculum, but the Lone Star Retractor System (Cooper Surgical, Trumbull, CT) can be used as well. A silk suture can be placed in the intended site of biopsy, usually approximately 3cm from the dentate line in the posterior rectal wall. By placing traction on this suture, an absorbable suture can be placed, tied, and left in place with the needle still on, just above the biopsy site. The biopsy may then be taken by cutting around the silk suture, removing a full thickness segment of rectal wall

approximately 1 cm in diameter. The previously placed absorbable suture is then used to close the defect in a running fashion and tied to itself. A frozen section is useful to confirm biopsy adequacy, but diagnosis awaits permanent section. The full thickness rectal biopsy should not interfere with future definitive operations for Hirschsprung's disease.[35] Complications include bleeding, infection, and pelvic sepsis, but these are rare.

Interpreting the Biopsy

The single most important pathological finding in Hirschsprung's disease is the absence of ganglion cells in the affected segment. In addition to aganglionosis, pathologists have found other features that can be useful in making the diagnosis.

Aganglionosis

In the affected segment, ganglion cells are absent within the myenteric and submucosal plexuses. The presence of muscularis, where myenteric plexuses reside, is not expected after suction biopsy.

Nerve hypertrophy

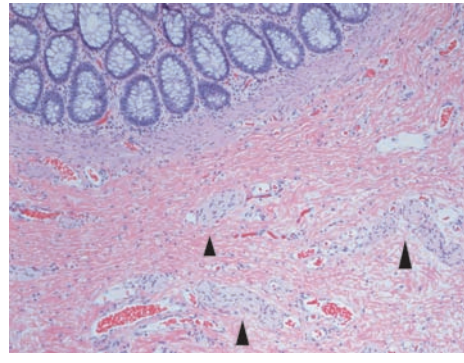
Hypertrophied nerve fibers ($\geq 40\,\mu m$) are usually, but not always, seen in the aganglionated bowel. This finding is seen with routine paraffin-embedded hematoxylin-eosin stain (Figure 3a).

Increased acetylcholinesterase staining

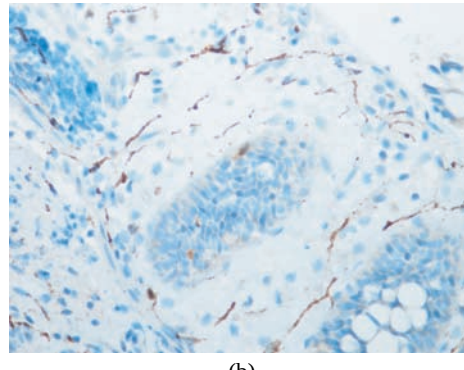
Histochemical staining for acetylcholinesterase (AChE) in specimens from aganglionated bowel reveals increased AChE-positive nerve fibers in the muscularis mucosae, although this technique requires a separate specimen for frozen section rather than the paraffin-embedded sections.[36]

Paucity of calretinin-staining fibers

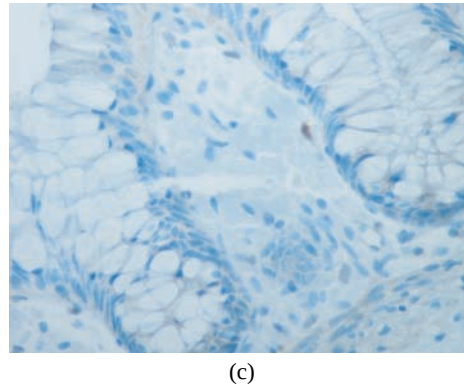
A newer technique gaining support is immunohistochemistry (IHC) targeting the calcium-binding protein calretinin.[33] In the aganglionated bowel, calretinin expression is completely absent, and IHC should not identify any binding (Figures 3b and 3c). In a small comparative study of calretinin IHC vs. AChE



(a)



(b)



(c)

Figure 3. (a) Hematoxylin-eosin stain of aganglionated bowel with hypertrophic nerve fibers (arrowheads) and an absence of ganglion cells. (b) Immunohistochemistry staining of calretinin in normal rectum. This is a normal distribution of calretinin fibers. (c) In comparison to (b), this immunohistochemistry image from an aganglionated segment of rectum shows a paucity of staining for calretinin, consistent with Hirschsprung's disease. (Special thanks to Dr. Morris Edelman for providing the micropathologic images.)

histochemistry, calretinin staining was shown to be an equivalent, if not superior, ancillary test in the pathologic diagnosis of Hirschsprung's disease (Ibid). IHC uses paraffin-embedded sectioning and does not require a separate specimen.

COUNSELING PARENTS

Incidence

Hirschsprung's disease occurs in approximately 1 in 5000 live births.[37,38] The male-to-female ratio is roughly 4:1 in short-segment (most common) disease, but in long-segment disease, that ratio may approach 1:1 in some reviews.[39] The incidence of Hirschsprung's disease increases among families with affected children. If a patient has the disease, there is a 4–6% chance of a subsequent child from the same parents having it. Siblings of a child with long-segment disease have a greater risk of approximately 17–33%, with the risk at the higher end of the range when the affected sibling is female and subsequent child male.[40]

When a parent has Hirschsprung's disease, the risk that a child is affected is roughly 4%, 200 times the expected risk.[41] The disease is much more likely to be inherited in long segment disease, with the length of aganglionosis felt to be one of the most consistent predictors of transmissibility.[42]

Genetics

Parents may wish to know why their child was born with Hirschsprung's disease. There is no suspected teratogen which results in the disease so parents can be reassured that they did nothing to cause their baby's condition. No single gene appears to be responsible for the development of the Hirschsprung's phenotype. A number of genes have been implicated including RET, EDNRB, GDNF, NTN, SOX10, ZFHX1B, and PHOX2B. The major susceptibility gene in Hirschsprung's disease is the RET proto-oncogene with sequence mutations found in roughly 50% of familial cases and 15% of sporadic cases.[41] RET is located on chromosome 10q11.2 and encodes a tyrosine kinase expressed in tissues of neural crest origin that is thought responsible for migration and differentiation of neural crest-derived cells.

Hirschsprung's disease is seen as an isolated phenotype in roughly 70% of patients. The incidence of patients with Hirschsprung's disease who have other congenital anomalies varies from 5–32% depending on the series with a mean of 21.1%,[43] and 12% of patients have known genetic diseases associated with Hirschsprung's disease.[44] There are numerous other syndromes and associated

abnormalities that can be seen with Hirschsprung's disease and are usually associated with mutations in particular genes. By far, the most common chromosomal abnormality is Trisomy 21 (Down syndrome). Approximately 5% of children with Hirschsprung's disease have Trisomy 21. Patients with Down syndrome have a 40-fold higher risk of having Hirschsprung's disease.[41] While the basis for this association is unclear, there is recent data showing that a variant allele on chromosome 21 may interact with RET and that the increased gene dosage in Down syndrome may cause the association.[45] Since children with Down syndrome are often constipated, clinicians may be slower in suspecting Hirschsprung's in these patients resulting in late diagnoses.

The various syndromes that have been associated with Hirschsprung's disease are too numerous to be described here, but the most common are the neurocristopathies, including multiple endocrine neoplasia syndromes and Waardenburg syndrome. The long-term prognosis for patients with these syndromes depends heavily on the associated anomalies.

Pre-Operative Rectal Irrigations

Rectal irrigations are a technique used to wash out gas and stool from the distal colon, as a treatment for enterocolitis. Some centers (the authors' included) initiate rectal irrigations 2–3 times daily in all patients considered high-risk for Hirschsprung's disease, and either stop them once the disease has been ruled out, or continue them up to the operation as a means to prevent enterocolitis. In a neonate who is undergoing irrigations and who has not been fed, bowel preparation for surgery is unnecessary.

Irrigations are not enemas. An enema is meant to clean out stool and is administered as one large bolus of fluid, which is retained for a period of time, and then expelled all at once. Irrigations are different, and are meant to wash out gas and help wash out the distal colonic flora so that pathogens causing enterocolitis do not accumulate.

The procedure is relatively simple. Normal saline is required and should be warmed slightly so that it is tepid, but not over body temperature. The child is placed supine on an absorbent pad with an assistant gently holding the legs up. A well lubricated, large bore (18–24 French), soft catheter, such as a Foley, is inserted a few centimeters into the rectum. Saline is drawn into a 60-cc catheter-tip syringe and is injected gently in 10–20 mL aliquots; and then the syringe is removed and the saline allowed to drip out. If the return is minimal, the syringe is reconnected and gently aspirated to withdraw the saline. The tube should be advanced a few centimeters and the procedure repeated, until resistance is encountered and the



(a)



(b)

Figure 4. (a) An infant with a distended abdomen who had a suspicious barium enema and was irrigated prior to biopsy that confirmed Hirschsprung's disease. (b) The scaphoid abdomen depicted after irrigation that decompressed the colon.

tube cannot go further. If an area is encountered where gas shoots out when the syringe is disconnected, that area should be washed several times before moving on again. When the returns become clear, the tube is slowly withdrawn and lower levels of the bowel are washed again, until the tube is completely withdrawn (Figures 4a and 4b).

THERAPEUTIC OPERATIVE PROCEDURES

Historically, Hirschsprung's disease was treated in a three-, and subsequently, a two-stage approach, with the first operation being a colostomy, diverting the fecal stream. This could be done proximally in the colon as the first of three stages or as a so-called leveling colostomy at the most distal point in the colon where normal ganglion cells are found. The second stage after a leveling colostomy is the resection of the aganglionated segment with takedown and pull-through of the ganglionated stoma and coloanal anastomosis. In 1980, Henry So *et al.* advocated correction in one-stage without colostomy.[46] The modern approach for patients identified early with normal caliber colon and no evidence of enterocolitis is often a one-stage transanal pull-through with either laparoscopic assistance or laparotomy for longer segment disease.

If a child has significant comorbidities, a delay in diagnosis with significant distension, or episodes of enterocolitis, a diverting stoma remains an excellent initial operation. For term or near-term patients diagnosed in the newborn period, no significant comorbidities, and minimal colonic distension, a primary pull-through without ostomy can be safely performed using one of the techniques to be described.

When a pull-through is performed, a critical component of the operation, regardless of technique chosen, is determining the precise level where transition zone ends and normal ganglionated bowel begins. The transition zone from ganglionated to aganglionated bowel may be irregular and ganglion cells may extend 2–3 cm distally along the antimesenteric border, while being absent on the mesenteric side.[47] For this reason, the authors routinely confirm with intraoperative frozen sections that ganglion cells are present in a normal distribution from the entire bowel circumference at the level where the anastomosis will be performed. This is done to avoid being fooled by sampling error and performing the anastomosis in transition zone bowel, which can result in long-term emptying dysfunction.

Leveling Colostomy

The purpose of a leveling colostomy is to alleviate the patient's functional obstruction in the most efficient way possible for patients who would do poorly with primary pull-through. It remains a sensible initial step in patients with significant comorbidities who would not tolerate a larger procedure, those with a late diagnosis and significant colonic dilation which may make colo-anal anastomosis technically risky due to size mismatch, and chronically dilated

colon, or in anyone with enterocolitis.[48] Ganglion cells must be confirmed at the site chosen for the stoma by frozen section before the child emerges from the anesthetic. If histopathology is not accurately checked, there is a significant risk of requiring a second operation to take down a nonfunctioning ostomy and create a new more proximal ostomy in normal ganglionated bowel. A leveling colostomy is always taken down at the time of the subsequent pull through procedure.

The first step in creating a leveling colostomy is locating the site proximal to the histological transition zone. This can be accomplished laparoscopically or by laparotomy, taking serial biopsies and obtaining frozen sections. If a transition zone was visualized on contrast enema, or is visible grossly, biopsies can be taken above and below to determine if it is indeed the transition zone (Figure 5). If no ganglion cells are encountered in the proximal biopsy, successive biopsies are taken every 5 cm until normal ganglion cells are encountered. This can be a time-consuming process so parents should be prepared for a potentially lengthy procedure. Biopsies are taken from the seromuscular layer, and the mucosa is not violated. If the mucosa is violated, the biopsy site should be repaired. If a biopsy shows ganglion cells but in sparse distribution, the biopsy was from transition zone bowel, and a more proximal biopsy is still needed.

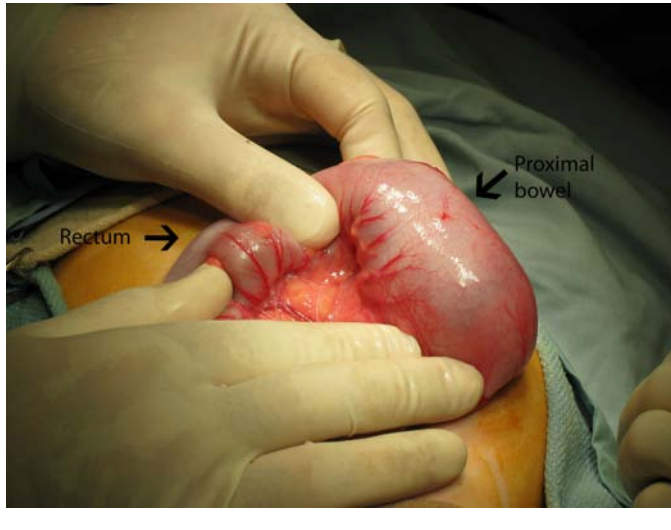


Figure 5. Operative appearance of the transition zone.

After locating the distal point where normal ganglion cells are encountered in normal distribution, an ostomy can be created there, either as a loop, or divided stomas. It is preferable to create a loop or divided stomas, as opposed to closing the distal bowel as a Hartman's pouch, so that the distal bowel can be irrigated in an antegrade fashion as needed. In creating the colostomy, it is important to suture the bowel circumference to the abdominal wall fascia to reduce the risk of parastomal hernia which can lead to evisceration in the early postoperative period. The stoma usually starts functioning within 24 hours and the patient can start feeding at that time.

Some children, even though they have a standard rectosigmoid transition zone, will benefit from an ileostomy. This applies to those with long-term constipation, a late diagnosis, and a megacolon. Fashioning an ileostomy may require irrigations of the diverted colon to prevent stasis and enterocolitis, but it can allow the colon to decompress and may be preferable to constructing a colostomy in a massively dilated colon.

Swenson Procedure

The Swenson procedure was a breakthrough in the management of Hirschsprung's disease as it represented a successful and definitive operative treatment. Originally described by Orvar Swenson and Bill in 1948,[10] it requires technically exacting dissection of the rectum to within 2 cm of the anodermal junction and may risk injury to adjacent genitourinary autonomic plexus. Because of this, the Duhamel and Soave procedures have been preferred by some surgeons, but the results of a properly performed Swenson procedure are as good.[49]

This operation was usually done after an initial colostomy had been fashioned. Preoperatively, the patient is admitted the day before and undergoes a formal bowel preparation. In the operating room, after induction of general anesthesia, the child receives a Foley catheter, a nasogastric tube, and a circumferential prep.

A generous paramedian or oblique incision is used to enter the peritoneum. As with the other definitive techniques, the aganglionated bowel above the peritoneal reflection is resected and the proximal bowel mobilized. The peritoneal reflection is then incised anteriorly. Using meticulous dissection, the surgeon dissects the full-thickness rectum circumferentially caudally down to within 2 cm of the anal verge. Blood vessels encountered in the dissection should be coagulated or ligated. The dissection must hug the serosa of the rectum. Judicious use of a bipolar cautery may limit injury to pelvic structures. This dissection is taken down to the perineum circumferentially.

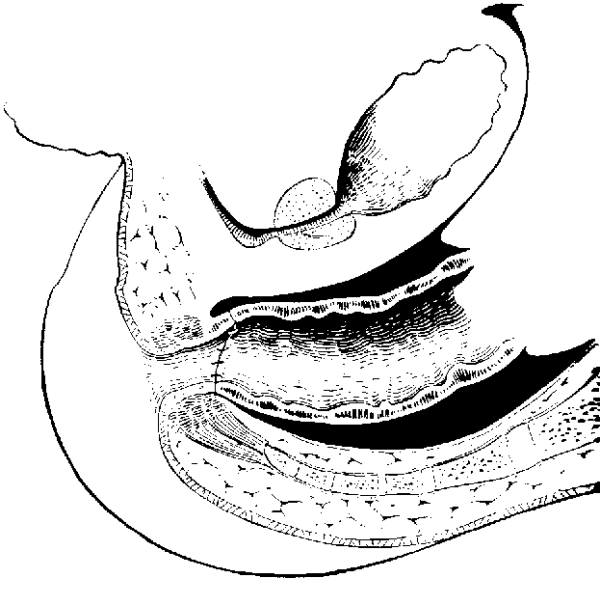


Figure 6. Completed Swenson procedure. The ganglionated bowel is anastomosed low in the pelvis, leaving only 1.5 cm of aganglionated rectum posteriorly and 2 cm anteriorly after resection of aganglionated colon and rectum. (Reprinted from *Rob & Smith's Operative Surgery,* 4th ed. with permission from the publisher.)

The full thickness rectum is then everted through the anus and opened 2 cm from the anodermal junction anteriorly. The proximal ganglionated colon that has been sufficiently mobilized is then pulled-through and an anastomosis is begun by sewing the anterior wall of the pulled-through ganglionated colon to the anterior wall of the aganglionated rectum. Then the circumferential incision through the distal rectum is completed posteriorly leaving 1.5-cm aganglionated rectum. The anastomosis is completed after the distal rectum has been excised. A single layer of interrupted 4–0 vicryl sutures is satisfactory. The anastomosis is allowed to return to the pelvis and the abdomen is closed. The result is a circumferential coloanal anastomosis with 2 cm of aganglionated bowel anterior and 1.5 cm posterior. The proximal side of the anastomosis is colon with normal ganglion cells (Figure 6).[50]

By everting the rectum, the Swenson technique allowed this "low" anastomosis to be effectuated at the perineum with ease. An argument made against this technique is the necessary meticulous extra rectal dissection deep in the pelvis. That is not a feature of the two standard options that evolved as alternative techniques, the Soave and the Duhamel procedures.

Soave Procedure (Endorectal Pull-Through)

The Soave procedure was first described in 1963[51,52] and was later modified by Boley[53] to include the primary anastomosis at the anus. Like the Duhamel procedure, the Soave procedure limits injury to the pelvic structures and avoids the deep pelvic dissection necessary for the Swenson procedure. The Soave procedure is usually performed at 6–12 months of age[4] after an initial colostomy has been made at the time of diagnosis. Serial rectal washouts and digital dilations are performed prior to the procedure.

As with the other techniques, the patient is placed supine and prepped circumferentially from the abdomen to the feet. A Foley catheter and a nasogastric tube are placed. The same abdominal incision can be made for the Swenson, Soave, and the Duhamel procedures. If the child did not previously undergo a leveling colostomy, the transition zone should be identified with frozen section. The proximal ganglionated bowel is mobilized.

An endorectal dissection of the distal rectum is begun by circumferentially removing surrounding fat and serosa from a 2-cm length of rectum starting 2 cm below the peritoneal reflection, incising the seromuscular layer, and, establishing a plane at the level of the submucosa. This endorectal dissection is carried distally to about 1–1.5 cm above the dentate line, depending on the age of the patient. A surgeon then places a clamp into the anus and grasps the end of the dissected submucosal/mucosal tube, which is then everted out over the perineum.

The anterior surface of the everted aganglionated rectal wall is incised above the dentate line and a clamp is inserted into the opening. The ganglionated bowel is then grasped by the clamp and pulled through with care taken not to twist the bowel in this process. The bowel is then anastomosed to a site about 1.5 cm above the dentate line, beginning with the anterior portion and working segmentally to the posterior while the everted tube is resected at the same time. The colon is allowed to return to the pelvis leaving the neorectum in a normal position. Attention is then returned to the abdominal cavity where the pulled-through colon is sutured to the native rectal muscular cuff to prevent prolapse. The abdominal incision is closed.

When the Soave procedure has been completed, ganglionated bowel has been joined circumferentially 1.5 cm above the dentate line. The ganglionated neorectum resides within a native rectal muscular sleeve devoid of its mucosa (Figure 7).[50]

Duhamel Procedure

The Duhamel procedure was first described in 1956 also as an alternative to the technically challenging pelvic dissection of the Swenson procedure.[54] Its putative

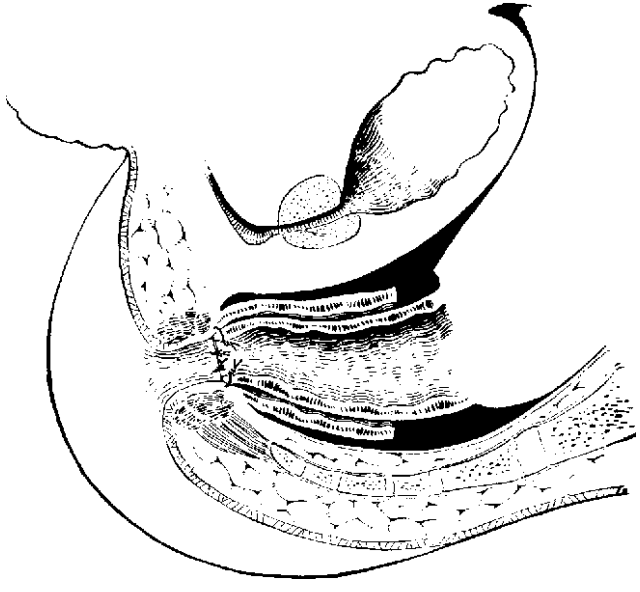


Figure 7. Completed Soave procedure. Normal bowel is pulled through an aganglionated native muscular cuff after mucosectomy of the distal rectum and an anastomosis is performed 1.5 cm above the dentate line. (Reprinted from *Rob & Smith's Operative Surgery,* 4th ed. with permission from the publisher.)

advantage is its technical ease and that there is little dissection anterior to the rectum avoiding injury to the autonomic plexus affecting the genitourinary system. Unlike the Soave, no mucosectomy is required.

Preoperatively, the patient often has had a leveling colostomy and should receive a formal bowel preparation in addition to rectal and colonic washouts to ensure that no residual stool is present at the time of operation. The operation itself is usually delayed several months after the initial colostomy to allow the patient to gain weight and for the dilated and hypertrophied colon to reduce to a normal caliber.

The patient is placed in the supine position, and a nasogastric tube and Foley are inserted; the patient should be prepped circumferentially. An oblique incision incorporating the colostomy can be used. The colon should be mobilized so that it reaches the level of the perineum. The ureters are protected and the peritoneal reflection between the bladder or uterus and rectum is incised. The rectum is then mobilized for about 4 cm below the reflection. A retrorectal space is created in the posterior midline so that an assistant's finger can be palpated when it has been inserted only 1–1.5 cm into the anus.

The aganglionated bowel is then transected at the peritoneal reflection and attention is turned to the patient's perineum. Using anal retractors for exposure, a full-thickness opening is made in the posterior midline of the distal rectum 1–1.5 cm proximal to the dentate line and extended laterally to either side. A clamp is placed through that opening in the posterior anorectum into the retrorectal space toward the abdominal field to assist the pull-through of ganglionated bowel. The proximal bowel is pulled through the rectal incision while the surgeon working in the abdominal field ensures the bowel does not rotate. The staple line from the pulled-through ganglionated colon is excised and an anastomosis is created. The anterior portion of the pulled-through bowel is sewn to the posterior native rectum and the posterior portion of pulled-through bowel to the distal native rectum. A GIA stapler is then inserted and fired to eliminate the common wall between the pulled-through colon and the native aganglionated rectum. Finally, a stapler is then fired across the proximal native aganglionated rectum to eliminate a proximal aganglionated spur that can lead to large fecalomas. The anastomosis is inspected and hemostasis is checked prior to closure.

When the Duhamel procedure has been completed, the neorectum consists of aganglionated rectum ventrally and ganglionated rectum dorsally with a coloanal anastomosis 1.5 cm from the dentate line (Figure 8).[50]

Transanal One-stage Pull-Through

At present, a popular approach for the newborn with Hirschsprung's disease is the single stage transanal pull-through. The procedure was initially described by De la Torre-Mondragon in 1998,[55] and then reported by Albanese[56] and Langer[57] the next year. Some studies suggested there was a greater incidence of incontinence in patients who underwent transanal endorectal pull-through (TERP), believed to be related to greater anal sphincter stretching.[58] However, in a recent large multicenter study, TERP was compared to the transabdominal approach which showed equal continence rates. In addition, patients who underwent TERP had lower rates of early and late complications, lower postoperative episodes of enterocolitis, and required fewer additional interventions.[59]

The patient is placed in the lithotomy position. The rectal mucosa is incised circumferentially with cautery 0.5 cm proximal to the dentate line in the neonate. The Lone Star self-retaining retractor is effective. The dissection is carried proximally in the submucosal plane until it is above the level of the peritoneal reflection. At this point, the rectal muscle is divided circumferentially and the full

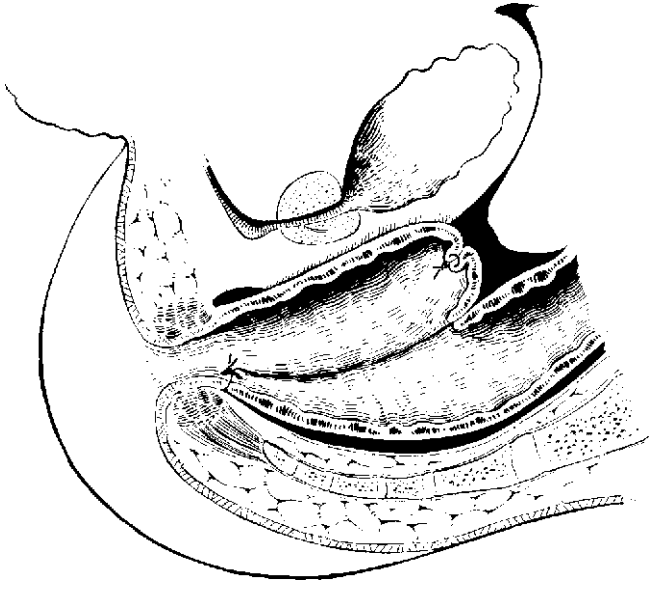


Figure 8. Completed Duhamel procedure. The ganglionated bowel is brought down posteriorly to the native rectum and an anastomosis is performed between the pulled-through bowel and the aganglionated rectum. (Reprinted from *Rob & Smith's Operative Surgery,* 4th ed. with permission from the publisher.)

thickness of the rectum and sigmoid is drawn through the rectal cuffout of the anus. Blood vessels to this portion of bowel can be divided with either cautery or ligatures. The transition zone is identified using full thickness biopsies and frozen section to confirm the presence of ganglion cells. Frozen sections of full thickness tissue confirm ganglion cells. The surgeon confers with the pathologist to ensure the site used for the anastomosis is above the transition zone. The same anastomosis is used as for the traditional Soave procedure.

A variant of this approach exploits the laparoscope. Biopsies of the colon can be done to identify the site with normal ganglion cells for the anastomosis. If needed, the splenic flexure is mobilized via the laparoscope and then attention is turned to the perineum for the mucosectomy. Some surgeons make a short mucosectomy and divide the rectum full-thickness circumferentially. The anastomosis is done to that site 1–2 cm above the dentate line. The final result is then the same as after the open Swenson operation. This is a laparoscopic-assisted endorectal operation. If a longer, more traditional mucosectomy is accomplished, it is a laparoscopic-assisted Soave procedure.

Operative Risks

Beyond the risks of associated comorbidities, the surgical correction of Hirschsprung's disease carries with it some significant risks. Risks vary with the choice of procedure. Ostomy complications include prolapse (by far the most common complication), stenosis, necrosis, retraction, obstruction, dehiscence, and parastomal hernia. The most important short-term complications specific to the pull-through are anastomotic leak and stricture. The most important complication, short- and long-term, enterocolitis will be addressed subsequently.

Postoperative Care

Postoperative care is similar for all the pull-through procedures. In the immediate postoperative period, the nasogastric tube can be removed as gastrointestinal function returns and the Foley can be removed on postoperative days 1–2, although this may be delayed after the Swenson procedure because the dissection was adjacent to the genitourinary autonomic nerves. In addition, the perineum should be inspected regularly for erythema as this can be a sign of anastomotic leak which would necessitate diverting stoma. Prior to discharge, the patency of the anastomosis can be assessed with a rectal examination using a cotton-tipped applicator or the small finger.

In the office, dilations can be started 3 weeks postoperatively to prevent anastomotic stenosis and limit the risk of enterocolitis.[60] Parents should be warned that frequent stools are expected immediately postoperatively, but should normalize by 1 year of age. These patients can develop very severe diaper dermatitis that demands careful attention and should be managed with barrier creams. Vigilance to prevent dermatitis is sensible.

TOTAL COLONIC AGANGLIONOSIS

The most common distribution of aganglionosis in Hirschsprung's disease is limited to the rectum with a rectosigmoid transition zone reported in 75% of cases.[4] However, the proximal extent of aganglionosis varies. It can be anywhere in the colon, can include the entire colon and can extend into the small intestine. When the entire colon lacks ganglion cells, the term total colonic aganglionosis (TCA) is applied. Some of these cases, although called TCA, include variable lengths of small intestine lacking ganglion cells. Very rarely, the entire gastrointestinal tract lacks ganglion cells, a condition called total intestinal aganglionosis.

TCA carries increased mortality and morbidity compared to the more standard forms of Hirschsprung's disease. TCA can be a difficult diagnosis to establish. Unlike the standard form of Hirschsprung's disease, the colon is not dilated. The typical patient with TCA has abdominal distention, and does not pass stool in the first days of life. There would be multiple distended intestinal loops on physical examination and abdominal radiograph. The contrast enema would not show a dilated colon. Nor would it show the microcolon from disuse seen in meconium ileus or distal small bowel atresia. The contrast enema in TCA shows a medium to small caliber colon. The colon in TCA is classically foreshortened, without well-formed flexures, an imaging appearance known colloquially as a "question mark-shaped colon" (Figure 9). Loops of small intestine are distended with gas. If contrast inserted into the rectum reaches the distended small bowel, the intestinal atresia is excluded from the differential diagnosis. The rectal contrast is less likely to reach distended small bowel if the aganglionated segment extends well proximal to the ileoceal valve. The surgeon needs an index of suspicion which promotes a rectal biopsy.

Rectal biopsy establishes the diagnosis of Hirschsprung's disease. The expected male predominance seen in Hirschsprung's disease may not pertain to



Figure 9. The "question mark-shaped colon" in total colonic aganglionosis. The colon is small to medium in caliber, foreshortened, without well-formed flexures. Also noted are loops of small bowel distended with gas.

these more extensive forms of aganglionosis, although the relatively large series of TCA from Indiana did have the same marked male predominance seen in the standard form of Hirschsprung's disease.[61]

After an initial ileostomy at a site with confirmed ganglion cells, the traditional types of pull-through procedures, Swenson, Soave and Duhamel, have all been applied to TCA. The small bowel with ganglion cells rather than the colon is brought down to the anus in these cases. Dehydration with loss of electrolytes and fluid has been a concern when the colon is removed and the small intestine is pulled-through. Surgeons have developed operations that leave aganglionated colon in place hoping to exploit its absorptive properties. The first of these was introduced by Lester Martin.[62] He originally described leaving the aganglionated descending colon and sigmoid. In this modification of the Duhamel operation, the normally innervated ileum is brought behind the aganglionated rectum and a long side-to-side anastomosis is done. In a standard Duhamel, the anastomosis is between colon with ganglion cells which is brought dorsal to the aganglionated rectum, and a side-to-side anastomosis is made between rectum and colon with ganglion cells. In the Martin operation for TCA, the ileum with ganglion cells is joined in a long side-to-side anastomosis to the aganglionated rectum, sigmoid, and descending colon. This creative approach taken by Dr. Martin was designed to leave the aganglionated descending and sigmoid colon despite the absence of ganglion cells hoping to benefit from water and electrolyte absorption from the aganglionated segment of colon and gain effective peristalsis from the ganglionated ileum, overcoming the functional obstruction. In order to gain even more absorption, Dr. Martin later described keeping the entire aganglionated colon in place thus making an even longer side-to-side anastomosis from normally innervated ileum to the entire aganglionated colon. This was conceived in an effort to limit diarrhea.[63]

Others suggested utilizing the aganglionated right colon because of its particular absorptive capacity, patching it in a long side-to-side anastomosis to the ileum.[64] Kimura suggested staging this by first making an ileostomy. Then he added a patch graft of cecum and ascending colon in a long side-to-side anastomosis to the ileum proximal to the ileostomy. He observed marked improvement in water absorption with decreased output through the stoma after this second operation. About 6 weeks later, he did a Swenson type pull-through but joining the ileum to the anus. Kimura divided the mesenteric pedicle to the patch of right colon when he performed the Swenson type pull-through. The right colon effectively parasitized blood supply from the ileum to which it was joined. The author explicitly chose a Swenson-type procedure because of his personal experience with that operation; but stated that the Duhamel or Soave

could have been used for his ileoanal anastomosis with a right colon patch graft to the side of the ileum.

Recently, a group from China published a report with four cases of single-stage neonatal primary laparoscopic endorectal pull-through for TCA. The number of cases is too small and the results too uncertain to generate much encouragement for this approach from that report.[65]

We lack evidence supporting one approach over another for the definitive surgical management of TCA.[66] Most surgeons would initially create an ostomy at the most distal site in the small intestine that has normal ganglion cells. Ultimately, some would choose an endorectal pull-through with small bowel. Others would add a J pouch such as is often done for ulcerative colitis or familial adenomatous polyposis. Some would patch right colon onto the small bowel and others would create a distal intestinal tract with the small bowel and the aganglionated sigmoid and descending colon as originally described by Dr. Martin and perhaps even the entire aganglionated colon as he subsequently advocated.

Total intestinal aganglionosis is very rare and often requires intestinal transplantation if the patient is to survive free of intravenous alimentation. Ziegler advanced an operation to improve function with multiple long myotomies and myectomies.[67]

ENTEROCOLITIS

Enterocolitis is a serious and potentially fatal complication of Hirschsprung's disease. It was first described by Bill and Chapman in 1962[68] who reported a mortality as high as 33%. Mortality has dropped significantly in the past 2 decades, owing to heightened awareness of this potential catastrophe, more prompt diagnosis and improvements in care. Enterocolitis is the major cause of death in Hirschsprung's disease. Death can occur quickly after the onset of this complication.

The reported incidence of enterocolitis averages 25%. The greatest risk for developing enterocolitis may be prior to the diagnosis of Hirschsprung's disease. Enterocolitis is also seen after pull-through procedures representing a significant long-term complication. The risk is greatest in the first year after surgery and decreases after that.[69] There appears to be an increased risk of enterocolitis in patients with Down's syndrome (about 50%).[70] Studies have shown no difference in the incidence of enterocolitis between the different pull-through techniques.[71,72]

The precise pathogenesis of enterocolitis has not been clearly perfectly clarified; and several theories have been proposed. Two theories are impaired immune

response to infection in the aganglionated colon and impaired mucosal defense. It has been shown that there is a decrease in the absolute neutrophil count in patients with Hirschsprung associated enterocolitis vs. controls.[73] In addition, increased natural killer cells are found in the lamina propria of ganglionated bowel in enterocolitis, as well as increased IgA-containing plasma cells but decreased luminal concentrations of IgA within the bowel in both patients and in animal models of Hirschsprung's disease[74,75] suggesting defects in both cellular and humoral immunity. Alternatively, the protective mucus barrier covering the luminal surface of the colon has been shown to be defective in patients with Hirschsprung's disease. Mucin precursors have a reduced turnover in patients with Hirschsprung's disease and this decreased turnover correlates with the development of enterocolitis.[76] Moreover, MUC-2, the predominant mucin expressed in the human colon, has been shown to have decreased protein expression in patients with Hirschsprung's disease versus controls and was found to be completely absent in patients with active Hirschsprung enterocolitis.[77] This defect in the mucin barrier has been theorized to allow for bacterial translocation and allow for invasion into the mucosal epithelium. The most commonly implicated organisms are *E. coli*, *C. difficile*, and *Cryptosporidium*. The common pathway appears to be bacterial adherence leading to invasion and subsequent disease.[78] Rectal dysfunction with stasis seems to be a precursor.

The diagnosis of enterocolitis is primarily clinical. Enterocolitis presents with abdominal distention and diarrhea. It can include pain, fever, and explosive foul-smelling, watery, green diarrhea. Lethargy may occur quickly and can be ominous. Physical examination reveals a distended, tympanitic abdomen and explosive discharge of malodorous diarrhea and flatus on rectal examination. Abdominal radiographs may reveal a distended loop of colon associated with small bowel dilation and possibly air-fluid levels. Contrast enema can reveal edema and an irregular mucosal lining, but it is not recommended because of the risk of perforation.[68]

Parents and pediatricians should be warned about enterocolitis. A variation in bowel habits may be the first alarm. Listlessness can predominate the clinical picture. Death from enterocolitis can occur quickly. Increased stool frequency, abdominal distention, any listlessness, demand a good rectal examination. Forceful expulsion of malodorous stool in this setting is diagnostic of enterocolitis. More mild variations have been referred to as syndrome of sphincter dysfunction and may not demand quite the same aggressive therapeutic interventions. The mistaken belief that a bout of enterocolitis is self-limited gastrointestinal dysfunction can be fatal.

Enterocolitis should be managed with adequate intravenous resuscitation, correction of fluid and electrolyte imbalances, and prompt initiation of broad

spectrum antibiotics (including coverage for *C. difficile*). Gastric decompression and gastrointestinal rest are appropriate. Decompression of the bowel is a priority. Decompression can initially be attempted using a large bore rectal catheter with repeated washouts if the patient does not have fulminant disease. If the bowel cannot be decompressed with rectal washouts and the patient fails nonoperative treatment, a diverting stoma may be life saving.

Dale Johnson *et al.* in Salt Lake City introduced routine rectal irrigation for several months post operatively in an attempt to reduce the risk of enterocolitis.[60] They successfully eliminated deaths and markedly reduced the incidence of postoperative enterocolitis. Today, surgeons often advocate routine dilatations to prevent anastomotic stricturing and to aid in rectal emptying, hoping to limit the complications of poor rectal function including enterocolitis after pull-through procedures for Hirschsprung's disease.

COMPLICATIONS AFTER PULL-THROUGH PROCEDURE

While a pull-through procedure is the standard management in Hirschsprung's disease, complications are common. Early complications include those associated with any abdominal procedure (bleeding, infection, risks of anesthesia etc.) or those associated with a stoma if one was created such as bleeding, prolapse, stenosis, retraction, and skin excoriation.[79] An anastomotic leak can occur and can present with perineal erythema in the early postoperative period. Perianal excoriation itself is a frequent complication, seen in as many as 50% of patients after pull-through procedures[80] and is managed using barrier creams. An effort to prevent perianal excoriation with compulsive protection of the perineum but avoidance of undue cleaning is sensible.

Late complications most commonly consist of constipation, gaseous distention, incontinence, and episodes of enterocolitis. A recently developed algorithm[81] for patients with late complications separates them into two groups, patients who are soiling and those who suffer from distention and enterocolitis. The patients with soiling are evaluated with a history, physical, contrast enema, and examination of the anal canal under anesthesia. If examination of the anal canal shows disruption of the dentate line (from a pull-through dissection begun too low) or if there is damage to the sphincters, unfortunately, there is small potential for eventual bowel control. These patients are usually given bowel management with enemas, constipating medications and diet, and can be considered for a Malone appendicostomy.

For those patients with fecal soiling with an intact anal canal, contrast enema will show a dilated hypomotile colon or a non-dilated hypermotile colon. Patients with a hypermotile colon should initially be treated with loperamide, pectin, and

a constipating diet. If patients are able to achieve voluntary bowel control with this regimen, they are considered to have been pseudo-incontinent. For those who fail this regimen, a small volume enema (200–500 mL daily) is added to their regimen. In a study by Levitt *et al.*, the authors found that 79% of patients were clean with this bowel regimen.[82]

Patients found to have a hypomotile dilated colon on contrast enema should be treated with a daily senna-based laxative and abdominal X-ray to assess whether the colon has emptied. The dosage should be titrated so that the child has one to two soft bowel movements daily and a radiograph showing the colon empty of stool. Again, patients who succeed with this regimen are considered pseudo-incontinent. Patients who fail this regimen will require daily large volume (500–1000 mL) saline enemas with glycerine or soap (phosphate enemas should be avoided due to reports of colitis in this setting).[83] In the same study, 85% of patients were able to stay clean with this regimen.

In the group of patients with recurrent enterocolitis and abdominal distention, the evaluation is similar, but should also include a full-thickness rectal biopsy. The biopsy looks for hypertrophic nerve fibers, ganglion cells, and abnormal acetylcholinesterase or calretinin staining. Correctable pathologic causes of distention and enterocolitis are an aganglionated site at the anastomosis or transition zone that has been used for the pull-through, both of which require a redo pull-through. Once histopathologic causes have been excluded, anatomic etiologies are considered, often in relation to the type of initial operation. Three such causes are stricture, usually at the anastomotic site, retained segment of dilated colon, or a twist or kink in the pulled-through bowel. The Duhamel procedure is associated with an aganglionated spur or megarectal pouch that can become impacted, leading to fecal stasis. With the Soave procedure, a fibrotic, constricting ring can form either if the muscular cuff is not adequately split or if it later scars down. Both of these complications can be diagnosed with a contrast enema, although the Soave cuff can also be palpated on rectal examination.[81]

In addition, patients can develop cutaneous, urethral, or vaginal fistulae after their initial operation, requiring redo operations, although a retrospective review found no fistulae associated with the Duhamel procedure in particular.[84] Redo operations in patients who encounter these serious complications can be difficult, and a posterior sagittal approach can be used. However, patients who require a redo operation have a far greater risk of permanent sequelae and a much smaller chance of becoming fully continent (Ibid).

There are a limited number of long-term studies examining the outcomes of Hirschsprung's disease into adulthood. A recent study interviewed patients who

underwent surgery for Hirschsprung's disease between 1950 and 1986 assessing their bowel function and quality of life and found patients to have significantly inferior bowel function compared with that of controls, including fecal soiling, constipation, short urgency period, and social problems associated with impaired bowel function.[85] There is a report of a small percentage of patients with Hirschsprung's disease suffering from micturition disturbances significantly greater than controls.[86]

The child with Hirschsprung's disease needs long-term commitment from the surgeon. The operation, although a critical step, does not satisfy the surgeon's obligation to the patient given the significant risks of enterocolitis and rectal dysfunction.

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CHAPTER 6

MECONIUM SYNDROMES

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INTRODUCTION

The meconium syndromes represent a broad category of diverse conditions affecting intestinal transit in the neonate that ultimately produce distal intestinal obstruction. Traditionally meconium syndromes included meconium ileus, meconium plug syndrome, and meconium peritonitis.[1] An additional entity, familiar to pediatric surgeons and neonatologists, demands inclusion in this category of conditions. It lacks a catchy name: meconium obstruction in the very small premature infant. Small left colon syndrome is a cause of distal intestinal obstruction in the newborn that has gained deserved independence as a distinct entity but does not fit more naturally in other discussions. Although not a true meconium-related condition, small left colon syndrome shares many features with meconium plug syndrome, including its manner of presentation early in the neonatal period and typical response to nonoperative management. In fact, the first descriptions of meconium plug syndrome included some cases that would now be recognized as small left colon syndrome.

Meconium syndromes have a wide range of clinical implications. These include distal intestinal obstruction in the first days of life (meconium ileus, meconium plug syndrome, small left colon), intestinal obstruction presenting a few days or weeks later (meconium obstruction in the very small premature infant), intestinal catastrophe with perforation and massive necrosis (severe

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cases of meconium peritonitis), and an asymptomatic patient with normal intestinal continuity (some cases of meconium peritonitis that have recanalized in utero). Meconium syndromes include conditions attributed to disorders of motility (small left colon syndrome) and abnormalities in the composition of meconium (meconium ileus). Some of these conditions usually are cured easily without operative intervention. Others require emergency operations. A thorough understanding of the clinical and radiographic differences among these distal intestinal obstructive syndromes is important to guide safe and effective treatment.

MECONIUM ILEUS

Meconium ileus (MI) is a common cause of neonatal obstruction which is due to inspissated meconium in the distal small bowel.[2,3] This entity accounts for approximately 10% to 25% of patients with neonatal intestinal obstruction.[2] Almost all cases are associated with cystic fibrosis (CF), and MI can be the earliest clinical manifestation in 10% to 15% of CF patients. Due to abnormal exocrine mucous secretion, meconium in MI contains lower concentrations of pancreatic enzymes, surcrase, and lactase, as well as less water content and becomes extremely viscid and protein rich. This thick tenacious meconium leads to obstruction of the distal ileum.[4] Patients presenting with MI require sweat chloride determination for the diagnosis of CF. The chloride sweat test is a simple noninvasive test which measures the chloride content of sweat. A sweat chloride concentration above 60 mEq/L indentifies affected infants with great accuracy which then can be clarified with genetic testing.[5]

Cystic Fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease with an incidence in some populations as high as 1 in 1150 live births.[6] This disease is more prevalent in Caucasians compared to people of African, Latin, or Asian descent. CF is due to a mutation located on the long arm of chromosome 7q leading to an abnormal gene named cystic fibrosis transmembrane regulator (CFTR). This gene codes for a cyclic adenosine monophosphate-activated chloride channel protein which regulates the flow of certain ions across the surface of epithelial cells. Patients with this mutation have thick viscous secretions in the lungs, pancreas, and intestine.[4]

Classification of MI

MI is either simple (uncomplicated) or complex (complicated), with each type occurring with equal frequency.[7] Patients with uncomplicated MI present similarly to other types of neonatal distal bowel obstruction. The inspissated meconium obstructs the ileum typically at or just proximal to the level of the ileocecal valve. Complicated MI results when distal ileal obstruction from thickened meconium leads to volvulus and intestinal necrosis with resultant perforation or atresia occurring *in utero*.

Clinical Presentation

Uncomplicated MI presents with abdominal distension, bilious vomiting or gastric aspirate, and failure to pass meconium in the first 24 to 48 hours of life. Afflicted patients exhibit abdominal distention, and often multiple loops of intestine are visible on abdominal examination. Other causes of neonatal distal intestinal obstruction such as Hirschsprung's disease, jejunoileal atresia, meconium plug syndrome, colonic atresia, and small left colon syndrome are in the differential diagnosis. Malrotation with midgut volvulus should always be considered as a cause of bilious emesis in neonates however, most neonates with malrotation and volvulus are able to pass normal stools within the first few days of life.

Complicated MI may appear dramatically after birth with clinical signs of intestinal necrosis or perforation including abdominal wall edema, tenderness, and erythema, as well as hemodynamic lability or overt shock.[4] These neonates may be in respiratory distress requiring ventilatory support and oxygen supplementation. They may also suffer hypovolemia from third space fluid losses requiring aggressive volume resuscitation.

Diagnosis

After a thorough history and examination, plain radiographs of the abdomen are the first step in standard evaluation of any neonate with intestinal obstruction. The presence of multiple distended bowel loops throughout the abdomen with a paucity of colonic or rectal gas signifies distal intestinal obstruction, such as seen with uncomplicated MI. Air-fluid levels are conspicuously absent on upright or cross-table abdominal radiographs in some cases of MI because the tenacious intraluminal meconium does not shift easily within the bowel in response to positional changes to create a visible air-fluid interface. A

"soap-bubble" appearance (Neuhauser sign) may be evident in the right lower quadrant as gas mixes with the tenacious meconium.[4,8] The "soap-bubble" sign is not pathognomonic, however, as it may be seen with other causes of distal intestinal obstruction. Radiographic findings in complicated MI may include calcifications (due to saponified extra luminal meconium within the peritoneal cavity after perforation), massive bowel dilation (from atresia which developed *in utero*), mass effect (from cystic meconium peritonitis), and ascites. Pneumoperitoneum equates to intestinal perforation and dictates emergent abdominal exploration.

Absent free air on plain radiographs or obvious clinical signs of intestinal necrosis or perforation warranting emergent operative intervention, further imaging is in order to delineate the exact level and nature of the obstruction. Ordinarily, the next diagnostic step when plain films suggest distal intestinal obstruction is contrast enema. Typically, contrast enema is performed under fluoroscopy with rectal installation of dilute Gastrografin solution (Bristol–Meyers Squibb, Princeton, NJ), which is less inflammatory to the peritoneum than barium if perforation complicates the study and may provide therapeutic benefit as an emulsifier in select cases of MI or other meconium-related syndromes (see below). Findings on contrast enema include a microcolon, resulting from disuse, and multiple small filling defects mostly located in the distal ileum reflecting inspissated meconium "pellets" unable to pass through the ileocecal valve[5] (Figure 1).

Treatment

Gastrografin enema has become the initial procedure for diagnosis and treatment of uncomplicated MI since its therapeutic benefit was reported in 1969 by Helen Noblett.[9] It establishes diagnosis and also allows liquefaction and evacuation of meconium in 40–90% of cases.[7] Gastrografin's benefit stems from its hyperosmolarity, which draws fluid into the bowel lumen, thus helping clear the thick inspissated meconium. However, this osmotic effect may also produce acute dehydration in neonates undergoing treatment. This potentially lethal complication was first demonstrated in a newborn puppy model reported by Rowe shortly after Noblett's report.[10] Therefore, infants undergoing this treatment should be adequately hydrated with intravenous fluid throughout the period of therapy. The therapeutic role of Gastrografin enema may be limited when contrast fails to reflux proximal to the level of obstruction and adequately mix with the inspissated meconium. Inability to reflux contrast into dilated small bowel may also indicate the presence of small bowel atresia which requires



Figure 1. Contrast enema from a patient with meconium ileus showing a microcolon with multiple filling defects in the distal ileum.

operative correction.[6,11] Complicated MI is a contraindication to nonoperative management in most cases. Before undertaking enema therapy, it should be determined that there is no clinical or radiographic sign of complicated MI.

Administration of therapeutic contrast enema should be done under fluoroscopic guidance to ensure the Gastrografin reaches the level of obstruction and to allow prompt recognition of intestinal perforation. Reported series include rates of perforation ranging from 5–14%.[11] This incidence of intestinal perforation warrants a warning to the family before proceeding with a nonoperative approach to simple MI. It also should prompt administration of prophylactic intravenous antibiotics that cover gut flora and close surgical supervision.[9] Serial abdominal films should be obtained initially every 8–12 hours to evaluate for late perforation, which may occur despite continuing evacuation of stool 24–48 hours after the Gastrografin enema. Abdominal radiographs can also assist in decision making for repeat enemas or need for operative intervention. Enemas may be repeated in 12–24 hours intervals if meconium evacuation is incomplete.

Despite reports of a fairly robust success rate with this management strategy for uncomplicated MI,[8] some authors have not been able to replicate these results. One such study showed success with contrast enema in only 1 of 18 of their more

recent patients.[12] Lower success rates may be due to radiologists approaching uncomplicated MI patients with more caution to avoid perforation or using less hyperosmolar agents for the procedure to avoid dehydration.[12]

Warm saline enemas with 10% N-acetylcysteine (Mucomyst, Bristol-Meyers Squibb, New York, NY) may supplement therapeutic contrast enema in the evacuation of inspissated stool. In addition, gastric 5–10% *N*-acetylcysteine can be used especially to mobilize proximal bowel meconium. The solution typically is administered in 5-ml doses every 6 hours via nasogastric tube until evacuation is complete.[4]

Operative Management

Indications for operative intervention are continued incomplete evacuation of uncomplicated MI, intestinal perforation, and evidence of complicated MI.[5] Several surgical strategies have been proposed for the management for each of these scenarios. Uncomplicated MI not resolving with enemas can be managed with an enterotomy and luminal irrigation to remove the obstructing meconium.[5,6] Saline, Gastrografin and *N*-acetylcysteine have been used most commonly as emulsifiers. Ziegler advocates using 2–4% *N*-acetylcysteine solution for intraoperative irrigation.[6] Following irrigation, a decision is made to perform an enterostomy or simply close the enterotomy. The choice between enterostomy and enterotomy closure often is dictated by surgeon experience and the overall clinical condition of the neonate; hemodynamic instability, extreme prematurity, presence of severe comorbid congenital abnormalities, and any intraoperative evidence of questionable intestinal viability or concern for postoperative intestinal dysfunction favor enterostomy. Complicated MI usually requires lysis of adhesions with bowel resection followed by enterostomy. Several traditional operative techniques for stoma creation have been described for these complicated cases.

One of the more popular technical options is a distal chimney enterostomy, or Bishop–Koop procedure[13] (Figure 2), which requires resection of the portion of ileum containing tenacious meconium followed by an anastomosis between the end of the proximal segment and side of the distal segment just proximal to the enterostomy. This configuration allows the egress of bowel contents through the distal stoma and intestinal access for irrigation postoperatively to manage the distal obstruction. When the obstruction resolves, this form of stoma allows the entire GI tract to function. Frequently, this type of stoma closes spontaneously or may be ligated locally at the bedside eliminating the need for further general anesthesia.

A Santulli enterostomy (Figure 2) has similar goals. It is essentially the opposite configuration from the Bishop–Koop, with the proximal intestinal

segment brought through the abdominal wall as a stoma, while the end of the distal segment is anastomosed to the side of the proximal segment just below the level of the abdominal wall fascia. Again, intestinal decompression and irrigation is possible with a Santulli enterostomy, but distal irrigation may be more cumbersome than with the Bishop–Koop configuration and spontaneous closure rarely occurs.[4]

Another option is to create a Mikulicz (Figure 2), double-barreled enterostomy in which the proximal and distal intestinal segments are brought through a single fascial opening in the abdominal wall as adjacent stomas. Their shared wall is later divided at the bedside without anesthesia. Classically, this was done with a spur-crushing clamp, placing one leg of the vise-like clamp into each stoma, crushing the shared intestinal walls. The principles of the Mikulicz enterostomy, like the Bishop-Koop and Santulli types, are to allow the egress of stool out of the stoma while ongoing distal obstruction remains and facilitate distal intestinal irrigation in the postoperative period to relieve obstruction. Similar to a Bishop-Koop stoma, distal passage of the fecal stream can return when the obstruction is relieved and stoma closure may occur without further operative intervention.

Harberg *et al.* in 1981 described the use of t-tube ileostomy as a surgical option to manage uncomplicated MI unresponsive to enemas.[14] In this technique, a t-tube is placed into the ileum through a small enterotomy just proximal to the obstruction and brought out the abdominal wall (Figure 2). Intestinal irrigation with *N*-acetylcysteine or pancreatic enzymes is instituted in the postoperative period to relieve the obstruction. Nineteen years later, this group from Houston reported an 87% success rate (20 of 23 patients) over 40 years experience with this management strategy for uncomplicated MI.[15]

Outcomes

Surgery was the only modality of treatment of MI for decades prior to the use of emulsifiers. Survival rates were poor in series published during this time period.[16] Prognosis for neonates with MI has improved markedly following introduction of Gastrografin enemas as initial management of uncomplicated MI along with improvements in neonatal intensive care strategies. Rescorla and Grosfeld in 1989 showed a 1-year survival rate of 92% (22 of 24 patients) from uncomplicated MI and 85% (23 of 27 patients) in complicated cases.[8] The outcome for CF patients presenting with MI was previously thought to be worse than those patients without MI. However, recent literature has shown equal outcomes in CF patients with or without MI,[17,18] likely related to additional improvements in CF management.

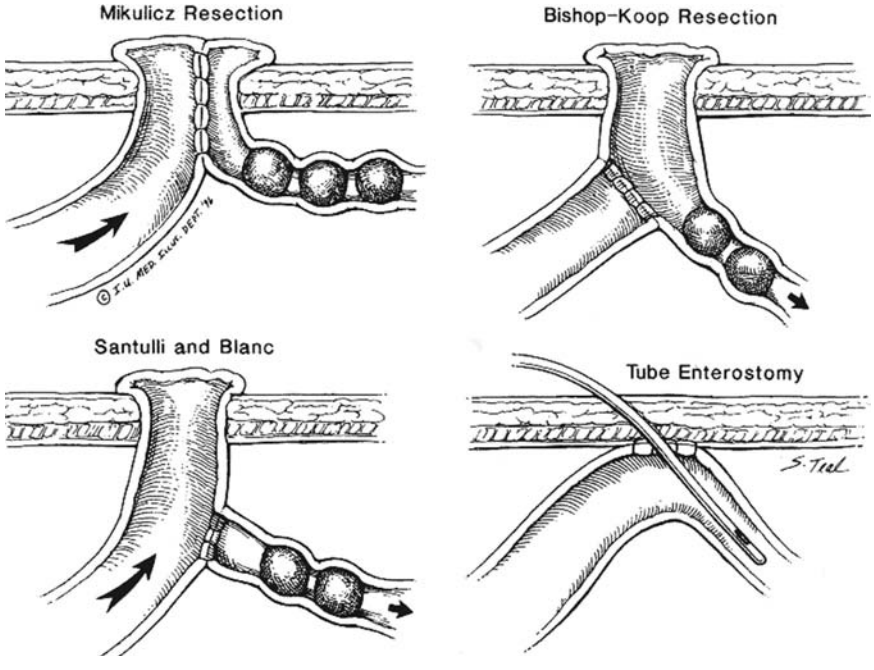


Figure 2. Some operative approaches to meconium ileus. Reprinted with permission of the publisher from Rescorla FR, Grosfeld JL (1993) Contemporary management of meconium ileus. *World J. Surg.* **17**: 318–325.

MECONIUM PLUG SYNDROME

Meconium plug syndrome is a common cause of distal intestinal obstruction in the newborn. The original description by Clatworthy from Columbus, Ohio in 1956 is striking for its clarity:[19]

"Newborn infants with intestinal obstruction due to the inability of the colon to rid itself of the meconium residue of nine months of fetal life are not uncommon. In such instances, it is presumed that either the meconium mass or the colonic motility is so altered that the normal unplugging process is impeded and deflation of the alimentary tract is retarded. This relatively benign form of obturation obstruction may vary from a mild stasis, which can be relieved by the insertion of a thermometer or a finger into the rectum, to a complete unrelenting form of mechanical obstruction. Infants who do not respond to anal stimulation rapidly develop the classical signs and symptoms of low intestinal

obstruction: abdominal distention with hyperactive intestinal patterning, bile-stained vomiting, and continued obstipation."

