General Hepatitis

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EDUCATION GAP

Hepatitis is responsible for significant morbidity and mortality in the pediatric population. It is fundamental that pediatricians understand the broad differential diagnosis of pediatric hepatitis and develop the ability to recognize the different signs and symptoms of disease, as well as initiate the primary evaluation.

OBJECTIVES *After completing this article, readers should be able to:*

1. Describe the broad differential diagnosis of pediatric hepatitis.
2. Recount the initial evaluation for suspected hepatitis.
3. Identify the signs and symptoms of acute and chronic hepatitis.
4. Describe the evaluation and initial management of acute liver failure.
5. Determine when to refer or consult.

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ABBREVIATIONS

AAT	α_1-antitrypsin
AIH	autoimmune hepatitis
ALF	acute liver failure
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CMV	cytomegalovirus
EBV	Epstein-Barr virus
GGT	γ-glutamyltransferase
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDV	hepatitis D virus
HEV	hepatitis E virus
Ig	immunoglobulin
INR	international normalized ratio
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
PCR	polymerase chain reaction
PT	prothrombin time
ULN	upper limit of normal
WD	Wilson disease

CASE

A previously healthy, fully vaccinated, 11-year-old girl presents with fever and sore throat for 3 days. She has a maximum temperature of 101.5°F (38.6°C) and notes throat pain with swallowing. The family denies any sick contacts, but the patient attended a birthday party 10 days before presentation. She denies any cough, congestion, vomiting, diarrhea, or rash.

On physical examination, enlargement of bilateral tonsils with erythema and white exudates is observed. No further diagnostic investigations were performed. She is diagnosed as having bacterial tonsillitis and is discharged with a 7-day course of oral amoxicillin at a dose of 50 mg/kg per day.

Four days later she returns with persistent fever, progressive fatigue, malaise, vomiting, vague right upper quadrant abdominal pain, and a diffuse rash. On physical examination she is febrile with otherwise stable vital signs. She has bilateral nontender posterior cervical lymphadenopathy and bilateral tonsillar enlargement with white exudates. Abdominal examination reveals right upper quadrant tenderness without guarding.

Laboratory analysis reveals a C-reactive protein level of 5.4 mg/dL (54 mg/L), alanine aminotransferase (ALT) level of 60 U/L (1.00 μkat/L), aspartate aminotransferase (AST) level of 245 U/L (4.09 μkat/L), alkaline phosphatase (ALP) level of 112 U/L (1.87 μkat/L), and albumin level of 3.4 g/dL (34 g/L). Cytomegalovirus (CMV) and hepatitis A serologies are negative. Epstein-Barr virus (EBV) serology testing is performed and reveals a positive immunoglobulin (Ig) M antibody consistent with acute infection.

Abdominal ultrasonography demonstrates a diffusely enlarged, hypoechoic liver, with a thickened gallbladder wall and mild splenomegaly. These findings are consistent with hepatitis secondary to EBV infection.

INTRODUCTION

Hepatitis is a general term indicating the presence of inflammatory liver injury, regardless of the cause. (1) The differential diagnosis is broad, encompassing infectious and noninfectious etiologies, both of which vary widely in severity and chronicity (Table 1). A thorough and efficient evaluation can be conducted by understanding the significance of laboratory tests and which values indicate a more severe disease state. This article describes a general approach to the diagnostic evaluation of pediatric hepatitis and indications for referral to a gastroenterologist. It also focuses on various disease manifestations in children of all ages, excluding neonatal hepatitis.

Evaluation

Presentations of hepatitis range from acute symptoms due to a self-limiting infection to subtle signs of progressive disease. Elevated transaminase levels, commonly included in basic laboratory panels, are often the first sign of liver damage or inflammation. When detected or when a patient's clinical presentation suggests hepatitis, it is imperative to obtain a thorough history identifying potential risk factors for liver disease and a physical examination directed at recognizing disease-specific manifestations. The decision to pursue further testing with additional laboratory studies, imaging, or biopsies is guided by assessing the constellation of signs, symptoms, history, physical examination findings, and pattern of laboratory test abnormalities.

History

A thorough history is crucial in identifying patients at increased risk for hepatitis. A history should encompass

Table 1. Differential Diagnosis for Elevated Liver Enzyme Levels in Pediatric Patients

CATEGORY	POSSIBLE ETIOLOGIES	
Infectious	Hepatitis A, B, C, D, E Herpes simplex virus Varicella zoster virus Epstein-Barr virus Cytomegalovirus Enterovirus Adenovirus Parvovirus	Human herpesvirus 6 Amebiasis Brucellosis Leptospirosis Fitz-Hugh-Curtis syndrome (perihepatitis) Yellow fever Sepsis
Drug-induced/ingestions	Acetaminophen toxicity Idiosyncratic drug reactions *Amanita phalloides* mushroom poisoning Herbal and dietary supplements	
Autoimmune	Autoimmune hepatitis Celiac disease Sclerosing cholangitis	
Genetic/metabolic/congenital	Hepatorenal tyrosinemia Mitochondrial hepatopathy Fatty oxidation disorders Galactosemia Neonatal hemochromatosis α_1 Antitrypsin deficiency Wilson disease Polyglandular syndrome, type 1	Cystic fibrosis Nonalcoholic fatty liver disease Nonalcoholic steatohepatitis Glycogen storage disease Inborn errors of bile acid metabolism Hereditary fructose intolerance
Endocrine	Thyroid disorders Adrenal insufficiency	
Ischemic/vascular	Sinusoidal obstruction syndrome (veno-occlusive disease) Budd-Chiari syndrome	Congestive hepatopathy Ischemic hepatopathy Heat stroke
Other	Inborn errors of muscle metabolism Polymyositis Seizures	Strenuous exercise Malignant infiltration Anorexia nervosa

the presence of any recent viral illnesses, sick contacts, and risk factors for viral hepatitis, including intravenous drug use, travel to endemic areas, and being born to infected mothers. Inquiry should explore possible hepatotoxin exposures, including prescription and over-the-counter medications, herbal and dietary supplements, alcohol, and recreational drugs, noting the amounts ingested and use duration. When obtaining medical histories, inquiry should include conditions associated with hepatobiliary disease, such as cardiac disease causing right-sided failure, diabetes mellitus, skin pigmentation, obesity, inflammatory bowel disease, celiac disease, and thyroid disease. Family history should be explored for the presence of autoimmune diseases, gastrointestinal diseases, hemochromatosis, and Wilson disease (WD).

