6A. Normal Anatomy, Development, Physiology

Christine Waasdorp Hurtado, MD, MSCS, FAAP

I. Introduction
A. The liver is divided into two lobes (right and left) by falciform ligament
B. The normal liver span is 7 cm in women and 10.5 cm in men. In infants, the normal liver span by percussion is 4–5 cm
C. Embryonic development of the liver:
   1. Liver is formed from endoderm
   2. Liver bud emerges from cranioventral portion of the endoderm
   3. Hepatocyte precursors—hepatoblasts—migrate into the septum transversum mesenchyme along with hematopoietic and endothelial precursors
      a. Hepatoblasts become hepatocytes
      b. Endothelial precursor cells develop into sinusoids
   4. Liver grows in volume and then is encapsulated and lobulated by 6th week of human gestation
   5. Lymphatic system develops at 15th week

II. The Blood Supply of the Liver
A. The majority of the blood supplied to the liver is venous. 70%–80% of the blood entering the liver is from the portal vein
   1. Portal venous blood is coming from small intestines, stomach, pancreas and spleen, and is rich in nutrients
B. Hepatic artery supplies the remaining 20%-30% of blood to the liver
   1. Arises from celiac artery
C. Terminal branches of the hepatic portal vein and hepatic artery empty together and mix as they enter sinusoids in the liver
   1. Sinusoids are lined with highly fenestrated endothelial cells and bounded circumferentially by hepatocytes
   2. Blood flows through the sinusoids, resulting in a substantial volume of plasma filtered into the space of Disse
D. Blood flows through the sinusoids to the central vein
   1. Central veins coalesce into hepatic veins
   2. Hepatic veins empty into the vena cava

III. Lymphatic Drainage
A. Lymph is created in the space of Disse
B. Lymphatics in portal tracts and wall of hepatic veins drain to lymph nodes in hilum and vena cava
C. Lymphatics in capsule drain across the diaphragm to esophageal lymph nodes

IV. Nerve Supply
A. Supplied by lower thoracic ganglia, celiac plexus, and vagus forming a plexus about hepatic artery, portal vein and bile duct
B. Arteries are mainly sympathetic fibers
C. Bile ducts have both sympathetic and parasympathetic fibers
D. Individual hepatocytes with unmyelinated sympathetic fibers

V. Biliary System (see section 5A)
VI. Liver Functions

The liver has many different functions. The major responsibility of the liver is to provide a source of energy for the entire body.

A. Carbohydrate metabolism (see section on Disorders of Carbohydrate Metabolism)
   1. Glycogen storage
   2. Gluconeogenesis – liver can produce 240 mg/day
      a. Fructose and galactose metabolism

B. Synthesis and metabolism of fatty acids (see section on Disorders of Lipid Metabolism)
   1. Fatty acid oxidation
   2. Ketogenesis
   3. Lipid transport

C. Bile acid synthesis (see section on Bile Acid Synthetic Disorders)

D. Protein synthesis
   1. Protein metabolism—deamination of AA, formation of plasma proteins, interconversion of AA
   2. Synthesis of nonessential AA
   3. Coagulation factors: Vitamin K–dependent
   4. Complement

E. Filter/detoxify
   1. Medication, toxin and xenobiotic elimination = first-pass metabolism
   2. Hormone metabolism
   3. Kupffer cells are macrophages and remove enteric organisms

F. Excretion of lipid-soluble waste products
   1. Excreted in bile

G. Hematopoiesis peaks in 3rd trimester
   1. Exocrine: secretion into biliary system
      a. Bile acids
      b. Cholesterol and phospholipids

Recommended Reading

6B. Microanatomy

Christine Waasdorp Hurtado, MD, MScS, FAAP

I. Normal Histology
   A. Majority of cells are hepatocytes (60%)
   B. Kupffer cells, endothelial cells, stellate cells and lymphocytes (40%)
   C. Liver organization—two ways to conceptualize the organization
      1. Lobules
         a. Lobules consist of hepatocytes, hepatic sinusoids (blood spaces), intralobular ducts and central vein (intralobular vein)
         b. Central vein surrounded by six portal triad areas (hepatic arteriole, portal venule, bile ductile). Hexagonal shape with central vein in center and portal triads at vertices
         c. Portal triads mark the junction of three lobules
         d. Lobules are separated by connective tissue
      2. Acinus
         a. Axis is two portal triads. Zone 1 is periportal with oxygen and nutrient rich blood. Zone 2 receives blood lower in oxygen and nutrients
   D. Hepatocytes are polygonal cells joined by anastomosing plate. Arranged in plates 1 cell thick
   E. Sinusoids run between rows of hepatocytes (Figure 1)
      1. Lined with fenestrated endothelial cells
      2. Blood flows from terminal branches of hepatic artery and portal vein at the periphery of lobules, and is delivered into central veins
   F. Kupffer cells are phagocytic cells (resident macrophages)
   G. Space of Disse is the area between endothelial cells and hepatocytes
      1. Lymph collects in this space
      2. Lymphocytes in this space
      3. Stellate cells are star-shaped, lipid-storing cells. They function as fibroblasts following cytokine stimulation
   H. Bile secreted at base of hepatocytes collects in canaliculi and flows into bile ductules and to the hepatic duct. Bile ducts have cuboidal epithelial cells (Figure 2)

Figure 1. Used courtesy of Kelly Capocelli, MD. Children’s Hospital Colorado.
Figure 2. Adapted from the Tokyo Institute of Technology's Department of Biomolecular Engineering Web site.

Recommended Reading

Histopathology of the Liver: 2 Volume Set Hardcover. Oxford University Press, USA; 1 edition (April 8, 1993)
6C. Jaundice

Rima Fawaz, MD

I. Overview
   A. Jaundice is the yellow discoloration of tissue due to deposition of bilirubin. The degree of discoloration is directly related to the amount of bilirubin deposition. Jaundice may be physiologic in infants or may be a sign of significant hemolysis, infection or liver failure
   B. Jaundice refers to a yellowish pigmentation of the sclera, mucous membranes and skin occurring when the plasma bilirubin exceeds 4–5 mg/dl in infants and 3 mg/dL in older children
      1. Other body fluids such as tears, saliva and cerebrospinal fluids may also have a yellowish hue
   C. An elevated bilirubin should always be fractionated into unconjugated (indirect) or conjugated (direct) bilirubin
      1. Direct bilirubin includes both the conjugated bilirubin fraction and bilirubin bound to albumin (delta bilirubin)
   D. Cholestasis occurs when there is failure of bile formation and/or flow
      1. Cholestasis and hyperbilirubinemia are not synonymous, although bile acid flux and bilirubin excretion are linked events in cholestasis

II. Mechanisms
   A. Jaundice can be broadly classified as prehepatic, hepatic or posthepatic
      1. Prehepatic jaundice occurs when excess bilirubin overwhelms the hepatocyte’s ability to conjugate bilirubin, as occurs in hemolysis
      2. Hepatic jaundice occurs when there is failure of bile formation or excretion, ie, at the cellular level
         a. Therefore, elevations of conjugated bilirubin may be seen in any type of liver disease
         b. In most liver diseases, both conjugated and unconjugated bilirubin fractions of the bilirubin are elevated
      1. Posthepatic jaundice occurs when there is interruption of drainage of bile into the biliary system, such as with a choledochal cyst

III. Bile Metabolism
   A. Bile is primarily an aqueous solution that is iso-osmotic to plasma
      1. It is the route of excretion of a range of endogenous compounds, including bile acids, bilirubin, cholesterol, steroids, xenobiotics and divalent heavy metals such as copper, iron, manganese and zinc
   B. Bile formation is a major function of the liver
      1. The major driving force for bile flow is the secretion and recirculation of bile acids
   C. Bile formation is also dependent upon ion flux in both hepatocytes and cholangiocytes
      1. In humans, up to 40% of bile is derived from bile ducts
      2. A main determinant of bile flow is the secretion of chloride, mainly through the apical CFTR gene product in cholangiocytes
   D. Bile formation and metabolism can be divided into four phases
      1. Hepatic uptake at the sinusoidal membrane (basolateral membrane)
         a. Initial site of bile formation
         b. Na-K ATPase is an inorganic ion transporter that creates a negative electric potential in the cell that helps facilitate diffusion
         c. Na-taurocholate cotransport peptide (NTCP) has a high affinity for bile acid uptake from the portal circulation
         d. The Solute Carrier Organic Anion Transport family, also known as Multispecific Organic Anion Transport Polypeptides (OATP; SLC21), are sodium independent carriers that facilitate uptake of a variety of organic compounds (both anions and cations), as they have broad substrate specificity
1) SLC21A6 transports bilirubin
2) Other carriers transport most drugs and unconjugated bile salts
   (Na-independent uptake system)

2. Hydroxylation
   a. Hydroxylation of lipid soluble constituents (bile and bilirubin) are mediated by
      cytochrome P450 (CYP) enzyme system
   b. Bile acids are formed from cholesterol via CYP7A1 and CYP8B1
   c. The majority of drugs are metabolized by CYP3A4

3. Conjugation
   a. Conjugation of bile acids with taurine or glycine is carried out by bile acid-CoA
      synthetase and bile acid Co-A amino acid N-acetyl transferase
   b. Bile acid conjugation also occurs with glucuronides and sulfates during
      cholestasis, which are substrates for the multidrug resistance–related protein 2
      and 3
      1) These reactions are mediated by uridine glucuronyl transferases
         (UGT2B4) and sulfotransferases (SULT2A1)
   c. Bilirubin is normally conjugated with glucuronides by UGT1A1
      1) Mutations in the promoter region of UGT1A1 result in reduced enzyme
         activity and Gilbert’s syndrome
      2) Mutations in the gene itself result in complete loss or very low level of
         enzyme activity and Crigler-Najjar syndrome

4. Canalicular excretion (apical membrane)
   a. Bile salt export pump (BSEP, ABCB11) is an ATP cassette transporter, which ef-
      ficiently secretes bile acids into the canalicular lumen
      1) The secretion of the bile acids against a steep concentration gradient is
         the rate-limiting step of bile secretion
      2) Mutations in BSEP result in a variety of cholestatic diseases, including
         progressive familial intrahepatic cholestasis (PFIC) Type 2, benign recur-
         rent intrahepatic cholestasis (BRIC-2) and intrahepatic cholestasis of
         pregnancy (ICP)
   b. The multidrug resistance protein 3 (MDR3) gene product, a flippase, functions
      as a phospholipid export pump
      1) Mutations in MDR3 result in variable forms of PFIC type 3, ICP, low
         phospholipid-associated cholelithiasis and adult biliary cirrhosis
      2) Cholesterol is secreted by two combined half transporters, ABCG5/G8
         a) Mutations of either half results in Sitosterolemia
   c. Multidrug resistance–related protein 2 (MRP2) multispecific transporter (ABCC2)
      excretes conjugated bilirubin
      1) MRP2 exports glutathione and other organic anions into the bile (usu-
         ally as conjugates with glutathione, glucuronide or sulfates)
      2) Mutations in MRP2 lead to Dubin-Johnson syndrome, while polymor-
         phisms may predispose to drug-induced cholestasis

IV. Differential Diagnosis
   A. The differential diagnosis for jaundice is age-specific
   B. See neonatal cholestasis and cholestasis in older child
V. Evaluation

A. Jaundice in the older infant and child is always pathologic and requires an investigation

B. History and patient age provide important clues as to the etiology of jaundice (Table 1)

1. A detailed physical exam may help direct the investigation by providing an assessment of global health and nutrition, assessing for dysmorphic features, and stigmata of chronic liver disease.

2. Initial laboratory might include a complete blood count with differential, chemistry, liver enzymes, albumin, total and direct bilirubin, and evaluation of liver synthetic function. More detailed testing can then be tailored according to suspected diagnoses.

3. Imaging evaluation might begin with an abdominal ultrasound as it noninvasive and without radiation. Ultrasonography can measure hepatic size and consistency. It can detect abnormal echotexture suggestive of fat, fibrosis or infiltration, and it can identify masses, cysts, abscesses and biliary tree abnormalities. Absence of the gallbladder in a fasting baby can be suggestive of biliary atresia, but is not diagnostic. Liver biopsy is often needed for definitive diagnosis.

Table 1. Patient History and Associated Differential Diagnosis

<table>
<thead>
<tr>
<th>History of:</th>
<th>Differential Diagnosis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal infection</td>
<td>TORCH infections, HIV, HBV</td>
</tr>
<tr>
<td>Abnormal fetal ultrasound</td>
<td>Choledochal cyst, ciliopathies</td>
</tr>
<tr>
<td>Cholestasis of Pregnancy</td>
<td>PFIC</td>
</tr>
<tr>
<td>Consanguinity or similar history in parents or siblings</td>
<td>Autosomal recessive genetic or metabolic diseases</td>
</tr>
<tr>
<td>History of feeding, irritability and vomiting</td>
<td>Metabolic disorders, such as galactose</td>
</tr>
<tr>
<td>Acholic stools</td>
<td>Obstruction or severe hepatocellular disease</td>
</tr>
<tr>
<td>Blood products transfusions/organ transplant</td>
<td>Infectious hepatitis</td>
</tr>
<tr>
<td>Sexual activity/ intravenous drug use</td>
<td>Hepatitis B, C, HIV, gonorrhea and syphilis</td>
</tr>
<tr>
<td>Foreign travel</td>
<td>Parasitic infections and/or liver abscesses</td>
</tr>
<tr>
<td>Shellfish ingestion</td>
<td>Hepatitis A</td>
</tr>
<tr>
<td>Drug intake: prescription or recreational drugs</td>
<td>Vitamin A, Tylenol, hepatotoxic medications</td>
</tr>
<tr>
<td>Chronic illnesses</td>
<td>Congenital heart disease, cystic fibrosis, diabetes mellitus, hematologic diseases, autoimmune diseases</td>
</tr>
</tbody>
</table>

Recommended Reading


6D. Elevated Aminotransferases

Isabel Rojas, MD
Norberto Rodriguez-Baez, MD

I. Serum aminotransferases are liver chemistry tests used to assess for liver injury. These enzymes are found in several different tissues. Increased levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) can assist in the identification of the liver injury and direct additional evaluation.

A. AST (aspartate aminotransferase) and ALT (alanine aminotransferase) are released from damaged hepatocytes, indicating liver injury.

B. AST is found in high concentrations in liver, heart muscle, skeletal muscle, kidney, brain, pancreas, lung, leukocytes and red blood cells.

C. ALT is more specific for liver disease, due to its presence in low concentrations in other tissues.

D. Elevation itself is not diagnostic of any disease, however, evaluated in conjunction with patient's history and physical exam, it can suggest a particular diagnosis and direct the evaluation.

E. Differential diagnosis of marked elevated aminotransferases (>1,000 U/L) include: viral hepatitis (A to E), toxic or drug-induced liver injury, ischemic hepatitis and, less commonly, autoimmune hepatitis, Wilson's and acute obstruction of biliary tract.

F. A disproportionately isolated increase in AST suggests: hemolysis, acute rhabdomyolysis secondary to a viral illness, myopathic process, myocardial disease and recent vigorous physical activity.

G. Although the value of the AST:ALT ratio is not well-documented in children, a ratio >4 in the appropriate clinical setting is highly suggestive of fulminant Wilson's disease.

H. Increased aminotransferases may be the only manifestation of celiac disease.

I. Non-alcoholic fatty liver disease may present with isolated increase in ALT.

J. Differential diagnosis of elevated transaminases in a transplanted patient include: acute or chronic cellular rejection, de novo autoimmune hepatitis, infection, and biliary or vascular complications.

K. There is poor correlation between degree of elevation of aminotransferases and extent of liver cell damage. A rapid decline in aminotransferases with increasing bilirubin and coagulopathy reflect massive liver damage and poor prognosis in a child with acute liver failure.

II. Causes

A. Chronic, mild elevation: ALT>AST (<150 U/L or <5X normal)
   1. Hepatic origin:
      a. α1-antitrypsin deficiency
      b. Autoimmune hepatitis
      c. Chronic viral hepatitis (B, C and D)
      d. Hemochromatosis
      e. Medications and toxins
      f. Steatosis and steatohepatitis
      g. Wilson's disease
   2. Nonhepatic origin:
      a. Celiac disease
      b. Hyperthyroidism

B. Severe, acute elevation ALT>AST (>1,000 U/L or >20–25 X normal)
   1. Hepatic origin:
      a. Acute bile ducts obstruction
   2. Acute Budd-Chiari syndrome
   3. Acute viral hepatitis
   4. Autoimmune hepatitis
   5. Hepatic artery ligation
   6. Ischemic hepatitis
   7. Medications/toxins
   8. Wilson's disease
C. Severe, acute elevation: (AST>ALT (>1,000 U/L or >20–25 X normal)
   1. Hepatic origin:
      a. Alcohol-related liver injury
      b. Cirrhosis
   2. Nonhepatic origin:
      a. Acute rhabdomyolysis
      b. Myopathy

D. Chronic, mild elevation: (AST>ALT (<150 U/L, <5 X normal)
   1. Hepatic origin:
      a. Alcohol-related injury
      b. Cirrhosis
   2. Nonhepatic origin:
      a. Hypothyroidism
      b. Macro-AST
      c. Myopathy
      d. Strenuous exercise

Recommended Reading


6E. Hepatomegaly

Rima Fawaz, MD

I. Increased liver size or hepatomegaly can be seen in many disorders, but is not a very reliable sign of liver disease, because of the variability of the size and shape of the liver.
   A. To determine if hepatomegaly is present, the liver span should be measured along the midclavicular line, with palpation of the lower margin and percussion of the upper margin.
   B. In children <2 years of age, the liver edge can extend up to 3.5 cm below the right costal margin in the midclavicular line. In older children, the liver edge rarely extends beyond 2 cm.
   C. The mean liver span is related to body weight, age and gender. At age 20, mean liver span for men is 7.7 cm and for women 6.3 cm. A liver span 2–3 cm smaller or larger than mean is considered abnormal.
   D. Hepatomegaly may be a transient finding during systemic infection, but persistent hepatomegaly should prompt a proper investigation.
   E. Mechanisms leading to hepatomegaly are similar to those leading to tissue growth and can be the result of alterations in cell number (hyperplasia), cell growth (hypertrophy) and/or cell death (apoptosis). In different disorders associated with hepatomegaly, many of all the above mechanisms can be at work at the same time.