Nine patients were included in this original description. All were cured with anal stimulation or enemas. None of these patients had CF or Hirschsprung's disease.

Ten years after this classic description, Ellis and Clatworthy updated the experience with 21 additional cases.[20] Meconium plug syndrome as originally described in these publications was colonic obstruction due to a meconium plug in a term infant. Clinical obstruction was evident in the first days of life. Contrast enemas were diagnostic and often therapeutic. In most cases, contrast enema identified a site of obstruction with decompressed colon distal to a single obstructing plug and dilated colon proximal to the plug. In some cases with multiple meconium plugs, there was no clear site of caliber change in the colon. Contrast enema (barium in early reports) relieved the obstruction in half of the cases. In other cases, cure was effectuated using hydrogen peroxide and dilute barium enemas. The authors suggested a possible role of rectal biopsy to rule out Hirschsprung's disease when diagnosis was uncertain.

In the years since these publications, meconium plug syndrome has gained prominence in differential diagnosis of an obstipated, full-term, newborn infant with a distended, soft, and nontender abdomen. Plain abdominal radiographs are nonspecific but suggest distal intestinal obstruction with multiple dilated loops of air-filled intestine. Contrast enema is performed with a water-soluble agent (Gastrografin). The absence of a microcolon on contrast enema helps to differentiate meconium plug syndrome from MI or jejunoileal atresia. If a plug of meconium is located at a site of obstruction in the colon, the diagnosis of meconium plug syndrome is practically established. In most cases, the plug is soon evacuated, classically with a pale leading end and forest green, long tenacious tail (Figure 3). Several hundred grams of meconium may be passed upon complete clinical resolution.

A word of caution: Hirschsprung's disease may have a similar appearance to meconium plug syndrome on contrast enema and should be highly suspected if complete evacuation of meconium does not occur or abnormal stooling persists despite meconium clearance. A series from Kansas City published in 2008 reviewed 77 cases of meconium plug syndrome diagnosed over a 13-year span.[21] Thirteen percent of these patients proved to have Hirschsprung disease; none had CF. The authors concluded that a persistent abnormal stooling pattern demanded investigations for Hirschsprung's disease (rectal biopsy) and CF (chloride sweat testing and chromosomal analysis).



Figure 3. Large meconium plug passed from a neonate with meconium plug syndrome following diagnostic and therapeutic contrast enema.

MECONIUM OBSTRUCTION IN THE VERY SMALL PREMATURE INFANT

In recent decades, attention has been paid to cases of distal intestinal obstruction with plugging of meconium in very low birth weight, premature infants.[22–25] Average reported birth weight of these patients is 800 g. Similar to meconium plug syndrome, obstruction occurs with plugging of the distal ileum and colon. Unlike meconium plug syndrome, meconium obstruction in these premature infants is attributed to functional immaturity and uncoordinated peristalsis in severely premature intestines. Since intestinal function is perturbed in premature infants, it is fairly common to see a delay in meconium evacuation for several days under normal conditions, while full-term neonates typically pass meconium on the first day of life. Clinically apparent obstruction, therefore, is delayed up to as much as two weeks after premature delivery. In a group of 21 premature infants reported from Galveston, Texas, the average age of onset of obstruction was 5.6 days with a range of 1 to 18 days of life.[25] In contrast, meconium plug syndrome classically manifests in the first few days of life. Thus, the main clinical features that distinguish meconium plug syndrome and meconium obstruction in very low birth weight, premature infants is the gestational age of the patient and timing of onset of clinically apparent intestinal obstruction.

Evaluation is essentially the same as other suspected meconium syndromes. Plain abdominal radiographs are nonspecific and show signs of distal intestinal obstruction. Contrast enema typically resembles that of meconium plug syndrome with visible filling defects representing meconium plugs in the colon; however, a small or microcolon may be present resembling the picture of MI.

Management strategy resembles that for MI. First-line treatment is enemas comprised of water-soluble contrast agents or dilute *N*-acetylcysteine solution. The group from Galveston seemed to have more success with Gastrografin enemas than with a 20% *N*-acetylcysteine solution. In some cases, enemas have been combined with Gastrografin or *N*-acetylcysteine gavaged into the infant's stomach.[23,24] Regimens and treatment duration vary. One group advocates instilling 1–5 mL of 10% *N*-acetylcysteine into the stomach every 6 hours.[24] Another group uses 1 mL of 10% *N*-acetylcysteine every 8 hours for 2 weeks after oral diluted Gastrografin.[22]

Operation is reserved for cases with perforation or progressive abdominal distention despite therapeutic efforts. The small premature infant is particularly prone to intestinal perforation while being managed for meconium obstruction. Perforation related to nonoperative management occurred in 6 of 21 patients reported from Galveston, all of whom required surgery. Operation entails creation of stomas unless the intestine can be easily emptied of meconium through an enterotomy in the dilated ileum. Primary closure after enterotomy is an option in this scenario. All but one of seven operations in Galveston's report included the formation of a stoma.[25]

Occasionally small premature infants undergo abdominal exploration for presumed small bowel atresia when they have meconium obstruction. Ideally, filling of the dilated ileum should be seen during performance of contrast enema, thereby excluding intestinal atresia. When dilated ileum does not fill and the patient remains obstructed, exploration may be undertaken. Perhaps in these cases, where an error in diagnosis leads to exploration, strong consideration can be given to enterotomy in the dilated ileum, followed by evacuation of meconium and closure of the enterotomy without creation of a stoma.

Neither Hirschsprung's disease nor CF is thought to be likely in these patients.[24,25] However, persistent abnormal stooling requires investigation to exclude these conditions.

SMALL LEFT COLON SYNDROME

In retrospect, Clatworthy's original description of meconium plug syndrome included some cases that would now be designated as small left colon syndrome.

Three of the original nine patients had a small left colon on imaging.[19] While not a "meconium syndrome", small left colon syndrome shares certain features with the meconium syndromes and warrants discussion among this group of disorders. Like meconium plug syndrome, it causes newborn colonic obstruction, is diagnosed with contrast enema, and ordinarily does not require operative therapy.

Small left colon syndrome was first described by Davis *et al.* in 1974.[26] It is considered a localized motility disorder. About half of inflicted infants are born to diabetic mothers. In a series of 105 infants of diabetic mothers, 6% were born with small left colon syndrome.[27] Interestingly, in a follow-up to Davis' original descriptive report, anatomically small left colons (not causing obstruction) were also observed in half of asymptomatic infants born to diabetic mothers.[28] Despite an intriguing correlation with maternal diabetes, the exact pathophysiology behind small left colon syndrome remains elusive.

Clinically, patients with small left colon syndrome fail to pass meconium in the first day of life. Abdominal distention and vomiting follow. Examination demonstrates a soft, distended abdomen without tenderness. Abdominal radiographs show the characteristic, multiple distended loops of intestine typically seen in newborns with distal intestinal obstruction. Contrast enema should be performed in this setting; it will reveal a small left colon with a transition to dilated colon at the splenic flexure. A plug of meconium may be visible at that location and pass after the enema, but the plug is not thought to be the cause of obstruction.

Small left colon syndrome is attributed to dysmotility of the descending colon. It resolves promptly and spontaneously. Since the contrast enema resembles Hirschsprung's disease with a presumed transition at the splenic flexure, rectal biopsy to assess for aganglionosis is required if GI function does not normalize. Some advocate suction rectal biopsy in all cases of small left colon syndrome.[29]

MECONIUM PERITONITIS

Meconium peritonitis is a diagnosis based on imaging that implies in utero intestinal perforation. Traditionally it meant that an abdominal radiograph showed speckled calcification in the neonate's abdominal cavity (Figure 4). Today, various types of imaging may show intraperitoneal, extra-luminal calcification in the neonate. Since extruded meconium undergoes saponification and calcifies quickly after entering the fetal peritoneal cavity, it is the presence of abnormal calcification that implies intestinal perforation.

Meconium peritonitis represents a spectrum of clinical scenarios that can range from the apparent healthy neonate with normal GI function to an infant



Figure 4. Abdominal film of a neonate with fetal intestinal obstruction and perforation showing speckled calcification in the right lower quadrant denoting meconium peritonitis.

with severe physiologic disturbance and intestinal obstruction. The healthy appearing infant with normal GI function likely experienced remote, *in utero* intestinal perforation that then healed spontaneously, leaving behind intact intestinal continuity and innocent intra-peritoneal calcification visible on imaging. These infants typically do well and need no intervention. Giant cystic meconium peritonitis occurs at the other end of the spectrum. Massive intestinal necrosis *in utero* produces a bile-filled, cystic cavity in the abdomen. Often, very little viable intestine may remain (Figure 5). Poor outcome is not uncommon in these extreme cases and survivors are often at risk for short bowel syndrome.[30,31]

Today, meconium peritonitis is often first recognized by fetal sonography. Like many other conditions, prognosis and natural history when meconium peritonitis is diagnosed in the fetus may be different than when diagnosis is made following birth. If the fetal sonogram shows intraperitoneal calcification without intestinal dilatation, ascites, polyhydramnios, or a pseudocyst, the prognosis is likely to be quite good. This has been termed "simple meconium peritonitis". None of five such patients in one report needed surgical intervention.[31] If meconium peritonitis is accompanied by any of these complicating factors, the possibility of a worse outcome and likely need for an operation is increased. Neonates with meconium peritonitis often have CF (7 to 40%); chloride sweat test and confirmative chromosomal analysis are required.[30]

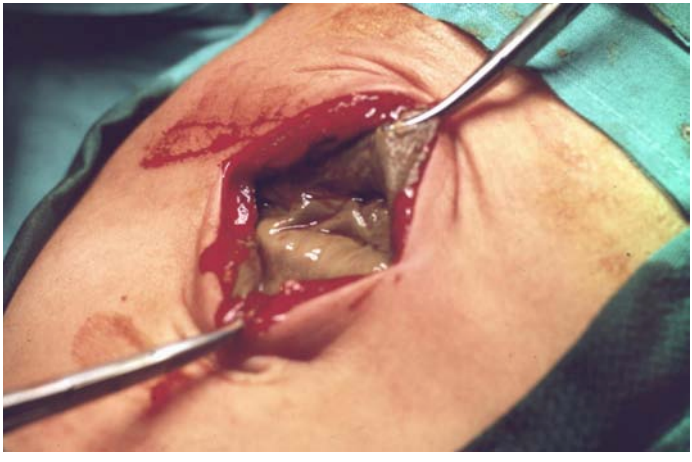


Figure 5. Intraoperative photograph of a neonate with distended, discolored abdomen and pneumoperitoneum. Laparotomy revealed giant cystic meconium peritonitis.

Pneumoperitoneum on abdominal radiograph demands exploration. Operation for meconium peritonitis can be treacherous. A thick inflammatory peel is expected. Adhesions should be thoroughly lysed to clarify the status of the intestines. Ideally, the perforation is distal and a stoma can be fashioned proximal to that site. In extreme cases, it may be difficult to delineate viable intestine to bring out as an ostomy; or the infant's clinical condition may not permit a prolonged exploration and adhesiolysis. In this case, peritoneal drainage may help alleviate the systemic inflammatory response and allow a more thorough second-look procedure once the neonate has stabilized. In either scenario, there may be substantial loss of intestine resulting in critical short gut syndrome and a guarded outcome.

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CHAPTER 7

ANORECTAL MALFORMATIONS

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INTRODUCTION

Overview

Anorectal malformations represent a wide spectrum of disease states due to abnormal development of the most distal portion of the intestinal and urogenital tracts. These malformations include all defects with an abnormal anal opening. There is a range of abnormalities of varying degrees of complexity. Careful physical examination initiates diagnostic and therapeutic steps that establish a management plan.

History

Historically, these malformations were approached with a limited understanding of the anatomy. Repairs involved rupturing an obstructing membrane with a finger or knife[1] or a making a perineal incision attempting to locate the bowel.[2] The first known record of anorectal malformations is from Aristotle in the third century BCE discussing imperforate anus seen in livestock.[2] In 1710, Littré suggested performing a colostomy in the setting of imperforate anus and in 1793, Duret performed the first colostomy for imperforate anus, fashioning sigmoid inguinal

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colostomy.[2,3] In 1835, Amussat advocated mobilizing the bowel through a perineal incision and suturing it to the skin.[4,5] In the 20th century, an abdominoperineal approach was used and, in 1953, Stephens advocated bringing the rectum through the puborectalis sling[6] to aid in the preservation of continence. The current approach to anorectal malformations was described by Peña *et al.* in 1982 which involved a posterior sagittal approach allowing the surgeon to better visualize and repair the entire malformation.[7,8] This technique is known as posterior sagittal anorectoplasty (PSARP) or posterior sagittal anorectovaginourethroplasty (PSARVUP).

TYPES OF MALFORMATIONS

The malformations are classified anatomically. Below is a brief discussion of the various defects in boys and girls. More complex defects are generally associated with poorer development of the sacrum and pelvic musculature and tend to have a poorer prognosis. In addition, patients with more complex defects tend to have a less defined groove between the buttocks, an almost absent anal dimple, or even a flat perineum on external examination.

Defects Common to Males and Females

Cutaneous perineal fistula

This represents the simplest defect and is associated with a good prognosis. It involves an abnormal opening either located anterior to the normal location of the anus, on the perineal skin, or in a normal location but stenotic. Some children may have a small loop of skin at the anal opening that resembles a bucket-handle. This finding is pathognomonic for perineal fistula. In addition, some boys may accumulate mucous or meconium within the fistula along the median raphe that can appear to be a black cord (meconium) or a string of pearls (mucous) (Figure 1). Associated defects are rare. Judging the "correct" size of the perineal body is a matter of clinical experience.[9]

Imperforate Anus without Fistula

This defect includes a blind-ending rectum that ends approximately at the level of the bulbar urethra without an associated fistula, but the rectum and urethra still share a common wall in the male. Interestingly, this defect has a strong association with Trisomy 21 (Down syndrome). More than 90% of patients with Trisomy 21



Figure 1. External appearance of a bucket-handle deformity and string-of-pearls. The presence of mucus along the median raphe can give the appearance of the so-called string-of-pearls defect. Also, a loop of skin at the expected location of the anal opening is known as a bucket-handle deformity. This is pathognomonic for a cutaneous perineal fistula.

and imperforate anus have this type of defect and about half the patients with this defect have Trisomy 21.[3,10,11] The prognosis for this malformation is good.

Rectal atresia

In this rare malformation, patients have a normal anal canal and the defect is not recognized until an attempt is made to pass a thermometer into the rectum and the atretic rectum obstructs passage of the thermometer or the child has abdominal distention and is investigated for distal obstruction. There is a total atresia or severe stenosis at the junction of the anal canal and the rectum. Because the sphincter mechanism is intact and fully formed, prognosis is excellent.

Male Defects

Bulbar urethral fistulas

A bulbar urethral fistula is a common defect in boys and is associated with a slightly higher incidence of associated defects, but the overall incidence is still

low.[10,12] The rectum opens into the posterior urethra in its lowest part and no external fistula is noted. Above the fistula, the rectum and urethra share a common wall.

Prostatic urethral fistula

In a prostatic urethral fistula, the rectum opens into the upper portion of the urethra. This abnormality is associated with a higher incidence of associated defects, less well developed muscles and sacrum, and an overall poorer prognosis. The diagnosis and initial management is the same as for a bulbar urethral fistula, but the definitive surgical procedure is different.

Bladder neck fistula

In a bladder neck fistula, the rectum opens into the bladder neck, above the levator muscles. The sphincter mechanism is poorly developed and this defect is associated with a poorly developed sacrum and a high incidence of associated defects. Fortunately, this defect represents only 10% of anorectal malformations in males as it carries a very poor prognosis.[10,13]

Female Defects

Vestibular fistula

In this, the most common variant in the female,[10] the rectum opens posteriorly within the female genitalia posterior to the hymen and within the vestibule. A portion of the rectum and vagina share a common wall. Because the fistula is external to the hymen, it is a vestibular, and not a vaginal fistula (solitary congenital rectovaginal fistulas are exceedingly rare).[10,13,14] When properly treated by an experienced surgeon, the prognosis for normal continence is good. A variant of vestibular fistula is a fourchette fistula in which the fistula is somewhere between a perineal fistula and a vestibular fistula with the fistula having a wet mucosal lining on its anterior aspect and dry perineal skin on its posterior half (Figure 2).

Cloaca

Persistent cloaca, the most complex malformation in females, represents a spectrum of defects. A cloaca includes a common channel that incorporates the



Figure 2. Fourchette fistula in a prone patient. A fourchette fistula represents a variant of a vestibular fistula in which the anterior aspect of the fistula has a wet mucosal lining while the posterior aspect has dry perineal skin.

urethra, vagina, and rectum leading to a single perineal orifice. This defect can be easily identified on physical examination, although the length of the common channel requires further investigation. The external genitals appear quite short with small labia and a small introitus (Figure 3). Both the rectum and vagina as well as the vagina and urethra share common walls. In addition, a significant portion of girls will have two hemivaginas and may have hydrocolpos. The dilated vagina can then compress the trigone of the bladder and interfere with drainage of the ureters, leading to megaureters as well. The malformation is distinct from persistent urogenital sinus, in which the urethra and vagina become a single common channel, without a rectal component.

Alberto Peña has categorized patients with cloacal malformations by the length of their common channel, which is measured cystoscopically and defined as the distance between the skin and the takeoff of the first opening that branches off of the common channel.[13] When the common channel is shorter than 3 cm, there is less likelihood of associated malformations, a greater likelihood of being able to repair



Figure 3. External appearance of a cloaca. A cloaca can be easily identified with a careful physical examination. On examination, the labia appear small and there is a short introitus. A single common external orifice is seen. The prognosis is directly correlated to the length of the common channel; channels longer than 3 cm are associated with a much poorer prognosis.

from a posterior sagittal approach, and a better prognosis for long term function. Long common-channel cloacae (> 3 cm) can be substantially more complicated and may require a laparotomy in addition to a posterior sagittal approach, and have poorer prognosis for long-term function. Persistent cloaca is usually identified on clinical exam in the neonate, but can also be suspected prenatally. In a female fetus with bilateral hydronephrosis, a poorly visualized bladder, and a cystic structure arising from the pelvis on prenatal ultrasound, diagnosis should be considered.[15]

An abdominal ultrasound in the newborn period is critical to determine if the child has hydrocolpos, which is present in a significant number of patients and must be drained. Undrained hydrocolpos can lead to infection, unnecessary urinary drainage procedures, and vaginal perforation which causes scarring and renders the native vagina unusable, committing the patient to eventual vaginal replacement. Once the prenatal workup is complete, a colostomy is performed and, if required, some form of vaginal drainage procedure is done concurrently, such as tube vaginostomy brought out either through the abdominal wall or through the cloacal orifice.

PRESENTATION AND PHYSICAL FINDINGS

VACTERL Association

The mnemonic VACTERL (V for vertebral, A for anorectal malformations, C for cardiac, TE for tracheal-esophageal fistula, R for renal, and L for limb anomalies)

refers to a variety of congenital malformations that are associated. The term serves no prognostic function. For example, a child can be born with a perineal fistula and a minor renal anomaly that requires no intervention and have a VACTERL association with an excellent prognosis and a normal quality of life. On the other hand, a child with a cloaca with a long common channel and no other anomalies, who does not carry the VACTERL label, faces a much worse prognosis and will require multiple operations and life-long impairment. While the mnemonic helps clinicians search for other occult anomalies, the term "VACTERL syndrome" can be a confusing label.[3]

Physical Examination

The majority of patients are identified shortly after birth. A small number of patients who have egress for stool will have a delayed diagnoses because a perineal fistula is misinterpreted as a normal anus. The most important diagnostic tool is a thorough examination that will aid in the characterization of the type of anorectal malformation.

A nasogastric or orogastric tube should be passed into the stomach to rule out esophageal atresia; and it should be attached to low continuous wall suction to avoid excessive gas or fluid accumulation. A cardiac examination should be performed to evaluate for murmurs. The abdominal examination should include palpation for masses (which can represent a dilated kidney or bladder, hydrocolpos, ectopic kidney, or other cystic structure). The limbs should be assessed for anomalies including the presence of extra digits.

External evaluation of the anorectal malformation can begin with qualitative evaluation of the buttocks. A flat bottom without a midline gluteal fold is a sign of a more complex malformation. The buttocks should be spread, as should the labia in females, and the presence or absence of every expected orifice identified. A pinhole opening may represent a perineal fistula, as may a "bucket-handle" of skin where the anus should be or a "string of pearls" along the median raphe. In babies with concern for a perineal fistula, meaning an abnormal opening of the rectum on the perineum either anterior to the normal location and/or narrow, the anus can be sized using Hegar dilators, starting small and moving up in size until just snug. A term infant's anus should be able to accept a 12-mm dilator without difficulty with preterm infants having correspondingly smaller anal diameters.[3]

The rectum, with rare exceptions, ends in one site only. This means that if there is an opening for stool on the perineum or in the vestibule, there will not be another fistula such as to the urinary system in males. Most female patients with anorectal malformations do have egress for stool on the perineum. Most males do not.

If a female patient does not have an anal opening on the perineum, a careful look at the area between the labia, posterior to the hymen, will often reveal an opening in the vestibule. Rectovestibular fistula is relatively common. A fine lubricated dilator can be passed into the vestibular fistula confirming this anatomy.

In the male, an opening on the perineum may not be evident immediately after birth. If there is no evident opening on the perineum a period of observation, perhaps 24 hours in duration, is appropriate. If meconium appears on the perineum during this time, the patient has no fistula to the urinary system and has a malformation that is less complex. This anatomic variant is usually amenable to a one-stage neonatal reconstruction without diverting colostomy. A bag should be placed to collect urine during this time of observation because if meconium appears in the urine, it establishes the presence of a rectourinary fistula and ordinarily dictates a staged repair with initial diverting colostomy.

ASSOCIATED MALFORMATION SURVEY AND FURTHER DIAGNOSTIC WORKUP

Plain X-Rays

Any patient with an anorectal malformation should undergo a thorough evaluation for associated malformations as a recent European study found that nearly half of patients with some form of anorectal malformation were found to have an additional congenital malformation.[16] A chest X-ray should be performed to confirm the position of the nasogastric/orogastric tube in the stomach and rule out esophageal atresia. If the radiograph includes the entire patient, it can be used to evaluate for bony malformations. Sacral X-rays, both AP and lateral, should be performed to determine the sacral ratio. The sacral ratio is calculated by dividing the distance from the lowest point of the sacrum to the inferior sacroiliac joint by the distance between the inferior sacroiliac joint to the superior iliac crest; a normal ratio is 0.74 on anterior–posterior view and 0.77 on lateral view[13] (Figure 4).

Ultrasound and Echocardiogram

Babies should also undergo spinal ultrasound, feasible as the spine has not yet ossified, to evaluate for a tethered cord, present in up to 24–39% of patients.[17,18] The presence of a tethered cord warrants a neurosurgical evaluation.[19] Patients should undergo abdominal ultrasound prior to surgery to evaluate the genitourinary tract as well as any other masses which can affect management. The ultrasound

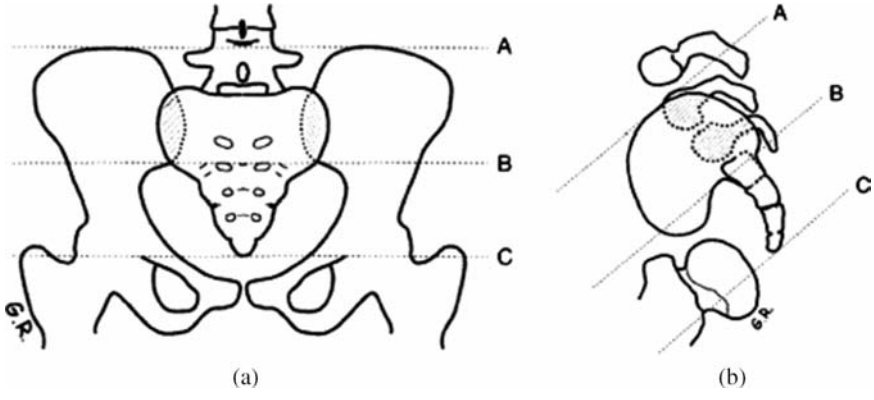


Figure 4. Sacral ratio. (a) The sacral ratio can be calculated on an AP film by measuring the distance between the lowest point visible on the sacrum to the inferior sacroiliac joint and dividing by the distance from the inferior sacroiliac joint to the superior iliac crest (BC÷AB). (b) The sacral ratio should also be calculated from a lateral film. A normal ratio is 0.74 on AP view and 0.77 on lateral view. Smaller ratios correlate with a worse prognosis for continence.

should be repeated after 72 hours as early studies may underestimate hydronephrosis due to vesicoureteral reflux. Pelvic ultrasounds in the female are done to evaluate for hydrocolpos and any other pelvic masses.

In a child without an audible murmur, who is well saturated on room air and without any hemodynamic instability, the echocardiogram should still be performed but can be deferred until after the initial surgery.

Cross-Table Lateral Prone Pelvic X-Ray

Patients without an anal opening on external examination should be observed for 24 hours to look for evidence of meconium staining on the perineum, suggesting a perineal fistula. In a male, meconium in the urine denotes that the rectum ends in a rectourinary fistula. If meconium is not observed on the perineum or in the urine the patient should undergo a cross-table lateral prone pelvic X-ray. It is performed with the baby in a prone position, a pad elevating the hips and a radio-opaque marker placed on the perineum where observation suggests the normal anus should be sited. This radiograph has replaced the previously popular invertogram in which the baby was held upside-down for a lateral film. If done correctly, this film, exploiting the air within the rectum as the contrast agent, can assess the distance from the rectal pouch to the anal marker (Figure 5). A colostomy should be performed for pouches farther than 1 cm from the marker, but

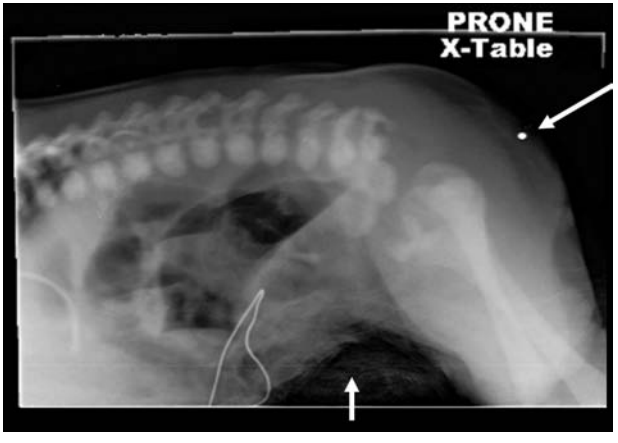


Figure 5. Cross-table lateral X-ray. A proper cross-table lateral X-ray is performed at least 24 hours after birth to allow time for the rectum to fill with air. A radio-opaque marker is placed over the anal dimple by the physician or NP (long arrow) and a rolled towel is used to elevate the hips (short arrow). If the rectal pouch is within 1 cm of the marker, a primary neonatal pull-through can be considered under the correct circumstances.

for pouches within 1 cm of the marker, primary repair is possible in the hands of an experienced pediatric surgeon.

Laboratory Tests

All children with imperforate anus should have a complete blood count (CBC), blood type, and serum electrolyte levels. In addition, all male infants with imperforate anus who have no visible external orifice or meconium staining should have a urinalysis for meconium. Meconium in the urine is diagnostic for a rectourinary fistula, and that child should undergo colostomy.

NEWBORN DECISION MAKING: COLOSTOMY OR PULL THROUGH?

The initial critical management decision centers around two factors: identifying other congenital anomalies and appropriately staging operative management for the patient's underlying anorectal malformation. The more complex the anorectal malformation, the more likely there will be other malformations;[20] and any life-threatening anomalies take precedence over the management of imperforate anus.

When no meconium appears on the perineum, approximately 24 hours is required to allow the rectum to distend with air to adequately evaluate the anorectal malformation. This time should be used to complete the above diagnostic work-up. In the meantime, the patient should be made NPO, receive intravenous hydration, and the stomach should be decompressed to prevent aspiration. If a urinary fistula is suspected, broad-spectrum antibiotics can be given, although anaerobic coverage is usually unnecessary.

Primary pull-through is reserved for infants with perineal fistula, rectovestibular fistula and a rectal pouch less than 1 cm from the perineal skin. A colostomy should be performed in children who are not amenable to primary pull-through due to the complexity of their malformation including any urinary fistula, cloaca in females, and in babies without fistula in which the cross-table lateral film shows a distance of greater than 1 cm from the perineal skin. Children with severe associated co-morbidity that requires management prior to definitive repair of the anorectal malformation should undergo colostomy. Finally, as the anatomy and malformations can be complex, primary repairs should not be attempted by surgeons without extensive experience in this area. An operation by a well-intentioned but inexperienced surgeon can jeopardize bowel control even in patients with initially good prognosis. If there is any doubt about the complexity of the defect, a colostomy should be performed (Figures 6 and 7).

COUNSELING PARENTS

Incidence

The overall incidence of imperforate anus is about 1 in 2000–5000 live births.[16,21] In females, the most common defect is a rectovestibular fistula followed by perineal fistula and then cloaca. The most common defect in males is a rectourethral fistula, again followed by perineal fistula and then by rectobladder neck fistulas. Imperforate anus without a fistula occurs in roughly 5% of all anorectal malformations in both boys and girls and is associated with Down syndrome as noted above.[11,13]

Genetics and Risks of Having Another Affected Child

The genetics of anorectal malformations is poorly understood; but it has long been recognized that a sibling of a patient is at increased risk.[22] It is felt that anorectal

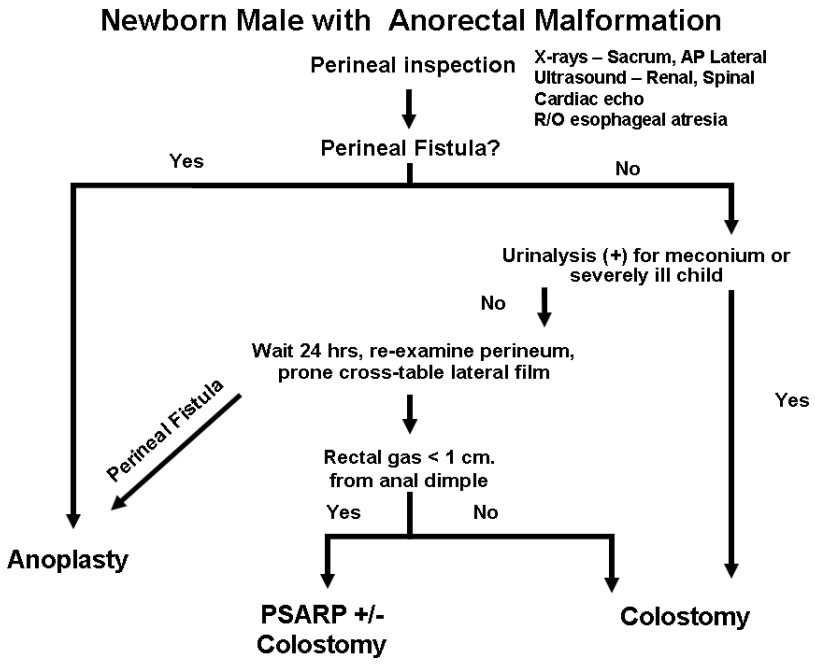


Figure 6. Algorithm for newborn males with anorectal malformations.

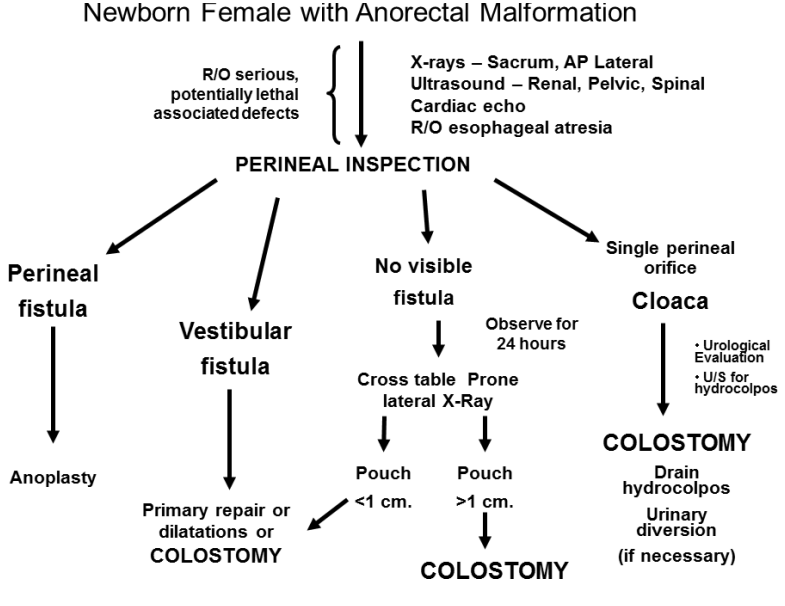


Figure 7. Algorithm for newborn females with anorectal malformations.

malformations likely develop through the interactions of a number of genes, but the precise mutations that give rise to the various phenotypes is unknown.

In a recent large retrospective study by Falcone *et al.*, the investigators stratified patients with different malformations and evaluated the risk of a family member with either an anorectal malformation or a different congenital anomaly. In their series, 2.4% of patients had at least one family member with a congenital anomaly and 1.4% had at least one family member with an anorectal malformation. In addition, children with perineal or vestibular fistulas, the risk of at least one affected family member was 5.6% for a congenital anomaly and 3.0% for an anorectal malformation.[23]

OPERATIVE RISKS

In children undergoing primary pull-through without a colostomy, there is risk of damaging the surrounding structures. Even in the absence of a fistula, the rectum and urethra share a common wall in males and careful dissection is required to prevent injury to these structures. Furthermore, these patients will require placement of a central line for total parenteral nutrition (TPN) during the postoperative period, which comes with its own attendant risks.

Parents of patients undergoing diverting colostomy with mucus fistula should be counseled regarding the standard long-term risks of this procedure including stoma prolapse, parastomal hernias, or stenosis. Skilled nurses are enormously valuable in helping families care for the ostomies.

Specific postoperative complications, both early and late, will be discussed later in this chapter.

NEWBORN TREATMENT/OPERATIVE TECHNIQUES

Colostomy and Mucus Fistula with Colonic Lavage

Colostomy with mucus fistula is indicated for neonates with imperforate anus not amenable to primary pull-through procedures. The colostomy is fashioned via a left-lower quadrant incision; and the colon is divided at the junction of the descending and sigmoid colon, leaving the sigmoid colon intact for later pull-through.

The mucus fistula should be made small and flush with the skin. In addition, it should be positioned far enough from the proximal colostomy that it can be separate from the appliance covering the colostomy. This is done to prevent fecal contamination of the urinary tract via the rectourinary fistula. Care is taken to



Figure 8. Appropriately fashioned colostomy with mucous fistula. A diverting colostomy should be fashioned with a left lower quadrant incision, dividing the colon at the junction between the descending and sigmoid colon and leaving the sigmoid intact for later pull through. The mucus fistula should be small and flush with the skin, far enough away from the proximal colostomy to be covered by a separate appliance in order to prevent fecal contamination of the urinary tract via a rectourinary fistula or impaction in the distal colon.

make sure that the mucus fistula is proximal enough that the pull through can be accomplished without tension or need to revise the stomas. When the colostomy is created, the distal colon is thoroughly irrigated to remove the impacted meconium in order to prevent urinary sepsis after the diversion and to allow for an effective distal colostogram later on (Figure 8).

Primary Newborn Pull-Through

Select patients may be able to undergo a primary repair of their defect via a posterior-sagittal approach as described below. Immediately prior to the pull-through procedure, all patients should undergo cystoscopy to clarify the anatomy and further evaluate for any additional malformation. Some have introduced primary repair without colostomy in neonates with more complex malformations such as some of the rectourethral fistulas in males. An argument has been proferred

that the chance for continence is enhanced by stimulating local nerves by allowing defecation from the earliest age. This practice has not become standard.

Postoperative Management

Once the colostomy has started to function and the patient is able to tolerate a regular diet, he or she can be discharged. The distal colostogram is done a few weeks later as an outpatient. Other malformations may be addressed.

Patients who have undergone primary repair initially should be kept strictly NPO and should be given parenteral nutrition for several days. A diet can be resumed as tolerated after about 1 week. Dilatations will be introduced after a few weeks.

Augmented Pressure Distal Colostogram

In patients who have undergone a colostomy in the newborn period, augmented pressure distal colostogram is the most important test to demonstrate the relevant anatomy in order to plan the definitive pull-through procedure. It is performed a few weeks after the creation of the colostomy. A Foley catheter is inserted into the mucous fistula and the balloon is inflated and pulled back to occlude the stoma during injection of contrast to avoid spillage. Water-soluble contrast is manually injected through the catheter under fluoroscopic control until sufficient pressure is reached to overcome the levator muscles. The contrast flows into the most distal portion of the colon and demonstrates any rectourinary communication. The injection is continued until the child voids and a film is taken to show the sacrum, rectum height, perineum, fistula location, vesicoureteral reflux, and urethra[24,25] (Figure 9). When performed properly, a voiding cystogram is unnecessary. In the authors' experience, having the surgeon present to administer the contrast ensures the study is performed correctly and that all of the important anatomy is well-visualized.

Cloaca

Once the child is thriving with a colostomy, and is stable for further workup and definitive treatment, a cloacagram is performed to clarify the anatomy and any associated malformation such as septated vagina, vesicoureteral reflux or ectopic ureter. This study includes the augmented pressure distal colostogram, but is complicated by rapid loss of injected contrast out the cloacal opening. Additional catheters may be inserted into the cloacal orifice to gather additional information during the study.



Figure 9. Augmented pressure distal colostogram. Lateral view of an augmented pressure distal colostogram demonstrating a rectourinary fistula with contrast draining into the urethra.

SECONDARY OPERATION

Surgical Technique

The present surgical approach to anorectal malformations has been championed by Dr. Alberto Peña who has offered detailed descriptions of the posterior sagittal anorectoplasty (PSARP).[26]

All but the least complex malformations are managed in his hands with initial colostomies. The key technical points in fashioning stomas are to create a widely separated double-barreled colostomy, leaving a long enough segment distal to the mucus fistula so the rectum can be mobilized for the eventual reconstruction.

Posterior Sagittal Anorectoplasty

The posterior sagittal anorectoplasty (PSARP) is done a few months after the initial stoma creation if the child is in good physiologic condition and associated malformations are not demanding attention. Some of the features that distinguish the PSARP in all its variations are a prone patient in a modified jackknife position. Transverse rolls elevate the pelvis. A transverse roll is placed under the upper chest to protect the neck from extreme flexion. A fine tipped needle cautery and

a muscle stimulator (Peña muscle stimulator, Model PS-1, Radionics) are required. A Foley catheter is placed to drain the urinary bladder. The incision is in the posterior midline centered over the site of the neoanus that is determined by identifying the place of maximal contraction when the muscles are stimulated. To contract the muscles, higher amperage is needed when the stimulation is applied across the skin. The skin must be moistened for satisfactory electrical contact. The incision is longer for the more complex malformations.

Minimal Posterior Sagittal Anoplasty

A perineal fistula in the male is usually treated in one operative stage (without initial colostomy) in the neonate by an approach Peña calls minimal posterior sagittal anoplasty. This is also used when radiographic evidence securely shows that the rectum, although without an opening to the perineum, ends less than 1 cm from the perineal skin.

Multiple fine sutures are placed circumferentially around the fistula. The distal rectum is sufficiently mobilized through a small sagittal midline incision to create a neo-anus without tension in the center of the site of maximal muscle contraction. Great care is required anterior to the rectum to avoid injury to the urethra that is anatomically opposed to the anterior wall of the rectum. The stimulator is used throughout to divide any skeletal muscle in the midline. The edges of the muscle complex are approximated both anterior and posterior to the rectum. The perineal body is reconstructed and the anoplasty done with carefully place interrupted sutures. Dr. Peña describes 16 interrupted sutures for the anoplasty.

PSARP, Male

The male with a more complex malformation needs a more extensive dissection and undergoes an initial double barreled colostomy and subsequent distal colostogram to delineate the anatomy. These patients usually have a rectourinary fistula but occasionally have a high blind ending rectum (no fistula). That is especially common in Down syndrome.

The incision for the more complex malformations is longer, starting well over the sacrum superiorly. The striated muscles are frequently assessed by the stimulator and divided in the midline. The rectum is opened vertically on its posterior wall and the fistula is isolated. The fistula exits at the inferior aspect of the rectum and should have been depicted on the distal colostogram. From the luminal

surface of the rectum, the fistula is separated with a submucosal dissection extending about 1 cm above the fistula, with care to avoid injury to the urethra, which is closely apposed to the anterior wall of the rectum above the fistula. The fistula is closed with interrupted sutures; and the colon is adequately mobilized. If necessary, a tapering rectoplasty is done posteriorly. The striated muscle complex is approximated ventral to the rectum and the rectum is placed behind this suture line. Dorsal to the rectum sutures approximate the posterior aspect of the vertically oriented striated muscle complex and the posterior rectal wall. The perineal body is reconstructed and the anoplasty performed.

Bladder neck fistulas require laparotomy combined with the posterior approach from the perineum. After the perineal dissection is done, a rubber catheter is secured behind the urethra and ventral to the levators. The muscles are approximated and the patient turned for the laparotomy. The rectum is mobilized and the bladder neck fistula is divided and closed. The end of the rectum is sewn to the catheter. The catheter is pulled down, leading the rectum to the perineum, and the anoplasty is performed.

PSARP, Female

A perineal or cutaneous fistula does not always demand repair if there is no stricture or an easily dilated fistula and a perineal body. The most common anorectal malformation is the rectovestibular fistula.[10,13] These malformations can be approached without an initial colostomy if the patient is in good physiologic condition and without limiting associated malformations.

The approach is very similar to what is described in the male. Here, the vagina has an intimate relation to the rectum and the required delicacy of the dissection separating the anterior wall of the rectum from the posterior wall of the vagina should not be underestimated. The dissection must completely separate the vagina from the rectum or else the rectum will be under tension and the fistula will recur. Any malformation more complex than these is managed initially with divided colostomies.

Minimally Invasive, Laparoscopic Approach

Minimally invasive approach to the male with rectourinary fistulas has been accomplished in many centers.[27,28] An initial colostomy allows clarification of the anatomy by a distal colostogram and decompression of the meconium from the distal colon. With a Foley catheter in place and a whole body preparation,

three trocars with 3-mm instruments can allow opening the peritoneum, dissecting the rectum and locating and dividing the fistula. The fistula can be closed on the urinary side with an endoloop.

The pelvic musculature is well visualized. At the perineum, using the muscle stimulator, the site for the anus is located and a small incision made just large enough for the anoplasty. A Veress needle within the expandable sheath of a STEP type trocar is passed from the perineum at the site of maximum muscle contraction. The surgeon at the abdomen watches to insure that the needle is passed safely just behind the urethra and in the center of the muscles which are not cut. The sheath is dilated with the blunt obturator to a 10 mm trocar. A grasper is directed from the perineum into the trocar and the operator at the abdomen directs the rectum into the grasper. The rectum is brought down to the perineum where the anoplasty is accomplished.

The clarity of the anatomy depicted on videos lends strong support to the value of this approach.

Cloaca

Definitive operations to repair the cloaca start with a cystovaginoscopy to directly clarify the anatomy. Once that is performed, if the common channel is less than 3 cm and the surgeon is confident the malformation is reparable completely through a posterior sagittal approach, the child is positioned prone. All other patients have a significant likelihood of requiring laparotomy and should have a total body preparation so they may be turned between prone and supine positions and remain sterilely draped during the procedure.

The operation is started with a posterior sagittal incision that is extended into the lumen of the cloaca. The incision is extended until the urethra is visualized and a Foley catheter is then inserted. At this point, the search begins for the rectum, which is the most posterior of structures. When a vaginal septum is present, the rectum reliably opens within the vaginal septum and may be found there. If there is difficulty finding the rectum, a Foley catheter may be inserted into the mucus fistula, and saline injected to facilitate locating the orifice. Once the rectal opening is identified, it is controlled with fine silk traction sutures and the rectum is carefully mobilized fully off of the other structures. Any vaginal septum present is resected. The total urogenital mobilization, a technique developed by Peña, is then started, by placing fine silk traction sutures all around the cloacal channel and the remaining common structure which is now essentially a urogenital sinus.[29] This sinus is mobilized as a single structure until the takeoff of the urethra is able to reach the tissue just beneath the clitoris. If there is enough vaginal length

with maximal mobilization to allow the urethra to reach, reconstruction may begin. If not, the vagina must be separated from the urethra, which requires a laparotomy and ureteral catheterization, and may necessitate vaginal augmentation or replacement. Intra-abdominally, it is prudent to assess patency of the fallopian tubes to prognosticate for future function, as well as identify any obstructed systems which may benefit from removal. Once the urethral and vaginal mobilization has been completed, reconstruction begins with delineating the borders of the muscle complex. The urethra and vagina are sewn into position. The perineal body is reconstructed. The rectum and neoanus are reconstructed similarly to other forms of imperforate anus.

Postoperative Care

A posterior sagittal incision is relatively painless. Those with a rectourinary fistula should keep the Foley catheter in place for 5–7 days. After definitive repair, the expected postoperative course is influenced by whether or not a laparotomy was performed. For those patients who have been diverted with a previous colostomy and whose definitive repair did not require a laparotomy, the postoperative hospitalization is usually brief and the patient can begin to eat after recovering from anesthesia. In more complicated repairs that required laparotomy, the postoperative course may be extended for several days while the children recover from paralytic ileus.

After discharge from the hospital patients are seen in 2 weeks. Parents are instructed how to obtain a set of Hegar dilators which are brought to the first office visit; and the surgeon measures the size of the anus. The parents are instructed how to perform twice daily dilations which are continued until the patient's anus has reached its goal size. Once dilations are complete, colostomy closure can be scheduled on an elective basis.

LONG-TERM MANAGEMENT

The major long-term complication of anorectal malformations is poor rectal function with incontinence for stool. Patients with anorectal malformations, in general, tend to suffer constipation and, as Dr. Peña has often reiterated, this may be most extreme in those with the more minor anorectal malformations who have an otherwise good prognosis.[30] Some patients develop pseudo-incontinence from constipation. They involuntarily leak stool around a fecal impaction. Constipation can also lead to fecal impaction, megarectosigmoid, and performance of unnecessary operations. Effective cleanout with a combination of enemas and laxatives

gets rid of the obstruction and allows the rectum to regain its tone and, with proper management, cures the pseudo-incontinence.[30] In the rare cases where megacolon has developed from long-standing constipation and impaction, resection may be beneficial.[31]

Those with more complex malformations, including most males with rectourinary fistulas and females with true rectovaginal fistuals and cloacas are expected to be incontinent and require bowel management to stay clean and maximize the chance for social adjustment. The goal of the bowel management program is to keep the children clean between daily enemas. If these regimens succeed the patients may be candidates for Malone procedures with antegrade colonic enemas (ACE).

Dr. Peña's group reviewed 294 children with fecal incontinence most of whom had anorectal malformations. Some had Hirschsprung's Disease and a few had spina bifida, sacrococcygeal teratomas and trauma.[32–34] His group utilizes a water-soluble contrast enema to assess the colon followed by daily enemas tailored to the individual patient, monitoring the effect with daily radiographs and checking if the child is dry between enemas. This week-long program distinguishes those who tend toward constipation, a group with a better prognosis, and those who tend toward diarrhea.

By contrast enema, the colon in those with constipation tends to be dilated. The colon in the child with diarrhea is more narrow. They advise larger volume enemas in the constipated child, half to one liter of normal saline, adding glycerin 10–30 ml and/or liquid soap 9–18 ml as needed. The volume and contents are varied as necessary until enemas have the desired result, an empty colon and a clean child.

Dr. Peña's group stopped using fleets except as a last resort after finding colitis in a few patients. The support and active participation of the patient's family requires a coordinated effort often spearheaded by nurse specialists.

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CHAPTER 8

NECROTIZING ENTEROCOLITIS

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INTRODUCTION

Necrotizing enterocolitis (NEC) is a major cause of morbidity and mortality in neonates. Although it is an acquired condition, NEC demands inclusion in this book. NEC represents a threat to the survival of newborns and especially to those with major malformations. It is one of the most common reasons a neonate needs surgical care. Despite advances made in caring for this patient population over the past several decades, mortality related to NEC has remained constant.[1] With advancements in neonatal intensive care, smaller and more premature babies are surviving, causing the incidence of NEC to increase.[2] The surgeon plays an important role in the management of NEC. Surgical intervention should not be viewed as a treatment of the disease, but rather as a way to manage associated complications. Skillful and thoughtful timing and selection of surgical interventions can markedly influence the course of the patient.

Epidemiology

The incidence of NEC is about 1 in 1000 live births.[3,4] Incidence is higher in selected populations; for example, it is as high as 7% in very low birth weight (VLBW) infants weighing less than 1500 g.[5,6] Incidence tends to increase with decreasing birth weight.[3] NEC is almost exclusively a disease of prematurity, with over 90% of cases occurring in premature infants. Full-term infants who develop NEC tend to have specific risk factors including congenital heart disease, sepsis, or hypotension.[7]

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NEC is associated with high a mortality rate (about 15–30%), which increases with lower birth weight and younger gestational age.[8] Certain demographic groups tend to have increased mortality rates, with the highest seen in VLBW black males.[3,4,9]

The majority of patients with NEC can be managed medically, while 20–40% require operation.[8] The vast majority of mortality and morbidity occurs in the group requiring surgical therapy compared to those who are successfully managed with medical therapy alone. Low birth weight predicts increased mortality in the surgically managed group as it does overall.[10]

Late complications include neurodevelopmental delay, growth restriction, and chronic gastrointestinal (GI) problems. These late complications are seen almost exclusively in the group requiring surgical intervention. Patients treated medically fare almost exactly the same as age-matched premature neonates without NEC.[11]

Pathophysiology

NEC is a severe inflammatory disorder of the intestine. It can involve any segment of the GI tract, but most commonly involves large and small bowel, usually distal ileum. Isolated small bowel involvement is the next most common presentation.[12] There is a small subgroup of patients who present with massive necrosis of the entire intestine, called "NEC totalis." NEC totalis describes total necrosis of the small and large bowel and is associated with mortality rates of nearly 100%.[13,14]

Classic histologic findings in NEC (seen in over 90% of specimens), include full thickness inflammation and coagulation necrosis (Figure 1).[12] These findings are nonspecific and provide little insight into the pathogenesis. The pathogenesis of NEC is multifactorial and not well understood. The preponderance of modern evidence now leads to a consensus that NEC results from an inappropriate or over-exuberant inflammatory response to some insult in the premature infant. This insult could be ischemia, infection, related to enteric contents introduced with feeds, or could be the translocation of normal enteric bacteria. It is not clear exactly what this insult is or why some infants exhibit a detrimental response and others do not. Evidence suggests that in the susceptible host, the insult leads to the disruption of intestinal epithelium and bacterial translocation, and the immature intestinal epithelial cells overreact.[15] There is an activation of stress pathways and the suppression of inhibitory pathways which leads to inappropriate mobilization of the host immune system and cytokine release. The result is an unfettered inflammatory response which has diffuse harmful effects.[2,16]

Several mechanisms implicate immaturity in the pathogenesis of NEC, many of which have to do with compromised integrity of the intestinal barrier in

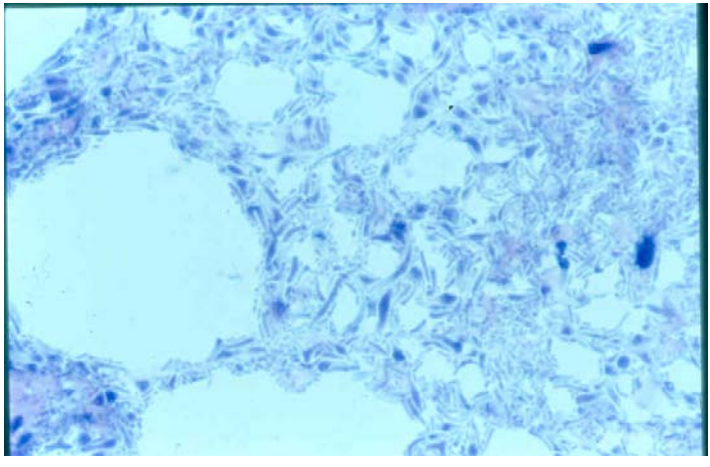


Figure 1. NEC histology. Pneumatosis with inflammation and coagulation necrosis.

premature infants. First, motility, which develops during the third trimester, is immature. Migratory motor complexes only begin to appear around week 34 of gestation.[17] Premature infants have not yet developed coordinated peristalsis; therefore, the intestinal epithelium may suffer from prolonged exposure to potentially noxious substances. Second, intestinal permeability is increased as a result of an immature mucous coat[18] and improperly formed tight junctions.[19] Lastly, contributing to weakness of the intestinal barrier is impaired regeneration after compromise.[20] All of these issues related to barrier integrity are further compounded by the fact that the GI tract immunologic defense is immature.[21]

Several substances mediate the pathogenesis of NEC, and many of these have potential implications for treatment and prevention of the disease. Nitric oxide in low levels has an important role in maintaining GI tract homeostasis, but under inflammatory conditions, it is produced in high concentrations and can have direct cytotoxic effects on enterocytes mediated by the oxidation intermediate, peroxynitrite (ONOO–).[22]

Platelet-activating factor (PAF) is an endogenous inflammatory mediator, regulated by PAF-degrading enzyme acetylhydrolase (PAF-AH). PAF can cause bowel injury via oxygen-derived free radicals.[23] It has been implicated in the pathogenesis of NEC, with higher circulating levels found in patients with NEC compared to age and disease-matched controls. The activity of the degrading enzyme PAF-AH is decreased in NEC patients.[24]

Lipopolysaccharide (LPS) the endotoxin component of gram-negative bacteria that are abundant throughout the GI tract, is another important

mediator. It impairs the barrier function of the intestine, and promotes release of inflammatory mediators such as nitric oxide, interferon gamma, and cyclooxygenase-2 which have direct toxic effects on enterocytes. It also potentiates effects of PAF.[25]

Epidermal growth factor (EGF) is essential in the development and maturation of the intestine, intestinal repair and adaptation, and prevention and treatment of inflammatory conditions. It is believed to play an important role in pathogenesis of NEC, and there is preliminary evidence that it has therapeutic potential for patients with NEC. In a randomized double-blind trial, eight neonates with severe NEC were treated with recombinant EGF. Repair of the intestinal epithelium was seen (inferred from rectal biopsy specimens), but there was no difference in clinical outcomes in this small group.[26] It is possible that EGF or related analogs could be used to prevent NEC in high-risk patients, as it provides balance in the inflammatory cascade and decreases the likelihood of bacterial translocation.

In addition to inflammatory mediators, several other important pathogenic mechanisms of NEC have been described, including intestinal ischemia and abnormal bacterial colonization. In the neonatal circulation, a delicate balance exists between vasodilation and vasoconstriction. The former is mediated by nitric oxide and the latter by endothelin-1 (ET-1). The baseline neonatal state is predominance of nitric oxide, which generates characteristic low systemic vascular resistance. Pathologic states cause endothelial dysfunction which leads to ET-1 activation and resultant vasoconstriction, promoting intestinal ischemia.[27] The relevance of this mechanism is supported by the histological finding of coagulation necrosis typically seen in NEC.

Abnormal bacterial colonization is another potential contributor to NEC. NEC usually occurs in the second week of life or later, after the neonatal intestine has been populated with flora. Flora which normally populate the intestine play an important role in maintaining the intestinal barrier, have the ability to dampen the inflammatory response, and are essential to proper maturation of intestinal epithelial cells.[28] Premature infants are more susceptible to having an imbalance of bacteria because they are exposed to a variety of nosocomial bacteria in the neonatal intensive care unit, and their immature immune systems are unable to respond appropriately even to normal bacterial colonization. Although cases of NEC are usually sporadic, outbreaks have been reported in crowded nurseries.[29,30] However, these outbreaks have never been reliably attributed to a specific infectious organism. NEC, therefore, is attributed to a failure of balance between pathogenic and commensal bacteria rather than a single infectious agent.

All of these theories underlying the pathogenesis of NEC revolve around some kind of insult leading to an inappropriate inflammatory response

which results in bowel injury. Several aspects of these theories explain the strong predilection for NEC to occur in premature infants.

Clinical Presentation

Traditionally, NEC has been described to occur in the second week of life, and almost always after start of enteral feeds. Although this may apply to infants born at 29 to 34 weeks' gestation, recent data suggest a subset of 23- to 28-week gestation infants will develop NEC at 1 to 4 months of age long after initiation of enteral feeding. Also, an increasing number of infants are developing NEC despite never having been fed.[31]

History and physical examination

Early nonspecific signs of NEC include lethargy, apnea, bradycardia, and temperature instability. These may progress to increased ventilatory requirements and poor perfusion requiring pressor support. Early GI tract signs include feeding intolerance, increased gastric residuals, abdominal distension, bilious vomiting or residuals aspirated via orogastric or feeding tube, and gross or occult blood in the stool. As the disease progresses, patients may develop abdominal wall tenderness or discoloration with erythema or ecchymosis (Figure 2), and palpable distended loops of bowel. Abdominal wall edema with concurrent discoloration is strongly



(a) (b)

Figure 2. Physical examination findings. (a) Right lower quadrant cellulitis indicating underlying perforation. (b) Abdominal wall changes consistent with massive perforation.

Table 1. Modified Bell's staging criteria for NEC.

Stage	Systemic signs	Intestinal signs	Radiographic signs
I: Suspected NEC	Temperature instability, apnea, bradycardia	Elevated gastric residuals, mild abdominal distention, occult blood in stool	Normal or mild ileus
II A: Mild NEC	Similar to Stage I	Prominent abdominal distention ± tenderness, absent bowel sounds, grossly bloody stools	Ileus, dilated bowel loops with focal pneumatosis
II B: Moderate NEC	Mild acidosis & thrombocytopenia	Abdominal wall edema & tenderness, ± palpable mass	Extensive pneumatosis, early ascites, ± PVG
III A: Advanced NEC	Respiratory & metabolic acidosis, mechanical ventilation, hypotension, oliguria, DIC	Worsening wall edema & erythema with induration	Prominent ascites, persistent bowel loop, no free air
III B. Advanced NEC	Vital sign & laboratory evidence of deterioration, shock	Evidence of perforation	Pneumoperitoneum

* DIC: disseminated intravascular coagulation; PVG: portal venous gas.
Adapted from Kleigman RM, Walsh MC. Neonatal necrotizing enterocolitis: pathogenesis, classification, and spectrum of disease, *Curr Probl Pediatr* **17**: 213, 1987.

predictive of NEC but present in only 10% of patients.[32] The course of the disease can be indolent or rapidly progressive.