CLINICAL MANIFESTATIONS

A review of signs and symptoms and physical examination directed at identifying clinical manifestations of liver disease may clue in the physician to possible etiologies and the chronicity of disease. Most patients are asymptomatic; however, acute hepatitis can present with signs and symptoms of fatigue, malaise, nausea, abdominal pain, anorexia, fever, and jaundice. Patients with chronic disease are more likely to present with growth failure secondary to the development of growth hormone resistance and low insulinlike growth factor 1 concentration. Patients with chronic liver disease may also have spider angiomas, most prominently on the face and chest. Spider angiomas are suspected to occur from the direct vasodilatory effects of hyperestrogenism, inadequate hepatic metabolism of steroid hormones, and angiogenesis due to elevated serum vascular growth factor levels in patients with cirrhosis. (2) Signs of cholestasis include jaundice, dark xurine, pale stools, and pruritus. Pruritis due to cholestasis can be generalized or localized, commonly affecting the palms and soles. (3) It tends to be worse at night and exacerbated by stress and heat. Increased portal resistance or increased portal flow can lead to portal hypertension. Signs and sequelae of portal hypertension imply chronicity of disease and include splenomegaly, ascites, caput medusae (dilated abdominal veins as a result of blood shunting from the portal venous system through the umbilical veins), esophageal and gastric varices and gastrointestinal bleeding. Progression to cirrhosis and, ultimately, liver failure is suggested by muscle wasting, ascites, bruising, prolonged bleeding, and hepatic encephalopathy (confusion, inattention, agitation, slurred speech, somnolence).

Hepatomegaly

Hepatomegaly in the pediatric population is determined by the extent of the liver edge below the costal margin. In the pediatric population, the normal liver edge can be felt up to 2 cm below the right costal margin. (4) The upper liver margin can be identified using percussion, with dullness starting around the level of the fifth rib in the right midclavicular line. (4) The average liver span, or distance between the upper liver margin and the lower liver edge, is 4 to 5 cm for newborns and 6 to 8 cm for children by 12 years of age. (4)(5) Examination of the liver should include assessment of the consistency, contour, and tenderness and for the presence of any masses.

Jaundice

Yellow discoloration of the sclera, skin, and mucous membranes is defined as jaundice and is indicative of hyperbilirubinemia. Jaundice becomes clinically apparent when the serum total bilirubin level reaches 2 to 3 mg/dL (34.21–51.31 μmol/L). Hyperbilirubinemia must be differentiated into conjugated and unconjugated etiologies. Conjugated hyperbilirubinemia can be due to decreased excretion by damaged hepatic parenchymal cells or to diseases of the biliary tract. Unconjugated hyperbilirubinemia is due to increased production (as seen with hemolysis), reduced hepatic removal, or altered metabolism of bilirubin. One example of benign unconjugated hyperbilirubinemia is Gilbert syndrome, an inherited disorder resulting from reduced glucuronidation of bilirubin. It is characterized by recurrent episodes of isolated hyperbilirubinemia and jaundice, often triggered by factors such as dehydration, fasting, infection, menstruation, and overexertion. Aside from the presence of jaundice, patients are typically asymptomatic and do not require further intervention. Carotenemia, secondary to excessive consumption of β-carotene–rich fruits and vegetables (eg, carrots, cantaloupe, squash, sweet potatoes), can cause yellow-orange skin pigmentation. Unlike jaundice, the yellow pigmentation seen in carotenemia spares the sclera and mucosa. (6)

LIVER BIOCHEMICAL PROFILES

In patients with suspected hepatitis, serum aminotransferase levels should be evaluated first, with special attention to their duration and extent of elevation. The extent of elevation and clinical context can help further guide the evaluation. If the transaminase elevation is acute, lasting less than 3 weeks, the etiology is likely infectious. Transaminase elevation for longer than 6 months is considered chronic. However, the presence of hepatic inflammation for longer than 10 weeks, evidenced by clinical presentation and laboratory studies,

decreases the likelihood of self-limited hepatitis and implies chronicity. (7) When transaminase elevations are identified, they should first be confirmed by repeated laboratory examination along with assessment of γ-glutamyltransferase (GGT) and creatinine phosphokinase levels (Fig 1). If elevations persist or the patient's clinical presentation suggests hepatitis, one should obtain direct and indirect bilirubin levels, ALP level, a complete blood cell count, albumin level, prothrombin time (PT), and international normalized ratio (INR). Prompt assessment of hepatic synthetic function with albumin, PT, and INR is crucial in identifying liver decompensation and timely referral and evaluation for liver failure, especially if the direct bilirubin level is greater than 3 mg/dL (>51.31 μmol/L), there is marked liver enzyme elevation (>100 U/L), or there is any presence of chronic liver disease.

Cytopathic injury to the hepatocytes can be detected with monitoring of serum levels of ALT and AST. With liver injury, necrotic hepatocytes release these aminotransferases into the circulation. ALT is present in the highest concentration in the liver, whereas AST can be found in the liver, cardiac muscle, skeletal muscle, brain, kidneys, pancreas, lungs, leukocytes, and erythrocytes and is less specific than ALT as a marker of liver disease. Elevations of ALT and AST levels must be differentiated from diseases affecting the muscle, such as rhabdomyolysis. Elevations in creatinine phosphokinase levels are more specific to muscle injury, whereas elevations in GGT and bilirubin levels would not be expected in muscle injury.

Cholestasis is defined by an elevated serum conjugated bilirubin level, which can be a result of abnormal bile flow secondary to inflammatory mediators and hepatocyte damage. Elevations of ALP, GGT, 5′-nucleotidase, and urobilinogen levels are also indicators of cholestasis. ALP, however, is nonspecific to hepatobiliary disease and can be considerably

