

PediatricsⁱⁿReview[®]

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Pediatrics in Review 2006;27;243

DOI: 10.1542/pir.27-7-243

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Biliary Atresia

Garret S. Zallen, MD,*
David W. Bliss, MD,*
Thomas J. Curran, MD,[†]
Marvin W. Harrison, MD,*
Mark L. Silen, MD,
MBA**

Author Disclosure
Drs Zallen, Bliss,
Curran, Harrison, and
Silen did not disclose
any financial
relationships relevant
to this article.

Objectives After completing this article, readers should be able to:

1. Recognize the signs and symptoms of biliary atresia.
2. Know the diagnostic tests for biliary atresia.
3. Discuss the management of biliary atresia.
4. Be aware of the role of transplantation in biliary atresia.

Clinical Presentation and Differential Diagnosis

Cholestatic jaundice presenting in the newborn period is a potentially serious disorder that may result from either a treatable or a nontreatable disorder. The clinician initially must recognize the presence of prolonged or pathologic jaundice. Many healthy infants have jaundice during the first postnatal week that resolves spontaneously, often referred to as physiologic jaundice. Persistence of jaundice or the presentation of jaundice after the tenth postnatal day should raise suspicion for pathologic causes. Conjugated hyperbilirubinemia also is of concern and should prompt early investigation.

The differential diagnosis of neonatal cholestasis is lengthy, with extrahepatic biliary atresia being the most common single cause (33%). “Idiopathic neonatal hepatitis,” a diagnosis made commonly in the past, is now an anachronistic term because the number of cases labeled “idiopathic” continues to diminish as more definitive genetic and molecular tests become available. The remainder of patients presenting with neonatal cholestatic jaundice have an anatomic abnormality, an obstructing extrahepatic lesion, an infectious cause, or an inherited or metabolic disorder as the explanation for their persistent jaundice. Toxic or hepatic vascular causes have been described rarely.

Jaundice and acholic stools may be the only specific signs of these disorders. Weight loss and appetite changes are common but not universal. Often, the sole finding on physical examination is jaundice. When present, the other findings may be mild hepatomegaly or the stigmata of certain inherited syndromes (eg, Alagille syndrome with the typical facies). If biliary atresia is discovered late, the clinician may detect a firm, enlarged liver and even splenomegaly.

The various anatomic or obstructive cholestatic disorders tend to be amenable to surgical correction. Included in this set of disorders are choledochal cyst, stenosis of a bile duct and sclerosing cholangitis of the newborn, and biliary atresia. Cholelithiasis can occur in infancy but is extremely rare. Spontaneous perforation of the common bile duct can present with jaundice alone.

Neonatal cholestasis also can result from infection. Viral infections, including adenovirus, enterovirus, hepatitis (A, B, C, D, and E), herpesviruses, human immunodeficiency virus, reovirus, rubella, and parvovirus, can present as neonatal jaundice. Bacterial septicemia can present with jaundice, as can infection with *Listeria monocytogenes*, syphilis, or tuberculosis. Parasitic infestation with toxoplasmosis also can result in neonatal jaundice.

A variety of familial intrahepatic cholestatic syndromes exists. Among these, Alagille syndrome (arteriohepatic dysplasia) is the best known. This disorder consists of jaundice, characteristic facies, pulmonary stenosis, butterfly vertebrae, growth and mental retardation, and hypogonadism. Again, the term “intrahepatic biliary atresia” is no longer used.

Among the various metabolic disorders that can present with neonatal jaundice are disorders of amino acid metabolism (hypermethioninemia, tyrosinemia), disorders of bile

*Division of Pediatric Surgery, Department of Surgery, Oregon Health & Science University, Portland, Ore.

[†]Department of Surgery, Wright State University, Dayton, Ohio.

**Editorial Board.

acid synthesis, and disorders of glucose metabolism (galactosemia, fructose intolerance, glycogen storage disease type IV). Metabolic disorders in the differential diagnosis of neonatal jaundice also include Zellweger syndrome (cerebrohepatorenal syndrome), disorders of oxidative phosphorylation, arginase deficiency, alpha-1-antitrypsin deficiency, and cystic fibrosis (which may cause inspissated bile and partial ductal obstruction). The diagnosis and management of extrahepatic biliary atresia is addressed in this article. More detailed discussions of neonatal cholestasis can be found in the articles listed as Suggested Readings.

