Hepatitis: General Principles
Maria Grazia Clemente and Kathleen Schwarz
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Hepatitis: General Principles

Maria Grazia Clemente, MD, PhD,* Kathleen Schwarz, MD†

Author Disclosure
Dr Clemente has disclosed that she is coinventor of a diagnostic technique for detecting F-actin immunoglobulin A antibodies. Dr Schwarz has disclosed no financial relationships relevant to this article. This commentary does contain a discussion of an unapproved/investigative use of a commercial product/device.

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

1. Describe the procedure and interpretation of the laboratory evaluation of hepatitis.
2. Recognize the signs and symptoms of acute and chronic hepatitis.
3. Describe the immediate and long-term complications of hepatitis.
4. List the multiple causes of hepatitis in an older child.

Introduction
Hepatitis is a term for inflammatory diseases of the liver, grossly subdivided into infectious and noninfectious, which are characterized by a wide variety of clinical and histologic manifestations, ranging from mild and self-limited to severe and progressive forms leading to liver failure, cirrhosis, or hepatocellular carcinoma.

Laboratory Evaluation
The liver typically has a similar response to any inflammatory injury, with some differences. The injury may be mostly hepatocellular (necrotic) or if it affects primarily the bile ducts and consequently the bile flow, cholestatic. In spite of injury, liver function is not necessarily compromised, and signs of liver failure might not appear until most of the hepatic cells are destroyed in the necrotic process. Disease-specific laboratory tests are available to diagnose the different causes of hepatitis.

Tests Reflecting Hepatocellular Necrosis
Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) are released from necrotic liver cells into the circulation, causing elevated serum concentrations. Usually, serum ALT values are higher than serum AST values unless cirrhosis already is present. Serum AST and ALT concentrations may rise dramatically with the progression of acute liver damage and subsequently decline to the normal range through depletion of their content in the liver. In the case of very slowly progressing chronic liver injury that results in cirrhosis, ALT and AST also may be in the normal range. Because AST and ALT can be derived from muscle, the clinician should verify that serum creatine kinase and aldolase values are within the normal range before assuming that the elevated serum AST and ALT values are hepatic in origin.

Tests Reflecting Cholestasis
Impaired bile flow due to cholestasis may result in very high serum concentrations of gamma-glutamyl transferase, serum alkaline phosphatase, and conjugated bilirubin.

Tests Reflecting Liver Failure
An elevated prothrombin time, despite administration of vitamin K, and low serum albumin concentrations are the most useful indicators of impaired synthetic liver function. Of note, the total serum protein concentration could be in the normal range in spite of low albumin values when the gamma globulins are increased substantially and the ratio of albumin to gamma globulins is inverted. Such an inversion is especially true in the autoimmune forms of hepatitis, which are characterized by hypergammaglobulinemia.
Disease-specific Laboratory Tests
Several disease-specific laboratory tests can identify the cause of hepatitis in some cases or characterize the nature of liver injury in others. Results of these tests can guide the selection of the most appropriate treatment. These tests are described in the sections of this article addressing specific diseases.

Diagnostic Procedures
Hepatic ultrasonography is the least invasive procedure and provides information about any degree of hepato-megaly, the presence of steatosis, and liver lesions such as parenchymal cysts or hemangiomas. Percutaneous liver biopsy is the gold standard for diagnosing almost all liver diseases. Hepatic histology not only can confirm the suspected cause of hepatitis, but it provides valuable information about the degree of inflammation and fibrosis, aiding the clinician in deciding the best therapeutic approach.

Clinical Symptoms
Hepatitis can manifest acutely or chronically. Fatigue and anorexia are characteristic, and gastrointestinal symptoms are common. Liver enlargement is the most common and often only manifestation of hepatitis on physical examination, followed by jaundice. When portal hypertension develops, splenomegaly usually is detected as well. Ascites and esophageal and gastric varices may occur if hepatitis progresses to cirrhosis and liver failure.