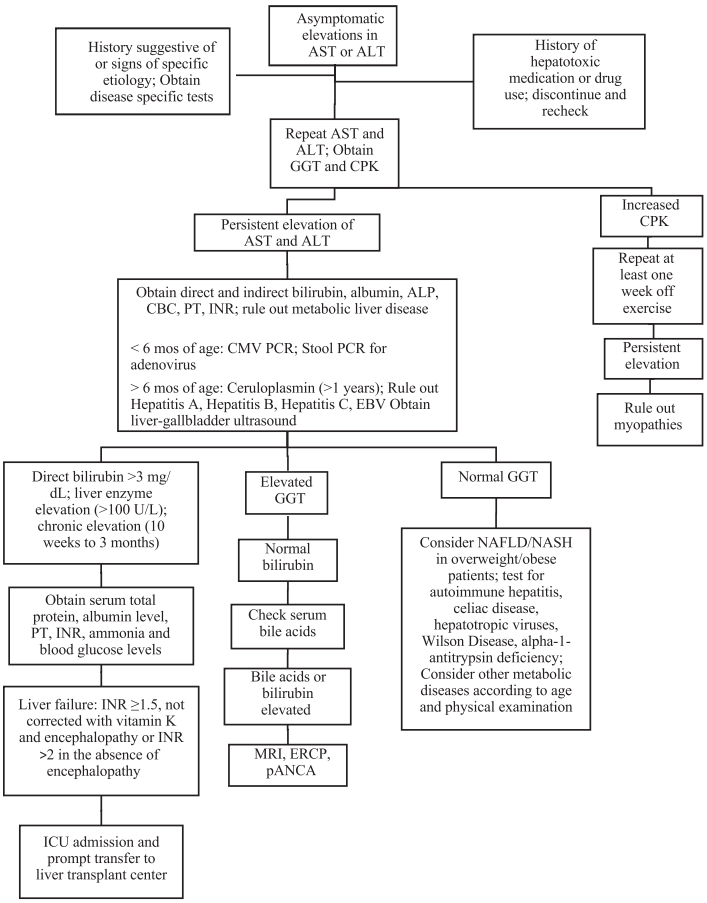

Figure 1. Suggested evaluation for patients with asymptomatic transaminase elevations. ALP = alkaline phosphatase, ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC, complete blood cell; CMV = cytomegalovirus, CPK = creatinine phosphokinase, EBV = Epstein-Barr virus, ERCP = endoscopic retrograde cholangiopancreatography, GGT = γ-glutamyltransferase, INR = international normalized ratio, MRI = magnetic resonance imaging, NAFLD = nonalcoholic fatty liver disease, NASH = nonalcoholic steatohepatitis, pANCA = perinuclear antineutrophil cytoplasmic antibody, PCR = polymerase chain reaction, PT = prothrombin time.

elevated in children, correlating with the rate of bone growth. Differentiation of the source of ALP elevation can be achieved by obtaining a serum GGT level. Serum GGT level is not influenced by bone turnover and is useful in supporting the presence of hepatobiliary disease. If GGT levels are elevated and bilirubin levels are within normal limits, serum bile acid levels should be checked as a sensitive marker of liver disease and impaired hepatic clearance. A more in-depth evaluation may include 5′-nucleotidase. (8) Increased 5′-nucleotidase, similar to GGT, is not influenced by bone growth. 5′-Nucleotidase activity is seen in obstructive jaundice, parenchymal liver disease, and hepatic metastases. (8) A normal 5′-nucleotidase level in the presence of an elevated ALP level does not rule out hepatobiliary disease because the 2 values may rise disproportionately in early hepatic injury. Urobilinogen is less useful in the differential diagnosis of hepatobiliary disease because it is influenced by bilirubin production, hepatic clearance, exposure of bilirubin to intestinal bacteria, biliary obstruction, cholestasis, and renal tubular reabsorption.

Altered synthetic function during acute or chronic liver injury is a significant marker of liver injury and should be monitored to determine the severity of the disease and progression to liver failure. This can be reflected by abnormal protein synthesis, metabolic disturbances, poor clearance of medications that depend on hepatic metabolism, and hepatic encephalopathy. Decreased hepatic synthetic function is reflected by the presence of a prolonged PT, high INR, or low serum albumin levels. Metabolic derangements can include hypoglycemia, lactic acidosis, and hyperammonemia. Patients with impaired hepatic synthetic function require immediate referral and evaluation for liver failure.

IMAGING

The initial imaging of choice for further evaluation of the liver is hepatic ultrasonography because it provides information about the presence of hepatomegaly, steatosis (infiltration of liver by fat), or other liver abnormalities, including lesions of the liver. Hepatic ultrasonography is indicated in patients with chronically elevated liver enzyme levels to characterize diffuse liver disease, in jaundiced patients or patients with laboratory evidence of cholestasis to visualize bile duct dilation, and in patients whose physical examination reveals an abdominal mass or organomegaly.

DIAGNOSTIC PROCEDURES

The gold standard for diagnosis of most liver pathology is a percutaneous liver biopsy and examination of hepatic histology, which can be performed safely in infants as young as 1 week. (9) A liver biopsy provides key information regarding the degree of liver damage, including inflammation, fibrosis, fat infiltration, and copper measurement. A biopsy is indicated when the result will influence clinical decision-making (ie, as a final investigation when laboratory tests are inconclusive or suggestive of treatable disease), in the presence of hepatomegaly or splenomegaly suggesting advanced liver disease, or before pharmacologic or surgical treatment. A transjugular or surgical wedge liver biopsy is preferred if coagulopathy is present.

ACUTE LIVER FAILURE

Acute liver failure (ALF) occurs in the setting of rapid deterioration of liver function in patients without known chronic liver disease or cirrhosis. It is characterized by evidence of coagulopathy and altered mental status and carries high morbidity and mortality. Patients with markedly elevated liver enzyme levels require prompt evaluation of PT/INR and assessment for altered mentation. An INR of 1.5 or greater (not corrected with vitamin K supplementation) and encephalopathy or an INR of 2 or greater (not corrected with vitamin K supplementation) and without encephalopathy is diagnostic for ALF. (10) It is important to closely monitor patients who meet the criteria for ALF in an ICU and to initiate planning for prompt transfer to a liver transplant center. Causes of ALF vary among age groups (Table 2). Metabolic and infectious causes, particularly herpes simplex virus, are more common in infants. Patients diagnosed as having WD or autoimmune hepatitis (AIH) less than 26 weeks before developing liver failure may meet ALF criteria, despite being considered chronic diseases. (10) In evaluating a patient for ALF, it is important to obtain a thorough history with attention to the onset of symptoms; family history of liver disease; exposure to medications, drugs, or toxins; recent travel; or exposure to viral illnesses. (11) Physical examination should include evaluation for hepatic encephalopathy (confusion, inattention, agitation, slurred speech, somnolence), ascites, edema, and heart murmur or gallop. An extensive laboratory examination evaluating the severity of disease and its etiology is indicated to guide management. Initial assessment should include blood chemistries, arterial blood gas, complete blood cell count, drug screen, acetaminophen level, viral serologies, tests for WD, and autoantibodies for the diagnosis of AIH. ALT, AST, and GGT levels should be evaluated as indicators of liver injury. (11) One also assesses liver function by obtaining PT/INR and levels of bilirubin (total and fractionated), total protein, albumin, glucose, and ammonia. It is important to monitor for complications of ALF, including sepsis, cerebral

Table 2. Differential Diagnosis and Laboratory Considerations for Pediatric Acute Liver Failure