Diagnostic Studies

The diagnosis of biliary atresia carries grave implications for the infant and family and cannot be left to probability; it must be established with certainty. No diagnostic studies other than operative cholangiography provide certainty in the time that permits effective, although not assured, long-term intervention (short of liver transplantation). The goal of diagnostic study, therefore, is limited not to a definitive statement as to the diagnosis, but rather to separating cholestatic jaundice in the infant from metabolic and hepatocellular causes of jaundice and providing a sufficiently sensitive differentiation in time to allow effective surgical intervention. Extrahepatic biliary

atresia is diagnosed in only 25% to 30% of neonates who have cholestatic jaundice (Table 1).

Separating physiologic from pathologic jaundice is the first step in diagnosis and is aided by knowing the natural history of physiologic jaundice, which usually resolves by 2 weeks of age. Therefore, the infant who is jaundiced and older than 2 weeks should be evaluated for potentially treatable forms of jaundice. Infants who have more than 20% of their bilirubin in the direct form have cholestasis or obstruction of bile flow. Accordingly, the initial step in the evaluation of prolonged jaundice in the infant is to measure total and fractional bilirubin concentrations, a procedure also worth pursuing in the baby younger than 2 weeks of age whose total bilirubin level is elevated beyond expectation.

The infant who has elevated conjugated bilirubin and cholestasis should be evaluated expeditiously to allow definitive diagnosis and surgical intervention before effective surgical drainage is precluded. Hospitalization should be considered for any infant who is clinically ill to complete the evaluation for cholestatic jaundice. Most children who have underlying metabolic disorders or infections as a cause of their cholestatic jaundice appear or act ill. Biliary cirrhosis in those who have obstructions progresses rapidly. By 4 weeks of age, the liver is firm and often enlarged; by 6 weeks of age, the spleen may be palpable in the left upper quadrant of the abdomen and the stool is acholic. Urine often is dark. However, the infant most often does not appear ill and is growing normally. Splenomegaly frequently is the first indication of developing portal hypertension, suggesting advanced portal fibrosis. Ascites and other manifestations of portal hypertension are late, appearing after 12 to 16 weeks in untreated infants.

Studies should be undertaken to identify hemolytic disease, infectious disease, and the genetic-metabolic disorders (Table 2). These tests may be diagnostic and may differentiate intrahepatic from extrahepatic cholestasis. When results of such evaluations are unrevealing, the biliary tract should be evaluated with ultrasonography and a technetium-99m diisopropyl iminodiacetic acid (DISIDA) or other hepatobiliary nuclear medicine scan. When infants have biliary atresia, the biliary system is not dilated and does not contain stones or sludge. If stones or sludge are present, surgical intervention may be appropriate. However, the prognosis is substantially less ominous if cholelithiasis or choledochal cyst is the preoperative diagnosis. The DISIDA scan confirms the absence of excretion of bile through the liver. Although this finding is not specifically diagnostic of biliary atresia, it

Table 1. Relative Frequency of Various Forms of Neonatal Cholestasis*

Clinical Form	Cumulative Percentage	Estimated Frequency [†]
Idiopathic neonatal hepatitis	30 to 35	1.25
Extrahepatic biliary atresia	25 to 30	0.70
Alpha-1-antitrypsin deficiency	7 to 10	0.25
Intrahepatic cholestasis syndromes (Alagille, Byler, etc)	5 to 6	0.14
Bacterial sepsis	2	<0.1
Hepatitis		
Cytomegalovirus	3 to 5	<0.1
Rubella, Herpes	1	<0.1
Endocrine (hypothyroidism, panhypopituitarism)	1	<0.1
Galactosemia	1	<0.1
Inborn errors of bile acid biosynthesis	2 to 5	<0.1

*Compilation of several published series (500 cases)
[†]Per 10,000 live births
 Modified from Balistreri WF, 1987.