II. Differential Diagnosis
   A. See Table 1

III. Evaluation
   A. Hepatomegaly should always be confirmed by a careful abdominal examination before extensive testing is undertaken. A detailed history can help direct further laboratory testing (see Table 2). If hepatomegaly is confirmed clinically further evaluation is recommended.
   B. A firm, enlarged liver may suggest a storage disease, infiltrative process, venoocclusive disease or neoplasia. Assessment of the liver edge may reveal firmness, irregularity, or frank nodules, suggestive of cirrhosis. Tenderness of an enlarged liver may indicate an inflammatory process.
   C. Laboratory evaluation should include a complete blood count with differential, comprehensive metabolic panel, liver enzymes including transaminases, glutamyltranspeptidase, alkaline phosphatase, albumin, total and direct bilirubin, and evaluation of liver synthetic function. More specialized testing can then be requested according to the suspected diagnosis.
   D. Imaging evaluation should always start with an abdominal ultrasound as it is the least invasive. This will help guide the need for further investigation.
   E. Ultrasonography can measure hepatic size and consistency. It can detect abnormal echotexture suggestive of fat, fibrosis or infiltration, and it can identify masses, cysts, abscesses and biliary tree abnormalities. Further imaging modalities may be needed for further elucidation, such as CT scan or MRI.
   F. Liver biopsy is often needed for definitive diagnosis.
Table 1. Differential Diagnosis of Hepatomegaly

<table>
<thead>
<tr>
<th>Increased Number of Cells in Liver</th>
<th>Increased Vascular Space</th>
<th>Increased Biliary Space</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflammation (hepatocyte or Kupffer cell enlargement, inflammatory cells)</td>
<td>Intrahepatic obstruction to hepatic vein outflow</td>
<td>Congenital hepatic fibrosis</td>
</tr>
<tr>
<td>• Viral: Hepatitis A-E, Cytomegalovirus, Epstein-Barr virus, Coxsackievirus</td>
<td>• Venoocclusive disease</td>
<td>Caroli disease</td>
</tr>
<tr>
<td>• Bacterial (sepsis, abscess, cholangitis)</td>
<td>• Hepatic vein thrombosis (Budd-Chiari)</td>
<td>Idiopathic (benign?)</td>
</tr>
<tr>
<td>• Toxic</td>
<td>• Hepatic vein web</td>
<td></td>
</tr>
<tr>
<td>• Autoimmune</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Storage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Nonalcoholic fatty liver disease, Reye syndrome/mitochondrial disease, Malnutrition (kwashiorkor), Hyperalimentation, Galactosemia, Cystic fibrosis, Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Glycogen storage diseases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Gaucher disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Niemann-Pick disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Wolman disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Alpha one antitrypsin deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Wilson disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hypervitaminosis A (Kupffer cell hyperplasia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infiltration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Extramedullary hematopoiesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Primary tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Hepatoblastoma, Hepatocellular carcinoma, Hemangioma, Focal nodular hyperplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Secondary or metastatic tumors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Lymphoma, Leukemia, Neuroblastoma, Wilms tumor, Hemophagocytic lymphohistiocytosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. History Intake for the Evaluation of Hepatomegaly

<table>
<thead>
<tr>
<th>Historical Information</th>
<th>Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal infection</td>
<td>Torch infections, HIV, HBV</td>
</tr>
<tr>
<td>Fetal ultrasound findings</td>
<td>Choledochal cyst, ciliopathies</td>
</tr>
<tr>
<td>Consanguinity/similar problems with parents or siblings</td>
<td>Risk for autosomal-recessive inheritance, genetic</td>
</tr>
<tr>
<td></td>
<td>diseases</td>
</tr>
<tr>
<td>Blood products transfusions/organ transplant</td>
<td>Infectious hepatitis</td>
</tr>
<tr>
<td>Sexual activity/ intravenous drug use</td>
<td>Hepatitis B, C, HIV, gonococcal and syphilis</td>
</tr>
<tr>
<td>Foreign travel</td>
<td>Parasitic infections and/or liver abscesses</td>
</tr>
<tr>
<td>Shellfish ingestion</td>
<td>Hepatitis A</td>
</tr>
<tr>
<td>Medication intake/nonprescription and recreational drugs</td>
<td>Vitamin A, Tylenol, hepatotoxic medications</td>
</tr>
<tr>
<td>Chronic illnesses</td>
<td>Congenital heart disease, cystic fibrosis, diabetes</td>
</tr>
<tr>
<td></td>
<td>mellitus, hematologic diseases, autoimmune diseases,</td>
</tr>
<tr>
<td></td>
<td>obesity</td>
</tr>
</tbody>
</table>

**Recommended Reading**


I. Ascites defined as the accumulation or retention of free fluid within the peritoneal cavity and it is one of the most common complications of cirrhosis.
   A. Ascites may also be associated with other diseases, such as cancer with peritoneum involvement, primary infections, autoimmune diseases and chylous ascites due to disruption of the abdominal lymphatics
   B. Prevalence is unknown

II. Pathogenesis: The accumulation of fluid in the peritoneal cavity represents a breakdown of intravascular volume homeostasis.
   A. The Associated factors to ascites are:
      1. Decreased plasma-colloid osmotic pressure
      2. Increased capillary pressure
      3. Increased colloid osmotic pressure of ascites fluid
      4. Decreased ascites fluid hydrostatic pressure

III. Causes of Ascites
   A. Portal hypertension
      1. Presinusoidal causes, eg, portal vein thrombosis (usually ascites is mild if present at all)
      2. Sinusoidal causes, eg, cirrhosis, vitamin A toxicity
      3. Postsinusoidal causes, eg, venoocclusive disease, Budd-Chiari syndrome, constrictive pericarditis, congestive heart failure
   B. Neoplastic causes
      1. Peritoneal carcinoma
      2. Lymphoma
      3. Hepatocellular cancer
   C. Inflammatory causes
      1. Infectious causes, eg, spontaneous bacterial peritonitis, tuberculosis
      2. Chemical causes, eg, talc peritonitis
      3. Immunologic disorders, eg, systemic lupus erythematosus, vasculitis
      4. Allergic causes, eg, eosinophilic gastroenteritis
   D. Miscellaneous causes
      1. Nephrotic syndrome
      2. Dialysis-associated ascites
      3. Thoracic duct obstruction

IV. Diagnosis
   A. Moderate and severe ascites may be detected on physical exam: fluid wave with percussion, ballotable liver and spleen and development of hydrocele and/or inguinal hernias are frequent findings
   B. Mild ascites may be confirmed by ultrasound
   C. An abdominal paracentesis is not necessarily indicated in a child with known chronic liver disease. However, it is indicated to rule out spontaneous bacterial peritonitis (SBP) or other less frequent etiologies
      1. The ascitic fluid associated with cirrhosis contains protein of <2.0 g/dL, serum-ascites albumin gradient (SAAG) is >1.1 g/dL (reflects portal hypertension) and the cell count is <250 cells/mm3. Glucose concentration resembles serum levels
   D. Paracentesis location: The left lower quadrant of the abdomen, two finger breadths cephalad and two finger breadths medial to the anterior superior iliac crest, is the best location for paracentesis because it has thinner abdominal wall and larger pool of fluid accumulation
E. Spontaneous bacterial peritonitis (SBP) is a primary bacterial infection of the ascites fluid
   1. Fever, irritability, abdominal tenderness, tense distension and erythema of skin are common signs
   2. >250 neutrophils/mm³ has the highest sensitivity for the diagnosis of SBP.
   3. Peritoneal bacterial cultures are only positive in ~60% of cases of SBP
   4. Bacterial organisms identified commonly include Gram-negative bacteria, Strep species, Enterococcus

V. Treatment
   A. Sodium restriction
      1. Sodium plays a central role in the pathogenesis of ascites
      2. Sodium restriction is the first step to treat ascites. However, this restriction should not affect nutrient ingestion, particularly of infants receiving formulas with specific sodium content. Children should have sodium restriction limited to 1,000 mg/day
   B. Diuretics
      1. The promotion of sodium excretion by means of diuretics is the second step
      2. Spironolactone (1–5 mg/kg/d divided in 2–4 doses in infants or 100–200 mg/d in two divided doses for children and adolescents) is a potassium-sparing diuretic
      3. Furosemide is indicated when spironolactone fails to improve ascites (1–4 mg/kg/d in infants or 40–240 mg/d in older children and adolescents).
      4. Complications of diuretics may be hypovolemia and electrolyte disturbance (hyponatremia for spironolactone and hyponatremia plus hypokalemia for furosemide)
   C. Large-volume paracentesis is indicated in refractory ascites or in children with restrictive respiratory failure

Recommended Reading


Primary tumors of the liver are rare and represent 0.3%–4% of all pediatric solid tumors.

I. Overview/Epidemiology
   A. Two-thirds of liver tumors are malignant, with the most common being hepatoblastoma
   B. The liver may also be the site of metastatic lesions from neuroblastoma, Wilms’ tumor, and lymphoma
   C. General signs and symptoms
      1. Abdominal distention, palpable right upper quadrant mass, anemia
      2. Jaundice and hepatic insufficiency are rare
      3. May see symptoms associated with specific tumor types
         a. Fever, thrombocytosis
         b. Precocious puberty
         c. High output cardiac insufficiency
         d. Skin findings (hemangiomas)
      4. Can occur within the presence of a genetic/metabolic syndrome

II. Benign Liver Tumors
   A. Differential diagnosis varies by age
      1. Infants: infantile hepatic hemangioma
      2. Toddlers: mesenchymal hamartoma, Focal Nodular Hyperplasia (FNH)
      3. School-aged children/adolescents: hepatic adenoma, FNH
   B. Other benign tumors: non-neoplastic cystic masses (biliary/simple hepatic cysts), hematoma, parasitic cysts, pyogenic/amoebic liver abscesses

III. Infantile Hepatic Hemangiomas (IHH)
   A. Most common benign hepatic tumor in infancy
   B. Vascular lesion, represents 12% of all childhood liver tumors
   C. Most cases (85%) are diagnosed within the first 6 months of life
      1. ~30% present within the first month
   D. Slight female predominance (F:M 1.3–2:1)
   E. Presentation
      1. Asymptomatic abdominal mass; normal labs, including alpha-fetoprotein (AFP)
      2. Cutaneous hemangiomas
      3. High output cardiac failure
      4. Coagulopathy
      5. Jaundice, failure to thrive, fever
      6. Hypothyroidism
   F. Varying degrees of hepatic involvement
      1. Focal: Well-defined, solitary, spherical tumor, usually asymptomatic
         a. Rarely accompanied by cutaneous hemangiomas
         b. Does not stain positive for glut-1
         c. Lesions should spontaneously involute
      2. Multifocal: Presence of, multiple individual spherical tumors with arteriovenous shunts
         a. Usually asymptomatic
         b. Accompanied by multiple cutaneous hemangiomas
         c. Should spontaneously involute
      3. Diffuse: Extensive hepatic involvement, near total replacement of hepatic tissue by hemangiomas
         a. More likely to have serious effects, including compression of inferior vena cava, respiratory compromise from compression of thoracic cavity, abdominal compartment syndrome, severe hypothyroidism, and high output cardiac failure
G. Treatment may include: resection, embolization, medical therapy (vincristine, steroids, management of hypothyroidism)
   1. Transplant should be considered in severe cases

IV. Mesenchymal Hamartoma (MH)
   A. Cystic/multicystic lesion, whose origin/biology are poorly understood
   B. The second most common benign liver tumor in children
      1. Accounts for 6% of all pediatric liver tumors
      2. 85% of lesions occur in children <2 years old
   C. Slight male predominance (M:F, 3:2)
   D. Presentation
      1. Abdominal distention, vomiting, anorexia, may have respiratory distress
      2. May be diagnosed by prenatal ultrasound
      3. May have increased AFP
   E. Clinical course is variable
      1. Tumor usually increases in size over first few months of life; then can stabilize, continue to grow, or spontaneously regress
      2. Small risk of malignant change into embryonal sarcomas
   F. Management is controversial, but includes:
      1. Nonoperative management in asymptomatic cases, as lesion will spontaneously regress
         a. Must consider potential transformation risk to malignant embryonal sarcoma
      2. Incision/drainage of individual cysts
      3. Complete tumor resection
      4. Transplantation in cases of unresectable lesions or severe symptoms
      5. Prenatal intervention

V. Focal Nodular Hyperplasia (FNH)
   A. Benign epithelial tumor, represents 2% of all pediatric liver tumors
      1. Well-circumscribed, lobulated lesion with central stellate scar
      2. Can vary in size from a few mm to 20 cm
      3. Has been seen with hepatocellular carcinoma, prompting consideration of tissue sampling to confirm diagnosis
   B. Presentation
      1. Usually diagnosed between 2–5 years, but can occur at any age
      2. More common in females
      3. Typically diagnosed on routine physical exam
      4. Patients may have abdominal pain
      5. Normal AFP
   C. Management
      1. Nonoperative management recommended for asymptomatic patients
      2. Excision of tumor may improve abdominal pain associated with FNH

VI. Hepatic Adenoma
   A. Usually occurs in young women on oral contraceptives or during pregnancy
   B. Also associated with glycogen storage disease
   C. Presentation
      1. Usually an incidental finding
      2. Larger lesions can present with pain or a right upper quadrant mass
      3. May also present with hemorrhage/rupture of adenoma
   D. Carries risk of transformation to hepatocellular carcinoma
   E. May be difficult to diagnose
      1. CT/MRI findings can be nonspecific (homogenous enhancement in arterial phase, hemorrhage, fat deposition, calcifications, lack of central scar)
      2. Can look like hepatocellular carcinoma, although AFP may help to differentiate these conditions
      3. May need to rely on tissue sample for diagnosis
         a. Histology: hepatocytes arranged in organized cords
         b. May also look like well-differentiated hepatocellular carcinoma
F. Management
   a. Surgical resection, radiofrequency ablation (RFA)

VII. Malignant Liver Tumors  (See Table 1)

VIII. Hepatoblastoma (HB)
   A. Most common malignant pediatric liver tumor
      1. 79% of all liver tumors in patients <15 years
   B. Male predominance (M: F, 6.1:1.2–3)
   C. Five histologic subtypes
      1. Fetal
      2. Embryonal
      3. Mixed epithelial
      4. Mesenchymal/macrotrabecular
      5. Small cell undifferentiated
   D. Multiple known risk factors:
      1. Birth weight <1,000 grams
      2. Familial adenomatous polyposis syndrome
      3. Beckwith-Wiedemann syndrome
      4. Many other metabolic/genetic associations
   E. Presentation can vary
      1. Asymptomatic right upper quadrant mass that is firm, non-tender, irregular
      2. Weight loss, anorexia, abdominal pain, vomiting, rarely jaundice
      3. Precocious puberty resulting from HCG
      4. Labs: anemia (70%), thrombocytosis (35%), elevated AFP (90%)
         a. Normal and high AFP levels can be associated with poor outcome
         b. Important to consider normal physiologic changes in AFP based on postgestational age
            1) Normal AFP: 25,000–50,000 ng/mL at birth (<25 ng/mL by 6 months)
      5. In high-risk groups, such as those with familial adenomatous polyposis or Beckwith-Wiedemann syndrome, screening with AFP and a liver ultrasound until age 4–5 years is recommended
   6. Biopsy needed to confirm diagnosis
   7. Management: (based on PRETEXT score)
      a. PRETEXT I/II: surgical resection followed by chemotherapy
      b. PRETEXT III/IV: chemotherapy followed by delayed primary resection
      c. Need to consider liver transplantation in patients with unresectable primary tumors despite chemotherapy, assuming they do not have metastatic disease
         1) Important prognostic factor: decreasing tumor size or reduction in AFP levels after chemotherapy
         2) Refer to liver transplant center if patients have multifocal PRETEXT IV tumors or unifocal PRETEXT II/III tumors (involving main hilar structures or all three hepatic veins)
         3) Contraindications to transplant include persistence of extrahepatic metastases despite chemotherapy

IX. Hepatocellular Carcinoma (HCC)
   A. The 2nd most common malignant pediatric liver tumor
      1. Represents <0.5% of all pediatric malignancies
   B. Usually occurs in older children/teenagers
   C. Most are de novo tumors, but can be associated with chronic liver diseases:
      1. Viral hepatitis (particularly hepatitis B)
      2. Inborn errors of metabolism (i.e., tyrosinemia)
      3. Biliary atresia
      4. Fanconi’s syndrome
   D. Other risk factors: androgenic steroids, oral contraceptives, methotrexate
   E. Presentation
      1. Abdominal distention, dull pain/discomfort, weight loss, weakness, hepatomegaly
      2. Often present with metastases at diagnosis (regional lymph nodes, lungs, bones)
      3. Labs: elevated AFP in 60%–80% of cases
F. Management:
   1. PRETEXT staging (similar to hepatoblastoma)
   2. Relatively chemoresistant tumor (only partial response in ~50% of patients)
   3. Surgical resection
   4. Consider liver transplantation for unresectable HCC

Table 1. Liver Tumor Summary

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Presentation</th>
<th>Labs</th>
<th>Imaging</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHH</td>
<td>Palpable mass, distention, CHF, hemangiomas (infant)</td>
<td>Normal</td>
<td>Focal, multiple or diffuse hemangiomas</td>
<td>Screening, ± /- steroids; will likely resolve (Glut-1 neg); may need resection/tx (diffuse)</td>
</tr>
<tr>
<td>MH</td>
<td>Abd distention + prenatal u/s (infant/toddler)</td>
<td>Normal ±/- high AFP</td>
<td>Single/multiple cysts; can look like solid tumor</td>
<td>Resection if possible (risk of malignancy)</td>
</tr>
<tr>
<td>FNH</td>
<td>Asymptomatic</td>
<td>Normal</td>
<td>Homogenous mass with central scar</td>
<td>Can occur with HCC If asymptomatic, no surgical intervention</td>
</tr>
<tr>
<td>Adenoma</td>
<td>Incidental finding, pregnancy, OCPs, rupture/RUQ mass</td>
<td>Normal +/- high GGT</td>
<td>Nonspecific findings</td>
<td>Resection vs ablation (risk of malignancy)</td>
</tr>
<tr>
<td>HB</td>
<td>Asymptomatic mass, f/wt loss/pain, FAP, BWS, prec pub, LBW</td>
<td>+AFP (10% with normal)</td>
<td>CT: solitary/multifocal mass; calcifications</td>
<td>Resection, chemotherapy (high risk may get chemotherapy, ?OLTx</td>
</tr>
<tr>
<td>HCC</td>
<td>Hepatomegaly, weight loss, pain, fatigue</td>
<td>+AFP (60%-80%)</td>
<td>Solid tumor with irregular margins</td>
<td>Chemotherapy, resection/liver transplant</td>
</tr>
</tbody>
</table>

Recommended Reading


Portal hypertension can be caused by a wide variety of conditions. It frequently presents with bleeding from esophageal varices, which is the most common cause of serious gastrointestinal hemorrhage in children.

I. Definition
Portal hypertension is defined as an increase in portal pressure >5 mm Hg

II. Etiology
Portal hypertension in children may arise due to problems at three different levels (Figure 1)
A. Prehepatic disease
   1. Portal vein thrombosis or occlusion by tumor and splenic vein thrombosis
B. Intrahepatic disease
   1. Intrinsic diseases of the liver, including those causing severe fibrosis and cirrhosis; i.e., congenital hepatic fibrosis
   2. Intrahepatic vascular or sinusoidal diseases, including schistosomiasis, veno-occlusive disease, nodular regenerative hyperplasia, hepatoporal sclerosis
C. Posthepatic disease
   1. Budd-Chiari syndrome, congestive heart failure, constrictive pericarditis
D. Other causes
   1. Arterialization of the portal venous flow by an arteriovenous fistula (e.g., as a congenital abnormality or acquired after liver biopsy)

III. Pathophysiology
A. Pressure gradient in the portal circulation (ΔP) is a function of portal flow (F) and resistance to flow (R)
   1. \( \Delta P = F \times R \)
B. Changes in portal flow and resistance originate from vascular and mechanical factors, which may be fixed (e.g., fibrosis and architectural distortion) or dynamic (e.g., sinusoidal vascular tone) (Figure 2)

IV. Vascular Factors
A. Raised intrahepatic vascular tone due to constriction of vascular smooth muscle cells, hepatic stellate cells, and hepatic myofibroblasts in response to changes in vasoactive substances (e.g., endothelin 1, reduced intrahepatic nitric oxide, increased thromboxane A2, reactive oxygen species)
B. Increased portal venous inflow due to splanchnic vasodilatation that increases bloodflow to the gut and spleen
C. Angiogenic mechanisms contributing to the development of portosystemic collaterals and varices

V. Mechanical factors
A. Fibrosis and nodularity of the cirrhotic liver, with distortion of the vascular architecture, causes remodeling in systemic and splanchnic vasculature, due to increased flow and shear stress that leads to a hyperdynamic circulatory state
VI. Clinical Presentation
   A. Splenomegaly
      1. On physical exam or ultrasound
   B. Variceal bleeding
      2. Presentation with hematemesis and/or melena
   C. Prominent vascular markings
      3. Caput medusa, spider hemangioma
   D. Ascites
   E. Associated lab findings
      1. Leukopenia and thrombocytopenia

VII. Complications of Portal Hypertension (Figure 3)
   A. Variceal bleeding
   B. Ascites
      1. Peritoneal fluid collection resulting from the combined effects of circulatory changes, including splanchnic dilatation, activation of the renin-angiotensin-aldosterone system, increased vasopressin secretion, water and sodium retention, increased portal hydrostatic pressure, and reduced intravascular oncotic pressure due to hypoalbuminemia (See section on Ascites)
   C. Hepatic encephalopathy
      1. Portosystemic shunting and liver dysfunction leads to delivery of blood to the brain containing increased concentrations of neurotoxic substances, such as ammonia

D. Hepatopulmonary syndrome
   1. Classically diagnosed by the triad of liver disease, hypoxemia and intrapulmonary vascular dilatations (identified by contrast-enhanced echocardiography or macroaggregated albumin nuclear medicine scan), but also seen in other causes of portosystemic shunting (e.g., congenital portosystemic shunt)

E. Portopulmonary hypertension: pulmonary hypertension in the setting of portal hypertension

F. Hepatorenal syndrome: renal failure in the setting of portal hypertension, primarily due to renal vasoconstriction in the absence of renal parenchymal damage

G. Mucosal edema leading to malabsorption and FTT

VIII. Diagnosis
   A. The presence of portal hypertension in children is usually a presumptive diagnosis based on findings on clinical examination (splenomegaly in the setting of known liver disease) and/or imaging:
      1. Abdominal US—confirms nonspecific features, such as abnormal hepatic echotexture, large collateral veins, and splenomegaly. Doppler flow studies provide information on direction and velocity of flow in the portal vein, hepatic veins, and vena cava, including presence of thrombosis or cavernous transformation of portal vein. Reversal of blood flow in the portal vein is usually a late finding
      2. CT & MRI—both useful in confirming Budd-Chiari syndrome (absence or diminutive hepatic veins, splenomegaly, ascites, patchy contrast enhancement of liver parenchyma, caudate lobe hypertrophy)
      3. Angiography—MR angiography is used to assess patency and caliber of veins throughout the portomesenteric system, and is particularly important when considering portosystemic shunt surgery and/or liver transplantation
      4. Endoscopy may be used to evaluate for gastroesophageal and anorectal varices, as well as portal hypertensive gastropathy characterized by mucosal hyperemia and dilated submucosal veins
         a. Large varices (>5 mm Hg) and varices of any size with red signs (including red spots, varices on varices, red wales) are at greater risk of bleeding
      5. Hepatic venous pressure gradient (HVPG) is measured via the transjugular approach, and is the difference between the wedged hepatic venous pressure (an indicator of portal venous pressure) and free hepatic venous pressure. A value >12 mm Hg is predictive of variceal bleeding. This measurement is rarely used in routine clinical practice in children; however it is the most accurate way to define portal pressure in the setting of cirrhosis (but is inaccurate in other causes of portal hypertension)
      6. Liver biopsy—may show mild periportal fibrosis in extrahepatic PVO
IX. Management

