Treatment Of Pediatric Patients With Jaundice In The ED

A 2-month-old infant presents to the emergency department with a chief complaint of jaundice. History reveals that the infant was full-term, had a normal birth, and was discharged from the nursery after 2 days. The infant is breastfed. During the last month, the parents have noticed progressive jaundice, and the infant’s stools seem lighter in color. The physical examination reveals a well-appearing, icteric infant without hepatosplenomegaly. The screening bilirubin test from the pediatrician’s office reveals that the infant’s total bilirubin level is elevated, but fractionation was not done.

You have seen many jaundiced infants, especially among breastfed patients. Does this infant warrant further evaluation, or is this a case of physiologic/breast milk jaundice? Is there something in the history that suggests this jaundice is worrisome? Should you discharge the infant for follow-up with the primary physician, or should you proceed with emergency department evaluation? If so, what is the next step in examining this patient? Does this infant have acute liver failure that warrants admission to the intensive care unit? Does he have an obstruction of the biliary tree or other surgical emergency? Is this a case of infectious hepatitis, and can the patient be discharged home after proper hydration?

Jaundice, or icterus, is a yellow-green discoloration of the skin, eyes, mucous membranes, and body fluids that results from excessive bilirubin. Jaundice is apparent in infants with a total serum bilirubin (TSB) concentration greater than 5 mg/dL and in older children with a TSB concentration greater than 2 to 3 mg/dL. Total serum bilirubin reflects the sum of unconjugated (ie, indirect) and conjugated (ie, direct) fractions. Conjugated hyperbilirubinemia, also called cholestasis, is defined as a conjugated bilirubin concentration greater than 1 mg/dL or more than 20% of the TSB concentration; it is always pathologic.

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Uncomprehended

Ja undice, or icterus, is a yellow-green discoloration of the skin, eyes, mucous membranes, and body fluids that results from excessive bilirubin. Jaundice is apparent in infants with a total serum bilirubin (TSB) concentration greater than 5 mg/dL and in older children with a TSB concentration greater than 2 to 3 mg/dL. Total serum bilirubin reflects the sum of unconjugated (ie, indirect) and conjugated (ie, direct) fractions. Conjugated hyperbilirubinemia, also called cholestasis, is defined as a conjugated bilirubin concentration greater than 1 mg/dL or more than 20% of the TSB concentration; it is always pathologic.
Early detection of cholestatic jaundice and a timely, accurate diagnosis are important for successful treatment and a favorable prognosis.

Although jaundice is a common finding in children, it also can be the presenting sign for a number of other disorders, hepatic as well as extrahepatic, reflecting either excessive bilirubin production or decreased excretion by the liver or biliary system. Binding to albumin prolongs the half-life of direct bilirubin, and even though the results of other liver tests may be normalizing, jaundice may be protracted.

Jaundice itself is harmful only in newborns, in whom the accumulation of unconjugated bilirubin may lead to kernicterus in the immature brain. The differential diagnosis is age specific. Neonatal jaundice occurs in up to 60% of term infants in the first week of life. Approximately 2% of newborns reach TSB levels in excess of 20 mg/dL.

The differentiation between nonpathologic and pathologic jaundice begins in the emergency department (ED). In recent years, a large body of evidence and updated guidelines have helped elucidate the pathophysiology of jaundice and outlined appropriate management options for children with cholestasis and related illnesses. This issue of Pediatric Emergency Medicine Practice provides the results of these evidence-based studies and the most up-to-date guidelines to assist the emergency clinician in caring for pediatric patients presenting with jaundice. These recommendations are general guidelines and are not intended as a substitute for clinical judgment or as a protocol for the care of all patients who present with jaundice.

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All studies, review articles, and meta-analyses were identified via MEDLINE® and Ovid MEDLINE® (eg, the Cochrane Database of Systematic Reviews, the ACP Journal Club®, the Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials, the Cochrane Methodology Register, the Health Technology Assessment Database, and the National Health Service Economic Evaluation Database). Terms used in the search included jaundice, cholestasis, neonate, infant, pediatric, child, guideline, and emergency department/room. More than 200 articles published from January 1991 to July 2008 were analyzed, providing the background for further review.

Although most population-based data come from well-designed, large-sample studies of infants with jaundice, only a few studies have been prospective in nature. In addition, differences in interhospital bilirubin testing and frequency of identified jaundice are significant. This has led to the development of benchmarking models that adjust for race, feeding method, and gestational age in order to compare incidence of hyperbilirubinemia between hospitals. Guidelines have been issued by the American Academy of Pediatrics (AAP) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) using the definitions for quality of evidence and balance of benefits and harm established by the AAP/NASPGHAN Steering Committee on Quality Improvement Management. These guidelines have undergone extensive peer review by committees, outside organizations, and experts in the field.

**Epidemiology**

Up to 15% of breastfed infants experience jaundice lasting more than 3 weeks. Male infants and older mothers are also associated with severe hyperbilirubinemia. Neonatal cholestasis occurs in 0.04% to 0.2% of live births. Although idiopathic neonatal hepatitis was historically the most common etiology of neonatal cholestasis, newer and more accurate diagnostic methods have reduced the number of infants diagnosed with this condition. In a recent Australian study of cholestatic infants, 25% had idiopathic hepatitis, 23% had a metabolic/genetic cause, 20% had biliary obstruction, 20% had total parenteral nutrition (TPN)-induced cholestasis, and 9% had an infection. Gilbert’s syndrome, found in about 5% of the population, also causes benign, mild unconjugated hyperbilirubinemia in the absence of hemolysis or evidence of liver disease.
Physiologic jaundice is often a transient elevation of bilirubin values during the first week of life, whereas pathologic hyperbilirubinemia often occurs during the first 24 hours of life and may be associated with anemia or hepatosplenomegaly, may demonstrate a rapid rise (> 5 mg/dL per day), may be prolonged (> 7-10 days in a full-term infant), or may present with elevated conjugated bilirubin level (> 1 mg/dL or > 20% of TSB).

The 3 main causes of unconjugated hyperbilirubinemia in the newborn are bilirubin overproduction, impaired bilirubin conjugation, and impaired hepatic bilirubin uptake. Newborns are especially prone to hyperbilirubinemia secondary to increased hemoglobin levels, which results from high red blood cell (RBC) volume, shortened RBC survival (and increased breakdown), or the relative immaturity of UDP-GT in the liver. (See Table 1.)

Fewer than 15 disorders account for more than 95% of neonatal cholestasis. Distinguishing between hepatocellular and obstructive cholestasis is especially important, as the diagnosis has implications for physiologic and anatomic disorders and between medical and surgical disease. The obstructive disorders require timely identification, as earlier surgical intervention can improve outcome. See Table 2 on page 4 for a helpful chart on the differential diagnosis of jaundice in children.

**Prehospital Care**

Prehospital care in cases of pediatric jaundice should focus on clinical assessment of the patient’s overall condition. Most patients are asymptomatic with jaundice noted incidentally and require little specific care in the

**Pathophysiology**

The daily production of unconjugated bilirubin is 250 to 350 mg, primarily from aging erythrocytes. The normal clearance rate is 5 mg/kg per day, or about 400 mg/d, in adults. The rate does not increase significantly with hemolysis. The half-life of unconjugated bilirubin is less than 5 minutes. The hepatic enzyme UDP-glucuronosyltransferase (UDP-GT) conjugates bilirubin. The conjugated bilirubin is actively excreted into bile via multidrug resistance-related protein and is essentially absent from blood in healthy individuals. Delta bilirubin (δ-bilirubin; also termed biliprotein) is produced by conjugation of bilirubin with albumin and has a half-life of about 17 to 20 days (the same as albumin). This accounts for prolonged jaundice in patients recovering from hepatitis or biliary obstruction. Upper reference limits for TSB increase throughout childhood and adolescence, reaching peak values at approximately age 20 years. (See Figure 1.) At all ages, upper reference limits are higher in men than in women, although the differences are minimal at the extremes of life. With recovery from hepatitis or obstruction, the conjugated bilirubin level falls quickly, while δ-bilirubin levels decline more slowly. Other factors affecting bilirubin values are summarized in Table 1.

**Differential Diagnosis**

In neonates, it is important to distinguish between physiologic jaundice and pathologic hyperbilirubinemia (ie, jaundice requiring treatment). The age of the infant and the duration of the abnormal bilirubin level may aid in differentiating the disorders.

![Figure 1. Age- And Gender-Related Changes In Bilirubin Levels](image)

**Table 1. Factors That Affect Bilirubin Levels**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Bilirubin Level</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day-to-day fluctuations</td>
<td>Varies by 15% to 30%</td>
<td>15</td>
</tr>
<tr>
<td>Fasting</td>
<td>Increases an average of 1- to 2-fold with fasting up to 48 hours, and by 20% to 25% after an overnight fast</td>
<td>16</td>
</tr>
<tr>
<td>Race</td>
<td>Is 33% lower in African-American men and 15% lower in African-American women</td>
<td>17</td>
</tr>
<tr>
<td>Exercise</td>
<td>Is 30% higher in men</td>
<td>13</td>
</tr>
<tr>
<td>Light exposure</td>
<td>Unconjugated bilirubin level decreases up to 50% in 1 hour</td>
<td>13</td>
</tr>
</tbody>
</table>
prehospital and ED settings.

In some cases, jaundice may result from a significant underlying infection/sepsis or surgical emergency. These children can deteriorate rapidly and should be transported as quickly as possible to a medical center with appropriate resources such as a pediatric ED or intensive care unit and pediatric hepatologists and surgeons.

**Emergency Department Evaluation**

**Initial Stabilization**
The evaluation should be guided by the clinical appearance of the patient and the timing of the jaundice, especially when it comes to newborns. Most patients presenting to the ED with jaundice are in stable condition. Table 3 on page 5 lists particularly worrisome features associated with the disorder. In the absence of any worrisome features, a full-term, well-appearing infant is at low risk of complications when presenting within a time frame that is consistent with physiologic jaundice. Although these patients may be given lower triage priority, they require laboratory evaluation and possibly imaging tests and therefore cannot be immediately discharged from the ED.