Acute Hepatitis
Flulike illness with fever, malaise, myalgia, arthralgia, and abdominal pain followed by the appearance of jaundice are typical symptoms of acute hepatitis. Cholestasis manifests with jaundice, dark urine, and acholic stools. Symptoms of acute hepatitis, however, can be milder, and often jaundice is absent, especially in children younger than 4 years of age. The most common causes of acute viral hepatitis are hepatitis A virus (HAV) and hepatitis E virus (HEV), the latter being an emergent public health problem, especially in developing countries. Enterovirus infection should be considered in febrile neonates who have hepatitis.

Chronic Hepatitis
Hepatitis that lasts more than 6 months is considered chronic and can progress to cirrhosis, liver failure, and hepatocellular carcinoma, which is rare in children. Symptoms can be absent and develop insidiously in most cases. Determining the cause is important because it is relevant to the overall prognosis and management as well as the short- and long-term complications of the disease. During childhood, for example, liver disease caused by hepatitis C virus (HCV) often is mild and slowly progressive, but autoimmune hepatitis (AIH) may present with bleeding due to previously unsuspected cirrhosis and liver failure.

Complications
Hepatitis may be complicated by serious conditions that require early recognition and appropriate intervention. Coagulopathy, esophageal bleeding, and acute encephalopathy are medical emergencies. Other complications, such as malnutrition, pruritus, and encephalopathy, are chronic and develop progressively over a longer period time.

Malnutrition
Nutrition is a major concern in children who have signs of hepatic dysfunction. A diet that has limited protein content and poorly absorbed disaccharides such as lactulose, which has significant therapeutic effects in reducing serum concentrations of ammonia and other potential cerebral toxins, must be balanced by adequate intake of

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>AIH</td>
<td>autoimmune hepatitis</td>
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<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
</tr>
<tr>
<td>ANA</td>
<td>antinuclear antibodies</td>
</tr>
<tr>
<td>APS-1</td>
<td>type 1 polyglandular syndrome</td>
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<tr>
<td>ASMA</td>
<td>antismooth muscle antibodies</td>
</tr>
<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
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<tr>
<td>CF</td>
<td>cystic fibrosis</td>
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<tr>
<td>CMV</td>
<td>cytomegalovirus</td>
</tr>
<tr>
<td>CYP</td>
<td>cytochrome P450 gene</td>
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<tr>
<td>EBV</td>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>HAV</td>
<td>hepatitis A virus</td>
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<tr>
<td>HBsAg</td>
<td>hepatitis B surface antigen</td>
</tr>
<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
</tr>
<tr>
<td>HCV</td>
<td>hepatitis C virus</td>
</tr>
<tr>
<td>HDV</td>
<td>hepatitis D virus</td>
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<tr>
<td>HEV</td>
<td>hepatitis E virus</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>IBD</td>
<td>inflammatory bowel disease</td>
</tr>
<tr>
<td>Ig</td>
<td>immunoglobulin</td>
</tr>
<tr>
<td>LKM</td>
<td>anti-liver and kidney microsomal antibodies</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>UGT</td>
<td>uridine diphosphate glucuronyl transferase</td>
</tr>
<tr>
<td>WD</td>
<td>Wilson disease</td>
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</table>
carbohydrates with supplements of zinc and branched-chain amino acids. Impaired bile flow in children who have cholestasis causes malabsorption of fat-soluble vitamins (vitamins A, D, E, and K) and lipids, necessitating adequate supplementation.

**Cirrhosis**
Cirrhosis represents the end stage of various liver diseases and may result in portal hypertension. The major and life-threatening complication of cirrhosis is hemorrhage from esophageal varices. Treatment includes endoscopic ligation or sclerotherapy. Surgical shunts are effective in reducing portal hypertension and preventing variceal bleeding, but liver transplantation is the preferred surgical solution in the modern era. Another common clinical problem in children who have end-stage liver disease is ascites. Ascites generally is treated with dual diuretic therapy using spironolactone and furosemide. Spontaneous infection of ascitic fluid is a serious complication and should be diagnosed by paracentesis in a febrile child who has ascites. Infection can be prevented by daily administration of norfloxacin.