Disease severity has traditionally been described using Bell's staging criteria (see Table 1).

These criteria describe stages I through III, based on systemic signs, intestinal signs, and radiographic signs, and are best used to allow more accurate stratification of patients for outcomes research. For practical purposes, patients can be thought of as having possible NEC (mild signs and symptoms without radiologic findings) sometimes called NEC scares or NEC alerts, NEC (radiologic findings or convincing clinical signs and symptoms), or perforated NEC. The fact that Bell's criteria are still in use over 25 years after they were introduced underscores the need to develop a more sophisticated understanding of NEC.

Laboratory findings

No specific laboratory abnormality is diagnostic for NEC. Possible findings include increased or decreased white blood cell count (often with increase in bands), thrombocytopenia (rapid drop in platelet count is a poor prognostic sign),[33] metabolic acidosis, hypo- or hyperglycemia, and electrolyte imbalance. In general, it is common to see nonspecific elevations in inflammatory markers, including C-reactive protein as well as white blood cell count. Bacterial and fungal cultures are not useful in making the diagnosis since no unique causative organism has been identified.

Several biochemical markers have been studied including interleukins, intestinal epithelial cell enzymes, stool endotoxin levels, urinary *D*-lactate, exhaled breath hydrogen, and others. None of these has proven to be clinically useful in making the diagnosis of NEC or predicting severity of illness.[34]

Imaging

Plain abdominal radiography is the traditional method of imaging used in the diagnosis of NEC. It can contribute important information about development of the disease process, but it is not essential to diagnosis, as patients can have extensive NEC without pneumatosis or free air. Initial radiographs are often non-specific. Plain films of the abdomen should be obtained and followed over time whenever there is suspicion of NEC. Both anteroposterior and dependent views (left lateral decubitus or cross table lateral) should be obtained as an isolated anteroposterior view is insufficient to rule out free air.

Early findings include air-fluid levels, dilated gas-filled loops of bowel, and thickened bowel walls. These same findings can also be present in sepsis with ileus, however. Pneumatosis intestinalis is the most specific radiographic finding that suggests diagnosis of NEC (Figure 3). This may represent the gaseous product of fermentation such as hydrogen gas produced by luminal bacteria acting on

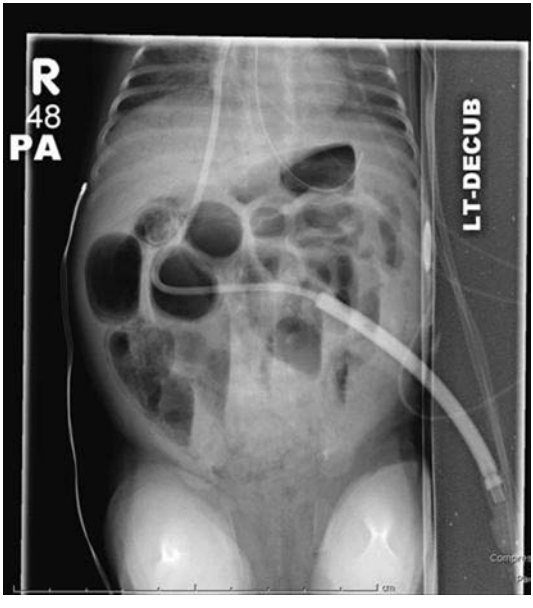


Figure 3. Pneumatosis.

ingested carbohydrate. Other findings include portal venous gas, which results from intramural gas passing into the portal venous or portal lymphatic system (Figure 4). Pneumoperitoneum can be seen in cases of frank perforation and is best visualized on the dependent view (see Figure 5). The anteroposterior supine film in the neonate with pneumoperitoneum classically may show a central lucency, known colloquially as a "football sign". "Fixed loops" of bowel that appear in the same place on serial films are suggestive of bowel necrosis, since they are not moving or peristalsing. A gasless abdomen is also concerning for advanced disease as it suggests fluid-filled loops of bowel or significant ascites, but it can also occur in a neonate who is simply on muscle relaxants and not swallowing air (Figure 6).

Abdominal ultrasound has been investigated over the last several years as a way to image NEC.[35] Potential advantages of ultrasound over plain films include ability to assess bowel perfusion using Doppler imaging, evaluate thickness and echogenicity of the bowel wall, identify free fluid or localized fluid collections, and determine if peristalsis is present to suggest bowel viability. Theoretically, ultrasound may be most useful to confirm or rule out NEC when plain films are equivocal or the patient's clinical course does not match the evolution of



Figure 4. Portal venous gas.

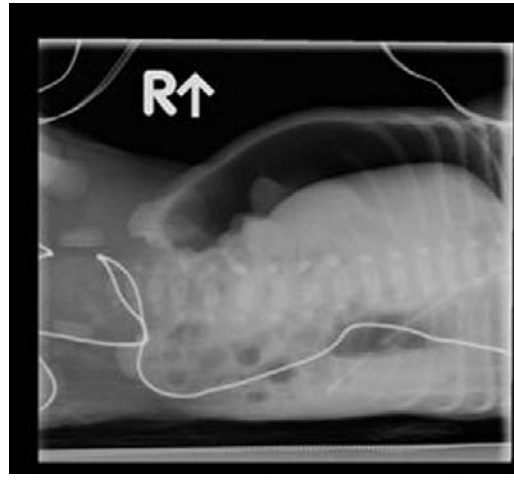


Figure 5. Pneumoperitoneum on dependent view.

radiographic findings.[36] It is important to emphasize that currently there is no evidence of any advantage of ultrasound over plain films. In fact, ultrasound may actually "over-read" some cases and lead to unnecessary operations. In addition, it is a highly subjective and operator-dependent test, and as yet no consensus has been reached regarding diagnostic criteria. The role of ultrasound in diagnosis

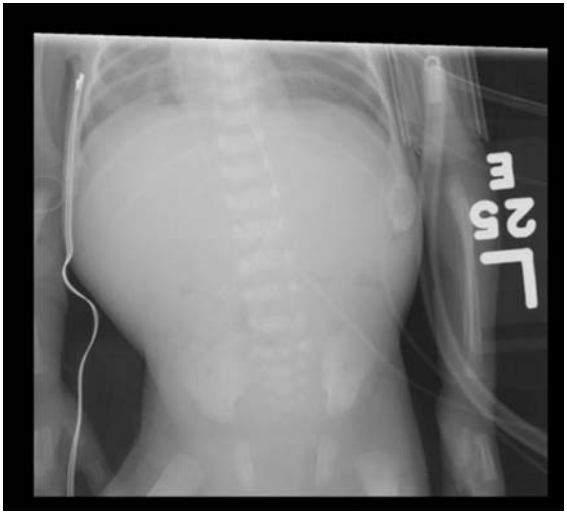


Figure 6. Gasless abdomen.

and management of NEC is still under investigation; plain films remain the gold standard at this time.

Contrast studies, CT, and MRI have been investigated but have not proven useful in diagnosing or following the course of patients with NEC.

Differential diagnosis

The most important alternative diagnosis to consider when evaluating a patient with potential NEC is septic ileus, as the initial presentation can be identical. Therefore, it is important to consider and treat alternative etiologies of sepsis. Differential diagnosis also includes other causes of abdominal distension that may be seen in neonates including Hirschsprung's disease, jejunoileal atresia, meconium ileus, volvulus, and intussusception. Clinical examination (peritonitis, abdominal wall erythema) and radiographic findings are helpful in distinguishing NEC from septic ileus or other causes of abdominal distention.

Focal intestinal perforation (FIP) has been described in premature infants in the first 7–10 days of life, often in those with patent ductus arteriosis receiving indomethacin. It is not clear whether this is a different disease entity or limited NEC. However, making this distinction is not necessary because management is essentially the same.

TREATMENT

As soon as the diagnosis of NEC is suspected, certain diagnostic and therapeutic measures should be undertaken immediately. These include bowel rest, decompression with an orogastric tube, blood, urine and sputum cultures, broad-spectrum antibiotics targeting enteric organisms, intravenous fluid resuscitation, and serial abdominal examinations and abdominal films. A pediatric surgeon should be involved early and see the patient regularly.

Medical Management

Patients without obvious radiographic signs of bowel perforation are treated with expectant management, close observation, serial abdominal examinations, and radiographs. As long as the clinical course is stable or improving, medical management can be continued. Increased ventilator support, hemodynamic support with pressors, and blood transfusions may be required and do not necessarily indicate failure of medical management. Surgical intervention should be considered for patients who deteriorate clinically in spite of optimal medical management or develop radiographic signs of bowel perforation. Patients with NEC who recover following medical management tend to have shorter lengths of hospitalization, with an average of 2 to 3 months versus 4 to 5 months for those requiring surgery.[37]

Surgical Management

Bowel perforation, diagnosed by pneumoperitoneum seen on abdominal films or paracentesis positive for stool or bile, is the only absolute indication for surgical intervention.[39] Paracentesis may be useful when patients deteriorate clinically in the absence of definitive radiographic evidence of perforation on plain films.[40] Relative indications for operation include clinical deterioration despite optimal medical management, peritonitis or abdominal wall erythema, extensive pneumatosis, portal venous gas, or fixed loops of bowel on serial abdominal films.[32] These signs and symptoms should be interpreted within the context of the patient's general clinical condition; none of them in isolation warrant surgical intervention. Ideally, surgical intervention should take place when bowel is nonviable but before it has perforated. It is extremely difficult to achieve this perfect timing, because often it is the perforation itself which leads to the clinical deterioration that prompts a trip to the operating room. Many severely ill neonates with NEC never progress to the point of perforation and recover without operation. A more aggressive approach promoting earlier operative intervention would likely subject

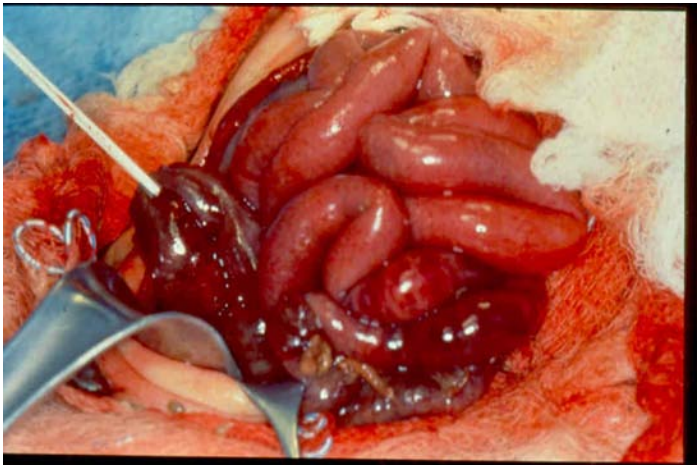


Figure 7. Intra-operative disease adjacent to normal bowel.

many infants to operation who would have recovered with medical therapy. Surgical treatment is reserved for cases where bowel necrosis or perforation is highly suspected.

Approach to operation

There are two commonly practiced approaches to surgical therapy in patients with NEC: laparotomy with resection of affected bowel and primary peritoneal drainage (PPD).

Laparotomy

The goal of laparotomy is to resect only frankly nonviable bowel and leave behind any bowel that has a chance of survival, even if it looks marginal in order to minimize the risk for short bowel syndrome (Figure 7). There is no role for histologic evaluation of margins or resection back to histologically normal bowel. Following resection, most commonly the intestinal stream is diverted by creating an ostomy proximal to the disease. Complex cases may be treated with multiple ostomies or even an ostomy proximal to compromised but viable bowel.

Several different strategies can lead to successful stoma creation. End stoma, stoma with mucus fistula, and loop enterostomy have all been advocated with no significant differences in complication rates.[40] Exteriorization techniques also

vary. A single stoma can be brought out through the surgical incision or a separate incision, while double barrel stomas can be fashioned at the same end or at opposite ends of the incision. Given the already tenuous blood supply to the exteriorized bowel, maturing the stoma is not recommended. Stoma complications are relatively common but usually can be managed successfully without significant morbidity. Very few centers advocate primary anastomosis in order to avoid stoma complications, and no reliable data support primary anastomosis in NEC.

Cases of diffuse intestinal involvement pose a unique challenge. In general, the principle is to preserve as much bowel as possible while resecting only the amount necessary to stabilize the patient. This can be achieved in several different ways. Some advocate the "clip and drop" technique, during which affected segments are resected and blind ends of intestine are dropped back into the peritoneal cavity. The patient is then re-explored 48–72 hours later, at which time further bowel is resected as necessary, and primary anastomosis is performed or stomas are created.[41,42] Primary diversion is another approach, where a single enterostomy is created proximal to the involved bowel without resection. In these cases, impressive recovery of apparently necrotic segments of bowel has been reported at the time of enterostomy closure.[43]

Primary peritoneal drainage

Peritoneal drainage was initially described in the late 1970s as a salvage procedure for patients who were "too sick to tolerate laparotomy".[44] When some of these patients survived and did not go on to require laparotomy, this approach rapidly evolved into a primary treatment strategy rather than a temporizing measure.

Peritoneal drainage is accomplished under local anesthesia by making a small (about half-centimeter) full-thickness incision in either the right or left lower quadrant of the abdomen, manually expressing and then irrigating stool or pus, and then placing a quarter-inch drain into the peritoneal cavity (Figure 8). In some cases, multiple drains are needed to provide effective drainage. Patients undergoing PPD often deteriorate before they get better. Some advocate salvage laparotomy in these cases, but this has not been shown to improve outcomes.[45,46] A certain proportion of neonates undergoing either PPD or primary laparotomy will survive but require delayed laparotomy for treatment of bowel obstruction or stricture.

Laparotomy versus PPD

Arguments in favor of PPD over laparotomy include the lack of general anesthesia, lower degree of invasiveness of the procedure, fewer accompanying fluid shifts

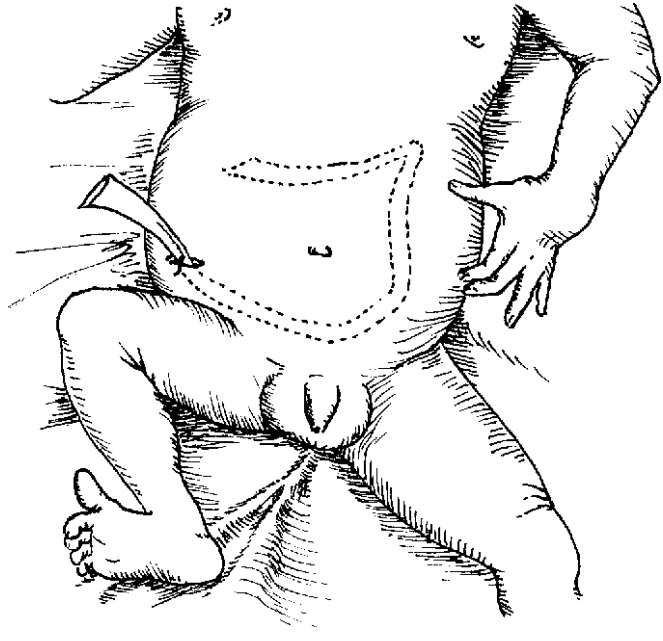


Figure 8. Peritoneal drainage.

and metabolic derangements, and potential avoidance of complications related to enterostomies or anastomoses as well as short bowel syndrome since no bowel is resected. The major argument against PPD is that undiverted perforated bowel segments remain *in vivo* and can be a source of ongoing sepsis.

Many small, retrospective, single-institution case series have been performed to evaluate laparotomy versus peritoneal drainage as a primary strategy in managing patients with surgical NEC. In general, these studies are not useful in forming treatment guidelines because of significant bias in the assignment of patients to one treatment or the other; for example, PPD only being used for infants who were thought to be too sick to tolerate a surgical procedure. Also, these studies usually evaluate only short-term outcomes.[47]

Three large prospective studies have been performed in an attempt to identify whether PPD or laparotomy leads to improved outcomes for patients with NEC, including one cohort study and two randomized controlled trials. The National Institute of Child Health and Human Development (NICHD) neonatal research network performed a 16-center, nonrandomized study of 156 extremely low birth weight (ELBW) neonates (less than 1000 g) with either NEC or FIP who

underwent PPD or laparotomy.[48] Eighty patients were treated with PPD and 76 with laparotomy at the discretion of the treating physician. Twenty-four percent of the PPD group went on to "require" laparotomy. Long-term mortality in the PPD group was 55% compared to 45% in the laparotomy group, but after adjusting for covariates, there was no statistically significant difference in mortality, need for prolonged enteral nutrition, or neurodevelopmental impairment at 18–22 months' adjusted age. This suggests that this study was vulnerable to similar biases as the previously described small case series, with smaller and sicker infants more likely to undergo PPD and, therefore, fare worse than healthier babies who had laparotomy.

Moss *et al.* published the first randomized controlled trial attempting to compare outcomes of laparotomy versus PPD for NEC.[49] The authors randomly assigned 117 infants less than 34 weeks' gestation and less than 1500 g at 15 pediatric centers to undergo PPD or laparotomy. An important feature of clinical management in this trial which distinguishes it from other prospective studies is that they discouraged salvage laparotomy in the PPD group. In the end, five patients in the PPD group (9%) had laparotomy between 2 and 45 days postdrainage for clinical deterioration, and 16 had elective, delayed laparotomy after 45 days for stricture, obstruction, or feeding intolerance. Mortality, dependence on total parenteral nutrition (TPN), or length of stay was no different between the two groups at 90 days.

Another randomized controlled trial was published by Rees *et al.*[50] In this trial, 69 ELBW neonates from 31 centers in 13 countries were randomized to PPD or laparotomy. All patients had pneumoperitoneum from NEC or FIP. In contrast to the study by Moss *et al.*, the authors were more liberal with the use of delayed laparotomy following PPD after at least 12 hours without clinical improvement, which was performed in nearly three-quarters of patients in the PPD group (26 of 35 patients) after a median of 2.5 days. This group had no statistically significant difference in six month survival (51.4%) compared to the primary laparotomy group (63.6%); however, a trend toward improved outcomes was observed with primary laparotomy. The study was limited by a small sample size. The authors suggested peritoneal drainage was not effective as a primary treatment or salvage technique.

Major differences in the two described randomized controlled trials are the rate of salvage laparotomy in the PPD group and standardization of care between groups. Moss *et al.* utilized salvage laparotomy in only 9% of PPD patients, while Rees *et al.* performed a laparotomy if there was no clinical improvement a minimum of 12 hours after PPD, which ended up being the case for close to 75% of patients. Moss *et al.* treated all patients under a standardized care pathway while Rees *et al.* allowed

more discretion to the treating center. This approach, and the fact that three-quarters of PPD patients in the later study ended up having laparotomy, makes it difficult to come to a conclusion about the efficacy of peritoneal drainage.

The overall conclusion based on outcomes of all three prospective trials seems to be that the rate of mortality or prolonged TPN dependence does not differ in patients with advanced NEC regardless of whether peritoneal drainage or laparotomy is used as initial surgical treatment. More data is needed to evaluate the incidence of long-term complications, such as short bowel syndrome and reoperation for strictures and bowel obstruction, in patients undergoing PPD versus laparotomy. At this juncture, it appears that the choice of surgical therapy is not a major determinant of outcome in patients with NEC.

Postoperative care

After patients undergo laparotomy or PPD, they are likely to have significant ongoing fluid requirements. Pressor and ventilator support should be provided as necessary. Decompression with an orogastric tube should be continued until there is evidence of bowel function, and antibiotics should be continued for at least 7 to 14 days postoperatively.

Patients who have enterostomies at the time of bowel resection should be evaluated for enterostomy closure anytime from 1 to 4 months postoperatively. In general, patients should weigh at least 2 kg and have demonstrated maintenance of adequate feeding and growth prior to stoma takedown.[51] Sometimes it is necessary to be more aggressive in reversing proximal enterostomies because of difficulties with fluid management and inadequate weight gain. The distal bowel should be evaluated with a contrast study to identify potential strictures prior to enterostomy closure so that these can be addressed at the time of surgery.

OUTCOMES

Many patients who survive their initial episode of NEC are challenged with a variety of short- and long-term complications. Recurrence happens rarely (about 5%) and is usually managed nonoperatively.[52] NEC may recur at the initial site of disease, but it is possible to have recurrence anywhere along the GI tract. Stoma complications are a common problem; they occur in at least half of patients who survive and include prolapse, stricture, and retraction.[53,54] In some cases, these complications require surgical intervention. Fluid losses from a proximal jejunostomy can cause problems with dehydration, electrolyte imbalance, failure to gain



Figure 9. Contrast enema showing sigmoid colon stricture from NEC.

weight, and peri-stomal skin breakdown. It is important to anticipate and manage these potential stoma problems aggressively in order to achieve successful outcomes. Wound infections and dehiscence are not rare in this setting.

Intestinal strictures are an intermediate-term issue. They typically are identified in an infant who develops signs of bowel obstruction despite an apparent successful recovery after medical management. They also can occur after surgical management of NEC regardless of initial treatment strategy with primary laparotomy or PPD.[48,53,57] Up to one-third of patients who survive stage II or III NEC may develop strictures,[55] which are most commonly found in the left colon.[13] Patients typically present in an insidious manner with progressive obstructive symptoms. Rarely, they will present acutely with signs of sepsis or peritonitis. Alternatively, a stricture may cause partial distal intestinal obstruction leading to bacterial overgrowth and chronic, progressive diarrhea. This potentially confusing presentation can result in delayed diagnosis; so any infant with progressive diarrhea who recovered from NEC as a neonate should be investigated with a contrast enema and, if not revealing, subsequent UGI-SBFT to rule out stricture.

Prior to enterostomy closure, patients who have had bowel resection should undergo routine contrast evaluation of the intestine distal to the stoma to evaluate for stricture (Figure 9). Few clinicians advocate routine imaging for patients with medically treated NEC.[57] The standard of care for treatment of symptomatic strictures is resection. Asymptomatic patients can be followed radiographically and undergo surgical intervention only if they become symptomatic or the

disease progresses significantly such that it is likely to cause symptoms. Balloon catheter dilatation has been described as an alternative to resection for focal lesions where the bowel lumen is still patent.[58] This technique should be considered investigative.

Several long-term complications have been described when patients with NEC are followed into their early childhood years. Up to one-quarter of patients with NEC suffer from short bowel syndrome as a result of inadequate bowel length following extensive resection or from poor function of remaining intestine despite seemingly adequate length. In fact, NEC is the most common cause of short bowel syndrome in childhood. Certain segments of intestine have an increased ability to undergo adaptation. The ileum has the greatest capacity; therefore, patients with jejunal disease tend to do better long-term than those requiring extensive ileal resection. It is unclear whether preservation of the ileocecal valve truly influences adaptation as data on outcomes for NEC patients with and without the ileocecal valve are mixed. Overall, adequate length and function of remaining bowel, as well as the presence of the distal ileum seem to be more important than preservation of the valve.

Long-term complications following NEC can involve more than just the gastrointestinal system. Neonates who survive stage II or III NEC are more likely to have impaired growth rates. This is a significant problem for children with short bowel syndrome, but even children with adequate intestinal absorptive capacity often fall below the 50th percentile for weight and height several years after suffering NEC.[59]

Neurodevelopmental delay is also common among NEC survivors, occurring in 15–30% of patients.[59,60] Reported problems include speech and motor impairment, intellectual delays, and problems with personal and social skills.[60–63] NEC patients who require surgery are almost twice as likely to have neurodevelopmental impairment as those treated medically. Furthermore, neurodevelopmental delay is no more prevalent in NEC patients managed medically than age-matched premature infants without NEC.[63]

PREVENTION

Prevention may have the greatest potential to impact adverse outcomes related to NEC. Many prevention strategies currently exist, but none of these are evidence-based.

Many studies have investigated the benefits of human breast milk in preventing NEC. Physiologically, it seems logical that human milk would be protective against NEC because of its antimicrobial and antiinflammatory properties.

However, proving efficacy in clinical trials has been challenging due to the lack of standardized definitions of what comprises human breast milk (maternal versus donor, fortified versus unfortified, human milk alone versus human milk supplemented with formula). Meta-analyses of several small randomized controlled trials suggest that human milk slightly reduces the risk of NEC,[64,65] while fortification of human milk does not increase the risk.[66] However, these studies should be interpreted with caution because they include small numbers of patients, nonuniform definitions of human milk, and variable incidences of NEC. Data from a large-scale prospective randomized trial is needed to definitively determine if human milk has any real benefit in NEC prevention.

The timing of initiation of enteral feeds also has been implicated as a possible causative or preventative factor. Early enteral feeding is advantageous in that it decreases need for TPN, reduces TPN-associated complications, and promotes growth in preterm infants. However, the effects of early enteral feeding on the risk of NEC are unclear. A meta-analysis of two small randomized controlled trials showed that early feeding had no impact on the incidence of NEC, but the sample size (82 patients) may not have been sufficient to demonstrate a difference.[67] In contrast, one larger prospective study found that early feeding was protective against NEC but only if human milk was used; early feeding of formula actually increased the risk of NEC by 20% for each day earlier formula feeds were started.[68] Early feeding may be beneficial, therefore, as long as human milk is used, but early initiation of formula should be considered with caution.

Similar concerns exist regarding the rate of advancement of enteral feeds. Rapid advancement may promote rapid weight gain, but also may lead to an increased incidence of NEC. Results have been mixed regarding the impact of rate of advancement of feeds on incidence of NEC. One randomized controlled trial was terminated early (after 141 patients) because the incidence of NEC was higher following rapid enteral feeding advancement.[69] On the contrary, a systematic review of three trials (372 patients) showed no difference in NEC rates regardless of whether a rapid or slow advancement feeding strategy was utilized.[70]

Some authors advocate supplementing enteral feeds with specific amino acids as a way to prevent NEC. However, randomized controlled trials evaluating arginine and glutamine supplementation have not shown any significant reduction in the incidence of NEC.

Multiple studies have evaluated the administration of oral antibiotics and probiotics as a prevention strategy based on the fact that an imbalance between pathogenic and commensal enteral bacteria is thought to play an important role in the pathogenesis of NEC. Although oral antibiotics may decrease the amount of pathogenic organisms populating the intestine, they also have the potential to

increase the development of resistant organisms. Five randomized controlled trials have investigated the impact of prophylactic enteral antibiotics, and none found a significant reduction in NEC. Even though one meta-analysis did achieve statistical significance, the potential adverse effects in terms of breeding resistant organisms were not reported.[71] Therefore, prophylactic enteral antibiotics are currently not recommended as a prevention strategy.

Probiotics similarly may help to prevent NEC by restoring the balance between commensal and pathogenic intestinal flora but may pose a risk of harmful effects in this immunocompromised patient population. Several studies have shown that probiotics do indeed influence intestinal colonization, and two meta-analysis of randomized controlled trials suggests that administration of these agents decreases the incidence of NEC.[72,73] These results seem promising. A large-scale trial has not yet been done, and safety considerations need to be evaluated before routine use of probiotics can be recommended with confidence.

CONCLUSION

NEC is a major cause of morbidity and mortality in the neonatal population. Even patients who survive the initial episode are plagued with intermediate to long-term complications such as short bowel syndrome and strictures as well as neurodevelopmental impairment and growth restriction. Despite extensive research efforts, outcomes have not significantly improved over the past 50 years since the disease was initially described. We are still unable to predict who will develop NEC or go on to require operation, and we can do little to prevent it. Further investigation exploring the molecular and genetic mechanisms that lead to NEC and determine severity of disease in individual patients remains crucial for development of successful preventative and treatment strategies. Ongoing efforts in prospective data collection also are essential to identify aspects of NEC management strategies that are more likely to lead to increased survival and improve short- and long-term outcomes.

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CHAPTER 9

ESOPHAGEAL ATRESIA

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INTRODUCTION

Esophageal atresia has remained the defining challenge for several generations of pediatric surgeons. Coveted by pediatric surgical fellows and featured in the commercial hit movie "M*A*S*H", these cases have epitomized a pediatric surgeon's ability to repair a catastrophic embryologic anomaly and restore normal life. Today, thanks to the contributions of many brilliant pediatric surgeons, anesthesiologists, and neonatologists, children with esophageal atresia cannot only survive but thrive as they head into early childhood. As a result of this work, associated anomalies have now surpassed esophageal atresia as the greatest barrier to survival and a rich quality of life.

Nearly one third of all infants with esophageal atresia have associated anomalies connected with the VACTERL syndrome. Hence, once the diagnosis is made it is critically important to perform a complete physical examination and obtain an echocardiogram as well as appropriate radiologic imaging to rule out associated Vertebral, Anal or Intestinal, Cardiac, Renal, and Limb/Lung anomalies. Additionally, genetic and neurologic screening should be done in every case. Moreover, since many infants are now diagnosed prenatally, it is often important to consult with the maternal fetal medical specialist or fetal radiologist who may have pertinent information to share concerning associated anomalies.

Historically, the incidence of esophageal atresia has been 1 in 5000 live births, although it does appear that, in developing countries, this rate may be declining

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as the result of selective termination used in conjunction with prenatal screening. This is difficult to assess due to regional differences in prenatal management and referral patterns. This emphasizes the need for pediatric surgical involvement in fetal care programs to educate prospective parents and healthcare providers about treatment options, risks, benefits, and expected outcomes for esophageal atresia.

History

The history of esophageal atresia is relevant to the many treatment options available to the pediatric surgeon today. Every case of esophageal atresia is different in terms of anatomy, gestational age, and associated anomalies; and surgical treatment has evolved through many iterations over the past six decades.

Esophageal atresia was uniformly fatal until 1939 when Leven[1] salvaged one patient using a three-staged repair including gastrostomy, extra-pleural division of an associated tracheoesophageal fistula, and cervical esophagostomy. Two years later, the first successful primary repair of esophageal atresia with fistula was performed by Haight[2] who very clearly described the technical innovations that would pave the way for future success, including meticulous mobilization of the proximal and distal ends of esophagus, an interrupted two layer closure, and attentive perioperative care including initial fluid restriction and esophagram prior to feeding.

Twenty years later, Waterston[3] proposed a risk classification (Table 1) based upon a large series of patients with esophageal atresia and tracheoesophageal fistula that demonstrated greater than 90% survival in infants greater than 2000 g without congenital anomalies compared to less than 50% survival in premature infants with congenital anomalies, especially cardiac.

At about the same time, Holder *et al.*[4] reported significantly improved survival in high-risk premature infants with esophageal atresia and tracheoesophageal fistula using a staged repair, including gastrostomy followed by fistula ligation, and then

Table 1. Waterston Risk Classification for infants with esophageal atresia and tracheoesophageal fistula.

Group A:	Over 5.5 lb birth weight and well.
Group B:	1. Birth weight 4–5.5 lb and well.
	2. Higher birth weight, moderate pneumonia and congenital anomaly.
Group C:	1. Birth weight under 4 lb.
	2. Higher birth weight and severe pneumonia and severe congenital anomaly.

delayed primary anastomosis when the infant's condition would safely permit. Using this strategy of repair, he achieved 66% survival in high-risk Waterston C infants. His strategy became the standard of care for high-risk infants with esophageal atresia and tracheoesophageal fistula and continues to be selectively used today by many surgeons both to maximize survival and minimize complications.[5] In that era, survival of high-risk infants with esophageal atresia and tracheoesophageal fistula ranged between 30% and 70% depending upon associated risk factors, while survival of contemporaneous low-risk infants approached 100%.

With improved technical support, surgical techniques, and perioperative care, surgeons began to have increasing success with primary repair in select high-risk infants. In 1972, Abrahamson and Shandling at the Hospital for Sick Children in Toronto[6] reported equivalent survival in groups of high-risk infants treated by primary versus staged repair. Although the study groups were not really comparable, the authors concluded that most high-risk infants could be safely treated by primary repair irrespective of weight, even when other complications were present. Ten years later, Louhimo and Lindahl at the University of Helsinki[7] reported similar findings and suggested a modification of the Waterston classification to exclude pneumonia and general condition from the criteria. Like the surgeons in Toronto, they reserved staged repair for infants who were desperately ill with severe respiratory problems or associated gross anomalies, any one of which were life-threatening. Using their modified risk classification, they reported incrementally increased survival in all categories: 100% survival in group A patients, 95% survival in group B patients, and 57% survival in group C patients. As these outcomes were emulated in many centers throughout North America, it became clear that some high-risk infants with esophageal atresia would not survive even with a repaired esophagus, and esophageal atresia was no longer a limiting factor in the survival of infants with prematurity or associated congenital anomalies.

One of the great unresolved technical challenges concerning esophageal atresia is long-gap atresia and so-called ultra-long-gap atresia, defined as a separation of greater than 6 cm between proximal and distal esophageal ends. Long-gap atresia may be found in association with tracheoesophageal fistula, but most commonly occurs in the absence of fistula, sometimes referred to as "pure" esophageal atresia. As discussed below, this anomaly is encountered much less frequently than esophageal atresia and tracheoesophageal fistula and may be temporized in virtually all infants by placement of a gastrostomy tube for feeding along with intermittent nasopharyngeal suction to prevent aspiration pneumonia.

Initial attempts at early primary repair of pure, long-gap atresia invariably failed. Attention soon turned to use of esophageal replacement procedures including the following: gastric pull-up, first performed at the Hospital for Sick Children in

Toronto in 1952 and later modified by Spitz;[8] colon replacement, first reported by Dale and Sherman in 1955[9] and subsequently advocated by Grosfeld,[10] Hendren[11] and others; and finally gastric tube reconstruction, first reported by Burrington and Stevens[12] in 1968 and later advocated by Anderson[13] and Ein.[14] These three procedures have been used concurrently for nearly 50 years and continue to be selectively used by some surgeons with variable success. Each of these procedures has its advocates and each its complications including leak, stricture, gastroesophageal reflux, and dysphagia requiring surgical revision in as many as 50% of all patients.[15]

In experienced hands, esophageal replacement may serve as an excellent substitute for the real thing, although even its staunchest advocates have admitted that the patient's own esophagus works best. In this regard, several early contributions set the stage for delayed primary repair of pure long-gap atresia that has become not only feasible but achievable in most cases. In 1965, Howard and Myers[16] reported a successful technique for elongating the proximal pouch using daily bougienage and delayed primary repair. Several years later, Livaditis[17] reported the ingenious technique of circumferential esophagomyotomy of the proximal pouch. Using these techniques to construct a well-vascularized single layer anastomosis under tension, a number of surgeons demonstrated excellent results using delayed primary repair in the 1980s.[18–20] Since then, the trend in North America has been toward delayed primary repair for long-gap atresia, utilizing esophageal replacement only for failures or extremely complicated cases.

ANATOMY AND EMBRYOLOGY

The normal esophagus arises from the proximal end of the foregut. The respiratory diverticulum emerges from the laryngeal groove on the ventral surface of the proximal foregut by the end of the fourth postconceptual week. A septating process occurs between the evolving ventral trachea and dorsal esophagus. The trachea and esophagus, therefore, share a common ancestry, the primitive foregut. The etiology of esophageal atresia is unknown but involves a mesenchymal field defect that results in several distinct anatomical patterns. Occurring in nearly 90% of cases, the most common form is a blind proximal esophageal pouch that ends at the 2nd–4th vertebral body and a tracheoesophageal fistula that leads to the distal esophagus and stomach. The blood supply to the proximal pouch originates from the thyrocervical trunk and reaches the caudal aspect of the blind ending pouch through the submucosal plexus allowing circumferential dissection and circular myotomy without interruption of the circulation. The distal tracheoesophageal fistula usually joins the back wall of the trachea just proximal to the carina but may enter the trachea cranial or caudal to that site and may even enter the right or left main stem bronchus below the carina. The blood supply of the

distal esophagus consists of fragile vessels that originate from the aorta and are easily damaged by surgical dissection.

In most cases, separation of the proximal pouch and distal tracheoesophageal fistula does not exceed three vertebral bodies, although it can be as many as six. In contrast, esophageal atresia without fistula (pure esophageal atresia) typically involves a separation of at least six vertebral bodies. Although pure esophageal atresia is the second most common type of major esophageal malformation, it occurs in only 5–7% of cases, and has a similar profile of associated anomalies compared to the more common form of esophageal atresia (with distal TEF). It is important to recognize that both forms of esophageal atresia may be associated with a right descending aorta which significantly affects exposure, mobilization, and ultimate reconstruction of the esophagus. Thus, it is critical to review aortic position on the preoperative echocardiogram before proceeding with operative repair.

Other forms of esophageal atresia and/or fistula are rare. For example, H-type fistula without atresia occurs in 2% of cases. Usually, this is a single fistula which is slanted cranially from the esophagus to the trachea and is located close to the 2nd–3rd vertebral body allowing exposure through the neck. Even less common is a double fistula with atresia, in which a fistula connects the blind proximal pouch to the trachea in addition to a distal tracheoesophageal fistula. Some surgeons have recommended routine preoperative endoscopy in order to rule out a possible proximal fistula prior to thoracotomy. An alternate approach is to perform a complete circumferential dissection of the proximal pouch extending to the thoracic inlet in order to rule out the possibility of a proximal fistula. Least common of all is a proximal tracheoesophageal fistula with distal esophageal atresia. This deformity is thought to be incompatible with life and has been diagnosed primarily at autopsy.

CLINICAL PRESENTATION

Those infants with esophageal atresia who are not diagnosed prenatally present shortly after birth with acute onset of respiratory distress. Within the first few hours, the infants usually develop coughing, excessive salivation, and drooling. If fed by mouth, they begin to choke and gag leading to a drop in oxygen saturation and cyanosis. If not treated, they will eventually develop acidosis, heart failure, and death.

Infants with proximal atresia and distal tracheoesophageal fistula may present with a more precipitous course than those with pure atresia. As their respiratory distress worsens, they often force air into their stomach which in turn causes gastric distension and reflux of acidic gastric contents through the fistula and into the endobronchial tree. This does not occur in infants with pure atresia who are not as sick as those with tracheoesophageal fistula and may survive longer without treatment.

Infants with H-type fistula (TE fistula with no atresia) usually do not present at birth but weeks to months later with upper airway congestion, gastroesophageal reflux, and recurrent pneumonia. Their symptoms are subtle and may be difficult to recognize initially; but most will present with a pattern of choking, coughing, and gagging with feeds or with persistent upper airway congestion or gas bloating minutes after feeding. Whether infants present in the newborn period or months later, these symptoms should provoke in the surgeon a high index of suspicion and low threshold for diagnostic investigation.

DIAGNOSIS

The diagnosis of esophageal atresia may be made with a 6–8 French nasogastric tube. If the tube can not be passed beyond 9–11 cm from the mouth or nose of an infant under suspicion, then the diagnosis is verifiably esophageal atresia. A "babygram" (chest and abdominal radiograph) will often show an air esophagram with the tube stopped or coiled in the blind end of the proximal esophageal pouch near the 2nd–4th vertebral body (Figure 1). More



Figure 1. Babygram of infant with esophageal atresia and tracheoesophageal fistula. Note coiled Replogle tube in blind ending upper esophagus at thoracic inlet.



Figure 2. Babygram of infant with pure esophageal atresia. Note absence of gas below the diaphgram and Replogle tube in upper esophagus.

importantly, the radiograph will demonstrate the presence or absence of intestinal gas beneath the diaphragm. If gas is present, the patient has a distal tracheoesophageal fistula. On the contrary, if there is no intestinal gas beneath the diaphragm (a gasless abdomen), the patient has pure esophageal atresia (Figure 2).

In addition to careful physical examination, a number of noninvasive studies should be obtained prior to definitive repair. On examination, particular attention should be paid to the possibility of a cardiac murmur (that may indicate a structural cardiac defect), genitourinary anomalies, and/or anorectal malformation and limb abnormalities. Following a complete physical examination and babygram as previously mentioned, several noninvasive studies should be performed prior to definitive repair. Most important of these is an echocardiogram to detect a possible associated structural cardiac defect (23%) as well as a possible right aortic arch (5%). Other studies that should be done prior to definitive repair of the esophageal atresia include renal ultrasonography as well as AP and lateral radiographs of the lumbosacral spine. Contrast esophagram is generally not required and, in fact, may be harmful. For example,

administration of oral barium to an infant with esophageal atresia could lead to barium aspiration and death.

Some surgeons recommend routine triple endoscopy including laryngoscopy to rule out a laryngoesophgaeal cleft, rigid esophagoscopy in order to rule out a proximal tracheoesophageal fistula, and rigid bronchoscopy in order to indentify the location of the tracheoesophageal fistula(s), especially in the new era of thoracoscopic repair. These procedures are not routinely performed by all surgeons prior to definitive repair, yet may provide important and relevant information. They require general anesthesia which may pose significant risk, especially to infants with proximal atresia and distal tracheoesophageal fistula, and thus are deferred until the time of anticipated repair.

On the contrary, contrast studies can be quite helpful in diagnosing an H-type fistula. Routine barium swallow in an upright position is unlikely to detect this deformity because of the variable size as well as slant of the fistula from cranial to caudal between the trachea and esophagus. More reliable results may be obtained from a tube esophagram performed with the patient in a prone position. In this study, an orogastric tube is passed into the stomach and contrast is injected as the tube is withdrawn. Fluoroscopy is used to immediately visualize any contrast material that extravasates through the fistula and into the trachea. This technique may be cumbersome but is the most effective radiographic study to diagnose H-type fistula. The prone esophagram may also be used to detect recurrent fistulas that are equally difficult to diagnose and often require repeated studies.

Whether H-type fistula is diagnosed or not by radiographic studies, most surgeons advocate endoscopy to confirm and localize this type of fistula when it is strongly suspected. Usually, the fistula is visualized through the bronchoscope in the membranous portion of the trachea close to the thoracic inlet. A ureteral catheter may be passed through the fistula to aid in operative identification. Alternatively, several drops of methylene blue dye may be instilled into an endotracheal tube of a fully anesthetized patient, and with positive pressure, blue dye may be seen by esophagoscopy draining through the fistula and into the esophagus. Diagnosis of tracheoesophageal fistula whether congenital or recurrent can be difficult and requires persistence as well as a high index of suspicion. Thus, if radiographic studies are negative, endoscopy should be seriously entertained.

Lastly, many cases of esophageal atresia may now be diagnosed prenatally. Depending upon geographic region and socioeconomic status, nearly 85% of all pregnant women now undergo prenatal ultrasound. Although ultrasound cannot accurately diagnose esophageal atresia, it is an excellent screening tool for

polyhydramnios which can be a marker of foregut obstruction. The finding of polyhydramnios should serve as an indication for prenatal MRI, which in the case of esophageal atresia will often demonstrate a dilated proximal esophageal pouch, sometimes associated with microgastria, as well as other associated anomalies. Because of their intimate knowledge about esophageal atresia, pediatric surgeons should play an important role in the process of prenatal diagnosis and counseling.

TREATMENT

Once the diagnosis of esophageal atresia has been made, treatment should begin immediately. A 10-French double lumen oropharyngeal tube (known as a Replogle tube) should be placed to intermittent suction, and the infant should be positioned with head up at a 20–30-degree angle to prevent aspiration. Broad-spectrum antibiotics should be administered and intravenous fluids should be carefully modulated in order to prevent fluid overload. Of course, careful monitoring by pulse oximetry is critical.

Some infants will require immediate intubation and ventilation due to either respiratory distress syndrome associated with prematurity and/or aspiration related to esophageal atresia and tracheoesophageal fistula. Infants with esophageal atresia aspirate saliva from their proximal blind pouch and have tracheomalacia due to distension of the proximal pouch, but infants with distal tracheoesophageal fistula are often much more compromised as a result of reflux of gastric content into the bronchial tree. It is preferable to manage these infants with oxygen supplementation as needed via nasal prongs or facial mask, since intubation entails positive pressure which may exacerbate gastric distension and reflux aspiration by forcing gas through the distal tracheoesophageal fistula into the stomach. If intubation is required, infants should be ventilated with the lowest possible peak inspiratory pressure.

Premature infants with esophageal atresia and tracheoesophageal fistula who develop respiratory distress syndrome are at greatest risk due to stiff, noncompliant lungs. As mentioned above, they may shunt greater minute ventilation through the fistula and into the stomach, causing distension and even rupture requiring immediate repair and gastrostomy tube placement. Even with a gastrostomy tube placed to 5–10-mm water seal, continued loss of minute ventilation may destabilize the patient and require immediate thoracotomy and ligation of the fistula as a life-saving procedure. This scenario illustrates a decision that must sometimes be made by the pediatric surgeon, whether or not to proceed with primary repair in critically ill infants with respiratory compromise. Ultimately, this judgment must be made intraoperatively in conjunction with the

anesthesiologist depending upon the infant's physiologic status once the fistula has been closed. It sometimes may be advantageous to proceed with definitive repair if the infant's physiology improves with fistula ligation, otherwise staged repair remains the safest alternative for infants who need further resuscitation. But what about infants who are physiologically stable? Today, few would disagree that physiologically stable infants should undergo primary repair without gastrostomy tube placement.

Esopahgeal Atresia with Tracheoesophageal Fistula

Definitive repair of esophageal atresia with tracheoesophageal fistula is typically performed through a right thoracotomy; alternatively, a left thoracotomy is used when there is a right aortic arch. Frequently, the latissimus dorsi muscle can be mobilized along its anterior border and retracted posteriorly, preserving muscle function; however, the muscle should be divided if a muscle-sparing technique would compromise exposure. Either an intra-pleural or extra-pleural approach to the posterior mediastinum can be used depending upon the status of the infant. An extra-pleural approach takes longer and is more tedious; thus, it would not be appropriate in an unstable infant. Yet this approach offers a number of advantages: it affords excellent exposure of the posterior mediastinal structures, protects the lung from retraction injury, and prevents empyema in the event of anastomotic leak.

Next, the azygos vein usually is divided, whereupon the vagus nerves are identified and scrupulously preserved. Dividing the azygous vein typically exposes the tracheoesophageal fistula. If the fistula is not clearly visualized, the distal esophagus can be identified just above the hiatus and followed proximally to the fistula's origin. The tracheoesophageal fistula is carefully mobilized from surrounding structures, taking care to preserve the medial perforating vessels originating from the aorta. The site of the fistula is sequentially divided as the trachea is repaired with interrupted 5.0 permanent sutures into the small remnant of fistula left on the trachea. To make sure that this closure is secure, saline can be poured into the mediastinum and the anesthesiologist asked to inflate the lungs as the surgeon looks for bubbles from the suture line that would indicate a leak.

Then, the proximal pouch is usually easy to find with the use of a nasopharyngeal tube, and a traction stitch is placed in the muscular tip of the proximal pouch to aid dissection. Some surgeons incorporate the tip of the tube in the traction stitch to minimize injury to the proximal esophagus with manipulation. Circumferential dissection is performed up to and above the thoracic inlet taking care to stay close to the esophageal wall so as not to damage the trachea, thoracic

duct, or recurrent laryngeal nerves. Electrocautery is used sparingly as dissection nears the thoracic inlet for the same reason. Careful attention is paid to the tracheoesophageal septum in order to ensure a proximal fistula is recognized if present.

Finally, if the decision is made to perform a primary repair, the proximal esophageal pouch is opened, the fistula is trimmed back to pink, well-vascularized esophageal tissue, and a single-layer anastomosis is performed. Prior to anastomosis a soft catheter, such as an 8-French red rubber tube, should be passed distally into the stomach to guard against an unrecognized distal stricture. The anastomosis is done by laying interrupted full-thickness sutures across the back wall leaving the knots on the luminal side. Many pediatric surgeons use 5.0 monofilament or braided nylon permanent sutures, but the choice of suture depends upon surgeon preference. The two ends of esophagus are gently held with noncrushing forceps while the back wall sutures are tied diffusing tension across the posterior aspect of the anastomosis. The front wall of the anastomosis is then completed in an interrupted fashion, again taking care to place full-thickness sutures. This is particularly important and challenging on the distal esophagus where the mucosa tends to retract from the cut edge of the esophageal wall. These sutures are tied leaving the knots on the extra luminal aspect of the esophagus, and the anastomosis is completed (Figure 3). If available, mediastinal fat or lymphatic tissue is placed between the trachea and esophagus to buttress the anastomosis and guard against fistula recurrence. A 10–12-French chest tube is inserted



Figure 3. Completed trans-thoracic repair of esophageal atresia and tracheoesophageal fistula.

through a separate stab incision, and the thoracotomy is closed in layers. Sutures around the ribs are not made tight, to limit future thoracic deformity. Esophageal stents in the form of nasogastric tubes are still used by many surgeons; however, there is no data to show they reduce the incidence of anastomotic stricture. However, trans-anastomotic nasogastric tubes can be useful to initiate continuous gastric feeds early in the postoperative period and reduce dependence upon parenteral nutrition. They can also help decompress the stomach.

As discussed above, it can be difficult to decide which infants in the modified Waterston C category may be safely treated by primary versus staged repair. Moreover, many high-risk infants may be safely temporized by gastrostomy tube drainage only without preliminary ligation of the distal tracheoesophageal fistula, followed by subsequent delayed primary repair. All these options must be considered in light of the patient's weight and physiologic status and with recognition that ligation of the fistula may potentially render subsequent primary repair more difficult. If the infant is not deemed a candidate for immediate primary repair, a gastrostomy may be placed to prevent reflux of gastric contents until the infant can be optimized for surgery. The gastrostomy tube should be at least 14-French in diameter to prevent occlusion and limit reflux of gastric contents into the bronchial tree. In addition, the infant should be positioned head up at 20–30 degrees with intermittent oropharyngeal suction to prevent antegrade aspiration. Delayed repair in premature infants is supported by studies which demonstrate that the two ends of esophagus continue to grow in length following delivery[19] and postoperative anastomotic complications related to tension including leak, stricture, and reflux may be minimized[5]. Weight alone does not preclude primary repair. However, if the infant weighs less than 1300–1500 g, most surgeons prefer to place a gastrostomy tube for drainage and parenterally feed the infant via a PICC line or Broviac® catheter until the infant reaches this general weight range when delayed primary repair may be more safely performed.

Thoracoscopic Repair

In the future, thoracoscopy may be more widely used to repair esophageal atresia. This was accomplished as a surgical first in 1999,[21] and several groups in the United States and Europe are routinely using this technique for esophageal atresia and tracheoesophageal fistula when the two ends are in close proximity. At this point, it is unclear whether the end result will justify the learning curve, and already there have been reported leaks and some fatalities using this technique.[22] As with any other technique, the surgeon must determine his/her level of comfort and ultimately choose the technique which yields the optimal long- and short-term outcomes in each individual case.

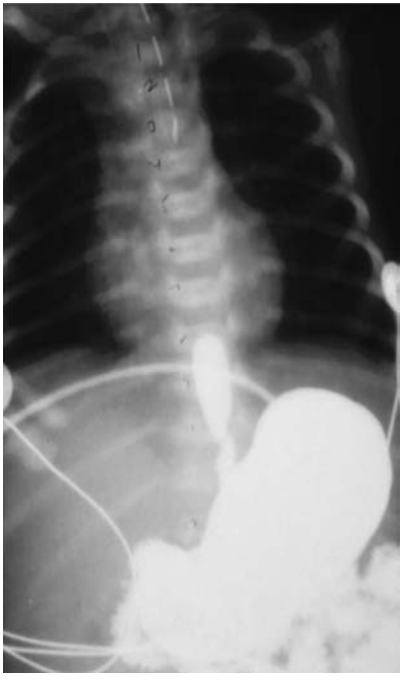


Figure 4. Gastrostomy tube contrast injection study demonstrating long-gap pure esophageal atresia.

Pure Esophageal Atresia

Infants with pure esophageal atresia are not nearly as sick as those with distal tracheoesophageal fistula yet require the same initial treatment as those with a fistula. Once the VACTERL evaluation has been completed, a gastrostomy tube should be placed for enteral feedings that may be given without risk of reflux. Shortly after this is done, a limited upper GI series may be performed via the gastrostomy with a Bougie placed in the upper pouch to assess the gap between the blind ends of the esophagus (Figure 4). Distance is usually measured using the vertebral bodies as a reference, and, in most cases, the separation is at least six vertebral bodies equating to a distance of 6–10 cm. At this point, there are several options. As previously discussed, historically there had been considerable enthusiasm for esophageal replacement procedures using a vascularized colonic segment (Figure 5), gastric tube, or gastric transposition. In many cases, these procedures were performed using a staged approach including cervical esophagostomy performed in the newborn period followed by colon replacement or gastric tube performed at one year

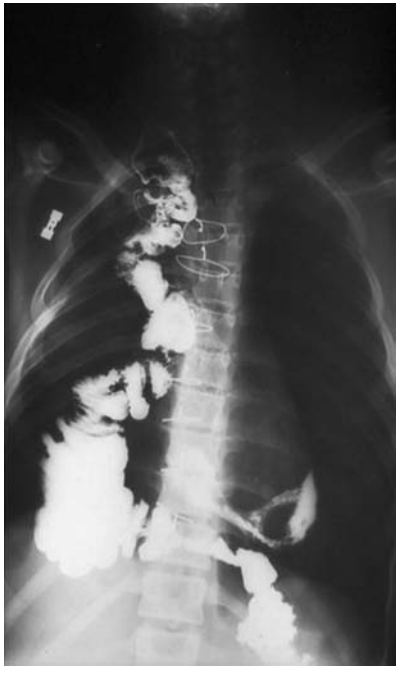


Figure 5. Tortuous colon replacement 2 years following repair in a child with dysphagia and reflux.

of age. On which side to place the cervical esophagostomy is purely surgeon preference: a left-sided esophagostomy may simplify subsequent replacement while thoracic duct injury may be avoided with right-sided placement.

More recently, these procedures have been successfully performed without cervical esophagostomy even in premature infants at 1–3 months of age.[23] The gastric tube is constructed using a GIA stapler on the greater curvature of the stomach based on the left gastroepiploic vessels with division of the short gastric vessels as necessary. The optimal colon conduit is constructed from the right and transverse colon based on the middle colic and arcuate vessels, preserving the ileocecal valve.[10] Both the gastric tube and colon conduit are often placed in the straight, substernal position with a proximal anastomosis in the neck. Both of these procedures require pyloroplasty to facilitate gastric emptying and minimize gastroesophageal reflux. In addition, the cervical anastomosis should be drained following either of these procedures until a postoperative esophagram demonstrates an intact anastomosis. Some surgeons prefer placing the conduit in the esophageal bed, a shorter route to the neck.

Another option for esophageal replacement in the newborn period is the gastric transposition or pull-up modified by Spitz.[24] This procedure involves the mobilization of the stomach, preserving the epiploic vascular arcades and ligation of the short gastric vessels and left gastric artery and vein. The stomach is then mobilized into a posterior mediastinal tunnel created from the neck above to hiatus below without thoracotomy. Then, anastomosis is performed between the proximal fundus and cervical esophagus using a single layer of fine polyglycolic acid sutures which is drained internally using a nasogastric tube. Once again, this procedure requires pyloroplasty and, in addition, feeding jejunostomy tube to allow enteral feedings in the first few weeks after repair.

The options discussed above have yielded reasonably good results in the past but have lost their appeal for all but the most complicated cases. There are a number of reasons for this including the desire to avoid a prolonged staged repair involving cervical esophagostomy, reluctance to invade the abdominal cavity, recognition of a 5–15% morbidity and mortality rate even in the best of hands, and realization that at least 50% of these patients will develop long-term dysphagia and reflux requiring remedial surgery.[15] Instead, most surgeons today embrace the concept that the infant's best esophagus is his/her own esophagus. For all these reasons, delayed primary repair has become the most popular and frequently performed reconstructive procedure for pure long-gap atresia.

The first step of delayed primary repair is to place a gastrostomy tube for feeding. After the gastrostomy tube is placed, the esophagus is lengthened. There have been a number of proposed techniques for this, but the most practical and least invasive of these is twice daily bougienage using a 20- or 22-French lead-weighted bougie. After not less than 2 weeks, the patient is taken to the operating room where, using a brief anesthetic, the gastrostomy tube is removed and a pediatric cystoscope is inserted under direct visualization into the gastrostomy tube site through the GE junction and into the blind distal esophagus. At the same time, a Bougie is passed into the proximal pouch, and the separation of the two ends is measured in terms of the number of intervening vertebral bodies. This procedure is performed intermittently for at least 2–6 weeks or until the separation has narrowed to two vertebral bodies (Figure 6). At that point, a definitive repair may be performed (Figure 7).

Another interesting approach to long-gap esophageal atresia, advocated by Dr. John Foker,[25,26] is to perform a mini-thoracotomy at the time of gastrostomy tube insertion in order to identify and hitch the upper and lower esophageal segments to pledgeted traction sutures. These sutures are then brought out of the chest above and below the incision. Tension on the external sutures is increased 1–3 times each day inducing "growth" of the esophageal ends over a period of

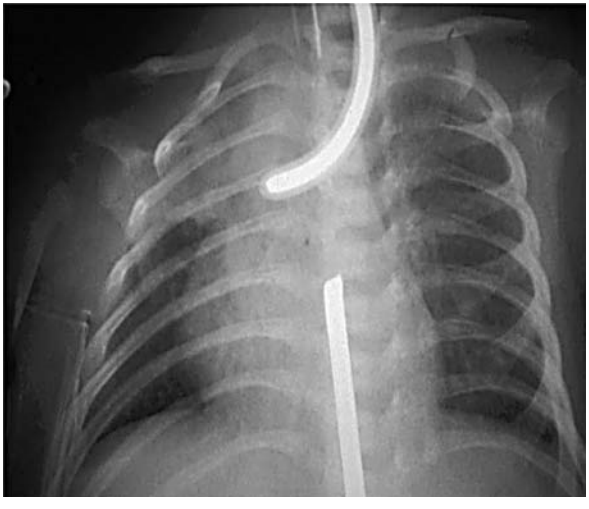


Figure 6. Same patient as in Figure 4 with long-gap atresia after 4 weeks of bougienage.



Figure 7. Same patient with long-gap atresia after completion of repair.

