Objectives

After completing this article, readers should be able to:

1. Describe the basic physiology of bilirubin metabolism, the two standard laboratory methods for its fractionation, and the classification of jaundice.
2. Characterize the features of Gilbert disease.
3. Identify the leading infectious cause of acute jaundice in older children and adolescents.
4. Delineate the clinical and biochemical features of Wilson disease and autoimmune hepatitis.
5. Compare and contrast liver function tests and tests of liver function.
6. Describe the "worrisome" clinical and laboratory signs of hepatic synthetic dysfunction in jaundiced patients that should prompt an immediate referral to a center where liver transplantation is available.

Introduction

Jaundice is defined as the presence of a yellow or yellow-greenish hue to the skin, sclera, and mucous membranes due to an elevation of serum bilirubin. In healthy individuals, the total serum bilirubin is less than 1 mg/dL (17 mcmol/L). Jaundice can be readily detected clinically when the total serum bilirubin is greater than 5 mg/dL (85 mcmol/L). Clinical jaundice occurs much less frequently in older children and adolescents than in neonates. Moreover, the differential diagnosis in this older age group differs markedly from that in newborns and young infants. This review provides a practical approach to the clinical evaluation of jaundice in the older child or adolescent. Because jaundice may be the presenting feature of life-threatening conditions such as fulminant liver failure, a prompt and logical evaluation is necessary to identify the more serious disorders that require urgent management.

Bilirubin Metabolism

Bilirubin is a product of heme metabolism. Heme is converted in the reticuloendothelial (RE) system to biliverdin and then to bilirubin by heme oxygenase and biliverdin reductase, respectively. Bilirubin is lipophylic and is bound to serum albumin in circulation from the RE system to the liver. The liver takes up the bilirubin-albumin complex through an albumin receptor. Bilirubin, but not albumin, is transferred across the hepatocyte membrane and transported through the cytoplasm to the smooth endoplasmic reticulum bound primarily to ligandin or Y protein, a member of the glutathione S-transferase gene family of proteins. There, the water-insoluble bilirubin is conjugated to water-soluble bilirubin monoglucuronide and diglucuronide by UDP-glucuronosyl transferase. The bilirubin conjugates are excreted through
the canalicular membrane into the bile duct system by an energy-dependent process. Conjugated bilirubin flows in the bile to the intestine, where it is broken down by gut flora to urobilinogen and stercobilin.

Total serum bilirubin consists of an unconjugated fraction and conjugated fraction of bilirubin and a fraction of bilirubin glucuronide that is bound covalently to albumin known as delta-bilirubin. The newer Ektachem® slide method for bilirubin fractionation accurately measures the levels of unconjugated, conjugated, and total serum bilirubin. Delta-bilirubin concentration can be calculated from these figures (Table 1). With the traditional Diazo® method for bilirubin fractionation, indirect and direct bilirubin are measured and the total bilirubin is calculated. m = measured.

**Table 1. Fractionation of Bilirubin**

**Diazo® Method**

Total bilirubin = Direct bilirubin\(^m\) + Indirect bilirubin\(^m\)

**Ektachem® Slide Method**

Total bilirubin\(^m\) = Conjugated bilirubin\(^m\) + Unconjugated bilirubin\(^m\) + Delta bilirubin

The Diazo method measures the direct and indirect bilirubin and calculates the total. In the Ektachem slide method, the total, conjugated, and unconjugated bilirubin fractions are measured and the delta bilirubin is calculated. m = measured.