AGE	ETIOLOGY	DIAGNOSTIC EVALUATIONS
All patients	Mitochondrial disease	Lactate, pyruvate
	Fatty acid oxidation defects	Plasma acylcarnitine profile
	Acetaminophen toxicity	Acetaminophen level
	Drug-, herbal or dietary supplement–induced injury	Drug history, urine toxicology screen
	Hemophagocytic lymphohistiocytosis	Soluble interleukin-2 receptor, ferritin, triglyceride level
	Vascular/anatomical abnormality	Abdominal ultrasonography with Doppler
	Sepsis/infection	Blood culture
	Viral infection	Viral PCR for EBV or anti-EBV capsid antigen IgM; CMV PCR; enterovirus blood PCR; adenovirus PCR; HHV-6 PCR; HSV types 1 and 2 PCR; parvovirus PCR; anti-HAV IgM; HBsAg, IgM anti-HBc, anti-HBs; HCV antibody, hepatitis C viral RNA; anti-HEV
	Urea cycle/metabolic	Serum amino acid profile
	Regardless of the age, if there is no clear cause of liver disease, consider genetic testing for heritable liver disease (mitochondrial, Niemann-Pick, hereditary fructose intolerance, etc)	
<3 mo	Neonatal hemochromatosis	Serum iron level and TIBC If transferrin saturation (serum iron/TIBC) is >45%, obtain a serum ferritin level Magnetic resonance imaging, liver biopsy, and genotype screening if indicated
	Tyrosinemia	Urine succinylacetone, confirm newborn screen results
	Galactosemia	Confirm newborn screen results
	Hepatitis B in newborn	Confirm maternal hepatitis B serology
	Cardiac dysfunction	Echocardiography
3 mo to 18 y	Wilson disease	Ceruloplasmin level, urinary copper quantitation, slit-lamp examination
	Autoimmune hepatitis	Antinuclear antibodies, anti–smooth muscle antibodies, anti-liver/kidney microsomal antibodies type 1, IgG

Anti-HBc=hepatitis B core antibody, anti-HBs=hepatitis B surface antibody, CMV=cytomegalovirus, EBV=Epstein-Barr virus, HAV=hepatitis A virus, HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus, HEV=hepatitis E virus, HHV-6=human herpesvirus 6, HSV=herpes simplex virus, Ig=immunoglobulin, PCR=polymerase chain reaction, TIBC=total iron-binding capacity.
Adapted with permission from Bhatt H, Rao GS. Management of acute liver failure: a pediatric perspective. *Curr Pediatr Rep.* 2018;6(3):246–257 (32) and Squires JE, Alonso EM, Ibrahim SH, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition Position Paper on the Diagnosis and Management of Pediatric Acute Liver Failure. *J Pediatr Gastroenterol Nutr.* 2022;74(1):138–158. (33)

edema, increased intracranial pressure, coagulopathy, renal failure, circulatory failure, and hypoglycemia.

CAUSES OF HEPATITIS

Infectious Causes

Viral Hepatitis.

Hepatitis A

Hepatitis A virus (HAV) is an RNA virus in the picornavirus family. It is responsible for acute hepatitis and does not typically result in chronic infection or chronic liver disease. Most children are asymptomatic or have mild disease. Symptomatic children can present with fever, abdominal pain, diarrhea, nausea, anorexia, arthralgias, and jaundice. Infection occurs through fecal-oral transmission or through ingestion of contaminated food or water. HAV is present globally but is more prevalent in developing countries with poor sanitary infrastructure and limited access to clean water. Infection rates worldwide have declined with the implementation of HAV immunization. In the United States, the HAV vaccine is routinely recommended as a 2-dose series, beginning at 12 months of age. Diagnosis is made with the detection of HAV antibodies. Treatment is supportive.

Hepatitis B

Hepatitis B virus (HBV) is a double-stranded DNA virus that causes acute and chronic hepatitis. Transmission is through contaminated bodily fluids. Vertical transmission (maternal-fetal route) is the most common form in pediatric cases. Diagnosis is made with the detection of viral markers (Table 3). The hepatitis B surface antigen (HBsAg) indicates either an acute or chronic infectious state. Hepatitis B

Table 3. Viral Markers of Hepatitis B

PHASE OF INFECTION	HBsAg	ANTI-HBs	HBeAg	ANTI-HBe[a]	ANTI-HBc	LIVER HISTOLOGY
Early	+	–	+	–	IgM	Acute inflammation
Recovery	–	+	–	+	IgG	Normal
Immune tolerance phase	+	–	+	–	IgG	Minimal inflammation
Inflammatory phase					IgG, IgM	Active inflammation
Inactive phase	+	–	+	–	IgG	Minimal inflammation

Anti-HBc=hepatitis B core antibody, anti-HBe=hepatitis B e antibody; anti-HBs=hepatitis B surface antibody; HBeAg=hepatitis B e antigen; HBsAg=hepatitis B surface antigen, Ig=immunoglobulin.
[a]Seroconversion of HBeAg to anti-HBe usually indicates resolution of the active hepatitis B virus replication phase.
Adapted with permission from Chang M-H. Hepatitis B virus infection. In: Suchy FJ, Sokol RJ, Balistreri WF, eds. *Liver Disease in Children.* 4th ed. Cambridge, England: Cambridge University Press; 2014:276–292. (34)

antigen and HBV DNA are markers of active viral infection. A positive IgM hepatitis B core antibody indicates a recent or acute infection with HBV. Hepatitis B surface antibodies are indicative of recovery and immunity to HBV by either vaccination or previous infection. Routine screening of all pregnant women for HBV has facilitated prophylaxis of newborns born to HBV-positive mothers. Newborn prophylaxis consists of hepatitis B vaccination and immunoglobulin administration within the first 12 hours of life. Infants who receive prophylaxis still require the complete HBV vaccine schedule. The infection rate is as high as 90% for infants born to mothers who are positive for HBsAg and do not receive appropriate prophylaxis at birth. Breastfeeding has not been shown to increase the risk of transmission. Presently available treatment options for children include interferon or nucleoside analogues. Due to the evolving nature of treatments, patients diagnosed as having HBV warrant gastroenterologist or hepatologist referral for management.

Hepatitis D

Hepatitis D virus (HDV) is rare in children born in the United States due to use of the hepatitis B vaccine in infancy. It is caused by an RNA virus that depends on the HBV for replication. Infection with HDV occurs only in individuals who are HBsAg positive. Infection can be as a co-infection (simultaneously) or as a superinfection (a chronic HBV carrier who is infected with HDV). It is recommended that patients with chronic HBV infection be tested for HDV, particularly those from endemic regions (Mediterranean basin, eastern Europe, Middle East, Amazonian basin, Asia, or Africa), those with a history of intravenous drug use, males who have sex with males, patients undergoing hemodialysis, or patients with clinical deterioration. (12) Diagnosis can be made by detection of HDV RNA with reverse transcriptase polymerase chain reaction (PCR) assays or by detection of antibodies to HDV. Pegylated interferon alfa is the treatment of choice.