6–10 days allowing a true primary repair. Dr. Foker describes the preliminary thoracotomy performed through a 3-cm incision and postulates the future application of thoracoscopy to accomplish this preliminary operation.

Definitive repair begins with extensive mobilization of the proximal pouch to the level of the thoracic inlet with circular myotomy as needed to add length. The distal esophagus is usually found lying just above the diaphragm as a small nubbin protruding above the hiatus. This is carefully mobilized taking care not to divide or injure the perforating vessels from the aorta. If there is not enough distal length, then the gastroesophageal junction is mobilized above the diaphragm taking care so as not to injure the vagal nerves. A back row of full-thickness interrupted fine permanent sutures is placed and then tied with the knots on the intraluminal side while holding both ends of the esophagus together using atraumatic ring forceps. The front wall of the anastomosis is completed, again taking care to include both the muscular and mucosal components of the esophageal wall, especially on the distal esophagus where the mucosa often retracts. The anastomosis is usually completed with a fair amount of tension which will nevertheless heal well as long as there is good tissue apposition and the cut ends of the esophagus are pink. Again a 10–12-French chest tube is placed through a separate stab incision, and the thoracotomy is closed in layers.

Postoperative Care

Regardless of which repair strategy is used, it is wise to leave the infant intubated at least 24 hours or until completely recovered from the anesthetic, whereupon the infant may be safely extubated. As in the preoperative period, the infant should be positioned at least 20–30-degrees in the upright position. Nasopharyngeal suctioning may be performed but should be done with a tube that has been clearly marked at the time of surgery to limit the depth of suctioning to at least 2 cm or more above the level of anastomosis.

The chest tube is left for drainage and not removed until an esophagram has been performed 5–7 days later. If the esophagram shows no evidence of a leak, oral feedings are cautiously started. Then the chest tube is removed. Infants with a gastrostomy tube may also be supplemented with tube feedings. If a small leak is found, oral feedings are withheld for several weeks, during which time the infant is supported with parenteral nutrition or fed by gastrostomy tube when present. Once oral feedings are initiated and advanced to sustainable levels, the infant is carefully followed for signs of esophageal stenosis which include choking, coughing, gagging, or excessive drooling. Once the infant has reached full feeds by mouth, supplemental parenteral or enteral nutrition is discontinued. When a gastrostomy tube is present, it is usually left in place for 6–12 months.

Any suspicion of esophageal stenosis should be investigated by esophagoscopy and treated by gentle esophageal dilatation. This can be easily and safely

accomplished using filiform and follower dilators passed through the esophagoscope under direct visualization, followed by Maloney dilators sized appropriately for the infant. Alternatively, balloon dilators may be passed through the esophagoscope, but extreme care should be taken to avoid esophageal perforation. It is not unusual for infants to require several dilatations within the first 3–6 months following primary repair; however, the need for further dilatation gradually diminishes. If stenosis persists despite multiple dilatations and the infant has clinical and radiologic evidence of severe gastroesophageal reflux, then fundoplication must be considered.

Infants with long-gap pure esophageal atresia who undergo preliminary esophageal lengthening via bougienage or Foker's technique of externalized traction sutures followed by delayed primary repair often will require repeated esophageal dilatation and many, if not most, will require fundoplication. Fundoplication can be relatively challenging in this group since the esophagus is short and many of these infants have microgastria which may be more amenable to Thal fundoplication as opposed to 360-degree Nissen fundoplication.

ISOLATED (H-TYPE) TRACHEOESOPHAGEAL FISTULA

As mentioned previously, isolated, or H-type, tracheoesophageal fistula has a single orifice typically located close to the 2nd–3rd vertebral body allowing exposure through the neck. A low right cervical incision is made along the anterior border of the sternocleidomastoid muscle, which is retracted posteriorly or divided as necessary to facilitate exposure. Dissection continues medial to the carotid sheath and often the inferior thyroid artery and middle thyroid vein will need to be divided to adequately expose the underlying tracheoesophageal groove. The recurrent laryngeal nerve must be carefully identified and preserved since it as well the contralateral recurrent laryngeal nerve branch may be damaged with circumferential dissection of the fistula.

Once the fistula is isolated, traction sutures are placed at the proximal and distal extents of the fistula on the tracheal side. The fistula is now divided close to the esophagus and the trachea closed with fine non-absorbable sutures. In this repair, as opposed to an esophageal anastomosis, a two-layer plicated repair of the esophagus is usually performed with fine absorbable sutures. Some surgeons buttress the repair with mediastinal fat or alveolar tissue to prevent recurrence. After this repair is performed, prompt return to regular diet for age and a relatively short hospital stay is expected. Rarely, the H-type fistula is located in the upper thorax and is best approached through a right thoracotomy.

OUTCOME

The pediatric surgical literature is replete with long-term retrospective outcome reports on esophageal atresia. Because of the relative rarity of cases, many of these reports span several technologic eras and include cases of variable risk, acuity, and surgical treatment making it difficult to assess current best practice. However, there is no question that improved technology, intensive neonatal care, and judicious use of primary or delayed primary repair has lead to vastly improved outcomes. For several decades, survival has been 100% for infants in Waterston and modified-Waterston groups A and B. Within the past decade, survival of higher-risk patients, modified-Waterston group C category, has caught up with their lower risk counterparts, approaching 100% in infants without chromosomal defects or other anomalies incompatible with life.[27] Delayed primary repair using temporary gastrostomy tube drainage still plays an important role in low weight micropremature infants (less than 1300 g) and those with life-threatening cardiac defects, but the role of staged division of distal tracheoesophageal fistula has all but been eliminated except in rare cases involving extremely unstable or potentially non-viable patients.

There is an emerging consensus that delayed primary repair is the treatment of choice for long-gap and ultra–long-gap pure esophageal atresia. Whatever the means of esophageal lengthening, the definitive repair requires patience and is technically challenging but produces superior functional results with significantly lower long-term requirement for surgical revision compared to esophageal replacement procedures. In the author's (unpublished) experience, bougienage followed by delayed primary repair was successful in 100% of 14 patients, all of whom had ultra–long-gap atresia with initial separation of greater than 6 cm. One patient had a small anastomotic leak found by postoperative contrast study that healed spontaneously within two weeks, and only three patients required subsequent fundoplication, although every patient developed symptomatic stenosis requiring repeated esophagoscopy and dilatation in the first 6 months following repair. All but one of these patients are alive and well and feeding normally for age without dysphagia. Using traction sutures to induce growth, Foker[26] achieved sufficient lengthening within 6–10 days to allow true primary repair with no discernible leaks by postoperative esophagram and 100% survival. Similar to the author's experience with bougienage, all patients in Foker's series required at least 2–4 esophageal dilatations within the first year following primary repair. However, all patients in this series required fundoplication compared to only 3 of 14 patients undergoing bougienage. In either series, all patients had good to excellent long-term function.

Esophageal replacement procedures are still used in cases where primary repair has failed, but, again, there is no consensus as to which procedure is best. To some extent, choice of replacement procedure depends upon training and experience of the surgeon. Nevertheless, most surgeons would agree that best results are obtained when gastric tubes and colon conduits are placed in the substernal or posterior mediastinal position and when gastric transposition is placed in the posterior mediastinum rather than the thorax. In addition, there is consensus that the proximal anastomosis should always be done in the neck rather than the thorax and that pyloroplasty should be done in all cases to facilitate gastric emptying and prevent gastric bloating and reflux.

Finally, H-type fistula repair results in 100% survival with minimal complications when properly performed. Esophageal leak and recurrent fistula are rarely reported.

COMPLICATIONS

Now that survival of infants with esophageal atresia has reached nearly 100%, most surgeons have turned their attention to reducing complications and hospital length of stay. Some complications such as gastroesophageal reflux and esophageal stricture are unavoidable, whereas others, including esophageal leak and disruption, are preventable. In any case, it is fair to say that the key to shortened length of stay is reduction or amelioration of complications.

Gastroesophageal reflux is the most common complication following repair of esophageal atresia occurring in virtually all infants, but becomes clinically relevant in 40–60%.[28] It is due in part to esophageal dysmotility and also esophageal mobilization and/or placement of a gastrostomy tube with disruption of the angle of HIS. In most cases, it responds well to medical management including H_2 receptor blockers, proton pump inhibitors, and the prokinetic agent metoclopramide (Reglan®). Approximately 20–30% of infants with esophageal atresia and tracheoesophageal fistula require fundoplication; however, as previously discussed, fundoplication may be required in a higher percentage of infants with ultra–long-gap atresia depending upon the strategy used for delayed primary repair. Fundoplication provides effective treatment for gastroesophageal reflux unresponsive to medical management but, unfortunately, may slip or disrupt in as many as 30% of all infants.[29] Another issue is the potential for dysphagia after fundoplication since all of these infants have an inborn dysmotility disorder. It is for this reason that some surgeons prefer to use a Thal technique or 270-degree fundoplication.

Reflux is often associated with and, in some cases, heralded by anastomotic strictures that occur in 30–50% of all cases of esophageal atresia.[30] Anastomotic

stricture is defined as a narrowing that impairs normal swallowing and usually requires esophagoscopy and dilatation. Dilatation has traditionally been done using progressive filiform and follower and Maloney dilators passed through the esophagoscope. Another option is to use balloon dilators passed through the esophagoscope and deployed by a pressure control device. With the addition of flouroscopy, contrast can be instilled into the balloon, demonstrating a waist seen at the site of the stricture when the balloon is dilated. Initially, strictures may be caused by local ischemia, foreign body reaction, and leak but are certainly aggravated by gastroesophageal reflux and usually resolve as the reflux abates. In some cases, persistent or recurrent strictures may require fundoplication for resolution and, along with cyanotic episodes and aspiration pneumonia, is an important indication for fundoplication.

Anastomotic leak usually indicates a technical problem. In the past, most leaks were assumed to be due to anastomotic tension, but recent results of primary and delayed primary repair of long-gap and ultra–long-gap atresia have demonstrated that this is not necessarily the case. In fact, we have learned that it is better to anastomose two pink esophageal ends under tension than two slightly cyanotic ends without tension. The keys to success are gentle tissue handling, meticulous dissection, proximal circular esophagomyotomy as necessary, and distal preservation of aortic perforators to the distal esophagus. A single-layer anastomosis should be employed consisting of properly placed full-thickness interrupted sutures. The back wall sutures are placed first, tied firmly but not tightly leaving the knots on the intraluminal surface, to diffuse tension across the anastomosis. Then the front wall sutures are carefully placed and tied as a unit leaving the knots on the extra luminal surface of the anastomosis. The suture line should be reinforced only sparingly with adjacent tissue as necessary and available.

Recurrent tracheoesophageal fistula occurs in up to 15% of cases[30] and presents similarly to an H-type fistula with coughing, choking, and congestion (especially after feeding) with or without recurrent pneumonia. In most cases, it presents within the first 6–8 weeks following initial repair and is more prevalent in patients who have developed an anastomotic leak. In some cases, recurrent fistula may occur months after initial repair in conjunction with esophageal dilatation for anastomotic stricture. Again, similar to H-type fistula, it may be difficult to establish the diagnosis. Prone esophagram through a tube in the proximal esophagus is helpful if positive; however, if the clinical index of suspicion is high and the esophagram is negative, then bronchoscopy and esophagoscopy with attempted passage of a catheter through the fistula site is essential for diagnosis. This technique can also be used for treatment with passage of a Bugbee electrode for cauterization of the fistula followed by injection of fibrin glue. This technique

may be successful, but if symptoms persist and/or follow-up esophagram remains positive for a fistula, then thoracotomy and operative repair is warranted. This is a delicate procedure which poses some risk for damage to the recurrent laryngeal nerve and requires the surgeon to confine his/her dissection of the cervical esophagus to the tracheoesophageal groove.

There are a number of other issues that may need to be addressed following definitive repair of esophageal atresia. Recurrent pneumonias and reactive airway raise the suspicion for tracheomalacia and gastroesophageal reflux. All infants have some degree of tracheomalacia which usually resolves spontaneously between 24 and 48 months of life. In some patients, it may never completely resolve and may manifest by persistent, barking cough classically described as a seal bark cough, often exacerbated by upper respiratory tract infection. Much less commonly, tracheomalacia may be associated with stridor due to innominate artery compression. In most infants, this may be placated by medical treatment including aerosols. If not, then it may require transthoracic aortopexy performed via a left lateral thoracotomy or thoracoscopic technique.

As already discussed, pneumonia and swallowing difficulties may result from gastroesophageal reflux, esophageal stricture, and dysmotility. Gastroesophageal reflux and esophageal strictures are treatable, but dysmotility is not and may persist for years. The etiology of esophageal dysmotility in this setting is unknown but may be related to an intrinsic abnormality versus disruption of vagal innervation of the esophagus. As long as esophageal continuity is reestablished within the first few months of life, these problems rarely interfere with an infant's avidity or ability to feed. On the other hand, if an infant incurs a serious complication such as a major leak or anastomotic disruption, then these problems may contribute to a possible feeding aversion requiring years of remedial feeding therapy and supplementation by gastrostomy tube feedings. Feeding aversion is far less common now that primary and delayed primary repair has largely replaced staged repair and esophageal replacement as the treatment of choice. Recent clinical and psychologic studies have demonstrated that most children with esophageal atresia grow up to be healthy, well-adjusted adults who live normal lives.[31,32]

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CHAPTER 10

ABDOMINAL WALL DEFECTS

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INTRODUCTION

Of the two major types of abdominal wall defects (AWD), omphaloceles were historically easier to manage because an intact sac afforded some protection to the viscera. When the occasional application of a topical escharotic agent to the omphalocele sac caused it to thicken and become epithelized, and if sepsis did not supervene, some infants were able to survive. In contrast, gastroschisis was almost uniformly fatal. Without the ability to contain the dehydration, heat loss, sepsis, and other consequences of exposed viscera, few infants with gastroschisis survived until relatively recently.

Until the 1940s, definitive surgical repair was only possible for small omphaloceles. Rupture of the sac invariably produced sepsis from which the infant often succumbed. As antibiotics became available, the prognosis from the once dreaded rupture of the omphalocele sac improved. The modern surgical management of omphaloceles began in the 1940s when Robert Gross first described a surgical procedure that permitted the repair of even large omphaloceles. The Gross procedure was done in two stages: first, he raised skin flaps to cover the defect and protect the viscera, and at a later stage he repaired the ventral hernia.[1]

As the Gross procedure was refined, mortality from omphaloceles dramatically declined, and was often due to associated cardiac and other malformations. Gastroschisis, however, remained a dismal challenge that was accepted with some resignation among pediatric surgeons. In fact, the textbook of pediatric surgery

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written by Gross, included a chapter on omphalocele but omitted any reference to gastroschisis. The fate of the infant with gastroschisis was a quiet and lonely death in a dark corner of the nursery. Fortunately, the 1960s brought a dramatic reversal in the prognosis for gastroschisis, due to a combination of factors. First, infant ventilators and better antibiotics became available. Secondly, the discovery of parenteral nutrition (PN) by Dudrick and colleagues made it possible to keep the infant alive during the prolonged period of postoperative ileus.[2] And finally, the development by Shuster of the silo constructed from an inner layer of polyethylene and outer layer of Teflon improved the options for treating large omphaloceles by allowing the gradual return of viscera to the abdominal cavity; a technique that was soon applied to gastroschisis.[3,4]

Before 1960, the survival for gastroschisis was less than 10%, but by 1970, it had already tripled, and steadily improved to the >90% obtainable today. Thus, the prognosis for AWDs has come full circle. Today, gastroschisis has a better outlook than omphalocele, which due to the severity of associated major malformations, has an overall survival that has yet to exceed 50–75%.

Omphalocele

Omphalocele (also known as exomphalos) is a central defect in the umbilical ring presenting as evisceration into the base of the umbilical cord. The pathogenesis is related to the failure of reduction of the physiologic herniation of the midgut that occurs at 6–10-week gestation. The exposed viscera are covered by a translucent sac comprised of fused visceral peritoneum and amnion, with an interspersed layer of Wharton's jelly (Figure 1). The major differences between omphalocele and gastroschisis are outlined in Table 1.

The size of the defect is usually 2–10 cm, or even larger. The sac can contain any portion of the gastrointestinal tract, and the liver in up to 50% of cases. Because much of these viscera developed within the sac, rather than in the abdomen, the residual abdominal cavity is relatively small. The smallest defects, often called umbilical cord hernias, usually contain only small bowel. These defects, covered only by a small sac and umbilical cord, are to be differentiated from umbilical hernia, which are covered by skin and usually become evident after the cord has separated. More extensive maldevelopment of the ventral body wall may produce larger omphaloceles associated with defects in the upper abdomen and chest, or lower abdomen and pelvis. The cephalic fold defects may include components of the pentalogy of Cantrell: sternal cleft, anterior diaphragmatic hernia, downward displacement of the heart, intracardiac defects, and omphalocele. The caudal fold defects may be associated with elements of the OEIS syndrome (omphalocele, exstrophy of the bladder, imperforate anus, and spinal defects).



Figure 1. An omphalocele consists of a defect through the umbilical ring, with exposed viscera covered by a translucent sac comprised of fused visceral peritoneum and amnion, with an interspersed layer of Wharton's jelly.

Table 1. Major differences between omphalocele and gastroschisis.

Factor	Gastroschisis	Omphalocele
Incidence	1:2500	1:5000
Location	Lateral to cord, usually to the right	Umbilical ring
Cord	Normal insertion	Inserts in sac
Sac	None	Present
Defect size	Small (2–4 cm)	Large (2–10 cm)
Contents	Bowel, stomach	Liver, bowel etc.
Bowel	± Matted, inflamed	Normal
Associated Anomalies	Unusual (bowel atresia 10%)	Common (30–70%)
Gestation	Moderate prematurity	Term

Other associated lower defects include vesicointestinal fissure (also called cloacal exstrophy), ambiguous genitalia, and colon atresia. In most cases of omphalocele the abdominal wall muscles, while displaced laterally, are well developed. However, an omphalocele may be associated with various degrees of poor muscle development, including the prune-belly syndrome (absent or deficient abdominal wall muscles, bilateral cryptorchidism, and urinary tract malformations) (Figure 2).

Associated congenital anomalies attributed to a single gene disorder, chromosomal anomalies, or genetic syndromes occur in up to 70% of cases of omphaloceles. These include chromosomal defects (trisomies 13, 18, and 21), or isolated defects involving he gastrointestinal tract, cardiovascular, genitourinary, musculoskeletal, and central nervous systems. Several other associated



Figure 2. A newborn with the prune-belly syndrome. The deficiency of the abdominal muscles is most pronounced on the right side. The omphalocele was very small and the sac had developed an eschar.

malformations are well known, including the Beckwith–Wiedemann syndrome, characterized by an umbilical defect, gigantism, macroglossia, visceromegaly, and pancreatic islet cell hyperplasia. Infants with the Beckwith–Wiedemann syndrome may therefore have significant hypoglycemia due to hyperinsulinism, while the associated pancreatic abnormality is a risk factor for the subsequent development of pancreatic neoplasia. Infants with Beckwith-Wiedemann also have increased risk of Wilms' tumor, neuroblastoma, and adrenocortical tumors. Omphaloceles containing liver are more likely to have coexisting cardiac, renal, and limb anomalies. Paradoxically, smaller omphaloceles tend to have a higher incidence of gastrointestinal and central nervous system malformations.

The overall incidence of omphalocele is estimated at 1:5000 live births and has been stable in recent epidemiologic studies. The odds of an infant being born with omphalocele is increased among males, twins or higher order multiples, and older mothers. Some ethnic differences in the incidence of omphaloceles have been reported and there are unconfirmed associations with higher socioeconomic status and maternal smoking and alcohol use during early pregnancy.[5] Familial recurrence of omphaloceles may also occur.

Gastroschisis

Gastroschisis is a defect in the abdominal wall lateral to the umbilical ring (usually to the right). The umbilical cord is normally inserted and separated from the defect,

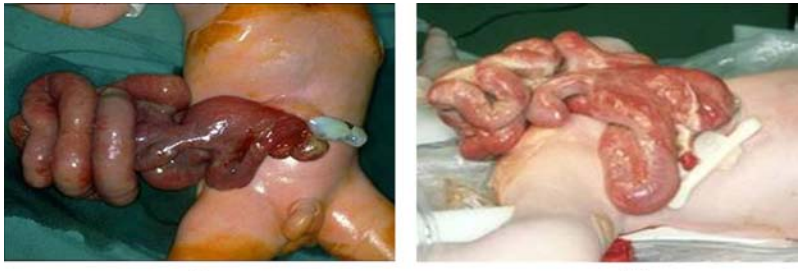


Figure 3. (a) Gastroschisis defect to the right of the intact umbilicus, with chemical peritonitis and inflammation of the exposed viscera. (b) An inflammatory exudate gives the characteristic appearance of a fibrinous peel around the viscera.

sometimes by an intact skin bridge. The etiology may involve ischemic insult to the right umbilical vein or an early rupture of a hernia of the umbilical cord.

Compared to omphaloceles, the size of the defect is relatively smaller (2–4 cm), and there is no covering sac. The exposed viscera, usually the stomach and intestines, may be significantly inflamed or matted together from chemical peritonitis caused by the amniotic fluid and congestion due to the tight ring caused by the defect in the abdominal wall (Figure 3). The liver is rarely eviscerated in gastroschisis, but the gonads (one or both ovaries, or undescended testes), may be exposed. The bowel is invariably nonrotated. An inflammatory peel may be noted, often associated with a foreshortened mesentery. In up to 10–15% of cases, there may be associated intestinal atresia (and less commonly, Meckel's diverticulum or duplications). Other than these gastrointestinal tract malformations, infants with gastroschisis are generally free from other major associated anomalies or chromosomal syndromes. They are usually born with moderate prematurity.

Gastroschisis occurs almost twice as commonly as omphalocele (1:2500 live births). While the incidence of omphaloceles has remained stable, several epidemiologic studies confirm a rising incidence of gastroschisis worldwide. The odds of an infant being born with gastroschisis is increased among young mothers (<20 years), and those with lower income and lower socio-economic status. Women who have offsprings with gastroschisis are less likely to be black, and more likely to have smoked, consumed alcohol, or taken nonsteroidal anti-inflammatory drugs during early pregnancy.[5]

The rising incidence of gastroschisis, particularly in low and middle income countries, has raised significant public health concerns. Studies indicate that additional risk factors may include unmarried mothers, early and unprotected sexual

intercourse, use of recreational drugs, and multiple pregnancies with different fathers. Among the most intriguing findings is the association between gastroschisis and maternal genitourinary and sexually transmitted infections.[6]

PRENATAL CONSIDERATIONS

Serum and Amniotic Fluid Assays

Elevation in the maternal serum alpha fetoprotein

Maternal serum alpha fetoprotein (MSAFP) is a marker for serious ectodermal defects in the fetus, and is employed in routine prenatal screening for neural tube defects. Alpha fetoprotein is produced by the fetus and passes into the amniotic fluid, from where it enters the maternal circulation. MSAFP is elevated in AWDs. The magnitude of MSAFP elevation is significantly greater in gastroschises, at more than nine multiples of the mean compared to only four with omphaloceles. Amniotic fluid acetylcholinesterase (AChE) is also elevated and follows a similar pattern. None of these tests are currently used for routine screening of AWDs.

Imaging

Ultrasound is the mainstay of prenatal diagnosis of AWDs. After the return of the physiologic midgut herniation, persistence of the small bowel in the umbilical cord is abnormal. Thus, an AWD containing bowel loops can be confidently detected by 15 weeks' gestation. However, the stomach and liver do not normally herniate at any stage; therefore the presence of any of these organs even during the first trimester is suspicious for omphalocele. The diagnosis of an abdominal wall defect is not made with confidence until the clinician is certain that normal physiologic herniation is complete.

Second trimester ultrasound screening is now performed routinely, and most cases of omphalocele or gastroschisis are detectable at this time and can be differentiated on the basis of the presence or absence of a sac (Figure 4). In a fetus with a gastroschisis, the loops of intestine floating in amniotic fluid, not enclosed within a sac, have a "brain" or "cauliflower" appearance on fetal ultrasound. Ultrasound allows more focused screening for other associated congenital anomalies. More specific diagnosis of chromosomal disorders requires karyotype analysis. Fetuses with AWDs have a greater risk of intrauterine growth retardation (IUGR), fetal death, and premature labor, so serial ultrasounds and

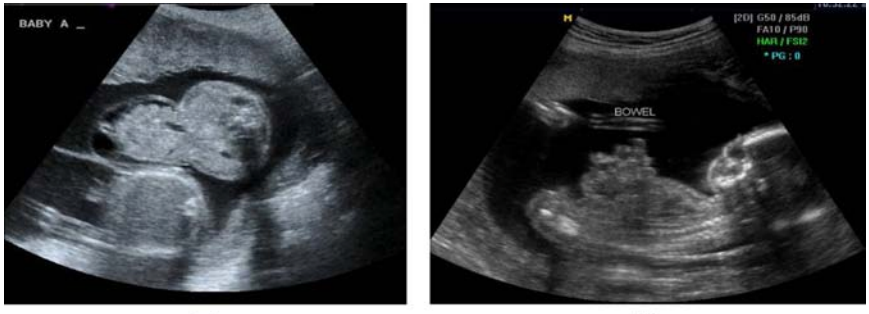


Figure 4. Second trimester prenatal sonograms of fetuses with abdominal wall defects. (a) Omphalocele, with arrow pointing at extruded viscera covered by an intact sac. (b) Gastroschisis, with the extruding bowel free within the amniotic fluid.

other tests of fetal well being are part of the standard repertoire of obstetrical management. Oligohydramnios is frequently noted in gastroschisis, and may be associated with IUGR, fetal distress, and fetal death. In contrast, the finding of polyhydramnios and gastric dilatation may reflect the presence of intestinal atresia.[7] Ultrasound also offers the ability to monitor the effect on the fetus of cardiac and other anomalies that increase the risk of intrauterine fetal death.

Another imaging modality occasionally used is an ultrafast magnetic resonance imaging (MRI). While not necessary for the routine identification of AWDs, it can give more detailed anatomic views of the organs, and help with the assessment of associated anomalies.

Prenatal Therapy

Currently, there is no routinely available prenatal intervention for AWDs. The few investigational treatments for gastroschisis are directed at: (a) relieving oligohydramnios, (b) reducing the inflammatory damage to exposed bowel caused by the amniotic fluid, and (c) relieving the constrictive effect of a tight defect on the bowel.

Oligohydramnios

This occurs in 25% of gastroschisis and is associated with poor fetal outcome. Amnioinfusion has been proposed to augment the volume of amniotic fluid with normal saline, and initial studies suggest that this treatment could improve the outcome of affected fetuses.[8]

Inflammatory damage

Putative noxious agents in the amniotic fluid include interleukins 6 and 8, ferritin, and fetal gastrointestinal waste containing enzymes and other toxic residues.[9] Amniotic fluid exchange with normal saline, performed repeatedly, during the third trimester is thought to ensure clearance of these inflammatory mediators and reduce the bowel damage that is believed to occur during this period. Although early experience has been promising, a randomized trial will be needed to demonstrate further efficacy and safety.[10,11]

Tight defects

Animal data using an iatrogenic gastroschisis model has shown the feasibility of performing a fetoscopic enlargement of the defect. This raises the prospect for enlarging tight defects in human cases, thereby preventing ischemia of the bowel caused by the tight ring.[12]

Prenatal Counseling

Early detection offers the opportunity for prenatal counseling of the parents and prompts more diligent screening for associated malformations. The diagnosis of AWD brings significant anxiety to parents. A multi-specialty counseling approach that includes the pediatric surgeon, neonatologists and nurse specialists is quite helpful. The overall survival is decreased with an earlier diagnosis.

In the EUROSCAN study of 19 European congenital malformation registries, 12% fetuses with prenatally diagnosed gastroschisis ended with intrauterine fetal death, with 21% of omphalocele cases meeting a similar outcome. Fetal death in gastroschisis is usually the culmination of associated intestinal atresia, volvulus, or severe bowel inflammation and perforation. At present, there is little that can be done to save these fetuses. Aside from cases of fetal death, those who survive to live delivery have a nearly 100% survival.[13] It is sobering that up to 44% of parents[14] (29% in the EUROSCAN study) chose termination for a condition with such excellent prognosis. Prenatal counseling, when successful, should allay parental anxiety and reduce the rate of unnecessary terminations. Fortunately, other studies have reported termination rates for gastroschisis of 5 % or less.[15,16] The prognostic implication for omphaloceles detected early in pregnancy is less certain and depends mostly on the presence of other anomalies. Data from a European registry revealed that one fifth of cases with omphalocele suffered fetal death, 37% were terminated, and only 41% were born alive.[17]

Prenatal counseling will help parents plan the timing and mode of delivery (see below) and anticipate the postnatal treatment course. Issues that should be covered include surgical treatment options, parenteral nutrition, and the likely duration of hospital stay. A recent survey shows that the average length of stay for gastroschisis was 41 days, versus 32 days for omphalocele, while death rate during initial hospitalization for gastroschisis was 3% and 6.8% for omphalocele.[18] The parents whose fetus has gastroschisis should expect a moderately premature delivery.

LABOR AND DELIVERY

Omphalocele

There is now broad agreement that after screening for chromosomal and catastrophic abnormalities, most omphaloceles should be allowed to proceed to term, but the manner of delivery remains a subject of controversy. Older literature empirically suggested caesarean delivery for omphaloceles because birth trauma would presumably increase the risk of rupture of the sac, damage the contained viscera, and expose the organs to contamination by vaginal flora. However, a meta-analysis that compared neonatal outcome based on mode of delivery found no supporting evidence for cesarean delivery of AWDs.[19] Yet, obstetric practice continues to favor cesarean delivery for the majority of omphaloceles.[20] In contrast, pediatric surgeons tend to favor vaginal delivery for most cases of AWD. There is greater consensus that "large" omphaloceles, especially those containing liver, are at greater risk of birth injury and should be delivered by cesarean section, but the threshold size has not been defined.

Gastroschisis

With respect to gastroschisis, there is greater controversy regarding the timing and mode of delivery. Advocates for elective preterm delivery cite reports of toxic substances in the amniotic fluid that could damage exposed bowel.[9] Further support comes from reports that amniotic fluid exchange reduces inflammatory injury to bowel.[10,11] Because bowel inflammation is believed to begin at about 33 weeks' gestation, the proponents of early delivery recommend elective delivery about this period. A prospective trial comparing 13 women nonrandomly selected for elective delivery at 32–34 weeks with an equivalent number of historical controls delivered at >36 weeks demonstrated some benefits for early delivery,

including a higher rate of primary closure (100% vs. 23%), earlier time to full enteral feedings (19.1 days vs. 35.1 days), and shorter length of stay (22.7 days vs. 35.6 days), compared to controls.[21] This study has the obvious flaws of a small sample size, poorly defined entry criteria, and exclusion of complex cases. The findings did receive some support by more recent studies.[22,23]

The timing of onset of the inflammatory changes to eviscerated bowel is also a matter of controversy, and some believe it is an entirely postnatal phenomenon that may be related to exposure to vaginal contents during delivery. Based on this hypothesis, some have advocated elective delivery at term followed by immediate postnatal surgical repair. Vegunta *et al.*, reported that such a protocol produced results superior to those reported for vaginal delivery.[24] However, studies supporting the practice of caesarean deliver (preterm or term) were often implemented as part of a clinical pathway that included intense obstetric monitoring and scheduled early postdelivery surgical repair. With these confounding variables, similar nonrandomized studies will likely be met with skepticism among many pediatric surgeons who have largely accepted the evidence, both from a meta-analysis,[19] and in the only randomized trial to date,[25] that there is no benefit from elective caesarean delivery. Furthermore, other studies continue to show no benefit for preterm delivery or cesarean section in gastroschisis.[26,27]

IMMEDIATE POSTNATAL CARE

Omphalocele

The immediate priority in newborns with omphalocele is to stabilize the infant, prevent heat loss, protect the sac and its contents, and undertake a thorough assessment of associated anomalies. While some surgeons advocate immediate repair, such a sense of urgency can rarely be justified when the sac is intact, particularly for larger defects where reduction of viscera can cause respiratory difficulties and abdominal compartment syndrome.

Routine neonatal care should be instituted to provide maintenance fluid and prevent heat loss. The umbilical vessels should not be used for access. Intestinal decompression is aided by early placement of an orogastric tube and the evacuation of meconium (aided by rectal examination, if necessary). The infant should be given prophylactic intravenous antibiotics and vitamin K. We perform a thorough physical examination, and obtain a cardiac echogram and renal ultrasound to search for other congenital anomalies. Determining whether there is a serious cardiac or other anomaly is helpful for anesthetic and operative planning, so it is rare that we proceed with emergency surgery without completing these

assessments. Rarely, the infant is born with a fatal syndrome that makes surgical repair a futile exercise.

To protect the sac from tear and infection, we apply Betadine® ointment and wrap large Kling® roll gauze around the front and back of the abdomen to make a snug and bulky dressing, taking care not to impede respiration. We avoid using moistened gauze because it predisposes to hypothermia. The dressing is changed once daily until operative repair is done, or continued until the sac is epithelized if an initial nonoperative approach is chosen.

A variety of topical agents have been applied to the omphalocele sac over the years, with the aim to produce desiccation, granulation, and epithelization of the sac. Mercurochrome®, once the mainstay of topical treatment, has all but been abandoned due to reports of mercury poisoning. Topical escharotic agents in current use include povidone iodine solution, silver sulphadiazine cream (Silvadene®), and Bismuth Tribromophenate (Xeroform®). Some surgeons apply a transparent adhesive dressing such as Tegaderm® or OpSite®, to protect the sac until epithelization occurs.

Gastroschisis

In addition to the obvious problem of dehydration, heat loss, sepsis, and risk of injury to the exposed bowel in gastroschisis, the bowel may be at risk for ischemia from volvulus. The appearance of the bowel is variable, from normal to being markedly inflamed with a thick peel. The bowel loops may also be matted together and the presence of atresia may be difficult to discern.

We immediately place the lower part of the baby, including the entire lower extremities, the eviscerated organs, and abdomen in a sterile bowel bag and tie the strings snugly around the chest at the level of the axillae (Figure 5). Being a free-standing pediatric facility, we receive our newborn babies from outside nurseries, which have all adopted the use of the bowel bag. Upon arrival, the profound fluid, electrolyte, and protein loss is quickly evident by the amount of fluid that has accumulated in the bag, and its turbid nature. We change the bag quickly to prevent hypothermia, taking care to use a sterile technique, and in the process collect the fluid so we can accurately determine the replacement volume.

Fluid resuscitation is initiated immediately, if possible prior to transfer from the delivery room. We begin with a 20 mL/kg bolus of 0.9% saline and repeat as necessary to restore normal perfusion and urine output. The infant is then given a one and one-half times maintenance solution of 5% dextrose in 0.25% saline until operative repair is undertaken. Intravenous antibiotics are



Figure 5. A sterile bowel bag is used to protect the exposed bowel from mechanical injury, infection fluid and heat loss; the entire body of the baby is placed in the bag and the strings tied snugly around the chest at the level of the axillae.

given and the infant is placed under a radiant warmer to further protect from heat loss.

A pediatric surgeon should be on hand to assess the condition of the bowel. The mesenteric stalk may be quite narrow and could easily twist as the eviscerated bowel flops to one side or the other. It is the surgeon's responsibility to ensure no ongoing mesenteric vascular obstruction. Arterial obstruction is easier to detect because the bowel quickly becomes dusky. The direction of the volvulus is not constant, but can usually be determined from careful inspection of the pedicle. The color of the bowel instantly improves if detorsion is performed in the correct direction. Isolated venous obstruction is more subtle but will increase the amount of bowel edema and make it harder to achieve primary closure.

SURGICAL REPAIR

Timing

Many observers have noted that the inflammatory condition of eviscerated bowel in gastroschisis is a postnatal phenomenon, and can be avoided by immediate repair after delivery. This is cited as a major rationale for elective cesarean delivery, because the newborn can be taken immediately to an adjoining operating room for a planned repair. In such cases, the bowel may be easier to reduce and the rate of successful primary closure higher (84–86%) than with

spontaneous vaginal delivery a term (65%).[23,24] Such a protocol-driven seamless transition from the delivery room to the newborn surgical suite is easier to implement when the infant is inborn. In our institution, where newborn patients are transferred from outside maternity units, we aim to repair the defect as soon as the infant is well resuscitated. Also, our treatment protocol makes no distinction whether they were delivered vaginally or by Caesarean.

With omphaloceles, emergent repair is indicated in cases of rupture of the sac. Sac rupture that occurs *in utero* may not be easily distinguished from gastroschisis if the liver is not involved. On occasion, we have identified a focal site of perforation of the sac and ligated it promptly, thus obviating the need for emergent repair. In most cases, however, immediate operative repair is the safest approach to avoid potentially catastrophic septic complications. With an intact sac, we proceed with an urgent repair in stable infants with small omphaloceles (defined as defects that appear amenable to primary skin closure, generally less than 5 cm in size, with liver "in"). Some surgeons prefer an urgent operative repair for even large omphaloceles, placing a silo or prosthetic patch if necessary. Alternatively, one can defer the repair of large omphaloceles or those associated with other life threatening anomalies, relying on topical escharotic dressings to thicken the sac and prepare for delayed definitive repair.

Primary Repair

Omphalocele

An orogastric tube should be in place to decompress the bowel and a rectal examination performed to encourage passage of meconium. An attempt should be made to reduce the viscera with an intact sac, but avoiding traction on the liver, which may be adherent to the sac. Next, a narrow rim of skin is incised around the defect to elevate skin flaps. The sac is excised, and the umbilical vessels and urachus ligated. If there is adherent sac on the liver, it is preferable to leave it rather than risk uncontrollable bleeding in the attempt to separate them. To facilitate reduction of the viscera, we create more intra-abdominal space by anteroposterior stretching of the abdominal wall and gently squeezing the colon to release more meconium through the anus. Whether primary fascial repair or skin closure only can be accomplished is a matter of intraoperative judgement. It is unhelpful to obtain fascial closure under tension as the predictable result is increased intra-abdominal pressure and all the well known consequences. Intra-abdominal pressure can be assessed

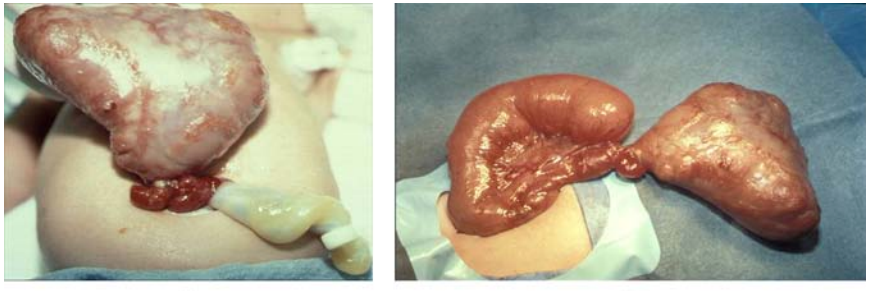
by monitoring intragastric, intravesical or airway pressures and a threshold pressure should be established beforehand, and if this is exceeded the attempt at primary closure should be abandoned. We use interrupted PDS sutures, taking full thickness bites through the rectus muscles. Before tying the knots, we simulate closure by pulling the alternate sutures to one side and ensure that the anesthesiologist can ventilate the infant with less than 25 mmHg airway pressure. When placing and tying sutures over the liver, care should be taken that the suture not "saw" through the liver and cause bleeding. It may, in fact, be preferable to avoid placing sutures in the most proximal aspect of the incision, as the liver fills the space.

Gastroschisis

An orogastric tube should be in place to decompress the bowel and a rectal examination may facilitate evacuation of meconium. Further colonic decompression from within the abdomen can also gain additional intra-abdominal space. We routinely stretch the abdominal wall as described previously and assess the eviscerated intestine for any anomalies, particularly intestinal atresia. In many cases, the viscera appear normal, with minimal inflammation or edema, and can be easily placed in the peritoneal cavity. When the bowel is inflamed, edematous, or matted it is often necessary to enlarge the defect in the fascia (and perhaps skin) to permit return of the viscera, care being taken to avoid iatrogenic injury. The fascia and skin are repaired as described for omphalocele, following the same principles to avoid closure under increased intra-abdominal pressure. The umbilicus may be preserved for the cosmetic benefit, but some surgeons remove it and create a neo-umbilicus with a purse-string skin closure. Use of a spring loaded silo (Bentec®, Figure 7b), inserted at the bedside without general anaesthesia, with gradual delayed closure, has become standard in some centers. When the viscera have obtained a domicile within the abdomen after several days of gradual tightening of the silo, then delayed primary closure is accomplished in the operating room under general anesthesia.

Intestinal atresia

Approximately 10% of gastroschises are associated with small intestinal atresia. The presence of atresia, however, may not be immediately obvious when the bowel is matted with an inflammatory peel (Figure 6). In such cases, the viscera should be reduced *en masse*, and no attempt should be made to separate the bowel at this time. Failure of bowel function persisting beyond 6 weeks should raise the



(a) (b)

Figure 6. (a) In this infant with gastroschisis, the entire bowel is surrounded by a fibrinous peel, and the presence of intestinal atresia may not be apparent for several weeks. (b) A separate case of gastroschisis with an obvious intestinal atresia; the distal bowel is covered with a thick fibrinous peel that may contain other atretic segments.

suspicion for atresia or other form of bowel obstruction. We generally obtain contrast studies at this stage to guide further intervention. In a stable infant with noninflamed bowel, it is reasonable to perform a primary repair of the atresia. If the bowel is inflamed but not matted, a condition not suitable for primary anastomosis, or when associated with ischemia or perforation, an end ileostomy can be brought out in the umbilicus or at a separate site. Many leave atretic small bowel and plan repair after the intestines have had time to recover.

Undescended testis

An undescended testis occurs in up to one-third of males with gastroschisis, the intra-abdominal location being twice as common as the inguinal testis.[28,29] Although primary orchidopexy at the time of gastroschisis repair has been advocated,[28] some surgeons prefer to replace the testis inside the peritoneal cavity in expectation that spontaneous descent will occur.[29] Immediate orchidopexy may be technically challenging due to the difficulty in mobilizing the thickened cord with its fragile vessels. Also, it could lead to an undesirably longer operation in a vulnerable neonate. If an orchidopexy is not performed, future descent is facilitated by positioning the testis as close to the internal inguinal ring as possible, without suture fixation.

Staged Repair

Some form of staged repair is indicated when primary repair is not feasible and as a means of avoiding closure under tension. The ideal temporary covering protects

the viscera from fluid and heat loss, resists infection, and allows gradual reduction of the viscera. As the eviscerated bowel becomes less congested and empties its luminal contents, spontaneous reduction gradually occurs. In a matter of weeks or even days, it is usually possible to perform delayed primary as the abdominal domain is established.

The methods used in staged repair include skin coverage without fascial closure, silo, biologic or prosthetic patches, and with giant omphaloceles, using the sac as a silo.

Silo

The traditional silo is constructed from Dacron-reinforced Silastic sheets that are sewn to the fascial edges on either side of the defect. Both sheets are then sewn together on all sides to house the viscera comfortably (Figure 7a). The defect in gastroschisis usually needs to be enlarged to ensure the silo is constructed on a wide base, thereby avoiding a funneling effect. We apply Betadine® ointment or



Figure 7. (a) The traditional silo constructed from Dacron-reinforced Silastic sheets. (b) A preformed spring-loaded silo.

Xeroform® gauze around the skin at the base of the silo and continue intravenous antibiotics until the silo is removed. Also, if the silo is tall and is at the risk of tilting (and potentially kinking the bowel), we support the silo by wrapping large Kling® roll gauze around the silo and the back of the abdomen to make a snug and bulky dressing, and change the dressing daily. We facilitate reduction by ligating the silo periodically (usually daily) by tying it with an umbilical tape (alternatives include suturing or stapling).

Although some surgeons still prefer the versatility of the hand-sewn silo, in many institutions it has been replaced by the preformed spring-loaded silo, of which there are several commercially available types (Figure 7b). These preformed silos are made with the base ranging in diameter from three to eight centimeters or greater. A preformed silo with a base larger than the size of the defect is chosen so that it will not easily dislodge when placed under the abdominal wall. For small gastroschisis defects, we enlarge the defect beforehand, to avoid having a base too narrow as to impede reduction of the viscera. Dislodgement of the silo in the nursery can be a nuisance in some infants. This can be prevented by sewing the ring of the silo to the fascia in rare cases.

The silo can be placed in the operating room under general anesthesia, and the infant maintained on ventilator support as the viscera reduce spontaneously. However, bedside insertion of the preformed silo is a popular option, and as mentioned, mechanical ventilation and muscle relaxation can be avoided. In fact, some surgeons advocate the routine use of the preformed silo placed at the bedside without anesthesia followed by delayed primary closure. A multicenter randomized trial of the preformed silo versus primary repair showed no differences with respect to the duration of parenteral nutrition, length of stay, or incidence of sepsis or necrotizing enterocolitis, and a trend toward fewer days on the ventilator.[30] However, there is some concern that the early fascial closure rate is reduced following the use of the preformed silo.[31]

Prosthetic patch

Biological and synthetic materials have been used as a temporary or permanent patch in both omphalocele and gastroschisis. Biological patches include AlloDerm® (human acellular dermis), Dura Gen® (human acellular dura), or Surgisis® (porcine small intestinal submucosa). These products are designed to provide an acellular matrix scaffold that support ingrowth of fibroblasts and vascular tissue. Because long-term data is not available, it is not yet possible to determine whether these biological materials prevent the need for ventral hernia repair in the future.

Synthetic materials such as polypropylene mesh and PTFE (Gore-Tex®) have been used most commonly to provide temporary fascial replacement until a definite reconstruction of the abdominal wall can be performed.

Delayed Repair of Ventral Hernia

When primary fascial closure has not been performed during the initial treatment, the short term goal is usually to obtain epithelial coverage and defer repair of the resulting ventral hernia (Figure 8) for several months or years. Definitive repair may be accomplished in a single session, but may require staged procedures. If a synthetic material had been used, it is removed and replaced with autologous tissue.

Careful assessment is essential to determine whether direct fascial apposition can be obtained, otherwise a variety of flaps or tissue expansion techniques may be considered. The component separation technique has been used to close defects 6–9 cm in size as reported in 10 patients with giant omphaloceles, with no recurrent herniation.[32] Tissue expanders made from Silastic® and similar materials, when implanted in the potential space between the internal oblique and transversus abdominis layers, help to stretch the abdominal wall fascia and muscles with minimal effect on intra-abdominal pressure.[33] A major risk of this procedure is thinning of the skin due to its relatively superficial location, leading to extrusion. An alternative location for the tissue expander is within the peritoneal cavity, as originally described by Bax and more recently by Foglia (Figure 9).[34,35] In a matter of several weeks, an intraperitoneal domain is re-established for



Figure 8. An infant whose giant omphalocele had been allowed to epithelize following application of escharotic agents. The resulting ventral hernia was repaired in multiple stages with tissue expanders in the intermuscular plane, followed by the component separation technique.

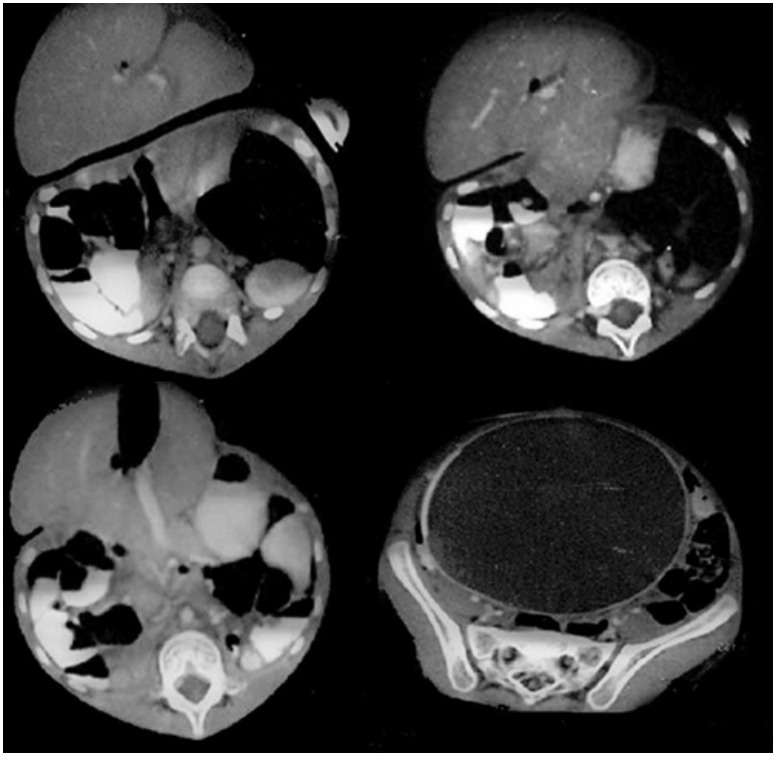


Figure 9. A case of giant omphalocele in which gradual reduction of the extraperitoneal viscera was facilitated by the placement of an intra-peritoneal tissue expander. Lower right image has 900 ml saline in tissue expander. *(From Foglia R, et al., J Pediatr Surg. 2006 Apr;41(4):704–9 with permission.*)

the viscera, allowing fascial apposition. We have used the tissue expander and component separation methods to deal with very large defects, sometimes combining both techniques in the same patient.

EARLY COMPLICATIONS

Abdominal Compartment Syndrome

Too tight a closure will cause an increase in intra-abdominal pressure and may produce the familiar syndrome of abdominal compartment syndrome. This is characterized by reduced lung compliance, impaired venous return, and reduced

visceral organ perfusion. Clinical signs include tachycardia, oliguria, poor peripheral perfusion, requirement for increased ventilatory pressures, and mixed acidosis. It is rarely necessary to measure intra-abdominal pressure in order to recognize the problem, and the infant should immediately undergo abdominal decompression and placement of a Silo. This is a complication largely preventable at the time of repair by ensuring that the closure does not cause an excessive increase in ventilatory pressure as discussed earlier.

NEC

Necrotizing enterocolitis occurs in up to 20% of infants with gastroschisis.[36] Putative factors associated with this increased risk include prematurity, low birthweight, inflamed bowel at birth, type of enteral feeds, and surgical closure technique. The incidence of NEC appears to be similar whether silos are used routinely or not.[30] Feeding the infant with expressed breast milk may reduce the risk of NEC in infants with gastroschisis.[37]

Bowel dysfunction

Although delayed enteral feeding in infants with gastroschisis is ascribed to prolonged ileus, a distinct group of these infants suffer from bowel dysmotility. In such cases, the inability to achieve full enteral feeding is not merely due to insufficient bowel length but due to persistent poor function. We generally begin enteral feeds when regular passage of stool indicates resolution of ileus. If unable to make progress with feeds in 4–6 weeks, we perform a complete gastrointestinal contrast evaluation, looking for atresia or other mechanical obstruction. A contrast agent that is water soluble and not highly osmolar is preferred. At this stage, slow transit of contrast without obstruction points to bowel dysmotility. Furthermore, chronic dilatation of segments of the bowel may be seen. Dysmotility may be a greater problem in infants with gastroschisis and associated intestinal atresia, even when there is adequate length and no persistent mechanical obstruction.[38] Easily digestible or elemental formula may be of help in these infants, sometimes given as tube feedings. Enthusiasm for the use of prokinetic agents to improve enteral nutrition has dampened since a multicenter randomized study failed to prove benefit for the use of erythromycin in infants with gastroschisis.[39] In some patients, enteroplasty of dilated bowel, creation of an enterostomy, revision of a stenotic bowel anastomosis, or other techniques may improve bowel function sufficiently to enable these infants to survive without parenteral nutrition.

LONG-TERM OUTCOMES

Advances in neonatal care, nutrition, and surgical technique have markedly improved the overall prognosis of infants with AWDs. Excluding omphaloceles associated with other anomalies, the vast majority of infants with isolated AWD have normal physical and mental development.[40] Nevertheless, there are potential long-term issues, particularly among a distinct group of infants with high-risk gastroschisis, comprising those with intestinal atresia, perforation, necrotic segments, or volvulus.[41]

Quality of Life

A survey of patients who had AWDs revealed an overall good quality of life and a prevalence of acquired disease comparable to the general population (with the possible exception of a 7% risk of rheumatoid arthritis). However, 50% of all AWD survivors reported functional gastrointestinal symptoms, such as transient abdominal pain, heartburn, and regurgitation.[42]

Cosmesis

Although most patients with AWD are satisfied with the cosmetic outcome, one-third complain of an ugly scar or loss of the navel.[42] Some patients will request umbilicoplasty or abdominoplasty procedures to improve cosmesis. Attention to the surgical technique during initial closure may be the most important factor in subsequent cosmetic outcome.[43]

Small Bowel Obstruction

The occurrence of late small bowel obstruction (SBO) and other bowel complications is of particular concern in infants with gastroschisis, with up to 20% in the high-risk category requiring laparotomy during a 15 year follow-up period.[44] Late SBO is due mainly to adhesions and anastomotic stenosis. Adhesive SBO occurs in up to 25% of gastroschisis and 13% of omphalocele, the majority within the first year of life.[45]

Intestinal Failure

Severe long-term morbidity in gastroschisis is principally due to intestinal failure, which causes a hidden late morbidity and mortality from catheter sepsis,

cholestasis, bacterial overgrowth, gastrointestinal bleeding, and complications following transplantation. Short bowel syndrome may occur as a result of intestinal atresia, volvulus, or bowel resections. A subset of patients develops intestinal failure due to severe malabsorption and intestinal dysmotility. Survival of these patients is now possible because of the availability of parenteral nutrition (PN), but long-term PN-dependency ultimately leads to severe complications particularly catheter infections and PN-associated liver disease (PNALD). Infants with PNALD who are unable to be weaned off from PN have a very high mortality.[46]

As an adaptive response, the residual bowel often becomes dilated, and could lead to bacterial overgrowth. Selected patients may benefit from an autologous intestinal reconstruction surgery (AIRS) in order to both taper and lengthen the bowel. Several AIRS techniques have been described including the longitudinal intestinal lengthening surgery (LILT or the Bianchi procedure),[47] the Iowa procedure,[48] and, serial transverse enteroplasty (STEP).[49] We find the STEP procedure technically easier than the other procedures, and the excellent results initially reported has been validated in many other centers.[50–52] Patients with intestinal failure, who develop severe PNALD can be rescued by means of intestinal transplantation, with 3-year survival currently at 72% for patients with gastroschisis.[53]

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CHAPTER 11

MALFORMATIONS OF THE LUNG

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INTRODUCTION

Congenital lung malformations comprise a challenging, variegated, and incompletely understood group of anomalies that most pediatric surgeons will treat on a regular basis. These lesions run the gamut from miniscule anomalies recognized in the fetus that may regress during the time of gestation and not be identifiable in the postnatal period, to large, space-occupying masses that lead to non-immune fetal hydrops (NIFH) and, ultimately, fetal demise. Although classically divided into several major groupings — cystic parenchymal lesions, sequestrations, lobar overinflation, and bronchogenic cysts — ongoing work has led to a better understanding of the hybrid nature of many lesions, particularly of congenital cystic adenomatoid malformation (CCAM), now often called congenital pulmonary airway malformation (CPAM), and bronchopulmonary sequestration (BPS).

The frequency of prenatal identification of congenital lung malformations has increased along with improvements in prenatal screening. Several groups have developed techniques for prenatal intervention in cases where mass effect appears to be restricting either normal lung development or venous return to the heart. While theoretically promising, these techniques remain in the arena of hyperspecialization and will require more investigation prior to adoption by the medical community at large.

This chapter reviews the anatomic basis of congenital lung malformations, identifies major groupings by histopathology and treatment, discusses some of the less common conditions, and highlights some of the important anesthetic and operative

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considerations in pulmonary resection. It is this author's opinion that our appetite for early resection, spurred by the promises of minimally invasive surgery (MIS), will soon be tempered by a better understanding of the natural history of these lesions.

EMBRYOLOGY

Embryologic lung development occurs in five stages: embryonic (3–7 weeks), pseudoglandular (7–17 weeks), canalicular (17–26 weeks), saccular (24–36 weeks) and alveolar (36 weeks to ≥ 2 years of age).[1,2] After the tracheal and esophageal grooves begin separating toward the end of the third gestational week, a diverticulum is noted off the caudal end of the laryngotracheal groove. This in turn gives rise to the trachea and lung buds, the latter of which form by the fourth gestational week. By the sixth week, bilateral lung buds have further divided into distinct lobar structures. The pseudoglandular phase of lung development takes place from the seventh to 17th gestational weeks, and ends with bronchial airway development. Canalicular differentiation follows from the 17th to 26th weeks, and at the end of this period, crude alveolar sacs are present. This is typically the earliest point at which gas exchange can occur, partly thanks to the development of types 1 and 2 pneumatocytes, the latter of which are responsible for surfactant production. Saccular development begins at the 24th week of gestation, resulting in maturation of alveoli and improvement in surfactant production, while the final stage of lung development (alveolar) continues postnatally, perhaps as long as 8 years, during which time alveolar maturation and multiplication take place.[3]

To understand bronchogenic malformations, one must also consider the embryology of foregut development, which originates as an epithelial-lined tube at the end of the third postconceptual week. During the following 2 weeks, the esophagus and trachea separate; the former being temporarily obliterated by proliferating foregut epithelium. Incomplete recanalization of the developing esophagus is thought to account for the appearance of foregut duplication cysts, which include enteric duplications cysts (lined with intestinal epithelium), bronchogenic cysts (lined with respiratory epithelium), and neuroenteric cysts (communicating with the nervous system).[3]

CONGENITAL LOBAR OVERINFLATION

Congenital lobar overinflation (CLO) is a rare disorder in which a pulmonary lobe is hyperinflated. This occurs despite histologically normal pulmonary alveolar architecture, which is why the conventional term "congenital lobar emphysema" is inaccurate.[4] Etiology is unclear, but proposed mechanisms include congenital

cartilage abnormalities as well as bronchial obstruction, either intrinsic from mucosal proliferation, or extrinsic from aberrant mediastinal blood vessels. The left upper lobe is most commonly involved, followed by the right middle lobe. Bilobar CLO has been reported in a handful of cases.[5]

As with other congenital lung lesions, CLO can be diagnosed antenatally on screening ultrasound, although it is less commonly identified than CCAM (CPAM) or BPS as the fetal lung is fluid-filled and not yet hyperaerated. Clinical presentation varies widely, from acute respiratory distress upon birth, to transient tachypnea in infants, to incidentally found lesions in older patients without physiologic impairment. CLO can also be confused with pneumothorax, leading to the possibility of thoracostomy tube placement with untoward results.