Older patients may present with altered mental status, coagulopathy, hypotension, or signs of sepsis. In these cases, particular attention should be paid to the ABCs of basic life support. Patients who are obtunded or hypotensive require immediate resuscitation, including possible intubation and adequate venous access.

**History**
The emergency clinician should conduct a careful

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**Table 2. Differential Diagnosis Of Jaundice In Children**

<table>
<thead>
<tr>
<th>Unconjugated Hyperbilirubinemia</th>
<th>Conjugated Hyperbilirubinemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased bilirubin production</strong></td>
<td><strong>Extrahepatic cholestasis</strong></td>
</tr>
<tr>
<td>• Hemolysis: blood group incompatibility, G6PD, sickle cell disease</td>
<td>• Cholestatic hepatitis, biliary sludge, inspissated bile syndrome</td>
</tr>
<tr>
<td><strong>Decreased excretion/conjugation</strong></td>
<td>• Intrinsic and extrinsic tumors: cholangiocarcinoma</td>
</tr>
<tr>
<td>• Crigler-Najjar syndrome (life-threatening) types I and II</td>
<td>• Primary sclerosing cholangitis</td>
</tr>
<tr>
<td>• Congenital hypothyroidism</td>
<td>• Acute and chronic pancreatitis</td>
</tr>
<tr>
<td>• Gilbert’s syndrome</td>
<td>• Strictures after invasive procedure</td>
</tr>
<tr>
<td>• Drugs: ketoconazole, ethinyl estradiol, amitriptyline, and HIV protease inhibitors</td>
<td>• Parasitic infections: ascaris, lumbricoides, liver flukes</td>
</tr>
<tr>
<td><strong>Impaired uptake</strong></td>
<td>• Extrahepatic biliary atresia</td>
</tr>
<tr>
<td>• Congestive heart failure</td>
<td>• Choledochal cyst</td>
</tr>
<tr>
<td>• Portal systemic shunts</td>
<td>• Alagille syndrome</td>
</tr>
<tr>
<td>• Drugs: rifampin, probenecid</td>
<td>• Cystic fibrosis</td>
</tr>
<tr>
<td><strong>Hyperbilirubinemia due to breastfeeding</strong></td>
<td>• Neonatal sclerosing cholangitis</td>
</tr>
<tr>
<td>• Breastfeeding jaundice</td>
<td>• Congenital hepatic fibrosis/Caroli disease</td>
</tr>
<tr>
<td>• Breast milk jaundice</td>
<td>• Spontaneous perforation of the bile ducts</td>
</tr>
<tr>
<td><strong>Intrahepatic cholestasis</strong></td>
<td><strong>Toxic</strong></td>
</tr>
<tr>
<td>• Idiopathic neonatal hepatitis</td>
<td>• Total parenteral nutrition-associated cholestasis</td>
</tr>
<tr>
<td>• Sepsis and hypoperfusion states</td>
<td></td>
</tr>
</tbody>
</table>
and thorough history of children presenting with jaundice. Familiarity with historical clues that place children at increased risk for severe hyperbilirubinemia will allow the emergency clinician to quickly assess these patients and initiate appropriate management.2 (See Table 4 on page 6)

Family history, including ethnicity, siblings with similar presentation, anemia, liver disease, or splenectomy can also provide significant clues about the source of the jaundice. Assessing the neurologic status of young infants is also important but can be very challenging. Emphasis should be placed on any behavioral changes, sleep cycle changes, or irritability. A detailed drug history should be obtained, including use of any prescribed, over-the-counter (OTC), and herbal medications. Many OTC drugs (eg, decongestants) contain acetaminophen. When combined with other acetaminophen-containing medications, they may lead to hepatotoxicity. Patients and parents frequently do not consider OTC and herbal remedies to be drugs; therefore, the history should include specific questions about their use.

Physical Examination

The physical assessment should begin with a careful and thorough clinical appraisal of the pediatric patient. Jaundice is best assessed by blanching the skin with digital pressure to reveal the underlying skin color and subcutaneous tissue.4 The AAP recommends that this evaluation be performed in a well-lit room.7 Jaundice follows a cephalocaudal progression, but visual estimation of bilirubin levels alone is unpredictable and imprecise.4,19 Therefore, accurate determination of bilirubin levels requires laboratory investigation. After the skin is assessed, other signs of pathologic jaundice should be evaluated. These include pallor, petechiae, weight status, and signs of blood loss (eg, excessive bruising, hepatosplenomegaly, or cephalohematoma).4

Table 5 on page 7 lists important components of the physical examination and their implications.

Examination of the head, eyes, ears, nose, and throat should focus on the presence of scleral icterus and any dysmorphic features such as those seen in Alagille syndrome. Fundoscopic and slit-lamp evaluations will better assess for ophthalmologic signs seen in congenital infections and Wilson’s disease (WD). Hydration status can be appreciated from mucous membranes.

Auscultation of the heart and lungs should be performed to assess for signs of pneumonia/infection or heart disease such as heart failure that can lead to congestive hepatopathy. The presence of murmurs or other congenital heart problems are associated with abnormalities such as extrahepatic biliary atresia and Alagille syndrome.

The abdominal examination should focus on evidence of distension, ascites, abdominal wall vasculature, liver size and consistency, spleen size and consistency, masses, or an umbilical hernia. Ascites is often seen in chronic liver disease in older children.

Nonphysical examination findings are also very helpful. Dark urine is suggestive of conjugated hyperbilirubinemia. Pale or clay-colored stools are suggestive of cholestasis and should prompt an evaluation for biliary obstruction.

Although difficult in young infants, the neurologic examination should assess vigor, tone, and overall symmetry.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome (HPS) is the association of liver disease, hypoxemia, and intrapulmonary vascular dilatations.46 The prevalence of HPS in cirrhotic children has been reported as 8% to 19% in recent studies.47 Clinically, HPS is evidenced by decreased oxygen saturation in the upright position (orthodeoxia) in patients with chronic liver disease and platypnea or improved dyspnea while lying down. Patients often manifest signs of pulmonary disease such as dyspnea, exercise intolerance, and digital clubbing. Echocardiography using agitated saline and macroaggregated albumin scanning are diagnostic measures. Although HPS is reversible months after transplant, it is associated with increased mortality and morbidity.48 Screening for HPS with upright saturation is recommended for children with cirrhosis and/or portal hypertension.

Physiologic Jaundice

Physiologic jaundice is a transient elevation of bilirubin level during the first week of life. It is a multifactorial condition resulting from increased serum bile salts secondary to decreased bile salt secretion,29 decreased bile flow, decreased bile acid synthesis, smaller bile acid pool size, decreased hepatic uptake of portal bile salts, and inefficient ileal uptake of bile salts.21 A recent study by
Bilirubin overproduction can result from increased breakdown of hemoglobin and other heme-containing proteins. It is important to exclude hemolytic diseases as a cause of indirect hyperbilirubinemia. Risk factors for hemolysis include a family history of significant hemolytic disease, a high-risk ethnic background, early or severe jaundice, or jaundice before 24 hours of life. Bilirubin levels that rise rapidly or are refractory to phototherapy may also be due to hemolytic processes.

In the infant, ABO blood group incompatibility is a common cause of hemolysis leading to hyperbilirubinemia; however, it is most often diagnosed before the newborn is discharged from the nursery. Although 15% of all newborns will be affected by ABO incompatibility, at most, only 2.2% will have some manifestation of the

Pathologic Jaundice

Unconjugated Hyperbilirubinemia

As mentioned previously, the causes of unconjugated hyperbilirubinemia can be best summarized as bilirubin overproduction, impaired hepatic bilirubin uptake, and impaired bilirubin conjugation.

Table 4. Important Historical Questions And Implications

<table>
<thead>
<tr>
<th>Questions About</th>
<th>Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history</td>
<td>Autosomal dominance, genetic cause, or nongenetic recurrence pattern: α1-antitrypsin deficiency, progressive familial intrahepatic cholestasis, Alagille syndrome, cystic fibrosis</td>
</tr>
<tr>
<td>Consanguinity</td>
<td>Autosomal recessive disorder</td>
</tr>
<tr>
<td>Maternal infection</td>
<td>TORCH, hepatitis B virus</td>
</tr>
<tr>
<td>Fetal ultrasound</td>
<td>Choledochal cyst and bowel anomalies</td>
</tr>
<tr>
<td>ABO or Rh disease</td>
<td>Hemolysis</td>
</tr>
<tr>
<td>Birth weight</td>
<td>SGA implies fetal involvement</td>
</tr>
<tr>
<td>Neonatal infection (urinary tract infection, sepsis, viral infection)</td>
<td>Associated conjugated hyperbilirubinemia</td>
</tr>
<tr>
<td>Feeding history/weight status</td>
<td>Neonatal hepatitis can cause failure to thrive; metabolic disease can cause failure to thrive, anorexia, jaundice</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Metabolic disease, pyloric stenosis, obstruction, variceal bleeding</td>
</tr>
<tr>
<td>Stooling</td>
<td>Delayed: cystic fibrosis, hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Diarrhea: infection, metabolic disease, progressive familial intrahepatic cholestasis, cystic fibrosis</td>
</tr>
<tr>
<td></td>
<td>Clay colored: biliary obstruction</td>
</tr>
<tr>
<td></td>
<td>Hematochezia/melena: variceal bleeding</td>
</tr>
<tr>
<td>Urine color</td>
<td>Dark: conjugated hyperbilirubinemia</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Breastfed or type of formula</td>
</tr>
<tr>
<td></td>
<td>Breast milk: physiologic jaundice</td>
</tr>
<tr>
<td></td>
<td>Galactose: galactosemia</td>
</tr>
<tr>
<td></td>
<td>Fructose/sucrose: hereditary fructose intolerance</td>
</tr>
<tr>
<td></td>
<td>Failure to thrive</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Portal hypertension, coagulopathy, vitamin K deficiency</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Biliary obstruction, cholangitis, pancreatitis</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Biliary obstruction, cholangitis, congenital intrahepatic cholestasis</td>
</tr>
<tr>
<td>Drug history</td>
<td>Prescribed, over-the-counter, and herbal medication use may lead to fulminating liver failure, hepatitis-like picture, and chronic liver disease; recreational drugs, alcohol use</td>
</tr>
<tr>
<td>Mental status changes, sleep disturbances, and school performance</td>
<td>Wilson’s disease, recreational drug use, encephalopathy, metabolic disease, hypothyroidism</td>
</tr>
<tr>
<td>Recent travel</td>
<td>Infection</td>
</tr>
</tbody>
</table>

Abbreviations: SGA, Small for Gestational Age; TORCH, toxoplasmosis, other (hepatitis B, syphilis, varicella-zoster virus, human immunodeficiency virus, and parvovirus B19), rubella virus, cytomegalovirus, and herpes simplex virus.