Evidence for the management of portal hypertension is primarily derived from adult studies, with most pediatric studies consisting of a small, uncontrolled case series

A. Primary prophylaxis: in patients at high risk of bleeding, adult studies show effective preventative therapy with either nonselective beta blockers or endoscopic variceal ligation (EVL). Endoscopic screening of adults is therefore recommended

B. Emergency management of variceal bleeding
   1. Airway, breathing, IV access and fluid resuscitation, NPO
   2. Do not overttransfuse (aim to maintain Hb at approximately 8 g/dL)
   3. Broad-spectrum antibiotic prophylaxis
   4. Vitamin K 1–10 mg slowly IV
   5. Intravenous proton pump inhibitor or ranitidine
   6. Octreotide infusion: to reduce splanchnic blood flow and portal pressure with minimal side effects
   7. Urgent EGD within 24 hours to confirm source of bleeding and to treat varices

C. Endoscopic management of varices (see section on Therapeutic Endoscopy)
   1. Endoscopic variceal ligation (EVL)
   2. Endoscopic injection sclerotherapy

D. Surgery for portal hypertension: surgery for portal hypertension is mostly considered in children with portal vein thrombosis, and only rarely in children with cirrhotic liver disease in whom criteria for liver transplantation are not met (Figure 4). Indications for surgery include:
   1. Esophageal variceal bleeding that is refractory to medical and endoscopic therapy in children with portal venous occlusion, or in children with chronic liver disease who do not fulfill criteria for liver transplantation
   2. Bleeding gastric or ectopic varices that cannot be controlled endoscopically
   3. Severe hypersplenism characterized by platelet count <10,000 and/or recurrent complications, including nonvariceal hemorrhage or infections
   4. Medically refractory portosystemic encephalopathy
   5. Hepatopulmonary syndrome or portopulmonary hypertension in children with portal vein thrombosis, if bypass surgery can be achieved (see below)
   6. Relative indications include symptomatic splenomegaly, restricted activity, large varices and poor access to health care, portal biliopathy, and unexplained failure to thrive

E. Description of surgical procedures:
   1. The mesenteric-left portal vein ("Rex") bypass is used to treat portal vein thrombosis, bypassing the thrombosed portal vein with a venous conduit from mesenteric vein to the left portal vein
      a. Restores portal venous blood flow to the liver and is therefore not complicated by encephalopathy
   2. The splenorenal shunt is the portosystemic shunt most often used in children because there is a lower risk of postoperative hepatic encephalopathy compared to mesocaval shunts
   3. Transjugular intrahepatic portosystemic shunt (TIPS) is a less invasive interventional radiology technique, in which a channel is created within the liver between a hepatic vein and portal vein

F. Liver transplantation:
   1. Transplantation is the treatment of choice for most children with variceal bleeding complicating end-stage chronic liver disease (e.g., biliary atresia), in whom criteria for liver transplantation are met
   2. Previous portosystemic shunting does not compromise survival after liver transplantation, although may complicate surgery and increase morbidity
Figure 1. Normal anatomy of the portal venous system. Courtesy of Kelly D. Diseases of the Liver and Biliary System in Children. 3rd ed. Hoboken, NJ: Wiley-Blackwell; 2008

Figure 2. Association between circulatory changes, portal pressure, and development of varices

Figure 3. Sites of collaterals formed as a result of portal hypertension. Varices may also develop at surgical sites, such as Roux-en-Y anastomosis created during the Kasai operation in children with biliary atresia or at the site of a gastrostomy tube.
Recommended Reading


**Shunt procedures for portal hypertension**

1. Portosystemic shunts
   - A Distal splenorenal
   - B Proximal splenorenal
   - C Side-to-side splenorenal
   - D Mesocaval splenorenal
2. Mesenterico-left portal (Rex) shunt
3. Transjugular intrahepatic portosystemic stent shunt (TIPSS)
6I. Fulminant Liver Failure

Naim Alkouri, MD

Acute liver failure (ALF) is rare in the United States. ALF accounts for 10%–15% of pediatric liver transplants.

I. Definition

A. Onset of hepatic encephalopathy and coagulopathy within 8 weeks of the onset of liver disease in absence of preexisting liver disease

B. In pediatrics, however, encephalopathy may be difficult to detect and liver failure may be first presentation of a previously unrecognized disease

1. The Pediatric Acute Liver Failure Study Group defines acute liver failure (ALF) in children as:
   a. Biochemical evidence of liver injury
   b. No history of known chronic liver disease
   c. Coagulopathy not corrected by vitamin K
   d. INR >1.5 if the patient has hepatic encephalopathy (HE), or >2.0 if the patient does not have HE

II. Etiology

A. A specific etiology cannot be identified in about 50% of pediatric cases

B. Toxins and Medications:
   1. Acetaminophen: dose-dependent hepatotoxicity. Conversion to highly reactive metabolite NAPQI; diagnostic criteria include toxic level on the Rumack nomogram and acute ingestion of 100 mg/kg within 24 hours. Aminotransferase levels are extremely high
   2. Anticonvulsants (phenytoin, carbamazepine, valproic acid): Can be accompanied by fever, skin rash, and eosinophilia. Valproic acid can induce ALF by unmasking a more generalized mitochondrial disorder
   3. Mushrooms
   4. Isoniazid
   5. Amiodarone
   6. Ecstasy

C. Metabolic:
   1. Wilson Disease: serum ceruloplasmin may be normal in ALF. Very low alkaline phosphatase, high bilirubin-to-alkaline phosphatase ratio, and hemolytic anemia are clinical clues. Poor prognosis with fulminant presentation
   2. Galactosemia
   3. Hereditary Fructose Intolerance: problems with introduction of fruit/sucrose. Some drugs and vitamins are in sucrose suspension
   4. Tyrosinemia
   5. Urea cycle defect: Ornithine transcarbamylase (OTC) deficiency is the most common and is X-linked. Very high ammonia levels without acidosis
   6. Fatty acid oxidation (FAO) defects: present with a Reyes-like syndrome and hypoketotic hypoglycemia
   7. Mitochondrial disorders: neurologic involvement, with severe hypotonia and myoclonus epilepsy (e.g., Alpers’ disease). Elevated lactate/pyruvate >20
   8. Neonatal hemochromatosis: affects the fetus and newborn. Severe coagulopathy, with relatively normal transaminases, and high ferritin and AFP. Abdominal MRI to demonstrate siderosis in the pancreas and liver or buccal mucosa biopsy

D. Immune:
   1. Autoimmune hepatitis (AIH): histology shows severe hepatic necrosis with interface hepatitis and plasma cell infiltration. Treatment with steroids may permit survival without liver transplantation
   2. Hemophagocytic lymphohistiocytosis (HLH)
E. Infections: viral hepatitis
   1. *Hepatitis A and E* are the most common cause of ALF in endemic areas
   2. *HSV* and *EBV* are more common in North America
   3. *Enterovirus adenovirus*
   4. *Sepsis*

F. Ischemic:
   1. Shock
   2. Budd-Chiari syndrome
   3. Congenital heart disease
   4. Cardiac surgery

G. Malignancy

H. Indeterminate (50%)

I. The etiologic agents vary by age, as seen in Figure 1 below:

**Etiology of Acute Liver Failure in Infants**
* Ages 0 to 3 years

**Etiology of Acute Liver Failure in Children**
* Ages 3 to 18 years

![Etiology of Acute Liver Failure in Infants](image1)

![Etiology of Acute Liver Failure in Children](image2)


III. Clinical presentation: varies based on etiology

A. Hepatic dysfunction with hypoglycemia, coagulopathy, and encephalopathy, with jaundice as a late feature

B. Typically a healthy patient who develops flu-like prodrome with malaise, myalgia, nausea, vomiting, and jaundice

C. Laboratory tests: increased transaminases, hyperbilirubinemia, coagulopathy
   1. Rapidly falling enzymes with worsening coagulopathy suggests exhaustion of hepatocyte mass

IV. Complications

A. Hypoglycemia: due to failure of synthesis and release, along with hyperinsulinemia due to failed degradation
   1. Maintain adequate glucose infusion rate

B. Hepatic encephalopathy (HE)
   1. Increased intracranial pressure (ICP) and cerebral edema are the major causes of mortality
   2. Factors that play a central role in the pathogenesis of HE
      a. Hyperammonemia, which is associated with increased levels of glutamine in astrocytes → results in cell swelling
      b. Increased cerebral blood flow may contribute to the development of cerebral edema
      c. Enhanced inflammatory response and inflammatory cytokines such as TNFα
   3. Symptoms include personality changes, regression, irritability, apathy, insomnia, disturbed sleep wake cycles, and poor oral intake
   4. May result in cerebral edema: prevention is critical with fluid restriction
      a. Mannitol and hyperventilation for temporary treatment
5. Coagulopathy; causes epistaxis, bleeding, hemorrhage
   a. Factor levels may help differentiate from DIC
   b. Treat with vitamin K, FFP, activated factor 7a

V. Management
   A. Treat above noted complications
   B. Specific therapy
      1. Acetaminophen → N-acetylcysteine
      2. Drug-induced → Remove offending drug
      3. Galactosemia → Remove dietary lactose
      4. Tyrosinemia → NTBC
      5. FAO defects → IV glucose and avoid fasting
      6. Wilson disease → Liver transplantation
      7. AIH → Corticosteroids
      8. Herpes → Acyclovir
      9. Neonatal hemochromatosis → Antioxidant cocktail

VI. Supportive Care
   A. Manage ICP and multiorgan failure while awaiting recovery of liver function or liver transplant
   B. IV fluids with glucose to avoid hypoglycemia
   C. Electrolyte replacement (hypokalemia, hypophosphatemia)
   D. Encephalopathy: medical therapy with lactulose. Minimize sedation, treat sepsis, and decrease protein intake. ICP monitoring is controversial. Consider mannitol, hyperventilation, hypothermia, or barbiturate coma for cerebral edema
   E. Coagulopathy: correct PT/INR with FFP or recombinant factor VII only in the setting of active bleeding or in anticipation of an invasive procedure
   F. Prophylactic acid-suppressive therapy
   G. Patients may develop hepatorenal syndrome or acute tubular necrosis and require dialysis or CVVH
   H. Obtain blood cultures and start antibiotics if indicated
   I. Consider acyclovir if suspecting infection with HSV

VII. Liver Transplantation
   A. Children with ALF fare poorly compared to those with chronic end-stage liver disease (average 6-month survival of 60% vs 90%).
   B. Indications for OLT include:
      1. Grade 3–4 encephalopathy
      2. Rising bilirubin (>20 mg/100 mL)
      3. Falling transaminases
      4. Coagulopathy with prolonged PT >100 seconds, and Factor II, V, VII decreased to <20% of normal values
      5. Acute renal decompensation

Table 1. A scale to Assess HE in Children <4 Years

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Signs</th>
<th>Reflexes</th>
<th>Neurologic Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (I and II)</td>
<td>Inconsolable crying, sleep reversal, inattention to task</td>
<td>Hyper-reflexic</td>
<td>Untestable</td>
</tr>
<tr>
<td>Mid (III)</td>
<td>Somnolence, stupor, combativeness</td>
<td>Hyper-reflexic</td>
<td>Most likely untestable</td>
</tr>
<tr>
<td>Late (IV)</td>
<td>Comatose, arouses with painful stimuli (IVa) or no response (IVb)</td>
<td>Absent</td>
<td>Decerebrate or decorticate</td>
</tr>
</tbody>
</table>

Recommended Reading


I. Overview of Neonatal Cholestasis
   A. Cholestatic jaundice in the neonatal period can be attributed to a variety of etiologies
   B. All jaundiced infants >3 weeks of age require measurement of direct (or conjugated) bilirubin
   C. Neonatal cholestasis is defined as a direct bilirubin of ≥2 mg/dL and ≥20% of the total bilirubin level
   D. In assessing the jaundiced infant, make sure to visualize the stool color, as acholic stools are associated with biliary atresia as well as other causes of biliary stasis
   E. All patients with cholestasis should be worked up for the underlying cause as expediently as possible. The most important reason for this urgency is based on the fact that the success of the Kasai portoenterostomy surgical procedure for biliary atresia is dependent on an early age at diagnosis
   F. Patients with neonatal cholestasis should have further liver evaluation, including serum AST, ALT, GGT, alkaline phosphatase, total protein, and albumin
   G. An abdominal ultrasound should be performed in order to rule out a choledochal cyst, biliary stones, sludge formation, or a tumor compressing the extrahepatic bile duct
   H. Other abdominal abnormalities found in <20% of biliary atresia patients includes polysplenia, intestinal malrotation, discontinuous inferior vena cava, and preduodenal portal vein

II. Differential Diagnosis of Neonatal Cholestasis
   A. The causes of neonatal cholestasis include anatomic abnormalities, metabolic disorders, infections, genetic syndromes and endocrinopathies
   B. Anatomic abnormalities:
      1. Choledochal cyst—five subtypes
         a. Most common are Type 1: saccular dilation of extrahepatic bile duct only; and Type 4: saccular dilations of intra- and extrahepatic biliary tree
         b. Jaundice, acholic stools, and a palpable mass; may present with cholangitis picture
         c. Diagnosis by US
         d. Surgical resection
         e. Increased risk of cholangiocarcinoma if untreated
      2. Spontaneous perforation of the bile duct
         a. Jaundice, poor weight gain, ascites, acholic stools, and vomiting
         b. Ill-appearing child with peritonitis
         c. Ultrasonography typically reveals ascites and fluid around the gallbladder
         d. Bile-stained ascitic fluid is a hallmark finding
         e. Alert surgery immediately
      3. Inspissated bile syndrome
         a. Stagnant flow of bile leading to cholestasis
         b. Often seen in the setting of intestinal disease and parenteral nutrition in the neonate
         c. Precipitation of cholesterol and calcium salts within bile can result in the formation of sludge
         d. Bile sludge can be detected by ultrasound
         e. Managed conservatively with ursodeoxycholic acid, a bile salt that acts as a choleretic agent to promote bile flow
         f. Bile sludge may be identified at cholangiogram, and saline flushes of the biliary tree at that time can improve flow
4. Biliary atresia  
   a. Diagnostic workup includes ultrasound (US), liver biopsy, and intraoperative cholangiogram. Rule out A1AT definitely  
   b. Ultrasound: to screen for associated anomalies (i.e., polysplenia)  
      1. Ultrasound: the size of the gallbladder by ultrasound is variable in biliary atresia (from absent to normal caliber)  
   c. Percutaneous liver biopsy—liver histology consistent with biliary atresia—fibrosis, bile duct proliferation, bile plugs in intrahepatic bile ducts  
   d. Alert surgery: intraoperative cholangiogram is the gold standard in the diagnosis of biliary atresia  
   e. Kasai portoenterostomy: it is generally regarded that effective bile drainage with resolution of jaundice can be achieved in up to 70% of biliary atresia patients if the portoenterostomy is performed prior to 60 days of life, as compared to 40%–50% of patients if performed at 60–90 days of life; 25% of patients at 90–120 days; and only 10%–20% of patients at 120 days  
   f. Complications post-Kasai:  
      1) Growth problems (see below)  
      2) Fat-soluble vitamin deficiencies (see below)  
      3) Cholangitis: fever, increase in bilirubin and other liver tests, acholic stools, RUQ abdominal tenderness, bacteremia; Rx - antibiotics  
      4) Pruritis: due to excess circulating serum bile acids; Rx - antibiotics: ursodiol ± rifampin  
      5) Portal hypertension is common: splenomegaly with hypersplenism, variceal bleeding, ascites  
      6) Bile lakes that may become infected  
      7) Cirrhosis with synthetic dysfunction (coagulopathy, hypoalbuminemia, hyperammonemia)  
   g. ~80% of cases lead to liver transplant in childhood  

C. Metabolic disorders  
   1. Alpha-1 antitrypsin (A1AT) deficiency  
      a. 10%–15% of patients with A1AT deficiency present with neonatal cholestasis  
      b. Defect in the ATZ molecule that results in abnormal accumulation of A1AT in the endoplasmic reticulum of hepatocytes  
      c. Diagnosed based on the serum A1AT level and phenotype (normal MM; abnormal ZZ, SZ, SS; heterozygote MZ or MS)  
      d. Important to obtain A1AT laboratory test early on in the evaluation of cholestasis, because if A1AT deficiency is confirmed, then there is no need for further workup  
      e. No known therapies  
   2. Inborn errors of metabolism (IEOM)  
      a. Enzyme deficiencies (usually autosomal-recessive transmission) involving multiple steps within metabolism of lipid, carbohydrate or protein  
      b. Examples include:  
         1) Galactosemia: part of the newborn screen and if suspected can be confirmed with the galactose-1-phosphate uridyl transferase serum level  
         2) Tyrosinemia: diagnosed with the urine succinylacetone level  
         3) Other IEOM can be screened for with serum amino acid and urine organic acid studies  
   3. Bile acid synthesis defects (BASD)  
      a. Defects in a number of enzymatic steps within the bile acids pathway results in abnormal bile acid synthesis and cholestasis  
      b. Screening test for BASD is total serum bile acids; this will be below normal in BASD as compared to elevated in all other cholestatic diseases  
      c. GGT also usually not elevated  
      d. Total serum bile acids are low, then BASD are confirmed with measurement of individual bile acid levels by fast atom bombardment (urine specimen)  
      e. Bile acid synthesis defects can generally be effectively treated by oral bile acid supplementation
D. Genetic disorders

1. Cystic fibrosis (CF)
   a. Cholestasis often associated with meconium plug syndrome
   b. Newborn screen (serum immunoreactive trypsinogen)
   c. Confirmed by sweat chloride test or genetic testing (CFTR gene mutation analysis)

2. Alagille syndrome
   a. Autosomal-dominant mutation of Jagged 1 gene on chromosome 20; variable penetrance of disease
   b. Constellation of physical findings, including cholestasis due to bile duct paucity, congenital heart disease such as peripheral pulmonic stenosis, abnormal facies, ophthalmologic abnormalities (posterior embryotoxon), and bony defects (butterfly vertebrae)
   c. Cholestatic neonates are screened for Alagille syndrome with an echocardiogram (if a murmur is detected), ophthalmologic exam, spine film, liver biopsy
   d. Characteristic findings on liver histology include paucity of bile ducts (may have bile duct proliferation early on in disease process, prior to paucity)
   e. Clinical course of liver disease in infancy is highly variable, with some children experiencing a gradual improvement in cholestasis in childhood, while others progress to cirrhosis, requiring liver transplant

3. Progressive familial intrahepatic cholestasis (PFIC)
   a. Specific transporter proteins on apical surface of the hepatocyte which are responsible for trafficking of bile components into the bile canaliculus. Defects in these proteins are associated with cholestatic disease
   b. PFIC type 1 (PFIC1): mutation in the gene coding for FIC1, a canalicular surface protein
      1) Clinically can present with cholestasis, diarrhea, and growth failure
      2) Low/nl GGT
   c. PFIC type 2 (PFIC2): mutation in the gene coding for BSEP interferes with bile salt trafficking into the canaliculus, leading to reduced bile flow and the toxic accumulation of hydrophobic bile acids within hepatocytes
      1) Clinical phenotype of cholestasis and pruritus in the first year of life
      2) Low/nl GGT
      3) Pruritus, a dominant clinical feature of both PFIC1 and PFIC2, is typically not problematic until after 6 months of age
   d. PFIC type 3 (PFIC3): mutation in the gene coding for the transporter MDR3, which is responsible for phosphatidylcholine secretion into the bile canaliculus
      1) The onset of cholestasis is variable in PFIC3, but is typically later than seen in PFIC1 and PFIC2
      2) High GGT

E. Infections:

1. TORCH infections: toxoplasmosis, syphilis, rubella, cytomegalovirus, and herpes-virus can all lead to a similar pattern of cholestasis and growth restriction
   a. Obtain a maternal history for TORCH infections, and perform diagnostic workup if history or physical exam warrants
   b. Screen for exposure to CMV with a urine CMV culture

2. Acquired infections after birth, in particular, Gram-negative sepsis

3. Urinary tract infections

F. Endocrinopathies:

1. Hypothyroidism
2. Panhypopituitarism
   a. Hypoglycemia often present
   b. Screening includes TSH, total and free T4, early morning cortisol level, and brain MRI (to assess pituitary gland)
   c. Associated with optic nerve hypoplasia, septo-optic dysplasia, microphallus
III. Management of Neonatal Cholestasis

A. Growth failure. Etiology:
   1. Increased metabolism
   2. Decreased fat absorption: reduced bile flow results in poor solubilization of dietary fats in mixed micelles, leading to fat malabsorption and steatorrhea
   3. Treatment: high medium-chain triglycerides (MCT)-containing formula/supplement (MCTs do not require bile for intestinal absorption)
      a. Consider nasogastric feeds for adequate caloric delivery
B. Fat-soluble vitamin deficiencies
   1. Pervasive in infants with chronic cholestasis, and should be aggressively managed
   2. Frequent monitoring of serum vitamin levels (PT- for Vitamin K, Vitamin E, Vitamin A, Vitamin D)
   3. Use of oral fat-soluble vitamin supplements
C. Ursodeoxycholic acid
   1. Hydrophilic bile acid that stimulates bile flow and displaces more toxic bile acids from the hepatocyte, thus potentially lessening the hepatocyte injury
   2. Ursodeoxycholic acid can decrease pruritus

<table>
<thead>
<tr>
<th>Disease</th>
<th>Diagnostic Workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary atresia</td>
<td>Abdominal US, liver biopsy, cholangiogram</td>
</tr>
<tr>
<td>Choledochal cyst</td>
<td>Abdominal US</td>
</tr>
<tr>
<td>A1AT deficiency</td>
<td>A1AT level and phenotype</td>
</tr>
<tr>
<td>IEOM</td>
<td>Newborn screen (galactosemia)</td>
</tr>
<tr>
<td></td>
<td>Urine succinylacetone (tyrosinemia)</td>
</tr>
<tr>
<td></td>
<td>Serum amino acids, urine organic acids (others)</td>
</tr>
<tr>
<td>BASD</td>
<td>Total serum bile acids; urine bile acid FAB</td>
</tr>
<tr>
<td>TORCH</td>
<td>Urine CMV culture; others as warranted</td>
</tr>
<tr>
<td>UTI</td>
<td>Urine bacterial culture</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Based on history, clinical picture, cultures</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>Newborn screen, sweat chloride test</td>
</tr>
<tr>
<td>Alagille syndrome</td>
<td>Echocardiogram (if murmur present), spine film, ophthalmology exam, liver biopsy</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Newborn screen, TSH, total and free T4</td>
</tr>
<tr>
<td>Panhypopituitarism</td>
<td>TSH, total and free T4, early a.m. cortisol, glucose, brain MRI (assess pituitary gland)</td>
</tr>
</tbody>
</table>

Recommended Reading


6J-2. Cholestatic Liver Diseases — Older Child

Ramya Ramraj, MD
Daniel H Leung, MD

The causes of cholestasis in the older child are varied, and the evaluation requires a judicial amount of laboratory testing, imaging, and other invasive studies to maximize diagnostic accuracy. Most of the metabolic and storage disorders present in early infancy; however, it is important to recognize that some of them have late presentations or may manifest as a result of decompensation during illnesses (Figure 1).