Table 2. Sequential Evaluation of Neonatal Cholestasis

- Clinical evaluation: History and physical examination, including ophthalmologic examination for posterior embryotoxon and cardiologic evaluation for structural heart disease and chest radiograph (all for possible Alagille syndrome)
- Stool color
- Fractionated bilirubin (\pm bile acids)
- Aspartate aminotransferase/alanine aminotransferase, gamma glutamyl transpeptidase
- Index of hepatic "synthetic function" (serum albumin and prothrombin time)
- Viral and bacterial cultures (blood and urine)
- Viral serology (hepatitis B surface antigen, TORCH, human immunodeficiency virus) and VDRL titers
- Alpha-1-antitrypsin and phenotype and level
- Thyroxine and thyroid-stimulating hormone
- Sweat chloride
- Metabolic screen (urine and serum amino acids, urine reducing substances, and succinyl acetone-tyrosinemia); ferritin
- Ultrasonography
- Nuclear medicine imaging (DISIDA or other hepatobiliary scan)
- Operative cholangiography and exploration with liver biopsy

Modified from Dellert SF, Balistreri WR, 2000.

mandates that the infant undergo the definitive diagnostic studies—laparotomy and operative cholangiography.

Percutaneous preoperative liver biopsy has been used to distinguish biliary atresia from other causes of neonatal cholestasis. Although biopsy can be interpreted correctly in 90% to 95% of cases and in some centers can be performed more expeditiously than a DISIDA scan, it is neither sensitive nor specific enough to provide a definitive diagnosis and carries its own set of risks. Nevertheless, biopsy often is used to direct the diagnostic evaluation of the jaundiced infant.

Operative Approach to Biliary Atresia

Although it is possible to suspect biliary atresia prior to the operative procedure, exploration often is both a diagnostic and therapeutic intervention. Preoperative percutaneous liver biopsy may demonstrate the classic histology of portal fibrosis with bile duct proliferation; magnetic resonance imaging or endoscopic retrograde cholangiography may display the characteristic ductal appearance. Regardless, the surgeon's first obligation is to investigate the diagnosis expeditiously with a limited

laparotomy. Preoperative preparation includes administration of vitamin K to minimize coagulopathy and intravenous antibiotics appropriate for upper gastrointestinal flora, as well as avoidance of hepatotoxic medications and anesthetics.

On entering the right upper quadrant, the liver and extrahepatic biliary tree are examined. Typically, a sclerotic gallbladder is encountered, although less common variants may have a normal-appearing gallbladder with sclerotic distal bile ducts. If a lumen can be found within the gallbladder, needle cholangiography should be performed to evaluate the biliary tree. Classically, the surgeon encounters a nondilated, proximally obliterated ductal system. If the biliary architecture is patent, other diagnoses such as Alagille syndrome, hepatitis, and cholestasis must be entertained. Entities other than extrahepatic biliary atresia do not benefit from additional operative intervention.

The liver often is enlarged and has a green hue. Occasionally, frank nodular cirrhosis may be found, although its presence is not an absolute contraindication to proceeding with the definitive operation. Unless a preoperative liver biopsy has been obtained, a wedge liver biopsy is performed. A 1-cm square piece is obtained from the anterior right lobe away from the bed of the gallbladder and is sent for frozen section examination. Classic histologic characteristics such as microscopic bile duct proliferation, periportal inflammation, and giant cell reaction should be documented before proceeding with the definitive procedure because the Kasai portoenterostomy has no value in other causes of neonatal jaundice. Any residual tissue should be saved for future studies such as electron microscopy or metabolic testing.

Once the diagnosis of biliary atresia is established, the liver is freed of its ligamentous attachments, and the biliary dissection is initiated. The gallbladder is freed from its bed and used to trace the biliary remnants within the porta hepatis. The tissue anterior to the portal venous and hepatic arterial branches is freed up to its insertion into the liver substance between the bifurcation of the portal vessels. A Roux-en-Y limb of jejunum at least 40 cm in length is brought up to reach the hepatic plate. The fibrous plate of the liver is transected in an effort to expose microscopic biliary radicals, and the limb of jejunum is sewn circumferentially around the exposed substance. Thus, the bile ductules drain passively into the small bowel without direct anastomosis. An orogastric or nasogastric tube is left in place for gastrointestinal decompression. Because the biliary flow is diverted to the jejunum, it is unusual to withdraw bile from the gastric

tube. Feedings are initiated once the child is stooling and the gastric tube output has waned.