Hepatitis C

Hepatitis C virus (HCV) is a blood-borne RNA virus. Maternal-fetal transmission during the birth process is the prevailing cause in infants and children. The incidence of vertical transmission is 1% to 5%, correlating to the mother's viral load. Individuals who require hemodialysis, receive tattoos in unsanitary conditions, participate in intravenous or intranasal drug use, and males who have sex with males are also at increased risk. Routine screening of blood products has virtually eliminated transmission of HCV through transfusions. Screening is recommended only for infants born to mothers with HCV. This should occur at 18 months of age (when acquired maternal antibodies are no longer present) by measuring serum anti-HCV antibodies. Diagnosis is made with the detection of serum HCV RNA by PCR and anti-HCV antibodies. Due to the slow progression of HCV, complications of liver disease such as cirrhosis and hepatocellular carcinoma rarely appear in childhood. The spontaneous clearance rate in children ranges from 20% to 45% and is more likely if the infection is acquired perinatally. Rates of spontaneous clearance decrease with infection at an older age. Treatment of HCV infection has evolved with the introduction of direct-acting antiviral agents and combination therapies now available to children as young as 3 years. Regimens vary based on genotype, disease severity, concomitant human immunodeficiency virus or HBV infection, and treatment history. Current combination therapy options for all genotypes include sofosbuvir-velpatasvir or glecaprevir-pibrentasvir. For HCV genotypes 1, 4, 5, or 6, ledipasvir-sofosbuvir can be administered. For children younger than 3 years, it is suggested that treatment be deferred until they are eligible for treatment with direct-acting antiviral agents. Patients diagnosed as having HCV should be referred to a

gastroenterologist or hepatologist for specific drug regimen determination.

Hepatitis E

Hepatitis E virus (HEV) is a single-stranded RNA virus. Transmission is through the fecal-oral route. HEV infection is rare in the United States; almost all HEV infections occur in resource-limited countries. One should consider HEV infection in patients who have recently traveled to Asia, Africa, the Middle East, or Central America or if no other explanation for elevated aminotransferase levels is found. (13)(14) HEV usually causes an acute, self-limited illness similar to HAV, but cases of fulminant hepatitis have been reported. Diagnosis is made by PCR or by detection of antibodies to HEV. Treatment is supportive.

EBV, CMV, and Herpes Simplex Virus. EBV and CMV are DNA viruses in the herpesvirus family. Transmission of EBV occurs through saliva. It is the offending agent in infectious mononucleosis. Liver involvement is present in most cases of EBV but is usually subclinical and self-limited. Acute or chronic EBV infection can lead to hepatitis, presenting with hepatomegaly, elevated transaminase levels, and even ALF. Liver involvement secondary to EBV infection can occur in isolation or in conjunction with symptoms of infectious mononucleosis (eg, fatigue, fever, tonsillar pharyngitis, lymphadenopathy). Transaminase elevations are typically mild, reaching 2 to 3 times the upper limit of normal (ULN). Severe cases have been observed, more frequently in immunocompromised individuals.

Transmission of CMV occurs through blood, secretions, or organ transplant. Maternal-fetal transmission can lead to severe congenital infection. Acquired infections tend to be asymptomatic but can lead to CMV hepatitis. Antiviral treatment, most commonly with ganciclovir, is recommended in severe cases and should be considered in patients with immunosuppression if clinically indicated. Herpes simplex virus type 1 has also been associated with acute hepatitis and should be considered in immunocompromised patients and those younger than 3 months. Treatment is with acyclovir.

Other Common Viruses. Other viruses have also been associated with hepatitis. Stool PCR for adenovirus should be obtained in patients younger than 6 months who have elevated transaminase levels or presentations suggestive of hepatitis. Hepatitis has also been associated as a complication of adenovirus in immunocompromised patients, particularly in pediatric liver transplant patients. There are presently no approved antivirals for the treatment of adenovirus infections; however, there have been reports on the successful use of cidofovir and ribavirin in severe cases of adenoviral disease in immunocompromised patients. (15) In addition, human herpesvirus 6 and parvovirus have also been associated with pediatric ALF.

Noninfectious Causes

Autoimmune Hepatitis. AIH is an immune-mediated inflammatory condition of the liver that may occur as a primary diagnosis or in association with other autoimmune disorders. Although it has a female predominance, AIH can occur in patients of all ages, sexes, and ethnic groups. The pathogenesis is hypothesized to be related to an exaggerated cellular and humoral autoimmune response to hepatocyte injury in the setting of an inciting trigger such as viral infection. (16) The diagnosis should be considered in any patient with elevated aminotransferase levels. It is important to exclude metabolic and infectious causes of hepatitis because the presentation of AIH is often indistinguishable from these causes, with nonspecific symptoms of malaise, anorexia, vomiting, abdominal pain, and jaundice. Some patients, however, may present with more fulminant liver failure with rapid development of severe liver injury and impaired synthetic function, with or without encephalopathy. (17) Diagnosis is made by the detection of elevated total serum IgG levels and the presence of circulating autoantibodies such as antinuclear antibody, anti–smooth muscle antibody, liver-kidney microsomal antibody, or anti–soluble liver antigen antibody. A liver biopsy should be obtained to establish the diagnosis of AIH. The presence of interface hepatitis, or inflammation of the hepatic parenchyma at its junction with portal tracts, portal tract lymphocytes, plasma cell infiltration into the parenchyma, hepatic rosette formation, and emperipolesis (intact cells in the cytoplasm of another cell) are typical findings. (17) Treatment of AIH consists of corticosteroids, usually with the addition of immunosuppressants.

There is often overlap between AIH and primary sclerosing cholangitis, a chronic, progressive disease characterized by inflammation and fibrosis of the bile duct system, often associated with inflammatory bowel disease, particularly ulcerative colitis. In patients with elevated GGT levels or biliary changes on histologic examination, it is advisable to do a further evaluation including magnetic resonance imaging or cholangiography to look for changes consistent with primary sclerosing cholangitis. (16)(18)

Celiac Disease. Celiac disease is an immune-mediated, gluten-sensitive enteropathy. Hepatic injury is a common extraintestinal manifestation, ranging from asymptomatic liver enzyme elevations to chronic liver disease. It is characterized by moderate elevations in transaminase levels, usually associated with mild, nonspecific lobular and portal tract lesions.

The mechanism of liver injury is postulated to originate from endogenous toxic compounds released through the portal circulation from the inflamed and permeable small intestine mucosa. (19) Affected patients have lifelong sensitivity to gluten found in wheat, barley, and rye. Symptoms suggesting celiac disease include diarrhea, bloating, poor growth, weight loss, irritability, decreased appetite, and ascites. Extraintestinal manifestations of osteopenia, arthralgias, dermatitis herpetiformis, erythema nodosum, and dental enamel defects may also be present. Screening is performed with IgA anti–tissue transglutaminase, IgA endomysial antibody, and deamidated gliadin peptide IgA and IgG. Total IgA must also be obtained to evaluate for accuracy of these tests, as IgA deficiency is more common in patients with celiac disease. In such cases, elevations of IgA anti–tissue transglutaminase or IgA endomysial antibody will not be seen. Small bowel biopsy showing characteristic villous atrophy and crypt hyperplasia before initiating a gluten-free diet is diagnostic. Resolution of gastrointestinal disease and liver inflammation is expected with gluten elimination from the diet; however, celiac disease can also be associated with other forms of liver disease, such as AIH. These patients require corticosteroid and immunosuppressant therapy in addition to gluten elimination. One should consider celiac disease in children with unexplained transaminase elevations and in those diagnosed as having AIH.