I. Causes of Cholestasis
A. Infections
   1. Hepatitis A, B, C, D, E viruses
   2. Adenovirus
   3. EBV, CMV, herpes viruses
   4. Influenza
B. Immunological
   1. Autoimmune hepatitis
   2. Primary sclerosing cholangitis
C. Bile duct obstructions
   1. Cholelithiasis
   2. Caroli’s disease
   3. Autosomal-recessive polycystic kidney disease (ARPKD)
D. Inherited cholestatic/hyperbilirubinemia syndromes
   1. Progressive familial intrahepatic cholestasis (PFIC) 1, 2
   2. Gilbert’s syndrome, Dubin-Johnson, Rotor syndrome, Crigler–Najjar syndrome
E. Metabolic
   1. Alpha 1 antitrypsin deficiency
   2. Wilson disease
   3. Cystic fibrosis
F. NAFLD
G. Storage disorders
   1. Glycogen storage disorders (types 1, 4)
   2. Lipid storage disorders
H. Urea cycle disorders
I. Mitochondrial disorders
J. Peroxisomal disorders
K. Drug-induced liver injury
L. Vascular
   1. Hepatic outflow obstruction (Budd–Chiari, myeloproliferative disorders)
   2. Portal vein thrombosis
M. Systemic
   1. Malignancies
   2. Immunodeficiency syndromes

II. History
A. Eliciting a complete history with the relevant details is important in ruling out important diagnoses. Below are some of the most pertinent questions to be asked and their possible etiologies
B. H/o Medications (Tylenol, amoxicillin, OCPs, steroids, testosterone, etc) – drug-induced liver injury
C. H/o IV drug use, blood transfusions, travel – Viral hepatitis
D. H/o Neuropsychiatric symptoms – Wilson disease
III. Physical Exam
A. A full physical exam is mandatory, and certain characteristic features, if present, point to specific diagnoses
B. Presence of KF rings (best seen with a slit lamp) and neurological signs like chorea will point to a diagnosis of Wilson disease
C. Presence of hepatomegaly and splenomegaly
D. Ascites in patients with portal hypertension

IV. Laboratory Testing
A. A full liver panel, with coagulation studies and hepatitis serology, needs to be drawn as part of the initial evaluation
B. Total and fractionated bilirubin to distinguish between the unconjugated hyperbilirubinemia vs conjugated hyperbilirubinemia
C. Creatine kinase levels to rule out muscular pathology
D. Based on the initial results and results of imaging, further labs looking for specific etiology such as AIH or Wilson disease need to be drawn
E. Check vitamin levels as part of nutritional assessment in chronic cholestasis
F. Low white blood cell counts and platelet count, especially thrombocytopenia, can be the first sign of chronic liver disease

V. Imaging
A. A full abdominal ultrasound with Doppler is very essential in the initial workup, to determine abnormalities in the hepatic architecture, as well as for the presence of any intrahepatic mass, ascites, or splenomegaly
B. The Doppler exam is a valuable diagnostic tool when there is a strong suspicion for abnormalities in the vasculature, or to determine portal venous blood flow
C. When there is strong suspicion for biliary tract disease (e.g., strictures, dilatations), choledocholithiasis, or previous evidence of biliary obstruction (presence of sludge in the gall bladder), further diagnostic evaluation with MRCP is warranted

VI. Biopsy
A. A core liver biopsy is often the gold standard in the diagnosis of cholestatic disorders in the older children
B. Biopsy can be delayed if the serological tests are positive for any of the viral hepatitis infections. Biopsy can also be delayed in patients who are overweight or obese, with a mild-to-moderate elevation of the liver enzymes, no other features of cholestasis, negative laboratory testing for metabolic disorders, and high suspicion for NASH

Figure 1. Algorithm for evaluation of cholestasis in the older child.
VII. Clinical Scenarios

A. An 11-year-old boy develops episodes of jaundice during viral illnesses. There is no history of pruritus, bleeding, or fatigue, and he is otherwise well. There is no history of medication use.
   1. Labs including transaminases, prothrombin time, ammonia, and complete blood count are normal, except for unconjugated bilirubin, which is 3 mg/dL, with a conjugated bilirubin of 0.5 mg/dL
      1. Most likely diagnosis – Gilbert's syndrome
   2. A benign form of inherited hyperbilirubinemia, and often manifests after puberty, especially during periods of illnesses and dehydration
   3. The history and the presence of elevated levels of unconjugated bilirubin (it is essential to get a fractionated bilirubin in the initial workup) establish the diagnosis, and no treatment is necessary
   4. It is important to recognize this condition while evaluating a child for jaundice, and thus avoid unnecessary testing

B. A 13-year-old girl presents with a few weeks history of fatigue and conjunctival icterus. She has no recent history of travel. She has a history of hypothyroidism, and is on hormone replacement therapy. A liver panel shows moderate elevation of transaminases and conjugated hyperbilirubinemia. Prothrombin time is normal. A liver US is unremarkable. Additional tests reveal an elevated IgG, elevated F actin level, and normal ceruloplasmin and MM alpha 1 antitrypsin phenotype. Liver biopsy shows interface hepatitis with plasma cell infiltration, confirming the diagnosis of autoimmune hepatitis
   1. Autoimmune hepatitis is one of the most common causes of cholestasis in older children, especially in females, and can occur in association with other autoimmune disorders. The presentation is often insidious, and hence it is important to recognize and make the diagnosis
   2. There are two types – Type 1 is characterized by antinuclear or smooth muscle antibodies, and type 2 is characterized by antiliver kidney microsomal type 1 antibodies

C. A 10-year-old boy is referred for elevation of transaminases. There is a history of declining school performance and occasional fatigue. No history of medication use. Liver panel shows moderate elevation of transaminases and conjugated hyperbilirubinemia. Physical exam is unremarkable except for mild tremor of the hands. Laboratory testing shows a normal ceruloplasmin level and an elevated 24-hour urinary copper excretion. A liver biopsy shows ballooning degeneration of hepatocytes, and total quantitative copper content of the liver is elevated (>250/Gm), confirming the diagnosis of Wilson disease
   1. Wilson disease is a rare autosomal-recessive disorder caused by excess accumulation of copper. Mutations in the ATP7B gene leads to defective copper transport, resulting in accumulation in liver, CNS, cornea, skeletal system, and other organs
   2. Wilson disease can present with nonspecific neurological or systemic symptoms, and hence it is essential to recognize the clinical spectrum and establish the diagnosis

D. A 3-year-old girl is seen for a WCC, and hepatomegaly is noted on exam. Liver panel shows mild elevation of transaminases and conjugated bilirubin. The history is otherwise unremarkable, except for episodes of sweating in the early mornings and mild developmental delay. There is no family history of liver disease. Imaging is unremarkable. Further laboratory testing is unremarkable. A liver biopsy is obtained, and shows ballooning of the hepatocytes with glycogen accumulation as detected by the PAS stain. The diagnosis is most likely GSD, and the liver tissue is sent for enzyme analysis to determine the subtype
   1. GSD (except for the infantile form of GSD 4) often presents in early childhood as organomegaly, asymptomatic elevation of transaminases, or intermittent periods of hypoglycemia
   2. A liver biopsy often establishes the diagnosis, and a multisystem evaluation with referral to genetics is essential
E. An 8-year-old boy presents to the ER with intense pruritus for a few weeks. He recently was diagnosed with a viral illness, that has since resolved. Physical examination is unremarkable except for mild scleral icterus. Liver panel shows elevated transaminases and conjugated hyperbilirubinemia. GGT is within normal limits, and US of the abdomen is unremarkable. Serum bile acids are elevated to 5x the upper limit of normal. A liver biopsy is performed, which shows features of intrahepatic cholestasis. EM shows granular bile, and the diagnosis is highly suspicious for BRIC 1 (benign recurrent intrahepatic cholestasis)

1. BRIC 1 is caused by missense or splice mutations in the ATP8B1 gene that codes for the FIC 1 protein. Severe mutations can lead to a complete absence or complete loss of function of the protein, leading to the more severe form of the disease, progressive familial intrahepatic cholestasis (PFIC 1)

2. Patients affected by BRIC 1 present with episodic cholestasis during illnesses, characterized by periods of intense itching, which can last for a few months

3. The characteristic history and the presence of low or normal GGT with cholestasis are important clues to the diagnosis

F. An obese teenager presents to the ER with severe right upper quadrant pain. An US of abdomen is obtained, which shows a dilated common bile duct of 6 mm, with sludge in the gallbladder. A liver panel shows elevated GGT with conjugated hyperbilirubinemia. An ERCP is performed on the patient, which shows choledocholithiasis, followed by removal of the stones

1. In patients with abnormal ultrasound findings and signs of acute obstruction, it is essential to proceed to ERCP without need for further imaging. The likelihood of finding bile duct stones in such clinical scenarios is high, and it is essential to relieve the obstruction to avoid further morbidity

G. A 7-year-old boy is seen in the clinic for fatigue and jaundice. His family has recently emigrated from Cambodia. Past medical history and family history are unremarkable. Liver panel shows elevated transaminases, and hepatitis serology is positive for HBs Ag and HBe Ag

1. Hepatitis B is an important cause of elevated transaminases and jaundice in children, and it is important to recognize the diagnosis, even in the absence of clear-cut risk factors

H. A 16-year-old teenager is referred to the clinic for abnormal liver panel and cholestasis. Imaging is unremarkable, and laboratory testing for most common etiologies as AIH, A1AT, and viral hepatitis is negative. Further questioning of the patient when alone revealed the use of hormone supplements for the past several months. The diagnosis is most likely hepatic injury secondary to steroid use. Liver biopsy is performed, which shows nonspecific hepatocellular damage

1. Drug-induced liver injury (DILI) is an important cause of cholestasis, and it is essential to recognize the entity through proper elicitation of history and maintaining a high suspicion for the diagnosis, especially when initial laboratory testing and imaging offer no clue to the diagnosis

Recommended Reading


6K-1. Infectious and Inflammatory Diseases — Congenital Infections of the Liver

Charles Vanderpool, MD

I. Bacterial Infections
A. Both Gram-positive and Gram-negative infections can cause liver injury, including hepatomegaly and jaundice
   1. Gram-negative infections are most common
   2. Hepatotoxicity is caused in part by endotoxin, including lipopolysaccharide complex (LPS), which causes cholestasis by diminishing bile flow
   3. *Escherichia coli* is the most common bacteria that causes neonatal hepatitis
      a. Galactosemia should be considered in infants with cholestasis and Gram-negative (especially *E. coli*) bacteremia
   4. Urinary tract infections are a common route of bacteremia, and can result in hepatitis and cholestasis
      a. Rarely have fever or urinary symptoms
      b. Often have irritability, lethargy, poor oral intake, and hyperbilirubinemia, with mildly elevated aminotransferases
B. Congenital Toxoplasmosis
   1. Maternal infection acquired by exposure to oocytes in cat feces or uncooked meat
   2. 70%–90% of affected patients are asymptomatic at birth, with hepatitis as the only sign
   3. In symptomatic patients, hepatic and neurologic effects predominate
      a. Hepatomegaly is common; jaundice is variable
   4. Liver biopsy shows nonspecific, generalized hepatitis and necrosis
      a. Toxoplasma organisms may be seen with immunofluorescence
   5. PCR or IgG/IgM testing of infant helps confirm diagnosis
C. Congenital Syphilis
   1. Transmission to fetus as high as 60%–100% with primary and secondary syphilis infections
      a. Up to 40% of infections result in fetal death
   2. Hepatomegaly, elevated aminotransferases, and conjugated hyperbilirubinemia are seen
   3. Liver biopsy classically shows intralobular dissecting fibrosis with centrilobular mononuclear inflammation
      a. Silver stain may highlight spirochetes
   4. Extrahepatic manifestations include skin lesions, snuffles, lymphadenopathy, anemia, thrombocytopenia
   5. Mother and infant should be tested with the same nontreponemal syphilis test (VDRL, RPR) to compare titers
   6. Primary treatment is parenteral penicillin

II. Viral Infections
A. Cytomegalovirus
   1. May be acquired transplacentally, at delivery, or postnatally
   2. Approximately 10% of infants manifest clinically apparent infections
      a. Hepatosplenomegaly and conjugated hyperbilirubinemia are common
      b. Extrahepatic manifestations include microcephaly, low birth weight, purpura, and thrombocytopenia
   3. Liver biopsy often shows nonspecific giant cell transformation, in addition to large characteristic intranuclear inclusions in bile duct epithelium or intracytoplasmic inclusion bodies in hepatocytes
4. Diagnosis is supported by culture of virus from urine, nasopharynx, or saliva
   a. Culture of liver tissue may be positive, but PCR has higher yield
5. Treatment options include ganciclovir and CMV immunoglobulin

B. **Rubella**
   1. Risk of infection-related birth defects is dependent upon timing of maternal infection
      a. Up to 85% of infants are affected if infection occurs during first 12 weeks of gestation, and this number decreases to 25% if infection occurs after second trimester
   2. Hepatomegaly is common, and is often associated with splenomegaly
   3. Elevated aminotransferases and conjugated hyperbilirubinemia are seen
   4. Extrahepatic findings include ophthalmologic (cataracts, chorioretinitis), hematologic (thrombocytopenia), dermal (blueberry muffin rash), cardiac (patent ductus arteriosus, septal defects), auditory (deafness), and neurologic (microcephaly, encephalitis) defects
   5. Liver biopsy has portal mononuclear infiltrates, giant cell transformation, focal necrosis, ductular proliferation
   6. Diagnosis is made by viral culture from the nose or throat, or IgM viral titer
   7. Treatment is supportive
      a. Majority of infants recover from hepatic disease without liver failure
      b. Morbidity/mortality associated with other organ system involvement

C. **Herpes Simplex**
   1. May be congenital, or present 4–8 days after birth, consistent with herpes virus incubation period
   2. Neonatal infections often occur from asymptomatic infection of mother, primarily from HSV 2
      a. 1/3 of infections are disseminated (with liver involvement), 1/3 of infections are limited to the cranial nervous system, and 1/3 are limited to skin, eyes, and mouth
   3. Clinical liver disease can result from either HSV 1 or 2
      a. May be quite mild and range to fulminant hepatitis with jaundice, hepatosplenomegaly and coagulopathy
      b. Liver biopsy shows multinucleated giant cells, multifocal or generalized necrosis, and characteristic intranuclear acidophilic inclusions
   4. Diagnosis is made by culture of mouth, nasopharynx, conjunctiva, and rectum
      a. Cultures of skin, urine, blood, and CSF specimens are also helpful
      b. Direct fluorescent antibody staining or immunoassay of antigens are specific, but are less sensitive than culture
   5. Treatment with IV acyclovir should be given to infants with any degree of symptomatic disease
      a. Approximately 25% of infants with disseminated disease die despite therapy
      b. Liver transplantation should be considered

D. **Enteroviral Hepatitis**
   1. Includes infections with coxsackievirus, echovirus, and enterovirus
   2. Transmission may occur during prenatal, intrapartum, or perinatal periods
   3. Maternal history of fever or viral syndrome just prior to birth may be elicited
   4. Clinical symptoms in newborn include poor feeding, fever, lethargy, diarrhea, and skin rash
   5. Liver involvement may be mild or can be severe, with jaundice, hepatomegaly, elevated aminotransferase levels, and coagulopathy with liver failure
   6. Diagnosis is made using culture from nasopharynx or rectum, or biopsy material from sites of involvement
      a. PCR testing is available and often used for CSF analysis
   7. Treatment is supportive, with no specific therapy options
      b. IVIG has been used in severe neonatal infections

E. Hepatitis A, B, C, D, and E are covered in the section on Viral Hepatitis
Recommended Reading


6K-2. Infectious and Inflammatory Diseases—Viral Hepatitis

Brandy Lu, MD
Cara Mack, MD

I. Hepatitis A: single-stranded RNA hepatitis A virus (HAV)
   A. Mode of transmission:
      1. Fecal-oral (foodborne or waterborne)
      2. There is no carrier state or chronic infection
   B. Incubation period: 15–40 days (mean 28)
   C. Clinical features:
      1. HAV infection is often asymptomatic (especially under the age of 6 years); only 30% of infants and preschool-aged children exhibit symptoms
      2. Acute, self-limited condition may be associated with anorexia, malaise, fevers, headache, emesis, diarrhea, and jaundice
      3. Acute HAV is characterized by clinical improvement with the onset of jaundice and a normalization of bilirubin and transaminases within 4–6 weeks
      4. Acute liver failure due to HAV is possible
         a. Consider hospital admission for any child with HAV and evidence of liver synthetic dysfunction (i.e., INR ≥2.0)
   D. Diagnosis:
      1. Confirmed with the presence of anti-HAV IgM antibody in serum
      2. Laboratories: check liver panel, PT/INR, and HAV-IgM
   E. Prevention:
      1. HAV vaccine:
         a. Universally recommended for all children between 12–24 months of age
         b. Catch up immunizations for older, unimmunized children
         c. Offer HAV vaccine to HAV-exposed family members or close contacts
      2. HAV immune globulin indications for use:
         a. Travel to endemic areas
         b. Postexposure prophylaxis within 14 days after exposure to food handled by someone with HAV, or persons exposed to family member with HAV

II. Hepatitis B: double-stranded DNA hepatitis B virus (HBV)
   A. Mode of transmission:
      1. Vertical, parenteral, or sexual
      2. Perinatal transmission rates vary from 20%–90%, depending on maternal HBsAg titer and HBeAg status
      3. Carrier state and chronic infection state
         a. A carrier state is a persistent infection with presence of HBsAg, but without biochemical or clinical signs of ongoing hepatic injury
         b. HBV carriers are infectious
      4. Special at-risk populations:
         a. Infants born to HBV-infected women
         b. Infants/children living in community groups with endemic HBV
         c. Immigrants/adopted children from regions of world with high prevalence of HBV
         d. Household contacts of individuals with chronic HBV
         e. Adolescents engaging in high-risk behaviors
5. The development of chronic disease varies based on age of HBV acquisition: infants have a 90% chance of developing chronic disease, children 1–5 years have 30% chance, and children >5 years have 6% chance