Table 5. Important Physical Findings In Jaundice And Their Implications

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Physical Finding/Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital signs, weight, length, global assessment</td>
<td>Acute illness</td>
</tr>
<tr>
<td>Head, eyes, ears, nose, and throat</td>
<td>Dystrophic findings: Alagille syndrome</td>
</tr>
<tr>
<td></td>
<td>Mucous membranes: hydration</td>
</tr>
<tr>
<td></td>
<td>Fundoscopic and slit-lamp examinations for posterior embriotoxon or Kayser Fleisher rings: sclera icterus</td>
</tr>
<tr>
<td>Chest/heart</td>
<td>Pneumonia: infection</td>
</tr>
<tr>
<td></td>
<td>Heart failure: congestive hepatology</td>
</tr>
<tr>
<td></td>
<td>Murms/heart disease: extra-hepatic biliary atresia, Alagille syndrome</td>
</tr>
<tr>
<td>Abdomen</td>
<td>Distension, ascites, tenderness, abdominal wall vasculature, liver size and consistency, spleen size and consistency, masses, umbilical hernia</td>
</tr>
<tr>
<td>Diaper examination</td>
<td>Dark urine: Conjugated hyperbilirubinemia</td>
</tr>
<tr>
<td></td>
<td>Pale stools: Cholestasis, possible biliary obstruction</td>
</tr>
<tr>
<td>Skin</td>
<td>Excoriation marks, petechiae, rashes, palmar erythema, spider angiomas, hemangiomas</td>
</tr>
<tr>
<td>Neurologic examination</td>
<td>Vigor, tone, and symmetry, reflexes, tremors, dysarthria ataxia, response to stimuli and pain</td>
</tr>
</tbody>
</table>


Certain inherited disorders may impair bilirubin conjugation and lead to unconjugated hyperbilirubinemia. The most common is Gilbert’s syndrome, estimated to affect 3% to 10% of the general population. The disorder is characterized by reduced bilirubin-UDP-glucuronosyl transferase activity. Patients present with mild jaundice and mild elevations of unconjugated bilirubin during times of stress, illness, or fasting. This condition is benign and requires no treatment. The diagnosis of Gilbert’s syndrome is usually clinical and one of exclusion, although genetic testing is available. A rare, hereditary form of unconjugated hyperbilirubinemia is Crigler-Najjar syndrome, an autosomal recessive disease characterized by either a complete loss or a partial deficiency of bilirubin-UDP-glucuronosyltransferase (type I and type II, respectively). Patients with Gilbert’s syndrome have TSB levels < 6 mg/dL, as opposed to levels between 6 and 20 mg/dL in patients with Crigler-Najjar syndrome type II and levels ranging from 20 to 45 mg/dL in those with Crigler-Najjar syndrome type I.

Hyperthyroidism may occasionally result in jaundice, although the cases presented have involved underlying liver disease or use of hepatotoxic medications. Certain drugs can also inhibit bilirubin glucuronidation. These include ketoconazole, ethinyl estradiol, amitriptyline, and human immunodeficiency virus (HIV) protease inhibitors.

Breast milk jaundice is the persistence of physiologic jaundice beyond the first week of life in breastfed infants. A factor in human breast milk is thought to increase the enterohepatic circulation and absorption of bilirubin, although the particular cause has not been identified. Unconjugated hyperbilirubinemia is usually characterized by a TSB > 5 mg/dL but with mildly increased levels that do not require intervention. It typically begins after the first 3 to 5 days of life, peaks within 2 weeks after birth, and improves to normal levels over 3 to 12 weeks. Breast milk jaundice is different from breastfeeding jaundice, which is caused by decreased milk intake and subsequent dehydration, with weight and fluid losses within the first 7 days of life.

**Diagnosis**

In addition to the initial workup for jaundice in the ED, infants with unconjugated hyperbilirubinemia should have a complete blood cell count (CBC), a peripheral blood smear, and a Coombs test to evaluate for anemia and hemolysis. Testing for G6PD deficiency may be added to the workup if suspicion is high, including in infants who do not respond to phototherapy. Genetic testing may also be done for Gilbert’s or Crigler-Najjar syndrome outside the ED setting, if warranted.

**Treatment**

The main goal in the treatment of unconjugated hyperbilirubinemia is the prevention of kernicterus. Phototherapy is the main treatment modality and
works by isomerization of bilirubin to water-soluble products that can be excreted in the urine and stool. Specific clinical practice guidelines for the management of hyperbilirubinemia in newborns were developed and published by the AAP in 2004. For markedly elevated serum bilirubin values, exchange transfusion may be necessary to keep the levels < 20 mg/dL. A study by Newman et al in 2006 determined that there were no adverse neurodevelopment outcomes when infants with high bilirubin levels (ie, between 25.0 and 29.9 mg/dL) were treated with phototherapy or exchange transfusion.33

The AAP recommends initiating treatment in cases of neonatal hyperbilirubinemia. These recommendations are summarized in Table 6, on page 8. The patient should be admitted to a pediatric service or neonatal unit where continued therapy and monitoring are available.

### Conjugated Hyperbilirubinemia

In an ill-appearing infant with conjugated hyperbilirubinemia, the most important initial step is to rapidly diagnose and treat potentially life-threatening disorders such as bacterial infection or sepsis, endocrine disorders (panhypopituitarism, hypothyroidism), and metabolic disorders/inborn errors of metabolism (eg, galactosemia).

### Intrahepatic Cholestasis

**Acute Liver Failure In The Pediatric Patient**

Fulminant or acute liver failure (ALF) occurs when liver function is severely compromised. It is a life-threatening condition manifested by jaundice, coagulopathy, hypoglycemia, and encephalopathy. Fulminant hepatic failure in children is a clinical syndrome that evolves over a period of 8 weeks or less from the onset of signs and symptoms of liver disease. In some cases of non A-E hepatitis, encephalopathy may occur later, often from 8 to 28 weeks after the onset of jaundice, and it may have a subfulminant course. Since hepatic encephalopathy (HE) may be subtle in infants and children and may not be clinically apparent until the terminal stages, the Pediatric Acute Liver Failure group came up with the following criteria for the definition of ALF in children: no evidence of a known chronic liver disease (except WD), vitamin K treatment refractory coagulopathy, and international normalized ratio (INR) > 1.5 in the presence of HE or an INR > 2 in

<table>
<thead>
<tr>
<th>Age</th>
<th>Total Serum Bilirubin Level (mg/dL)</th>
<th>Consider phototherapy.</th>
<th>Initiate phototherapy.</th>
<th>Initiate exchange transfusion if intensive phototherapy fails.</th>
<th>Initiate exchange transfusion and intensive phototherapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-48 hours</td>
<td>≥ 12</td>
<td>≥ 15</td>
<td>≥ 20</td>
<td>≥ 30</td>
<td></td>
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<tr>
<td>49-72 hours</td>
<td>≥ 15</td>
<td>≥ 18</td>
<td>≥ 25</td>
<td>≥ 30</td>
<td></td>
</tr>
<tr>
<td>&gt; 72 hours</td>
<td>≥ 17</td>
<td>≥ 20</td>
<td>≥ 25</td>
<td>≥ 30</td>
<td></td>
</tr>
</tbody>
</table>

Etiologies of ALF vary by age, with metabolic and infectious diseases prominent in the first year of life and acetaminophen overdose and WD occurring in adolescence. In almost 50% of cases, however, ALF has an indeterminate cause. Hepatitis A, B, D, and E viruses are a common cause of identifiable fulminant hepatic failure worldwide; however, they are found in only 5% of children in North America and the United Kingdom. Viral infections are identified more frequently in infants and immunodeficient patients and include herpes simplex, human herpesvirus, parvovirus B19, cytomegalovirus, adeno-associated virus, varicella-zoster, enterovirus, and paramyxovirus. Epstein-Barr virus (EBV) occurs more frequently in older patients.

Fulminant hepatic failure may also result from use of some hepatotoxic drugs and chemicals. Risk factors for drug-induced hepatotoxicity are age (very young children or adolescents), abnormal renal function, concurrent use of other hepatotoxic agents, drug interactions, and preexisting liver diseases. Drug-induced hepatotoxicity can be dose-dependent, idiosyncratic, or a synergistic reaction. Drugs that commonly induce an idiosyncratic toxicity include isoniazid, sodium valproate, carbamazepine, penicilllin, erythromycin, tetracyclines, sulfonamides, quinolones, amiodarone, and pemoline. Toxins that induce ALF include Amanita phalloides (mushroom poisoning), herbal medicines, and carbon tetrachloride.

Metabolic causes of ALF are more common in infants but may be observed in all age groups. Galactosemia, hereditary tyrosinemia type I, mitochondrial disorders, fatty acid oxidation disorders, hereditary fructose intolerance, neonatal hemochromatosis, inborn errors of bile acid metabolism, congenital disorder of glycosylation, and other inherited metabolic disorders can all cause hepatic failure. Wilson’s disease is currently the most common metabolic disorder presenting with ALF in older children and adolescents. Autoimmune hepatitis can also present as ALF, most often in patients with positive liver/kidney microsomal antibody tests. Fulminant hepatic failure may also be associated with sepsis, vascular occlusion (Budd-Chiari syndrome and veno-occlusive disease), congestive heart failure, cyanotic congenital heart disease, obstructive lesions of the aorta, circulatory shock, heat stroke, and hemophagocytic lymphohistiocytosis.