Wilson Disease. WD is an autosomal recessive genetic disorder characterized by abnormal storage of copper in the liver. It is caused by mutations in the *ATP7B* gene, which encodes for a protein that functions as an ATP-driven copper pump. A defect in the *ATP7B* gene results in toxic accumulation of copper in the liver, leading to hepatocellular injury, central nervous system dysfunction, and hemolytic anemia. The diagnosis should be considered in children older than 1 year with elevated transaminase levels or other signs of liver injury and in those with unexplained cognitive, psychiatric, or movement disorders. (20) Neurologic manifestations can include tremor, decline in academic performance, psychiatric disturbances, and micrographia. Hepatic manifestations range from jaundice and spider hemangiomas to portal hypertension and hepatic failure. The presence of dark pigment rings encircling the iris of the eyes on slit-lamp examination, known as Kayser-Fleischer rings, is highly suggestive of WD. The diagnosis is made by low serum ceruloplasmin concentrations, high 24-hour urinary excretion of copper, and elevated quantitative hepatic copper determination via biopsy (determined by measuring the dry weight of the tissue sample). However, serum ceruloplasmin levels may remain within normal limits. (10) In acute presentations of WD with ALF, laboratory evaluation will reveal a high total bilirubin level to ALP ratio (>2). (10) Low total ALP levels are thought to result from zinc deficiency. (20) Copper estimation in the liver tissue may be a helpful indicator in children when the diagnosis remains uncertain. (20) The normal estimated hepatic copper concentration is less than 50 μg/g dry weight, whereas a hepatic copper concentration of 250 μg/g dry weight or higher is diagnostic of WD. Molecular testing for common mutations or whole gene sequencing should be obtained, especially if laboratory and biopsy results remain equivocal. Treatment consists of copper-chelating drugs such as penicillamine or trientine, or zinc salts to reduce copper absorption and prevent progressive liver and CNS damage. Early diagnosis and treatment is important in the avoidance of irreversible neurologic damage. Copper-rich foods such as shellfish, tofu, mushrooms, nuts, sweet potatoes, dark chocolate, and organ meats should be avoided until there is remission of symptoms and normalization of liver enzyme levels. (20) Liver transplant is often indicated in cases of ALF secondary to WD.

α_1-Antitrypsin Deficiency. α_1-Antitrypsin (AAT) deficiency is an autosomal codominant disorder affecting the lungs and liver. It is caused by a mutation of the protease inhibitor gene encoding for AAT. A single amino acid substitution leads to misfolded protein aggregates that cannot be released into circulation, causing accumulation in the hepatocellular endoplasmic reticulum and reduced serum concentrations. Accumulation of the defective, hepatotoxic AAT in the liver leads to inflammation, which can eventually progress to cirrhosis and fibrosis, and places the patient at increased risk for developing hepatocellular carcinoma later in life. (21) AAT deficiency is the leading genetic disorder in children requiring liver transplant. (21) AAT deficiency should be ruled out in children presenting with faltering growth, poor feeding, and respiratory pathology. Infants may present with prolonged jaundice with mild to moderate elevations in conjugated bilirubin and aminotransferase levels. This can make it difficult to distinguish AAT deficiency from biliary atresia. Toddlers may have mild elevation of aminotransferase levels, which can progress to severe liver dysfunction and portal hypertension through childhood and adolescence. Laboratory tests will reveal diminished serum levels of AAT; however, serum concentrations can be misleading during the host response to inflammation. An absence of the α-1 peak on serum protein electrophoresis is suggestive of the disorder. Diagnosis is confirmed by determining AAT phenotypes using isoelectric focusing, which is a technique for separating different molecules by differences in their isoelectric point. (16)

The normal gene product is PiM. PiZ and PiS are the most common mutations, with ZZ and Z null phenotypes most frequently associated with liver disease. Although orthotopic liver transplant is curative, current treatment of liver disease is otherwise supportive.

Nonalcoholic Steatohepatitis. Nonalcoholic steatohepatitis (NASH) is a complication of nonalcoholic fatty liver disease (NAFLD), highly associated with obesity and the metabolic syndrome. With the rise in childhood obesity, NAFLD has become the most common liver disease in children and a leading reason for liver transplant in adults. Although data are limited in the pediatric population, studies suggest that individuals with NAFLD are at greater risk for more severe severe acute respiratory syndrome coronavirus 2 disease, likely related to the obesity associated with NAFLD. (22)(23) Screening for NAFLD with ALT measurement is recommended in obese children starting at 9 years of age and for overweight children with additional risk factors such as prediabetes, diabetes, dyslipidemia, sleep apnea, or family history of NAFLD or NASH (Fig 2). (24) Patients are usually asymptomatic but may present with fatigue, malaise, and right upper quadrant pain. Central adiposity, hepatomegaly, and acanthosis nigricans may be seen on physical examination. Diagnosis is made in overweight or obese children, with ALT at least 2 times the sex-specific ULN for children and evidence of hepatic steatosis and inflammation in the absence of other causes. GGT level may also be elevated and is directly correlated with the degree of fibrosis. Serum ALP level can be elevated as well, but bilirubin levels and INR are typically within normal limits. NASH is characterized by macrovesicular hepatocellular steatosis with the additional histopathologic features of portal inflammation, with or without fibrosis. First-line treatment includes lifestyle modifications and weight loss. Patients and families should be advised to consume a well-balanced diet, avoid sugar-sweetened beverages, engage in moderate- to high-intensity exercise daily, and limit screen time to less than 2 hours per day. (24) For asymptomatic patients with an ALT level greater than the ULN but less than 80 U/L (<1.34 μkat/L), lifestyle modifications to promote weight loss can be recommended with repeated screening within 6 months. Referral to a gastroenterologist is advisable if the ALT level is greater than 80 U/L (>1.34 μkat/L) or 2 times the ULN for at least 3 months or if the patient is exhibiting