B. Incubation period: 50–180 days

C. Clinical features:
   1. Perinatal HBV acquisition is usually asymptomatic; however, if mother is HBeAg positive at birth, ~6% of infants will develop acute liver failure by 2–3 months of age
2. Chronic active hepatitis is associated with persistence of HBsAg >6 months and elevated ALT and AST levels
3. Of the neonates who become chronic carriers, many will develop an immune tolerant phase, represented by a normal ALT/AST despite high HBV DNA levels and persistent HBsAg & HBeAg positivity (and negative antibodies)
4. Acute liver failure has been reported, with the highest incidence in neonatal period
5. Co-morbidities: Gianotti-Crosti syndrome (acrodermatitis of face, trunk, and extremities; and lymphadenopathy); polyarteritis nodosa and glomerulonephritis

D. Diagnosis: see Table 1 at end of section for details
   1. Confirmed with detection of HBV surface antigen (HBsAg) on two separate testings at least 6 months apart
2. Laboratories: check liver panel, HBV: sAg, sAb, eAg, eAb
   a. Positive HBsAg represents active infection
   b. Positive HBeAg represents high infectivity
   c. HBeAg negative and HBeAb positive reflects seroconversion, with clearance of actively replicating virus
   d. HBsAb is rare, but represents protective immunity
3. Annual rate of spontaneous clearance (convert to HBeAg negative and HBeAb positive): 0-3 years of age <2%; >3 years of age ~5%
4. Check HBV DNA if considering treatment
5. Check liver histology if considering treatment; classic finding of HBV infection is ground glass appearance of hepatocytes

E. Treatment:
   1. Subcutaneous weekly pegylated interferon-alpha injections for 24 weeks
2. Treatment response: nondetectable HBV DNA and seroconversion to HBeAb positive (HBeAg negative)
3. Pegylated interferon therapy approved for ≥3 years of age

F. Prevention:
   1. HBV vaccine:
      a. Universally recommended for all infants; series of three doses over 6–9 months
      b. Catch up immunizations for older, unimmunized children
      c. HBV-exposed family members or close contacts
2. HBV immune globulin indications for use:
   a. Infants born to HBsAg positive mothers
   b. Postexposure prophylaxis within 24 hours after exposure (if no history of vaccination in past)
3. Household contacts: avoid sharing of tweezers, shavers, toothbrush, nail clippers
4. Universal precautions for handling abrasions, bleeding, etc
5. Screening for hepatocellular carcinoma (HCC): increased risk for HCC in setting of chronic HBV hepatitis. Screening modalities include annual alpha fetoprotein, liver ultrasound

III. Hepatitis C: single-stranded RNA hepatitis C virus (HCV)

A. Mode of transmission:
   1. Vertical, parenteral, or sexual
   2. Carrier state and chronic infection exist
   3. Perinatal transmission rates are ~5%, and increase to 15%–20% if the mother is coinfected with HIV

B. Incubation period: 30–150 days
C. Clinical features:
1. Chronic infection will develop in 60%–80% of exposed children
2. Majority of patients are asymptomatic in childhood
3. End-stage liver disease with decompensated cirrhosis has been described in children with chronic HCV hepatitis
4. Acute liver failure from HCV infection in immunocompetent patients has not been reported
5. Comorbidities: glomerulonephritis, cryoglobulinemia, autoimmune hepatitis, and Sjogren's syndrome

D. Diagnosis:
1. Laboratories: check liver panel, screen with HCV IgG antibody (after 18 months of age) and HCV RNA (after 2 months of age)
   a. Positive anti-HCV antibody (IgG) after >18 months of age reflects exposure to HCV
   b. Active infection can only be confirmed with positive HCV RNA
2. HCV genotype analysis indicated if treatment is being considered
3. HCV RNA testing in the first 2 months of life is problematic: both false positives (due to transient viremia) and false negatives (low levels not detectable) have been reported; wait until after 2 months of age to check HCV RNA, and repeat test 6 months later
4. Variable rates of spontaneous clearance after perinatal acquisition have been reported

E. Treatment:
1. Subcutaneous weekly pegylated interferon-alpha injections for 48 weeks (genotypes 1 or 4) or 24 weeks (genotypes 2 or 3), plus oral ribavirin
2. Treatment response: nondetectable HCV RNA by 24 weeks of age
3. Pegylated interferon/ribavirin therapy approved for ≥3 years of age

F. Prevention:
1. HCV vaccine: none available
2. HCV immune globulin: none available
3. Household contacts: avoid sharing of tweezers, shavers, toothbrush, nail clippers
4. Universal precautions for handling abrasions, bleeding, etc
5. Screening for hepatocellular carcinoma (HCC): increased risk for HCC in setting of chronic HCV hepatitis. Screening modalities include annual alpha fetoprotein and liver ultrasound

IV. Hepatitis D: defective RNA hepatitis D virus (HDV)
A. Mode of transmission:
1. Vertical, parenteral, or sexual
2. Carrier state and chronic infection exist
3. HDV cannot replicate without a coexisting infection with hepatitis B

B. Incubation period: 20–90 days

C. Clinical features: coinfection with hepatitis D is more severe than hepatitis B alone, and can progress more rapidly to liver failure and cirrhosis

D. Diagnosis: confirmed with the presence of anti-HDV antibody

E. Prevention: HDV vaccine or immune globulin. Not available

V. Hepatitis E: single-stranded RNA hepatitis E virus (HEV)
A. Mode of transmission:
1. Fecal-oral (foodborne, waterborne). Reports of contaminated blood products
2. There is no carrier state or chronic infection

B. Incubation period: 15–40 days

C. Clinical features:
1. Acute, self-limited condition may be associated with anorexia, malaise, fevers, headache, emesis, diarrhea and jaundice
2. Infection can be very severe in pregnant women (3rd trimester), with 20% mortality

D. Diagnosis:
1. Confirmed with the presence of anti-HEV IgM antibody in serum
2. Laboratories: check liver panel, PT/INR, and HEV-IgM

E. Prevention: no HEV vaccine is available
Table 1. The Hepatitis Viruses: Characteristics and Terminology of Associated Antigens and Antibodies

<table>
<thead>
<tr>
<th>Marker</th>
<th>Definition</th>
<th>Significance of Marker</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serologic Markers of HAV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HAV IgM</td>
<td>Antibody (IgM) directed against HAV</td>
<td>Current or recent infection</td>
</tr>
<tr>
<td>Anti-HAV IgG</td>
<td>Antibody (IgG) directed against HAV</td>
<td>Previous infection/vaccine and protective immunity</td>
</tr>
<tr>
<td><strong>Serologic Markers of HBV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBsAg</td>
<td>Hepatitis B surface antigen; found on surface of intact virus and in serum as free particles</td>
<td>Active HBV infection</td>
</tr>
<tr>
<td>HBeAg</td>
<td>Hepatitis B e antigen; soluble antigen produced during self-cleavage of HBcAg</td>
<td>High infectivity</td>
</tr>
<tr>
<td>HbcAg</td>
<td>Hepatitis B core antigen; found within virus core</td>
<td>Detectable in liver tissue</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>DNA of HBV (PCR test)</td>
<td>Active HBV replication</td>
</tr>
<tr>
<td>Anti-HBs IgG</td>
<td>Antibody (IgG) to HBsAg</td>
<td>Protective Immunity</td>
</tr>
<tr>
<td>Anti-HBC IgM</td>
<td>Antibody (IgM) to HBCAg</td>
<td>Early infection</td>
</tr>
<tr>
<td>Anti-HBC IgG</td>
<td>Antibody (IgG) to HBCAg</td>
<td>Indicates infection</td>
</tr>
<tr>
<td>Anti-HBe</td>
<td>Antibody to HBeAg</td>
<td>Resolution of active viral replication</td>
</tr>
<tr>
<td><strong>Serologic Markers of HCV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Antibody (IgG) to HCV</td>
<td>Exposure to HCV; Not protective</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>RNA of HCV (PCR test)</td>
<td>Active HCV infection</td>
</tr>
<tr>
<td><strong>Serologic Markers of HDV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDVAg</td>
<td>Hepatitis D antigen</td>
<td>HDV infection</td>
</tr>
<tr>
<td>Anti-HDV</td>
<td>Antibody (IgM/IgG subclass) to HDV</td>
<td>Exposure to HDV</td>
</tr>
<tr>
<td>HDV RNA</td>
<td>RNA of HDV (PCR test)</td>
<td>Active HDV replication</td>
</tr>
<tr>
<td><strong>Serologic Markers of HEV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEVAg</td>
<td>Antigen associated with HEV</td>
<td>Stool test; recent infection</td>
</tr>
<tr>
<td>HEV RNA</td>
<td>RNA of HEV (PCR test)</td>
<td>Early HEV infection</td>
</tr>
<tr>
<td>Anti-HEV</td>
<td>Antibody (IgM) to HEV</td>
<td>Early HEV infection</td>
</tr>
<tr>
<td>Anti-HEV</td>
<td>Antibody (IgG) to HEV</td>
<td>Protective immunity</td>
</tr>
</tbody>
</table>
**Recommended Reading**


HAV, hepatitis A virus; HBV, hepatitis B virus; HBCAg, hepatitis B core antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; PCR, polymerase chain reaction.

6K-3. Infectious and Inflammatory Diseases—Bacterial, Parasitic, and Other Infections of the Liver

Sabina Ali, MD

I. Pyogenic Hepatic Abscess
   A. Overview:
      1. It is a life-threatening condition
      2. Delay in or failure to recognize this condition results in high mortality and morbidity
      3. Liver abscess often occurs in patients with underlying medical conditions:
         a. Perforated appendicitis
         b. Crohn disease
         c. Immunodeficiency
         d. Sickle cell disease
         e. Neonates with UVC catheter and necrotizing enterocolitis
         f. Patients with VP shunts and with penetrating injuries
   B. Pathogenesis:
      1. Biliary disease
      2. Infection via the portal system
      3. Hematogenous (via the hepatic artery)
      4. Cryptogenic
   C. Microbiology:
      1. Cultures from blood and/or abscess contents are mostly positive
      2. Lesions can be polymicrobial
      3. E coli is the most commonly reported single bacteria
      4. Anaerobic accounts for 30%–50% of cases
      5. Other usual organisms: Salmonella, Haemophilus, and Yersinia
      6. Fungal liver abscesses are seen in patients with neutropenia and in patients with leukemia
      7. Patients with AIDS are at increased risk for mycobacterium-related infections. Tuberculous liver abscess is uncommon, but should be considered in patients when other organisms are not recovered
      8. Amebiasis: should be considered in patients who are from or have traveled to an endemic area within the past 6 months
   D. Clinical Features:
      1. Fever 79%–90%
      2. Chills
      3. Abdominal pain
      4. Nausea
      5. Vomiting
      6. Chest pain
      7. Weight loss
      8. Cough and dyspnea
      9. Diarrhea
      10. In neonates, it appears to have similar features as neonatal sepsis
The NASPGHAN Fellows Concise Review of Pediatric Gastroenterology, Hepatology and Nutrition

E. Laboratory Findings:
1. Anemia
2. Leukocytosis
3. Abnormal transaminases are common
4. Elevated ESR 100%
5. Elevated prothrombin time
6. Hypoalbuminemia is a poor prognostic sign
7. Diagnostic imaging
8. Chest x-ray
9. Elevated hemidiaphragm, right pleural effusion, atelectasis
10. Ultrasound
11. Round, oval, or elliptoid lesion
12. Irregular margin
13. CT scan
14. Sensitivity 94%
15. Lesions show reduced attenuation, and may enhance with contrast
16. MRI: Sensitive for smaller lesions

F. Management and Prognosis:
1. Antibiotic therapy as a sole treatment modality has been successful
2. Treatment should not be delayed pending the abscess drainage procedure
3. Blood culture should be taken prior to initiation of antibiotic therapy
4. Surgical intervention may be required if the patient fails to respond to antibiotic therapy

G. Complications:
1. Septicemia
2. Septic shock
3. ARDS
4. Renal failure
5. Liver abscess rupture is rare and is more commonly reported with amoebic liver abscesses, at a rate of 5%–20%
6. Metastatic abscess

II. Other Bacterial Infections
A. Typhoid fever
1. Fever, diarrhea, abdominal pain, and hepatosplenomegaly
2. Patients can also present with encephalopathy, seizures, myocarditis, and circulatory failure

B. Brucellosis: consumption of infected unpasteurized milk or milk product
C. Perihepatitis (Fitz-Hugh-Curtis syndrome):
1. Occurs as a complication of PID
2. Can occur both with N gonorrhea and Chlamydia
3. Acute sharp RUQ pain, fever, mimics acute cholecystitis
4. Serum hepatic enzymes and bilirubin may be normal
5. Laproscopic finding: violin sign – adhesions from the liver to the right costal margin

D. Weil syndrome: severe form of leptospirosis associated with hepatic dysfunction, renal failure, hemorrhagic manifestations, and pulmonary involvement

III. Amebic Liver Abscess
A. Overview:
1. Caused by Entamoeba histolytica
2. Transmission occurs via the fecal-oral route, either directly by person-to-person contact (e.g., diaper changing, sexual practices), or indirectly by eating or drinking fecally contaminated food or water
3. Commonly reported in the tropical regions such as Africa, Asia, and Central and South America
4. 7%–20% have contiguous pulmonary infection
5. Liver abscess is 10x more common in men, and rare in children
Section 6 - Liver

273

B. Clinical Features:
1. May have preceding amoebic colitis (10%–30%)
2. Fever, malaise, rigors, diaphoresis
3. Right upper quadrant pain: sharp, constant, relieved by lying on left side
4. Radiating to shoulder tips and scapulae
5. Pleuritic component
6. Hepatomegaly
7. Chronic presentations: weight loss and vague abdominal discomfort

C. Diagnosis:
1. Hyperbilirubinemia – uncommon
2. Leukocytosis
3. Anemia
4. Abnormal transaminases
5. Abnormal ESR

D. Imaging:
1. Ultrasound or CT can provide anatomic verification
2. Usually solitary in the right hepatic lobe (75%). Amebic abscess has a better defined margin with a peripheral halo
3. Aspiration of abscess: The abscess contains sterile pus, and reddish-brown “anchovy paste” liquefied necrotic liver tissue

E. Serological Tests:
1. Indirect hemagglutination assay (IHA)
2. Combination of a positive immunofluorescent antibody test (IFTA) and positive cellulose acetate precipitin test (CAP) correlates 100% invasive amebic disease

F. Treatment:
1. Usually with drugs alone: metronidazole, tinidazole, or chloroquine
2. Luminal amebicides must always be used following the above regimens
3. Diloxanide furoate or paromomycin

IV. Hydatid Disease of Liver
A. Overview:
1. Worldwide distribution
2. It is a chronic and potentially dangerous condition
3. Echinococcus granulosis is the most common form of hydatid disease in humans
4. Host: dog

B. Clinical Features:
1. May be asymptomatic
2. Right upper quadrant pain and/or mass
3. Fever
4. Jaundice

Figure 1. Lifecycle of *E histolytica*
5. Anorexia
6. Weight loss
7. Vomiting
8. Pruritis
9. Cysts may rupture and anaphylaxis may occur
10. Eosinophilia
11. Abnormal liver enzymes
12. Ultrasound is useful in diagnosis: cyst may be anechoic, round, and septated
13. IHA and ELISA are 75%–94% sensitive

C. Complications:
1. Rupture and leakage of cyst
2. Cholangitis
3. Secondary infection

D. Management:
1. Surgery remains as the mainstay treatment. Complications of surgery are high
2. Drug therapy includes: albendazole or mebendazole

Recommended Reading


Autoimmune hepatitis is an idiopathic chronic inflammatory disorder involving the liver is often associated with autoimmune inflammation of other organs.

I. Basics
   A. Autoimmune hepatitis (AIH) is found in all ethnic groups
   B. There are two major types of autoimmune hepatitis—Type 1 and Type 2. Each is recognized by distinct serological markers and characterized by subtle differences in presentation and clinical course
   C. Overall incidence in North America is 2/100,000 and AIH can present at all ages
   D. 60%–75% of patients are female

II. AIH in Children
   A. 40% of patients present at <20 years of age
   B. In children, mean age at presentation is 10–14 years, though it has been described in infants
   C. 5% of children with chronic liver disease have AIH
   D. 3.5% of children undergoing transplant have AIH

III. Presentation
   A. Acute hepatitis is most common presentation, approximately 40%
   B. 20%–25% present with features of chronic liver disease
   C. Fulminant failure is an uncommon presentation
   D. 20% are asymptomatic, and AIH is discovered serendipitously at routine exam
   E. 5%–10% are diagnosed in course of evaluation of other autoimmune diseases

IV. Etiology
   A. Thought to occur in genetically susceptible individuals in response to a variety of triggers via molecular mimicry. These triggers include:
      1. Drugs, viruses—hepatitis A, EBV, CMV, HCV among others, and possible environmental factors
   B. Genetic factors include MHC class II antigens, such as:
      1. Type 1 AIH—DR3, 4 in Europe, N. America, and Japan; and DR13 in South America and India (especially associated with HAV)
      2. Type 2—DR7 and DQ2
   C. Also polymorphisms in a variety of cytokines and in the complement system

V. Diagnosis
   (Codified by International Autoimmune Hepatitis Group)
   A. Exclude metabolic disease—e.g., Wilson, alpha-1-antitrypsin deficiency
   B. Exclude infectious causes
   C. Exclude alcohol or drugs
   D. Demonstrate hepatitis process—e.g., elevated transaminases
   E. Demonstrate immune process—e.g., elevated gamma globulin, autoantibodies
   F. Describe characteristic histological features
   G. Normal cholangiogram
VI. Characteristic Histology
   A. Interface hepatitis
   B. Mononuclear cell infiltrate
   C. Piecemeal necrosis
   D. Plasma cells
   E. Multilobular (bridging) collapse

VII. Characteristic Autoantibodies
   Titers in children are typically lower than adults—1:10 is significant
   A. Type 1 AIH
      1. Antinuclear antibody (ANA)
      2. Antismooth muscle antibody (SMA)
      3. p-ANCA
      4. Antiactin antibody
   B. Type 2 AIH
      1. Antiliver kidney microsomal antibody (LKM)
      2. Antiliver cytosol antibody
   C. Soluble liver antigen (SLA) may be present in both types and may connote a worse prognosis
   D. Very rarely, no antibodies are found—seronegative AIH

VIII. Type 1 AIH
   A. 70%–95% of all cases
   B. May present at any age
   C. ANA, SMA, and pANCA are the most common antibodies, and are nonpathogenic
   D. Target antigen unknown
   E. Genetic associations—DR3 more severe than DR4; DR13 often associated with HAV

IX. Type 2 AIH
   A. 5%–30% of cases—much more common in Europe than North America
   B. Most patients are children
   C. LKM antibodies are pathogenic—ANA, SMA, pANCA are absent
   D. Target antigen—CYP2D6
   E. Initial presentation may be more severe, and fulminant failure more common than Type 1
   F. Response to treatment is similar, although these patients may be less likely to be taken off medications altogether
   G. 25% of patients with autoimmune polyendocrinopathy have Type 2 AIH
      1. Target antigen different
      2. More severe disease, less responsive to treatment

X. Treatment—Standard Regimen
   A. Prednisone 2 mg/kg/day; azathioprine (AZA) 1–2 mg/kg/day
   B. After liver tests near/normalize, then begin slow steroid taper over several weeks. Goal is to eventually stop steroids if possible; patients may need continuous low-dose prednisone; azathioprine at therapeutic levels
      1. Endpoints—normal LFTs for two years without flares, and normal biopsy
   C. Labs should be monitored biweekly initially, and then every 1–3 months as treatment progresses
   D. Consider d/c therapy (AZA ± prednisone) only if inflammation has resolved on biopsy (histologic remission)
   E. Biochemical remission in 80% by 18 months, histological remission in 90% by 48 months
   F. Flares of disease activity occur in 40% during treatment, and require transient increase in steroid doses. Consider noncompliance, especially in teenagers
   G. Worse long-term outcome with any recurrence—some now recommend only one or no attempts to stop all therapy
   H. 15%–20% Type 1 and fewer Type 2 patients can stop treatment permanently
XI. Treatment Failure
A. Relapse despite Rx or inability to taper steroid to acceptable levels
B. 11% adults, 17% children
C. Again, consider noncompliance
D. Indication for other treatment
   1. MMF as substitute for AZA, not as monotherapy
   2. CSA, tacrolimus
   3. Possible TNF ab, rituximab, IVIG, IL-2 ab—anecdotal reports only

XII. Transplant
A. 5%–15% patients require transplant, children > adults
B. Indications—disease progression to decompensation, despite treatment or fulminant failure
C. Type 2 has higher incidence of fulminant presentation compared to Type 1
D. Disease recurrence in up to 50%

XIII. Overlap Syndromes
A. AIH + characteristics of another liver disease, usually PSC or PBC
B. Seen in 20% of adults
C. 35%–40% children with PSC present with features of AIH
D. Antibody profile consistent with Type 1 AIH
E. UC commonly associated
F. Parenchymal inflammation improves with standard AIH therapy, but biliary lesions typically progress. Outcome worse than AIH, and transplant more common

Recommended Reading


I. Hepatic granulomas are found in 2%–10% of livers biopsied for any indication. They are associated with disorders of the liver outlined below, but may also be an incidental finding. Histologically, granulomas consist of a central accumulation of mononuclear cells, mainly macrophages, with a surrounding rim of lymphocytes and fibroblasts. When activated, macrophages may become epitheliod cells. These cells may fuse under the influence of certain cytokines and become multinucleated giant cells.