The child with fulminant hepatic failure is often
Electrolyte disturbances are common, including hypokalemia, hyponatremia, hypophosphatemia, hyperammonemia, metabolic acidosis, and respiratory alkalosis. Renal function may be impaired as a result of tubular injury, hypovolemia, or hepatorenal syndrome (HRS). Serum acetaminophen levels after 4 hours of ingestion are useful in identifying high-risk patients but are not informative in patients in whom toxicity is secondary to long-term administration. Myelosuppression is associated with non–A-E hepatitis etiology for ALF and non-immune hemolytic anemia with WD. a-Fetoprotein and selective clotting factors with short half-lives may serve as markers of liver regeneration.

**Treatment**

The treatment of fulminant hepatic failure consists primarily of supportive care. Numerous complications may also be identified and should be promptly treated. (See Table 8 on page 10.) Patients who are significantly disoriented or comatose often require endotracheal intubation to prevent aspiration, reduce cerebral edema with hyperventilation, or prevent aspiration of secretions. Patients should be monitored in an intensive care unit. A quiet environment is necessary to avoid an increase in intracranial pressure. Cerebral edema is an extremely serious complication that responds poorly to measures commonly used to treat it in the presence of other disorders. Initial management includes minimizing excessive stimulation, treating suspected sepsis, and removing sedative medications that affect mental status. The role of hypothermia in clinical practice remains unclear. Hyperventilation may actually worsen oxygen availability to the brain, but osmotic diuresis may be useful in maintaining cerebral perfusion pressure. The placement of an intracranial pressure monitor may be useful in guiding treatment. The gut should be purged with lactulose, a nonabsorbable disaccharide thought to lower blood ammonia concentrations by decreasing microbial ammonia synthesis and trapping ammonia in acidic colonic

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Presentation</th>
<th>Reflexes</th>
<th>Neurologic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Irritability, poor feeding, change in sleep rhythm, child not acting like self (according to parents)</td>
<td>Normal or hyper-reflexive</td>
<td>Tremor, apraxia, impaired handwriting (difficult to test adequately in infants)</td>
</tr>
<tr>
<td>II</td>
<td>Drowsiness, inappropriate behavior, decreased inhibitions</td>
<td>Normal or hyper-reflexive</td>
<td>Dysarthria, ataxia (difficult to test adequately in infants)</td>
</tr>
<tr>
<td>III</td>
<td>Somnolence, stupor, combativeness,</td>
<td>Hyper-reflexive, positive Babinski sign</td>
<td>Rigidity</td>
</tr>
<tr>
<td>IV</td>
<td>Coma, arousal with painful stimuli (4a) or no response (4b)</td>
<td>Absent</td>
<td>Decerebrate or decorticate rigidity</td>
</tr>
</tbody>
</table>

**Diagnosis**

In patients with ALF, direct and indirect serum bilirubin levels are variably increased. Although extremely high serum aminotransferase activity levels are often found, the peak level does not correlate well with the severity of the illness. In metabolic disorders, liver failure may be present with only a modest elevation in activity. A coagulopathy is always present with prolongation of prothrombin time. Hypoglycemia can occur, particularly in infants. A number of

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Table 7. Stages Of Hepatic Encephalopathy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Presentation</th>
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<th>Neurologic Findings</th>
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<td>Decerebrate or decorticate rigidity</td>
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</table>
Lactulose should be dosed to produce several loose acidic bowel movements each day. Nonabsorbable antibiotics such as rifaximin may also be given to decrease the level of enteric bacteria that produce ammonia and are superior to nonabsorbable disaccharides in improving HE.

Renal dysfunction commonly occurs as a result of dehydration, acute tubular necrosis associated with the initial toxic insult, and HRS. Renal replacement therapy with continuous venovenous hemofiltration or dialysis may be necessary, but only liver transplantation can reverse HRS. Intravenous fluids should be restricted and should represent only 85% to 90% of maintenance fluids to avoid overhydration. Electrolyte- and glucose-containing solutions should be administered intravenously to maintain urine output, correct electrolyte abnormalities, and prevent hypoglycemia, as the liver is the primary organ for gluconeogenesis. In addition, 10% dextrose should be administered, and blood glucose levels should be monitored hourly until stabilization. Hyponatremia is usually dilutional and not a reflection of sodium depletion. Parenteral infusion of calcium, phosphorous, and magnesium is also often required.

Intravenous, subcutaneous, or intramuscular vitamin K should be given to help correct the coagulopathy (2-2.5 mg in infants, 5 mg in older children and adolescents). Intravenous vitamin K has been associated with acute hypotension and therefore needs to be given slowly in infants, not more than 1 mg/min, although other studies have not supported this finding. Disseminated intravascular coagulation may be present in these patients as a result of liver failure as well as infection. Infusion of fresh frozen plasma (FFP), recombinant activated factor VII, or platelets may be necessary in the setting of active bleeding or in anticipation of an invasive surgical procedure rather than treating laboratory abnormalities. Patients can rapidly become fluid overloaded with infusions of large amounts of FFP.

Gram-positive and gram-negative bacteria or fungal infections commonly occur and may be fulminating for patients with liver failure. At least 50% of patients experience a serious disorder such as sepsis, pneumonia, peritonitis, or a urinary tract infection. Infection may present subtly with tachycardia, intestinal bleeding, reduced renal output, or changes in mental status. Fever may not be present. Blood cultures should be obtained with any evidence of clinical deterioration and antibiotics initiated with a clinical concern for sepsis. Prophylactic administration of H2-receptor blockers is usually advised because of the high risk of gastrointestinal tract bleeding.

Ascites can be managed with fluid restriction and diuretics. The diuretic of choice is spironolactone, an aldosterone antagonist, at a starting dose of 1 mg/kg to be increased gradually up to 6 mg/kg per day. It may take 2 to 4 days for full effect. The most significant side effects are hyponatremia and hyperkalemia. Furosemide (1-2 mg/kg) can be used to control the hyperkalemia and to promote a strong and rapid response. Thiazide diuretics can be used at a dosage of 2 to 3 mg/kg per day, although in the authors’ experience they are rarely needed. Large-volume paracentesis should be reserved for those patients who experience tense ascites, respiratory compromise, or renal failure. Up to 100 mL/kg can be removed while replacing the protein and volume loss with albumin at a concentration of 1 g/100 mL. Overly aggressive diuresis may precipitate HRS.

Specific therapies for the unique causes of ALF are limited and are summarized in Table 9. Other therapies in use include activated charcoal; copper chelation, plasmapheresis, and antioxidant therapy for WD; lamivudine or entecavir for acute hepatitis B; hemodynamic support for shock or ischemic liver injury; and decompressive surgery or transjugular intrasheptic portosystemic shunts for acute Budd-Chiari syndrome. Currently, the only effective cure for ALF is liver transplantation.

A variety of approaches has been used to assist the liver in removing toxins that may cause encephalopathy. Plasmapheresis and perfusion of the patient’s plasma through an ion-exchange resin or a column of charcoal have been used in several studies. In uncon-

<table>
<thead>
<tr>
<th>Table 8. Extrahepatic Complications Of Fulminant Hepatic Failure</th>
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</thead>
<tbody>
<tr>
<td>• Hepatic encephalopathy</td>
</tr>
<tr>
<td>• Complex coagulopathy</td>
</tr>
<tr>
<td>• Cerebral edema</td>
</tr>
<tr>
<td>• Cardiovascular abnormalities</td>
</tr>
<tr>
<td>• Acid-base disturbances</td>
</tr>
<tr>
<td>• Gastrointestinal tract bleeding</td>
</tr>
<tr>
<td>• Electrolyte imbalances</td>
</tr>
<tr>
<td>• Renal failure</td>
</tr>
<tr>
<td>• Sepsis</td>
</tr>
<tr>
<td>• Pulmonary problems</td>
</tr>
<tr>
<td>• Hypoglycemia</td>
</tr>
<tr>
<td>• Pancreatitis</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Table 9. Treatment Of Acute Liver Failure According To Etiology</th>
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</thead>
<tbody>
<tr>
<td>Cause Of Acute Liver Failure</td>
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<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Herpes virus infection</td>
</tr>
<tr>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Amanita phalloides</td>
</tr>
<tr>
<td>Tyrosinemia type I</td>
</tr>
<tr>
<td>Wilson’s disease</td>
</tr>
<tr>
<td>Galactosemia</td>
</tr>
<tr>
<td>Fatty acid oxidation</td>
</tr>
<tr>
<td>Hemophagocytic syndrome</td>
</tr>
<tr>
<td>Neonatal hemochromatosis</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
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</tbody>
</table>
trolled studies, patients experienced some clinical improvement, but no impact on neurologic outcome or the ability of the liver to recover spontaneously was found.\textsuperscript{45} Albumin dialysis is suggested in selective patients.\textsuperscript{47} Gastrointestinal tract hemorrhage, infection, sedative use, electrolyte imbalance, and hypovolemia may precipitate or exacerbate HE and should be prevented or aggressively treated.

A number of liver assist devices are under evaluation: non-cell-based systems (molecular absorbent recycling systems), cell-based bioartificial liver systems, hepatocyte bioreactors, and stem cell transplantation. These methods are used to support patients until regeneration of their liver or to bridge the gap until a suitable organ donor can be found.

### Toxin- And Drug-Induced Liver Injury

Drug-induced liver injury (DILI) can be acute or chronic. Acute DILI is more common and can present with a variety of injury patterns including hepatocellular, cholestatic, or a mixture of the two.\textsuperscript{84} Acute cholestatic patterns often mimic those of extrahepatic obstructive jaundice, with patients presenting with both jaundice and pruritus. Common drugs associated with cholestasis-type damage in pediatric patients are listed in Table 10.\textsuperscript{51,52}

Acetaminophen use is the most common cause of DILI in the United States as well as the second most frequent etiology of ALF in children. Hepatotoxicity results when the patient’s ability to conjugate and metabolize acetaminophen is saturated; the cytochrome P-450 2E1 pathway is then stimulated to form N-acetyl-benzoquinoneimine, which rapidly binds to available intracellular glutathione (an effective hepatoprotectant), leaving the liver susceptible to injury by reactive intermediates.\textsuperscript{55} Although patients often present with a hepatocellular pattern, the emergency clinician should obtain a serum acetaminophen level in any patient with an acute elevation in liver enzymes. As mentioned previously, overdosing can be intentional or unintentional in pediatric patients. Many OTC drugs, especially cold remedies, contain acetaminophen, and they may unknowingly be combined with other acetaminophen-containing medications, leading to hepatotoxicity. Patients with acetaminophen levels above the possible toxicity line of the Rumack-Matthew nomogram require a full course (72 hours) of N-acetylcysteine (a 140-mg/kg loading dose, then 70 mg/kg every 4 hours for 17 doses). (See Figure 2.) Patients with evidence of hepatic injury at the time of presentation (eg, increased level of liver enzymes, hypocoagulability, or encephalopathy) must be treated in an inpatient setting.