Early operative success is defined by the appearance of colored stools and a declining serum bilirubin concentration. However, the high rate of progression of liver disease and portal hypertension requires close observation by either the surgeon or a pediatric gastroenterologist over several years. Early failure is manifested by inexorable worsening of hepatic synthetic function, failure to thrive, and progressive jaundice. Late failure is characterized by signs of portal hypertension and liver failure. Both circumstances require careful nutritional care, vitamin supplementation, and early referral to a liver transplantation center.

Recently, several surgeons have reported series of robotically assisted laparoscopic portoenterostomy. Thus far, in early follow-up, the results seem to be comparable to open surgery, with a 33% long-term success rate. However, the newer techniques may result in fewer adhesions and, therefore, may facilitate liver transplantation. Ultimately, two thirds of children progress to liver

changes in stool color. The prompt recognition of cholangitis is essential to avoid scarring. Treatment is administration of broad-spectrum intravenous antibiotics. Some authors recommend prolonged oral suppressive treatment with penicillin or sulfamethoxazole. Pulse-dose steroids have been used by some clinicians. The use of steroids in cholangitis may not be feasible if significant sepsis is involved, and steroids have not been shown definitively to improve outcome. All patients should receive fat-soluble vitamin (A, D, E, and K) supplementation due to the likelihood of poor absorption. Diets containing a predominance of medium-chain triglycerides may be necessary if fat malabsorption is evidenced.

Long-term follow-up is essential. Despite early excellent results, patients often develop progressive liver deterioration. The timing of this decline varies, depending on the initial success of the operation. Even patients who have had an excellent response to the portoenterostomy may develop late-onset liver failure. This failure occurs most often during adolescence, when the need for transplantation may exceed 50% of patients. Female survivors of biliary atresia can become pregnant, but need close follow-up because significant liver deterioration can occur during pregnancy. There have been no reports of second-generation biliary atresia.

The development of portal hypertension is common in biliary atresia, due to progressive hepatic fibrosis. Treatments vary from sclerotherapy or banding for bleeding esophageal varices to portosystemic shunts for recalcitrant portal hypertension. The use of percutaneous transhepatic portal system shunts is an excellent option and often is a successful bridge until liver transplant can be performed.

Reoperation for a failed portoenterostomy remains controversial. At this time, no preoperative test can determine if reoperation will be successful. More operative interventions are associated with more scarring, making subsequent liver transplantation more difficult. Some patients, however, benefit from a re-exploration and removal of either granulation tissue or an anastomotic stricture. Reoperation for a primary failure is unlikely to be successful; liver transplantation may be better.

Transplantation and Future Options

Currently, the best long-term outcome for a patient who has biliary atresia is achieved by the Kasai portoenterostomy followed by orthotopic liver transplantation, when indicated. This situation is likely to remain true until the pathophysiology of the disease is better understood and

The prompt recognition of cholangitis is essential to avoid scarring.

failure and require transplantation, although results may be better at more experienced centers.

The treatment of biliary atresia does not end with the creation of a portoenterostomy. The success rate of portoenterostomy varies from 30% to 50%. A significant number of infants have primary nonfunction of the portoenterostomy and require evaluation for liver transplantation as a lifesaving procedure. Evidence suggests that the number of operative failures can be decreased by careful postoperative management. The use of postoperative steroids at immunosuppressive doses appears to improve survival. It is hypothesized that this therapy may decrease the inflammatory response in the bile ducts and promote bile flow. Ursodeoxycholic acid also augments bile flow and should be started once oral feedings are initiated. The dose ranges from 15 to 30 mg/kg per day. Administration of prophylactic long-term antibiotics can help prevent the development of cholangitis.

Cholangitis is a frequent complication seen after portoenterostomy and often is manifested by fever, increasing bilirubin values, and abnormal liver function test results, as well as abdominal pain and, occasionally,

new treatments can be designed. The primary care practitioner can play a significant role in improving the outcome of portoenterostomy by diagnosing biliary atresia early and referring the patient to an appropriate center. Studies have shown an improved success rate if the procedure is performed prior to 7 weeks of age.