Diagnostic imaging in the postnatal period typically begins with a simple chest x-ray. Findings suggestive of CLO include hyperaeration of the affected lobe with mediastinal shift and ipsilateral flattening of the diaphragm (Figure 1). Computer tomographic (CT) angiography is perhaps the most useful imaging modality, providing confirmation of the diagnosis and allowing for identification of obstructive vascular structures, if present (Figure 2). The possible need for general anesthesia for this diagnostic test challenges the clinician to weigh its risks and benefits.



Figure 1. Chest X-ray demonstrates hyperlucency of the left upper lobe with mediastinal shift and depression of the ipsilateral diaphragm.



Figure 2. Computer tomographic scan demonstrates left upper lobe overinflation.

Although surgical excision of the affected lobe is considered standard treatment, there are reports of observation in patients who are mildly or not at all symptomatic.[6,7] Proponents of observation argue that since some lesions may involute, early resection is not absolutely necessary.[6,8] Desire to spare an infant an unnecessary operation must be tempered by the appreciation of potential complications of an unresected CLO, including mass effect with impaired alveolar development of adjacent lung tissue or infection. In patients with CLO who are to be managed nonoperatively, particularly those older patients in whom lobar hyperinflation is an incidental finding, bronchoscopy may be prudent to exclude foreign body or mucous bronchial obstruction (Figure 3).

Occasionally, newborns that present with profound respiratory distress and tamponade physiology will require emergency thoracotomy to relieve these symptoms. Once the chest is opened, the crisis should immediately resolve, allowing for a more normally-paced lobar resection (Figure 4). Although not impossible, thoracoscopic resection of CLO is quite difficult due to hyperexpansion of the affected lobe.[9–12]

CONGENITAL CYSTIC ADENOMATOID MALFORMATION (CONGENITAL PULMONARY MALFORMATION)

CCAM (now often called CPAM, congenital pulmonary airway malformation) occurs in an estimated 1:10,000 to 25,000 live births.[13,14] It consists of air-filled and solid lung tissue, and is morphologically diverse. Terminal

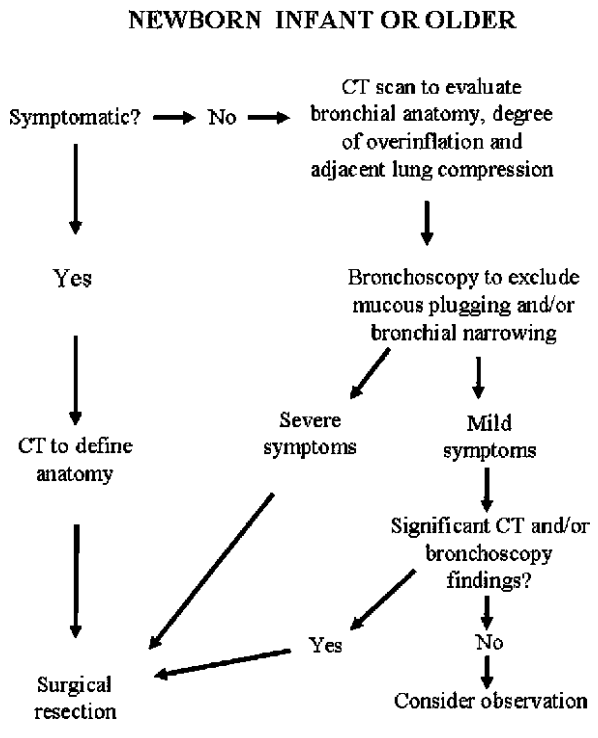


Figure 3. Treatment algorithm for congenital lobar overinflation seen on X-ray. *CT: computer tomography.



Figure 4. Resected left upper lobe. The patient had an uncomplicated recovery.

bronchiolar overgrowth is a histological hallmark.[4] CCAM tends to be unilobar. Various classification schemes exist but are not particularly useful in clinical practice. The malformation can simply be characterized as being principally cystic, principally solid, or of a mixed variety. In addition, growing literature on the etiology of congenital lung lesions suggests a common origin with multiple areas of overlap; thus, CCAM may be pure or hybrid, sharing features in common with other lesions such as BPS.[4,15,16]

CCAM tends to present in three fashions: respiratory distress in the newborn, recurrent lobar pneumonia in older infants and young children, and asymptomatic lesions identified incidentally on imaging.[17] Newborn respiratory distress typically is seen with large, dominantly cystic forms of CCAM. *In utero*, this large lesion may cause a mediastinal shift with contralateral lung hypoplasia and polyhydramnios, perhaps due to esophageal compression or from increased fluid production from the abnormal developing lung. Some of these neonates suffer such profound respiratory embarrassment that they require selective ventilation of the contralateral mainstem bronchus. In the most severe of cases, needle aspiration of a dominant cyst may be lifesaving until definitive surgical resection is undertaken. Large cystic lesions also can cause nonimmune fetal hydrops (NIFH) *in utero* through mass effect on the superior vena cava. Because NIFH is almost uniformly fatal in the prenatal period, some surgeons advocate prenatal intervention in such cases, either through fetal surgical resection or placement of a thoracoamniotic shunt (see below "Antenatal Intervention").

The second typical clinical presentation is that of recurrent infection in the same lobe. This clinical picture is often seen in older infants and young children. Since CCAM is rarely encountered in any given pediatric practice, and plain radiographic findings may be confounded in the face of active infection, diagnosis may be delayed until more definitive imaging (ultrasound or CT scan) is obtained. Once an anatomic abnormality is identified, lobar resection can be undertaken after adequate treatment of the superimposed infection.

Third and perhaps most interesting among types of presentation is that of an asymptomatic lesion, either noted on antenatal sonography or on postnatal radiography (Figures 5 and 6). Although CCAM is cited as a risk factor for either recurrent infection or malignant transformation, the true incidence of either of these conditions is unknown and perhaps overstated.[18,19] Because a variety of lung neoplasms, including pleuropulmonary blastomas, rhabdomyosarcomas, and bronchoalveolar carcinomas have been reported in adults with underlying CCAM, ongoing surveillance of patients with unresected CCAM appears warranted, although no clear guidelines exist on the frequency or modality of surveillance.[1,17]

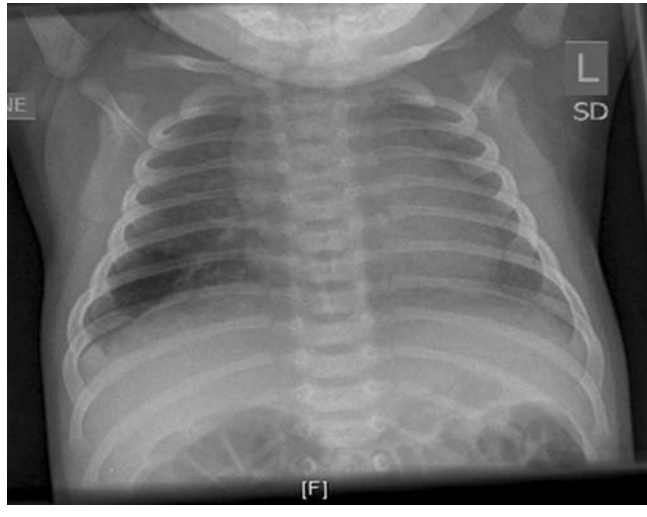


Figure 5. Right lower lobe CCAM in an asymptomatic 6-week-old. His prenatal ultrasound showed a right lower lobe abnormality.

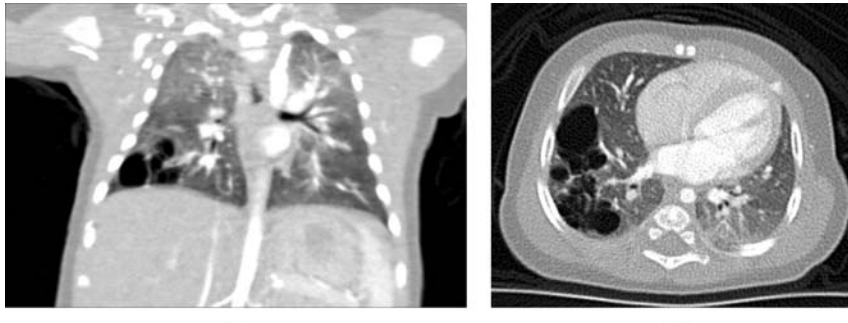


Figure 6. Computer tomographic images of the patient in Figure 5. (a) Coronal and (b) axial images better define the lesion seen on plain radiography.

Management of CCAM may be divided into complicated and uncomplicated presentations. Complicated presentations include both fetuses with hydrops and newborns with respiratory compromise. Uncomplicated presentations that present for elective resection include a CCAM incidentally identified in the postnatal period or infected CCAM that improves readily with antibiotic therapy.

A large CCAM can restrict adjacent lung development resulting in hypoplasia, as well as compress the superior vena cava leading to NIFH. Since NIFH

associated with congenital lung lesions is nearly uniformly fatal, the groups at Children's Hospital of Philadelphia and the University of California, San Francisco, among others, had been strong proponents of antenatal intervention. They proposed that fetuses between the gestational ages of 20 and 32 weeks undergo either thoracoamniotic shunting (in the case of macrocystic lesions) or open maternal–fetal surgery for fetal thoracotomy and lobectomy. Fetuses beyond the 32nd week of gestation with NIFH are treated with early delivery with or without an EXIT (*ex utero* intrapartum treatment) procedure, where the fetus is supported on placental circulation or extracorporeal membrane oxygenation while a lobectomy is performed immediately after delivery.[2,14,20–22] The use of maternal steroids when a fetus has a large microcystic CPAM (CCAM) with hydrops has rendered fetal lung resection less promising. Steroids given to the mother have had significant benefits in shrinking these fetal malformations in early reports.

Patients that present with asymptomatic CCAM are an interesting group to consider. Ample evidence exists to support regression of congenital lung malformations, both in the latter stages of pregnancy and early postnatal period.[17,24] However, the CCAM that seems to disappear on plain radiograph often may be detectable on CT scan. Still, long-term natural history of these lesions is unclear, with some authors championing a "wait and see" approach,[24,25] while others suggest that because CCAM are connected to the airway, they pose a life-long risk of air-trapping and infection and thus, should all be resected.[26] The incidence of malignant transformation is absolutely unclear, and mostly evidenced by case reports. Given uncertainty surrounding the clinical significance of asymptomatic CCAM, it may be reasonable to perform CT at 6 months of age.

Resection of CCAM typically requires formal lobectomy, and rare bilobar CCAM have been treated with pneumonectomy with significant morbidity. A single lobectomy, performed either thoracoscopically or through a muscle-sparing incision, is extremely well-tolerated by the infant, and the remaining lobe(s) expand rapidly and sufficiently.

BRONCHOPULMONARY SEQUESTRATION

BPS is a lung segment that shares no direct communication with the tracheobronchial tree. The blood supply derives from a systemic arterial blood supply, usually a branch of the descending aorta, and the venous drainage can be either into the systemic circulation (via the azygos or hemiazygos veins, or the inferior vena cava) or into the pulmonary veins.

Table 1. Intralobar vs. extralobar bronchopulmonary sequestration.[27]

	Intralobar	Extralobar
Gross	Invested within normal lung, No separate pleura	Separate from normal lung, Invested by its own pleura
Sex (M:F)	1:1	4:1
Other anomalies	Rare	Frequent
Location	Lower lobe	2/3 between lower lobe and diaphragm; 10% intra-abdominal
Arterial supply	Descending aorta (95%); Celiac or splenic (20%)	Descending aorta (75%)
Venous drainage	Pulmonary veins (95%)	Systemic veins (75%)
Age at presentation	Rare < 1 year of age	Most < 6 months of age
Presentation	Recurrent infection; Rare: CHF, FTT, PTX	Respiratory distress, CHF

CHF: congestive heart failure; FTT: failure to thive; PTX: pneumothorax.

Etiology of BPS is unclear. Researchers have proposed a wide variety of causes including additional tracheobronchial budding, anomalous pulmonary arterial development, acquired infections, lung bud duplication, coalition of bronchogenic cysts, and many others. Coexistence with congenital diaphragmatic hernia (CDH), itself thought to arise prior to the sixth week of gestation, makes the concept of additional early tracheobronchial budding attractive.[27]

BPS can be classified as either intralobar or extralobar. This nomenclature arises from whether the sequestration is invested by the visceral pleura of adjacent normal lung (intralobar) or has its own, separate pleural lining (extralobar). In addition, a small minority of sequestrations (usually extralobar) have been previously referred to as bronchopulmonary foregut anomalies because they demonstrate fistulous connections to the gastrointestinal tract via the esophagus or stomach. Major features of intralobar and extralobar BPS are discussed below and summarized in Table 1.

Extralobar BPS

With advances in prenatal screening, many extralobar BPS may be identified prior to delivery (Figure 7). Among those that are not, a majority present within the first 6 months of life, typically with respiratory distress. Other symptoms, such as feeding difficulty, may be caused by mass effect. In rare cases, high arterial blood

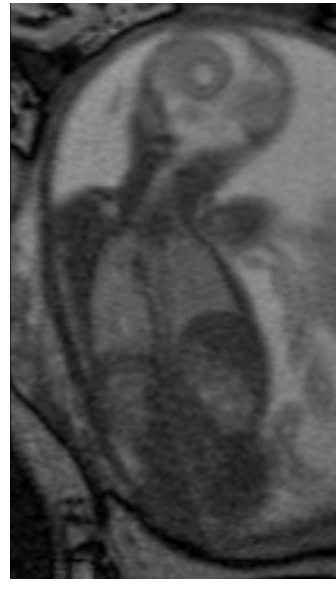


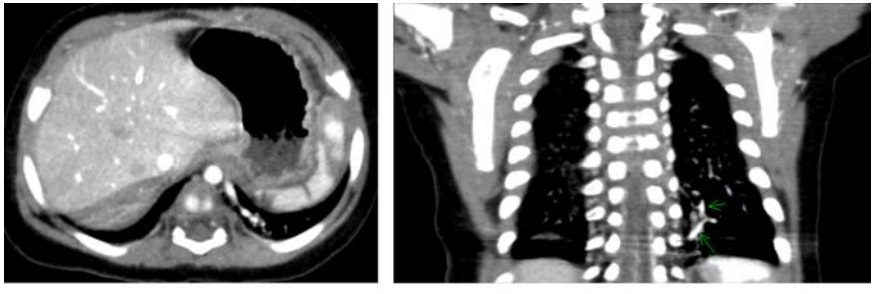
Figure 7. Fetal MRI demonstrating hyperechoic left lower lobe lesion, suspicious for a pulmonary sequestration. The fetus is shown in the prone position.

flow from the systemic feeding artery can cause arteriovenous shunting and high output cardiac failure.

Extralobar BPS is found most commonly in the left lower hemithorax (65–90%) (Figure 8). It typically lays between the lower lobe and the diaphragm, although as many as 10% are discovered below the diaphragm in the peritoneal cavity.[28] Extralobar BPS also has been reported in other thoracic locations, including within the pericardium.[29]

Co-existing anomalies occur in up to 60% of patients, including CDH (10–15%) and other congenital lung anomalies, such as lung hypoplasia, CCAM, and CLO. Nonpulmonary associated malformations include pectus excavatum, dextrocardia, truncus arteriosus, total anomalous pulmonary venous drainage, pericardial defects, accessory spleen, and enteric duplication cysts.[27]

At operation, extralobar BPS can range in size from subcentimeter lesions to greater than 10 cm in diameter. It is completely separate from adjacent normal lung parenchyma, and appears typically grey or pink with a smooth surface. Arterial supply is systemic, with at least 75% arising from the descending aorta. Other sources include subclavian, brachiocephalic, splenic, gastric, and intercostal arteries. Venous drainage is either systemic (75%), via the azygos or hemiazygos



(a) (b)

Figure 8. Intralobar pulmonary sequestration with systemic arterial blood supply, seen in the computer tomographic angiogram in the (a) axial and (b) coronal views.

vein or inferior vena cava, or pulmonary (25%). A large systemic vein may follow a course through the diaphragm; thus, surgeons must be cautious in securing any possible vessel on the inferior surface of a lower lobe extralobar BPS. Bleeding can occur uncontrolled and unseen into the abdominal cavity if a vessel is unknowingly divided without ligation. Histologic examination reveals irregular, atypically large bronchi, bronchioles, and alveoli, although the bronchial structures may be unrecognizable or absent. Dilated lymphatics are typical as well.

Intralobar BPS

Intralobar BPS tends to present later in life, rarely prior to one year of age. Most common presentation is that of recurrent pulmonary infection, although failure to thrive and congestive heart failure can also occur. This type of sequestration is rarely associated with other anomalies and is found almost always in the lower lobes (approximately 90%). Blood supply is usually systemic. Often a large feeding vessel can be identified on pre-operative imaging coursing through the inferior pulmonary ligament. Venous drainage is typically to the pulmonary veins.

Imaging

Prenatal ultrasound may identify up to a quarter of BPS.[30] An unknown proportion of sequestrations appear to involute toward the end of pregnancy as demonstrated by serial ultrasound,[31,32] but it is unclear how many completely disappear; thus, definitive postnatal imaging is recommended for all antenatally visualized lesions. After birth, chest X-ray is the natural first step in evaluating lung fields

either when antenatal sonography suggests a BPS or the clinical scenario, such as recurrent pneumonia, prompts further investigation. Although ultrasonography can often identify these pulmonary lesions and may occasionally well delineate feeding systemic arterial vessels, CT angiography is perhaps the best modality for precisely outlining the operative anatomy.

Pulmonary Resection

Proponents of resection for all suspected BPS suggest that resection is mandatory to confirm diagnosis and avoid future complications, such as recurrent infection or potential malignant transformation, probably due to a hybrid lesion containing features of CCAM. While these arguments have merit, several authors propose observation may be an appropriate recommendation based particularly on the ill-defined natural history of BPS and evidence suggesting some of these lesions may indeed involute over time. There are a handful of case reports of pulmonary resection for BPS in adults; most of these are discovered in the setting of infection.[33]

Resection of intralobar BPS invariably requires formal lobectomy in the infant or small child. Extralobar BPS is amenable to direct resection without formal lobectomy, but the procedure carries the potential for added morbidity and mortality from uncontrolled bleeding if a retracted systemic vessel goes unrecognized. For this reason, preoperative vascular imaging is helpful.

BRONCHOGENIC CYSTS

Bronchogenic cysts are thought to arise from abnormal budding of the bronchial tree. As such, they must contain hyaline cartilage plates. Although they derive from and, at resection, most frequently attach to the tracheobronchial tree, they do not communicate with the airway or participate in gas exchange. The gestational age at which this abnormal budding occurs dictates whether the cyst will be mediastinal (early) or peripheral (late). In addition to expected locations abutting the main tracheobronchial tree, bronchogenic cysts have been described in varied locations such as adjacent to the adrenal gland and other retroperitoneal locations, within the pleura, neck, base of the tongue, and others.[4] These cysts have a thin wall covered with ciliated columnar epithelium and may contain an assortment of tissue including cartilage, smooth muscle, or intestinal mucosal elements.[17]

Bronchogenic cysts may be identified prenatally, but often present later in life with infection. Thoracic imaging typically shows a well demarcated lesion with an air-fluid level (Figures 9 and 10). Depending on their location, large

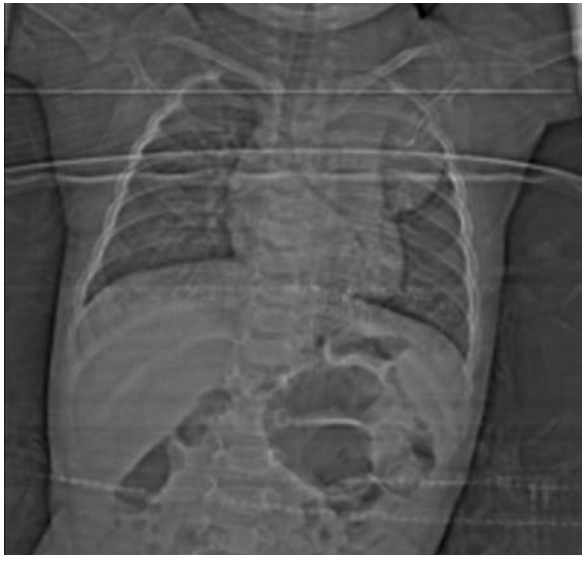


Figure 9. Scout image demonstrating left upper thoracic cystic mass in a 9-month-old patient that presented with fever and cough.

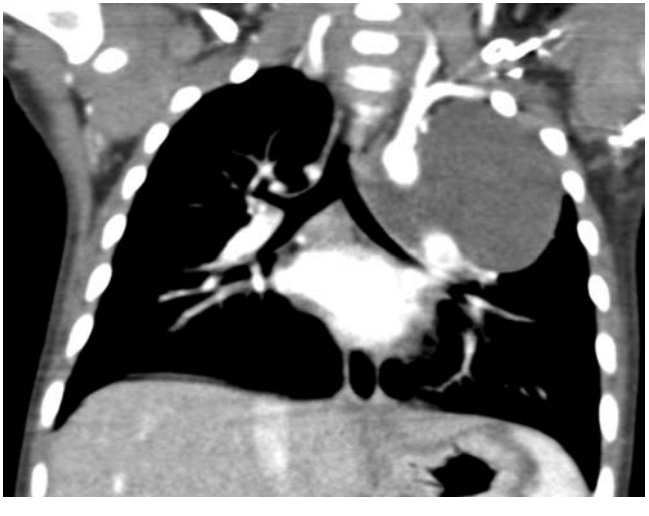


Figure 10. Computer tomographic image demonstrating bronchogenic cyst in the patient shown in Figure 9.

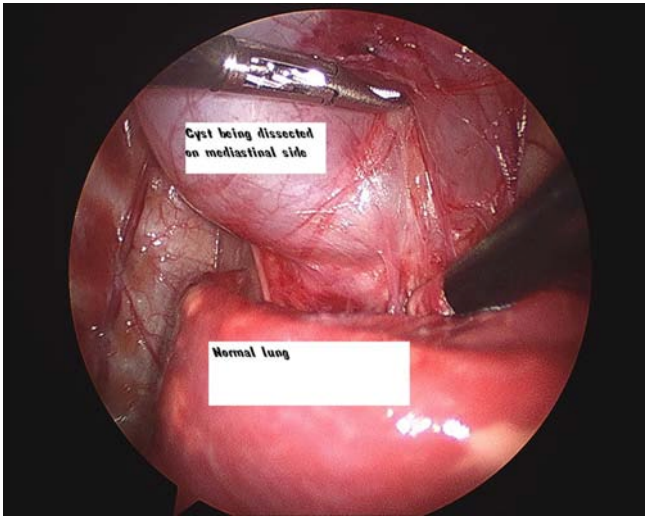


Figure 11. Thoracoscopic, intra-operative image demonstrating bronchogenic cyst in the patient shown in Figures 9 and 10.

bronchogenic cysts may displace surrounding structures and cause respiratory compromise or swallowing difficulty due to obstruction. In addition, if infection leads to wall necrosis, the rare bronchogenic cyst may present with hemoptysis or hemo-, pneumo-, or pyothorax. They can be discovered incidentally on imaging performed for unrelated reasons. Once identified, surgeons recommend resection almost uniformly because of the high incidence of infection.

Most bronchogenic cysts are ideally suited to thoracoscopic resection, particularly in cases that have only fibrous attachments to the tracheobronchial wall (Figure 11). Infected bronchogenic cysts may require percutaneous, image-guided drainage and antibiotic therapy prior to resection.

MISCELLANEOUS CONDITIONS

The most difficult to characterize, congenital or acquired pulmonary cysts include lymphatic or lymphangiomatous cysts, mesothelial cysts, and peripheral cysts, the last perhaps consequent to indefinable *in utero* or peri-partum infections.[4] Many other rare congenital pulmonary lesions are only documented in case reports. Pulmonary arteriovenous malformations, often found in association with hereditary telangiectasia (Rendu-Osler-Weber syndrome), have been described and may

present with hemoptysis, infection, and/or mass effect.[34,35] Pulmonary lymphangiectasia is a primarily sporadic disorder characterized by pathologic dilatation of pulmonary lymphatics.[36] These present clinically with respiratory failure and chylous pleural effusion; treatment is generally supportive. Despite advances in critical care support, prognosis is very poor.

It is important to recognize postinfectious pneumatocele that can occur after bacterial pneumonia, most often from staphylococcus species. These acquired lesions rarely require operative intervention. They can be large and still resolve after the infection has been adequately treated.

IMAGING

Increasing frequency and sophistication of prenatal sonography has greatly increased the number of antenatal consultations regarding various lung lesions. Although visible as early as 18 weeks into pregnancy, most lung lesions are identified by the latter half of the second trimester. Lesions appear either hyperechoic (suggesting a microcystic CCAM or BPS) or cystic (suggesting a macrocystic CCAM or bronchogenic cyst).[1,37] Accuracy with which prenatal sonography precisely predicts lung anomalies is heavily user-dependent. Sensitivity for prenatal sonography in detecting congenital lung lesions is hard to estimate, but results from the United Kingdom, where populations may be better captured than in the Unites States, suggest a sensitivity of 81%.[13] Despite its limitations, screening ultrasound can be helpful in guiding the need for more sophisticated imaging, such as magnetic resonance imaging (MRI), as well as identifying associated anomalies that may affect outcome.

Despite comprising up to 15% of congenital lung lesions, CLO is uncommonly identified on prenatal sonography due to the echogenic texture of surrounding, normal lung tissue. When identified, CLO characteristically appears as a uniformly echogenic lesion with associated mass effect.[38] Initial postnatal evaluation, typically performed in the setting of progressive respiratory distress, starts with a simple, plain chest X-ray. Plain chest films obtained just after birth will likely show a solid infiltrate that progresses to hyperinflation in the ensuing days. If chest radiographs are equivocal, CT imaging can confirm diagnosis and help define the anatomy precisely.

Similar to CLO, bronchogenic cysts are rarely identified prenatally. Plain chest radiography may identify cysts as mediastinal or hilar masses, occasionally with air-fluid levels if they are infected. Bronchogenic cysts are best characterized by CT imaging, which helps both to distinguish these cysts from other soft-tissue masses within the mediastinum and plan operative approaches.[38]

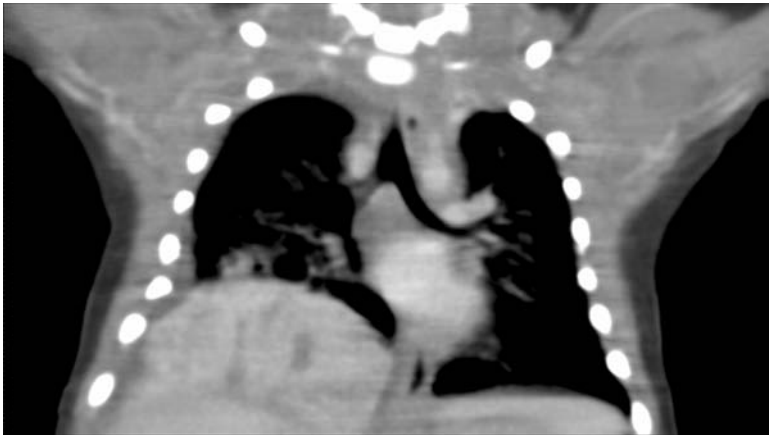


Figure 12. Coronal CT image in a 2.5-week-old infant who was suspected of having a right lower lobe congenital cystic adenomatoid malformation on prenatal sonography, suggests that right-sided congenital diaphragmatic hernia (CDH) is a more likely diagnosis. The patient underwent diagnostic thoracoscopy and ultimately thoracoscopic repair of the right-sided CDH.

The appearance of CCAM (CPAM) on prenatal sonography is perhaps more consistent and predictable than the previous two entities. Specific characteristics depend on the type of CCAM and relative composition of cystic and solid components. These lesions may be indistinguishable from CDH on prenatal ultrasound as CCAM tend to be confined to the lower lobes and their cystic components may resemble bowel. Fetal MRI has the advantage over sonography of better differentiation between lung tissue and bowel or liver, making the distinction between CCAM and CDH theoretically easier to make[37] (Figure 12). It is also much more precise than ultrasound in determining lung volumes and lung-to-thorax ratios, although the utility of these measures in predicting postnatal lung function is limited at best. Although MRI avoids the use of ionizing radiation associated with CT scan, the effect of magnetic field exposure on the developing fetus is unknown; thus, fetal MRI is usually reserved until after the first trimester. Postnatal imaging may include plain chest radiography for an initial general view, but often CT is required to better define anatomic characteristics postnatal.

BPS may also be difficult to definitively diagnose by prenatal ultrasound characteristics alone. These lesions appear echogenic on sonography and, because of their lower thoracic location, may be confused with infra-diaphragmatic lesions such as adrenal hemorrhage or neuroblastoma.[38] Extralobar BPS may be

associated with CDH, which can impact the approach to surgical therapy. For all the aforementioned reasons, fetal MRI may be indicated to clarify diagnosis and therapeutic strategy. Postnatal imaging should include some modality that readily identifies systemic feeding vessels — this includes CT angiography or sonography with Doppler analysis.

Multiple investigators have tried to develop prenatal prognostic indicators for this group of lesions based on sonographic characteristics or measurements. Included in these assessments are cyst size and character, lesion echogenicity, presence of polyhydramnios, and presence of hydrops.[39,40] Some groups measure normal transverse lung-to-thorax area ratio during the course of pregnancy in an effort to develop an absolute ratio number or relative change in ratio that may predict poor outcome.[39,41] Still others measure total lung volume on MRI in attempt to do the same. While some trends have been noted, none of these methods are consistent enough yet to merit strict adoption in the general community.

Imaging of congenital lung lesions must balance the need for precise diagnosis and anatomic localization against the increasingly appreciated perils of radiation over-exposure, particularly in early life. CT remains the most useful modality due to its rapidity, reproducibility, ability to define vascular structures, and capability for three-dimensional reformatting. It is hoped that ultrasound and/or MRI techniques will improve enough to supplant modalities requiring significant exposure to radiation.

A final word of caution: a significant proportion of antenatally visualized lesions may not be visible on postnatal plain chest radiography.[42,43] While appreciation for the "disappearing lesion" has grown and willingness to adopt an observational strategy for select lung lesions has increased, it is incumbent on the consulting surgeon to maintain contact with families seen in prenatal counseling to monitor for development of symptoms. Strong consideration should be given to obtain a postnatal chest CT to definitively characterize the lung abnormality when diagnosis or resolution is in doubt. If the patient has no symptoms, this can be advised at 6 months of age.

ANESTHETIC CONSIDERATIONS

A meaningful discussion of pediatric anesthetic considerations for operations to remove congenital lung lesions is beyond the scope of this chapter. However, several cautionary observations may be helpful. CLO and its associated physiologic embarrassment produce perhaps the only true life-threatening emergency encountered among all the lesions discussed in this chapter, and therapeutic measures short of thoracotomy may fail. Obstruction is the mechanism behind

hyperinflation and mediastinal compromise; any maneuvers that worsen hyperinflation should be avoided, particularly aggressive ventilation and allowing the patient to cough during intubation. Ventilation-perfusion mismatch in the affected lobe may delay onset of general anesthesia using inhalation agents.[44] In addition, extrinsic cardiac compression may already compromise cardiac function; therefore, agents that further depress myocardial function should be avoided. Once the chest is opened, however, the sequelae of hyperinflation resolve promptly, allowing for application of standard anesthetic techniques. It is wise for the surgical team to scrub and gown and be at the bedside prior to induction. If positive airway pressure causes an acute decline in cardiopulmonary function, the patient is urgently positioned with the affected side up. An immediate thoracotomy allows the lobe to herniate and relieves compromise.

When undertaking minimally invasive surgery (MIS) pulmonary resection for congenital abnormalities, pre- and intraoperative communication between the surgeon and anesthesiologist is essential. Selective hypoventilation of pulmonary lobes in the operative field is critical to success of thoracoscopic pulmonary resection. In the neonate and infant, this can often be achieved simply by gentle insufflation with carbon dioxide (often no more than 3 mm Hg pressure) and application of gentle ventilation maneuvers. In older patients, bronchial blockers or selective bronchial intubation of the contralateral side can be tremendously helpful, although the team must be vigilant about loss of selective intubation or blocking during patient positioning. Lastly, permissive hypercapnia is an accepted and necessary technique when performing MIS pulmonary resection. In select cases, high frequency oscillating ventilation may be of benefit, although this has not been formally reported.

OPERATIVE CONSIDERATIONS

Advances in MIS for congenital lung lesions over the past 15 years have been remarkable, although putative advantages beyond cosmetic ones have been hard to identify. To date, there are no randomized studies comparing open to MIS resection. Multiple case series have shown longer operative times and only marginally shorter lengths of hospital stay for MIS procedures. Even the theoretically expected improvement in patient discomfort with MIS techniques has been hard to demonstrate. Despite marginal advantages at best for MIS techniques thus far, these same case series have not shown significant differences in complication rates.[9–11,25] One final theoretical advantage that MIS techniques promise is a decrease in long-term chest wall deformity and/or acquired thoracic dystrophy. Longer-term follow-up studies will hopefully provide these data.[45]

Pulmonary resection remains among the most difficult MIS procedures to master due to the small operative space involved, unique anesthetic challenges, challenging three-dimensional anatomy, and risk of catastrophic bleeding. Although MIS principles of pulmonary resection are no different from those of open resection, a clear understanding of standard anatomy and expected variants is critical; even experienced surgeons may be well served by reviewing expected relationships of pulmonary vessels and airway structures immediately prior to operation.

Depending on patient size, selective mainstem intubation or independent lung ventilation with double-lumen endotracheal tubes can be quite helpful to minimize unwanted lung expansion in the operative field although not presently applicable to neonates. In the smallest patients, carbon dioxide insufflation usually provides enough lung collapse under a gentle tension pneumothorax to allow the operation to proceed. After decubitus positioning, port placement is dictated in part by the anticipated resection location. The first port is placed typically in the mid-axillary line in the 5th or 6th intercostal space. Final number and size of ports is variable, but typically include a total of 3–5 ports. Ligasure (Valleylab, Boulder, CO) has proven to be a very useful device capable of safely sealing and dividing blood vessels several millimeters in size, as well as lung tissue in the fissures. Power source technology is in constant evolution, but has greatly helped to eliminate the need for MIS staplers, which typically require 12-mm ports and are hard to deploy in the neonate's small thoracic cavity. In order to visualize hilar structures well, surgeons may resort to cyst aspiration or fenestration in the case of macrocystic CCAM or hybrid lesions.

Surgeons are cautioned to look for and safely divide systemic vessels coming off the aorta in the case of BPS. Further dissection is dictated by the location of planned lobectomy. If possible, pulmonary artery branches should be secured first to avoid venous congestion. Then the corresponding pulmonary vein is ligated. Bronchi are divided last, either accomplished with a stapling device in older patients or by sharp transection and ligature with long-term absorbable suture (such as PDS).

LONG-TERM OUTCOMES

As with many pediatric surgical diseases, the natural history and long-term outcomes for non-operative management of congenital pulmonary anomalies, as well as results with resection are only starting to be addressed seriously in the literature. Stanton *et al.* published a systematic review and meta-analysis of available literature on postnatal management of congenital cystic lung lesions.[25] They estimate that 4%

of fetuses with known cystic lung lesions will die *in utero*, while another 2% will succumb in the postnatal period. Mortality is equally divided among patients treated with resection and those who were observed only. Several centers advocate continued observation for asymptomatic lesions, although preliminary results from at least one longitudinal study suggest a significant proportion of patients in the observation group developed symptoms within the first year of life, leading to resection. Continued observation carries risk of excessive radiation exposure from surveillance X-rays, as well as conversion of an elective operation to an emergent one if clinical status deteriorates during the observational period. This in itself carries an inherently higher risk of complication.[25] Stanton *et al.* also found that symptoms develop at an average age of 10 months, suggesting that if elective postnatal resection is to be undertaken to prevent future complications, it should be done during this time period. The reader is reminded that much of what is published and taught about management of congenital lung lesions is based on case reports and surgeon preference. Adequate evidence-based guidelines simply do not yet exist.

Patients who undergo pulmonary resection through thoracotomy are thought to be at high risk for the development of spinal anomalies[45] and thus should have long-term follow-up and referral to an orthopedic specialist as needed. This risk is thought to be reduced through MIS, although long-term follow-up is yet not available.

ANTENATAL THERAPY

Multiple prenatal interventions have been proposed to either directly or indirectly address problems caused by large congenital pulmonary lesions.[46] They are listed here briefly for completeness. Maternal betamethasone administration has been reported in several small series to arrest and even cause regression of NIFH in association with CCAM.[14] The evidence for its efficacy is increasing.[23] Other options for treatment of NIFH include placement of a thoracoamniotic shunt,[22,47,48] percutaneous laser ablation of large lesions,[22,49] and open fetal pulmonary resection.[17,22] These therapies are still mostly viewed as experimental. They have not been widely adopted in the medical community due to extraordinarily complex ethical and logistical issues surrounding their implementation, as well as inconsistent benefit reported in the literature. Thoracoamniotic shunting results in demonstrable reduction of cyst volume and is most frequently utilized in fetuses with macrocystic CCAM who develop NIFH. Placement is performed after the 20th week of gestation to avoid added complication of postnatal chest wall abnormalities. Putative salutary effects on lung development have not been

born out yet in the literature.[47] Although fetal surgery is technically feasible, any advantage of prenatal pulmonary resection over conventional techniques similarly has not been realized, in part due to a high rate of fetal deaths and ongoing problems with induction of premature delivery. Ongoing research seeks to define better selection criteria, improve fetal intraoperative monitoring, and battle premature delivery. Maternal steroids may be replacing this invasive approach.[23]

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CHAPTER 12

CONGENITAL DIAPHRAGMATIC HERNIA

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INTRODUCTION

This chapter will focus on the current trends in medical and surgical therapy for congenital diaphragmatic hernia (CDH). CDH was traditionally classified as a surgical emergency.[1] In 1940, Ladd and Gross emphasized the importance of early surgical intervention as essential.[2] This is no longer the case. While CDH can carry a grave prognosis, overall survival has improved to 70–95%.[3] This improvement in survival is due to new strategies such as delayed repair with preoperative stabilization and the avoidance of barotrauma.[4] This approach is probably superior to the historical practice of rushing these immensely compromised newborns to the operating room soon after birth. In addition, the use of ECMO and other advanced ventilatory strategies have made significant contributions.[5] Our understanding of CDH now recognizes that it is not the herniated viscera causing respiratory compromise at birth but rather pulmonary hypertension and pulmonary hypoplasia, which determine outcome. Persistent pulmonary hypertension of the newborn (PPHN) is the most treatable element present in CDH and is the target of most therapies.[6] The treatment of congenital diaphragmatic hernia has evolved dramatically since the early reported successful repair by Dr Gross,[1] and medical management has become the focal point of current care.

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Epidemiology and Genetics

The incidence of CDH is approximately 1 in 2000–5000 live births.[7] Although familial cases have been reported, most are sporadic.[8] Many genetic deletions and gene overexpressions have been implicated in individual cases of CDH. However, most cases represent complex inheritance patterns in which a combination of environmental and genetic factors are likely involved.[9] The best studied gene associated with CDH is the *WT1* gene on chromosome 11p13 which encodes a transcription factor important in diaphragmatic development. Cases of CDH caused by mutations of *WT1* have been reported in children with various clinical settings such as WAGR (Wilms' tumor, Aniridia, Genitourinary malformations mental Retardation), Denys-Drash, Frasier and Meacham syndromes. Nevertheless, these represent a small subset of CDH patients.[7]

There is no known racial predisposition and the etiology of CDH is unknown. Environmental exposures to agents such as thalidomide, cadmium and lead have been reported.[10] The incidence of associated anomalies was previously thought to be low. However, more recent data suggests that 10–50% of babies born with CDH have associated malformations. Cardiac anomalies are present in about 25% of infants and include ventricular septal defects, tetralogy of Fallot, transposition of the great vessels, double outlet right ventricle, and coarctation of the aorta.[11] The embryology of diaphragmatic development is incompletely understood but closure of the pleuroperitoneal canals with formation of a pleuroperitoneal membrane occurs at about the eighth week of gestation. Failure of the pleuroperitoneal membrane to close or failure of the rudimentary diaphragm to muscularize leaves this area prone to herniation.[12]

Pathophysiology

The advent of the nitrofen model for studying CDH has been critical in the understanding of the pathophysiology of the disease.[13] The agent itself, nitrofen, implies that an environmental toxin may be critically important to the induced pathology. Moreover, the reproducible findings seen in the model, namely a diaphragmatic defect in combination with hypoplastic lungs and pulmonary hypertension, imply a field defect affecting both lungs, ipsilateral more than contralateral, and the entire foregut. We now realize that the degree of pulmonary hypoplasia is probably not strictly related to the volume of herniated viscera. There is also increased muscularization around peripheral arterioles which is thought to contribute to the severe pulmonary hypertension that is usually present.[14]

The diaphragmatic defect itself usually features a completely open space between the abdomen and the chest. The defect may involve a small portion of the

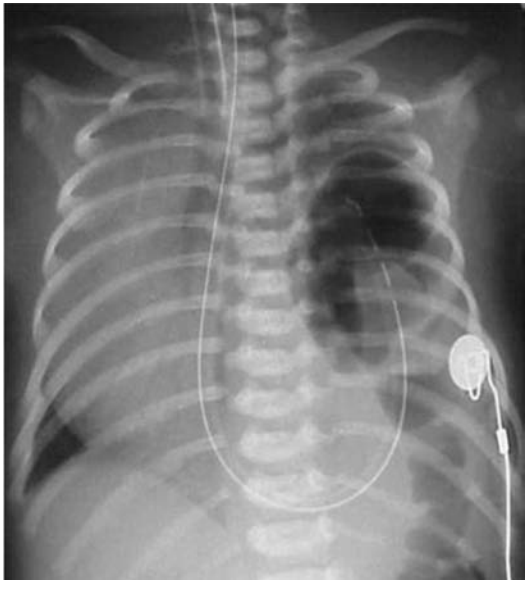


Figure 1. Left congenital diaphragmatic hernia; note nasogastric tube within the stomach located in the left hemithorax and mediastinum shifted to the right.

diaphragm or the entire diaphragm may be absent. A peritoneal hernia sac may be present in 10–15% of patients. With left-sided hernias, the stomach, small intestine, colon or liver may herniate into the left hemithorax (Figure 1). The spleen is also a frequent visitor. While the herniated viscera may exacerbate the concomitant pulmonary hypoplasia and pulmonary hypertension, it does not appear to be the direct cause of these problems. Rather, the field defect present affects both the herniation and lung maldevelopment.

Clinical Presentation and Diagnosis

About 90% of CDH's are left sided. Morgagni hernias often present later in life and have few pulmonary symptoms at birth. The diaphragmatic defect in left-sided hernias is usually postero-lateral (Foramen of Bochdalek). The anterior rim of diaphragm is usually quite prominent but the posterior rim may be narrow or absent, and is often rolled up like a window shade. There is a small subset of right sided, non-Morgagni type congenital diaphragmatic hernias that may have the worst overall prognosis due to severe unrelenting pulmonary hypertension and particularly challenging pulmonary hypoplasia.[15] With left-sided defects, a true hernia sac is

present about 10–15% of the time and should be excised during the repair.[16] Both lungs are hypoplastic with the ipsilateral lung more severely affected.

Most CDH's are now diagnosed prenatally with ultrasound.[17] Between 11–24 weeks of gestation, one can easily visualize stomach or intestinal loops in the fetal left hemithorax adjacent to the heart. Polyhydramnios may also be present and suggestive of a diaphragmatic defect. Most babies can be delivered vaginally, which remains the standard of care. However there may be some advantages to scheduled caesarian section delivery.[18] Fetal intervention techniques such as tracheal occlusion performed both open and laparoscopically have been attempted but have not shown any improvement in survival.[19] There has been a renewed interest in fetal tracheal occlusion and there is good evidence that lung growth can be achieved *in utero* with minimal morbidity.[20] Still, there remains no evidence of any survival advantage at this time. The search for clinically reproducible and valid prognostic factors has become vitally important during the age of potential fetal interventions so that babies can be stratified appropriately. Lung to head ratio is now a generally accepted prenatal prognosticator with a number below 1.0 portending a particularly poor prognosis.[21, 22] Liver in the left hemithorax, seen on ultrasound and other congenital defects, particularly complex cardiac anomalies diagnosed on prenatal echocardiography, also reflects a negative disposition.[23]

Postnatally, the first sign of CDH is usually respiratory distress within the first few hours of life due to severe pulmonary hypertension and pulmonary hypoplasia. Physical examination may reveal a schaphoid abdomen with an increased anteroposterior diameter of the chest. Breath sounds may be absent on the side of the hernia. Heart sounds may be loudest on the right. Occasionally, bowel sounds may be auscultated in the chest. The chest radiograph is usually diagnostic and reveals abdominal viscera in the left hemithorax with displacement of the heart to the contralateral side. The nasogastric tube may be seen to coil in the chest (Figure 1). There is typically a relative paucity of bowel gas below the diaphragm. No other studies are necessary to confirm the diagnosis. Children may exhibit a "honeymoon period" with improved respiratory status immediately after birth for about 24 hours.

PREOPERATIVE TREATMENT

Initial Management

Immediate resuscitation of infants born with CDH is undertaken. Intubation followed by mechanical ventilation is instituted and the blood pressure is supported

with volume and inotropic support if needed. Intensive hemodynamic monitoring of arterial blood pressure, pre- and postductal oxygen saturation, and mixed venous oxygen saturation is begun. A nasogastric tube should be placed immediately to decompress the stomach. This simple maneuver can greatly aid ventilation and is often overlooked during the acute period. A chest X-ray confirms the stomach is decompressed. If it is not, manipulations of the NG tube are undertaken and the chest X-ray is repeated until one can visualize a decompressed stomach. The chest X-ray will also visualize the position of the endotracheal tube and confirm the presence of a CDH. The position of the liver is of particular importance, with the liver in the chest suggesting a more difficult clinical course.

A urinary catheter is placed to monitor urine output. An echocardiogram is done to rule out any structural cardiac defects and to evaluate the degree of pulmonary hypertension. Mask and bag ventilation should ideally be avoided as this may distend the herniated viscera. The use of a prophylactic chest tube is unnecessary. However, symptomatic pneumothoraces in the contralateral lung must be treated aggressively with immediate chest tube placement. Once stabilized and with the diagnosis confirmed, the child should be transferred to a neonatal center, preferably one with extracorporeal membrane oxygenation (ECMO) capabilities. Babies diagnosed prenatally with CDH should be delivered at an ECMO center to expedite care and avoid the hazards of transport should ECMO be required.

Ventilator Management

Historically, it was thought that the ideal way to treat persistent pulmonary hypertension of the newborn (PPHN) was with hyperventilation to induce alkalosis and inflate atelectatic alveoli. However, this strategy leads to barotrauma and may worsen the pulmonary hypoplasia. Ventilation strategies utilizing permissive hypercapnia and low airway pressures without paralysis may help to avoid the problem of barotrauma.[4] This management strategy may contribute to the improved survival rates noted in some centers. This approach can be combined with high frequency oscillatilatory ventilation (HFOV) which allows for adequate gas exchange at lower airway pressures. Nevertheless, the entire gamut of ventilation strategies (conventional IMV, jet ventilation) is utilized in different high volume centers with no one strategy clearly superior to any other. The goal of therapy should be a preductal oxygen Po_2 greater than 60 mm Hg ($Sao_2 > 88\%$) with a corresponding Pco_2 less than 60 mm Hg.

Pharmacologic Therapy

Historically, pharmacologic agents such as tolazoline (alpha blocker) have been used to reduce pulmonary hypertension.[24] While these agents induce pulmonary vasodilation, none have been shown to definitively improve patient survival. Moreover, these agents act peripherally on all vasculature and may lead to systemic hypotension. Inhaled nitric oxide is a potent vasodilator which, because of its short half-life (bound to hemoglobin), is selective for pulmonary vasculature. It has been used extensively in all etiologies of PPHN, including CDH.[25] Surfactant deficiency has been shown to be present in CDH in animal models. However, this has not been replicated in human studies.[26] Surfactant replacement therapy may improve gas exchange, particularly when combined with nitric oxide in animal models, and initial use of this combined strategy has been encouraging in some centers. It is important to note that neither nitric oxide nor surfactant, alone or in combination, has demonstrated improved survival in infants with CDH.[27]

Extracorporeal Membrane Oxygenation (ECMO)

ECMO serves as an alternative form of oxygen delivery and allows for a period of time to "rest" the hypoplastic/hypertensive lungs so they can heal and mature while avoiding barotrauma. Improved survival in children with CDH placed on ECMO is documented[5] although some portion of this is attributable to other improvements in respiratory care strategies. Some centers have not seen a survival benefit. Criteria for initiation of ECMO varies among institutions. Some use an oxygenation index (OI) of greater than 40 as an important factor while other centers do not even calculate the OI. The OI is calculated by multiplying the fraction of inspired oxygen by the mean airway pressures and dividing that number by the partial pressure of oxygen in the arterial blood gas. Perhaps the best indication for ECMO is failure of medical management in the setting of a potentially viable baby. This can be difficult to assess and some children born with very severe pulmonary hypoplasia may be denied ECMO since their predicted survival is so low. Babies who never reach a preductal oxygen saturation of 90%, despite full medical management, or have very high P_{co_2} may not be good candidates for ECMO because of their low chance of survival.[28] Alternatively, many have advocated that all babies should be given a chance and placed on ECMO.

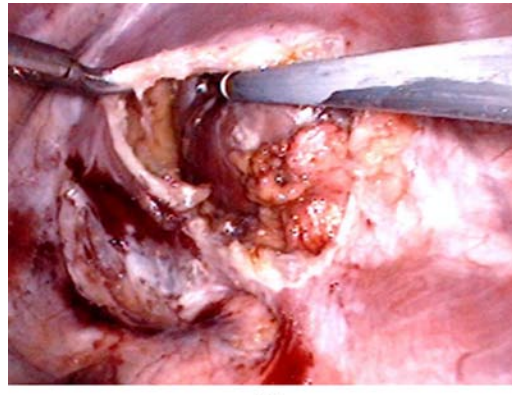
Absolute contraindications for ECMO include known intraventricular hemorrhage (Grade 2 or higher), prematurity of less than 35 weeks' gestation, and associated lethal anomalies including some congenital cardiac abnormalities.

Babies on ECMO require anticoagulation which is associated with an increased risk for intracranial or generalized bleeding. Cannulation may be either veno-arterial or veno-venous, often depending on cardiac function. There is no difference in survival between VV and VA ECMO although neurologic complications may be lower with VV ECMO.[29] The timing of operative repair in babies requiring ECMO for CDH is variable. Surgery should be done when the infant is determined to have derived the maximal benefit from ECMO. Repairing the hernia on ECMO is associated with significantly more bleeding complications, some of which may be severe. The use of aminocaproic acid may minimize bleeding complications. Many surgeons wait until the child is off ECMO before undertaking the repair which may improve overall survival.[30] However, many babies will develop some respiratory insufficiency post-repair, even if they had improved preoperatively.

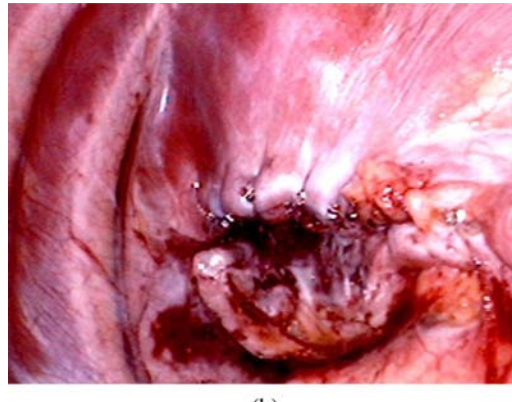
Operative Procedures

Following initial stabilization, which may require several days or longer as the hypoplastic lungs mature, operative repair is undertaken with the goal of returning herniated viscera to the abdominal cavity and minimizing the chance of hernia recurrence. Most surgeons favor a transabdominal approach. A subcostal incision is made, the herniated viscera are reduced into the abdomen and the diaphragmatic defect is visualized. The edges of the diaphragm are approximated with nonabsorbable suture material. If the defect is large, a prosthetic patch may be required to close the defect without tension. Gore-Tex has been the most common material used in patch repairs but many other materials are being tested. The incidence of hernia recurrence is increased in children repaired with a prosthetic patch.[31] Some groups have advocated the use of a split abdominal wall muscle flap for repair of large defects in babies who are on ECMO since this may have less bleeding complications.[32] Some babies may experience a significant loss of intrabdominal domain and placement of the viscera back into the abdominal cavity can lead to an abdominal compartment syndrome. Babies whose abdominal cavities after repair are very tight or whose peak airway pressures increase markedly after hernia reduction may benefit from a temporary Gore-Tex patch closure of the abdomen followed by removal of the patch within 1–2 weeks once the abdomen accomodates.

Thoracoscopic repair of CDH both in the newborn period and in children diagnosed later is now being performed at many centers[33–35] (Figure 2). The feasibility of this approach has been established although there is no long-term data comparing the durability of thoracoscopic versus open repairs. Some groups are suggesting lower morbidity and improved respiratory status following thoracoscopic repair.[36] A major concern during thoracoscopic repair is



(a)



(b)

Figure 2. Thoracoscopic repair of left congenital diaphragmatic hernia. (a) Hernia reduced into abdomen; defect defined. (b) Defect closed primarily with permanent suture.

worsening of pulmonary hypertension intraoperatively and elevated P_{CO_2} due to insufflation. There are some babies who may not tolerate thoracoscopic repair hemodynamically and should be converted to an open procedure. However, there are attempts to repair all babies thoracospically in some centers, even those with significant pulmonary hypertension. The advisability of this approach is debated. Laparoscopic repair is also feasible but may be more difficult technically and is less commonly used by those surgeons who favor a minimally invasive approach. Lung transplantation, particularly for babies with critical pulmonary hypoplasia, has been performed successfully, but a shortage of organs, as well as very limited experience in patients with CDH, makes this a rarely used option at present.[37]

LONG-TERM OUTCOME

The hypoplastic lungs may take many years to mature and often never achieve "normal" status in terms of complete respiratory function. However, most CDH survivors do not manifest clinically significant respiratory compromise over the long term. Gastroesophageal reflux is the most common complication affecting approximately 50% of patients.[38] Most children with GE reflux can be managed medically and will not require an antireflux procedure. Neurologic and developmental status are adversely affected in a significant number of children who survive CDH and this number may be increasing as a subset of more severe, post ECMO patients survive.[39] Disabilities may include seizure disorders, hearing loss, visual problems and cognitive deficits. The etiology of these problems is unclear although neonatal hypoxia and complications of ECMO (microthrombi) are suspected. Nevertheless, the majority of babies who survive CDH can be expected to lead a normal and productive life with minimal or no long-term sequela.

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CHAPTER 13

EXTRA HEPATIC BILIARY ATRESIA

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SURGICAL HISTORY OF BILIARY ATRESIA

Sir Everard Home provided one of the earliest descriptions of neonatal obstructive jaundice in 1813 when he described a child who was "without a gallbladder, or even a duct of any kind leading from the liver to the duodenum".[1] In later years, Professor John Burns of the University of Glasgow provided evidence for the extreme danger of neonatal jaundice and encouraged further understanding on the failure of the biliary apparatus. It was not until the great treatise of John Thomson, University of Edinburgh, in 1892 detailing the clinical and post mortem account of a 3-month-old jaundiced infant, that the surgical community became widely aware of congenital obliteration of the bile ducts as a distinct disease.[2] Absence of the bile ducts remained a fatal disease until decades later in 1928 when Ladd published 8 of 11 cases amenable to surgical correction with a bilioenteric anastomosis.[3]

Patient phenotypes were divided into "correctable" and "non-correctable" disease types, both with poor surgical outcomes. Donovan published his experience in 1937 with 18 cases of congenital atresia of the bile ducts and noted only two survivors after operation.[4] He concluded that despite poor surgical success, all patients with presumed biliary atresia (BA) deserved an exploratory celiotomy. He hoped that enough of the ductal system was present to attain drainage as the

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alternative was universally fatal. Gross followed with his surgical text in 1953 describing 27 of 146 infants with "correctable" pathology; however, he documented only 12 jaundice-free survivors. All infants with "non-correctable" BA died in infancy.[5] With these failures, the surgical community sought other techniques including artificial bile duct placement, anastomotic tube splints, partial hepatectomy with intrahepatic cholangio-jejunostomy, enteric lymphatic drainage of the liver, and drainage to the thoracic duct which all proved unsuccessful.[6–10]

A paradigm shift in the surgical approach to BA occurred with Kasai and Suzuki's work during the 1950s. Professor Kasai described the progressive destruction of intralobular bile ducts when examining the histology of patients with BA. In addition, he identified the presence of microscopic bile ducts within the fibrous remnant of the atretic extraheptic biliary tree between 2 and 12 months of age.[11] Kasai proposed that if the extrahepatic bile ducts were removed while there was biliary continuity between the intraheptic ductal system and the ductal plate, internal drainage could be achieved arresting the progression of BA.[11] Internal drainage with Roux-en-Y reconstruction became known as the Kasai portoenterostomy.[12] In the United States, Lilly and Altman championed the Kasai portoenterostomy for BA as they attained a 90% success rate of internal drainage in children less than 3 months of age if microscopic biliary ductules were identified in the excised fibrotic remnant of extrahepatic bile ducts.