II. Giant Cell Hepatitis
A. The giant cells seen in granulomatous hepatitis should not be confused with giant cell hepatitis, such as in neonatal giant cell hepatitis, which is characterized by ballooning degeneration of hepatocytes with fusion of hepatocyte membranes and nuclear transformation into multinucleated giant cells. The etiology of these giant cells is unclear. A recent study has identified nuclear proliferation markers in the hepatocytes of patients with giant cell hepatitis, suggesting that nuclear proliferation contributes to the pathogenesis of these giant cells. Multinucleated giant cells are also believed to be the response of immature hepatocytes to injury, as seen commonly in neonatal giant cell hepatitis.

III. Autoimmune Disorders
A. Sarcoidosis
1. Systemic granulomatous disease of unknown etiology characterized by noncaseating epithelioid granulomas
2. Gastrointestinal system involvement (usually hepatic) occurs in 0.1%–0.9% of patients
3. Hepatic manifestations include hepatomegaly (40%); less commonly elevated serum aminotransferases; least common chronic liver disease, cirrhosis, cholestatic liver disease, portal hypertension, and hepatic vein thrombosis
4. Liver pathology: noncaseating granulomas mainly in portal tracts and with increased hepatic copper. Decreased number of interlobular bile ducts, with periportal fibrosis and micronodular biliary cirrhosis, are long-term complications
5. Granulomatous phlebitis of the portal and hepatic veins occurs rarely
6. Serum angiotensin-converting enzyme (ACE) level is high in 75% of untreated cases
7. Treatment: corticosteroids, ursodeoxycholic acid
B. Primary biliary cirrhosis (PBC)
1. Immunological attack on intralobular bile ducts that leads to cirrhosis and liver failure
2. Biochemical liver profile and hepatic histology may mimic sarcoidosis
3. Usually distinguished from sarcoidosis by presence of antimitochondrial antibodies

IV. Systemic Infections
A. The most common infections causing granulomatous liver disease in the United States are tuberculosis and infections associated with acquired immunodeficiency syndrome (AIDS). Schistosomiasis, leprosy, brucellosis, and Q fever also cause granulomatous liver disease
B. AIDS-related causes
1. Patients with AIDS are susceptible to infections associated with hepatic granulomas, including Mycobacterium tuberculosis and Mycobacterium avium complex (MAC), Cryptococcus neoformans, Cytomegalovirus (CMV), histoplasmosis, and toxoplasmosis
2. Some of the medications used to treat these infections also produce hepatic granulomas, particularly sulfonamides and isoniazid
C. **Tuberculosis – Mycobacterium tuberculosis**
   1. Hepatic granulomas occur in >90% of patients with miliary tuberculosis
   2. Alkaline phosphatase levels are high in approximately 75% of cases, and aminotransferase levels are high in 35%
   3. Liver histology is variable. Most common findings are small hepatic granulomas in portal areas. Early granulomas are composed of lymphocytes and epithelioid cells. Later, giant cell formation and central necrosis (caseation) may predominate
   4. Acid-fast bacilli can be identified in granulomas on histologic examination
   5. Biliary obstruction may result from perihilar adenopathy
   6. In congenital TB, the liver is the usual primary site of infection

D. **Brucellosis – B melitensis, B abortus, B suis**
   1. 25% of affected children have hepatosplenomegaly. 84% have elevated serum transaminases, but jaundice is rare
   2. Lymphocytosis and elevated erythrocyte sedimentation rate are common
   3. Liver histology: portal inflammation and focal hepatocyte necrosis in 90% of patients. Noncaseating granulomas occur in 70%, primarily within the first 100 days of illness
   4. Treatment: with tetracycline or doxycycline in conjunction with rifampin. Trimethoprim-sulfamethoxazole may be used in children aged <9 years

E. **Q fever – Coxiella burnetii**
   1. Liver usually involved in acute infections. 70%–85% have elevated serum transaminases; 11%–65% have symptoms referable to the liver; 5% present with jaundice
   2. Liver histology: fibrin ring granulomas, characterized by a central clear space surrounded by histiocytes and a fibrin ring. Early lesions may contain neutrophils. Giant cells appear in later lesions. Steatosis, and mononuclear infiltration of portal tracts with Kupffer cell hyperplasia, are nonspecific histologic findings. Fibrosis and chronic hepatitis are rare
   3. Treatment: disease can be self-limited, but doxycycline is efficacious in shortening the clinical course

V. **Fungal Disease**
   A. **Hepatosplenic candidiasis**
      1. Occurs almost exclusively in neutropenic oncology patients, often as a consequence of seeding during generalized fungemia
      2. Fever occurs in 85% of patients; abdominal pain in 57%, hepatomegaly in 44%, and splenomegaly in 43%. Serum alkaline phosphatase is elevated in 60%. Leukocytosis is present in 30%. Serum total and direct bilirubin may be very high, but aminotransferases are less frequently elevated
      3. Computerized tomography early in infection often shows areas of variably enhancing diminished attenuation. Ultrasound examination is less sensitive, but so called “bull's-eye” lesions are characteristic
      4. Liver pathology: early lesions are composed of pseudohyphae and yeast forms, surrounded by neutrophils and an outer fibrous rim. Lesions progress to well-formed granulomas, with giant cell change. Fungal organisms may be seen using periodic acid-Schiff (PAS) or silver stains
      5. Treatment: amphotericin B, often in conjunction with 5-fluorocytosine
   B. **Coccidioidomycosis – Coccidioides immitis**
      1. Endemic in southwestern United States, parts of Mexico, Central America, and South America
      2. Transmission usually via inhalation of arthrospores. Pulmonary infection is the most common manifestation
      3. Disseminated infection seen most often in immunocompromised patients
      4. Hepatic involvement in 45%–60% of patients with disseminated disease. Hepatomegaly occurs in conjunction with elevated serum aminotransferases, and less commonly with elevated serum alkaline phosphatase and bilirubin
      5. Serology often useful for diagnosis disseminated disease
      6. Liver pathology: granulomas and giant cells containing PAS or methenamine silver-staining spherules are seen, surrounded by normal-appearing hepatic parenchyma
      7. Treatment: amphotericin B
C. **Cryptococcus infection – Cryptococcus neoformans**
   1. Liver may be involved in disseminated disease. Primary hepatic infection is rare
   2. Gross examination of the liver reveals white nodules
   3. Liver pathology: granuloma formation surrounding fungal organisms
   4. Treatment: usual agent is amphotericin B. Other agents include 5-fluorocytosine and fluconazole

D. **Histoplasmosis – Histoplasma capsulatum**
   1. Endemic in the Ohio and Mississippi River valleys in the United States
   2. Inhalation of spores is the usual route of infection. The gastrointestinal tract is rarely the portal of entry
   3. Hepatic involvement occurs in conjunction with disseminated disease
   4. Laboratory findings include pancytopenia, and mild-to-moderate elevations of serum aminotransferase and alkaline phosphatase
   5. Liver pathology: Kupffer cells loaded with fungal spores, prominent in sinusoids and periportal areas, causing compression and necrosis of adjacent hepatocytes. Kupffer cell infiltration of veins and arteries may be present. Granuloma formation most common in chronic disease
   6. Treatment: amphotericin B or itraconazole

E. **Malignancy**
   1. Hodgkin lymphoma and, less commonly, non-Hodgkin lymphoma and renal cell carcinoma have been associated with hepatic granulomas
   2. Lesions are distinct from the primary lymphomatous tumor
   3. Granulomas are not pertinent to the staging of Hodgkin and non-Hodgkin lymphomas

VI. **Drugs**
   A. The most common drugs associated with hepatic granulomas are allopurinol, sulfa drugs, chlorpropamide, and quinidine

VII. **Idiopathic**
   A. Idiopathic granulomatous hepatitis is characterized by recurrent fever, weight loss, myalgia, arthralgia, and vague abdominal pain, with granulomas in the liver when other causes of hepatic granulomas have been excluded
   B. Diagnosis is one of exclusion. Evaluations include clinical history, skin testing for fungal and bacterial pathogens, and microbiological, serological and biochemical screening to rule out other causes
   C. Laboratory findings are usually nonspecific, with elevations of transaminases and bilirubin. Sedimentation rate is often markedly elevated
   D. Liver pathology: granulomas in all cases. A common finding is multiple lesions consisting of typical focal nodular aggregations of lymphocytes, mononuclear cells and epitheloid cells. Caseation is absent. Most granulomas are distributed randomly throughout the liver parenchyma, although periportal granulomas are also seen
   E. Treatment: some patients benefit from immunosuppression with corticosteroids or methotrexate
   F. The natural history of the disease is chronic, with multiple remissions and exacerbations. The condition can resolve spontaneously in some patients
Recommended Reading


I. Congenital hepatic fibrosis (CHF) is characterized by ductal plate malformation, variable degrees of periportal fibrosis, and irregularly shaped proliferating bile ducts, resulting in portal hypertension and increased risk of ascending cholangitis.

II. Associated Anomalies
   A. Autosomal-recessive polycystic kidney disease (ARPKD) is most common. Mutations of PKHD1, which encodes the large, integral membrane protein; and fibrocystin that appears to be a ciliary/basal body protein, although its role is not fully determined
   B. Autosomal-dominant kidney disease (ADPKD). Mutations of PKD1 or PKD2. PKD1 accounts for 85% of ADPKD cases and is associated with more severe renal disease. The proteins encoded, polycystin-1 and-2, are thought to play a role as a flow detector on primary cilia in kidney and biliary ducts
   C. Meckel-Gruber syndrome. Recessively inherited lethal condition with central nervous system (occipital meningoencephalcele) abnormalities, bilateral large multicystic kidneys, CHF, and polydactyly. Gene loci: MKS1, MKS2, MKS3
   D. Ivermark syndrome. Renal-pancreatic-hepatic dysplasia
   E. Jeune syndrome. Asphyxiating thoracic dystrophy, rare, autosomal-recessive skeletal dysplasia leading to respiratory insufficiency, with constricted thoracic cage
   F. Bardet-Biedl syndrome. Retinal dystrophy; obesity, developmental delay, cystic renal disease
   G. Bold Joubert syndrome. Hypoplasia of cerebellar vermis, retinal dystrophy, subset with medullary cystic disease of the kidney and CHF. Gene: NPHP1
   H. Caroli’s disease
   I. von Meyenburg complexes
   J. Choledochal cyst

III. Clinical Manifestations
   A. Age of presentation and the severity of symptoms vary greatly, with patients usually being diagnosed in childhood or early adulthood
   B. Most patients are asymptomatic
   C. Physical examination findings include hepatomegaly, predominantly left lobe; splenomegaly, and nephromegaly
   D. The liver is firm, with a mildly nodular surface
   E. Four clinical forms have been defined:
      1. Portal hypertension (most common, more severe with portal vein abnormalities)
      2. Cholangitic: cholestasis and recurrent cholangitis
      3. Mixed
      4. Latent (presentation at a late age)

IV. Diagnosis
   A. Mild elevation of liver enzymes
   B. Patients with a predominant cholangitic clinical picture may have marked elevations in alkaline phosphatase (ALP), \( \gamma \)-glutamyl transpeptidase (GGT) and bilirubin
   C. Varying cytopenias secondary to hypersplenism
   D. Abnormal renal function tests are associated with extensive cystic renal disease, which may progress to end-stage renal failure
   E. Ultrasound: most informative, often reveals increased echogenicity of the liver, cysts in the hepatic parenchyma, enlarged spleen, and accompanying fibrocystic changes in the kidneys.
F. Magnetic resonance cholangiopancreatography (MRCP) typically shows cystic or fusiform dilatations and irregularities of the intrahepatic bile ducts, abnormally large left lobe of the liver extending anteriorly under the xiphoid and to the left over the spleen, fusiform dilation of the extrahepatic bile ducts, elongation of the gall bladder, and enlarged spleen, which can be quantified by calculating volume and accompanying fibrocystic changes in the kidneys.

V. Histopathology
   A. Varying degrees of hepatic fibrosis with nodular formation, which may become extensive as the disease progresses and may be mistaken for cirrhosis.
   B. Widened fibrous bands may be seen in the portal tract, containing an increased number of irregularly shaped proliferating bile ducts lined by normal cuboidal epithelium.
   C. Signs of cholestasis may be observed in the setting of cholangitis.
   D. Other findings include cystic dilatation of the bile ducts (Caroli’s disease), and hypoplasia of the portal vein branches in association with supernumerary hepatic artery branches.

VI. Treatment
   A. As yet, there is no treatment that has been shown to stop or reverse the process in CHF. It remains a progressive debilitating condition.
   B. Endoscopic treatment is the mainstay for primary and secondary prophylactic management of esophageal and gastric varices, as well as in the setting of acute bleeding.
   C. Portosystemic shunts are considered for patients with refractory bleeding. Liver transplantation is the only known cure for CHF, and is indicated at the later stages of the disease, with the development of liver failure.

Recommended Reading


6M. Vascular Disease of the Liver

Lina Maria Hernandez, MD
Lesley Smith, MD

I. Budd-Chiari Syndrome
A. Characterized by hepatic venous outflow tract obstruction in the absence of right heart failure or constrictive pericarditis (which must be carefully excluded)
B. The obstruction can be located at the level of the small or large hepatic veins, or the suprahepatic portion of inferior vena cava (IVC)

C. Pathogenesis
   1. Primary: hepatic expression of underlying prothrombotic conditions
      a. Myeloproliferative diseases (MPD): mutation in the Janus Tyrosine Kinase-2 (JAK2) gene in myeloid cells
      b. Inherited conditions: Factor V Leiden deficiency (accounts for 7%–25% of Budd-Chiari Syndrome (BCS patients), G20210A prothrombin gene mutation, deficiencies in protein C and S, and antithrombin
      c. Other acquired conditions: Bechet’s disease, paroxysmal nocturnal hemoglobinuria, antiphospholipid syndrome, hyperhomocysteinemia, oral contraceptives, pregnancy, polycythemia vera
      d. Systemic diseases: sarcoidosis, hypereosinophilic syndrome
   2. Secondary: invasion or compression by a tumor, paracytic or non-paracytic cyst, or abscess
   3. Hepatic veno-occlusive disease must also be excluded

D. Presentation
   1. Classic presentation: abdominal pain and distension with ascites
   2. May be asymptomatic (15%), fulminant, or chronic (more common)
   3. Common symptoms: abdominal pain, ascites, hepatomegaly, splenomegaly, portal hypertension, prominent dilation of subcutaneous veins of the trunk, lower extremity edema
   4. Aminotransferases and bilirubin are minimally elevated

E. Diagnosis
   1. Demonstration of an obstructed hepatic venous outflow tract or inferior vena cava (IVC) obstruction
   2. Doppler-ultrasound, triphasic CT scan, or MRI is usually sufficient to show diagnostic features
   3. Direct or retrograde venography rarely used

F. Treatment
   1. Prompt recognition and treatment of underlying disease, and in all patients:
      a. Initiate anticoagulation therapy
      b. Refer to hematologist for paroxysmal nocturnal hemoglobinuria and MPDs
      c. Stop oral contraceptives
      d. Therapy for portal hypertension
      e. Treat ascites with diuretics
   2. Angioplasty (balloon dilatation), with or without stenting in patients with short length stenosis in hepatic vein or IVC
   3. Transjugular Intrahepatic Portosystemic Shunt (TIPS)
   4. Liver transplantation if there is no improvement with above measures
II. Hepatic Veno-Occlusive Disease
   A. Please refer to the section on venoocclusive disease vs graft host disease.

III. Hemangioma
   A. Most common benign hepatic tumor
   B. Lesions are usually focal, but can be multifocal or diffuse
   C. May have estrogen receptors, resulting in accelerated growth during puberty, pregnancy, oral contraceptive use, and with androgen treatment
   D. Tumor consists of multiple, large vascular channels lined by a single layer of endothelial cells and supported by collagenous walls, with blood supply arising from the hepatic artery

   E. Clinical Presentation
      1. Mostly asymptomatic, and diagnosed as an incidental finding on ultrasound
      2. In symptomatic patients, right upper quadrant pain or fullness is common, and intermittent symptoms may occur secondary to necrosis, infarction, or thrombosis of the tumor
      3. May rarely present as a large abdominal mass, cardiac failure, spontaneous rupture, or jaundice from compression of biliary ducts
      4. Patients with giant hemangiomas may present with Kasabach-Merritt syndrome
      5. Laboratory evaluation is usually unremarkable, including a normal alpha-fetoprotein, CA 19-9, and CEA, but may demonstrate thrombocytopenia or hypofibrinogenemia
      6. Infantile hemangiomas may present with cardiac failure secondary to high-volume shunting, hypothyroidism secondary to overproduction of type III iodothyronine deiodinase, fulminant hepatic failure, respiratory compromise, and/or abdominal compartment syndrome

   F. Diagnosis
      1. The majority of hemangiomas can be diagnosed accurately by imaging studies alone
         a. Ultrasound shows a well-defined, lobulated, homogeneous hyperechoic mass
         b. Findings inconsistent with this description are confirmed by triple phase CT or MRI
      2. Liver biopsy contraindicated in most circumstances because of increased risk of hemorrhage, and should be used only when radiology study results and alpha fetoprotein testing are equivocal

   G. Management
      1. Most hepatic hemangiomas may be safely left alone
      2. Asymptomatic patients with focal or multifocal disease should be observed, with follow-up ultrasonography to document regression
      3. Indications for treatment include severe symptoms, complications, and inability to exclude malignancy
      4. Treatment includes surgical enucleation, resection, transarterial catheter chemoembolization, hepatic irradiation, and transplantation
         a. Surgical resection and enucleation are applicable for single hemangioma
         b. Transplantation may be necessary in large unresectable lesions, multiple lesions, or those involving the hepatic hilum

IV. Infantile Hemangioendothelioma
   A. The 3rd most common hepatic tumor in childhood
   B. It is usually detected before 6 months of age, with 85% detected by age of 2 months
   C. 2:1 female predilection
   D. These tumors are composed of vascular channels lined by a single layer of neoplastic endothelial cells, often with entrapped hepatocytes, bile ducts, and areas of extramedullary hematopoiesis
   E. Most tumors continue to grow during the 1st year of life, and then spontaneously regress, probably due to thrombosis and scar formation

   F. Clinical Presentation
      1. Most common presenting signs of are hepatomegaly, abdominal mass, cutaneous hemangiomata, and congestive heart failure
      2. Patients may also have splenomegaly, jaundice, ascites, gastrointestinal bleeding, anemia, feeding difficulties, failure to thrive, elevated transaminases, respiratory difficulties, and hepatic bruit
      3. Hemangiomas can be seen at distant sites, including skin, lung, pancreas, lymph nodes, and bone
4. Serum alpha fetoprotein levels are normal or slightly elevated
5. Associations with chromosome 6q deletion, diaphragmatic hernia, Trisomy 21, transposition of the great arteries, extranumerary digits, and Kasabach–Meritt syndrome
6. Risk of degeneration into malignant hemangiendothelial sarcomas
   a. Infantile hemangiendothelioma (IHE) in older children are at higher risk for malignancy

G. **Diagnosis**
   1. Ultrasound shows heterogeneous, septated lesion with iso- and hypoechoic areas, with increased blood flow on Doppler
   2. Biphasic contrast CT and dynamic gadolinium-enhanced MRI show rapid peripheral enhancement during the arterial phase, with delayed central filling during the venous phase
   3. Liver biopsy should only be performed if there is doubt of the benign nature of a vascular lesion

H. **Management**
   1. Intervention is unnecessary for asymptomatic masses
   2. Yearly ultrasound should be performed until complete resolution occurs
   3. Options for medical therapy include steroids and interferon to accelerate the natural involution of the mass, radiation therapy or chemotherapy, and supportive care for congestive heart failure and coagulopathy
   4. Hepatic artery embolization can be used to reduce tumor vascularity and arteriovenous shunting. Surgical resection is indicated for life-threatening symptoms or if the mass cannot be distinguished from a malignant tumor radiologically
      a. Single lesions may be managed with hepatic lobectomy or local resection
      b. Orthotopic liver transplantation should be considered if other therapies fail

**Recommended Reading**


I. Bile acids are synthesized by the liver from cholesterol through a complex series of reactions involving multiple enzymatic steps in the bile acid synthetic pathway.