**Pruritus**
Pruritus is an annoying itch that frequently develops during hepatic cholestasis. Because its origin has not yet been clarified, no truly effective treatment is available. Local use of moisturizing lotions or creams to avoid excessive dry skin is highly recommended. Some relief can be achieved with oral intake of medications such as rifampin (not approved for this indication) and ursodeoxycholic acid, both of which decrease intrahepatic concentrations of bile salts. Oral naltrexone also is effective but not approved for this indication or for children younger than 18 years. If itching is severe, surgical management by partial external biliary diversion may provide some relief.

**Encephalopathy**
Encephalopathy develops when increasing serum concentrations of ammonia and other potential cerebral toxins become toxic to the brain. These substances are produced by normal metabolism but cannot be metabolized properly and excreted because of the liver dysfunction. The goal of treatment is to reduce the production of ammonia derived from the intestinal bacteria using either oral nonabsorbable antibiotics, such as neomycin or rifaximin (not approved for this indication or for children younger than 12 years of age), or lactulose. Encephalopathy can be overt, manifesting as seizures and coma in children who have acute liver failure, or much more subtle (“minimal hepatic encephalopathy”), manifesting as poor concentration, forgetfulness, and poor school performance in the child who has chronic liver failure.

**Causes**
Hepatitis in an older child is due to multiple causes that can be subdivided into infectious and noninfectious (Tables 1 and 2). The latter includes nutritional, autoimmune, genetic, and drug-induced hepatitis. General treatment recommendations for hepatitis of different causes is summarized in Table 3.

### Table 1. Causes of Acute Hepatitis

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Noninfectious</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Hepatitis A, B, C, D (coinfects with hepatitis B), E</td>
<td>● Metabolic/genetic</td>
</tr>
<tr>
<td>● Cytomegalovirus</td>
<td>–Hepatorenal tyrosinemia</td>
</tr>
<tr>
<td>● Epstein–Barr virus</td>
<td>–Mitochondrial hepatopathy</td>
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<tr>
<td></td>
<td>–Fatty acid oxidation disorders</td>
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<td></td>
<td>–α−1-antitrypsin deficiency</td>
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<tr>
<td></td>
<td>–Wilson disease</td>
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<tr>
<td></td>
<td>–Polyglandular syndrome, type 1</td>
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<tr>
<td></td>
<td>● Autoimmune hepatitis</td>
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<tr>
<td></td>
<td>● Drug–induced hepatitis</td>
</tr>
</tbody>
</table>

### Table 2. Causes of Chronic Hepatitis

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Noninfectious</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Hepatitis B, C, D (with hepatitis B)</td>
<td>● Metabolic/genetic</td>
</tr>
<tr>
<td>● Cytomegalovirus</td>
<td>–Hepatorenal tyrosinemia</td>
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<tr>
<td>● Epstein–Barr virus</td>
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<td></td>
<td>–Wilson disease</td>
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<td></td>
<td>–Cystic fibrosis</td>
</tr>
<tr>
<td></td>
<td>–Polyglandular syndrome, type 1</td>
</tr>
<tr>
<td></td>
<td>● Autoimmune hepatitis</td>
</tr>
<tr>
<td></td>
<td>● Celiac disease</td>
</tr>
<tr>
<td></td>
<td>● Drug–induced hepatitis</td>
</tr>
<tr>
<td></td>
<td>● Nonalcoholic steatohepatitis</td>
</tr>
</tbody>
</table>
Infectious Hepatitis

HEPATITIS A.
HAV is an RNA virus transmitted primarily through the fecal-oral route. Contaminated uncooked food and water are the most common means of transmission. HAV infection never results in chronic hepatitis; it causes only acute disease. Clinical symptoms range from mild and asymptomatic to severe and fulminating hepatitis, especially when the infection is contracted as an adult. Measurement of immunoglobulin M (IgM) and IgG anti-HAV antibodies allow detection of recent or past exposure to HAV. HAV RNA is detectable by polymerase chain reaction (PCR) during viremia. Treatment is supportive. HAV vaccine is available for all children at age 1 to 18 years and for adults at risk. HAV vaccine is recommended for all children who have any chronic liver disease. (2)