However, doubts still remained about the benefits of Kasai portoenterostomy. Campbell *et al.* reviewed 12 infants with surgically corrected BA and identified no postoperative increase in bile excretion and a mean total survival of only 15 months, no different than those children not receiving surgery.[13] Biliary drainage with Kasai portoenterostomy is associated with two major morbidities leading to management failure: cholangitis and portal hypertension.[14–16] One series demonstrated the absence of cholangitis if a portocholecystostomy was completed.[17] Portocholecystostomy was described for the anatomic variant with an intact distal biliary tree and an atretic hepatic duct, allowing neobiliary enteric communication by joining the porta to the gallbladder instead of jejunum. With this reconstruction, the sphincter at the distal end of the common bile duct serves to prevent reflux of gastrointestinal (GI) contents into the biliary tree. Other methods to decrease cholangitis include an intussuscepted antireflux valve; however, this has proven ineffective.[18,19]

With the introduction of liver transplantation by Starzl, patients with end-stage liver disease from BA had hope of cure.[20] BA is the most common indication for orthotopic liver transplantation in children.[21]

Epidemiology

BA has a variable worldwide incidence ranging from 1 in 19,600 live births in France to 1 in 6,800 live births in Taiwan. In the United States, the estimated incidence is 1 in 14,000 live births. French Polynesians seem to have the highest reported incidence of BA: 1 in 3400 live births.[22] Infants are significantly more likely to be female, approximately 60% of cases, and more likely to be first born.[23,24] Incidence varies across racial lines and according to birth weight, with rates higher among nonwhite compared to white infants (0.96 vs. 0.44 per 10,000 live births) and term, low birth weight compared with term, normal birth weight infants (2.62 vs. 0.75 per 10,000 live births).[25] Infants at highest risk are those born preterm with low birth weight (RR 3.24, 95% CI 2.20–4.76).[26]

Several studies have observed seasonal variation in the incidence of BA. Over a 16-year study period in New York City, spring births had a significantly increased rate of BA, while fall births had an increased incidence across the rest of the state.[26] In a separate study from Atlanta, seasonal clustering was found with rates of BA three times higher from December through March compared to April through July.[25] Other studies have failed to demonstrate seasonality, time-clustering, or time-space clustering in BA incidence.[22,27] The significance of time clustering may be related to viral infection outbreaks as a potential candidate in etiology of BA.[28]

BA may be related to pre- and perinatal risk factors, including maternal reproductive and family history, as well as gestational age and weight status of the neonate at delivery. Multivariate analysis of the Swedish national health database has identified four independent risk factors for BA: maternal age, parity of at least 4, prematurity, and low birth weight for gestational age.[29] In addition, low maternal intake of vitamin E, copper, iron, phosphorus, and beta tocopherol had borderline significance in their association with isolated BA.[30]

Embryology

The extrahepatic biliary system is generated as a ventral outgrowth from the distal end of the foregut along with the liver primordium and gallbladder. Concurrently, intrahepatic ducts are created from differentiated hepatocytes, first appearing at the liver hilum and spreading peripherally. The caudal aspect of the hepatic diverticulum produces the cystic duct and gallbladder primordium by the end of the 4th week of gestation. The common bile duct and hepatic ducts can be identified at the beginning of the 5th week; the ducts become a solid cord that elongates to

reach the liver and recanalizes between the 6th and 12th weeks. Continuity of the intrahepatic and extrahepatic biliary systems is evident commonly by 5 months gestation when bile can be seen within the fetal intestine.[31]

Pathogenesis

If untreated, the inflammation and fibrosis that obliterates the extrahepatic biliary tree in BA progresses to end stage biliary cirrhosis in most patients. Etiology and pathogenesis are still largely unknown.[32] The theory that BA is caused by an immune response to a variety of genetic, infectious, inflammatory, and toxin mediated insults is widely shared.[33–35] Each arm of the immune system, innate and adaptive, has been implicated in the pathogenesis of BA after exhaustive study on the rhesus rotavirus group A (RRV) murine model established by Petersen.[36] Shivakumar *et al.* further elucidated the significance of immunologic potentiation by demonstrating improved survival in an immunologically incompetent, interferon (IFN)-γ knockout mouse model of BA.[37]

Recently, the innate, or nonspecific, immune response has attracted attention as a key component in pathogenesis of the disease. Cellular markers specific to many of the cellular mediators of innate immunity, including natural killer (NK) cells, mast cells, eosinophils, basophils, and phagocytic cells such as macrophages, neutrophils, and dendritic cells, have been observed within the region of the portal tracts at various stages of disease progression. NK cells become activated early, populating the portal tracts of infants with BA at diagnosis. In an experimental murine model, NK cells are the most abundant inflammatory cell in the extrahepatic ducts and undergo hyperplasia during the inflammatory and obliterative process leading to BA.[38] Blocking the powerful NK cell regulating receptor, NK group 2d (NKG2D) receptor, prevents the BA phenotype and duct injury in the murine model. Cluster of differentiation receptor 14 (CD14), a differentiation marker found on the surfaces of macrophages and neutrophils, is expressed strongly in BA patients with clinically evident cholestasis.[39] CD14 expression appears to be specific for BA and dynamic throughout disease progression, with strong activation early on and quiescence in later stages, supporting a theory of endotoxin susceptibility in infants with BA.[40,41] The role of macrophages has yet to be fully elucidated. However, they promote neutrophil chemotaxis for bile duct destruction in the murine model, improve outcome if heavily infiltrated at the portoenterostomy core after Kasai portoenterostomy, and contribute to inflammatory complications including cholangitis and fibrosis after biliary decompression.[42–44] Pattern recognition molecules that mediate innate immunity, toll like receptors (TLR), also have been shown to be highly

expressed in the early stages of BA.[45] Activation of these receptors, specifically TLR7, leads to a signaling cascade for the induction of type I IFN, co-stimulatory molecules, and other inflammatory cytokines also thought to play a role in pathogenesis of BA.

The adaptive, or specific, immune system is comprised of both cellular and humoral defenses against antigenic challenges. Activation of both components of adaptive immunity is evident in ductal tissues from experimental models and afflicted infants. Oligoclonal expansions of CD4(+) and CD8(+) T cells occurs to a yet undetermined stimulus within the liver and extrahepatic bile duct remnants of infants with BA.[46] In the murine model, CD8(+) cells primed with RRV preferentially migrate to extrahepatic bile ducts and drive the phenotypic expression of BA, while depletion of CD8(+) cells suppresses duct injury.[47] Analysis of extrahepatic bile duct remnants in infants with BA has shown deposits of immunoglobulins, specifically IgG and IgM, supporting a role of the humoral response in pathogenesis of the disease.[48] Similar IgG immune deposits as well as serum antibodies reactive to bile duct epithelial proteins have been identified in the murine model.[49] Additional support for an immune response includes recent evidence of maternal microchimerism. BA patients exhibit varying intensities of antimaternal human lymphocyte antigens (HLA) class I antibodies to bile duct epithelium and hepatocytes compared to controls. While the immune system is clearly involved, the antigen causing this response is still in question.

Though there has not been a direct genetic link to BA, several studies suggest that genetic error or polymorphism may lead to development of a genetically susceptible host. The case for a genetic basis was bolstered in 1993 with discovery of the inversin gene, a situs inversus mutation, in a family of transgenic mice.[50] These *inv* mice develop ductal plate malformation and increased conjugated bilirubin. Similar pathologic changes are observed in some clinical cases of BA, suggesting a possible genetic link may also exist in humans.[51] BA with splenic malformation (BASM) represents 10% of BA cases in European and US series. This syndrome appears to be related to a heterozygous transition mutation in the CFC1 gene.[33,52] Other syndromic relationships to BA include chromosome 22 aneuploidy (cat eye syndrome), trisomy 18, and trisomy 21.[33,53–55] DNA polymorphisms potentially responsible for BA alter the functions of certain molecules necessary for normal immunologic response. Arikan *et al.* identified an association between BA and a polymorphism in the gene coding for intracellular adhesion molecule-1 (ICAM-1). Altered ICAM-1 function brought about by this polymorphism has previously been shown to impair immunity in other inflammatory diseases.[56] Another genetic polymorphism responsible for upregulation of CD14, a cell surface receptor for endotoxin, has been found in much higher

frequency in infants with BA versus healthy neonates. CD14 overexpression may confer a susceptibility to endotoxin leading to stimulation of hepatic Kupfer cells, aggrevation of portal inflammation, and the pathologic changes seen in BA.[41]

Intrahepatic cholestasis in neonates has been associated with certain viral triggers, specifically Cytomegalovirus (CMV) and Reovirus type 3 (Reo III), as demonstrated by high titers of anti-CMV IgM and anti-Reo III IgM.[57,58] Although this association has not been shown in BA, it lends credence to the proposal that similar viral triggers may be responsible for stimulating immunologically mediated destruction of the intra- and extrahepatic biliary tree in BA. The best evidence for viral triggering has come from the murine model established by Petersen. This model has provided a better understanding of the cascade of events that follow the introduction of RRV into mice. Cholangiocyte infection and apoptosis in this model appears to follow the mitogen-associated protein kinase (MAPK) signaling pathway with downstream transcription factor upregulation, specifically nuclear factor-kappa B, and subsequent caspase activation.[59–61] In addition, RRV induces a hepatocyte specific type I IFN- γ inflammatory reaction against bile duct cells leading to biliary obstruction.[37,62] Interestingly, maternal vaccination against RRV prevents BA in the murine model, thus highlighting the specificity of RRV to induce the clinical phenotype.[63]

Other authors suggest that viruses do not play a major role in pathogenesis of BA in humans. Rauschenfels *et al.* screened a large number of liver samples of BA patients for common human hepatotropic viruses. They found the presence of seropositivity for one or more of theses viruses in less than half of patients despite 92% of samples expressing Mx proteins in hepatocytes, bile ducts, and epithelium.[34] Previous work from this group noted Mx protein, a sensitive marker for type I IFN-mediated immune response to viral infection, in liver biopsies of all neonates with BA but not in specimens from children with neonatal cholestasis of other etiologies (e.g. inspissated bile syndrome).[64] They conclude the presence of Mx protein may be the result of a viral-like pathway, while the presence of hepatotropic viruses in liver specimens from BA patients is likely a secondary phenomena.[34,64] Other evidence against the role of viruses comes from Schweizer *et al.* who found only small leukocyte infiltrations in tissue blocks from the porta hepatis and liver biopsies of children with BA. The leukocyte infiltration appears to be predominately macrophages, while immunocompetent lymphocytes and antigen presenting cells remain scarce.[65] Given the current controversy surrounding the role of viruses in the pathogenesis of BA, further study is warranted to better understand the pathologic immunoreation that leads to biliary duct destruction and possibly identify any potential causative agent(s) that could be targeted for cure.

Pathology and Classification

Gross pathological examination of the liver with BA demonstrates a lack of continuity between intrahepatic and extrahepatic bile ducts as a result of progressive fibrosis. In some cases, the gallbladder is also atretic. Histology of a normal "portal plate" typically shows two large biliary ducts, mucinous and columnar cells within the largest bile ducts, and minimal signs of bile ductular proliferation.[66] In liver specimens from BA patients, ductular proliferation, bile duct and ductular bile plugs, and portal fibrosis are identified. Portal fibrosis is shown to be the best discriminator between BA and neonatal hepatitis.[67] Additional histologic features include bile stasis, focal necrosis with intralobular portal fibrosis, giant cell transformation, and hypertrophy of hepatic arterial branches in the portal region.[68–71] Although the term "biliary atresia" implies a static process with complete obstruction or absence of the bile ducts, it is more a dynamic process of progressive obliteration and sclerosis of bile ducts. As the severity of BA increases, the liver may be large, firm, and congested with nodular changes indicative of cirrhosis.

Severity of disease is often classified by using the macroscopic appearance and cholangiography findings to stratify patients into three main categories according to the level of obstruction: Type I, atresia of common bile duct (CBD) (5% of cases); Type II, atresia of proper hepatic duct (PHD) (2% of cases); and Type III, atresia involving the biliary plate at the porta hepatis (> 90% of cases).[33] Type III is by far the most common. Type I (and sometimes II) may be associated with a cystic remnant that resembles a choledochal cyst (Figure 1). In all cases, microscopic biliary ductules maintain communication with the intrahepatic biliary system.

Two distint clinical subtypes are defined: embryonal and acquired. Embryonal subtype presents usually at birth and is associated with several congenital anomalies in the Biliary Atresia Splenic Malformation syndrome (BASM) syndrome, including cardiac anomalies, heterotaxia, malrotation, polysplenia, aberrant arterial anatomy, preduodenal portal vein, and absent retrohepatic vena cava with a dominant hemiazygous vein draining the abdomen (Table 1).[72]

Approximately 10% of BA manifests as the embryonal subtype. Aquired "perinatal" subtype is isolated and due to an unknown triggering event.[73] This form of the disease is typical of the vast majority of cases.

DIAGNOSIS

Differential Diagnosis

Diagnostic evaluation of BA is summarized in Table 2.

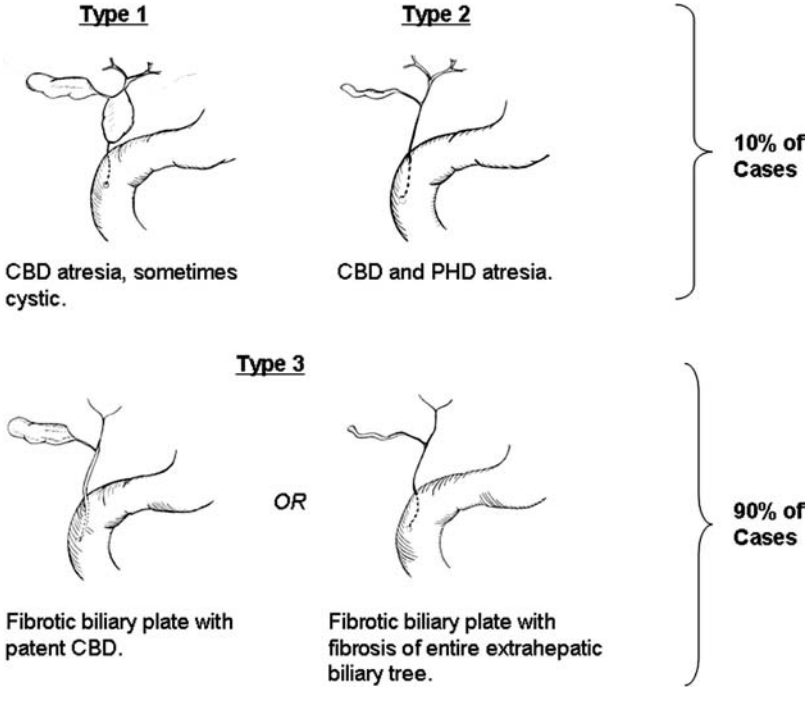


Figure 1. Classification of biliary atresia.

Table 1. Biliary atresia splenic malformation syndrome.*

- Cardiac anomalies
- Heterotaxia
- Polysplenia
- Absent retrohepatic inferior vena cava
- Intestinal malrotation
- Unusual hepatic anatomy
  - — Aberrent hepatic arteries
  - — Preduodenal portal vein
  - — Unusual shape of lobes of liver

*Represents about 20% of cases and may be referred to as the genetic form of biliary atresia. Some or all of the components of the syndrome may be present.

Jaundice related to neonatal indirect (unconjugated) hyperbilirubinemia, known as breast milk jaundice or physiologic jaundice, is a normal finding within the first few weeks of life that resolves with time. All term infants with jaundice persisting after 14 days, preterm infants with jaundice lasting greater

Table 2. Diagnostic evaluation of possible biliary atresia.

- History and physical examination
  - — Acholic stool
  - — Consistency of liver
  - — Jaundice and scleral icterus
- Laboratory
  - — Elevated conjugated bilirubin
  - — Liver biochemistry: total/direct bilirubin, transaminase (AST, ALT), GGT, alkaline phosphatase
  - — Coagulation time PT, INR
  - — Special biochemical studies: Hepatits A, B, C: TORCH titer, A1-Antitrypsin level, Serum lipoprotein X, serum bile acid
- Confirmation of patency of extrahepatic bile ducts
  - — Duodenal fluid aspiraion
  - — Ultrasound
  - — Hepatobiliary scintigraphy (HIDA scan)
  - — Cholangiogram (percutaneous, laparoscopic, ERCP, or open surgical)
- Histopathology
  - — Liver biopsy
    - ▪ Bile plugs
    - ▪ Biliary ductular proliferation
    - ▪ Progressive fibrosis in advancing disease

GGT: gamma glutamyl transpeptidase; INR: international normalized units; PT: Prothrombin time; TORCH: toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex virus.

than 21 days, and breast-fed infants with jaundice persisting longer than 21 days should be evaluated for direct hyperbilirubinemia with a measurement of the conjugated fraction of serum bilirubin.[74] Jaundice in the neonate is pathologic when the conjugated fraction of bilirubin (direct bilirubin) is greater than 20% of total serum bilirubin.[75] Several etiologies exist and can be distinguished by clinical findings among viral, congenital, metabolic, genetic and familial causes. These clinical findings include jaundice, dark urine, hepatomegaly, ascites, coagulopathy, and failure to thrive. Acholic stools are variable, appearing in about half the cases, while splenomegaly is a rare finding unless the patient is presenting late and portal hypertension has ensued.[33] Early diagnosis is essential as late diagnosis in biliary atresia is associated with poor survival, failure of surgical therapy, and greater need of liver transplantation.[76]

Laboratory Evaluation

Laboratory and serological evaluation is an initial step in identifying BA in the cholestatic child. Intrauterine infection may lead to postnatal jaundice; therefore, a search for TORCH (toxoplasmosis, other viruses, rubella, cytomegalovirus, and herpes simplex virus) antibody titers should be completed. Laboratory studies identify elevated indirect and direct fractions of bilirubin, alkaline phosphatase, gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) in the cholestatic child. The albumin level and prothrombin time are typically normal, reflecting preserved liver synthetic capacity. Tang *et al.* demonstrated that levels of GGT are significantly higher in BA than neonatal hepatitis, with GGT levels > 300 IU/L indicative of BA with 98% specificity.[77] Hyaluronic acid is another biochemical marker which may aid in serological diagnosis of BA; however, as of now, no serological or laboratory analysis is sufficient to accurately diagnose BA independently.[78]

Radiographic Imaging

Ultrasound

Ultrasonography is a noninvasive modality useful in the identification of BA in cholestatic infants. The "triangular cord" sign, a triangular structure located cranial to the portal vein bifurcation on ultrasound examination, has a 70–86% sensitivity, 96% specificity, 94% positive predictive value, 92% negative predictive value, and 91% accuracy in diagnosis.[79–80] When present this sign is forceful evidence of BA, but it is not always appreciable in these patients. Another accurate diagnostic sign on sonography is the "gallbladder ghost triad", defined by gallbladder length < 19 mm, lack of a smooth echogenic mucosal lining, and an indistinct wall with irregular contour.[81,82] Secondary ultrasonic findings that may help differentiate BA from other causes of neonatal jaundice include increased hepatic subcapsular flow on color Doppler ultrasound imaging, increased hepatic artery diameter, decreased gallbladder length (< 15 mm), and decreased gallbladder contractility (< 68% for infants < 12 weeks and < 25% for infants > 12 weeks).[83–85] In addition, ultrasonography allows the diagnostician to exclude BA if other findings are present such as choledochocyst or intrahepatic ductal dilatation. In some cases, sonography reveals cystic remnants of the biliary tract associated with EHBA.

HIDA scan

Hepatobiliary scintigraphy using technetium-labeled iminodiacetic acid (HIDA) is useful in excluding BA from other causes of cholestasis by demonstrating patency of the biliary tree.[74] When used alone, HIDA has a low accuracy of 67% in identifying BA; however, when used in combination with single photon emission computed tomography (SPECT) and phenobarbital stimulation the accuracy increases to 91–98%.[86,87]

Cholangiography

Direct imaging of the biliary tree by cholangiography is feasible in children by magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP). Although these modalities have been used extensively to evaluate hepatobiliary disease in adults, the safety and accuracy of MRCP and ERCP in children recently have been validated.[88,89] MRCP is quite appealing to clinicians as it is noninvasive, often does not require anesthesia in small infants, does not subject the patient to ionizing radiation, and has very few complications. Despite the appeal, its utility is questionable due to less sensitivity, specificity, and accuracy to diagnose BA than either ultrasound or scintigraphy.[87] ERCP may be performed in children of all ages but typically requires sedation or general anesthesia, and successful cannulation of the papilla of Vater is not always feasabile in neonates. As such, ERCP requires the collaboration between skilled gastroenterologists or surgeons and pediatric anesthesiologists, which often is not available outside of specialized pediatric centers. Despite these limitations, ERCP is effective in evaluation of neonates with possible BA, with sensitivity and specificity of 92% and 73%, respectively, when correlated to intraoperative findings. In fact, ERCP may lead to a 12–25% reduction in unnecessary surgical procedures.[90] Complications are few in children (4%) or even less when therapeutic interventions are not employed. Mild pancreatitis is most common and can be managed expectantly.[89] While ERCP does not replace noninvasive imaging, it may be most useful when other imaging studies prove inconclusive.

Percutaneous cholecystocholangiography (PCC) is another safe alternative to differentiate obstructive from hepatocellular causes of neonatal cholestatic jaundice when non-invasive imaging is not diagnostic[91,92] (Figure 2). Alternatively a laparoscopic-assisted cholangiogram is possible,[93] although we prefer ultrasound guided PCC in the interventional radiology suite because of the ease with which it can be perfomed with simple conscious sedation rather than general anesthesia.[91]

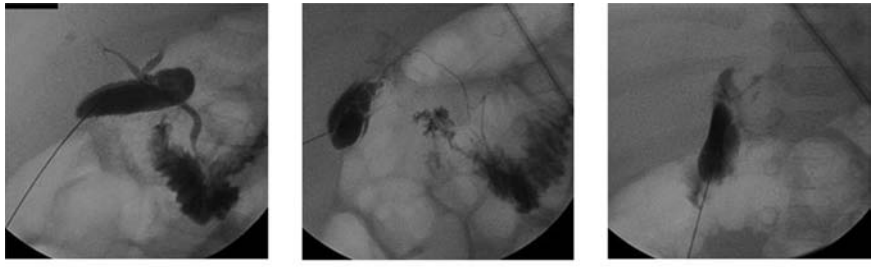


Figure 2. Percutaneous cholecysto-cholangiogram. (a) Normal cholangiogram. (b) Type III biliary atresia with patent CBD. (c) Type III biliary atresia with fibrosis of entire extrahepatic biliary tree.

Duodenal Tube Test

The duodenal tube test (DTT) is another modality that can be used to evaluate the patency of the biliary tree and diagnose BA in cholestatic infants. A nasoduodenal tube is placed in the distal duodenum beyond the ampulla of Vater and fluid is collected over 24 hours. If no bile is collected, the biliary tree is obstructed and laparotomy is indicated. The DTT method has a reported sensitivity of 97%, specificity of 94%, positive predictive value of 92%, and negative predictive value of 99% for diagnosis of BA.[94]

Liver Biopsy

Percutaneous liver biopsy with subsequent histological analysis is an invasive yet highly accurate diagnostic modality with reported accuracy rates approaching 97%.[87] In many centers, liver biopsy is regarded as suggestive but not diagnostic because of the overlapping histologic patterns from different causes of cholestasis. Recently, a 7-feature scoring system demonstrated good diagnostic accuracy in the histological evaluation of neonatal cholestasis. This scoring system evaluates portal ductal proliferation, bile plugs in portal ductules, portoportal bridging, portal lymphocytic infiltration, multinucleated hepatocytes, neutrophilic infiltration, and hepatocellular swelling to differentiate the causes of cholestasis.[95] However, atypical histological features may lead to inaccurate analysis of liver biopsy samples taken prior to 6 weeks of age; and therefore, these samples must be interpreted with caution.[96] When diagnosis remains uncertain in neonatal cholestasis, operative cholangiography remains the gold standard of diagnosis for BA. This should not be delayed for excessive testing.

TREATMENT

Preoperative Medical Management

Success of surgical correction for BA is directly dependent on the patient's age at the time of surgery.[76] Increased age at surgery has a direct negative impact on the likelihood of establishing meaningful biliary flow; hence, prolonged attempts at medical management are discouraged once a diagnosis has been made or is highly suspected. Prompt work up and treatment especially is required when the patient presents toward the end of the second month of life or later. If the history, physical examination, and laboratory tests are suggestive of BA, ultrasonography followed by liver biopsy and then operative exploration is appropriate without delay for further imaging or medical therapy. If diagnosis of BA is made in the operating room, Kasai is performed.

There are some medical measures, however, which can be useful during the diagnostic phase of the workup. Phenobarbital and ursodeoxycholic acid (Ursodiol, Actigall) have been used as choleretics to promote bile flow. Vitamin K is given to help restore normal coagulation. ADEK fat soluble vitamins are administered. Meticulous attention to the infant's nutrition is most important.

Surgical Management

Kasai portoenterostomy has been the surgical gold standard for the past 30 years. Operation begins with a right subcostal incision, which usually affords adequate exposure for careful inspection of the biliary tree remnant, hepatic parenchyma, and exploration for associated anomalies of possible BASM syndrome (Table 1). The incision can be enlarged through an epigastric, midline, vertical extension or bilateral, subcostal extension, or both, as dictated by the baby's anatomy. Care should be taken to minimize the incision as much as possible until cholangiogram has definitively confirmed diagnosis. Once diagnosis is certain, the incision is then enlarged to allow full unrestricted access to the porta hepatis being cognizant of the need to make an incision that can be reused for liver transplantation in the future should that become necessary. In the early stages of both neonatal hepatitis and BA, the liver may simply look purple, swollen, and inflammed. As each disease progresses, a liver with neonatal hepatitis becomes smooth, swollen and chocolate brown, whereas a liver with BA is firm, fibrotic and greenish brown. In equivocal cases, a repeat liver biopsy may be helpful to definitively exclude neonatal hepatitis.

Operative cholangiogram

Cholangiogram may not be feasible or necessary when only a fibrous ductal remnant remains, with no lumen or identifiable biliary tree. However, most infants will have a remnant of gallbladder filled with clear mucoid liquid. In these infants, a catheter is placed into the gallbladder lumen and secured with a pursestring suture. If completely clear, bile is aspirated from the gallbladder then atresia is highly likely and cholangiogram may not be necessary. Any greenish hue or ambiguity to the bile warrants cholangiogram which is performed with water soluble contrast (Isovue or Hypaque). If contrast extravasates promptly and no remnant of biliary tree can be opacified, diagnosis of BA is confirmed. The filling of the duodenum and intrahepatic biliary radicles with contrast confirms patency of the common bile duct and rules out BA. In this case, the catheter is removed, the pursestring closed, and the operation terminated. In cases of Type 3 BA, the cholangiogram occasionally may show distal flow into the duodenum but no filling of proximal biliary radicles (Figure 2). Repeat injection can be made with gentle distal occlusion to promote proximal filling. Although it is anatomically feasible to perform a cholecysto-portoenterostomy in babies with unequivocal cholangiographic evidence of distal patency, this procedure is reported to carry an excess long-term failure rate and is rarely recommended.[97] Occasionally, biliary hypoplasia will be seen; and in such a situation, a Kasai procedure is NOT recommended.

Kasai portoenterostomy

Successful results demand meticulous dissection with as complete as possible excision of the fibrotic biliary plate remnant to ensure maximum continuity with any tiny remaining intrahepatic ductules. Dividing the triangular ligaments and bringing the liver up onto the abdominal wall improves exposure for dissection and anastomosis. Kasai portoenterostomy begins with the resection of the gallbladder remnant and fibrotic remains of the extrahepatic biliary tree. Dissection of the fibrotic cord is followed proximally up to the plug of scar tissue filling the "biliary plate," reliably located immediately cephalad to the bifurcation of the right and left portal veins (Figure 3). A few small posterior perforating branches of the left and right portal vein are divided. Traction sutures may be placed in the fibrotic plug of tissue at the biliary plate to provide upward tension on the tissue to facilitate complete excision. The most important areas of complete excision are not so much deep as lateral in the portal plate. It is supremely important to carry this dissection at least as far lateral as the umbilical fissure on the left and to the hepatic arterial branch to segment 5 on the right. The tiny delicate left hepatic artery branch to

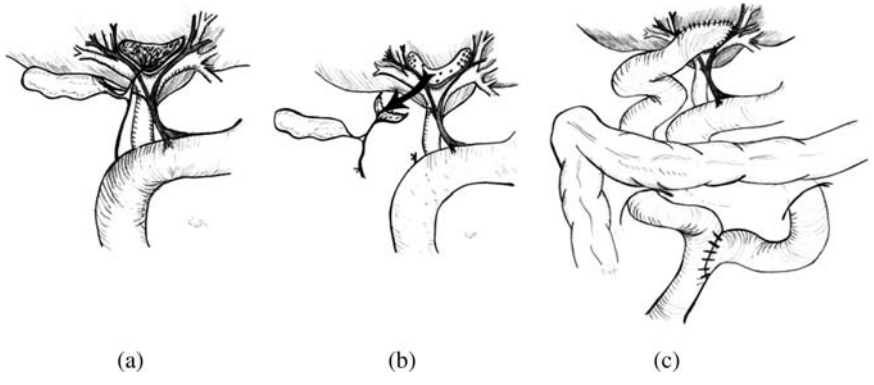


Figure 3. Kasai portoenterostomy. (a) Biliary atresia type III, with atresia of proper hepatic duct and common hepatic duct. (b) Resection of atretic exterahepatic biliary tree and resection of plug of fibrotic tissue at biliary plate. (c) Roux-en-Y anastomosed to biliary plate.

segment 4 and right hepatic artery branch to segment 5 must be carefully mobilized and retracted laterally to facilitate complete lateral excision of fibrotic tissue in the hope of exposing the microscopic ductules draining the left lateral and right posterior sectors of the liver. Excessive dissection deep into the parenchyma and or excessive use of electrocautery promotes scarring and should be avoided.[98]

A Roux-en-Y limb of jejunum 30–40 cm in length is passed into the Morrison's pouch through a defect created in the transverse mesocolon, typically to the right of the middle colic vessels. The portoenterostomy is constructed with fine absorbable sutures approximating the Roux limb to the rim of resected fibrous tissue being careful not to occlude any potential areas of drainage. Either the end of the Roux limb or the antimesenteric side of the jejunum near the closed end can be used for the anastomosis. The back row of sutures is placed just to avoid the portal vein at the bifurcation. These sutures can be left untied to allow the limb of jejunum to be parachuted down to the liver. After these sutures are tied, the front row of sutures is placed. At completion, the entire cut liver surface is contained within the jejunal lumen. This single layer reconstruction is essentially the only way contemporary operation differs from Kasai's original description.[99] The defect in the transverse mesocolon is now closed to prevent kinking, twisting, tension, or obstruction of the Roux limb, as well as to prevent the risk of future internal herniation. Closed suction drain of Morrison's pouch is advisable in case of anastomotic leak from the portoenterostomy.

Roux-en-Y limb

The technique for constructing the Roux-en-Y limb has been a source of intense interest in the past. Some enthusiastic proponents support externalizing the Roux as a drainage stoma to minimize cholangitis and allow close monitoring of bile flow. However, variceal hemorrhage has been a frequent problem in patients with an external stoma, stemming from progression of portal hypertension. Others favor construction of an antirefluxing intussusception valve in the Roux limb to prevent cholangitis. While a valve is conceptually attractive, evidence has been mixed supporting its effectiveness to prevent cholangitis. Furthermore, cholangitis has NOT been a problem in liver transplant patients using standard Roux limbs without antirefluxing valves; therefore, it has to be assumed that cholangitis is due to biliary obstruction and NOT the presence of refluxed intestinal contents.[100,101] Muraji has reported instances of failed drainage secondary to obstruction by adhesion or twisting of the Roux limb in the retrocolic tunnel.[102] In cases of poor drainage, this should be considered. Yamatakal *et al.* stress the importance of performing the anastomosis at the very end of the Roux limb to prevent the formation of an afferent blind limb from intestinal growth.[103]

A handful of reports document the potential use of the appendix as a conduit in place of a Roux limb of jejunum.[104] The technique has not gained wide appeal but may be useful in a select few cases in which concomitant short bowel syndrome precludes taking a long segment of jejunum out of continuity. Long-term results of the appendiceal conduit may be inferior.[105]

Biliary atresia splenic malformation syndrome

In genetically inherited, or embryonic, cases of BA possible concomitant congenital anomalies (heterotaxia, polysplenia, absent retrohepatic vena cava, malrotation, aberrant hepatic arterial and parenchymal anomalies, and preduodenal portal vein) should be sought for and carefully documented (Table 1). Hepatic arterial anomalies are common and should be anticipated to prevent inadvertent injury. Malrotation may preclude the need for a retrocolic tunnel for the Roux limb and should be addressed with the Ladd procedure at the time of portoenterostomy. A preduodenal portal vein should be carefully handled to prevent kinking, twisting, tension, or obstruction.

Primary liver transplantation

A salient case can be made to forgo the Kasai and move directly to primary liver transplant in infants with a very late diagnosis or advanced bridging fibrosis.[106] In most infants, however, Kasai offers up to a 30% hope of cure and a chance that transplant can be delayed for many months and even years.[107]

Minimally Invasive Techniques

Laparoscopic-assisted cholangiogram

As discussed above, diagnostic cholangiogram is sometimes done as a separate minimally invasive procedure: either ultrasound-guided PCC with intravenous sedation,[91,92] ERCP with intravenous sedation, or laparoscopic-assisted cholangiogram with general anesthesia.[93,108] However, when liver biopsy is not definitive, perhaps suggesting neonatal hepatitis but not definitively ruling out BA, a minimally invasive cholangiogram can be considered. If laparoscopic evaluation confirms BA, Kasai portoenterostomy can be accomplished under that anesthetic.

Laparoscopic portoenterostomy

With advances in laparoscopic techniques, a few centers have reported feasibility of laparoscopic Kasai portoenterostomy. While early reports claimed equivalent results when comparing laparoscopic and traditional open techniques,[109,110] over time this has turned out not to be true. If success is measured as restitution of some kind of biliary drainage, early results were promising indeed. However, a landmark, recent report from a high volume center with mature experience in both techniques raised serious concerns about laparosocopic portoenterostomy. They found patients in the minimally invasive group suffered early failure requiring liver transplantation in the first year of life almost twice as often as patients in the open group (66% vs. 38%).[111] Regarding postoperative complications, one patient who underwent laparoscopic Kasai portoenterostomy suffered intestinal volvulus after initial surgery while another developed internal herniation of the Roux limb. Thus, laparoscopic Kasai portoenterostomy seems to be associated with more postoperative complications and worse early clinical outcome. As a result, we remain guarded about the present-day technique of laparoscopy for BA.

POST-KASAI MANAGEMENT

Medical Management

Postoperative management is directed at measures designed to increase bile flow, reduce cholangitis, and maintain nutrition. Common measures aimed at increasing bile flow are restoration of enteral nutrition, low-dose phenobarbital, ursodiol to thin bile and dissolve biliary plugs, and steroids. Ursodiol should be used if there is some evidence of biliary drainage and is usually given at a dose of 10 mg/kg/dose twice daily. Ursodiol has a choleretic, cholelitholytic, and hepatoprotective effect that may be very valuable, although prospective randomized trials

are lacking.[112] Steroids are used both for their choleretic effect and to reduce inflammation and fibrosis at the biliary plate. Immediate postoperative steroids are given intravenously as glucocorticoids and then transitioned to oral preparations which are continued for several weeks in the outpatient setting. Results of a controlled trial by the Biliary Atresia Research Consortium (BARC) are anticipated. Many variations of the postoperative steroid protocol have been published.[113–118] We use Solu-Medrol in a high dose, perioperative pulse (10 mg/kg tapered over 5 days as 8 mg/kg, 6 mg/kg, 5 mg/kg, and 4 mg/kg) transitioned to oral prednisone 2 mg/kg daily for the next 4–8 weeks.[118] Broad-spectrum intravenous antibiotics are given in the perioperative period, and some authors have even advocated prolonged administration. Usually, intravenous antibiotics are transitioned to oral amoxicillin, metronidazole, and/or trimethoprim-sulfamethoxazole for long-term prophylactic bacterial suppression within the obstructed biliary pool. Although multiple case series recommend long-term postoperative use of antibiotics and steroids, neither treatment has yet been reported in prospective, randomized trials. Bile is essential for the absorption of fat-soluble vitamins A, D, E, and K. Therefore, supplemental A, D, E, and K are usually given daily (1 mg/day) to prevent vitamin deficiency.

Surgical Reoperation "Redo Kasai"

Reoperation for recurrent cholangitis may be indicated in very select circumstances.[119] Although attractive in theory, reoperation is difficult in practice and seldom successful at achieving durable drainage.[120] Successful reoperation has been achieved occasionally when excellent postoperative bile flow is followed by an abrupt cessation of flow indicated by a change from pigmented to acholic stool.[120] In this situation, a pulse of steroids is given initially; consideration is then given to the possibility of resection of recurrent fibrosis at the biliary plate if bile flow does not improve. Recurrent cholangitis related to Roux limb stasis may also benefit from reoperation and revision of the jejunal limb if bile flow and stasis fail to improve with other treatment measures or mechanical obstruction cannot be ruled out by other means.

Complications

Cessation of bile flow

Reappearance of acholic stool following Kasai portoenterostomy is an ominous sign when prior evidence of pigmented stools existed in the postoperative period.

Prompt re-establishment of bile flow is imperative to avoid cholangitis and liver damage. Parents should be encouraged to report changes in stool color or signs of cholangitis. If there is an abrupt cessation of bile flow, a pulse of intravenous steroids can be very helpful in two ways: as a choleretic agent, they promote bile flow, and as an anti-inflammatory agent they may reduce fibrosis.[113,114] If bile flow is not re-established within a few days, steroids are stopped. At this time, a redo procedure with debridement of obstructing fibrotic tissue at the biliary plate might be considered if the child previously had good bile flow. However, multiple reoperations with repeat attempts to re-establish bile flow are probably not helpful.

Cholangitis

Cholangitis is seen in about 40% of children and is most common in the first year following portoenterostomy. Poor bile flow and partial biliary obstruction combined with enteric bacteria is a perfect recipe for cholangitis. Prophylactic antibiotics are often used to reduce gut flora in hopes of altering this milieu and prevent cholangitis.[118,121] Initial signs are fever, decreased bile drainage, elevated serum bilirubin, and acholic stools. Blood work may show leukocytosis, elevated serum bilirubin, and elevated hepatic enzymes (especially alkaline phosphatase and GGT). Clinical and laboratory changes may lag, however, so unexplained fever in BA patients who are post-Kasai is assumed to be cholangitis in the absence of another explanation. After initial blood cultures are drawn, prompt treatment with broad-spectrum intravenous antibiotics covering gram-negative and anaerobic bacteria is necessary to prevent liver damage. If stools become acholic, a pulse of steroids is given.[114]

Portal hypertension and ascites

Portal hypertension is common after Kasai, even in infants with good bile flow. The idiopathic inflammatory process affecting the extrahepatic biliary tree also damages the intrahepatic biliary ductules, albeit at variable rates.[122] Onset may be acute, or more commonly insidious with increase in abdominal distension secondary to accumulated ascites and progressive splenomegaly with its attendant hypersplenism and thrombocytopenia. Esophageal variceal hemorrhage may be the first sign of the progressive increase in portal pressure. Medical management includes control of ascites as necessary with a combination of furosemide and spironolactone, and when needed, intermittent paracentesis to exclude spontaneous primary peritonitis or simply to decrease intra-abdominal pressure in some cases. Propanolol may be used to decrease portal pressure. Interestingly, susceptibility to complications of portal hypertension seems to decrease over time, probably as a result of developing

spontaneous portosystemic shunts. Therefore, frequency and/or severity of GI bleeding often decrease over time. In the presence of poor hepatic function, complications of portal hypertension are an indication for liver transplantation.[123]

Intrahepatic cysts

Biliary cysts or "bile lakes" (Figure 4) may develop and are often a source of recurrent attacks of cholangitis.[124] Percutaneous drainage, antibiotics, and ursodiol may be used to prevent cholangitis in this setting. In most patients, however, infected cysts and bile lakes are an indication to proceed with liver transplantation.

Hepatopulmonary syndrome (HPS)

In the setting of prolonged portal hypertension, some children may develop diffuse intrapulmonary shunting. These shunts are postulated to result from the release of vasoactive compounds into the mesenteric circulation that bypass hepatic inactivation due to increased portal pressure. Children present with clubbing, dyspnea on exertion, nighttime desaturation, and hypoxia. Initial diagnosis is usually made with contrast bubble echocardiography.[125] Intrapulmonary shunts can become progressive and are generally considered an indication for liver transplantation once detected. In a recent large experience from Kings

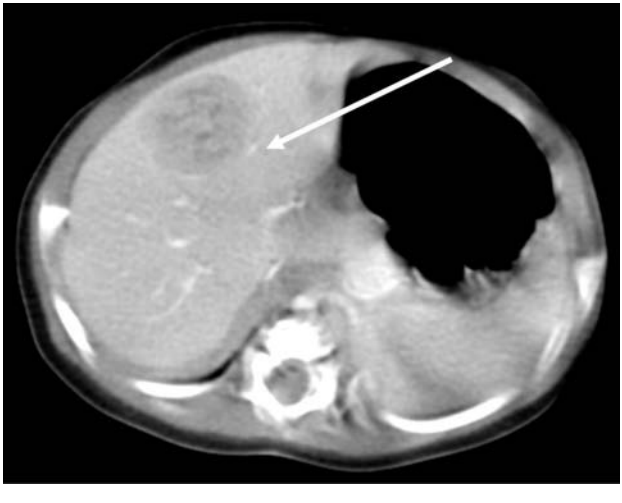


Figure 4. Intrahepatic inspissated bile cyst.

College, a total of 18 patients with HPS were reviewed. Pulmonary symptoms resolved in 13 of 14 patients who underwent liver transplantation in this study.[125]

Nutrition

Metabolic problems may develop from malabsorption of fat, protein, vitamins, and trace minerals.[126,127] Essential fatty acid deficiency and rickets are especially common. Weight gain is often impaired and supplemental tube feeds are commonly needed. Formulas enriched with medium-chain triglycerides (Pregestamil, Portagen, Alimentum, EleCare) are more easily absorbed in the absence of bile micelle formation. In children with advanced liver failure, however, growth may not be achievable even with adequate caloric intake. Liver transplantation is indicated in this situation.

Hepatocellular carcinoma

Hepatocellular carcinoma has been reported in the chronically inflamed, cirrhotic liver of a child who has undergone Kasai portoenterostomy in infancy.[128] The incidence is exceedingly rare.

Liver Transplantation

Common indications for liver transplant are complications of portal hypertension refractory to medical management (bleeding, thrombocytopenia, HPS), growth failure, and hepatic synthetic failure (jaundice, coagulopathy, hypoalbuminemia). In the presence of hepatic synthetic failure, little can be done to improve liver function short of transplantation. Oral vitamin K supplementation is standard, but it becomes less and less effective as liver failure progresses. A multidisciplinary team at Columbia University recently published their experience with pediatric liver transplantation in which seventy-one children (average age: 25 months, range: 3–216 months) with BA underwent 77 liver transplants.[123] Sixty-one patients had a previous Kasai, and 10 had primary transplant without prior Kasai. Overall patient survival and overall graft survival was 94.4% and 87%, respectively, at median follow-up of 58 months (range, 6–111 months). Living donor liver transplantation was performed in 32 of these children with 91% patient and graft survival. Four patients died, while 6 required retransplantation. Outcome was associated with the pediatric end-stage liver disease (PELD) score.

Children with a PELD score greater than or equal to 10 had worse outcome, while all children with a PELD score less than 10 survived with their original grafts. Therefore, the PELD score should be determined when a child with BA is deemed a candidate for liver transplant. A PELD score that approaches 10 should trigger discussion of living donor liver transplantation with the family.[123]

OUTCOMES AND LONG-TERM PROGNOSIS

About one-third of patients may hope to be "cured" by Kasai portoenterostomy. "Cure" equates to achieving durable long-term bile flow and stable liver disease which may or may not require medical management for portal hypertension. In the remaining two-thirds of patients, cholestasis and fibrosis lead to progressive cirrhosis, portal hypertension, liver failure, and eventually liver transplantation. Even with adequate early bile flow, recurrent bouts of cholangitis may herald progressive fibrosis.

Patients usually can be stratified into prognostic groups within 2–3 months after Kasai hepatoenterostomy. Infants with bile-colored stool who clear their jaundice in this time frame have a good chance of long term survival with their native liver. Other infants may improve but fail to clear their jaundice completely. In this group, hepatic synthetic function may be relatively stable but slowly deteriorates over time in association with progressive biliary cirrhosis, portal hypertension, and growth retardation. Liver transplant is required in time. In a third group, Kasai portoenterostomy may fail to offer any palliation. Postoperative bile flow may be trivial or completely absent, and progression of liver failure leads to early liver transplant between 6 and 18 months of age.

Successful outcome depends upon many clinical factors, but age at time of Kasai portoenterostomy appears to have the greatest significance. Other prognostic factors which have at times been shown to influence outcome include: volume of operative experience of the surgeon and hospital, degree of hepatic fibrosis at time of operation, microscopic size of residual biliary ductules at the portal plate, presence of intrahepatic biliary cysts, associated anomalies, magnitude of postoperative biliary excretion, and use of adjuvant steroids in medical management.

Age at Time of Kasai Portoenterostomy

Ultimately, clinical success of Kasai portoenterostomy is judged by the need for liver transplantation. With wide availability of pediatric liver transplantation in developed countries, overall 5-year survival rates for children with BA now

exceeds 90% in high volume centers.[123] Survival with the native liver, however, is much less common. A recent multi-institutional, 15-year (1986–2002) French study analysed the impact of age at time of portoenterostomy on outcome in 743 children with BA. Survival rates without liver transplantation (i.e. alive with native liver) at 2, 5, 10, and 15 years were 57%, 38%, 32%, and 29%, respectively.[76] Most notably, the likelihood of survival into adolescence with the native liver decreased as age at time of Kasai portoenterostomy increased. Interestingly, this relationship was linear with the greatest survival benefit occurring in the youngest patients. Best results were obtained when surgery was performed before the age of 30 days. Nevertheless, patients operated beyond the age of 90 days still had a 13% chance of survival with their native liver until adolescence. Although several large studies verify that late performance of Kasai portoentrostomy worsen results,[129–133] the linear relationship between younger age at surgery and improved outcome is perhaps most convincingly shown in the French study.[76]

Volume of Surgical Experience

McKiernan *et al.* first noted the association between outcome of Kasai portoenterostomy and volume of surgical experience at institutions treating infants with BA. Their multi-institutional experience included 91 children with BA operated on at 15 different centers in the United Kingdom over a 3-year period (1993–1995).[134] Early success was significantly higher in children whose operation was performed at centers with an annual case load of more than five cases. As a result of this study, all infants with suspected BA in England and Wales, UK, were referred to one of five designated high volume centers since 1999. Davenport *et al.* in 2004 reported the follow-up, 4-year experience after implementation of centralization of care to super-regional centers in the United Kingdom.[135] Following centralization of care, patient survival with the native liver improved greatly to 51% from 30%. Overall patient survival only improved marginally to 89% from 85%.[134,135] It must be noted that these data reflect 4-year actual survival as compared to 5-year actual survival in McKiernan *et al.*'s report.

Liver Histology

Liver histology at the time of surgery has been proposed as a prognostic determinant. Although older studies failed to show a correlation between the extent of hepatic fibrosis and outcome,[107] these studies may be limited by the methods

available at the time to accurately quantify hepatic fibrosis. More contemporary studies have employed electron microscopy and novel immunohistochemical techniques to better characterize the cellular architexture and degree of fibrosis at the portal plate. These studies suggest that increased biliary duct proliferation and a greater degree of fibrosis in the portal plate at the time of Kasai portoenterostomy portend a worse prognosis.[136–139]

Size of Remnant Biliary Ductules at Biliary Plate

Biliary ductules with diameters greater than 150 microns have been associated with greater surgical success when compared with smaller ductules, while the findings of a few or no ductal remnants and absence of portal inflammation were predictors of poor prognosis.[107,140,141] However, Mirza *et al.* did not find the same relevance between ductule diameter and outcome. Instead, they found that the number of bile ducts, maximal length of measureable ductal strictures, and degree of histologic bile ductular proliferation are better prognostic predictors of success than ductule diameter.[66]

Cystic BA

Cystic BA associated with extrahepatic choledochal cyst is a clinically distinct variant that develops early in prenatal life. Cystic BA has a better prognosis than isolated BA despite its earlier onset, particularly with early surgery.[142] Conversely, intrahepatic biliary cysts, seen either pre- or post-Kasai, represent trapped intrahepatic collections of inspissated bile. Intrahepatic biliary cysts, unlike true cystic BA, are associated with an increased risk of recurrent cholangitis and a worse prognosis.[143] Increased risk of cholangitis seen in children with intrahepatic bile lakes may be pronounced in long-term follow-up.[144]

Associated Anomalies

The presence of syndromic-associated anomalies has traditionally been thought to be a poor prognostic factor.[145] This is in part related to congenital heart disease and a postulated increase in HPS. Not all studies support this outcome. BASM has been suggested to not be such a poor prognositic factor with 5-year survival rate reported with native liver up to 46%.[146] Other chromosomal abnormalities, such as cat eye syndrome and trisomy 22, have recently been recognized in a small cohort of patients with as yet unknown prognositic significance.[147]

Postoperative Steroids

Multiple single and multicenter studies, with retrospective and prospective design, have shown improved bile flow and/or improved outcome with the administration of postoperative Solu-medrol[113–115,118,148] or dexamethasone.[116,117] Many of these studies have also used long-or short-term ursodiol and antibiotics in variable doses and durations. Although none of these studies using multi-drug therapy were randomized, accumulated experience is highly suggestive of improved bile flow, and possibly improved outcome, with a postoperative course of steroids. The potential impact of adjuvant steroids is the subject of an ongoing randomized trial by the multi-institutional, NIH funded, United States BA research consortium (BARC).

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CHAPTER 14

OVARIAN CYSTS

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INTRODUCTION

Sonographic depiction of a fetal ovarian cyst was first reported in 1975.[1] The management decisions made by the authors are provocative and reverberate across the ensuing decades and raise issues about the best management that remain unresolved. In that report, a fetal sonogram showed a 9-cm "sonolucent" mass. The clinicians aspirated it through the fetal abdominal wall, draining 3 mL of fluid. The patient was born with a palpable abdominal mass that was aspirated transabdominally in the neonate. Finally, the patient was surgically explored. The "cystic mass was found to represent the ovary". It was excised and called a "lutein cyst" by the histopathologist. Although an ovariectomy was performed, there is no suggestion of torsion or necrosis.

This report is often cited because it was the first time an ovarian cyst was recognized in the fetus. It is particularly relevant because it marks the birth of an explosion of reports describing fetal ovarian cysts, unearthed by sonography, and prompting clinicians to intervene even though the natural history and risks and benefits are unclear. It illustrates that clinicians tend to intervene when images show pathology. We have learned some things about the natural history of fetal ovarian cysts since this report, but we still have uncertainty about the likely expectations and role for intervention either pre or post-natally. This was not the last time that ovariectomy was done inappropriately. Authors have frequently noted that when neonates are explored for ovarian cysts, unnecessary ovariectomy often eventuates. This argument is raised by those who suggest leaving ovarian cysts alone or simply

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aspirating them since histologic study often reveals viable ovarian tissue when gonadectomies have been done. This chapter will review the causes of fetal ovarian cysts and consider the options in management and recommend a therapeutic approach. This is a classic clinical challenge. The fetal or neonatal sonographic imaging is done and families need our help, but we don't have quite enough facts about the natural history and risks and benefits of alternate approaches to chart a therapeutic course with complete confidence.

Some of the essential questions needed to give sound clinical advice are not fully answered. What happens if an ovarian cyst is left alone? Is the size of the cyst relevant to this question? How likely is it to resolve without intervention? How often does torsion and necrosis occur? How likely is that event to cause symptoms? In other words, can ovarian cysts be left alone or should intervention be undertaken. Should they be treated *in utero* and/or postnatally? What intervention, if any, should be offered?

PATHOPHYSIOLOGY

Fetal ovarian cysts arise from fetal follicles. The rich hormonal milieu stimulates fetal follicles through the actions of HCG, fetal pituitary FSH and LH, and estrogen.[2] Some clinical scenarios associated with elevated hormonal levels have been linked to fetal ovarian cysts: maternal diabetes, rh isoimmunization, and toxemia.[3,4] However, in published series of fetal and neonatal ovarian cysts, these conditions are rarely present. Fetal ovarian cysts are generally construed to be an unexplained aberration of normal physiology given the stimulating hormonal environment of the fetus. Ovarian cysts are usually noted in the third trimester. One group proposed that physiologic imbalance is not the cause of ovarian cysts in the fetus, suggesting instead that they represent malformations of the ovaries, but that is an exceptional opinion.[5]

The stimulatory milieu of the fetus offers an eclectic array of hormones activating the fetal follicle. FSH and LH arise from the fetal pituitary, while HCG from the placenta. The androgen precursor of fetal estrogen (DHEA) is manufactured in the fetal adrenals and converted to estradiol in the placenta. Because estradiol gets sulfonated in the maternal liver and estrogen is secreted in maternal urine, it is often misnamed maternal estrogen. Estrogen, interestingly, has a stimulating effect on the fetal follicle by activating receptors to FSH.[2]

The evolution of fetal sonography has led to the fairly common diagnosis of fetal ovarian cyst. Autopsy study before the era of fetal sonography had already shown that most fetal ovaries have small cysts larger than 1mm. These are normal follicles.[3] A sonographic study of ovaries in neonates and infants found cysts ranging from 1 mm to 1.4 cm in 84% of ovaries, confirming that small radiolucent thin-walled cysts

represent normal physiology in this age group.[6] What size constitutes a pathologic cyst in the fetus is not clear, but 2 cm, often used as a size criterion to define a pathologic cyst in postnatal ovaries, seems to be the most common designation.

CLASSIFYING FETAL OVARIAN CYSTS

Nussbaum distinguished between uncomplicated and complicated ovarian cysts in the neonate.[7] That designation, often called simple vs. complex, persists as the standard and is applied to ovarian cysts in the fetus, as well as neonates and older patients. This designation has had considerable importance for clinicians. The following is the description provided by Nussbaum:

> "An uncomplicated cyst is anechoic and its wall is imperceptible. A complicated cyst invariably contains a fluid-debris level, a retracting clot, or septa, and often has an echogenic wall associated with infarction."[7]

The authors conclude that the complex appearance results from hemorrhage into the cyst, always implies torsion of the adnexa, and usually means infarction of the ovary has occurred. Subsequent series disagree, suggesting that while the sonographic image of a complex cyst suggests hemorrhage, torsion is present in about 90% of cases; so infarction, although likely, is not inevitable. In the remaining 10%, perhaps, hemorrhage does represent torsion that spontaneously resolved before infarction occurred.

THE NATURAL HISTORY OF SIMPLE OVARIAN CYSTS IN THE FETUS AND NEONATE

Estrogen and HCG levels rapidly plummet at birth. As expected from the loss of negative feedback, FSH and LH actually rise after birth since estrogen declines, but then they drop after a few months. Since stimulation from this array of hormones disappears, spontaneous resolution of simple ovarian cysts is expected in infancy.

The main clinical concern when a neonate has a simple ovarian cyst is torsion and infarction. Cancer in not an important consideration. Even the benign teratoma of the ovary is extremely rare in the fetus and neonate. Consequences of infarction can be atrophy without any acute physiologic sequelae or an array of more serious events: major hemorrhage, peritonitis, intestinal obstruction when the infracted ovary adheres to the mesentery, urologic obstruction, and a calcified wandering tumor. In addition, error in diagnosis is an important consideration when a fetal sonogram is interpreted as showing an ovarian cyst. Urologic malformations, mesenteric or other lymphatic malformations, intestinal duplications and

choledochal cysts represent most of the other diagnostic considerations. Brandt gives the following extensive listing of causes of fetal abdominal cystic masses:

> "The differential diagnosis of a cystic abdominal mass in the female fetus includes intestinal duplication, hydronephrosis, bladder distention, cystic meconium peritonitis, intestinal obstruction, hydrometrocolpos, duodenal atresia, lymphangioma, anterior meningomyelocele, and renal, mesenteric, urachal, omental, choledochal and ovarian cysts.[8]"

Critical information needed to decide how to manage a fetal or neonatal ovarian cyst includes the risk of a simple cyst becoming complex and the likelihood of a complex cyst causing physiologic problems. Most published series include relatively small numbers of cases and are retrospective. That authors reach several differing conclusions confirms the inadequacy of this evidence for clinical decision making.

In 1992, a multi-institutional German study reported that 50% (18/36) of simple ovarian cysts identified by prenatal sonogram converted to complex cysts on postnatal imaging.[9] More recent series confirm that *in utero* conversion of fetal ovarian cysts from simple to complex is fairly common, ranging from 18% (9/49) to 51% (28/55).[10–12] However, the size of the cysts does not consistently seem to be a useful factor in predicting torsion. Interestingly, in opposition to these reviews, another series shows no conversion in 33 simple fetal ovarian cysts less than 5 cm in diameter.[4] Since the authors intervened for most larger cysts, the risk of torsion in the larger ones could not be quantified.

Some things are clear from the literature. Cancer in the fetal and neonatal ovary almost never occurs. There is one report of a stillborn from the German literature in 1945 with bilateral cancer of the ovary, perhaps granulosa cell.[13] An occasional benign teratoma or benign serous cystadenoma appear within reported series. Neoplasm in the fetal or neonatal ovary is a rarity and cancer is an obscurity so remote as not to be an issue in a clinical algorithm.

APPROACH TO MANAGEMENT OF THE FETAL OVARIAN CYST

Once a fetal ovarian cyst becomes complex, it has usually infarcted, so salvage of the ovary becomes unlikely. It is the propensity for conversion *in utero* from simple to complex that leads some authors to advocate *in utero* aspiration of simple fetal ovarian cysts, hoping to save the ovary from infarction. Bagolan in Rome strongly supports aspiration of simple fetal ovarian cysts in order to salvage the involved ovary.[14] Bagolan *et al.* believe their evidence supports using size as a

criteria to judge the risk of torsion and advocate aspiration *in utero* of cysts larger than 4–5 cm in diameter. How safe is that step? In a series of 73 fetal ovarian cysts, this group aspirated 14 simple fetal cysts larger than 5 cm, saving 12 (86%) of the ovaries without a complication. Although the results appear excellent, that experience does not answer the question of whether or not the risks outweigh the benefits. Since the track record for fertility in women with a solitary ovary is good.[15] and many simple ovarian cysts will resolve without intervention, major risks including serious fetal injury or induced premature labor would have to occur quite rarely to warrant a procedure that may save an ovary. Case numbers are too small and evidence is too weak in the literature to be confident about the safety of aspirating a fetal ovarian cyst. The most common approach to fetal ovarian cysts, whether simple or complex, small or large, is to follow with prenatal sonograms and perform a confirmatory sonogram in the neonate. As more experience accrues, advantages and safety of *in utero* aspiration may be clarified.