The use of herbal remedies must be considered as an etiology in any setting of liver injury. Unlike medications that must pass Food and Drug Administration approved clinical trials before release to the public, herbal products do not need FDA approval.\textsuperscript{57} Although herbal-induced toxicity may present with nonspecific symptoms, extracts of kava-kava, a plant in the pepper family that is often used for anxiety and sleep problems, have been linked to ALF and death.\textsuperscript{55,58,62} Similarly, excessive ingestion of vitamin A has been shown to cause liver cirrhosis and portal hypertension.\textsuperscript{63,65}

### Diagnosis And Treatment

No clinical sign or laboratory value is pathognomonic for DILI. Often the temporal relationship between initiation of a drug and the onset of liver injury or the resolution of hepatotoxicity upon withdrawal of the drug are the most telling clues.\textsuperscript{55}

### α1-Antitrypsin Deficiency

α1-Antitrypsin deficiency (A1ATD) is a common genetic disorder; 1 in 4455 people have the ZZ phenotype.\textsuperscript{66} Approximately 12% of patients with the disorder present with obstructive jaundice, and 7% have minor liver dysfunction.\textsuperscript{67} In patients with A1ATD, α1-Antitrypsin levels are usually low. However, the criterion standard is protein or genetic analysis (homozygous Pi type ZZ or SZ or other rare deficiency variant). Half of patients with liver dysfunction eventually develop cirrhosis, and em-

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### Table 10. Common Pediatric Drugs Associated With Cholestatic Injury

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>Amoxicillin-clavulanate, Cloxacillin, dicloxacillin</td>
</tr>
<tr>
<td>Estrogens</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td></td>
</tr>
<tr>
<td>Anabolic steroids</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Amoxicillin-clavulanate, Cloxacillin, dicloxacillin, Clindamycin, erythromycin, Nafcillin, nitrofurantoin, rifampin, trimethoprim-sulfamethoxazole, tetracycline</td>
</tr>
<tr>
<td>Herbal Remedies</td>
<td>Chaparral leaf (Larrea tridentata), glycyrrhizin, Helvola majus</td>
</tr>
<tr>
<td>Haloperidol</td>
<td></td>
</tr>
<tr>
<td>Phenothiazines</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen</td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td></td>
</tr>
<tr>
<td>Angiotensin inhibitors</td>
<td>captopril, enalapril</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>amitriptyline, imipramine</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
</tr>
</tbody>
</table>

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Physema commonly presents by the fourth or fifth decade of life.66

**Cystic Fibrosis**
Cystic fibrosis (CF) is a multisystem disease affecting 1 in 2000 Caucasians. From 20% to 50% of patients with CF develop liver disease, ranging in severity from asymptomatic derangement of liver function tests and focal biliary fibrosis to cirrhosis with portal hypertension and chronic liver failure.68 Features of advanced clinical liver disease are most prominent in adolescents and young adults with CF.

**Wilson’s Disease**
Wilson’s disease, also known as hepatolenticular degeneration, is an autosomal recessive disorder of copper metabolism. The carrier frequency for WD is about 1 in 150 to 180 individuals, with a prevalence of 1 in 30,000.69,70 The liver is both the site of the metabolic defect in WD and the initial target of copper toxicity. Liver diseases range from asymptomatic in patients with elevated aminotransferase levels or hepatomegaly to fulminant liver failure in others, whose only option may be liver transplantation. Initial presentation may include nonspecific symptoms (anorexia, fatigue, jaundice, ascites, variceal bleeding, amenorrhea, or poor school function), and misdiagnosis and lack of appropriate treatment may lead to disease progression. Acute hepatitis (resembling an acute viral hepatitis) is the mode of presentation in 25% of patients.71 From 10% to 30% of children with WD present with signs and symptoms of chronic liver disease and evidence of cirrhosis, either compensated or decompensated.70 No single test confirms the diagnosis of WD, and referral to a pediatric hepatologist is warranted. Often, laboratory tests will demonstrate elevated levels of liver enzymes and conjugated hyperbilirubinemia, along with an extremely low serum ceruloplasmin level, elevated urinary copper excretion, and an elevated serum copper concentration. A liver biopsy may be necessary for quantification of hepatic copper or gene testing.

The medical management of WD is based on the use of copper chelators (penicillamine or trientine) or zinc to reduce copper absorption. Liver transplantation is a life-saving therapy for WD patients with fulminant liver failure, those with fulminant liver failure after discontinuing copper chelation therapy, and those with decompensated liver disease unresponsive to medical therapy. Liver transplantation corrects the hepatic metabolic defects of WD and may serve to initiate normalization of extrahepatic copper metabolism.

**Metabolic Disease**
Patients with hypothyroidism or panhypopituitarism may also present with jaundice.8 Infants with a metabolic disease such as galactosemia may present with vomiting, diarrhea, lethargy, and hypotonia within hours of milk ingestion. Continued galactose ingestion leads to hemolysis, jaundice, liver disease, lactic acidosis, and renal tubular acidosis. Neonates may present with *Escherichia coli* sepsis. Failure to thrive, hepatosplenomegaly, cirrhosis, and cataracts develop over time. Diagnosis is usually based on newborn screening and positive non-glucose urine reducing substances and is further confirmed by low activity of galactose-1-phosphate uridyl transferase in RBCs. It is managed medically with a galactose-free diet.68 Presentations and diagnoses of other common metabolic diseases associated with jaundice are listed in Table 11.

**Autoimmune Hepatitis**
Autoimmune hepatitis may present or progress to jaundice. It is characterized by elevated levels of transaminases and total immunoglobulin G (IgG) and positive autoimmune markers (antinuclear antibodies, anti-smooth muscle, or antiliver-kidney microsomal antibodies). A diagnosis requires a liver biopsy to reveal interface hepatitis with predominance of plasma cells. Immunosuppressive therapy with steroids is a first-line treatment.72

**Caroli Disease**
Caroli disease is a congenital disorder characterized by multifocal, segmental dilatation of large..
Jaundiced infant 2 to 8 weeks old

Is the patient acutely ill? Require urgent care?

- Manage the acute illness
- Consider urinary tract or other infection, galactosemia, tyrosinemia, hypopituitarism, fructosemia, iron storage disease, metabolic disorders, acute common duct obstruction, hemolysis.

Is there direct hyperbilirubinemia?

Measure serum direct bilirubin

Cholestatic Jaundice

History, physical exam, Urinalysis, urine culture

Findings of specific disease?

Evaluate further (See AAP guideline)

Evaluate further

Consult Pediatric GI
- CBC, platelet count
- Total and direct bilirubin, ALT, AST, alkaline phosphate, glucose
- Prothrombin time, albumin
- Urine reducing substances
- Abdominal ultrasound

Choledochal cyst?

Low α-1 antitrypsin?

Consider:
- Percutaneous liver biopsy
- Scintiscan
- Duodenal aspirate
- ERCP

Is there evidence of biliary obstruction?

No hyperbilirubinemia

No hyperbilirubinemia

Does bilirubin normalize by 6 weeks of age?

Pi typing
- Further management

Yes

No

No

Yes

Consent Pediatric surgeon.
- Operative cholangiogram

ABNORMAL

NORMAL

Indirect hyperbilirubinemia

NATIONAL CENTER FOR BIOMEDICAL RESOURCES, NIH, Public Access Participation Program

Clinical Pathway For The Treatment Of Jaundice In 2- To 8-Week Old Infants

to 20% of all cases are associated with congenital anatomic abnormalities, most commonly splenic malformation syndrome. Typically, biliary atresia presents shortly after birth with persistent jaundice, pale stools (white to beige), and dark urine in term infants with normal birthweights. Splenomegaly is not usually a feature unless presentation is late, and it is then a sign of portal hypertension. An antenatal maternal ultrasound with abnormal findings (ie, a cyst related to the porta hepatis, bile duct, or liver) is associated with about 5% of biliary atresia (cystic biliary atresia) in infants. Some patients with missed diagnosis may present with failure to thrive, hepatomegaly, ascites, and coagulopathy.