A. Chemistry and Physiology
   1. The two primary bile acids synthesized by liver are cholic acid (3α, 7α, 12α, trihydroxy-5β cholanolic acid) and chenodeoxycholic acid (3α, 7α–dihydroxy-5β-cholanoic acid)
      a. These bile acids are extensively conjugated to the amino acids glycine and taurine
      b. The primary bile acids enter the distal small intestine and colon, where a portion are deconjugated and dehydroxylated by bacterial enzymes to produce the secondary bile acids, deoxycholic and lithocholic acid
   2. Bile acids perform several important functions
      a. They are the major catabolic pathways for elimination of cholesterol from the body
      b. They provide the primary driving force for the promotion and secretion of bile, and are essential to development of the biliary excretory route for the elimination of endogenous and exogenous toxic substances, including bilirubin and drug metabolites
      c. Within the intestinal lumen, the detergent action of bile acids facilitates the absorption of fats and fat-soluble vitamins

B. Clinical Presentation
   1. There are nine identified defects in the bile acid synthetic pathway, resulting in blocked production of normal bile acids, accumulation of unusual bile acids and intermediary metabolites, reduced bile flow, and decreased intraluminal solubilization of fat and fat-soluble vitamins
   2. Liver disease occurs as increased hepatotoxic bile acid intermediaries are created because of blockage in pathways
   3. Bile acid synthetic defects should be considered in all cholestatic infants. Clinical suspicion should be raised in particular if:
      a. Total serum bile acids are low or normal, as they are usually high in cholestatic infants
      b. GGT is normal or minimally elevated, as it is usually high in cholestatic infants
      c. Pruritus, which is a common and distressing component of most cholestatic disorders, is absent

C. Diagnosis
   1. Requires high index of suspicion, as above
   2. If serum bile acids are normal or low, urine bile acids should be measured by Fast Atom Bombardment Ionization Mass Spectrometry (FABMS), which allows identification of a profile of the bile acids in urine
   3. FABMS can be complemented by Gas Chromatography-Mass Spectrometry (GC-MS) of urine, bile, and serum, to establish absence or reduction of primary bile acids in conjunction with the presence of atypical bile acid and sterols that are synthesized as a result of enzymatic deficiency
   4. Liver biopsy may demonstrate suggestive features (see below)
D. **General Treatment Principles**
1. Down regulate hepatocyte bile acid synthesis by negative feedback inhibition, thereby diminishing the toxic products of intermediate metabolism, such as monohydroxy bile acids
2. Nutritional support, including fat-soluble vitamins and medium-chain triglyceride-containing formula
3. Liver transplant may be an option in some cases

II. **Specific Inborn Errors of Bile Acid Synthesis (BAS)**

A. **3β Hydroxy C-27 Steroid Oxidoreductase/Dehydrogenase Deficiency (3βHSD)**
1. Most commonly reported defect in BAS 3βHSD catalyzes the conversion of 7α hydroxy cholesterol to 7α hydroxy-4-cholesten-3-one
2. Presents in neonates with progressive jaundice, increased aminotransferases, normal GGT, conjugated hyperbilirubinemia, and low/normal total bile acids
3. Hepatomegaly with or without splenomegaly, malabsorption with steatorrhea and fat-soluble vitamin deficiency, rickets
4. Urine bile acid profile shows decreased primary bile acids and increased di- and trihydroxy chenolic acids
5. Liver biopsy: giant cell hepatitis/portal inflammation, perilobular fibrosis, canalicular bile plugs
6. Enzyme activity can be measured in fibroblasts and is undetectable in affected patients
7. Molecular techniques allow for genetic diagnosis
8. Treatment with cholic acid can improve liver function and resolve jaundice if fibrosis has not yet occurred

B. **Oxysterol 7α Hydroxylase Deficiency**
1. Only one reported case in literature
2. Clinical presentation of severe progressive liver failure, cholestasis, and hepatosplenomegaly
3. Urine bile acids show absent primary bile acids, and increased sulfate and glycosulfate conjugates of 3 beta-delta 5-monohydroxy bile acids
4. Liver biopsy shows lobular disarray, giant cell transformation, and moderate portal inflammation

C. **Δ4-3 oxosteroid 5β Reductase Deficiency**
1. Δ4-3 oxosteroid 5β reductase catalyzes conversion of the intermediates 7α hydroxy 4-cholesten – 3-one & 7α, 12α-dihydroxy-4-cholesten-3-one to their corresponding 3-oxo-5β (H) intermediates
2. Present with neonatal cholestasis, increased aminotransferases, conjugated hyperbilirubinemia, coagulopathy, and normal GGT
3. Liver biopsy typical of neonatal hepatitis
4. Enzyme not expressed in fibroblasts or leukocytes. Diagnosis must be made by FABMS, which shows increased 3-oxo-7α bile acids. Urine and serum concentration of normal bile acids are low. Accumulated Δ4-3-oxo-7α bile acids cause hepatotoxicity
5. Treatment with cholic acid, as it suppresses endogenous synthesis of bile acids and accumulation of toxic metabolites

D. **Cerebrotendinous Xanthomatosis**
1. A defect in bile acid side chain modification
2. Slowly progressive disease of lipid accumulation, characterized in adults by progressive neurologic dysfunction, dementia, ataxia, cataracts, and xanthomata in the brain and tendons
3. Liver disease is not generally a feature of this condition, but a self-limiting neonatal cholestasis may occur, consisting of increased ALT, AST, conjugated bilirubin, and normal GGTP and liver enzymes, and usually resolves by 6 months of age because of increased cholic acid production by compensatory alternative 25 hydroxylation pathway
4. Treatment with chenodeoxychoic acid or cholic acid is recommended, with the addition of a statin to suppress cholesterol synthesis. Without treatment, tendinous and CNS xanthomata occur, with neurologic dysfunction in adulthood
E. **Alpha Methylacyl-CoA Racemase Deficiency**
   1. Defect results in inhibition of cholesterol side chain oxidation
   2. Key enzyme required for racemization of trihydroxycholestanoic acid and pristanic acid into their stereoisomers
   3. Present with cholestatic liver disease, severe fat-soluble vitamin deficiencies and coagulopathy. If undiagnosed in infancy, may later present as adults with peripheral neuropathy
   4. Urine bile acids show decreased primary bile acids and increased trihydroxycholestanoic and pristanic acids
   5. Liver biopsy shows neonatal hepatitis with giant cell transformation. Electron microscopy shows decreased numbers of peroxisomes
   6. Treatment options include cholic acid and, with severe presentation, liver transplant

F. **Bile Acid Conjugation Defects**
   1. Conjugation of cholic and chenodeoxycholic acid into taurine and glycine is the final step in primary bile acid synthesis
   2. The enzymes that catalyze this conjugation are the rate-limiting Co-A ligase and CoA: amino acid N-acyltransferase
   3. Patients have symptoms of malabsorption and fat-soluble vitamin deficiency. May have conjugated hyperbilirubinemia, severe cholestasis, and liver failure
   4. Diagnosis is based on urine FABMS, with complete absence of usual glycine and taurine conjugated BA
   5. Treatment with oral primary conjugated bile acids and fat-soluble vitamins

**Recommended Reading**


6N-2. Metabolic/Genetic Liver Diseases—Disorders of Bilirubin Metabolism

Asha Willis, MD
Stephanie Page, MD
James Daniel, MD
Fred Suchy, MD

I. The metabolism of bilirubin involves many enzymes and receptors. Defects in the bilirubin transport or enzyme defects lead to jaundice, and are seen in several different scenarios.

Bilirubin is the end result of the breakdown of heme. Hemoglobin contributes 80% of the total amount of heme in the body with smaller contributions by myoglobin, cytochromes, catalases, and tryptophan. Heme oxygenase converts heme to biliverdin and biliverdin reductase changes biliverdin to bilirubin.

Bilirubin is bound to albumin within the bloodstream and upon uptake by hepatocytes, is conjugated by UDP-glucuronosyltransferase to mono and di-glucuronides. These are then excreted into the lumen of the intestines and some are changed by bacteria into urobilinogen and excreted in feces and some are reabsorbed in the ileum via enterohepatic circulation (after deconjugation by intestinal enzymes).

In the neonate increased enterohepatic circulation is the likely cause of significant physiologic jaundice. However, jaundice usually resolves unless there are other abnormalities as well. Evaluating the direct and indirect components of bilirubin points the diagnostician in the appropriate direction for diagnosis.

II. Breast Milk Jaundice

A. The persistence of physiologic jaundice beyond the first week of life, due to an unknown factor that promotes increased intestinal absorption of bilirubin

1. Beta-glucuronidase is one proposed substance: deconjugates intestinal bilirubin, increasing its ability to be absorbed (i.e., increasing enterohepatic circulation)

B. Typically begins after the first 3–5 days of life, peaks within two weeks after birth, and progressively declines to normal levels over 3–12 weeks

C. Severe in 2% of cases, where serum bilirubin levels can reach 15 mg/dL

D. Not associated with kernicterus

E. Different from breastfeeding jaundice, which occurs because of inadequate intake of breast milk, leading to significant weight and fluid loss resulting in hypovolemia and hyperbilirubinemia

F. Cessation of breastfeeding for 24–48 hours will decrease bilirubin

III. Gilbert’s Syndrome

A. A defect in bilirubin glucuronidation resulting in chronic recurrent, mild, unconjugated hyperbilirubinemia, with otherwise normal liver function tests

1. Inherited as autosomal-dominant or autosomal-recessive

2. Heterogeneous group of disorders, with at least a 50% decrease in hepatic bilirubin UDP glucuronyl transferase (BUGT) activity

B. Clinical diagnosis in which mild, fluctuating, unconjugated hyperbilirubinemia occurs with otherwise normal liver function tests and no evidence of hemolysis

C. Patients are often identified when elevated serum bilirubin is noted on screening blood chemistry

D. Mild jaundice or scleral icterus may occur during a period of fasting or viral illness

E. Most often clinically apparent after puberty

F. Serum unconjugated bilirubin levels usually range from 1–4 mg/dL
G. Genetic screening for UGT1A1 mutations is available
H. Benign condition, with affected patients not at increased risk of morbidity or mortality related to condition
I. No specific treatment is required

IV. Crigler-Najjar Syndrome
A. Glucuronidation defect resulting in a severe unconjugated hyperbilirubinemia in the immediate neonatal period, with a high risk of kernicterus
B. Autosomal-recessive condition
   1. Type I: complete absence of functional UGT1A1 activity
   2. Type II: markedly reduced but not absent UGT1A1 activity
   3. Type I can be differentiated from Type II by response to phenobarbital, which can stimulate endoplasmic reticulum hyperplasia: those with Type II will decrease serum bilirubin, while Type I will not
C. Patients with one normal allele have normal bilirubin metabolism
D. Evaluation begins in the immediate neonatal period, when serum bilirubin levels are >20 mg/dL, without a conjugated fraction
   1. Evaluation should include the exclusion of other causes of unconjugated hyperbilirubinemia, such as hemolysis, hypothyroidism, infection
E. Neonates should be treated with phototherapy and/or exchange transfusion to prevent kernicterus
F. Requires lifelong treatment with phototherapy, 6–12 hours daily, to maintain serum bilirubin <20 mg/dL
G. Phenobarbital (4 mg/kg/d) may be used as an adjunct therapy in Type II patients
H. Oral administration of binding agents such as agar, cholestyramine, or calcium phosphate have also been used to bind bilirubin in the intestinal lumen and prevent enterohepatic recirculation
I. Orthotopic liver transplantation is curative

V. Rotor Syndrome
A. Defect of intracellular binding of bilirubin and its conjugates
B. Autosomal-recessive defect of glutathion S-transferase (GST), though genetic defect is unknown
C. Chronic elevation of both conjugated and unconjugated serum bilirubin fractions
   1. Total serum bilirubin concentrations range from 2–7 mg/dL, with ≥50% conjugated
D. Consider diagnosis in individuals with elevations of both conjugated and unconjugated serum bilirubin fractions, but otherwise normal liver function, and no hemolysis
E. The diagnosis made by measuring urinary coproporphyrin levels: 2.5–5x higher than in normal individuals
   1. Urinary coproporphyrin Isomer I will be <80% of the sum total of Isomer I and III
F. Jaundice is lifelong, but not associated with morbidity or mortality
G. No specific therapy is required

VI. Dubin-Johnson Syndrome
A. A defect of hepatic excretion of non-bile salt organic ions at the apical canalicular membrane by the ABC transport system (CMOAT/MRP2/ABCC2)
B. Autosomal-recessive condition
C. Elevation of both conjugated and unconjugated serum bilirubin fractions
   1. Total bilirubin levels range from 1.5–6 mg/dL, with >50% conjugated
   2. Levels as high as 25 mg/dL may occur during intercurrent illness
D. Usually diagnosed after puberty, though may occur in neonates
E. Male predominance, with earlier age of presentation
F. Patients may have abdominal complaints
G. Hepatomegaly may occur, but liver function tests are otherwise normal
H. Jaundice may be worsened by pregnancy and oral contraceptives
I. Patients have an increase in the urinary excretion of coproporphyrin I (80%), with a decrease in the excretion of coproporphyrin III
J. Liver has a brown-to-black discoloration, due to pigment in lysosomes
K. Jaundice is lifelong, but not associated with morbidity or mortality
L. No specific therapy is necessary
   1. Avoidance of oral contraceptives is recommended
   2. Anticipatory guidance regarding pregnancy should be provided
Recommended Reading


I. Carbohydrate Metabolism
   A. A central role of the liver is glucose homeostasis (See figure 1)
   B. Glucose can be generated via pathways of gluconeogenesis and by degradation of stored glycogen
   C. Hormones such as insulin, glucagon, and epinephrine regulate the uptake and release of glucose
   D. The majority of dietary carbohydrates are absorbed in the form of glucose, galactose, and fructose
   E. Glucose is stored primarily in the form of glycogen, a branched-chain glucose polymer primarily located in liver and muscle

II. Common Features of Disorders of Carbohydrate Metabolism
   A. Neonates and infants may present with hypoglycemia, vomiting, diarrhea, poor feeding, poor weight gain, seizures, hepatomegaly, and liver failure
   B. Older children may present with hepatomegaly, abnormal feeding behaviors such as sugar avoidance, poor weight gain and growth, and developmental delay
   C. May present after an acute illness or prolonged period of fasting

III. Disorders of Galactose Metabolism
   A. Epidemiology/Pathogenesis
      1. Most common defect of galactose metabolism is a deficiency of galactose 1-phosphate uridyl transferase (GALT). This defect is responsible for classic galactosemia (See figure 2)
      2. Occurs in 1 of every 30,000–50,000 live births
      3. Autosomal-recessive condition
      4. Other galactose metabolism defects include a defect of galactokinase (the enzyme responsible for the first step in galactose metabolism)

   B. Clinical Features
      1. Failure to thrive, vomiting, diarrhea are most common
      2. Patients may present with hypoglycemia and encephalopathy shortly after birth, and then develop jaundice, ascites, hepatosplenomegaly, and liver failure
      3. Hemolytic anemia can be seen
      4. Cataracts can develop with galactokinase deficiency due to accumulation of toxic metabolites (galactitol) in the lens
      5. E coli sepsis should prompt an evaluation for galactosemia
      6. Renal tubular dysfunction can also occur
      7. Mental retardation is the most significant long-term effect. IQ is highly correlated with adequate dietary control
      8. Hypergonadotropic hypogonadic ovarian failure can also occur with GALT deficiency

   C. Diagnosis
      1. Most patients are detected via the newborn screen
      2. Positive urinary reducing substances, without glucosuria
      3. Decreased GALT activity in the red blood cells
D. Management/Treatment
   1. Elimination of dietary galactose
      a. Switch infants to soy or protein hydrolysate formula
      b. Older children and adults should avoid products that contain milk and milk products. Food labels must be read carefully to look for these ingredients
      c. Legumes such as garbanzo and black beans should also be avoided because they contain increased amounts of galactose
      d. Calcium and Vitamin D supplementation is recommended
   2. Annual ophthalmologic exams and neurodevelopmental assessments are recommended

   **Figure 1.** Galactose metabolism. Galactose is phosphorylated to galactose 1-phosphate, by galactokinase (1). This is then further converted to uridine diphosphate (UDP) galactose and glucose 1-phosphate by galactose-1-phosphate uridylyl transferase (GALT) (2). UDP-galactose is converted to UDP-glucose by uridine diphosphate galactose-4-epimerase (3). UDP-glucose is converted to glucose 1-phosphate by uridine diphosphate glucose pyrophosphorylase (4). In the absence of GALT, galactitol and galactonate are over-produced.


IV. Hereditary Fructose Intolerance
   A. Epidemiology/Pathogenesis
      1. Caused by a deficiency of fructose-1,6-bisphosphate aldolase (aldolase B) (See figure 3)
      2. Occurs in approximately 1 in 20,000 live births
      3. Autosomal-recessive condition
   B. Clinical Features
      1. Symptoms develop once fructose is introduced into the diet (switch to sucrose-containing formula or the initiation of baby foods)
      2. Most common symptoms include poor feeding, vomiting, diarrhea, and abdominal pain
      3. Chronic exposure or large fructose loads can lead to seizures, failure to thrive, liver failure, and renal tubular dysfunction
      4. Older patients and adults may go undiagnosed, because these patients may purposefully avoid fructose-containing foods
   C. Diagnosis
      1. Definitive diagnosis requires tissue enzyme assay
   D. Management/Treatment
      1. Complete avoidance of fructose and sucrose. Must take particular notice of food additives, pill coatings, and medication suspensions
      2. In acutely ill patients, correct hypoglycemia, metabolic acidosis, and coagulopathy

   **Figure 2.** Fructose metabolism. Fructose is metabolized to glycogen or to components of the Krebs cycle. A deficiency in aldolase B, as in hereditary fructose intolerance, results in the accumulation of fructose 1-phosphate.

V. Fructose 1,6-Bisphosphatase Deficiency
   A. An autosomal-recessive condition resulting in impaired gluconeogenesis
   B. A slight female predominance (1.5:1) exists
   C. Parental consanguinity has been reported in some cases
   D. Symptoms develop when glycogen stores are low (such as in newborns or in periods of prolonged fasting or illness)
   E. Approximately 50% of affected patients will develop symptoms shortly after birth, including hypoglycemia, hyperventilation, and metabolic acidosis
   F. Definitive diagnosis is made by liver biopsy
   G. Treatment includes avoidance of prolonged periods of fasting, and limitation of dietary fructose and sucrose

VI. Glycogen Storage Diseases (GSDs)
   A. Epidemiology/Pathogenesis
      1. Caused by deficiencies of enzymes in the pathways of glycogen metabolism. Ten different types of GSDs have been identified, with Types I, III, IV, and VI primarily affecting the liver (See Table 1)
      2. Autosomal-recessive conditions
      3. Type Ia occurs in 1 of every 200,000 live births

Table 1.

<table>
<thead>
<tr>
<th>Type</th>
<th>Enzyme Defect</th>
<th>Affected Tissues(s)</th>
<th>Main Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia (Von Gierke disease)</td>
<td>Glucose-6-phosphatase</td>
<td>Liver, kidney</td>
<td>Classic form of GSD; hypoglycemia &amp; metabolic acidosis 3–4 hours post meal; hepatomegaly with protuberant abdomen and lordosis; elevated triglycerides; doll facies and xanthomas; impaired platelet function/bleeding; elevated uric acid</td>
</tr>
<tr>
<td>I b-c</td>
<td>Glucose-6-phosphatase related transport</td>
<td>Liver</td>
<td>Ib – neutropenia and recurrent infections; association with IBD lc – impaired insulin secretion</td>
</tr>
<tr>
<td>II (Pompe disease)</td>
<td>Acid-α-glucosidase</td>
<td>Heart, muscle</td>
<td>Cardiorespiratory failure, cardiomyopathy</td>
</tr>
<tr>
<td>III (Forbes disease)</td>
<td>Debranching enzymes</td>
<td>Liver, muscle</td>
<td>Hepatomegaly, fasting hypoglycemia, hyperlipidemia, progressive myopathy</td>
</tr>
<tr>
<td>IV (Andersen’s disease)</td>
<td>Branching enzyme (α-1,4-glucan 6 glucosyl-transferase)</td>
<td>Liver</td>
<td>Hypoglycemia is RARE; liver disease and cardiomyopathy are common</td>
</tr>
</tbody>
</table>

Figure 3. Type 1 glycogen storage disease (A) Glycogen-filled hepatocytes seen on periodic acid-Schiff stain. (B) Plantlike mosaic patter of hepatic lobules on hematoxylin stain. Courtesy of Dr. H. Melin-Aldana

B. Diagnosis
   1. Liver biopsy: histological exam of GSD type I patients will demonstrate glycogen-filled hepatocytes that are periodic acid-Schiff stain positive
   2. Molecular genetic tests available for GSD types I through V
C. Management/Treatment
   1. GSD Type I
      a. Continuous glucose source (small frequent feeds in infants, continuous or overnight enteric tube feeds, cornstarch)
      b. Allopurinol and lipid-lowering agents are rarely needed
      c. Recombinant G-CSF for neutropenia
   2. GSD Type III
      a. Continuous glucose source
      b. Annual alpha-fetoprotein and ultrasound due to risk of hepatocellular adenomas
      c. Annual echo and EKG for patients with cardiomyopathy
   3. GSD Type IV
      a. Liver transplantation is the only effective therapeutic modality for these patients

Recommended Reading


I. Tyrosine Metabolism
A. Degradation of tyrosine is catalyzed by a series of reactions yielding acetoacetate and fumarate. The complete pathway only occurs in hepatocytes and renal proximal tubules. Conditions leading to elevated serum tyrosine levels include: transient tyrosinemia of the newborn (most common cause of hypertyrosinemia resulting from immaturity of the liver and the enzymes required for tyrosine degradation); any severe hepatocellular dysfunction; congenital deficiencies or dysfunction of enzymes related to tyrosine metabolism, hyperthyroidism and vitamin C deficiency.