**Table 2. Causes of Hyperbilirubinemia in Older Children**

**Unconjugated Hyperbilirubinemia**

- Hemolytic anemias
- Gilbert syndrome
- Crigler-Najjar syndrome

**Conjugated Hyperbilirubinemia**

**Viral Infections**

- Hepatitis viruses A, B, C, D, E
- Epstein-Barr virus
- Cytomegalovirus
- Herpes simplex

**Metabolic Liver Disease**

- Wilson disease
- Alpha-1-antitrypsin deficiency
- Cystic fibrosis

**Biliary Tract Disorders**

- Cholelithiasis
- Cholecystitis
- Choledochal cyst
- Sclerosing cholangitis

**Autoimmune Liver Disease**

- Type 1 (anti-smooth muscle antibody)
- Type 2 (anti-liver-kidney-microsomal antibody)

**Hepatotoxins**

- Drugs: Acetaminophen
- Anticonvulsants
- Anesthetics
- Antituberculosis agents
- Chemotherapeutic agents
- Antibiotics
- Oral contraceptives

**Other:** Alcohol, insecticides, organophosphates

**Vascular Causes**

- Budd-Chiari syndrome
- Veno-occlusive disease

Differential Diagnosis

The differential diagnosis of jaundice in an older child is extensive, encompassing some common conditions and many rare disorders (Table 2). A key practical first step is to classify the jaundice as unconjugated (indirect) or conjugated (direct) hyperbilirubinemia by using the previously noted Diazo or Ektachem method.

**Unconjugated Hyperbilirubinemia**

Older children and adolescents who present with jaundice due to unconjugated hyperbilirubinemia are most likely to have a disorder associated with excessive hemolysis, such as hereditary spherocytosis, a red blood cell enzyme defect of pyruvate kinase or glucose-6-phosphate dehydrogenase, or a hemoglobinopathy (eg, sickle cell anemia and thalassemia). In these conditions, significant hemolysis leads to excess heme production and consequent increased circulating unconjugated bilirubin load.

Gilbert syndrome, an autosomal recessive disorder seen in 5% of the population, is another important cause of unconjugated hyperbilirubinemia in this age group. This inherited disorder of bilirubin metabolism is characterized by a mild unconjugated hyperbilirubinemia (usually 5 mg/dL [<85 mcmol/L]) due to a UGT1 gene mutation that impairs the function of the UDP glucuronosyl transferase enzyme. In affected adolescents or young adults, jaundice appears most often in associa-
tion with an intercurrent mild infectious illness, fasting, or physical stress. Other than the modest elevation in unconjugated bilirubin, patients who have Gilbert syndrome are healthy and have no clinical or laboratory evidence of liver disease or hemolysis. An associated family history, although not always present, is diagnostic for the condition. There are no specific diagnostic laboratory tests. The prognosis is excellent, with no long-term sequelae.

The Crigler-Najjar syndromes types 1 and 2 are extremely rare autosomal recessive diseases that result from a complete absence (type 1) or limited activity (type 2) of the UDP-glucuronosyl transferase enzyme. Both conditions typically manifest as an unconjugated hyperbilirubinemia in the first few days of life, although exceptional cases of Crigler-Najjar type 2 presenting at an older age have been reported. Without the ability to conjugate and excrete bilirubin, patients who have type 1 disease exhibit markedly elevated serum bilirubin levels (25 to 35 mg/dL) [425 to 600 mcmol/L]), are at high risk to develop kernicterus, and require aggressive phototherapy. In contrast, patients who have type 2 disease usually have total serum bilirubin levels below 20 mg/dL (350 mcmol/L) because of the partially functioning UDP-glucuronosyl transferase enzyme, whose activity can be induced by phenobarbital. Indeed, the two types of Crigler-Najjar syndrome may be distinguished by treatment with phenobarbital. Patients who have type 1 disease show no response; those who have type 2 disease exhibit a dramatic decrease in serum bilirubin levels following the administration of phenobarbital.