HEPATITIS B.
Hepatitis B virus (HBV) is a blood-borne, double-stranded DNA virus that is transmitted by vertical transmission (maternal-fetal route) in most pediatric cases. Horizonal household transmission accounts for fewer cases. Diagnosis is made by detection of viral markers. Hepatitis B surface antigen (HBsAg) is indicative of HBV infection; hepatitis B e antigen and HBV DNA are markers of active viral replication. IgM anti-HB core antibody is positive in recent HBV infection, and the presence of IgM antihepatitis D virus (anti-HDV) is indicative of HDV coinfection. Anti-HBs IgG is the hallmark of permanent immunization against HBV that can occur naturally, especially after an acute HBV infection; can be induced by treatment of chronic hepatitis; or can follow successful HBV vaccination of unexposed individuals.

Maternal screening of all pregnant women for HBV has allowed prophylaxis for all newborns of HBV-positive women. Prophylaxis is provided by a combination of passive (IgG) and active immunization (first dose of the vaccine) of the newborns in the first 12 hours after birth, followed by the complete HBV vaccine schedule. Breastfeeding does not increase the risk of transmission. (3) HBV infection contracted early in life by vertical transmission usually results in chronic infection (90% to 95%). When contracted later, only 5% to 10% of infections progress to chronic hepatitis; 90% to 95% of patients clear the virus. Treatment for immunoactive HBV is with interferon or nucleoside analogs.

HEPATITIS C.
HCV is a blood-borne RNA virus that exists in six different major genotypes. Genotype 1 is the most aggressive and most resistant to antiviral therapy. A high rate of spontaneous mutations in the viral genome is the reason for the lack of an effective vaccine. HCV infection is investigated by measuring anti-HCV antibody and is confirmed by the detection of serum HCV RNA by PCR.

The maternal-fetal route is the principal route of transmission in infants and children, and injection during drug abuse is the most common mode of transmission in adults. The rate of vertical transmission is 4% to 7% if the mother has viremia. Coinfection of HCV/human immunodeficiency (HIV) increases the rate of transmission if the mother is not treated effectively for HIV. Screening of infants born to HCV-infected mothers is recommended by measuring serum anti-HCV antibody at 18 months of age, at which time passively acquired maternal antibody is no longer present in the infant serum. (4) For most children, HCV hepatitis is mild and slowly progressive. Each case should be considered individually for determining antiviral treatment. Treatment is with pegylated interferon plus ribavirin.

HEPATITIS D.
HDV depends on HBV to be infective. Very rare in pediatric patients, HDV is transmitted primarily through blood and sexual contact in HBsAg-positive individuals, in whom it dramatically worsens the pre-existing liver disease. Treatment is interferon.

Table 3. Management Principles According to Cause of Liver Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment/Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A virus infection</td>
<td>No specific antiviral treatment required; passive and active immunization of household contacts</td>
</tr>
<tr>
<td>Hepatitis B virus infection</td>
<td>α-interferon and lamivudine are the only FDA-approved treatments for children</td>
</tr>
<tr>
<td>Hepatitis C virus infection</td>
<td>Pegylated interferon and ribavirin</td>
</tr>
<tr>
<td>Hepatitis E virus infection</td>
<td>Supportive</td>
</tr>
<tr>
<td>Epstein-Barr virus infection</td>
<td>Supportive</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Supportive</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Corticosteroids and azathioprine</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Gluten-free diet</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Supportive</td>
</tr>
<tr>
<td>α-1-antitrypsin deficiency</td>
<td>Supportive</td>
</tr>
<tr>
<td>Wilson Disease</td>
<td>Copper-chelating agents such as penicillamine or trientine</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Drug withdrawal</td>
</tr>
</tbody>
</table>

**HEPATITIS C.** HCV is a blood-borne RNA virus that exists in six different major genotypes. Genotype 1 is the most aggressive and most resistant to antiviral therapy. A high rate of spontaneous mutations in the viral genome is the reason for the lack of an effective vaccine. HCV infection is investigated by measuring anti-HCV antibody and is confirmed by the detection of serum HCV RNA by PCR.