Laboratory studies typically identify cholestatic liver function tests with elevated levels of direct bilirubin, serum \( \gamma \)-glutamyltransferase (higher than in other causes of neonatal cholestasis), alkaline phosphatase, and cholesterol; however, hepatic synthetic function is usually normal. An abdominal ultrasound typically shows hepatomegaly, absence of biliary dilatation, and absent or contracted gallbladder after a 4-hour fast (20% of patients may have a normal gallbladder). Up

### Table 11. Common Metabolic Diseases Associated With Jaundice

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical Presentation</th>
<th>Diagnostic Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galactosemia</td>
<td>Vomiting and hypoglycemia after ingesting lactose (breast milk)</td>
<td>Results of newborn screening</td>
</tr>
<tr>
<td></td>
<td>Fulminant liver failure</td>
<td>Positive non-glucose urine reducing substances</td>
</tr>
<tr>
<td></td>
<td>Escherichia coli sepsis</td>
<td>Low activity of galactose-1-phosphate uridyl transferase in red blood cells</td>
</tr>
<tr>
<td></td>
<td>Cataracts</td>
<td></td>
</tr>
<tr>
<td>Hereditary fructosemia</td>
<td>Vomiting</td>
<td>Low fructose-1-phosphate aldolase B activity in liver tissue</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia and tremor after exposure to fructose (fruit)</td>
<td>Liver biopsy with EM</td>
</tr>
<tr>
<td></td>
<td>Fulminant liver failure</td>
<td>Genetic analysis</td>
</tr>
<tr>
<td></td>
<td>Renal dysfunction</td>
<td></td>
</tr>
<tr>
<td>Tyrosinemia</td>
<td>Fulminant liver failure</td>
<td>Results of newborn screening</td>
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<tr>
<td></td>
<td>Cirrhosis</td>
<td>High serum tyrosine and methionine levels</td>
</tr>
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<td></td>
<td>Early hepatocellular carcinoma</td>
<td>High serum ( \alpha )-fetoprotein level</td>
</tr>
<tr>
<td></td>
<td>Neurologic crisis</td>
<td>Succinylacetone detection in urine</td>
</tr>
<tr>
<td></td>
<td>Renal dysfunction</td>
<td></td>
</tr>
<tr>
<td>Neonatal hemochromatosis</td>
<td>Fulminant liver failure</td>
<td>High ferritin level (&gt; 1000 µg/L)</td>
</tr>
<tr>
<td></td>
<td>Coagulopathy in the presence of near-normal transaminase levels</td>
<td>Low total iron-binding capacity</td>
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<tr>
<td></td>
<td></td>
<td>Liver biopsy with iron stain or buccal mucosal biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MRI (of the abdomen for typical pattern of iron deposition)</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Cirrhosis and portal hypertension</td>
<td>Results of newborn screening</td>
</tr>
<tr>
<td></td>
<td>Pulmonary disease</td>
<td>Sweat chloride test</td>
</tr>
<tr>
<td></td>
<td>Steatorrhea</td>
<td>Genetic analysis</td>
</tr>
<tr>
<td>Progressive familial intrahe-</td>
<td>Progressive pruritus</td>
<td>Low serum ( \gamma )-glutamyltransferase level in disease types 1 and 2</td>
</tr>
<tr>
<td>patic cholestasis</td>
<td>Hearing loss</td>
<td>Liver biopsy with EM</td>
</tr>
<tr>
<td>Inborn errors of bile acid</td>
<td>Jaundice without pruritus</td>
<td>Genetic testing</td>
</tr>
<tr>
<td>metabolism</td>
<td></td>
<td>Low serum ( \gamma )-glutamyltransferase and bile acid levels</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urinalysis for bile acids</td>
</tr>
</tbody>
</table>

Abbreviations: EM, electron microscopy; MRI, magnetic resonance imaging.
known as the triangular cord sign, is a specific finding in almost all cases, but it is operator-dependent, with reported sensitivities of 49% to 73%.\(^2\)

Early diagnosis of biliary atresia is essential, as the outcome of the Kasai operation, or portoenterostomy, is more likely to be successful (defined as a normal bilirubin concentration within 6 months of the procedure) if done before 60 days of life.\(^3\)

**Pancreatitis**

Obstructive jaundice may be among the symptoms seen with pancreatitis. In contrast to adults, who present with constant pain from pancreatitis, children more frequently exhibit recurrent epigastric abdominal pain, nausea, and vomiting.\(^7\) The most common etiologies of pancreatitis in children, regardless of age, are systemic illness, biliary disease, trauma, and medication side effects, with the remainder classified as idiopathic.\(^7\) Obstructive jaundice can also be the presenting feature in other pancreatic diseases including annular pancreas, pancreatic duct anomalies, and more rare entities such as autoimmune pancreatitis and idiopathic fibrosing pancreatitis.\(^7\)

Upon admission, all patients should have screening laboratory tests including amylase and lipase levels, triglyceride levels, calcium level, and liver chemistries (bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase). The American Gastroenterological Association (AGA) published guidelines on acute pancreatitis in 2007 and recommends an abdominal ultrasound to assess for cholelithiasis or choledocholithiasis.\(^7\)

For most cases of pancreatitis, treatment consists of pain relief, intravenous hydration with limitation of oral intake, and observation for complications. The AGA also recommends nasojejunal tube feedings with an elemental or semi-elemental formula rather than TPN for those patients likely to remain on “nothing by mouth” status for more than 7 days. In those patients unable to tolerate enteral nutrition, total parental nutrition (TPN) should be given.\(^7\) Endoscopic retrograde cholangiopancreatography (ERCP) may be required if gallstones are the inciting factor. Prophylactic antibiotics may be considered in cases of severe acute pancreatitis with necrosis, though it remains controversial, with no standardized practice guidelines.

**Choledochal Cyst**

A choledochal cyst is a congenital dilatation of the extrahepatic and/or intrahepatic biliary trees. The classic presentation in a child with a choledochal cyst is jaundice, abdominal pain, and a palpable right upper-quadrant mass.\(^7\) A single-center study by Edil et al examined choledochal cysts seen in patients over a 30-year period.\(^7\) They found that children most commonly presented with jaundice and only rarely with the complete triad. In contrast, adults presented with jaundice only 25% of the time and were more likely to report abdominal pain. Concurrent pancreatitis occurred in 30% of both children and adults.\(^7\)

The recognition and management of choledochal cysts must occur in a timely manner, as these patients have a substantial risk of developing cholangiocarcinoma; complete excision of the cyst is the standard of care to reduce the risk of malignancy.\(^7\)

**Cholelithiasis**

Cholelithiasis is rare in infants and children, although the prevalence is increasing along with childhood obesity rates.\(^7\) One population-based study estimated the prevalence of gallstones and biliary sludge in children at 1.9% and 1.46%, respectively.\(^7\) Cholelithiasis may be an incidental finding, or it may be asymptomatic. Jaundice occurs in approximately 50% of children with the disease.\(^7\) Hemolytic disorders account for most of the cholelithiasis seen in children. Other etiologies include prolonged TPN use, ileal resection, short bowel syndrome, obesity, adolescent pregnancy, and idiopathic causes.\(^8\) Choledocholithiasis is also rare in children and most commonly occurs with biliary tract malformations (eg, choledochal cysts), hemolysis, chronic liver disease, and infection. Patients who are symptomatic often require ERCP as therapeutic intervention.

**Diagnosis**

Diagnosis of extrahepatic biliary obstruction versus intrahepatic causes of hyperbilirubinemia can be accomplished through various imaging modalities. (See Table 12.)

**Infectious Causes**

The so-called TORCH agents (toxoplasmosis; other [hepatitis B, syphilis, varicella-zoster virus, HIV, and parvovirus B19]; rubella virus; cytomegalovirus; and herpes simplex virus) account for about 5% of hepatitis cases due to congenital infections.\(^10\)

**Bacterial**

Bacterial infections are a well-known cause of concomitant conjugated hyperbilirubinemia, most likely due to the effect of bacterial endotoxins on bile formation.\(^7\) The most frequent bacterial organism causing neonatal hepatitis is *E. coli*. Group B streptococci are rarely implicated.\(^9\) In most cases, the child will present with symptoms other than jaundice that are suspicious for infection (ie, fever, lethargy). In such cases, the initial evaluation should include bacterial cultures as appropriate. As the cause of jaundice is most likely related to the underlying illness rather than to primary liver disease, in the acutely ill child management should be geared toward the underlying disease.\(^7\) In infants, jaundice can be an early sign of urinary tract infections in the absence of other symptoms. Otherwise asymptomatic infants presenting to the ED with jaundice should be tested for a urinary tract infection as part of the initial evalu-
tion, particularly if the onset of jaundice occurs after 8 days of life.\textsuperscript{83}

Bacteremia and sepsis with cytokine formation may induce cholestasis. Cholestasis with cytokine release results from decreased expression of sodium, potassium, and adenosine triphosphatase and the downregulation of transport proteins critical to bile formation.\textsuperscript{39} Other infections such as cholangitis, cholecystitis, and pancreatitis can directly obstruct the biliary tree and present with jaundice.

\textbf{Viral}

Infection with any of the hepatotropic viruses (A, B, C, D, or E) may cause jaundice in the pediatric population, specifically older children and adolescents. With these infections, jaundice is secondary to conjugated hyperbilirubinemia resulting from intrahepatic cholestasis.\textsuperscript{82}

\textbf{Hepatitis A}

\textbf{Clinical Features:} The severity of hepatitis A viral (HAV) infections is age dependent. In older children and adolescents, HAV is the most common infectious cause of acute jaundice\textsuperscript{82} and usually presents with an abrupt onset of fever, headache, anorexia, nausea, and right upper-quadrant pain. Older children may also exhibit significant elevations in AST and ALT levels as well as conjugated hyperbilirubinemia.\textsuperscript{82} In infants and preschool-aged children, the presentation may be clinically unapparent and mostly asymptomatic, with possible scleral icterus.\textsuperscript{85,86} Although HAV infection is usually self-limiting, in some cases it can cause jaundice that relapses or persists for months.

\textbf{Diagnosis:} Serologic markers for anti-hepatitis A viral antigen (anti-HAV) should be sent on presentation, including anti-HAV immunoglobulin M (IgM) and anti-HAV IgG. Anti-HAV IgM is found during the acute phase of hepatitis A infection, is present for only 3 to 6 months after infection, and is seldom found after vaccination.\textsuperscript{83} Anti-HAV IgG may be found during the early onset of infection but is accompanied by positive IgM test results. When found alone, anti-HAV IgG indicates past infection or immunization. It can persist for decades and represents recovery and resistance to reinfection.\textsuperscript{83} Although viral hepatitis can present as fulminant liver failure, hepatitis A infection is rarely the cause, occurring in less than 1\% of such cases.\textsuperscript{82}

\textbf{Treatment:} Treatment of hepatitis A infections is supportive, focusing on the hydration status of patients with vomiting and fatigue. Clinical symptoms as well as biochemical abnormalities will completely resolve within 3 to 6 months and, in most patients, as early as 4 weeks.\textsuperscript{83,86} Although this approach may require additional ED visits for evaluation, hepatitis A infection does not lead to chronic hepatitis (ie, infection lasting more than 6 months).