Conjugated Hyperbilirubinemia
Infections

Infection with any of the hepatotropic viruses (A, B, C, D, or E) may cause jaundice in older children and adolescents. In these instances, the jaundice is due to conjugated hyperbilirubinemia resulting from intrahepatic cholestasis. Hepatitis A virus (HAV) infection, a self-limited illness induced by an RNA virus, is the most common infectious cause of acute jaundice in this age group. Young infants rarely develop jaundice when infected with HAV. Infants and young children who have HAV infection are usually asymptomatic or simply manifest signs and symptoms of viral gastroenteritis without icterus. In contrast, older children and adolescents have a prodrome of fever, headache, and general malaise followed by the onset of jaundice, abdominal pain, nausea, vomiting, and anorexia. There is biochemical evidence of a profound hepatitis characterized by significant elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) as well as a conjugated hyperbilirubinemia. Clinical symptoms and biochemical abnormalities completely resolve within 4 weeks in most patients. In rare cases, HAV can cause relapsing or persistent jaundice for months. However, HAV infection never leads to a chronic hepatitis, defined as hepatitis lasting for more than 6 months. Fulminant HAV infection, heralded by encephalopathy and significant hepatic dysfunction (ie, coagulopathy), is distinctly unusual, occurring in fewer than 1% of cases. Indeed, although viral or presumed viral hepatitis accounts for 75% to 80% of all cases of fulminant liver failure in children, most of these are the result of non-A through G hepatitis viruses.

The majority of pediatric patients who have hepatitis B virus (HBV) infection are asymptomatic. However, jaundice may occur in acutely infected older children. The most important routes for acquiring acute HBV infection in adolescence are horizontal—from highly infectious family members, from improperly sterilized syringes, or when adolescents practice high-risk sexual behavior with multiple partners and infrequent use of condoms. Many older children and adolescents chronically infected with HBV are foreign immigrants from endemic regions who had acquired infection through perinatal transmission. Older children who have chronic HBV infection are often asymptomatic carriers or they may have a limited, subclinical, biochemical hepatitis, evidenced by increased hepatic transaminase levels. Jaundice is an unusual manifestation in children who have chronic HBV infection, except in the rare instance of fulminant liver failure or end-stage liver disease and cirrhosis developing at a young age.

Most children who have hepatitis C virus (HCV) infection are older than 8 years of age and have contracted the infection through contaminated blood and blood products prior to 1992. With improved processing of blood and blood products, the chance of contracting HCV through these sources is now low, estimated at 1 per 100,000 units transfused. The more important source for pediatric HCV infection is through maternal-infant transmission. This indolent disease takes many decades to progress to end-stage liver disease. Thus, the vast majority of older children infected with this virus are asymptomatic. However, as with chronic HBV infection, jaundice may manifest in those very rare patients who have HCV infection and develop cirrhosis at an early age. Hepatitis D virus infection is uncommon in the United States, occurring only in patients already infected with HBV. Hepatitis E virus is prevalent in developing countries and typically presents acutely with jaundice, in a manner similar to HAV infection.
Epstein-Barr virus (EBV) infection can cause acute hepatitis and jaundice in older children and adolescents as a part of the infectious mononucleosis syndrome. Any child or adolescent who presents acutely with jaundice, especially in association with lymphadenopathy, sore throat, and mild splenomegaly, should be evaluated for EBV infection. In immunocompromised hosts, infection with herpes simplex virus, cytomegalovirus, or rare opportunistic agents can cause hepatobiliary disease with clinical jaundice, but a discussion of these is beyond the scope of this article. Jaundice with hepatic dysfunction as a result of gram-negative bacterial infections and sepsis is much more common in infants and young children than in older children and adolescents.