The maternal-fetal route is the principal route of transmission in infants and children, and injection during drug abuse is the most common mode of transmission in adults. The rate of vertical transmission is 4% to 7% if the mother has viremia. Coinfection of HCV/human immunodeficiency (HIV) increases the rate of transmission if the mother is not treated effectively for HIV. Screening of infants born to HCV-infected mothers is recommended by measuring serum anti-HCV antibody at 18 months of age, at which time passively acquired maternal antibody is no longer present in the infant serum. For most children, HCV hepatitis is mild and slowly progressive. Each case should be considered individually for determining antiviral treatment. Treatment is with pegylated interferon plus ribavirin.
HEPATITIS E. HEV is transmitted by the fecal-oral route and is a major health problem, especially in developing countries, where HEV outbreaks have been reported. HEV is endemic in Asia, the Middle East, and Africa, where it is primarily a self-limiting disease. Travel to countries that have high endemicity accounts for most of the sporadic cases detected in the United States and in other developed countries, where the infection is clinically more severe and has a higher mortality rate. Chronic HEV infection is rare but possible in immunocompromised patients. IgM and IgG anti-HEV antibodies allow detection of recent or past exposure. HEV RNA is detectable by PCR during viremia. Treatment is supportive management only. A recently developed vaccine is not yet available but is under study for safety and efficacy.

HERPESVIRUSES. Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are DNA viruses of the human herpesvirus family. Transmitted through saliva, EBV is responsible for human diseases, including infectious mononucleosis, Burkitt lymphoma, and lymphoproliferative disorders in immunocompromised children. Hepatitis commonly occurs during acute or chronic EBV infection, manifesting mostly with hepatomegaly and elevated serum liver enzymes and, in rare cases, with acute fulminant liver failure.

CMV is transmitted through blood, secretions, or transplanted organs. Vertical transmission may result in severe congenital infection. Acquired infections usually are asymptomatic but sometimes are responsible for what is called CMV hepatitis, CMV mononucleosis, or EBV-negative infectious mononucleosis syndrome, which is similar to EBV infection. Herpes simplex type 1 virus may cause acute hepatitis at any age and requires prompt administration of acyclovir.

A rapid mononucleosis slide test can be used to screen for EBV infection. In the case of equivocal test results, IgM and IgG for viral capsid antigen and nuclear antigens can be measured as well as PCR for EBV DNA. IgM and IgG anti-CMV also are useful in the diagnostic evaluation for viral hepatitis, as are CMV blood culture and PCR for CMV DNA.

Antiviral treatment is recommended in the most severe cases. Ganciclovir is used most frequently, although its efficacy is limited.

Autoimmune Hepatitis

AIH is a type of severe and progressive hepatitis in which the liver becomes the target organ of autoimmune inflammatory reactions. The diagnosis usually is made by exclusion of other causes of hepatitis and is suggested by the presence of hypergammaglobulinemia and circulating autoantibodies. Negative findings for all of the viral markers in the presence of hypergammaglobulinemia are highly indicative of AIH. Autoantibodies are IgG, and their presence in the serum at a high titer is responsible for the hypergammaglobulinemia. According to the patterns observed by indirect immunofluorescence assay, three major types of autoantibodies are associated with AIH: antinuclear antibodies (ANA), antismooth muscle antibodies (ASMA), and anti-liver and kidney microsomal antibodies (LKM). Analysis of the target antigens by different techniques has revealed that ANA, ASMA, and LKM have high heterogeneity.

ASMA have been detected frequently in viral hepatitis as well, where they react with different components of the intracellular cytoskeleton, but when their concentrations are high and directed toward actin filaments (F-actin), they are highly indicative of AIH. This particular anti-F-actin antibody has recently been reported in individuals who primarily have celiac disease. Such antibodies in these patients are primarily IgA compared with exclusively IgG in AIH. Therefore, ASMA-positive hepatitis may arise spontaneously, be triggered by a virus, or be associated with sensitivity to gluten. Only highly specialized laboratories can characterize ASMA fully to assist the clinician in the differential diagnosis.