\textbf{Hepatitis B, C, D, And E}

\textbf{Clinical Features:} Pediatric patients with hepatitis B (HBV) and hepatitis C (HCV) infections are asymptomatic. Nevertheless, jaundice may occur in older children with acute HBV infection or in those with chronic HBV or HCV infection who develop cirrhosis at an early age. Hepatitis D infection is rare in the United States and occurs only in those already infected with HBV. Acute hepatitis E infection can present with jaundice similar to that seen in HAV infections, but this disorder is prevalent mostly in developing countries.\textsuperscript{82}

\textbf{Hepatitis B:} In the general population, acute HBV infections result from horizontal transmission, namely via highly infectious family members, improperly sterilized syringes, accidental needle sticks, or unprotected sexual activity. Chronic HBV infection is usually acquired through perinatal transmission. Older children with chronic HBV infection are often asymptomatic carriers or have limited subclinical, biochemical hepatitis, evidenced by increased hepatic transaminase levels.\textsuperscript{82}

\begin{table}[h]
\centering
\begin{tabular}{|l|l|l|}
\hline
\textbf{Study} & \textbf{Advantages} & \textbf{Limitations} \\
\hline
Liver ultrasound & • Quick & • Operator dependent (best done at a referral center) \\
 & • Inexpensive & \\
 & • Noninvasive & \\
 & • No radiation & \\
 & • No sedation & \\
\hline
MRCP & • Noninvasive & • Image artifacts \\
 & • As sensitive and specific as ERCP & • Lower resolution than direct cholangiography \\
 & • Lower cost and risk vs ERCP in adults & • Can miss small stones (< 4 mm), small ampullary lesions, primary sclerosing cholangitis, and strictures of the ducts \\
 & & • Sedation needed \\
 & & • Diagnostic, not therapeutic \\
\hline
ERCP & • Diagnostic and therapeutic capabilities & • Available only in specialty settings \\
 & • Can be combined with endoscopic ultrasound & • Invasive \\
 & & • Significant radiation exposure \\
 & & • Significant side effects \\
 & & • Expensive \\
\hline
\end{tabular}
\caption{Imaging Modalities For Diagnosis Of Extrahepatic Obstruction}
\end{table}

(\textsuperscript{Abbreviations: MRCP, magnetic resonance cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography.)
**Hepatitis C:** Prior to 1992, most children contracted HCV infection through contaminated blood products. Today, the most important source of HCV infection in the pediatric population is maternal-infant transmission.

**Treatment:** Hepatitis viral infections are diagnosed by serologic antibody tests, which are summarized in Table 13. Once the diagnosis is made, patients with no other reason for admission should be discharged with instructions for appropriate follow-up with a pediatric gastroenterologist/hepatologist who specializes in chronic hepatitis infections. In the case of HBV infection, specific serologies will help determine acute versus chronic varieties.

**Epstein-Barr Virus, Cytomegalovirus, Herpes Simplex Virus, Varicella-Zoster Virus**
Jaundice and acute hepatitis can be presenting signs in older children and adolescents infected with Epstein-Barr virus and are usually seen as part of infectious mononucleosis syndrome. Jaundice in conjunction with lymphadenopathy syndrome, sore throat, and splenomegaly in any pediatric patient should be evaluated with Epstein-Barr virus serologies. Cytomegalovirus, herpes simplex virus, and varicella-zoster virus should be considered in immunocompromised patients and neonates presenting with jaundice and hepatobiliary disease.

**Diagnostic Studies**

**Bilirubin**
Serum bilirubin is typically measured using 2 assays: total and direct. The terms direct and indirect reflect how the 2 types of bilirubin react to certain dyes. Conjugated bilirubin is water-soluble and reacts directly when dyes are added to the blood specimen. Non-water-soluble free bilirubin does not react with the reagents until alcohol is added to the solution. Therefore, the measurement of this type of bilirubin is indirect. Subtracting the direct bilirubin level from the TSB level gives the indirect bilirubin value. The direct bilirubin assay measures the majority of α-bilirubin and conjugated bilirubin, as well as a small but variable percentage of unconjugated bilirubin. Direct spectrophotometry (dry film method) measures conjugated and unconjugated bilirubin levels individually. Some have suggested that the conjugated bilirubin value is better than the direct bilirubin level for measuring recovery from liver disease, as it is cleared from serum more rapidly. Assays for bilirubin should have a total analytical error of ≤ 20% (or 6.8 μmol/L [0.4 mg/dL]) at the upper reference limit.

**Urobilinogen**
Conjugated bilirubin is hydrolyzed in the small intestine to unconjugated pigment, which is further reduced by anaerobic bacterial flora to urobilinogen. In all, 20% of urobilinogen is reabsorbed via the enterohepatic circulation, and most is excreted into the bile, with a small amount excreted into the urine. The urobilinogen concentration increases in the urine when it escapes hepatic uptake in liver dysfunction. With biliary obstruction, bilirubin delivery to the intestine is decreased, thus reducing the urinary urobilinogen level. Low urinary pH, antibiopic use, and diarrhea may also decrease urinary urobilinogen levels.

**Aminotransferases**
Aminotransferases are the most common serum tests for diagnosing hepatocellular injury and are also sensitive for hepatocyte necrosis. The enzymes ALT and AST catalyze the reversible transfer of the α-amino group of the amino acids alanine and aspartic acid to the α-keto group of α-ketoglutaric acid. This action leads to the formation of pyruvic acid (in the case of ALT) and oxaloacetic acid (in the case of AST) plus glutamic acid.

**AST**
The enzyme AST is present in high concentrations in multiple organs. In addition to the liver, it is found in muscle (heart and skeletal), the kidney, and the pancreas. It is also found in red blood cells. Injury to any of these due to trauma, ischemia, or drug use can result in an elevation of serum AST levels. Therefore, care must be taken when diagnosing liver injury solely on elevated AST values, as they may also rise in the face of hemolysis, rhabdomyolysis, and acute kidney injury.

**Table 13. Hepatitis Serologies**

<table>
<thead>
<tr>
<th>Hepatitis</th>
<th>Anti-HAV IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>Anti-HBc antibodies: (+) IgM for acute infection, (+) IgG for previous or ongoing infection</td>
</tr>
<tr>
<td></td>
<td>Anti-HBs: resolution or immunity</td>
</tr>
<tr>
<td></td>
<td>HBeAg: increased viral replication</td>
</tr>
<tr>
<td></td>
<td>Anti-HBe: waning viral replication</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Anti-HCV</td>
</tr>
<tr>
<td></td>
<td>HCV RNA</td>
</tr>
<tr>
<td>Hepatitis D</td>
<td>Anti-HDV</td>
</tr>
<tr>
<td>Hepatitis E</td>
<td>IgM anti-HEV</td>
</tr>
<tr>
<td>Other viruses</td>
<td>CMV, VZV, EBV, HSV</td>
</tr>
</tbody>
</table>

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, hepatitis A virus antigen; HBc, hepatitis B core; HBeAg, hepatitis B antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HSV, herpes simplex virus; IgG, immunoglobulin G; IgM, immunoglobulin M; RNA, ribonucleic acid; VZV, varicella zoster virus.

1. “This 2-month-old breastfed infant probably has breast milk jaundice.”
   Diagnosis of neonatal cholestasis must be done promptly, as patients with early diagnosis of biliary atresia (< 60 days of life) have a better prognosis following portoenterostomy. A missed diagnosis of biliary atresia leads to progressive liver disease and the need for liver transplantation.

2. “The patient’s stools are pigmented; therefore, the diagnosis of biliary atresia can be excluded.”
   Although patients with biliary atresia classically have acholic stools, the presence of pigmented stools does not rule out biliary atresia.

3. “TSB levels are sufficient to screen neonates with jaundice.”
   With neonatal jaundice, it is extremely valuable to differentiate between indirect hyperbilirubinemia, which may be benign, and direct hyperbilirubinemia, which is always pathologic and requires urgent workup.

4. “This small, breastfed infant with jaundice has an elevated AST level. This finding is indicative of significant hepatocellular injury.”
   Although AST is present in large amounts in the liver, it is also present in heart and skeletal muscle, the kidney, the pancreas, and red blood cells. Thus, while elevated AST levels may be indicative of liver injury, they can also be elevated in situations such as acute rhabdomyolysis during a systemic viral illness.

5. “This patient with new-onset jaundice and an INR of 2 can be discharged and seen as an outpatient.”
   Patients with jaundice and evidence of hepatic dysfunction (coagulopathy or hypoalbuminemia) have impending liver failure. These patients should be closely monitored in an intensive care setting. If liver dysfunction is progressive and unresponsive to vitamin K, the patient should be transferred promptly to a liver transplant center.

6. “If a patient or family member states that no high-dose acetaminophen was ingested, an overdose is unlikely.”
   Many cold and pain medications contain acetaminophen, and unintentional overdosing may occur. Therefore, acetaminophen levels should be checked in any child presenting with liver failure, as early initiation of N-acetylcysteine may be lifesaving.

7. “If a child seems alert, HE is unlikely.”
   Diagnosis of hepatic encephalopathy (HE) in young children may be very challenging, as evidence may be subtle. Patients in the early stages present with irritability, poor feeding, and a change in sleep rhythm.

8. “The transaminase levels are trending downward; therefore, the patient is improving.”
   Patients with fulminant liver failure and massive hepatic necrosis may have transaminase levels that trend downward as a consequence of loss of hepatocytes and worsening liver function (ie, rise in bilirubin level and INR). These patients should be transferred immediately to a liver transplant center.

9. “The patient’s albumin value is normal; therefore, the liver synthetic function is intact.”
   The half-life of albumin is 21 days, and in cases of fulminant liver failure, it can be less than 7 days.

10. “All coagulopathy needs to be corrected with fresh frozen plasma.”
    Patients with cholestasis and coagulopathy may be vitamin K deficient and responsive to subcutaneous or intravenous administration of vitamin K. The INR is an important marker of the liver’s synthetic capability and is important for evaluation of disease progression and prognosis. Coagulopathy should be corrected with fresh frozen plasma (FFP), platelets, or factor VII in cases of active bleeding or prior to an invasive procedure such as a central line placement.