**METABOLIC LIVER DISEASE**

A variety of metabolic diseases of the liver may present with jaundice in older children. Wilson disease is an autosomal recessive disorder of copper metabolism, characterized by excess accumulation of copper in the liver, central nervous system (CNS), kidney, cornea, and other organs. The hepatic manifestations are protean, ranging from an acute hepatitis to fulminant hepatic failure with coagulopathy, ascites, and hepatic encephalopathy or a more indolent course with chronic hepatitis and cirrhosis. Wilson disease must be considered in the differential diagnosis of every older child or adolescent who presents with conjugated hyperbilirubinemia. Neuropsychiatric features may be dramatic, including motor system disturbances such as tremor, incoordination, and dystarthritis, along with poor school performance, depression, neurosis, or psychosis. The CNS manifestations may present in concert with or independent of the hepatic symptoms. Kayser-Fleischer (KF) rings, a golden brown discoloration in the zone of the Descemet membrane of the cornea, is virtually always present when neurologic or psychiatric symptoms develop. However, KF rings may be absent in patients who have Wilson disease without neurologic involvement but who present with hepatic symptoms. Renal involvement is characterized by proximal tubular dysfunction, decreased glomerular filtration rate, and decreased renal plasma flow. Patients may manifest proteinuria, glucosuria, phosphaturia, uricosuria, aminoaciduria, renal tubular acidosis, and microscopic hematuria. Severe renal insufficiency may occur in patients who have fulminant or end-stage liver disease. Intravascular hemolysis with a Coombs-negative hemolytic anemia may develop because of the oxidative injury to red blood cell membranes induced by excess copper. Cardiac involvement, including ventricular hypertrophy and arrhythmias, has been reported in Wilson disease.

Skeletal manifestations resulting from bone demineralization are not uncommon.

Alpha-1-antitrypsin deficiency, an autosomal codominantly inherited disease, can present with a conjugated hyperbilirubinemia at any age. Approximately 20% of patients who have the ZZ protease inhibitor phenotype will have liver disease. Although neonatal cholestasis is a more common presentation for this disorder, older children may have new-onset jaundice in association with alpha-1-antitrypsin deficiency, chronic hepatitis, or cirrhosis.

Hepatobiliary disease may occur in up to two thirds of patients who have cystic fibrosis. Pancreatic insufficiency and pulmonary disease used to be the dominant features of cystic fibrosis, which was associated with high morbidity and mortality at a young age. With improved treatments and longer life expectancy, liver disease has assumed greater importance, especially for older children and adolescents. The spectrum of hepatobiliary disorders in cystic fibrosis includes steatohepatitis, focal biliary and multilobular cirrhosis, cholethiasis and cholecystitis, sclerosing cholangitis, and common bile duct stenosis. Any of these complications may be heralded by a conjugated hyperbilirubinemia.

**BILIARY TRACT DISORDERS**

Extrahepatic biliary tract disorders may cause an obstructive type of jaundice that is manifested by icterus, dark urine, acholic stools, and pruritus in association with a conjugated hyperbilirubinemia. Cholethiasis can occur in older children, albeit infrequently. Gallstones in this age group may be idiopathic or may develop due to hemolytic disorders, cystic fibrosis, obesity, ileal resection, or long-term use of total parenteral nutrition. Although many children who have gallstones are asymptomatic, jaundice, periumbilical or right upper quadrant abdominal pain, vomiting, and fever may develop in cases of acute cholecystitis, choledocholithiasis, or pancreatitis. Ultrasonography is the safest, most sensitive, and most specific method of identifying gallstones.

Choledochal cysts are congenital cystic dilatations of the intrahepatic or extrahepatic biliary ducts. At least five subtypes have been described based on the anatomic site of cystic dilation along the biliary tree. Patients may present at any age with epigastric pain, fever, and jaundice. The most useful diagnostic study is abdominal ultrasonography. In older children, acute jaundice may develop in cases of intrahepatic cystic duct lesions that are associated with congenital hepatic fibrosis and autosomal recessive polycystic kidney disease.

Primary sclerosing cholangitis is a chronic fibro-
obliterative disease of unknown etiology that involves the extrahepatic and intrahepatic bile ducts. In older children, this condition occurs most often in association with inflammatory bowel disease, although it may present rarely in otherwise healthy teenagers or in patients who have congenital or acquired immunodeficiency. Clinical features include jaundice, anorexia, fatigue, abdominal pain, and pruritus. The diagnosis is confirmed by cholangiography that shows a characteristic beading and stenosis of the common or intrahepatic bile ducts in the absence of choledocholithiasis.