LKM target antigens are the enzymes of phase 1 (cytochrome P450 superfamily) and phase 2 (uridine diphosphate glucuronyl transferase [UGT]) hepatic metabolism involved in the detoxification of endogenous compounds and xenobiotics. LKM-1 autoantibodies, reacting specifically with CYP2D6, are the most commonly detected LKM autoantibodies and are diagnostic for type-2 AIH, although they also can appear in the course of HCV-positive hepatitis. Type 2 AIH not associated with HCV is classified as type 2A and is treated with immunosuppression. Type 2 AIH associated with HCV is classified as type 2B and is treated with antivirals. Less commonly, type 2 AIH also may present with liver cytosol autoantibody, alone or in combination with LKM-1. Type 3 AIH is soluble liver antigen antibody-positive and is treated with immunosuppression. LKM-3 directed against UGT1 has been described during HDV infection.

Finally, “antibody-negative” AIH is possible. Liver biopsy shows typical plasma cell infiltrates along with Ig deposits, and the patient responds to immunosuppressants. However, the classic serum antibodies are not detectable at the time of presentation and may not occur later in the course of the disease.

Liver histology typically demonstrates plasma cell in-
filtrate, and liver biopsy should be performed before initiating treatment with corticosteroids or immunosuppressants.

Celiac disease, or gluten intolerance, often is accompanied by mild chronic hepatitis. The origin is not known, but it has been suggested that gluten-induced inflammation of the small intestinal mucosa generates endogenous toxic compounds that enter the liver through the portal circulation. Liver inflammation usually responds well to elimination of gluten from the diet. In a few cases, however, celiac disease is associated with AIH, and treatment with corticosteroids or immunosuppressants is required along with the gluten-free diet. Because the intestinal symptoms of celiac disease might not be evident at the time of the liver involvement, celiac serology should be performed in all children who have otherwise unexplained elevations of serum aminotransferases as well as in children in whom AIH is diagnosed. Screening for celiac disease is accomplished by measuring serum antiendomysial antibody and tissue transglutaminase.

AIH also may be an extraintestinal manifestation of inflammatory bowel disease (IBD). IBD also is associated with primary sclerosing cholangitis. Symptoms of IBD usually are already present at the time of the hepatobiliary disease diagnosis. Treatment is as specified for AIH.

**Genetic Hepatitis**

Wilson disease (WD) is a genetic disorder of copper metabolism that typically manifests during childhood only with abnormal serum aminotransferase values. Hepatitis accompanied by low serum ceruloplasmin concentrations and high urinary excretion of copper usually indicates WD. At slitlamp examination of the eyes, the dark pigment rings encircling the iris of eyes (Kayser-Fleischer rings) are highly suggestive of WD, but these occur rarely in childhood. Liver histology may show a variety of findings, ranging from mild hepatitis with characteristic microsteatosis to fully developed cirrhosis. An elevated concentration of copper in the liver is the gold standard for diagnosis. The gene for WD is known, but diagnostic screening for mutations is not recommended because of the large number of mutations. Treatment is copper-chelating agents such as trientine or penicillamine or zinc to prevent absorption of dietary copper.

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations of the CFTR gene on chromosome 7, which encodes for cyclic adenosine monophosphate-regulated chloride channels. Although pulmonary and pancreatic insufficiency are the most common disease manifestations, liver involvement due to focal inspissation of bile, which obstructs the intrahepatic bile ducts, is common. The most common liver injury in children who have CF is a cholestatic injury, characterized by eosinophilic concretions in the intrahepatic bile ducts. CF liver disease usually manifests initially with serum aminotransferase values above the normal range, but it progresses slowly to biliary cirrhosis with portal hypertension and can be one of the causes of death from the disease. An abnormal sweat chloride test result is suggestive of CF and usually is confirmed by genetic analysis for the most common mutations. There is no known therapy for CF liver disease, although administration of ursodeoxycholic acid reduces elevated serum aminotransferase concentrations.