11. “A serum sodium level of 120 mEq/L should be rapidly corrected with hypertonic saline.”
    Hyponatremia in patients with chronic liver disease is usually dilutional and not a reflection of sodium depletion. Therefore, fluid restriction is warranted. Parenteral infusion of calcium, phosphorous, and magnesium is often required.
domyolysis, or other processes that affect other organs. Measurement of elevated levels of serum lactate and lactate dehydrogenase will draw attention to hemolysis whereas elevated creatinine phosphokinase and aldolase will draw attention to myopathy as the cause of AST elevations in these circumstances. Notably, AST has a short half-life of 17±5 hours (mitochondrial, 87 hours) and is the first liver enzyme to decline.

ALT
Alanine aminotransferase is present in relatively low concentrations in tissue other than the liver, with muscle being the most significant. It is more specific than AST for the presence of liver disease, and although it tends to increase and decrease concurrently with AST levels, it may increase alone in the face of hepatocellular disease. The level of ALT correlates with body mass index, and its normal value in healthy children is now considered to be less than 30 U/L in boys and less than 19 U/L in girls. The half-life of ALT is 47±10 hours, meaning its value has an almost 2-day lag time.

Although elevations in AST and ALT levels may be the first or only laboratory evidence of liver disease, one must remember that significant liver diseases such as cirrhosis or fulminant liver failure with previously elevated AST and ALT levels may present with normal liver enzyme values. Therefore, measurement of serum aminotransferase levels have little value in determining a specific diagnosis; instead, their value lies in detecting the presence of hepatocellular damage and monitoring overall clinical progress through value trends. For example, rapidly decreasing aminotransferase levels in combination with an increasing bilirubin level and prolongation of prothrombin time could suggest submassive hepatic necrosis and poor outcome.

Diagnostic Modalities

Ultrasound
Ultrasound is useful for evaluating liver structure, size, and composition. Extrahepatic anomalies may also be detected, as well as gallbladder anatomy, obstructing gallstones, sludge, or cystic dilatations in the biliary tree.

Magnetic Resonance Cholangiopancreatography
Magnetic resonance cholangiopancreatography (MRCP) can be used to diagnose pancreatic and biliary disorders including choledochal cyst, cholelithiasis, choledocholithiasis, biliary atresia, Caroli disease, PSC, and anomalies of the pancreas and pancreatic duct. The test is noninvasive and has been shown to be as sensitive and as specific as ERCP, with lower cost and less risk in adults. Published studies of MRCP use in children are limited, especially studies comparing MRCP with ERCP, largely because of the infrequent indications for either method. Tipnis and Werlin reviewed 10 studies involving 221 children and found the overall sensitivity of MRCP for pancreatobiliary disease was 88% and the specificity was 91%.

Endoscopic Retrograde Cholangiopancreatography
The main advantage of ERCP is its therapeutic capability. Data regarding its use in children are limited because of the low incidence of childhood diseases requiring ERCP and the scarcity of tertiary care facilities or endoscopists experienced with the technology. Additional disadvantages include significant radiation exposure, significant potential side effects, high cost, and the invasiveness of the procedure. The largest study to date was done by Cheng et al and included 245 children (mean age, 12 years) who underwent 329 diagnostic or therapeutic examinations for a variety of biliary or pancreatic disorders. There were 32 complications (9.7% of patients), 31 of which were pancreatitis. No mortality was related to use of ERCP.

Special Circumstances

Neonatal jaundice has a unique differential diagnosis, workup, and therapy, all previously discussed. In newborns, prompt diagnosis is necessary to prevent the devastating consequences of untreated indirect hyperbilirubinemia on the developing brain (kernicterus) as well as metabolic disease. Biliary atresia diagnosed early in life has a higher likelihood of successful surgical intervention (Kasai operation) and less likelihood of progression to liver disease and liver transplantation.

Patients receiving TPN may present with TPN-induced cholestasis (TPN-IC), defined as a direct serum bilirubin level > 2 mg/dL. The condition is more common in children than adults, with an incidence of 7.4% to 84%. Bilirubin levels may begin to rise as early as 2 weeks after the initiation of TPN, and in some patients, liver cirrhosis may develop in a few months. In most cases, TPN-IC improves after cessation of TPN and resumption of full enteral feeding. In cholestatic patients on TPN, other causes such as cholelithiasis and sepsis need to be considered.

Jaundice in liver transplant recipients poses a diagnostic dilemma. The incidence of biliary complications is 15% to 30% and includes strictures and bile leaks. Jaundice may be the presenting symptom in acute and chronic liver rejection, recurrence of liver disease (eg, PSC), drug toxicity, and posttransplant lymphoproliferative disease. Infection within the first month after liver transplant is usually nosocomial (eg, methicillin-resistant Staphylococcus aureus, Pseudomonas). After the first month, opportunistic infections (eg, cytomegalovirus, Toxoplasma) become
Disposition

The decision to discharge or admit the pediatric patient with jaundice is difficult and depends on the patient’s age, etiology, clinical appearance, and bilirubin level as well as jaundice onset (especially for neonates). Similar to patients with bilirubin levels that meet the criteria for phototherapy and exchange transfusion, ill-appearing infants or infants with anemia, regardless of the bilirubin level, should be admitted and monitored, as these conditions may conceal an ominous underlying disease. As mentioned earlier, patients with jaundice and fever require admission and evaluation for a possible underlying infectious disorder. More importantly, jaundice in an otherwise asymptomatic newborn can be an early indicator of sepsis or urinary tract infection and requires evaluation. With the identification of a bacterial cause, antibiotics should be started immediately. Early and timely diagnosis is crucial in cases of biliary atresia and biliary obstruction (e.g., cholelocal cyst) to ensure proper surgical intervention.

For pediatric patients beyond the newborn period, vital signs, clinical presentation, laboratory data, and the suspected underlying cause of jaundice will influence disposition from the ED. Cases of hepatocellular injury, biliary obstruction, and recent hemolysis require stabilization, admission, and further evaluation and treatment. Patients with elevated transaminase levels may or may not require admission. The decision should be based on the patient’s clinical picture, other supporting laboratory values, and access to follow-up.

Mild elevations of liver enzymes without signs of coagulopathy can be followed on an outpatient basis. In contrast, admission and close monitoring should be considered in patients with significant elevations, as well as for those patients with vomiting, pain, altered mental status, or signs of coagulopathy. In the absence of any other symptoms or significant laboratory test abnormalities, most pediatric patients with jaundice, especially older children and adolescents, can be discharged with appropriate follow-up with a pediatric gastroenterologist or hepatologist.

As mentioned previously, the emergency clinician must not only assess pediatric patients who need admission but must also be conscious of patients requiring special care at a tertiary facility with appropriate resources. Ill-appearing neonates with bilirubin levels elevated above treatment thresholds would be better served at an institution with experienced neonatologists and a neonatal intensive care unit. Any pediatric patient with evidence of ALF or who is at risk for the development of liver failure should be immediately transferred to the nearest facility with staff experienced in pediatric liver transplantation.

Time-And Cost-Effective Strategies

Not all patients with jaundice require an extensive workup. Patients with indirect hyperbilirubinemia without evidence of hemolysis or other liver enzyme abnormality are likely to have Gilbert’s syndrome, a lifelong benign condition with a prevalence of 5% of the general population.

Summary

The differentiation between nonpathologic and pathologic jaundice often begins in the ED. Jaundice, along with excessive crying and rash, are the 3 chief reasons for neonatal visits to the ED. Neonatal jaundice can occur in up to 60% of full-term infants in the first week of life. The emergency clinicians’ ability to distinguish between causes of conjugated and unconjugated hyperbilirubinemia and to recognize signs of serious conditions leading to jaundice can be lifesaving for their pediatric patients. Emergency clinicians must feel comfortable knowing when to admit the jaundiced patient and when transfer or referral to a transplant center is necessary.

Case Conclusion

You figure since the 2-month-old with progressive jaundice has acholic stools, he warrants a careful examination and further laboratory and imaging tests to rule out biliary atresia. Laboratory tests reveal a normal CBC, a TSB level of 10 mg/dL, and a direct serum bilirubin value of 8 mg/dL. His ALT level is 200 IU/L, his AST level is 220 IU/L, his GGT value is 500 IU/L, his albumin value is 3 g/dL, and the INR is 1.4. These laboratory results are consistent with biliary obstruction, so you send the infant for an ultrasound of the liver. Sonography reveals that the gallbladder and common bile ducts cannot be visualized. You are concerned about biliary atresia. You are aware that the infant is 2 months old and the window of opportunity for performing a successful portoenterostomy (Kasai operation) is narrow. You call a pediatric gastroenterologist/hepatologist for an emergent consult.
Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

3. The main goal in the treatment of unconjugated hyperbilirubinemia is:
   a. Prevention of cirrhosis
   b. Prevention of Wilson’s disease
   c. Prevention of kernicterus
   d. Prevention of Gilbert’s syndrome

4. Which etiologies of acute liver failure are most prominent for adolescent patients?
   a. Acetaminophen overdose
   b. Metabolic disease
   c. Infectious disease
   d. Wilson’s disease
   e. Both a and d
   f. Both b and c

5. Which of the following is NOT an extrahepatic complication of fulminant hepatic failure?
   a. Cerebral edema
   b. Cardiovascular abnormalities
   c. Electrolyte imbalances
   d. Hyperglycemia

6. Which laboratory value or study is most pathognomonic for drug-induced liver injury?
   a. Ultrasound
   b. Magnetic resonance cholangiopancreatography (MRCP)
   c. Endoscopic retrograde cholangiopancreatography (ERCP)
   d. No laboratory value or study

7. Which group of patients most often present with constant pain from pancreatitis?
   a. Children
   b. Adults

8. The most frequent bacterial organism causing neonatal hepatitis is:
   a. E coli
   b. S aureus
   c. Streptococcus pyogenes
   d. None of the above
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Needs Assessment: The need for this educational activity was determined by a survey of medical staff including the editorial board of this publication; review of morbidity and mortality data from the CDC, AHA, NCHS, and ACEP; and evaluation of prior activities for emergency physicians.

Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Goals & Objectives: Upon reading Pediatric Emergency Medicine Practice, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

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