**AUTOIMMUNE HEPATITIS**

Autoimmune hepatitis is a chronic progressive inflammatory liver disease of unknown etiology. Two major subtypes have been identified based on circulating autoantibodies. Type 1 disease, defined by the presence of anti-smooth muscle antibodies (ASMAs) and antinuclear antibodies (ANAs), typically presents in adolescent females as an acute hepatitis with symptoms of malaise, nausea, anorexia, fatigue, abdominal pain, and jaundice. Type 2 autoimmune liver disease, associated with the liver-kidney microsomal antibody, is a more rapidly progressive form that usually presents with similar symptoms in younger children and infants.

**HEPATOTOXINS**

A variety of drugs or environmental agents may be hepatotoxic and cause jaundice in children and adolescents. Acetaminophen overdose is a leading cause of fulminant hepatic failure in these age groups. Hepatotoxicity develops in the face of glutathione depletion, after which any excess acetaminophen is metabolized by the hepatic P450 pathway to produce the hepatotoxic product NAPQI (N-acetyl-p-benzoquinoneimine). A distinct clinical course ensues, with initial nausea and vomiting, followed progressively by a quiescent period and acute liver dysfunction with jaundice and coagulopathy. Hepatic failure may develop with progressive encephalopathy and coma. Other hepatotoxic agents that can cause jaundice include erythromycin, sulphonamides, halothane, methotrexate, chemotherapy, anticonvulsants such as valproate and phenytoin, the antituberculous drug isoniazid, and oral contraceptives.

**VASCULAR DISEASES**

Vascular diseases of the liver may present with jaundice in older children. Veno-occlusive disease causing hepatic congestion and jaundice may be seen in children in the first few weeks following bone marrow transplantation.

**Clinical Evaluation**

Distinguishing between conjugated and unconjugated hyperbilirubinemia is a most important first step in diagnosis. Whereas the presence of dark urine, pale stools, or pruritus in a jaundiced patient suggests hepatobiliary disease with a conjugated hyperbilirubinemia, the absence of these symptoms does not specify the underlying type of jaundice, and laboratory studies are required. If the jaundice is associated with abdominal pain, it is important to document the nature, site, and severity of the pain. Cholecystitis or choledocholithiasis due to gallstone disease usually presents with severe epigastric or right upper quadrant pain, often accompanied by vomiting. For acute viral hepatitis, the abdominal pain characteristically is a dull ache in the right upper quadrant. Personality changes, inappropriate behavior, and disturbed sleep-wake cycle or worsening school performance in a child who has jaundice may indicate hepatic encephalopathy, suggesting fulminant hepatitis, or may represent features of the CNS complications of Wilson disease.

In reviewing the past history, it is important to inquire about risk factors for viral hepatitis, such as maternal-infant transmission, transfusion of contaminated blood products, intravenous drug abuse, high-risk sexual activity, travel history, or a history of infectious contacts. A detailed review of all medications is essential to search for potential hepatotoxic agents, especially acetaminophen abuse or misuse. Consanguinity or a family history for jaundice may suggest inherited metabolic conditions such as Wilson disease, alpha-1-antitrypsin deficiency, cystic fibrosis, or Gilbert syndrome.

The physical examination should focus on signs of chronic liver disease; the acute onset of jaundice in any child may be an initial clinical manifestation of previously unrecognized chronic liver disease. Pallor may suggest an...
Jaundice in children

Laboratory Evaluation and Diagnosis

Bilirubin fractionation by the Ektachem or Diazo method is a necessary first step in the laboratory evaluation of any older child or adolescent who has jaundice (Table 3). Unconjugated hyperbilirubinemia in this age group is due most often to hemolytic disease. A complete blood count, reticulocyte count, direct and indirect Coombs tests, measurement of serum haptoglobins, and hemoglobin electrophoresis should be requested. Exceptionally, a Coombs-negative hemolytic anemia may be the sole presenting feature of Wilson disease. In the absence of hemolysis or elevated liver enzyme levels, Gilbert syndrome should be considered in the adolescent who has mild unconjugated hyperbilirubinemia.