Hepatic failure from biliary atresia is the leading indication for liver transplantation in the pediatric age group. Approximately 20% of patients undergoing portoenterostomy survive into adulthood without liver transplant. Fortunately, the results of pediatric liver transplantation have improved consistently over the past 2 decades. Ten-year survival has been reported at 81%, but current techniques likely will improve this result. An older age at transplant also has been shown to improve outcome, reinforcing the value of portoenterostomy as a first-stage therapy. Recent series have reported up to 100% 1-year survival for patients 6 years of age and older. The increased success is attributed to better surgical techniques, improved intensive care, better understanding of infectious diseases, and new immunosuppressive agents such as cyclosporine and FK 506. Patients must be followed very closely, particularly in the first several months after transplant. The balance is delicate between the immunosuppression required to avoid graft rejection and the toxic and infectious complications of the agents used.

The shortage of donor organs has led to the development of several creative alternatives to whole organ transplantation in children. Reduced-size cadaveric liver transplantation enables an adult donor to provide a graft to a child, with the left lobe of the donor liver being used. Split-liver transplantation extends this capability by creating two allografts from a single donor to benefit two recipients. These concepts also have been used to develop living-related or even living-nonrelated donor programs, whereby a parent, relative, or friend can serve as the donor. Morbidity to the living donor has been minimal, and the graft function of these other methods has been comparable to whole organ transplants.

Although there are not many long-term outcome studies, most children who have had liver transplants attend school and function normally. A few recent stud-

ies performed 1 to 2 years after liver transplantation have shown some speech and language delays. This finding warrants additional study, and affected patients may benefit from seeing child development and behavioral specialists for early intervention. The primary cause of extrahepatic biliary atresia remains elusive but is the subject of numerous ongoing collaborative studies.

Summary

Extrahepatic biliary atresia is a rare and highly morbid condition. When unrecognized, it progresses inexorably to liver failure and death unless liver transplantation is available. However, expeditious evaluation of the jaundiced infant that excludes other disorders and determines the biliary anatomy and function, employing nuclear, ultrasonographic, magnetic resonance, or other modalities, may lead to earlier referral for the appropriate operative intervention, the Kasai procedure. When successful, this procedure may delay or forestall the need for liver transplantation and its attendant morbidity. Improvements in the future may come from venues such as improved diagnostic techniques, determination of causes, better operative technique (including the application of robotics), and refinements in transplantation.

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PIR Quiz

Quiz also available online at www.pedsinreview.org.

1. A 15-day-old male infant presents with yellow discoloration of the skin and sclera. The infant is breastfed and otherwise has appeared normal. For the last 4 days, he has been having three to four stools per day, which appear clay-colored. Physical examination findings are normal except for jaundice. Which of the following is the *most* likely diagnosis?
 - A. Cholestasis.
 - B. Human milk jaundice.
 - C. Hypothyroidism.
 - D. Occult isoimmune ABO blood group incompatibility.
 - E. Prolonged physiologic jaundice.
2. The infant described previously has a serum bilirubin concentration of 8.5 mg/dL (145.4 μ mol/L), with a direct component of 4.8 mg/dL (82.3 μ mol/L). Which of the following is the *most* appropriate next step?
 - A. Discontinue breastfeeding and re-examine in 1 week.
 - B. Order abdominal ultrasonography.
 - C. Order endoscopic retrograde cholangiopancreatography.
 - D. Schedule for laparotomy and operative cholangiography.
 - E. Start phototherapy and re-examine in 1 week.
3. A mother is concerned about her 2-day-old daughter's jaundice because her neighbor's child recently was diagnosed with biliary atresia. Which of the following is *most* likely to be observed in a child who has extrahepatic biliary atresia?
 - A. Abnormal facies.
 - B. Decreased serum alpha-1-antitrypsin concentration.
 - C. Indirect bilirubin component greater than 90% of total bilirubin.
 - D. Onset of jaundice within first week after birth.
 - E. Presence of light-colored stools after 2 weeks of age.
4. You are asked to see a 21-day-old boy who has jaundice. Physical examination findings are normal except for yellow discoloration of the skin and sclera. Serum bilirubin is 10 mg/dL (171 μ mol/L), with the direct component of 5 mg/dL (85.5 μ mol/L). Serum alpha-1-antitrypsin concentrations are normal. Ultrasonography of the abdomen shows a nondilated biliary tract. Which of the following is the *most* appropriate next step?
 - A. Computed tomography of the abdomen.
 - B. Doppler velocities measurement of hepatic artery and venous blood flow.
 - C. Endoscopic retrograde cholangiopancreatography.
 - D. Hepatobiliary nuclear medicine scan.
 - E. Magnetic resonance imaging of the abdomen.

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