Alpha-1-antitrypsin deficiency is an autosomal recessive disease caused by mutation of the protease inhibitor gene on chromosome 14 encoding for α-1-antitrypsin, a serine protease inhibitor produced by hepatocytes and released into the circulation. Liver disease results from accumulation of the defective α-1-antitrypsin in the liver, with consequent severe inflammation and sometimes even cirrhosis.

The absence of the α-1 peak at serum protein electrophoresis is strongly suggestive of α-1-antitrypsin deficiency, which usually is confirmed by determining α-1-antitrypsin phenotypes. N2Z and P2S are the most common deficiency alleles. The phenotypes usually associated with liver disease are ZZ and Z null; occasionally, patients who have the SZ phenotype can develop liver disease. Treatment is supportive.

Type 1 polyglandular syndrome (APS-1) is an autosomal recessive disorder caused by mutations of the autoimmune regulator AIRE gene on chromosome 21, which encodes a transcription factor. Clinical manifestations appear at different ages during childhood and include autoimmune diseases affecting parathyroid and adrenal glands, chronic mucocutaneous candidiasis, and ectodermal dystrophy. In 20% of children, liver involvement is present as part of the syndrome as AIH or acute liver failure, which is also one of the causes of death. Serum liver microsomal autoantibodies reacting with cytochrome P4501A2 are highly specific for the form of AIH associated with APS-1 and allow differentiation from the other forms of LKM-positive hepatitis. Treatment is with immunosuppressants.

The list of causes of acute liver failure associated with inborn errors of metabolism is long and beyond the scope of this article. More common metabolic causes include hepatorenal tyrosinemia, mitochondrial hepatopathy, and fatty acid oxidation deficits.

**Nutritional Hepatitis**

Nonalcoholic steatohepatitis is a complication of fatty liver, a condition associated with obesity. The condition
Drug-induced hepatitis is subdivided into two major groups. Drugs can have a direct toxic effect on the liver or they may induce an immunoallergic AIH. Although the liver damage in the first category usually is dose-dependent and there is no specific predisposition, drug-induced AIH affects only genetically predisposed individuals, is not dose-dependent, and usually reverses after drug withdrawal. Acetaminophen causes hepatitis by direct hepatic injury; isoniazid and methyldopa may induce immunoallergic hepatitis in predisposed individuals.

In the immunoallergic process, the drug-metabolizing cytochrome P450 (CYP) enzyme becomes an autoantigen (CYP2C9, CYP3A4, CYP2E1), triggering the production of specific LKM autoantibodies. The history of drug intake is critical in making the diagnosis. Treatment is withdrawal of the responsible drug. Autoimmune drug-induced hepatitis that does not respond to withdrawal may require treatment as for AIH.

References

Suggested Reading
Manns MP, Vogel A. Autoimmune hepatitis, from mechanisms to therapy. Hepatology. 2006;43(suppl 1):S132–S144
11. Which of the following laboratory tests is most likely to yield a positive result in a person who has been fully immunized against hepatitis B?

A. Anti-HBs IgG.
B. HBeAg.
C. HBsAg.
D. HBV DNA.
E. IgM anti-HB core antigen.

12. Which of the following hepatitis-causing viruses is correctly matched with its primary mode of transmission in the pediatric population?

A. Hepatitis A and contact with blood.
B. Hepatitis B and fecal-oral transmission.
C. Hepatitis C and vertical transmission.
D. Hepatitis D and fecal-oral transmission.
E. Hepatitis E and vertical transmission.

13. An abnormal result in which of the following laboratory tests is most indicative of cholestasis?

A. Alanine aminotransferase.
B. Albumin.
C. Aspartate aminotransferase.
D. Gamma-glutamyl transferase.
E. Prothrombin time.

14. The pathology report for a liver biopsy performed on a patient who has jaundice and elevated aminotransferase values reveals eosinophilic concretions in the intrahepatic bile ducts. Which of the following is the most likely diagnosis?

A. Autoimmune hepatitis.
B. Cystic fibrosis.
C. Hepatitis C infection.
D. Parenteral nutrition–induced cholestasis.
E. Wilson disease.
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