Conjugated hyperbilirubinemia suggests hepatobiliary disease. The initial laboratory investigations should include a complete blood count, liver function tests (AST, ALT, alkaline phosphatase [ALP], gamma-glutamyltransferase [GGT]), total protein, serum albumin, and a prothrombin time (PT). Although there is considerable overlap, predominant elevation of the AST and ALT suggests hepatocellular injury, and a prevailing elevation in the ALP and GGT suggests biliary tract disease. It is important to remember that the so-called “liver function tests” are a misnomer; they do not reveal anything about the synthetic function of the liver. Tests for liver function include a coagulation screen and measurements of serum glucose, cholesterol, ammonia, and albumin. Of these, the most sensitive test for synthetic liver function is the PT. Prolongation of the PT despite administration of vitamin K suggests significant hepatic dysfunction. Patients who have acute hepatitis and a marked coagulopathy that is not responsive to vitamin K or who manifest other “worrisome signs” (Table 4) should be referred promptly to a center that has expertise in the management of children who have advanced liver disease and where liver transplantation is readily available. For these more urgent cases, intensive supportive care and liver transplantation hold the greatest potential for survival.

Further laboratory investigations are directed toward establishing a diagnosis. Every patient who presents with conjugated hyperbilirubinemia should undergo abdominal ultrasonography to examine the hepatic architecture and to exclude biliary tract disease. Screening for the viral hepatitides should include serology for hepatitis A immunoglobulin M (IgM), hepatitis B surface antigen, IgM antibody to hepatitis B core antigen, anti-HCV, Monospot®/EBV titers, serum ceruloplasmin, 24-hour urinary copper excretion, serum IgG, autoantibodies (ANA, ASMA, anti-liver-kidney-microsomal antibody), serum alpha-1-antitrypsin level and phenotype, liver biopsy, and to exclude biliary tract disease. Screening for the viral hepatitides should include serology for hepatitis A immunoglobulin M (IgM), hepatitis B surface antigen, IgM antibody to hepatitis B core antigen, and anti-HCV. A Monospot® test or serology for EBV is also highly recommended for the adolescent who presents with conjugated hyperbilirubinemia. Measurement of serum alpha-1-antitrypsin levels and protease inhibitor pheno-
typing should be requested to exclude alpha-1-antitrypsin deficiency. Patients who have autoimmune hepatitis, jaundice, and an elevated ALT usually exhibit a high serum total protein relative to the albumin, reflecting an increased globulin fraction. This is a result of the significant hypergammaglobulinemia often found in association with autoimmune hepatitis. Aside from measuring the serum IgG, other tests for autoimmune hepatitis should include an ANA, ASMA, and anti-liver-kidney-microsomal antibody. A liver biopsy is recommended to confirm the diagnosis.

Serum ceruloplasmin is a valuable screening test for Wilson disease. A decreased serum ceruloplasmin level is found in up to 80% of affected patients. Another useful diagnostic test is the 24-hour urinary copper excretion. In Wilson disease, the urinary copper excretion is typically greater than 100 mcg/24 h. Serum copper levels are not helpful in diagnosing Wilson disease except for those rare patients presenting with fulminant liver failure, in whom serum copper levels are significantly elevated. Other laboratory abnormalities often seen in Wilson disease include a low serum ALP, particularly when fulminant hepatic failure is present, and low serum phosphate and uric acid due to the associated Fanconi syndrome. Quantification of hepatic copper concentration in a liver biopsy tissue specimen (>250 mcg/g of dry weight liver) remains the gold standard for diagnosing Wilson disease.

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Specific treatment of the hyperbilirubinemia depends on the precise etiology. A detailed discussion of therapy for each individual disease state is beyond the scope of this article. In general, acute hemolytic crises require hyperhydration and close monitoring of renal function. Immunosuppressive agents, such as prednisone, azathioprine, or cyclosporine, are used to treat autoimmune hepatitis. Penicillamine is the drug of choice for Wilson disease, although zinc replacement and trientine also have been prescribed. N-acetyl-cysteine is recommended for the treatment of acetaminophen overdose. Patients who have acute viral hepatitis, especially hepatitis A, are prone to dehydration and require adequate fluid support. Passive immunoprophylaxis should be administered to all close family contacts of patients who have acute hepatitis A.