APPROACH TO MANAGEMENT OF THE NEONATAL OVARIAN CYST

What should the clinician advise for the newborn with an ovarian cyst? Occasionally, cysts are symptomatic, sometimes so large as to be visible, palpable, or obstruct breathing or GI function. Some have developed hemorrhage and/or torsion, causing mass effect, bleeding or peritonitis. These obviously demand intervention.

Most often neonatal ovarian cysts would not be recognized except for the fetal sonogram that unearthed them. They should be followed with postnatal ultrasounds expecting spontaneous resolution. One approach is to intervene for large simple cysts, usually more than 4–5 cm in diameter, and for all complex cysts.[8] The idea is to save the ovary from infarction due to torsion when it has a large simple cyst. Not all agree that size is relavant to the risk of torsion. The basis is largely retrospective and since groups often intervene when cysts are large there is no certainty about the size criteria.[16] When the cyst is complex the ovary is not likely to be salvageable (although occasionally it has bled and not infracted). Intervention for a complex ovarian cyst is recommended to prevent the dangers of complications. This advice is not universal.

Several authors have questioned whether size is a valid criteria for judging the risk of torsion. In Zampieri's series from Verona, none of 33 simple ovarian cysts, less than 5 cm, became complex.[4] Shimada in Ohmura Japan saw no size correlation following 11 simple fetal ovarian cysts.[10] Galinier in Toulouse found no relation of natural history to size following 55 simple fetal ovarian cysts.[11] Other series can't weigh in on this subject since practitioners intervened when cysts met certain size criteria.

Authors of the multicentered retrospective review from Germany advocate leaving the cysts alone whether simple or complex, large or small.[9] They feel resolution is likely for both simple and complex cysts regardless of size. The physiologic reasoning is that since delivery removes the patient from the stimulatory fetal hormonal milieu, resolution of simple fetal ovarian cyst is likely in the first year of life. Those ovaries that have infarcted will atrophy and are presumed unlikely to cause problems. Authors of a retrospective series of 82 fetal ovarian cysts from France support leaving simple ovarian cysts and most complex cysts alone.[11]

Since surgeons may often sacrifice the ovary, many who regard large simple neonatal ovarian cysts as dangerous advocate ultrasound-guided aspiration as an appealing middle ground.[17,18] Because the milieu is no longer rich in stimulating hormones, recurrence is thought to be unlikely after aspiration of simple cysts in the neonate. One striking case report of an attempted aspiration of a presumed ovarian cyst serves as a horror story warning of the danger in this procedure when combined with an error in diagnosis.[19] The cyst proved to be an intestinal duplication. Bleeding resulted from the needle aspiration. Intestinal volvulus occurred and the patient died. Granted, a horror story does not satisfy the proponents of evidence based medicine, but the literature is laden with small cases series with happy endings. A single case that has a catastrophic outcome may be of more value by confirming possible dangers inherent in some procedures described as safe in small series.

To be certain of the diagnosis and view both ovaries, aspiration can be accomplished in the neonate with a laparoscope. One downside is the need for general anesthesia. However, this approach allows the surgeon to confirm if a cyst is simple or complex, aspirate under visualization if it is simple, or perform gonadectomy when indicated. A laparoscope can be passed through a 3-mm trocar at the umbilicus. Other trocars are not needed. An aspirating needle, probe, grasper or other devices can be passed through abdominal stab wounds (Figures 1–4). Once aspirated by the laparoscopic technique, the cyst can be removed through a small transumbilical incision if the surgeon prefers.[20] This makes sense if there is apprehension that it will recur. Aspiration alone of neonatal simple ovarian cysts is advocated, but not enough cases with significant follow-up are reported to be certain about the risk of recurrence. By all means, ovariectomy should be avoided unless there is certainty that no viable ovarian tissue persists. This is especially true since some authors feel an infarcted ovary is unlikely to cause difficulties. Aspirating the simple cyst might have less chance of ovarian loss than a more definitive procedure such as cystectomy, although that is not proved.

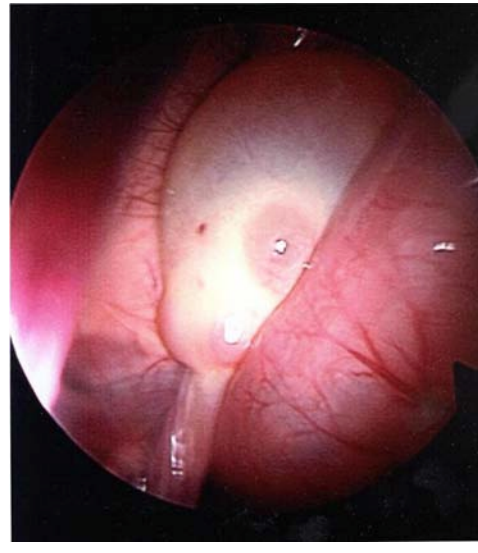


Figure 1. Laparoscopic view of simple ovarian cyst in a neonate that appeared complex on sonogram.

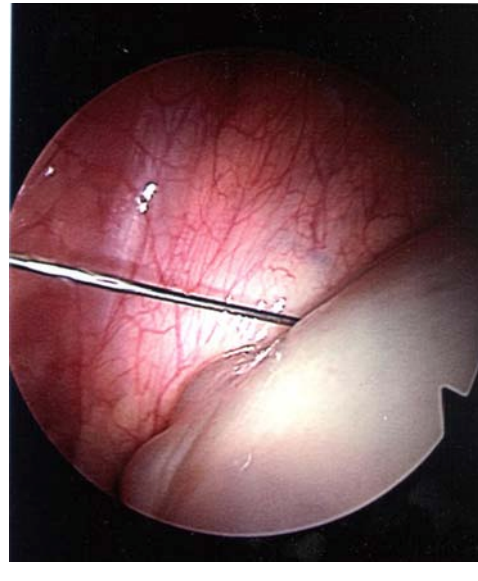


Figure 2. Laparoscopic guided needle aspiration.



Figure 3. Patient after laparoscopic needle aspiration.

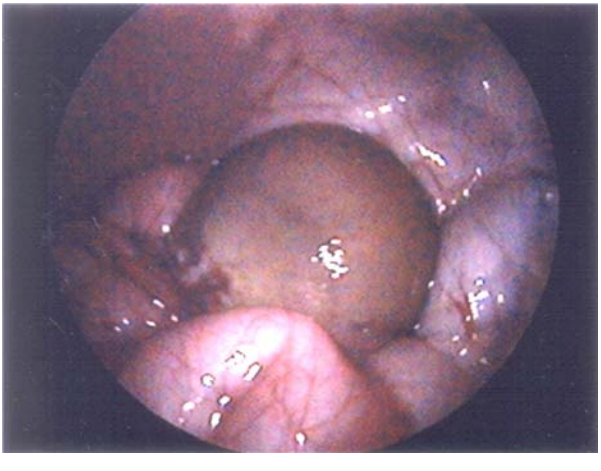


Figure 4. Laparoscopic view of infarcted ovary with old blood in a neonate with a complex cyst found in the fetus.

COMPLEX CYST IN THE NEONATE

Many advocate intervention for any complex ovarian cyst. Saving the ovary is not expected, although about 10% of ovaries with a complex cyst on sonography are not infarcted. Those who would leave even complex cysts alone are concerned that intervention might lead to unnecessary gonadectomy.[11] As a safety measure, some

suggest intervention after several months if, sonographically, the mass persists (the ovary has not involuted).[11]

An operative approach, preferably with the laparoscope, confirms the pathology, examines the other ovary, and allows aspiration of a simple cyst or evacuation of a blood filled cyst (Figures 1–4). If ovariectomy is done, it should be limited to the situation where the gonad is unequivocally dead. After decompression, ovariectomy can be done through a tiny incision.

SUMMARY

Although simple fetal ovarian cysts often resolve spontaneously during infancy, they may become complex before and after birth. This usually implies torsion and most often infarction of the ovary. Cancer is not an important consideration. Laparoscopic inspection of a simple neonatal cyst more than 4–5 cm and any complex cyst allows absolute confirmation of the diagnosis, aspiration or evacuation, and possible cystectomy or gonadectomy. Gonadectomy should be done only when infarction is unequivocal. Evidence supporting these choices is retrospective, and even when studies are described as prospective they may have some selection bias. Reported numbers are too few to know with certainty the risk of leaving large simple or complex cysts alone. Likewise, the recurrence rate after aspiration is uncertain. Families should be well informed of all options as there is limited, weak support in the literature upon which to base most of these clinical decisions.

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CHAPTER 15

VASCULAR AND LYMPHATIC ANOMALIES

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INTRODUCTION

First proposed in 1982, the current biologic classification system for vascular anomalies correlates cellular features with clinical characteristics and natural history.[1,2] Vascular anomalies are divided into two categories: tumors and malformations (Table 1).

Tumors are characterized by increased endothelial cell turnover. Hemangioma is the most common vascular tumor. Vascular malformations occur due to errors in embryonic vascular morphogenesis and exhibit normal, slow endothelial cell turnover. Malformations are further subdivided based on predominant channel type and flow characteristics into either fast-flow or slow-flow malformations. Examples of slow-flow lesions are capillary, lymphatic, and venous malformations. Fast-flow lesions include arteriovenous malformations and arteriovenous fistulas. History and physical examination alone yield an accurate diagnosis in more than 90% of infants.[3] The majority of vascular anomalies are apparent at birth since they often involve the skin. In addition to cellular and clinical behavior, tumors and malformations also exhibit their own unique radiographic findings and immnohistochemical properties.[3] Increasingly, vascular anomalies are being diagnosed antenatally due to advances in fetal medicine. Pediatric surgeons may

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Table 1. Classification of vascular anomalies.

Tumors	Slow-flow malformation	Fast-flow malformation
Infantile hemangioma	Capillary	Arteriovenous fistula
Congenital hemangioma	Lymphatic	Arteriovenous
Rapidly involuting congenital hemangioma (RICH)	Microcystic	
Noninvoluting congenital hemangioma (NICH)	Macrocystic	
	Lymphedema	
Kapisoform hemangioendothelioma (KHE)	Complex-combined	Complex-combined
Kaposiform lymphatic anomaly (KLA)	Capillary lymphaticovenous (CLVM)	Capillary arteriovenous
Pyogenic granuloma (PG)	Lymphaticovenous	

be called upon to diagnose, manage, and treat vascular anomalies antenatally, postnatally, and throughout childhood.

VASCULAR TUMORS

Vascular tumors are distinguished from vascular malformations by their proliferating endothelium. Additionally, many vascular tumors are not present at birth but appear in the first weeks of life and exhibit postnatal expansion.[4]

Infantile Hemangioma (IH)

Clinical features

Infantile hemangioma (IH), a benign tumor of the endothelium, is the most common tumor of infancy. Precise incidence figures are unavailable, since the few early studies performed likely counted some vascular malformations as well as hemangiomas. Thus, the oft-quoted figure of 4–10% of Caucasian infants is likely inflated.[5] The incidence is lower in dark skinned infants. Extremely low birth weight infants (<1000 g) appear to have the highest incidence of IH approaching 23%.[6] IH occur three times more commonly in girls than boys.[3] The majority of IH present as single lesions (80%) and are located in the head and neck (60%) followed by the trunk (25%) and the extremities (15%)[2] (Figure 1). IH uncommonly

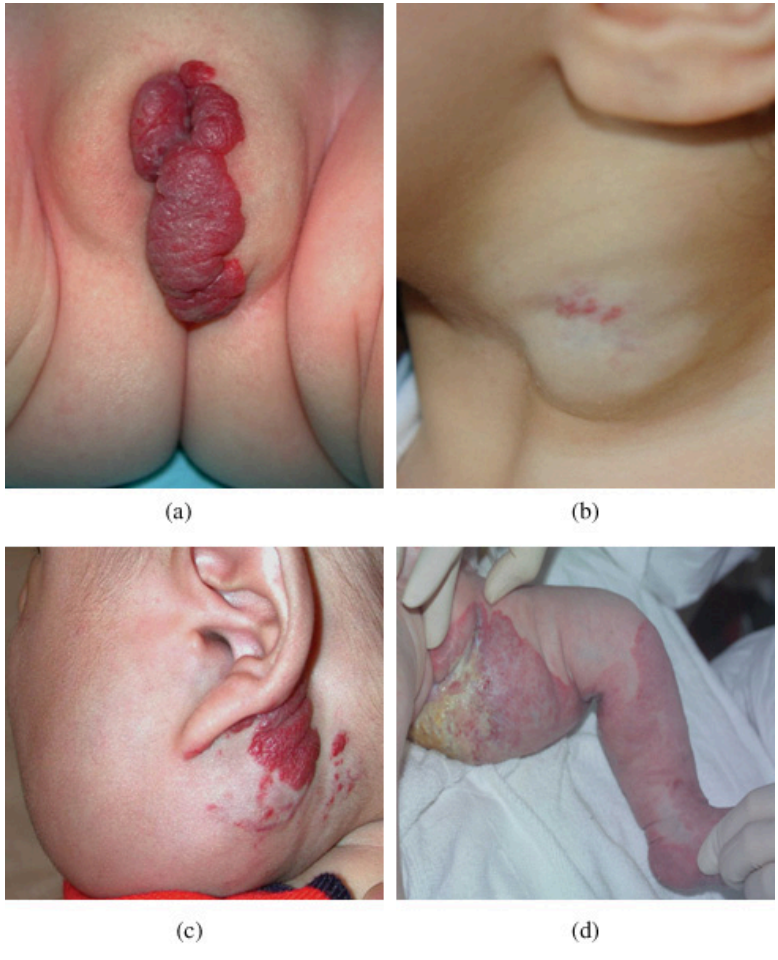


Figure 1. Morphologic variation of infantile hemangioma. (a) Tumor of labia majora. (b) Deep tumor of the neck. (c) Deep and superficial tumor of the parotid. (d) Reticular hemangioma of the extremity with ulceration in the perineum and posterior thigh.

involves the viscera. The median age of appearance is 2 weeks after birth, however, about 50% of IH are visible at birth by the presence of a faint macular stain, small pale spot, or ecchymotic area[3] (Figure 2). Ninety percent of IH are small, localized, and do not involve aesthetically or functionally vital structures.[3,7]

IH exhibit a unique growth pattern which is divided into three phases: proliferating, involuting, and involuted phases. The proliferating phase is marked by rapid growth of the IH and lasts until approximately 10 months of age. Tumors



Figure 2. Progression of an infantile hemangioma during the proliferating phase. (a) Normal appearance at birth. Two weeks of age; notice macular stain over left eye. (b) Five weeks of age; notice raised crimson tumor. Six weeks of age; small area of ulceration appearing at the inferior aspect. (c) Continued ulceration at 8 weeks of age.



Figure 3. Life cycle of infantile hemangioma. (a) Red macule. (b) Proliferation with increase in size and change in color. (c) Continued proliferation. (d) Involuting stage notice decrease in size and change in color.

that permeate the superficial dermis are crimson, raised, and firm. Those occupying the deep dermis may be more subtle, exhibiting a bluish hue in the overlying skin. By 10–12 months of age, growth of the IH plateaus, and thereafter, tumor growth is proportionate to the growth of the child. During the involuting phase, the first signs indicating regression appear: the crimson color fades to a dull purple, the center becomes pale, and overall the lesion is less tense (Figure 3).[3] Involution is complete in 50% of children by 5 years of age and 70% of children by 7 years of age. Gradual improvement may continue until 10 to 12 years of age.[8] When the IH has ceased involuting, it enters the involuted phase. Fifty percent of patients have permanently damaged skin, scarring, excess skin, telangiectasias, discoloration, or a fibrofatty residuum[3] at the end of involution.

Ten percent of hemangiomas are estimated to be endangering or life-threatening.[9] Complications include destruction, distortion, and obstruction and usually arise in cervicofacial IH. Ulceration may cause tissue destruction and distortion of the eyelid, nasal tip, lip, or ear. A large IH may cause mass effect



Figure 4. Infantile hemangioma in a beard distribution in a 5-month-old infant requiring tracheostomy.

and expansion of tissue. Even a small IH can be devastating and potentially life-threatening. A small subglottic IH is a common life-threatening lesion which is characterized initially by potential hoarseness and later by biphasic stridor around 6–12 weeks of age.[3] Many of these infants will have an associated cutaneous cervical IH often in the "beard distribution" (Figure 4). Even a seemingly trivial periorbital IH can block the visual axis and cause deprivation amblyopia. An IH of the upper eyelid or supraorbital area can distort the cornea producing astigmatic amblyopia. A pediatric ophthalmologist should examine any infant with a periorbital hemangioma. High-output cardiac failure, hypothyroidism, or abdominal compartment syndrome may be caused by hepatic hemangiomas.

The presence of multiple IH, usually greater than four, is called hemangiomatosis (Figure 5). The cutaneous IH are frequently small (<5 mm), dome-shaped, and firm. Occult visceral lesions may be present when multiple cutaneous IH are found. Screening ultrasonography may be indicated. The liver is the most frequently involved location.

Etiology

The exact etiology and pathogenesis of IH is yet to be determined. The endothelial cells involved in IH are clonal, derived from a single precursor cell,[10] but their exact origin is unknown. Some evidence suggests that hemangioma endothelial cells may be of placental origin or have a common precursor to placental microvillous endothelium[11–14] since their immunophenotypes are similar, and



Figure 5. An infant with hemangiomatosis. Characteristic appearance of multiple dome-shaped infantile hemangiomas which may indicate the presence of associated visceral hemangiomas.

both express several markers such as glucose transporter-1 (GLUT-1), type III iodothryonine deoidinase, Fcγ-RIIb, merosin, and Lewis Y antigen.[13,14] A placental origin would help clarify the increased incidence of IH seen with pre-eclampsia, chorionic villus sampling, and placenta previa which are all conditions that disrupt the maternal–fetal barrier.[15]

Associated structural abnormalities

The majority of IH occur sporadically and are not associated with dysmorphic syndromes, however, larger hemangiomas and those encountered in the midline deserve attention. Large cervicofacial hemangioma can be associated with posterior fossa abnormalities, arterial cerebrovascular anomalies (e.g. aneurysm, occlusion, stenosis, persistent intra- and extracranial embryonic arteries), cardiac defects (e.g. aortic coarctation, right sided aortic arch), ocular abnormalities (e.g. microphthalmia, cogenital cataract, or optic nerve hypoplasia), and sternal defects (clefting) or supraumbilical raphé.[16–18] The acronym for this constellation of finding is PHACES association (posterior fossa abnormalities, hemangioma, arterial cerebrovascular anomalies, cardiac defects, eye abnormalities, sternal defects and/or supraumbilical raphe). Hemangioma of the lumbosacral region may signal the presence of an underlying occult spinal abnormality such as tethered cord or lipomeningocele. Ultrasonography is used to screen infants less than 4 months

of age for the presence of occult spinal dysraphism; MRI may be necessary in older children. Perineal hemangioma may be seen with anorectal and genital anomalies. A macular, network-like IH of the lower extremity can be associated with structural anomalies of the ventral-caudal region, visceral hemangiomas, and cardiac overload.[19]

Radiologic features

Ninety percent of neonatal and childhood vascular tumors can be diagnosed by history and physical examination. Radiographic studies will assist with classifying the remaining 10% of indistinguishable lesions. Ultrasonography is the first-line study for the majority of vascular anomalies in part because it is widely available and noninvasive.[20] Ultrasonographic features of IH include a discrete soft tissue mass, decreased arterial resistance, and increased venous flow.[20] It may be difficult to distinguish between hemangioma and arteriovenous malformations since both are fast-flow lesions. MRI is the second-line study and is used to confirm the extent and tissue characteristics of the lesion, however, sedation is often necessary in children less than 6 year of age.[21] Proliferating IH on MRI are well-circumscribed, enhance uniformly, and have dilated feeding and draining vessels. They are isointense on T1 and hyperintense on T2 (Figure 6). Flow voids

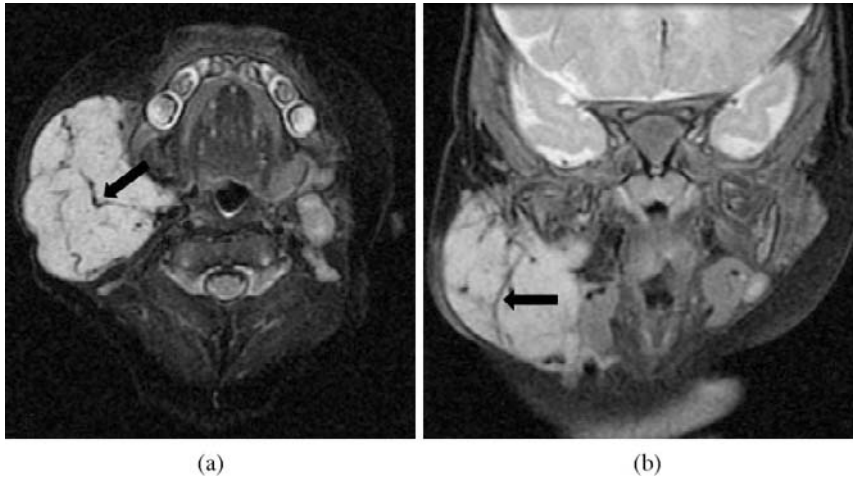


Figure 6. T-2 weighted fat-saturation MRI sequences of a parotid infantile hemangioma. (a) Axial view shows well-circumscribed uniformly hyperintense mass with dilated feeding and draining vessels (arrows). (b) Coronal view.

are seen around and within the mass.[22] Involuting IH shows vessels that are decreasing in size and number. Involuted IH on MRI appears as an avascular fatty mass.[21] IH are usually not identified antenatally since they are typically invisible or small until they exhibit postnatal proliferation.

Treatment

Observation is the mainstay of management since approximately 90% of IH are small, localized, and do not involve aesthetically or functionally vital structures.[3] The remaining 10% can cause major deformity or severe complications.[9] Disfiguring hemangiomas, particularly when located on the face, frequently evoke strong parental emotions of loss and grief. The consultant plays a crucial role in providing guidance and support.[23] Regularly scheduled follow-up is imperative. Serial photographs are useful to document progression, response to treatment, and subsequent regression.

The most frequently encountered complications associated with IH are epithelial breakdown, ulceration, and necrosis occurring in about 5% of patients during the proliferative phase. Ulceration is most common on the lips, perineum, and parotid area.[24] Local treatment includes daily cleansing and application of hydrated petrolatum with intermittently applied topical viscous lidocaine for pain control. Eschars should be sharply débrided and treated with wet-to-dry dressings to stimulate granulation tissue. Superficial ulceration usually heals within days to weeks, whereas, a deep ulceration may take several weeks.[3] Healing may be expedited by the administration of corticosteroid. Flashlamp pulsed dye laser is also reported to alleviate pain and aid healing for ulcerated IH. Surgical resection of ulcerated IH is usually reserved for lesions of the chest, scalp, extremity, and rarely for facial lesions when primary closure is possible.

For endangering or problematic IH, pharmacologic intervention may be required. The rationale behind drug therapy is inhibition of angiogenesis in the IH. Intralesional injection of corticosteroid should be considered for small IH of the nasal tip, cheek, lip, or eyelid in an effort to minimize expansion. Periorbital injection of corticosteroid should be performed cautiously due to the risk of retinal artery occlusion presumably from embolic material resulting in blindness and eyelid necrosis.[25,26] Triamcinolone (25 mg/mL) is injected slowly at a low pressure with a 3-mL syringe and 25 gauge needle. A total of 3–5 mg/kg per treatment is used.[27] Compression at the periphery of the lesion will minimize the chances for embolization of the colloidal particles. Three to five additional injections at 6- to 8-week intervals may be necessary.[27] Response rates are similar to that of an oral corticosteroid.

Systemic corticosteroid should be used for larger life-threatening or ulcerated IH. Orally administered prednisone or prednisolone is administered in the morning at 2–3 mg/kg/day for two weeks. If the IH stabilizes, the dosage is tapered every 2–4 weeks. Treatment is usually terminated by 10–11 months of age. Occasionally, rebound growth of the tumor is noted when the dose is tapered and the prior dose must be continued for somewhat longer. Stabilization of growth or accelerated regression is noted in approximately 90% of IH treated systemically. Corticosteroid administration is not without side effects. Some of the more common ones include Cushingoid facies, irritability, GI reflux, a slowing in the rate of height and weight gain, steroid induced cardiomyopathy, and hypertension.[28–30] After cessation of corticosteroid therapy, children return to their pretreatment curves for height and weight by 14–24 months.[29] Live vaccines (such as polio, measles, mumps, rubella, and varicella) should be withheld during corticosteroid treatment.

Recombinant interferon α2a or 2b, previously considered second-line pharmacologic therapy, has fallen out of favor due to the high incidence of spastic diplegia that may occur in 5–20% of treated infants .[31,32] For IH that are recalcitrant to corticosteroid, a more suitable second-line therapy is chemotherapeutic agents with anti-angiogenic properties, such as vincristine, in a low-dose, high-frequency regimen.

Recently, propranolol, a nonselective β-blocker, for the treatment of IH has come into favor after a serendipitous discovery made when it was observed to induce changes in color and softening of the lesion.[33] Stabilization and inhibition of growth were also noted. Additional reports indicate that propranolol may be as efficacious as corticosteroid for the treatment of problematic IH.[34,35] The mechanism of action for propranolol has yet to be elucidated, however, theories include vasoconstriction or possibly downregulation of angiogenic proteins such as VEFG and bFGF.[33,35] A large prospective randomized controlled trial is underway to address the efficacy, tolerability, and safety of propranolol.

Embolization of IH is reserved for those lesions causing severe congestive heart failure such as seen in hepatic hemangioma. Embolization is usually used as an adjunct to pharmacotherapy, and its effectiveness depends on the ability to occlude a large percentage of the shunts.

Despite its popular appeal, flashlamp pulsed dye laser does not play a role in the treatment of nascent or proliferating hemangioma. Flashlamp pulsed dye laser penetrates only 0.75–1.2 mm into the dermis, thereby treating only the superficial component of the IH. Purely superficial IH are frequently the very tumors that require no treatment. After involution, they leave behind nearly normal skin. More commonly, cutaneous IH involve or are deep to the middle dermal layer

leaving them impenetrable. Laser therapy carries risks of scarring, ulceration, and hypopigmentation which may result in a poorer cosmetic result than observation alone. On the other hand, pulsed dye laser is an effective therapy for telangiectasias that persist during the involuted phase. Continuous wave carbon dioxide laser can be used to partially excise subglottic IH.[36] Intralesional laser photocoagulation with a bare fiber (Nd:YAG) can be used when rapid shrinkage is necessary such as an eyelid hemangioma causing visual obstruction.

Surgical indications for excision of an IH vary by patient age and hemangioma stage. During the proliferative phase (infancy), resection may be indicated for obstruction, ulceration, and bleeding. Excision may also be considered for well-localized or pedunculated lesions especially when the scar formed would be similar to that if the excision were to occur at a later stage. Skin of the scalp, trunk, and extremity in an infant is lax, facilitating closure of these sites. Indications for resection during the involuting phase include cases for which excision is inevitable (e.g. expanded inelastic skin or the presence of a fibrofatty residuum), ability to hide the scar, and desire to avoid an altered self-image.[3] Preschool age children become aware of body differences at this age, and the presence of an obvious involuting IH can lead to low self-esteem. Since many IH involute completely, waiting until the involuted phase is a reasonable approach barring any endangering or life-threatening complications. Surprisingly, the involuted skin can look normal, however, if ulceration occurred during the proliferative phase, significant scarring may be present. Additionally, a protuberant IH may leave behind excess skin and tissue. Resection may be considered during late childhood (involuted phase) for damaged skin and contour deformity.

Despite debate on indication, timing, and resection technique, most would agree that the scar for resection of an IH should be minimized.[37] Lenticular excision with linear closure is the conventional method for removal of a spheroidal mass. Frequently, the incisional length extends beyond the lesional border into normal skin in an effort to prevent terminal dog-ears. Lenticular excision can be used when a transverse incision is indicated. In areas of convexity such as the cheek or forehead, lenticular excision with linear closure should be avoided since it may result in central flattening. Circular excision and intradermal purse-string closure can minimize scar size (Figure 7). Staged excisions using this method can be performed. Radial folds may be evident initially and usually smooth-out rapidly within weeks.[37] Hemangiomas of the forehead, eyelid, cheek, lips, nose, nasal tip, ear, and neck require surgical expertise.

IH of the stomach, small intestine, or colon can present with mild or life-threatening GI bleeding. Localization with endoscopy or laparoscopy or both may be necessary to identify lesions of the small intestine.[38] Many infants can be

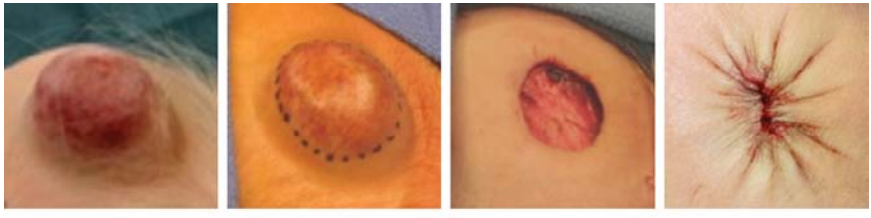


Figure 7. Circular excision of an infantile hemangioma located on the scalp. (a) Preoperative photo. (b) Intra-operative photo demarcates path for excision. (c) After circular excision. (d) Circular closure.

treated nonoperatively with corticosteroid and intermittent blood transfusions. Focal IH of the GI tract which are refractory to medical management may be treated endoscopically (e.g. band ligation or multipolar thermocoagulation) or surgically (e.g. segmental bowel resection or wedge resection). Diffuse, patchy involvement of the GI tract is unfortunately the more common pattern, making endoscopic and surgical intervention problematic.[39] These infants require pharmacotherapy and often repeated blood transfusions. Extensive enterectomy should not be performed, since involution and cessation of bleeding will eventually occur.

Congenital Hemangioma

Congenital hemangiomas, unlike IH, are present at birth and do not exhibit postnatal growth. There are two types of lesions: rapidly involuting congenital hemangioma (RICH) and noninvoluting congenital hemangioma (NICH). They are usually solitary and have no gender predilection. Histopathologically, these lesions are further distinguished from IH by staining negatively for GLUT-1. As its name implies, RICH are characterized by earlier onset of involution, often beginning before birth and completing on average between 6 and 14 months of age.[40] RICH affects the head or neck (42%), limbs (52%), or trunk (6%).[40,41] On physical examination, RICH are raised, pink to violaceous with central pallor and a surrounding peripheral pale halo. Telangiectasias are often present, and the lesions are firm to rubbery on palpation.[40] Due to accelerated involution, the residual area often appears deflated and is not accompanied by the usual fatty component seen in IH.[41] Given the intrauterine onset of these lesions, prenatal detection is possible and has been reported in several series.[40,42,43] NICH tend to

present as plaques in shades of pink to purple with overlying coarse telangiectasia averaging 5 cm in size.[44] NICH affect the head or neck (43%), limbs (38%), and trunk (19%). NICH does not undergo involution.[44] These lesions persist essentially unchanged or with slight expansion. RICH and NICH are fast-flow by Doppler evaluation. On MRI, some RICH exhibit large flow voids near the surface as well as areas of inhomogenous enhancement. Angiography of RICH can also reveal arterial aneurysms and direct arteriovenous shunts.[45] The radiographic appearance of NICH is indistinguishable from IH. Congenital hemangioma can be confused with infantile fibrosarcoma.[46] When the diagnosis is in doubt, biopsy must be performed. The biopsy specimen should include the periphery of the lesion since the lobular architecture is preserved here in congenital hemangioma.[45]

Hepatic hemangioma

Unlike adult hepatic hemangiomas which are actually venous malformations, hepatic hemangiomas (HH) of infancy are true vascular tumors. Their life cycle is similar to their cutaneous counterparts. They generally present in one of three patterns: focal, multifocal, and diffuse with each category exhibiting its own unique imaging, histopathologic, and physiologic characteristics.[47] Not all HH are life-threatening. The majority of HH cause no clinical sequelae and involute completely with minimal to no distortion of the hepatic parenchyma. Knowledge of the common presentations and imaging findings facilitates proper management and treatment.

Focal HH is likely the hepatic equivalent of the cutaneous rapidly involuting congential hepatic hemangioma (RICH). Like their cutaneous counterpart, these tumors are fully grown at birth and involute faster than the typical infantile hemangioma. There is no gender bias, and they can be detected on antenatal ultrasound.[48] Cutaneous IH are rarely present. Some infants exhibit transient anemia and thrombocytopenia which is likely due to intralesional central thrombosis. Focal HH are GLUT-1 negative. Many of these tumors are of no clinical significance, however, their presentation can be alarming when an otherwise healthy infant presents with an abdominal mass. Occasionally, focal HH can cause high-output cardiac failure due to the presence of high-flow shunts (arteriovenous or portovenous). These shunts may cause steal accounting for blood flow demands above and beyond what would be expected when looking at the volume of involved hepatic parenchyma. The shunts usually close as the tumor involutes. Embolization may be necessary to occlude the larger shunts in the face of heart failure. Skilled pediatric interventional radiologists can frequently successfully



Figure 8. CT angiogram of an infant with a focal hepatic hemangioma. Peripheral enhancement (*arrows*) with sparing centrally due to thrombosis or necrosis (*star*).

embolize these symptomatic shunts while protecting major hepatic vessels. It is unclear if the administration of corticosteroid is beneficial because these tumors tend to involute rapidly. Resection is rarely necessary. Focal HH are heterogeneous on computed tomography (CT), frequently with large hepatic arteries and hepatic veins. The enhancement pattern is usually centripetal with sparing centrally due to thrombosis or necrosis (Figure 8). If there are macrovascular shunts, large hepatic arteries and hepatic veins will be seen. There is often evidence of high flow exhibited by dilation of the proximal abdominal aorta, hepatic arteries, and hepatic veins with a reduced caliber aorta distally. Calcifications can also be evident.[49] Focal HH on MRI reveals a well-defined, solitary, spherical tumor that is hypointense relative to liver on T1-weighted sequences and hyperintense on T2-weighted sequences (Figure 9). They exhibit centripetal enhancement on gadolinium sequences. The solid, noninvoluted, portions which are usually at the periphery of the lesion demonstrate intense homogeneous enhancement. Heterogeneous enhancement may be found centrally where areas of necrosis, thrombosis, or intralesional hemorrhage have occurred.[47]

Multifocal HH is a true infantile hemangioma both by histopathology and natural history. Unlike focal HH, there is a gender bias toward females. These lesions are GLUT-1 positive. Many infants remain asymptomatic and require no treatment. Frequently, multifocal HH is only detected while screening for visceral hemangioma based on finding multiple cutaneous IH. Some of these infants can

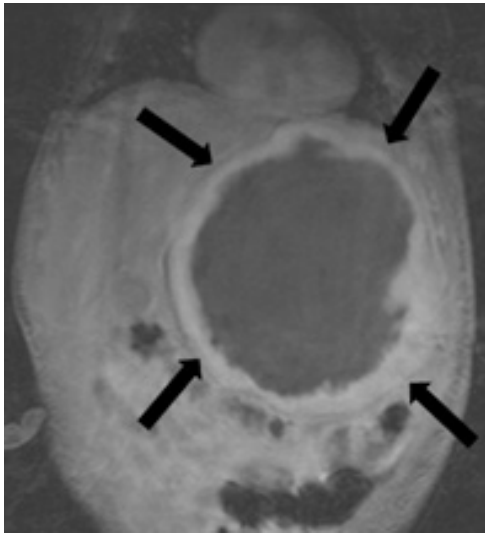


Figure 9. Coronal image of focal hepatic hemangioma shows well-defined, solitary, spherical tumor on MRI with gadolinium ultrafast spoiled gradient echo sequence. The periphery of the lesion demonstrates intense homogenous enhancement (*arrows*).

present in high-output cardiac failure due to macrovascular shunting. Because these multifocal lesions are true IH, corticosteroid can be used to treat symptomatic infants in an effort to close shunts. In cases refractory to medical management or if time is insufficient to wait for clinical improvement, embolization can be performed to ameliorate heart failure. Infants with multifocal HH should be followed closely with serial abdominal ultrasonography until involution of their hemangioma. Multifocal HH on CT appear as well-defined, spherical lesions. Prior to contrast administration they are hypodense compared to liver. With contrast, they enhance centripetally. A large supraceliac aorta with tapering distally is frequently observed and in conjunction with enlarged hepatic arteries and veins can indicate the presence of shunting.[49] Flow-voids are variably seen in and adjacent to the lesions. MRI reveals homogenously enhancing tumors that are hypointense relative to liver on T1-weighted sequencing and hyperintense on T2 (Figure 10).[49]

Of the three types of HH, the diffuse form is the most feared. Diffuse HH are also true IH with a strong female bias. These infants are the most likely to have a serious clinical course. Presenting symptoms are usually abdominal distention and respiratory compromise. CT and MRI findings for diffuse HH reveal hepatomegaly with near-total hepatic parenchymal replacement by innumerable, densely

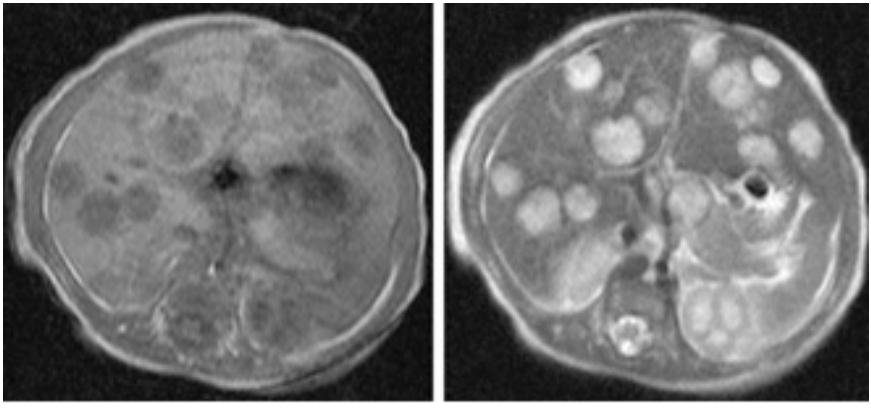


Figure 10. MRI evaluation of multifocal hepatic hemangioma. (a) Axial T1-weighted image of multifocal hepatic hemangioma. Lesions are hypointense relative to liver. (b) Axial T2-weighted image at same level shows lesions that are hyperintense relative to liver.

packed nodular lesions. Like multifocal HH, diffuse lesions also exhibit homogenous or centripetal enhancement.[49] The massive hepatomegaly can cause compression of the inferior vena cava and thoracic cavity leading to abdominal compartment syndrome and multiorgan failure. All IH express type 3 iodothyronine deiodinase which inactivates biologically active thyroid hormone.[50] Accelerated breakdown of thyroid hormone in infants with diffuse HH and sometimes with multifocal HH can lead to an acquired hypothyroidism. Levels of type 3 iodothyronine deiodinase are directly proportional to tumor burden. Despite the adaptive capacity of the thyroid endocrine axis, it is unable to replace thyroid hormone adequately and profound hypothyroidism develops.[50] Initial serum thyroid-stimulating hormone (TSH) concentrations can be greater than 50 μU/mL. Hypothyroidism of this magnitude can lead to profound mental retardation and cardiac failure.[50] Seemingly supranormal exogenous thyroid replacement and endocrinologic consultation are imperative. All patients with multifocal and diffuse HH should be screened by measurement of serum TSH. Corticosteroid should be administered to infants with diffuse HH to hasten tumor involution. Response to therapy can be followed with serial TSH measurements; hypothyroidism resolves with tumor involution. These infants often respond poorly to pharmacologic therapy, and in such cases, consideration should be given to hepatic transplantation.[47]

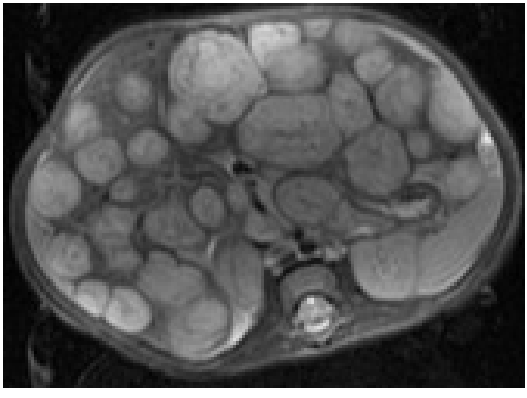


Figure 11. MRI evaluation of diffuse hepatic hemangioma. Axial T2-weighed fast spin echo sequences of diffuse hepatic hemangioma shows near-total hepatic parenchymal replacement with densely packed lesions.

A liver hemangioma management treatment algorithm may facilitate improved outcomes for infants with HH.[47] Regardless of treatment regimen selected, close follow-up is mandatory since clinical deterioration is possible, especially in the first few months of life. In some instances, it is necessary to perform both CT and MRI to look for the aforementioned imaging patterns. In the face of diagnostic uncertainty, percutaneous needle biopsy may be necessary to evaluate for malignancy. The differential diagnosis of HH is broad and includes arteriovenous malformation, arterioportal fistula, mesenchymal hamartoma, hepatoblastoma, angiosarcoma, and metastatic neuroblastoma.

Pyogenic Granuloma

Pyogenic granuloma is a common acquired vascular lesion of the skin and mucous membranes in the pediatric age group.[51] The average age of onset is 6.7 years. Pyogenic granulomas are rare before 6 months of age. There is usually no antecedent history of trauma or predisposing dermatologic condition. The lesions are frequently small and are commonly located in the head and neck area. On physical examination, these lesions appear as small (less than 1 cm) red sessile papules in the early phases and can quickly evolve into pedunculated lesions that bleed easily. Treatment options include curettage, full-thickness excision with linear closure, shave excision and cautery, cautery alone, and laser phototherapy.[52] Recurrences rates can approach 45% when the pyogenic granuloma is not completely excised.[51]

Kaposiform Hemangioendothelioma and Kasabach-Merritt Phenomenon

Kassabach-Merritt phenomenon (KMP) occurs with more invasive vascular tumors such as kaposiform hemangioendothelioma (KHE), kaposiform lymphatic anomaly (KLA), and tufted angioma (TA).[53–55] Unlike common IH, the endothelial cells of these invasive tumors do not xpress GLUT-1 nor Lewis Y antigen,[56] indicating they are a distinct type of vascular tumor. The cardinal features of KMP include an enlarging infantile vascular lesion, thrombocytopenia, microangiopathic hemolytic anemia, and a mild consumptive coagulopathy.[57] The term "KMP" is frequently misapplied to describe thrombocytopenia associated with hepatic hemangioma as well as a localized intravascular coagulopathy seen with some extensive venous and lymphatic malformations.

KHE appears as a single lesion at birth or early infancy with an equal gender ratio. It has a predilection for the trunk, extremities, and retroperitoneum. KHE can expand rapidly. The superficial component of the tumor visible in the skin appears as a tense, edematous, and violaceous plaque (Figure 12). Palpation reveals a warm lesion. Infants with associated KMP are at risk for intracranial, pleural, pulmonary, peritoneal, and gastrointestinal hemorrhage. Thrombocytopenia can be profound (less than 10,000 cells/μL) and is unresponsive to platelet transfusion due to intralesional trapping. The prothrombin time and activated partial thromboplastin time are usually normal to mildly elevated.

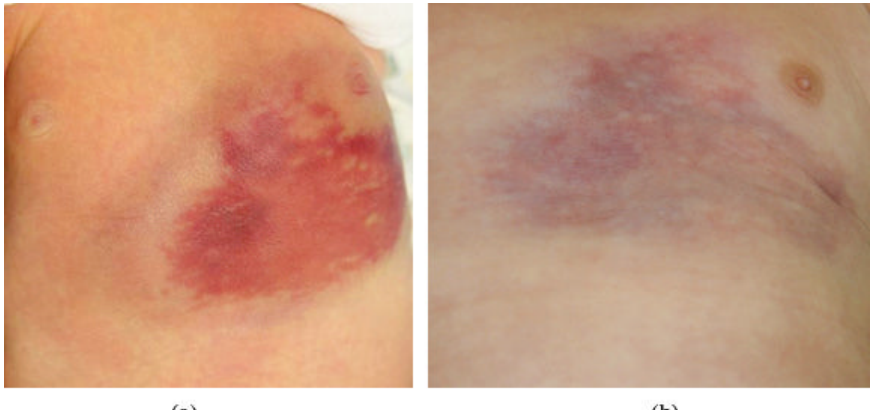


Figure 12. KHE of the chest wall. (a) Two months of age. (b) Four months of age after 2 months of treatment with vincristine.

D-dimer is increased while fibrinogen is low. Not all KHE are associated with KMP. Those less than 8 cm are more commonly spared.[58] Histopathology reveals aggressive infiltration of normal tissues by sheets or lobules of oval or spindled endothelial cells, dilated lymphatic channels, and slit-like vascular spaces filled with hemosiderin and compacted erythrocytes suggesting stasis.[55] When lymphatic channels predominate, it is a KLA. MRI demonstrates enhanced signal on T2-weighted images with ill-defined tumor margins and small feeding and draining vessels relative to tumor size. The tumor does not respect tissue planes and passes through skin down to muscle with stranding in the subcutaneous fat due to lymphatic obstruction or invasion. When KHE is adjacent to bone, osteolysis may be evident.[55]

The treatment for KHE with KMP is primarily medical as the tumor is usually too large to safely resect. Pharmacologic options include corticosteroid, interferon, or vincristine. Response to treatment is variable with all agents. In a small series, improved platelet counts were noted in all subjects who received vincristine.[57] For KHE not associated with KMP, the decision to treat should be based on size, location, and treatment side effects.[58] Platelet transfusions should be avoided unless there is active bleeding. Heparin should not be given since it can stimulate tumor growth, thus exacerbating platelet trapping and thrombocytopenia. Because mortality rates remain high (20–30%), careful monitoring is essential. KHE continues to proliferate into early childhood followed by incomplete regression in mid-childhood.

Tufted Angioma

Tufted angioma shares many clinical and histologic features with KHE indicating that they exist within the same spectrum. There is no gender bias. They are most commonly encountered in the neck and upper trunk. TA appears as erythematous macules or plaques; KMP may be evident. The microscopic appearance shows tufts of capillaries in the middle to deep dermis.[59] Well-localized lesions may be amenable to resection. Medical treatment and imaging patters are identical to KHE.

VASCULAR MALFORMATIONS

Vascular malformations are congenital errors of vascular development affecting arteries, capillaries, lymphatics, and veins that usually manifest themselves during infancy and childhood. They are named according to the abnormally developed

channel. Unlike vascular tumors which exhibit postnatal proliferation and expansion, vascular malformations tend to exhibit growth commensurate with that of the child. The prevalence of congenital vascular malformations is 1.2–1.5%.[60] The majority are sporadic but those with a clear genetic basis often follow autosomal dominant patterns of inheritance. Unlike sporadic forms which usually present as a solitary lesion, multiple lesions are frequently observed in the familial forms.[61,62] Many vascular malformations enlarge during puberty and recur after treatment. These lesions can be locally destructive, causing bleeding, obstruction, infection, heart failure, and even death. The most common complication, though, is psychological morbidity due to disfigurement.[63] Management strategies are focused on minimization of morbidity rather than cure.

Capillary Malformations

Capillary malformation (CM) is the modern term for the antiquated 19th century phrase "port-wine stain." CMs can be confused with the most common vascular birthmark called nevus flammeus neonatorum more popularly known as "angel kiss" (on the forehead) and "stork bite" (on the nuchal area). These faint macular stains are seen in 50% of caucasion neonates. They are attributed to transient dilation of dermal vessels and fade predictably during infancy. CMs present at birth as pink-red, flat, cutaneous patches. They affect 0.3% of infants.[64] with an equal sex distribution. Most CMs occur sporadically, but some are inherited in autosomal dominant pattern with incomplete penetrance.[65] They can be localized or extensive and occur anywhere on the body. CMs are composed of dilated capillary-to-venule sized vessels in the superficial dermis. Histopathology demonstrates a decreased number of nerves surrounding these vessels.[66] The lack of sympathetic innervation leads to vessel ectasia and explains the observed color change and nodular expansion seen with aging.[67] This phenomenon is most striking in facial CMs. Associated hypertrophy of the subcutaneous tissue, muscle, and bone underlying a CM is common. Extensive CM in an extremity may result in increased girth and limb length discrepancy (Figure 13).

Similar to some infantile hemangioma, a CM may signal an underlying structural abnormality. A CM overlying the cervical or lumbar spine can be a red flag for occult spinal dysraphism or tethered cord. An occipitally located CM can cover an encephalocele of ectopic meninges. Any child with a CM affecting trigeminal dermatomes, particularly the ophthalmic and maxillary distribution, should be evaluated for Sturge-Weber syndrome. This syndrome is composed of a facial CM with ipsilateral ocular and leptomeningeal vascular anomalies which can be capillary, venous, or arteriovenous malformations. Extensive



Figure 13. Capillary malformation. (a) Anterior view of an infant with an extensive CM of the right leg, trunk, arm, and face. Right leg is hypertrophic compared to left. Initial examination does not indicate leg length discrepancy. (b) Posterior view shows full extent of capillary malformation with overgrowth of right leg and buttock.

leptomeningeal involvement can manifest as seizures, contralateral hemiplegia, and variable motor and cognitive delays. Choroid involvement leads to an increased risk for retinal detachment, glaucoma, and blindness. Ophthalmic examination should be performed every 6 months until 2 years of age and then yearly in children at risk. Medically refractory seizures may require evaluation by an experienced epilepsy service, but surgical options may be limited given the diffuse nature of the seizure foci. CMs are also seen in complex-combined vascular malformations such as in capillary-lymphaticovenous malformations (CLVM), and capillary-malformation-arteriovenous malformation (CM-AVM), and Parkes Weber syndrome.

Radiographic features of cutaneous CM are nonspecific. Soft tissue and skeletal hypertrophy can be appreciated by CT and MRI. Sturge-Weber syndrome in

children can be suggested by MRI showing pial vascular enhancement. In later stages, gyriform cortical calcifications and cerebral atrophy can be seen.

Treatment for CM is usually focused on lightening the stain with the use of vascular-selective pulsed dye lasers. Early, thin CMs, such as in the neonate, respond well to flash lamp pulsed dye lasers which penetrate up to 2 mm into the skin. In general, the lateral face is the most responsive location. Complete eradication of any CM is difficult to achieve. Most laser-treated CMs continue to darken if left untreated.[68] Multiple sessions are required. The timing of therapy remains controversial, however, initiating treatment prior to 6 months of age is an option and short-term follow-up appears promising.[69] Soft tissue hypertrophy and limb length discrepancy may require tailored surgical intervention.

Lymphatic Malformation

Lymphatic malformation (LM) is commonly improperly termed "lymphangioma", implying that it has proliferative potential such as a tumor, but LM is not a tumor. Thus, the term lymphangioma should be abandoned. The pathogenesis for the formation of LM is largely unknown. For LMs in the neck and axilla, it is theorized that the principal lymphatic sacs lose or fail to re-establish communication with the central venous system from which it arose; peripheral lesions may be due to sequestration of lymphatic buds. The molecular basis for LMs is yet to be elucidated. No evidence for inheritance of typical LMs exists, but heritable forms of lymphedema, also a type of LM, have been identified.[61]

LMs are seen in various forms ranging from discrete sponge-like masses to areas of diffuse infiltration of a single or multiple anatomic locations. They are classified as microcystic, macrocystic, or combined macro- and microcystic. The difference between a micro- and macrocystic LM is of therapeutic importance. Size is relevant in determining whether or not the cystic cavity can be successfully aspirated to accomplish visible decompression. LM is usually noted at birth or within 2 years but can be discovered at any age. They tend to occur in areas of major lymphatic channels especially the cervical and axillary locations. With the exception of the central nervous system, which does not have lymphatics, LMs can be found in all tissues and organ systems. The overlying skin is often normal but a bluish hue can be present (Figure 14). Puckering or cutaneous dimpling can be seen with dermal involvement. LMs of the subcutis or submucosa appear as tiny clear to white vesicles which can weep fluid. Intravesicular bleeding changes the vesicles to appear as tiny red dome-shaped nodules. Histologically, LMs are composed of thin-walled vascular channels lacking pericytes or smooth muscle. Their lumens may be empty or filled with a protein rich fluid containing macrophages



Figure 14. Neonate with bilateral axillary lymphatic malformations. Extensive LM of the left axilla and upper extremity with bluish discoloration likely representing intralesional bleeding (*arrow*).

and lymphocytes.[70] Lymphatic endothelial cells comprising the wall of the LM are immunopositive for podoplanin (D2–40) and lymphatic vessel endothelial hyaluronan receptor LYVE-1.[71]

Increasingly, mass lesions[72] and vascular anomalies are detected on antenatal ultrasound.[42] An important distinction exists between what perinatologists refer to as fetal "cystic hygroma" and LMs seen postnatally by pediatric specialists. Today first trimester sonographic screening for fetal aneuploidy using nuchal translucency measurement is commonplace making the diagnosis of "cystic hygroma" more frequent.[72] "Cystic hygroma" is due to aberrant development of the cervical lymphatic sacs. Nuchal scanning, performed between 10–14 weeks, gestation, with nuchal thickness of ≥ 2.5 mm is considered abnormal. Slight variations in the measurement depend upon crown-rump length. Some authors reserve the term "cystic hygroma" for only those with visible septations while the remaining are simple increased nuchal translucency.[72] Average sizes of fetal "cystic hygroma" range from 6.5 to 7.9 mm.[72,73] Fetal "cystic hygroma" definitively is shown to be associated with a higher risk of aneuploidy, cardiac malformation, and perinatal death over simple increased nuchal translucency.[72] Fifty percent of fetuses with "cystic hygroma" will have a chromosomal abnormality, predominantly Down syndrome or Turner Syndrome, however, 17–25% of these pregnancies will result in the birth of a healthy newborn with normal chromosomes.[72,73] The resolution of fetal "cystic hygroma," usually between 16–20 weeks, gestation may have as high as a 95% chance of a normal outcome.[72]

Fetal "cystic hygroma" and simple increased nuchal translucencies are always situated in the posterior neck and can extend down the entire dorsum of the fetus.[72] This posterior location is distinct from cervical LMs located in the submandibular, supraclavicular, and anterior/lateral neck regions which can be found antenatally during second or third trimester scanning or postnatally (Figure 15). Although not thoroughly studied, lymphatic malformations are usually not detected until the second trimester.[42] This is in contradistinction to the more concerning fetal "cystic hygroma" seen by 14 weeks. Due to continued use of the imprecise term "cystic hygroma" to describe a form of increased nuchal translucency associated with adverse fetal outcome as well as in reference to LMs, some families receive misinformation regarding their true diagnosis, leading them to incorrectly believe that their fetus cannot survive or will have chromosomal abnormalities. Antenatal consultation with pediatric specialists familiar with vascular anomalies can be beneficial and educational for families when the diagnosis of a LM is made *in utero*. This also allows for specialists and families to begin planning for delivery and postnatal care especially when a large cervicofacial LM is diagnosed.[42] Most importantly, it should be emphasized that LM is not associated with chromosomal derangement or developmental disorders. The term "cystic hygroma" should not be used after a child is born. Lymphatic malformation is preferable.

Large cervicofacial LMs (Figure 16) diagnosed *in utero* should raise concern about potential airway obstruction leading to asphyxia in postnatal life. In many cases, it is possible to prognosticate the likelihood of airway difficulties at birth based on results from prenatal ultrasound and fetal MRI. If the probability of airway obstruction is high, consideration should be given to deliver the fetus via an *ex utero* intrapartum treatment (EXIT) procedure.[74] The mother is placed under deep inhalation anesthesia which preserves uteroplacental gas exchange. The anesthesiologist's goal is to ensure adequate fetal anesthesia and uterine relaxation. A Cesarean section is performed and the neonate is partially delivered. The umbilical cord is not transected allowing for maintenance of fetoplacental circulation for up to an hour allowing for airway assessment, endotracheal intubation, and if necessary tracheostomy. After securing the airway, the umbilical cord is clamped and delivery is completed.[74] Though EXIT was used somewhat frequently for LM in the early years after development of this technique, experience has shown that most LMs are compressible lesions allowing intubation after delivery if there is airway compromise. Thus, differentiation from teratoma, which is usually firm and non-compressible, is important in delivery planning.