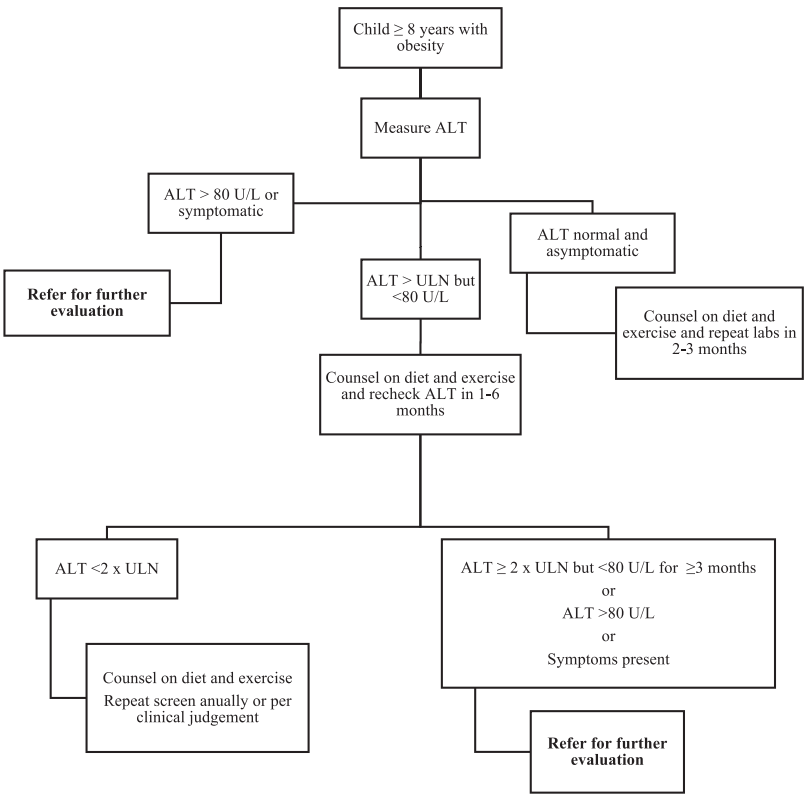

Figure 2. Suggested algorithm for patients with suspected nonalcoholic fatty liver disease. ALT=alanine aminotransferase, ULN=upper limit of normal. Adapted from Vos MB, Abrams SH, Barlow SE, et al. NASPGHAN Clinical Practice Guideline for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease in Children: recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). *J Pediatr Gastroenterol Nutr.* 2017;64(2):319–334. (24)

signs of advanced liver disease. Liver biopsy is not routinely recommended but should be considered to assess for steatosis, inflammation, and fibrosis in children who are at increased risk for NASH. Ultrasonography has poor sensitivity and specificity in quantifying steatosis but may be useful in ruling out anatomical abnormalities and assessing for portal hypertension. Magnetic resonance elastography and transient ultrasound elastography (ultrasound technique used to measure the elastic properties of tissue) are newer noninvasive imaging modalities to assess fibrosis. However, there are limited data in the pediatric population. (24) There are presently no approved medications for the management of NAFLD or NASH in the pediatric population. Bariatric surgery may be an option for select adolescents with a BMI of 35 or greater and other comorbid conditions. (24) Weight reduction medications, insulin sensitizers, lipid-lowering drugs, antioxidants, and cytoprotective therapies are under investigation in the adult population and may become available in the future. (25)

Metabolic Diseases. Metabolic diseases account for approximately 30% of cases of pediatric ALF. (11) Those associated with ALF include galactosemia, Niemann-Pick type C, tyrosinemia, glycosylation defects, mitochondrial hepatopathies, hereditary fructose intolerance, and urea cycle defects. (26) ALF secondary to WD and fatty oxidation defects is more common in older children and adolescents. Patient history of vomiting, diarrhea, poor growth, developmental delay, and seizures should increase the index of suspicion for metabolic disease. (11)(26)

Drug-Induced Hepatitis. There are a multitude of medications and supplements associated with drug-induced liver injury. Classes commonly implicated include antibiotics, analgesics, antiepileptics, and antineoplastic drugs. A detailed history concerning all prescription, over-the-counter, and recreational drugs, as well as herbal and dietary supplements, should be obtained. It is imperative to note the dosage, amount taken, and timing of the last dose.

Acetaminophen ingestion is the most common identified cause of ALF in the pediatric population. (11) The mechanism of injury is attributed to hepatic glutathione store depletion, allowing the acetaminophen derivative *N*-acetyl-*p*-benzoquinone imine to accumulate and cause hepatocellular damage. Acetaminophen toxicity develops at 7.5 to 10 g/d or 140 mg/kg. (27) Patients may experience early symptoms of nausea and vomiting; however, they may remain asymptomatic for hours after ingestion before progressing to ALF and death. Laboratory evaluations will reveal significantly elevated aminotransferase levels. For patients who present within 4 hours of a known or suspected acetaminophen overdose, activated charcoal can be given before starting *N*-acetyl cysteine. *N*-acetyl cysteine should be started promptly in all patients when the amount of acetaminophen ingested, serum drug level, or rising aminotransferase levels suggest impending liver injury. (10)

Although acetaminophen hepatotoxicity is intrinsic and dose-dependent, most drug hepatotoxicities are idiosyncratic, and the liver injury caused is unpredictable. Liver injury typically occurs within the first 6 months of drug initiation. (10) Diagnosis is made on the exclusion of other causes of liver injury. When suspected, all possible offending agents should be discontinued immediately. There are currently no particular antidotes for idiosyncratic drug reactions.

Herbal and dietary supplements are often perceived as natural and safe by consumers. It is important for physicians to be vigilant and suspect herbal and dietary supplements when evaluating patients with unexplained liver injury and to make patients aware of the potential hepatotoxic effects of herbal and dietary supplements. The list of known hepatotoxic herbal and dietary supplements is extensive; examples include Jin Bu Huan, Ma-Huang, germander, mistletoe, valerian, skullcap, chaparral, comfrey, green tea extracts, pennyroyal oil, kava, weight loss supplements, and androgenic corticosteroids. (28)(29) Further information can be found through *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury* (https://www.ncbi.nlm.nih.gov/books/NBK547852/). (30)

MANAGING HEPATITIS IN THE PRIMARY CARE CLINIC AND WHEN TO REFER

Most children presenting with hepatitis warrant referral to a pediatric gastroenterologist or hepatologist for specialist review, particularly patients with persistent, unexplained elevations in liver enzyme levels or who have any suspected differential diagnoses that may require further investigation and pharmacologic and/or surgical intervention.

In cases when the etiology is self-limited or does not require specific treatment, patients can be monitored in the primary care setting. Examples of such conditions include infectious causes of hepatitis such as HAV, HEV, CMV, and EBV that are mostly managed conservatively, and noninfectious causes such as NAFLD that is primarily managed with lifestyle modification. Patients with Gilbert syndrome can also be followed in the primary care setting.