Any child who has conjugated hyperbilirubinemia and encephalopathy or biochemical features of hepatic synthetic dysfunction, best evidenced by a prolonged PT, is at high risk to develop a more fulminant course that has a fatal outcome. Close supervision and intensive supportive care are required, preferably by physicians who have expertise in the management of advanced pediatric liver disease.

Summary
The spectrum of diseases causing jaundice in older children and adolescents differs from that in the neonate and young infant. A sound knowledge of the differential diagnosis of unconjugated and conjugated hyperbilirubinemia in this age group provides the framework for a sensible approach to the clinical evaluation and laboratory investigation of these children. For patients who have acute hepatitis, a careful assessment of liver function is of critical importance. Signs and symptoms of liver dysfunction in a jaundiced patient should prompt an immediate referral to a tertiary center where expertise in the management of pediatric liver disease and hepatic transplantation is readily available.

Suggested Reading

Table 4. “Worrisome” Signs and Symptoms in the Jaundiced Older Child or Adolescent who has Acute Hepatitis

- Onset of hepatic encephalopathy
- Vitamin K-resistant prolongation of the prothrombin time
- Cerebral edema
- Serum bilirubin 18 mg/dL (>300 mcmol/L)
- Rising serum bilirubin with decreasing ALT/AST
- Rising serum creatinine
- Hypoglycemia
- Sepsis
- Ascites
- pH<7.3 in acetaminophen overdose

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PIR Quiz
Quiz also available online at www.pedsinreview.org.

1. You are seeing a 13-year-old girl who has acute onset of jaundice. She previously has been healthy, but had a mild viral illness 1 week ago. She appears well and has mild scleral icterus. Laboratory testing reveals a total bilirubin of 4 mg/dL (68.4 mcmol/L) that is all unconjugated. There is no evidence of hemolysis on a peripheral smear. Which of the following is the most likely diagnosis?

A. Autoimmune hepatitis.
B. Crigler-Najjar syndrome.
C. Gilbert syndrome.
D. Hepatitis A.
E. Wilson disease.

2. A 10-year-old boy comes to your office with a 4-day history of abdominal pain, nausea, and jaundice. He appears mildly ill and is notably jaundiced. His laboratory values are as follows: conjugated bilirubin, 10.5 mg/dL (179.6 mcmol/L); aspartate aminotransferase, 800 U/L; and alanine aminotransferase, 950 U/L. Which of the following is the most likely diagnosis?

A. Alpha-1-antitrypsin deficiency.
B. Cholelithiasis.
C. Epstein-Barr virus infection.
D. Hepatitis A.
E. Hepatitis B.

3. Which of the following statements about Wilson disease in adolescents is true?

A. Central nervous system symptoms are always present with hepatic insufficiency.
B. Elevated serum copper levels are pathognomonic of the disease.
C. Kayser-Fleischer rings are almost always present with neurologic involvement.
D. Patients typically are asymptomatic at the time of diagnosis.
E. The gold standard for diagnosis is an elevated ceruloplasmin level.

4. Which of the following laboratory tests is the most sensitive indicator of liver function?

A. Alanine aminotransferase.
B. Albumin.
C. Alkaline phosphatase.
D. Prothrombin time.
E. Total bilirubin level.

5. You are evaluating a 15-year-old patient who has had a 2-week history of worsening jaundice. She shows signs of depression. You are concerned about the possibility of fulminant liver failure. Which of the following is most likely to prompt you to refer her to a liver transplant center immediately?

A. Increasing conjugated bilirubin and liver enzyme levels.
B. Persistently elevated prothrombin time despite administration of vitamin K.
C. Presence of ascites.
D. Presence of splenomegaly.
E. Rising levels of ammonia.
# Jaundice in Older Children and Adolescents

Dinesh Pashankar and Richard A. Schreiber

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