LMs occur in recognized patterns. Consequences are anticipated depending upon anatomic location and extent. Periorbital and orbital LMs can lead to

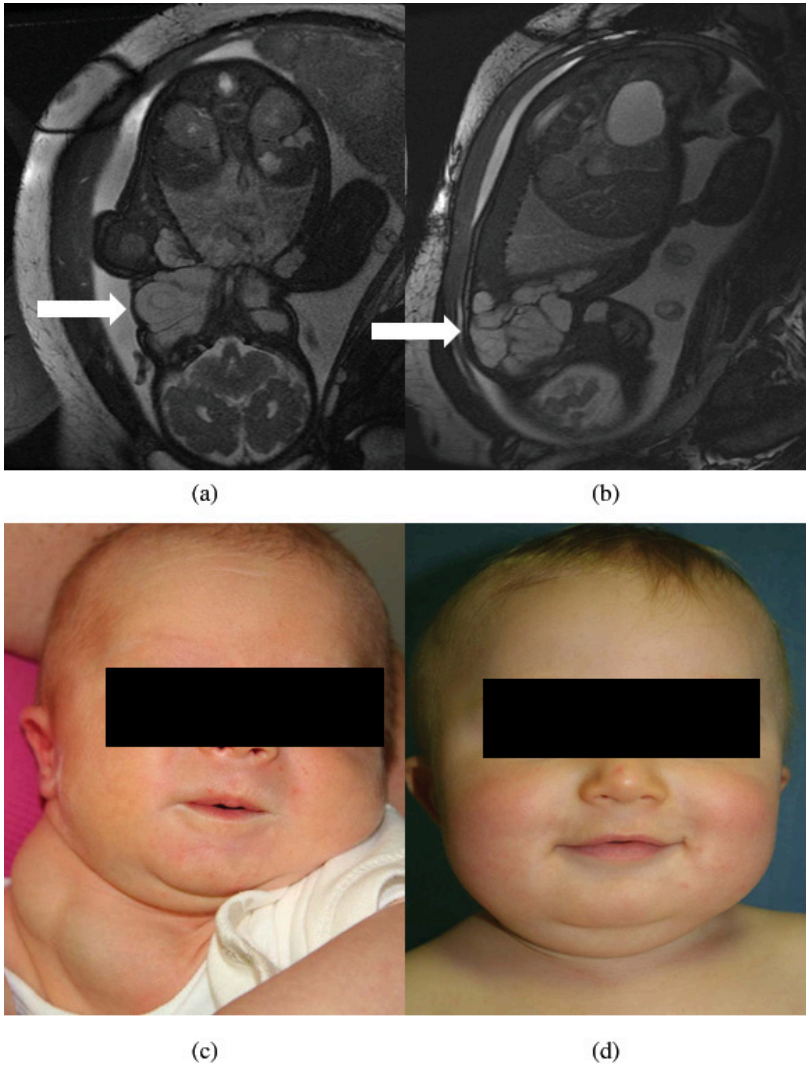


Figure 15. Cervical LM. (a) Coronal prenatal MRI FIESTA sequence shows a fetus with a right cervical LM (*arrows*). (b) Macrocysts are more clearly delineated on the axial view. (c) Postnatal photo of the same infant with cervical LM at 2 weeks of age. (d) Spontaneous resolution by 11 months.

proptosis. Lower facial LMs are often associated with skeletal overgrowth, macroglossia, and macrocheilia.[7] LMs of the lingual base and oral floor can cause chronic airway problems, recurrent infection, and functional issues related to



Figure 16. Cervicofacial LM. Infant with a diffuse LM involving bilateral mandible, tongue, and floor of mouth requiring tracheostomy due to airway obstruction.

speech, oral hygiene, and malocclusion.[75] Mediastinal LMs frequently accompany cervical or axillary LMs. Diffuse thoracic lymphatic anomalies or rare abnormalities of the thoracic duct or cysterna chyli can manifest as recurrent chylous pericardial and pleural effusions and chylous ascites. LMs of the gastrointestinal tract can cause chronic protein-losing enteropathy resulting in profound hypoalbuminemia. In the pelvis, LMs can cause recurrent infections, constipation, and bladder outlet obstruction. Similar to CMs, LMs of the extremity can result in overgrowth and limb length discrepancy.

Lymphedema is also a type of LM. Lymphedema is characterized by localized accumulation of protein-rich fluid in the interstitial space of skin and subcutaneous tissue, followed by deposition of fat and fibrous tissue.[76] It may be primary (idiopathic) or secondary (acquired). Primary lymphedema comprises a heterogenous group of disorders. The vast majority of patients with primary lymphedema have no family history and present without other signs and symptoms,[77] but some do have a genetic basis. Milroy's disease, a congenital form of lymphedema, is an autosomal dominantly inherited condition which has been linked to chromosome 5q35.3 which codes for a mutation in the vascular endothelial growth factor receptor 3 gene.[78,79] Sporadic forms occur as well. Greater than 90% of patients with Milroy's disease present with lymphedema, predominantly below the knees. Hydrocele occurs in less than 30% of affected men.[62] Intrauterine pleural effusion

and hydrops fetalis can be seen in rare pregnancies in these families.[80,81] Skin biopsy from the swollen feet of patients with Milroy's diease shows the presence of abundant skin lymphatics suggesting malfunction.[82] Meige disease, typically a pubertal onset form of lymphedema, is also an autosomal dominant disorder with variable penetrance and phenotype. Some patients with primary lymphedema of the limbs present with systemic involvement such as intestinal lymphangiectasia, ascites, pleural or pericardial effusions, and pulmonary lymphangiectasia.[82]

Well-localized and superficial LMs can be characterized by ultrasonography (Figure 17). MRI, however, provides the most reliable diagnosis and allows for determination of extent and type of LM (micro- vs. macrocystic). Like all vascular anomalies, LMs are hyperintense on T2 weighted and turbo-STIR images.[83] Macrocystic LMs frequently have fluid-fluid levels due to layering of blood, protein, or both (Figure 18). Cystic rims and septae may enhance with contrast. Microcystic LMs show an intermediate signal on T1 and intermediate to high signal on T2 spin echo sequences.[83] The differential diagnosis of an LM in an infant includes teratoma, infantile fibrosarcoma, and infantile myofibromatosis. Magnetic resonance lymphangiography is a useful method for evaluating the lymphatic channels, especially in the limbs. Conventional contrast lymphangiography has largely been abandoned because of its excessive morbidity and technical

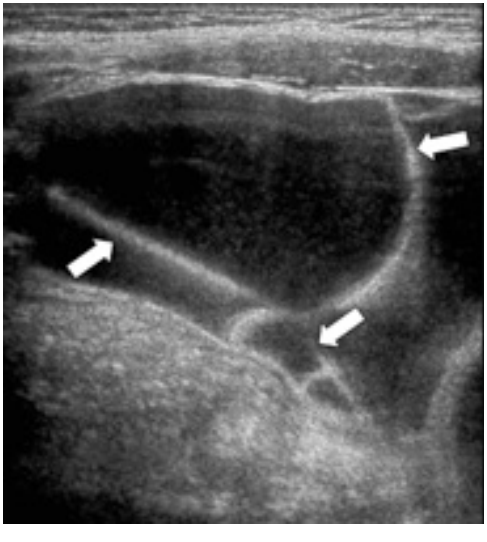


Figure 17. Ultrasonographic image of an intra-abdominal LM in a 2 year-old presenting with vague abdominal complaints. Notice septations separating macrocysts (*arrows*).

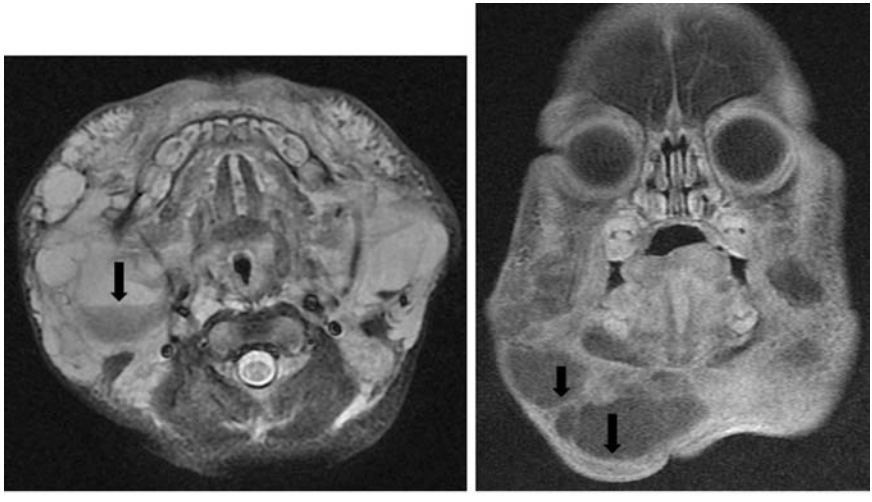


Figure 18. MRI of cervicofacial LM. (a) Axial short T1 inversion recovery image of an extensive cervicofacial LM (same patient as Figure 16). Macrocystic component (*arrow*) with fluid-fluid levels. (b) Coronal T1 fat saturation spin echo image with gadolinium shows contrast-enhancement of septations and rims of cysts (*arrows*).

difficulties in small children; it can be useful, though, to characterize lymphatic anomalies of the thoracic duct and chylous effusions, allowing for localization of abnormal channels or sites of leakage.[84] Lymphoscintigraphy can be used as an adjunct to history and physical examination when the diagnosis of lymphedema is uncertain. It can confirm the diagnosis and delineate the pathogenesis by defining anatomic and functional derangements.[85] Lymphoscintigraphy is also minimally invasive, safe, and reliable and can be performed in infants and children.[86]

Treatment of LMs is varied and must be tailored according to size, location, and extent. The most common complications include bleeding and infection. Intralesional bleeding whether spontaneous or due to local trauma can result in expansion of an LM. On physical examination, the LM can be firm and ecchymotic. Analgesia, rest, and time may be all that are needed. Depending on location or risk for infection, prophylactic antibiotics may be indicated.[3] Intralesional bleeding can also transform a macrocystic LM into a microcystic LM.

LMs can also swell in response to viral or bacterial infection anywhere in the body. Frequently, there are no sequelae to this passive engorgement; however, the rapid onset of localized swelling, tenseness, erythema, and systemic signs of

infection should prompt initiation of antibiotics. Infection of previously occult retroperitoneal and mesenteric LMs can present in frank septic shock. Bacterial cellulitis is a serious complication particularly of cervicofacial and perineal LMs. Infection in a cervicofacial LM can be life-threatening due to obstruction of the airway and may require emergent intubation. Oral antibiotics may be effective, but prolonged intravenous antibiotics are often necessary. The choice of antibiotic therapy is based on the presumption of oral pathogens in the head and neck or enteric organisms in the abdomen and perineum.[60]

The two strategies for treating LMs are intralesional sclerotherapy and surgical resection. Sclerotherapy works by causing direct endothelial damage with subsequent luminal obliteration and fibrosis.[87] Success depends in part on the efficacy of the sclerotic agent. Common sclerosants include pure ethanol, sodium tetradecyl sulfate, and doxycline. Ethanol has long been considered an effective sclerosing agent, however, injection is painful often requiring general anesthesia and post-treatment analgesics. A retrospective review of doxycycline has shown that it is a safe and effective sclerosant, producing an 83% reduction in size with high patient satisfaction.[88]

Intralesional sclerotherapy works best for LMs with macrocystic components and can even be curative for well-localized lesions. Multiple punctures, aspirations, and injections are frequently necessary. For more diffuse and complex lesions, staged sclerotherapy sessions can minimize toxicity and discomfort while still achieving a significant reduction in size. Microcystic LM is unfortunately less responsive to intralesional sclerotherapy. Superficial lymphatic vesicles can be treated with local intravesicular injection, although leakage generally resumes in 6 to 24 months. Intralesional sclerotherapy should be performed by knowledgeable personnel familiar with the inherent risks and discomforts such as need for general anesthesia, post-therapy swelling especially near the airway or in contained anatomical compartments, and potential toxicities of the sclerosants. Systemic ethanol absorption can cause cardiac arrest, pulmonary vasoconstriction, or systemic hypotension. Edema and pain at the site of sclerotherapy are expected consequences. The duration of post-treatment symptoms is believed to correlate to an improved therapeutic effect. Unfortunately, however, many LMs re-expand after treatment and require multiple sclerotherapy sessions. Other complications include skin and soft tissue necrosis, blistering, and local neuropathy.

The only potential for a definitive cure of an LM is surgical resection. Staged excisions are often required.[3] In each resection, a surgeon should aim to limit the resection to a defined anatomic region, perform as thorough a dissection as possible without injuring vital structures, minimize blood loss, and perform closed

suction drainage of the resection cavity. Surgeons must also be committed to reoperation as the "recurrence" rate after incomplete excision is 40% and 17% after macroscopically complete excision.[89] Recurrence after apparently thorough excision is thought to be due to growth and expansion of affected lymphatics in the remaining, seemingly normal appearing tissue. After resection, typical cutaneous "warty" vesicles can develop, seen in the scar. These can be treated by intravesicular sclerotherapy, cauterization, laser coagulation, or scar excision.

LMs in each anatomic area demand specialized surgical expertise. Surgical resection of cervicofacial LMs with maxillary and mandibular overgrowth can require staged orognathic procedures to improve bite and speech impediments. Cervical and axillary LMs demand experience in dissection of the brachial plexus. Mediastinal LMs can be challenging due to proximity near the great vessels and vagus and phrenic nerves. Anatomical understanding of the ischiorectal fossa and sciatic nerve is necessary for excision of pelvic and anorectal lesions. A nerve stimulator can be a useful adjunct to prevent injury.[13] Gastroenterologists are vital to providing thorough evaluation of the GI mucosa when evaluating for intestinal LM. A symptomatic focal GI LM is sometimes cured with segmental bowel resection. Sclerotherapy preceding resection can shrink LMs resulting in a less morbid surgical procedure. The resultant scarring can make dissection of important neurovascular structures in a previously sclerosed area challenging.

Venous Malformation

Venous malformations (VMs) are the most common of all vascular anomalies. Although present at birth, they may go unrecognized until later in life depending on location. Commonly incorrectly labeled as "cavernous hemangioma", VMs are slow-flow lesions consisting of venous channels that can develop anywhere in the body. They commonly appear as soft, bluish, easily compressible masses. VMs grow proportionately with the child and can expand slowly over time. They are variable in their presentation presenting as simple varicosities and ectasias, discrete masses, or as complex collections of channels permeating any tissue or organ system. Phlebothrombosis is common and can be associated with pain. Phleboliths can also be easily palpated in many VMs. Patients frequently complain of pain and stiffness in the area of the VM, especially with wakening in the morning.[3] Histologically, VMs are composed of attenuated thin-walled, dilated vascular channels. The mural architecture is distorted due to a paucity of and clumping of vascular smooth muscle cells which may be responsible for the progressive, gradual expansion of VMs. There is often evidence of clot formation and fibrovascular ingrowth.

The majority of VMs, greater than 90%, are sporadic. Somatic mutations in the tyrosine kinase receptor TIE2 have been discovered in approximately 50% of sporadic VMs.[90] Only 1–2% of VMs are due to an autosomal dominantly inherited form termed cutaneomucosal venous malformation. Cutaneomucosal VM has been shown to be mediated by two mutations in the *TEK* gene, encoding for TIE2.[91,92] The VMs appear as tiny-to-several centimeter-sized dome-shaped lesions. The VMs are progressive and the degree of venous irregularity increases with age. Rapid expansion can be observed during puberty or after trauma. Glomovenous malformations comprise 5% of VMs and have an autosomal dominant pattern of inheritance.[62] These superficial lesions may be scattered occurring as multiple blue nodules or as a confluent plaques. Glomovenous malformations usually are deep-purple in color and have a matted cobblestone appearance frequently affecting the trunk or extremities.[27] Glomovenous malformations are caused by loss-of-function mutations in glomulin which disrupts differentiation of vascular smooth muscle cells towards rounded "glomus" cells which are seen lining the ectatic vascular channels.[93] The glomus cells express smooth muscle actin and vimentin. Cerebral cavernous malformation is familial. The cerebral lesions are characterized by dilated channels with endothelial cell layers that have defective tight junctions. The venous malformations occur in the brain, retina, and spinal cord and can result in headaches, seizures, and cerebral hemorrhage. A subset of individuals with cerebral cavernous malformation has cutaneous hyperkeratotic capillary-venous lesions.[94]

Like all vascular anomalies, complications of VMs are related to their location. Cervicofacial VMs are often unilateral and can produce distortion of facial features (Figure 19), exophthalmia, dental malalignment, and obstructive sleep apnea. VMs of the extremities can result in leg length discrepancy or hypoplasia of the affected side due, in part, to disuse.[27] VMs in the synovial lining of the knee can cause episodic pain as a result of repeated bloody effusions. Hemarthrosis can be debilitating and can ultimately lead to degenerative arthritis.[3] Intraosseous VMs cause structural weakening of the bony diaphysis, predisposing to pathologic fracture.

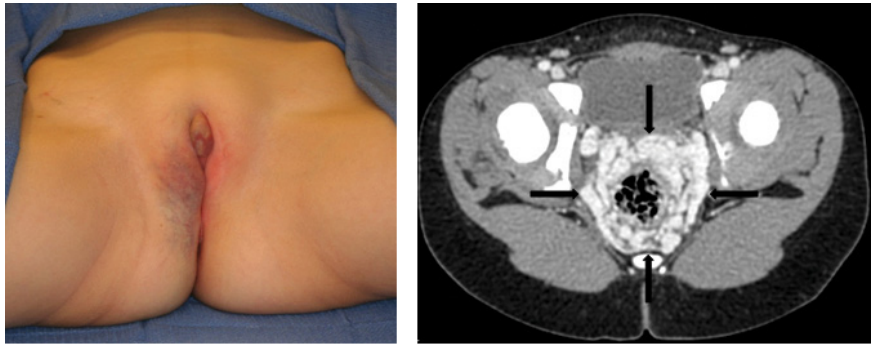
VMs of the GI tract can be solitary or multifocal and variably involve any or all layers of the bowel wall. The size ranges from minute to massive. VMs can be located anywhere along the GI tract, but the majority occurs as transmural lesions of the left colon and rectum with variable local extension into pelvic structures.[3,39,95] GI VMs can go unrecognized until they manifest with GI bleeding. Occasionally, external cues, such as bluish discoloration in the perineum, can indicate the presence of a rectal VM in an infant (Figure 20). GI VMs, particularly of the foregut and hindgut, can be associated with central



Figure 19. Facial VM in an infant. (a) Anterior view shows distortion of left upper lip. (b) Lateral view shows faint bluish hue indicative of VM. (c) Gradual expansion of the VM at 2 years of age. The tongue, floor of mouth, and buccal mucosa are involved. (d) Tracheostomy was necessary due to airway compression.

mesenteric and portal venous anomalies. The presence of a rectal VM and associated ectatic mesenteric veins is a risk factor for developing portomesenteric venous thrombosis.[96]

Blue-rubber bleb nevus syndrome (BRBNS) is a rare, sporadic disorder consisting of multifocal venous malformations in the skin, soft tissues, and GI tract. The cutaneous lesions of BRBNS are small, measuring 1–2 cm and blue to purple in color which can range from several to hundreds.[97] The cutaneous VMs are commonly found on the palms and soles of the feet (Figure 21). Often, there is a large isolated cutaneous VM. Of greater clinical significance, however, are the GI VMs. These lesions are distributed throughout the gut, most commonly in the small bowel, but can be encountered in the stomach, colon, mesentery, liver, gallbladder, and retroperitoneum. Patients usually exhibit chronic GI bleeding resulting in anemia, requiring lifelong iron replacement and repeated blood transfusions. Massive sudden hemorrhage is rare. GI VMs are usually diagnosed during



(a) (b)

Figure 20. (a) Faint discoloration in the perineum can indicate the presence of an underlying vaginal or rectal VM. Further investigation in this infant revealed a rectal VM. (b) Axial image of a contrast enhanced CT scan of the same patient shows VM (*arrows*) surrounding the rectum.



(a) (b)

Figure 21. Photos of blue rubber bleb nevus syndrome. (a) Characteristic dome-shaped plantar lesions. (b) Serosal view of VMs in the small intestine.

endoscopy. In addition, the polypoid GI VMs of BRBNS can also cause intussusception and volvulus.[98]

VMs can alter coagulation profiles, especially when extensive. Constant activation of coagulation due to blood stagnation in abnormal venous channels leads to the production of thrombin and conversion of fibringogen into fibrin. The resultant fibrinolysis causes an elevation in fibrin degradation products and can be measured by obtaining a D-dimer level. This process has been called localized intravascular coagulopathy (LIC).[99] A more severe form of LIC with not only elevated D-dimer levels but also low fibrinogen levels has been observed in extensive VMs of the extremity.[100,101] Prior to any interventional procedure, coagulation studies (prothrombin time, activated partial thromboplastin time, and D-dimer and fibrinogen levels) should be reviewed. Consideration should be given to treatment with low-molecular weight heparin during the perioperative period to improve the hematologic status for those patients with elevated D-dimer levels. Platelet counts can be minimally diminished, in the 100,000–150,000/mm^3 (unlike Kasabach-Merritt phenomenon).[99]

Radiologic modalities useful for the diagnosis of VMs include ultrasonography, MRI, and venography. MRI is the most informative to document the location and extent. Characteristic MRI findings include focal or diffuse collections of high T2 signal, often containing identifiable spaces separated by septations (Figure 22). Fluid-fluid levels may be present. Contrast enhancement (albeit sometimes slow) of the vascular spaces of VMs distinguishes them from LMs. Phleboliths are often seen as signal voids on all MRI sequences and are most prominent on gradient images. Flow-sensitive sequences show no high flow vessels within or around the lesions. Magnetic resonance venography is useful to clearly delineate deep venous anatomy, especially of the extremity.[21] VMs appear as soft, compressible masses with monophasic low-velocity flow on Doppler ultrasonography.[27]

Indications for treatment of VMs include pain, functional loss, bleeding, and appearance. Therapuetic modalities include compression, sclerotherapy, resection, and a combined approach. No pharmacologic agents will induce involution of a vascular malformation. The unfortunate persistent use of the inappropriate term "cavernous hemangioma" to describe VMs results in some patients receiving medications which have no potential for benefit and some risk of toxicity. The term "cavernous hemangioma" should be abandoned. It has no appropriate use.

Conservative management with graded elastic compression aids in reducing swelling and pain in VMs of the extremities. A garment can be worn while upright during the day and removed during recumbency. Intralesional sclerotherapy is the



Figure 22. MRI evaluation of a VM of the knee. Coronal fast spin-echo inversion recovery image shows diffuse involvement of the quadriceps muscle with pathognomonic phleboliths (*arrows*).

mainstay of interventional treatment for most symptomatic VMs. Sclerosing agents are similar to those used for LMs. Large VMs are accessed by direct puncture and the sclerosant is injected under fluoroscopy with the use of compression or tourniquets to limit venous drainage and prevent the systemic delivery of the sclerosant. These procedures should be performed by an experienced interventional specialist. Local complications of sclerotherapy include blistering, full-thickness cutaneous necrosis, and nerve injury.[102] Systemic complications include hemolysis, sudden pulmonary hypertension, and cardiac and renal toxicities. Cure with sclerotherapy is rare since many VMs will recanalize and expand after treatment. Multiple sclerotherapy sessions are often required. Results from treatment are usually stated in terms of patient satisfaction related to a decrease in pain, an improvement in appearance, or both. Excision of well-localized VMs is usually successful. For larger lesions, it may be preferable to shrink them with sclerotherapy prior to surgical resection.[102] In some cases, staged subtotal resections are necessary. GI VMs of the bowel wall resulting in transfusion dependent bleeding

should be evaluated for surgical resection. Complete resection of multifocal VMs of BRBNS provides the only chance for possible cure. Bowel resection is rarely indicated. Rather, wedge excision and polypectomy by intussusception of successive lengths of intestine are the preferred methods of resection.[97] The location of the lesions can be identified by intraoperative enteroscopy at the time of resection. Colorectal VMs causing significant bleeding may be treated with colectomy, anorectal mucosectomy, and coloanal pull-through.[103]

Arteriovenous Malformation

Arteriovenous malformations (AVM) are fast-flow malformations that develop between the 4th and 6th week of gestation due to defective embryonic vasculogenesis and angiogenesis. The result is a collection of abnormal communications between arteries and veins (shunts) which bypass the high-resistance capillary bed. These shunts form the epicenter of the AVM, called the nidus. It is well known that an AVM can enlarge rapidly after proximal ligation.[104,105] Collateral vessel formation also increases the size and extent. Most AVMs are sporadic, however, they can be inherited in an autosomal dominant pattern as part of the disorder, capillary malformation-arteriovenous malformation (CM-AVM), caused by mutations in *RASA1*.[106] The hallmark of CM-AVM is the randomly distributed, pink to red, multifocal CMs (Figure 23) which can be accompanied by a fast-flow vascular lesion such as an intracranial AVM, extrcranial AVM of the face and extremities, Parkes Weber Syndrome, or a vein of Galen aneurysmal malformation in one-third of patients.[107]



Figure 23. Characteristic appearance of multifocal CMs which are seen in CM-AVM.



Figure 24. AVM of a foot. A faint pink stain over the dorsal aspect of the left foot is present. The left foot is also slightly larger than the right.

Intracranial AVMs are more common than extracranial AVMs in the head and neck region. Other areas affected by AVMs in decreasing frequency are the limbs, trunk, and viscera. AVMs are usually noted at birth but are commonly misdiagnosed as CM or IH. Occasionally, an AVM will present at birth with life-threatening high-output cardiac failure. More frequently, AVMs become evident during childhood and adolescence as a warm, pink cutaneous patch with an underlying palpable thrill or bruit (Figure 24). With continued growth, the AVM can become more mass-like accompanied by ulceration of the overlying soft tissue, bleeding, pain, or heart failure. The natural history of AVMs can be documented by a clinical staging system introduced by Schobinger (Table 2).[105]

Ultrasonography and Doppler imaging are efficient tools to detect fast flow of an AVM and can help distinguish it from a VM. IH also exhibit fast flow, however, a thorough history and physical examination should distinguish between them. Radiographically, AVMs are characterized by the presence of dilated feeding arteries and draining veins. The enlarged vessels are seen as areas of contrast enhancement on CT, signal flow voids (black tubular structures) on spin echo MR images, and as areas of signal enhancement (white tubular structures) on gradient sequences including MR angiography. The nidus may or may not be visible. There is not a parenchymal mass as seen with IH.[21] Edema, increased fat, muscle

Table 2. Clinical staging system for arteriovenous malformation.

Stage	Clinical findings
I (Quiescence)	Pink-bluish stain, warmth, arteriovenous shunting by Doppler
II (Expansion)	Stage I plus enlargement, pulsations, thrill, bruit, tense and tortuous veins
III (Destruction)	Stage II plus skin ulceration, tissue necrosis, bleeding, pain
IV (Decompensation)	Stage III plus cardiac failure

enlargement, and bony changes are variably noted on imaging. Superselective angiography can be used for diagnosis, however, due to its invasiveness, it should not be performed until intervention is scheduled.[3]

The majority of AVMs will require treatment due to continued life-long expansion. The mainstays of treatment are angiographic embolization with or without surgical resection (Figure 25). The timing of intervention for AVMs is controversial. Treatment is rarely indicated during infancy and childhood, except in rare cases of postnatal heart failure. After a complete diagnostic evaluation, infants and children should be followed annually. Extremity AVMs can result in a limb length discrepancy. Resection of AVMs in infancy and childhood is rarely advocated. The usual recommendation is to observe stage I and stage II AVMs. Intervention is usually delayed until stage III when distortion or symptoms such as pain and ulceration develop. Regardless of stage or method of treatment, proximal feeding arteries must not ever be ligated or embolized. Even though ligaton may result in temporary improvement of bleeding and heart failure, it will preclude any future embolizations. Furthermore, the nidus of the AVM will recruit nearby arteries resulting in continued growth and expansion.[108]

Angiography should precede interventional therapy or surgical extirpation. Superselective arterial or retrograde venous embolization can ameliorate pain, bleeding, and heart failure.The preferred treatment of AVMs consists of arterial embolization for temporary occlusion of the nidus followed by surgical resection 2–3 days later. Preoperative embolization diminishes bleeding but does not diminish the limits of resection. The surgical goal is complete resection of the nidus and overlying soft tissue and skin to minimize the chances of recurrence. The best results are seen with well localized AVMs. Follow-up evaluation with physical examination complemented by MRI or ultrasongraphy is necessary to evaluate for recurrence. Regrettably, many AVMs are extensive and permeate all



Figure 25. Angiography and embolization of an AVM in the foot. (a) Anterior tibial arteriogram with digital subtraction delinates the nidus of the AVM (same patient as in Figure 24). (b) After superselective embolization, the nidus has been occluded. (c) Characteristic appearance of embolic material post-embolization.

tissue planes rendering them unresectable. Embolization can be palliative. Amputation is a last resort for difficult to manage AVMs of the extremities.[3,27,108] Pharmacologic therapies aimed at angiogenesis inhibition and remodeling are being explored given the difficulty for cure with other modalities.

COMPLEX-COMBINED VASCULAR MALFORMATIONS

Combined vascular malformations are classified as either slow-flow or fast-flow. These more complex disorders are usually associated with hypertrophy and skeletal overgrowth.

Capillary-Lymphaticovenous Malformation

Klippel-Trenaunay syndrome is a well-known eponym for capillary-lymphaticovenous malformation (CLVM).[3] Unfortunately, it is often incorrectly



Figure 26. CLVM of bilateral lower extremities. Note the hypertrophy of the right leg and the CM on the lateral aspect of the left leg.

called Klippel-Trenaunay-Weber syndrome suggesting a relation to Parkes Weber syndrome, a fast-flow malformation. CLVM, diagnosed prenatally or at birth, is associated with soft tissue and skeletal hypertrophy usually of a single lower extremity but can be bilateral, involve the trunk, or upper extremities (Figure 26). The CMs are often multiple, occurring predominantly on the lateral side of the extremity, buttock, or thorax. In the newborn, the CM component is macular. As the infant ages, lymphatic vesicles erupt through the CM. Lymphatic anomalies can present as lymphedema, lymphatic cysts (macro- or microcystic), or lymphatic hypoplasia. CLVM of the lower extremity is frequently associated with a large lateral vein, termed the marginal vein of Servelle, which is a persistent embryonic vessel. Branches of the lateral vein become prominent due to incompetent valves. Anomalous deep system veins may be hypoplastic or absent. Thrombophlebitis occurs in 20–45% [109,110] of patients and pulmonary embolism in 4–25%.[111] Limb hypertrophy is usually present at birth and tends to be progressive. Infrequently, patients with classic CLVM have a short or hypotrophic limb.

Pelvic involvement is common with CLVM of the lower extremity. The lymphatic and venous components can involve the perineum, urethra, external genitalia, bladder, and rectum. Many patients remain asymptomatic, however, some present with recurrent infection with gut flora, hematuria, bladder outlet obstruction, hematochezia, and constipation. Portomesenteric venous thrombosis has been observed in patients with a rectal venous malformation.[96] The venous abnormalities in patients with CLVM frequently extend proximally from the leg veins and can include the iliac veins and inferior vena cava. CLVM of the torso and arms frequently involves the mediastinum or retropleural space.

Imaging plays an important role in the evaluation of patients with CLVM. Serial plain radiographs are used to evaluate and follow limb-length discrepancies. MRI and magnetic resonance venography are used to determine the specific type of malformation as well as distribution (Figure 27). Findings are variable given the wide range of severity. Hypertrophic fatty tissue in areas of overgrowth is seen on MRI. CLVM of the lower extremity typically presents with macrocystic LMs in the pelvis and thigh. Microcystic LMs are predominantly encountered on

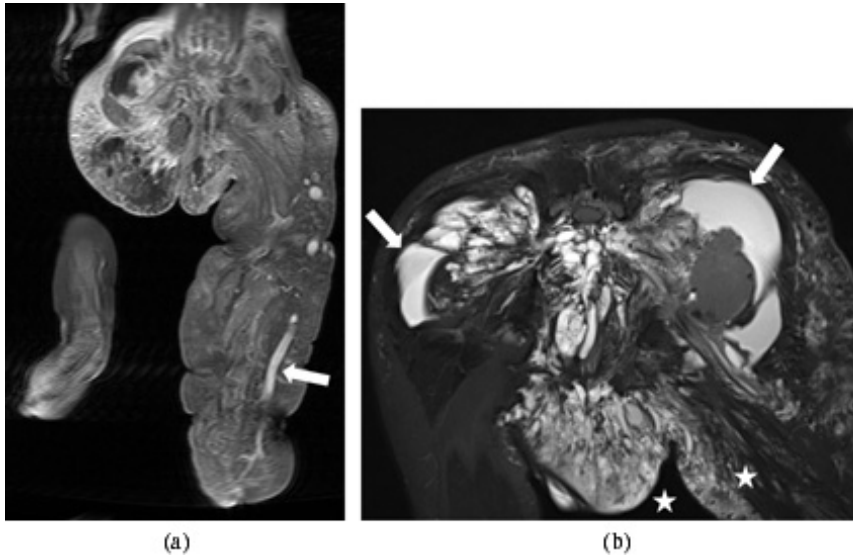


Figure 27. MRI of CLVM. (a) Coronal TI-weighted post-gadolinium image showing hypertrophy of fatty tissue and enlargement of left lower leg. Marginal vein of Servelle is seen (*arrows*). (b) Coronal short T1 inversion recovery image through the pelvis shows macrocystics in the buttocks (*arrows*) and microcysts in the scrotum and thigh (*stars*).

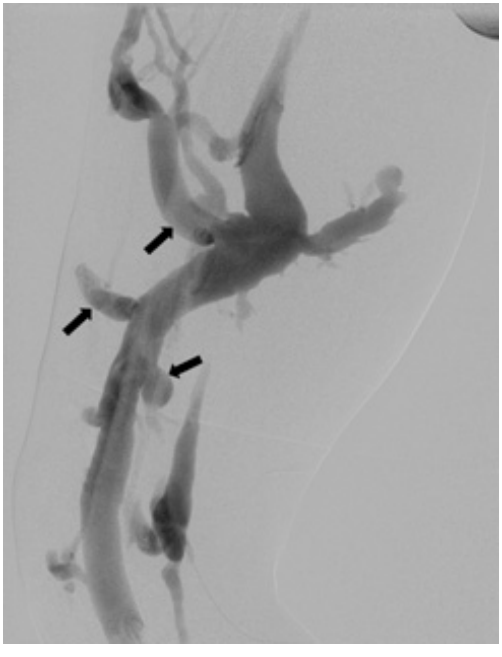


Figure 28. Lateral projection of a venogram of the right upper thigh in a patient with CLVM showing a capacious marginal vein of Servelle with large perforators (*arrows*).

the abdominal wall, buttock, and distal extremity. Magnetic resonance venography can delineate the anomalous venous channels of the extremities, pelvis, rectum, and mesentery. The marginal vein of Servelle can be seen coursing along the lateral calf and thigh. Venography may be useful for mapping the venous drainage of the extremity when resection or sclerotherapy is being considered (Figure 28).

Treatment for CLVM is usually conservative since there is no single curative procedure. Compression is the hallmark of conservative management for CLVM of the extremity when there is venous insufficiency or a lymphedema component. Small lymphatic vesicles that do not improve with compression can be sclerosed. Sclerotherapy can also be used to treat focal VMs as well as macrocystic LMs. Multiple sessions are usually necessary as the malformations tend to recur. Persistent embryonic and other anomalous veins of the lower extremity frequently cause pain and heaviness of the affected extremity and serve as a source for pulmonary emboli. Patients with massive veins with direct connections to the inferior vena cava or iliac veins are at exceptionally high risk for pulmonary

embolism. Patients with this pattern should be considered for pre-emptive ablation or resection.

Surgical resections are tailored to symptoms. Gross foot enlargement that impairs ambulation and the ability to wear shoes requires orthopedic corrective procedures and partial amputations to permit the use of custom footwear.[108] These procedures can be performed during infancy. Staged, contour resection of the calf, thigh, buttock, and perineum can improve function and decrease infection. Leg length discrepancy should be followed annually by an orthopedic surgeon. Leg length discrepancy of less than 0.5 cm is usually asymptomatic. Shoe lifts are recommended to prevent limping and scoliosis if the discrepancy is greater than 1.5 cm at 2 years of age. If necessary, epiphysiodesis at the distal femoral growth plate is performed around 12 years of age. It is not necessary to correct upper extremity limb-length discrepancies. Truncal and thoracic wall CLVM can be resected in stages. The mediastinal and intrathoracic components should be treated only if symptomatic. Rectal venous or combined lymphaticovenous malformations resulting in transfusion dependent anemia can be treated with colectomy, anorectal mucosectomy, and coloanal pull-through.[103]

Postoperative healing is often problematic for CLVM regardless of location. Prolonged closed-suction drainage should be expected. Perioperatively, anticoagulation and potentially temporary inferior vena cava filter placement to prevent deep venous thrombosis and pulmonary embolism should be considered for CLVM patients requiring significant surgical procedures.[108]

CLOVES Syndrome

Congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal anomalies is a newly described syndrome.[112,113] The main features of this syndrome are truncal lipomatous masses, vascular malformations, and acral/musculoskeletal anomalies. CLOVES syndrome is usually obvious at birth due to the presence of a truncal lipomatous mass which can be mistaken for LM (Figure 29). Unlike LM, however, the lipomatous masses in CLOVES are hypervascular and exhibit rapid postresection recurrence. These lesions are also infiltrative and frequently extend from the trunk into adjacent areas such as the retroperitoneum, medastinum, and pleural cavity. Many of the lipomatous growths involve the spinal column and present with extension of the mass into the epidural space which can result in compression of the cord, thecal sac, and nerve roots. Of the initial 25 documented cases, all have had slow-flow vascular malformations.[112,113] CMs can be seen on the trunk. LMs and vesicles are frequently seen

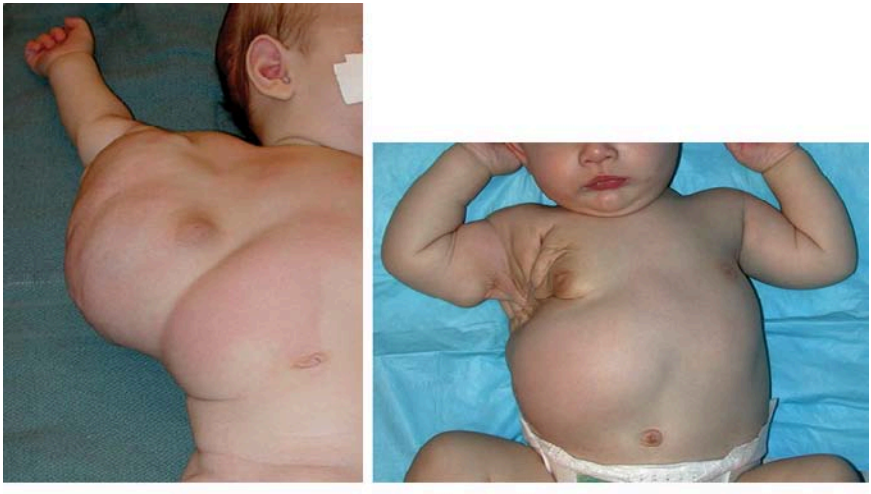


Figure 29. Infant with CLOVES syndrome. (a) Preoperative photo with characteristic lipomatous truncal masses of the right axilla and trunk which can easily be mistaken as LM (as in Figure 14). (b) Postoperative photo after resection of axillary component.

within and around the truncal lipomatous masses. VMs, in the form of phlebectasia, can course over or around the truncal lesions. Spinal and paraspinal AVMs have been observed. Acral deformities include large, wide feet and hands, macrodactyly, and a wide sandal gap. Scoliosis, neurological, renal, and musculosketal malformations can also be present. The truncal lipomatous growths can be seen antenatally.[112]

Parkes Weber Syndrome

Parkes Weber syndrome is characterized by the presence of a confluent or patchy CM with an underlying complex AVM that permeates an extremity. The malformation is evident at birth with symmetric enlargement of the involved limb, usually a lower extremity. The ipsilateral buttock or trunk may be involved.[107] The stained areas are usually warm. The diagnosis can be confirmed by the detection of a bruit or thrill. Parkes Weber syndrome was previously believed to be sporadic and nongenetic. Mutations in RASA1, either *de novo* or inherited, have been identified in those patients with multifocal CMs.[107] On imaging, the affected extremity usually has fusiform subcutaneous, muscular, and bony overgrowth with diffuse microfistulas. The bony overgrowth can result in a limb length discrepancy.



Figure 30. Photo of a patient with Parkes Weber syndrome of the right leg. Notice geographic CM covering the distal portion of the right leg with fusiform, symmetric hypertrophy of the entire leg and foot.

Generalized arterial and venous dilation can be seen on angiography and venography. Angiography can demonstrate discrete arteriovenous shunts, particularly around joint structures.[27] Parkes Weber syndrome is frequently misdiagnosed as either a CM with overgrowth or a CLVM due to the prominence of superficial veins. The distinction is important, though, given that 30% of patients with Parkes Weber syndrome exhibit signs of cardiac volume overload.[107] The cardiac overload is generally well tolerated, however, in rare instances, cardiac failure can develop secondary to shunting through the arteriovenous fistulas. Infants and children are observed annually with monitoring for axial overgrowth, signs of cardiac failure, and cutaneous problems related to ischemia. Ultrasonography and color Doppler evaluation of the arterial flow can be performed in infancy. Treatment is predicated on symptoms. Repetitive superselective embolization is the mainstay of therapy.[3] Though reduction of flow may be accomplished with embolization, significant reduction of cardiac failure may require limb amputation.

CONCLUSIONS

Over the past 3 decades, the cloud of terminologic confusion has been supplanted by a standardized classification system allowing for improvements in diagnostic accuracy. The formation of multidisciplinary vascular anomaly centers combines medical, surgical, radiologic, and pathologic expertise, facilitating treatment and management of what were previously unsolvable problems for many patients. Continued collaboration between clinicians and basic scientists is essential for continued advancements in the field.

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CHAPTER 16

SACROCOCCYGEAL TERATOMA

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INTRODUCTION

Sacrococcygeal teratomas (SCT) are the most common solid neoplasm of the neonate.[1] Teratomas arise from totipotential cells. Primordial germ cells give rise to some teratomas. They originate in the area of the allantois of the embryonic yolk sac endoderm and migrate to the genital ridge of the posterior abdominal wall at 4–5 weeks' gestation. Unusual locations of extragonadol germ cell tumors may be attributed to aberrant migration of these cells. Extragonadol germ cell tumors are most commonly found in the sacrococcygeal region followed by the anterior mediastinum, pineal gland, retroperitoneum, and neck. SCT may arise from totipotential cells in the primitive streak as opposed to primordial germ cells. Teratomas are composed of cells from more than one germ cell layer and often all three (ectoderm, endoderm, and mesoderm). Extragonadol tumors tend to occur primarily in neonates and young children. Gonadal tumors occur more commonly in adolescents.[2] The sacrococcygeal location is said to be the most common site for a teratoma in childhood accounting for up to 60% in several series.[3] That claim is arguable since ovarian teratomas, albeit quite rare in neonates, are much more common than SCT. SCT is widely recognized as the most common solid neoplasm of the neonate. The sacrococcygeal location and the ovary are the two most common sites for teratomas overall in childhood. The predominance of the sacrococcygeal location in multiple pediatric series may represent a selection bias in tertiary centers.

SCT are located at the caudal aspect of the spine and can be quite obvious and dramatic. These arise much more commonly in girls with a ratio of 3–4:1.[4]

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The incidence is thought to be approximately 1 in 40,000 live births. The aim of this chapter is to describe the presentation, management, and outcomes of SCT.

PRESENTATION AND DIAGNOSIS

The clinical presentation of these lesions has changed due to the advancement of prenatal imaging. The most common clinical presentation had been a large exophytic skin-covered mass arising from the sacrococcygeal region in the newborn. The anus and vagina are often pushed anteriorly (Figure 1). Larger tumors may have evidence of rupture or skin ulceration. Of importance though, Beckwith *et al.* composed a list of up to 20 entities that can enter into the differential diagnosis.[5] Most of these are very rare but it is important to consider them. The main lesion to be ruled out is a meningocele. Although they usually occur more superiorly and are covered by dura, they can be lower and skin covered. On close physical examination, it is thought that gentle pressure on the lesion can produce bulging of the fontanelle in the case of meningocele. Lipomas, lymphatic and vascular malformations, and remnants of the vestigial tail are also possibilities in this location. Associated congenital anomalies can occur in up to 18% of cases. They can involve the musculoskeletal, renal, or nervous systems most frequently.[6] Lesions that are predominantly or completely pelvic or internal will often present later since they are not obvious on examination at birth. They usually are identified by the age of four.

The morphology, location, and extent of SCT can vary significantly. Their composition can range from primarily cystic to mostly solid. There may be varying degrees of external exophytic component and internal pelvic-abdominal extension.



Figure 1. Large exophytic skin covered mass. Anus is pushed anteriorly.

An important classification was developed in the 1970s and it is still used today when describing SCTs. Altman *et al.* surveyed the membership of the American Academy of Pediatrics' Surgical Section in 1973 and were able to accumulate data from over 400 cases. A classification was devised that divided the lesions into four distinct anatomic types.[6] Figure 2 illustrates this and shows the four types as: (I) predominantly external; (II) external but with a significant intrapelvic component; (III) mass

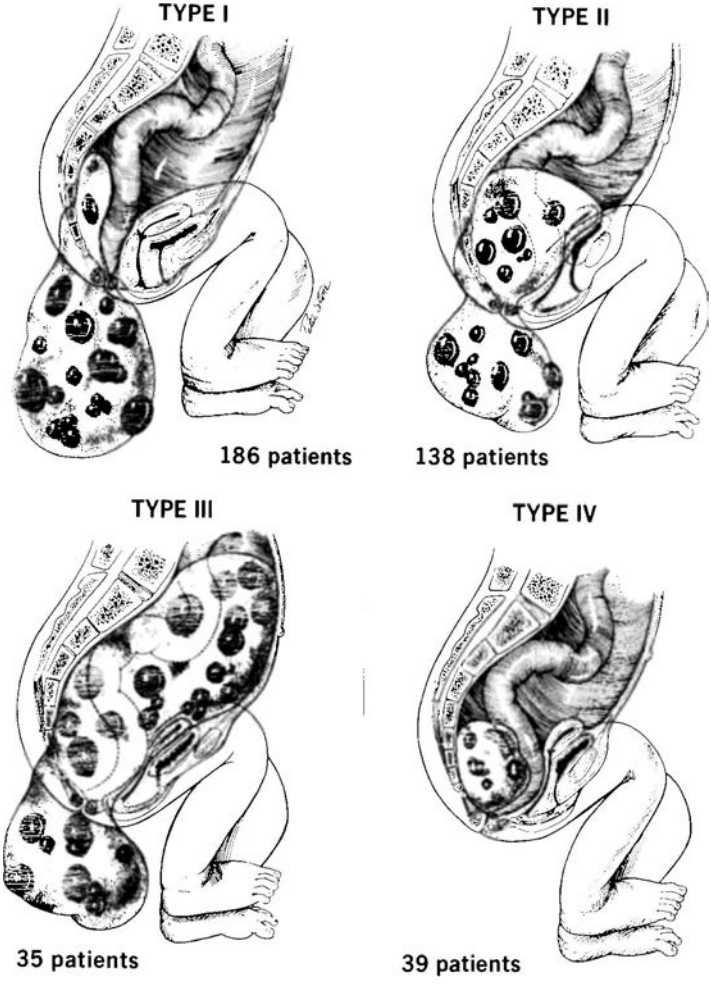


Figure 2. Illustration of the Altman Classification of Sacrococcygeal Tumors. The numbers for each type of SCT represent the results of the AAP survey. Borrowed from Altman PR, *et al.* (1974) Sacrococcygeal teratoma: American Academy of Pediatrics Surgical Section Survey 1973. *J Pediatr Surg* **9**: 389–398. Reprinted with kind permission from Elsevier.

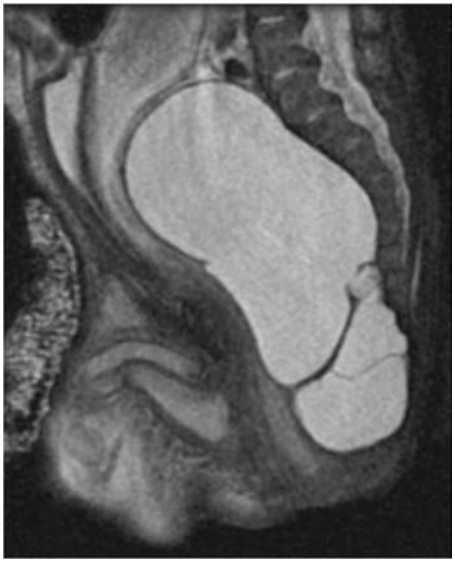


Figure 3. MRI of large Type IV sacrococcygeal teratoma.

predominantly intrapelvic and abdominal with a minor external component as well; (IV) presacral only with no external component. Types I and II were found much more frequently making up a combined total of 82% of all the tumors.

Physical examination must include rectal examination to feel for a presacral pelvic mass or extension. An ultrasound of the lesion as well as the abdomen and pelvis can further characterize the consistency and extent of the mass. That is usually the first study done. Plain radiographs reveal calcifications that can be present within the tumor. Sacral anomalies can be visualized. If a significant pelvic component is found by ultrasound, MRI (Figure 3) can be helpful to further elucidate its precise anatomy including the uncommon circumstance of spinal canal invasion. It is an important study if the child is manifesting any neurological symptoms or signs. Also, it is particularly helpful to discriminate between the meningocele and primarily cystic teratoma if the distinction between these is uncertain. However, it is not considered a mandatory preoperative study especially if a CT scan has been obtained.

PRENATAL DIAGNOSIS AND THERAPY

SCTs tend to be identified on prenatal ultrasound at around 20-weeks gestational age on average. They have a disorganized appearance with solid, cystic, or mixed



Figure 4. Fetal U/S of large sacrococcygeal teratoma coming off spine.

elements. They can also appear quite vascular. They are located at the distal aspect of the spine and have a characteristic appearance[7] (Figure 4). Magnetic resonance imaging (MRI) provides additional and important information and helps identify the intrapelvic component.[8] Both modalities, as well as fetal echocardiography, are recommended for evaluating these fetuses. Serial ultrasounds and echocardiograms are used to follow the fetus who has a SCT.

Most newborns with SCT tend to do quite well after resection. However, SCTs diagnosed prenatally have a poor prognosis with a mortality rate of up to 50%.[9,10] This is thought to be multifactorial. First, mass effect from a larger tumor or one that grows rapidly can have deleterious effects on the fetus. This can be compounded by polyhydramnios in these pregnancies. Preterm labor can result with its multiple associated morbidities including pulmonary immaturity. Dystocia can lead to tumor rupture and hemorrhage, especially during delivery. This often results in a fatal outcome. There are also significant hemodynamic effects caused by a large lesion. These are thought to be due to the large blood flow with resultant arteriovenous shunting and high output cardiac failure. This can result in vascular "steal" away from the placenta and fetus. Any intratumoral hemorrhage resulting in anemia can compound the condition. These factors can lead to placentomegaly and hydrops with fetal compromise.[9] Maternal preeclampsia, proteinuria, and edema can accompany this process. This has been called "mirror syndrome" as if the physiologic impairment of the mother mirrors that of the fetus. That the neo-

nate with SCT fares better than the fetus implies that these are different populations and that, historically, fetuses with SCT were often lost as still births.

Over the past 15–20 years, with the advent of fetal surgery, the goal became to understand which fetuses warranted an intervention, to elucidate the nature of that intervention, and to determine the best timing. The first successful fetal SCT resection was reported in 1997 from the Children's Hospital of Philadelphia. That surgery was done at 26 weeks' gestation and actually led to a reversal of fetal hydrops and placentomegaly within 10 days of the surgery. That fetus went on to be delivered at 29 weeks' gestation weighing 1.3 kg.[11] This same group proposed an algorithm for *in utero* surveillance of SCTs. They recommended detailed ultrasound as well as fetal ultrafast MRI, amniocentesis, and fetal echocardiogram. Fetuses without high output cardiac failure would be followed closely with serial ultrasounds. The development of hydrops and placentomegaly are ominous. For fetuses greater than 32 weeks' gestations with high output cardiac failure, emergency Cesarean delivery is recommended. *In utero* tumor resection is recommended for fetuses less than 32 weeks' gestation with high output cardiac failure or evolving placentomegaly and hydrops.[9] The same group published their series of prenatal SCT surveillance reviewing 23 cases from 2003–2006. The mean gestational age at diagnosis was 20 weeks. These masses were predominantly solid and mainly Type II. The overall perinatal mortality was 48%, with four terminations. There were three intrauterine deaths and four neonatal deaths. No fetal surgeries were performed in this group, although amnioreduction or infusion was performed in five cases. Rapid tumor growth of greater than 150 cm^3 per week was found to carry significant risk of mortality. Another group recently confirmed that large, fast-growing SCTs with rich vascularity were associated with higher perinatal morbidity and mortality than smaller slower growing lesions.[12]

POSTNATAL DIAGNOSIS AND SURGICAL THERAPY

The great majority of tumors not identified prenatally will be noted at delivery either by simple inspection and/or rectal examination. However, when dealing with purely internal SCTs, the diagnosis is often delayed.[6] In these cases, children can present with symptoms due to the space occupying nature of the lesion, such as constipation, urinary retention, or abdominal mass. Appropriate imaging should be done as discussed in a previous section of this chapter. It is important to obtain a preoperative baseline alpha fetoprotein (AFP) level. It can then be followed postoperatively to verify that it falls at the appropriate rate.[13] Clinicians who rarely do this determination in the neonate must be reminded of the normal ranges in different age groups. AFP is the predominant serum protein in the fetus and it is normally at relatively high levels in the first months of life. At birth levels

range from about 10,000 to over 100,000 mg/mL and gradually decrease to about 10 mg/mL by 10 months of age.

Operative therapy is rarely emergent and should be carefully planned with respect to the external and internal components of the lesion. For newborns, it should be done within the first few days of life. Occasionally, the timing is more pressing, such as in the case of a ruptured or hemorrhagic tumor. The goal of the surgery is complete resection. The surgeon therefore has to plan the positioning accordingly. If there is any chance that a laparotomy may be necessary for the internal component, the patient should be prepared and draped from the chest down so that access will be possible in both the prone and supine positions. If the internal component clearly necessitates a laparotomy, this should often be done first to gain control of the middle sacral artery. Some authors advocate using open or laparoscopic approaches to ligate this artery before resecting even the external tumor component.[14,15] Most SCT resections are done completely in the prone position with the pelvis bumped upward. The positioning and pressure point padding is very similar to that used for imperforate anus procedures. Urinary catheterization should be done. The incision most commonly used is the inverted "V" with the apex at around the level of the sacrococcygeal junction. A midline incision is satisfactory for smaller tumors. All skin is preserved at first. The dissection is taken around the bulk of the tumor and down to the fascia. Skin and subcutaneous tissue flaps are usually created during this dissection. The dissection is taken down toward the sacrococcygeal region in the midline. A Hegar dilator is often inserted into the rectum as a landmark. The sacrococcygeal junction is ascertained and then undermined carefully with a clamp hugging the inner aspect. The sacrococcygeal ligament is then divided. The coccyx will be removed en bloc with the tumor. It has been taught for a long time that omission of the coccygeal resection increases the recurrence rate significantly.[16,17] This step also helps to expose the middle sacral artery, which should then be ligated. The tumor then needs to be dissected off of the gluteal, levator, and pelvic musculature. If there is an internal component, it should then be pushed anteriorly off the sacrum; and this can often be done with blunt dissection. The lateral extent is then dissected free and then the anterior part is taken carefully off the rectum. After resection, the muscular layers are carefully re-approximated anatomically. The wound is closed in layers. A drain may be left in place. Depending on the amount of redundant skin, some can be excised.

FURTHER THERAPY, FOLLOW-UP, AND PROGNOSIS

The subsequent treatment and prognosis of the sacrococcygeal teratoma depends largely on the pathologic characteristics of the resected tumor as well as the clinical staging of the disease. The American Academy of Pediatrics Surgical Section

Survey that included 398 patients showed that the presence of distant metastasis was quite related to the Altman Type. Type I lesions had no patient with distant metastasis while Type III had the most at 20%. Types II and IV had 6% and 8%, respectively.[6] In that same survey, 19% of tumors were found to be malignant. Histopathologically, these tumors are divided into three groups: mature teratoma, immature teratoma, and malignant teratoma. The malignancies are predominantly composed of endodermal sinus tumors but embryonal carcinoma has also been described. The occurrence of malignancy is related to age at resection. A quite dramatic difference between malignancy rates can be found in children resected over the age 2 months.[6,18] Data from the Children's Cancer Group (CCG) showed that only 9% of newborn tumors were malignant versus 27% of older children. Multiple studies over many years have shown similar data with respect to this age — malignancy relationship.[19,20] Rates of malignancy and metastases in tumors presenting after the neonatal period, and thus in clinical scenarios other than the typical and obvious exophytic lesions, are significantly higher.[21] In Altman's large study, Type I tumors had only an 8% malignancy rate while the rate in Type IV was 38%. Pathology specimens must be very carefully examined by an experienced pediatric pathologist. It has been shown in many studies where pathology has been re-reviewed, that tumors originally thought to be benign have harbored malignant elements.[6,22]

The overall prognosis for neonatal SCT is excellent. However, there is morbidity and mortality associated with resection of the large neonatal SCT reported in almost every series. This is due to several factors, the most important of which is thought to be hemorrhage.[18,21,24] Multiple reports have described methods to increase the safety of these operations.[14,15,23] There are also complications associated with prematurity. However, the long-term survival rate from an oncologic standpoint remains very high. This is especially true for the most common benign lesions. Even with malignant primaries and malignant recurrences in both young and older patients, survival rates are excellent. A large study of 74 malignant SCTs showed an overall survival rate of 90%.[24] These favorable cure rates are thought to be due to the modern era's standard chemotherapeutic regimen for germ cell tumors, including cisplatin, etoposide, and bleomycin.[25,26] This chemotherapeutic regimen is used in an adjuvant fashion for resected malignant SCTs. Recurrence is a well-known phenomenon. Recurrences after resection of benign tumors have been well-documented and found to be either benign or malignant lesions. The occurrence of subsequent malignancy is thought to be due to either unnoticed malignant elements in the primary tumor or from malignant transformation of residual tissue. Recurrence rates are between 11% and 21% with a median time of around 10–12 months.[18,21,27] Factors that have been



Figure 5. Cosmetic result after resection through inverted V incision.

associated with higher recurrence rates are immature and malignant histology, incomplete resection, intraoperative tumor spill, and omission of the coccygeal resection.[21]

Recurrent disease is best detected by serial AFP measurements as well as rectal examinations. These should be done every 3 months. Since the longest interval to recurrence has been documented up to almost 3 years postoperatively,[16] children should be followed closely for this length of time and then less intensely thereafter. Abnormalities on physical examination or increasing AFP levels prompt further work-up.

The long-term functional sequelae of SCT have been examined, mainly with respect to bowel and urinary issues. Some studies reported a fairly high incidence of impaired bowel function and urinary incontinence (above 40%). However, these symptoms improved with time.[28,29] Gait analyses of such patients revealed only very subtle disturbances measurable with sophisticated analysis. Their everyday gait patterns were found to be normal.[30] Cosmetic results are often quite acceptable given the size of these lesions (Figure 5).

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