Patients with EBV or CMV may warrant referral if the affected child is immunocompromised. Referral is recommended in NAFLD for children with normal BMI, persistent ALT elevation above 80 U/L (>1.34 μkat/L) or 2 times the ULN for more than 3 months, or signs of advanced liver disease. Referral is also warranted for any cases with

diagnostic uncertainty. Treatable causes of liver disease, such as infectious (eg, HCV, bacterial causes, fungal/parasitic causes) and noninfectious (eg, WD, celiac disease, drug-induced hepatitis) conditions, should be referred promptly to ensure timely examination and treatment to minimize long-term complications.

Patients managed in the primary care setting should be followed regularly to assess progress and to repeat laboratory examinations of liver function (eg, AST, ALT, ALP, GGT, albumin, total and fractionated bilirubin). The frequency of follow-up should correlate with the severity of the disease and the underlying condition of the patient. Close monitoring of patients with mostly self-limiting presentations enables observation for any signs of ALF that may develop in rare cases. If signs of ALF are noticed, urgent referral is imperative to avoid life-threatening complications.

Summary

- *Hepatitis* is a general term that indicates the presence of inflammatory liver injury, the causes of which are wide-ranging.
- Most patients are asymptomatic; however, acute hepatitis can present with signs and symptoms of fatigue, malaise, nausea, abdominal pain, anorexia, fever, and jaundice.
- When transaminase elevations are identified, they should be confirmed on repeated laboratory examination along with assessment of γ-glutamyltransferase and creatinine phosphokinase levels to differentiate alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations from diseases affecting the muscle.
- If elevations in ALT/AST levels persist on repeated examination or if the patient's clinical presentation suggests hepatitis, initial evaluation should include direct and indirect bilirubin levels, alkaline phosphatase level, complete blood cell count, albumin level, PT, and international normalized ratio.
- Altered synthetic function is a significant marker of liver injury and should be monitored to determine disease severity and progression to liver failure.
- If laboratory results suggest altered liver synthetic function, immediate referral and evaluation for liver failure is indicated.
- Based on moderate research evidence, hepatic ultrasonography is not recommended for the determination or quantification of steatosis but may be useful for further evaluation of other causes of liver disease and anatomical abnormalities. (24)
- Based on strong evidence, the gold standard for diagnosis of most liver pathology is a percutaneous liver biopsy and resulting hepatic histologic analysis. (9)
- Based on strong research evidence, children should receive all age-appropriate immunizations, including hepatitis A and hepatitis B vaccines. (31)
- Based on some research evidence and general consensus, it is strongly recommended that infants born to hepatitis C virus–positive mothers undergo antibody testing at 18 months of age. (31)
- Based on moderate research evidence as well as consensus, it is strongly recommended that screening for NAFLD with ALT measurement be performed in obese children 9 to 11 years of age and for overweight children with additional risk factors. (24)
- Children with NAFLD should be referred to a specialist if they have a normal BMI, persistent ALT elevation above 80 U/L (>1.34 μkat/L) or 2 times the upper limit of normal for over 3 months, or if they have signs of advanced liver disease.
- Prompt referral is warranted for treatable causes of liver disease, such as infectious (eg, hepatitis C virus, bacterial causes, fungal/parasitic causes) and noninfectious (eg, WD, celiac disease, drug-induced hepatitis) conditions.
- *LiverTox* (https://www.ncbi.nlm.nih.gov/books/NBK547852/) is a helpful resource for physicians and patients seeking further information on the diagnosis and management of liver injury secondary to various medications and herbal and dietary supplements. (30)

References and teaching slides for this article can be found at https://doi.org/10.1542/pir.2021-005279.

PIR QUIZ

1. A 16-year-old boy presents to his pediatrician for a 7-month history of fatigue and intermittent yellowing of his eyes. He has no medical history and has had no previous surgeries. He takes no medications or supplements. He has a BMI of 32. His liver edge is palpable 3 cm below the right costal margin. A metabolic profile is notable for an aspartate aminotransferase level of 103 U/L (1.72 μkat/L) and an alanine aminotransferase level of 117 U/L (1.95 μkat/L), with elevated direct and total bilirubin levels. The next step is to order:

   A. Abdominal radiography.
   B. Cholangiography.
   C. Endoscopic retrograde cholangiopancreatography.
   D. Hepatic ultrasonography.
   E. Magnetic resonance cholangiopancreatography.

2. You are seeing a term infant in the newborn nursery who was born 10 hours ago. The newborn's mother is known to have hepatitis B. The newborn has already received a dose of the hepatitis B vaccine intramuscularly (IM) along with hepatitis B immunoglobulin IM. You are most likely to recommend that the infant:

   A. Avoid breastfeeding.
   B. Complete the remainder of the hepatitis B vaccination series.
   C. Undergo abdominal ultrasonography.
   D. Not receive the hepatitis A vaccination series.
   E. Receive oral antiviral therapy for the first 3 months of life.

3. You are seeing a 2-year-old child for his health supervision visit. His mother is known to have hepatitis C, and previous testing has shown the infant to be hepatitis C RNA positive, hepatitis C antibody positive, and human immunodeficiency virus negative. His mother is concerned about him having hepatitis C and asks what should be done. You are most likely to recommend the child undergo:

   A. A 12-month course of IM pegylated interferon and oral ribavirin.
   B. Liver biopsy.
   C. Observation until 3 years of age.
   D. Screening for celiac disease.
   E. Therapy with oral ledipasvir-sofosbuvir for 3 months.

4. A 17-year-old girl has been undergoing evaluation for worsening school performance and behavioral changes. She was found to have elevated liver enzyme levels, and the consulting hepatologist recommended a liver biopsy. With such, it was determined that her hepatic copper concentration was elevated at 385 μg/g dry liver tissue. You are most likely to recommend that she:

   A. Avoid wheat, rye, and barley in her diet.
   B. Avoid shellfish, nuts, dark chocolate, and liver in her diet.
   C. Receive oral antiviral therapy.
   D. Start daily oral vitamin K therapy.
   E. Undergo an endoscopic retrograde cholangiopancreatography.

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5. A 14-year-old girl is in the ICU after purposeful oral ingestion of 12 g of acetaminophen 80 hours earlier. Her most recent international normalized ratio is 2.2 despite previous vitamin K therapy. Due to worsening mental status, she is intubated, sedated, and mechanically ventilated. She is requiring supraphysiologic amounts of glucose in her intravenous fluids to maintain normoglycemia. She has been receiving *N*-acetyl cysteine at the advice of the toxicology service. The primary mechanism of liver injury in this patient is due to

   A. An idiosyncratic reaction.
   B. Hepatic glutathione depletion.
   C. Interface hepatitis with plasma cell infiltration.
   D. Macrovesicular steatosis with portal inflammation.
   E. Misfolded proteins accumulating in the endoplasmic reticulum.