![Tyrosine degradation pathway](image)

**Figure 1.** Tyrosine degradation pathway demonstrating fumarylacetoacetate hydrolase, a defect of which is responsible for tyrosinemia type 1. In addition, the inhibitory effect of abnormal metabolites on porphyrin metabolism and the site of action of NTBC are also demonstrated. Abbreviation: NTBC, 2-(2-nitro-4-trifluoromethylbenzol)-1, 3-cyclohexanedione


II. Hepatorenal Tyrosinemia (Hereditary Tyrosinemia Type 1)
A. Epidemiology/Pathogenesis
1. Incidence of 1 in 100,000, with higher incidence in Northern Europeans (1 in 8,000) and in Saguenay-Lac Saint-Jean region of Quebec, Canada (1 in 1,846)
2. Autosomal-recessive condition caused by defect in fumaryl acetoacetate hydrolase (the last enzyme in tyrosine degradation), resulting in accumulation of fumarylacetoacetate and maleylacetoacetate, and their derivatives succinylacetoacetone (SAA) and succinylacetone (SA)
3. Maleylacetoacetate induces renal Fanconi syndrome
4. Maleylacetoacetate and fumarylacetoacetate are reactive unstable compounds that may form glutathione adducts, which allow free radical formation. This may be the source of DNA damage and the increased risk of hepatocellular carcinoma
5. Succinylacetone inhibits synthesis of porphobilinogen from δ-aminolevulinic acid (δ-ALA). Accumulation of δ-ALA is the source of neurotoxicity as in acute intermittent porphyria

B. Clinical Features

1. Acute manifestations are those of acute liver failure with vomiting, diarrhea, hepatosplenomegaly, edema, ascites, mild elevations of bilirubin and transaminases, and severe hepatic synthetic dysfunction–producing coagulopathy, hypoglycemia and hypoalbuminemia

2. Chronic Form
   a. Growth failure
   b. Renal tubular dysfunction from Fanconi syndrome with phosphaturia and renal rickets resulting from maleylacetoacetate accumulation
   c. Neurological crises, pain with paresthesias and posturing result from delta aminolevulinic acid accumulation. Often precipitated by infection. Can last up to a week and may progress to flaccid paralysis and respiratory failure resembling acute intermittent porphyria
   d. Main causes of death are liver failure, especially recurrent bleeding, 
      Hepatocellular carcinoma and neurological crises

3. Hepatocellular carcinoma (HCC) is usually a long-term complication occurring in less than 1/3 of patients. Cases as young as 15 months have been reported. Abdominal ultrasound or CT scan can identify HCC. Cirrhotic nodules may be a confounder, but are not a reliable indicator of HCC

C. Diagnosis

1. Elevated urine succinylacetone is most diagnostic. Urine δ-ALA also elevated but is elevated in other disorders. Serum α-fetoprotein elevation variable with or without HCC

2. Coagulopathy (with normal factors V and VIII), hypoalbuminemia and hypoglycemia out of proportion to milder elevation of bilirubin and transaminases

3. Hemolytic anemia

4. Renal tubular dysfunction (hyperphosphaturia, glucosuria, proteinuria and aminoaciduria)

5. Liver biopsy
   a. Acute → fatty infiltration of liver, iron deposition and varying degrees of hepatocyte necrosis
   b. Chronic → multilobular cirrhosis, bile duct proliferation and regenerative nodules

D. Management/Treatment

1. Coagulopathy is NOT responsive to Vitamin K

2. Dietary restriction of phenylalanine and tyrosine. In infants, Tyrex® or Tyros® formula is used

3. NTBC (2-(2-Nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione)
   a. Inhibits 4-hydroxyphenylpyruvate dioxygenase (2nd step in tyrosine degradation)
   b. >95% of patients respond with significant hepatic and renal improvement
   c. Need frequent monitoring, including LFTs and urine succinylacetone
   d. Recurrent ophthalmological evaluations and abdominal imaging
   e. Serum alpha-fetoprotein every 6–12 months
   f. NTBC started early may decrease the incidence of HCC, but careful monitoring is still required for all Type I cases

4. Liver transplantation
   a. Reserved for those patients who do not respond to medical therapy
   b. Reported 1-year survival is high: 88%–100%
   c. Renal tubular dysfunction, renal rickets and poor growth may persist after transplantation
III. Other Forms of Tyrosinemia

A. Liver failure: nonspecific elevation of many urine and serum amino acids, including tyrosine
B. Transient tyrosinemia of the newborn: immaturity of 4-hydroxyphenylpyruvate dioxygenase (4HPPD) causes self-limited elevation of tyrosine. Treat with lower protein diet and vitamin C
C. Vitamin C deficiency: Vitamin C is a cofactor for 4HPPD
D. HP Type III: congenital defect in 4HPPD
E. HP Type II (oculocutaneous tyrosinemia) autosomal-recessive deficiency of tyrosine aminotransferase. Hyperkeratosis of palms and soles, corneal thickening, developmental delay with normal hepatic and renal functions

Recommended Reading


**I. Physiology of Fatty Acid Oxidation**

A. Mitochondrial β-Fatty acid oxidation (FAO) provides most of the energy needed in the heart and muscle, and is an essential pathway to maintain blood glucose during periods of fasting

1. FAO leads to the production of ketone bodies, which are an important secondary energy source for many tissues, including the brain, when glucose supplies are low. This is particularly important in childhood when glycogen stores are limited

B. The initial step in fatty acid metabolism is lipolysis, in response to fasting, resulting in free fatty acids (FFAs)

1. FFAs are transported across the plasma membrane and are esterified to coenzyme A (CoA) by the enzyme acyl-CoA synthetase, to form acyl-CoA esters before entry into the mitochondria for further metabolism
   a. Long-chain fatty acids (LCFAs) require the carnitine cycle and transesterification to acylcarnitines to cross the mitochondrial membrane

2. Within the mitochondria, the acyl-CoA esters enter the β-oxidation cycle, and carnitine is reshuffled back across the inner mitochondrial membrane to bring more LCFAs across the membrane
   a. Medium-chain fatty acids (MCFAs) and short-chain fatty acids (SCFAs) can traverse the mitochondrial membrane without conversion to acylcarnitines

**Figure 1.** Overview of fatty acid import and metabolism. Adapted from Walker WA, Goulet O, Kleinman RE, Sherman PM, Shneider BL, Sanderson IR. *Pediatric Gastrointestinal Disease: Pathophysiology, Diagnosis, and Management.* 4th ed. Hamilton, Ontario: BC Decker Inc;2004. Chapter 55-3.

ACS = acyl-CoA synthetase; CACT = carnitine acylcarnitine translocase; CoA = coenzyme A; CoASH = unacylated coenzyme A; CPT1 = carnitine palmitoyltransferase 1; CPT12 = carnitine palmitoyltransferase 2; FA = fatty acid; FA-CoA = fatty acyl CoA; FATP = fatty acid transport protein; MCAD = medium-chain acyl-CoA dehydrogenase; Mit = mitochondrial; M/SCHAD = medium-/short-chain 3-hydroxyacyl-CoA dehydrogenase; SCAD = short-chain acyl-CoA dehydrogenase; SCEH = short-chain enoyl-CoA hydratase; SKAT = short-chain ketoacyl-CoA thiolase; TFP = trifunctional protein; VLCAD = very-long-chain acyl-CoA dehydrogenase.

**Figure 1.** Overview of fatty acid import and metabolism. Adapted from Walker WA, Goulet O, Kleinman RE, Sherman PM, Shneider BL, Sanderson IR. *Pediatric Gastrointestinal Disease: Pathophysiology, Diagnosis, and Management.* 4th ed. Hamilton, Ontario: BC Decker Inc;2004. Chapter 55-3.
C. The β-oxidation cycle is a 4-step cyclical process. Each turn of the β-oxidation cycle results in the cleavage of two carbon fragments from the original LCFA in the form of acetyl-CoAs that are then directed into ketone body synthesis
   1. An important byproduct of the β-oxidation cycle is the production of electrons for the electron transport chain
   2. There are four major enzyme families responsible for each turn of the β-oxidation cycle
      a. Acyl-CoA dehydrogenases
      b. Enoyl-CoA hydratases
      c. 3-Hydroxyacyl-CoA dehydrogenases
      d. 3-Ketoacyl-CoA thiolases
   3. Enzymes responsible for long-chain metabolism (e.g., VLCAD, LCHAD, LKAT) are associated with the inner mitochondrial membrane
   4. Enzymes responsible for short- and medium-chain metabolism (e.g., MCAD, SCAD, MCHAD, SCHAD, MCKAT) are associated with the mitochondrial matrix
   5. The rate-limiting step in the β-oxidation cycle is the first reaction catalyzed by the family of acyl-coA dehydrogenases. Riboflavin (Vitamin B2) is a precursor to these enzymes
D. The following are the recognized defects in fatty acid oxidation:
   1. Fatty acid transporter
   2. Carnitine transporter
   3. Carnitine palmitoyltransferase 1 (CPT1)
   4. Carnitine-acylcarnitine translocase
   5. Carnitine palmitoyltransferase 2 (CPT2)
   6. Very long chain acyl-CoA dehydrogenase (VLCAD)
   7. Long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD)
   8. Mitochondrial trifunctional protein
   9. Medium chain acyl-CoA dehydrogenase (MCHAD)
   10. Short chain acyl-CoA dehydrogenase (SCHAD)
   11. Short chain 3-hydroxyacyl-CoA dehydrogenase (3 types)
   12. Multiple acyl-CoA dehydrogenases
   13. Riboflavin-responsive multiple acyl-CoA dehydrogenase
   14. 2,4 Dienoyl-CoA reductase deficiency
   15. HMG-CoA synthase
   16. HMG-CoA lyase

II. Epidemiology/Genetics
   A. Autosomal-recessive inheritance, with an incidence of approximately 1 in 10,000 and a recurrence risk of 25% in subsequent pregnancies by the same couple
   B. MCAD deficiency is the most common and best studied FAO disorder, with 1 point mutation accounting for approximately 80% of cases

III. Clinical Features/Associations
   A. In general, the more proximal the defect in the FAO pathway, the earlier the clinical presentation and the more severe the clinical course
   B. Most symptoms appear after a period of fasting and/or vomiting, typically associated with an acute infection or illness
   C. Hypoketotic hypoglycemia is a hallmark of most FAO disorders
   D. Symptoms at presentation include vomiting, lethargy, apnea, seizures, encephalopathy and respiratory arrest
   E. May also presence with a metabolic crisis, cardiac arrhythmia, skeletal or muscle myopathy
   F. Physical exam can be significant for marked hepatomegaly but NO splenomegaly, hypotonia, and a gallop rhythm and poor perfusion if the heart is affected. Jaundice is rare
   G. One-third of patients will have a family history significant for SIDS, Reye syndrome, sudden cardiac decompensation, or early infant death due to acute liver failure or sepsis. An estimated 1%–5% of SIDS cases are due to an underlying FAO disorder
   H. SCHAD and SCAD deficiencies allow for multiple turns of the β-oxidation cycle, which allows for the formation of ketones
   I. Several case of LCHAD, CACT and MCKAT have presented in acute liver failure, although this is an overall uncommon presentation for FAO disorders
J. Some patients with SCAD deficiency may have persistent vomiting, gastroesophageal reflux and failure to thrive. Mild types of MCAD and SCAD may have a cyclic vomiting syndrome–like presentation.

K. Several cases of LCHAD and CPTII deficiencies have been linked to repeated episodes of pancreatitis.

L. Pregnancy and FAO Disorders
   1. Acute fatty liver of pregnancy (AFLP)
      a. Disorder with significant morbidity and mortality in women during the third trimester of pregnancy.
      b. Women typically present with nausea, vomiting and abdominal pain, and quickly progress to fulminant hepatic failure with coagulopathy and encephalopathy.
      c. Liver histology reveals microvesicular hepatic steatosis and mitochondrial disruption.
      d. Management includes prompt delivery.
   2. HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome
      a. Complication of preeclampsia that occurs in the third trimester.
      b. Better prognosis than AFLP.
      c. Liver histology reveals periportal hemorrhage and fibrin deposition.
      d. Management includes prompt delivery.
   3. There is a well-documented association between FAO disorders and complications, such as AFLP and HELLP syndrome, particularly in those women carrying LCHAD-deficient fetuses. A common mutation in G1528C has been found.
      a. Offspring of women who develop these third trimester complications should be screened for this mutation.

IV. Diagnosis
   A. Urine organic acids and serum acylcarnitine profile have the best diagnostic yield.
   B. Labs significant for elevated ammonia, mild elevation in transaminases, normal or very mild elevation in bilirubin, and mild to moderate increase in BUN, uric acid and CPK.
   C. Urinary ketones during a metabolic crisis may be useful.
   D. Serum free fatty acids and β-hydroxybutyrate (increased FFA concentrations in FAO disorders).
   E. Tissue assays (liver, muscle, skin fibroblasts) to measure enzyme activity.

V. Management/Treatment
   A. Acute
      1. Reverse hypoglycemia with dextrose infusions.
      2. Dextrose also raises insulin levels and inhibits FAO and lipolysis.
      3. Avoid drugs that inhibit FAO (e.g., valproic acid, NSAIDs, and salicylate) and drugs that increase the release of FFA (e.g., epinephrine).
      4. Avoid IV propofol, IV fat emulsions and parenteral nutrition.
      5. Carnitine (IV or enterally) if there is no vomiting or diarrhea, particularly for those with a carnitine transport defect.
   B. Chronic
      1. AVOID fasting. A low-fat, high-carbohydrate diet is recommended. Overnight NG or gastrostomy tube feeding may be helpful. These patients often need to be admitted if they are going to be NPO for a prolonged period of time (e.g., prior to surgery).
      2. High carbohydrate load prior to cold exposure or prolonged aerobic activity.
      3. MCT supplementation for long-chain defects.
      4. Daily carnitine supplementation (100 mg/kg/day) for those with carnitine transport defects.
      5. Riboflavin supplementation (100 mg/day) for those with defects in the first step of the β-oxidation cycle.
   C. Prognosis
      1. Those who present in neonatal period have a poor prognosis, with a mortality rate as high as 60% (even before diagnosis is made).
      2. If diagnosis can be made early, then appropriate measures can be taken to prevent acute episodes.
Table 1. Differential Diagnosis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Ammonia</th>
<th>Metabolic Acidosis</th>
<th>Anion Gap (Na- (Cl- Bicarb))</th>
<th>Ketones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea Cycle Disorders</td>
<td>High</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>FAO Disorders</td>
<td>High</td>
<td>Yes</td>
<td>Elevated</td>
<td>Too Low</td>
</tr>
<tr>
<td>Organic Acidemias</td>
<td>High</td>
<td>Yes</td>
<td>Elevated</td>
<td>Too High</td>
</tr>
</tbody>
</table>

Recommended Reading


I. Ammonia/Hyperammonemia
   A. Ammonia is a degradation product from amino acid metabolism. Some is reused, but most is
detoxified by the urea cycle and excreted as urea
   B. Hyperammonemia is toxic to the immature nervous system, and repeated prolonged episodes of
elevated ammonia can lead to permanent neurologic impairment
   C. Differential Diagnosis of Hyperammonemia
      1. Urea cycle defects (elevated ammonia, NO metabolic acidosis)
      2. Fatty acid oxidation disorders (elevated ammonia, + metabolic acidosis, elevated anion
gap, NO ketones in urine)
      3. Organic acidemias (elevated ammonia, + metabolic acidosis, elevated anion gap,
ELEVATED ketones in urine)
      4. Transient hyperammonemia of the newborn (rapid neurological deterioration right after
birth, possibly due to decreased hepatic blood flow)
      5. Reye’s syndrome (also have hypoglycemia and coagulopathy)
      6. Liver failure
      7. Severe systemic illness

II. Pathogenesis/Epidemiology
   A. The urea cycle converts ammonia into urea and produces arginine
   B. 6 different enzymes involved
      1. Carbamyl phosphate synthetase (CPS)
      2. Ornithine transcarbamylase transferase (OTC)
      3. Argininosuccinate synthetase (AS)—citrullinemia
      4. Argininosuccinate lyase (AL)
      5. Arginase
      6. N-acetylglutamate synthetase
   C. All urea cycle disorders are inherited in an autosomal-recessive pattern, except for OTC
deficiency, which is inherited in an X-linked dominant pattern
   D. OTC deficiency is the most common urea cycle disorder
   E. Urea cycle defects occur in 1 of every 25,000–30,000 newborns

---

III. Clinical Features
   A. Infants → rapid sepsis-like deterioration after protein feeds, food refusal, vomiting, tachypnea, seizures, lethargy, coma
   B. Older children → vomiting, neurological changes

IV. Diagnosis
   A. Elevated ammonia levels
   B. Citrulline level (low in OTC and CPS deficiencies, high in AS deficiency)
   C. Elevation in transaminases and prothrombin time during acute exacerbations
   D. Diagnosis is confirmed by the measurement of tissue enzyme activity
   E. OTC deficiency
      1. Expressed in liver and intestinal mucosa
      2. Males have virtually absent enzyme activity
      3. Females are heterozygous

V. Management/Treatment
   A. REDUCE serum ammonia levels
      1. Discontinue all protein intake and supply sufficient glucose (IV or orally) to limit catabolism
      2. Provide alternatives for nitrogen excretion
         a. Sodium benzoate (1 mole of nitrogen excreted for each mole of benzoate given)
         b. Phenylbutyrate (2 moles of nitrogen excreted for each mole of phenylbutyrate given)
   B. Dietary
      1. Protein restriction (<700 mg/kg/day)
      2. Cyclinex® (free nonessential AA formula)
   C. Arginine supplementation (except for those with arginase deficiency)
   D. Citrulline supplementation (excretes additional nitrogen) for OTC and CPS deficiencies
   E. Some may require anticonvulsants
   F. Regular monitoring of serum ammonia and amino acids
   G. Caution during periods of fasting, illness, infections, anesthesia, or surgery
   H. Transplantation reserved for those with recurrent or poorly controlled hyperammonemia, but does NOT correct existing neurological injury

VI. Outcomes
   A. Duration of hyperammonemia is related to subsequent intellectual ability of the patient
   B. Severity of hyperammonemia is NOT related to subsequent intellectual ability of the patient

Recommended Reading


6N-7. Metabolic/Genetic Liver Diseases—Alpha-1 Antitrypsin Deficiency

Christine Waasdorp Hurtado, MD, MSCS, FAAP
Michael Narkewicz, MD

I. Alpha-1 antitrypsin deficiency (α1-ATD)
   A. A common metabolic liver disease in childhood. The diagnosis should be considered in all adults and children with chronic hepatitis or cirrhosis of unknown etiology and in infants with cholestasis. Alpha-1 antitrypsin deficiency is associated with chronic liver disease in 10% of affected adults and 10%–15% of affected children.

II. Genetics and Function
   A. Alpha-1 antitrypsin (AT) deficiency is an autosomal co-dominant disorder affecting 1 in 1,800 live births encoded by a gene on the long arm of chromosome 14 q31-32.2
   B. PiMM (PI = protease inhibitor), the normal phenotype which is present in 95% of the population and is associated with normal serum levels of α1-AT
   C. The Z α1-AT protein is caused by a single nucleotide substitution (glu to lys). The gene is most common in those of northern European descendants. PiZZ and PiSZ phenotypes are associated with severe deficiency and liver disease, while the PiMZ phenotype leads to an intermediate deficiency without liver disease
   D. There are more than 100 allelic variants of AT. Not all variants are associated with clinical disease
   E. Alpha-1 antitrypsin is an inhibitor of neutrophil proteases and elastases

III. Clinical Presentation
   A. α1-ATD predisposes children and adults to pulmonary and liver disease
   B. Liver involvement is often first identified in the newborn period due to persistent cholestatic jaundice. Affected infants tend to be small for gestational age. The jaundice generally clears. 10%–15% of PiZZ individuals present with liver disease in the first years of life
   C. 10%–30% of those presenting with neonatal liver disease develop moderate to severe liver disease with coagulopathy, poor growth, portal hypertension and ascites in childhood
   D. Serum aminotransferase levels, alkaline phospha park and gamma glutamyl transpeptidase may all be elevated
   E. Emphysema develops in 60%–70% of α1-ATD adults over the age of 25 years with the peak in the 4th and 5th decades

IV. Pathogenesis and Diagnosis
   A. Liver disease is associated with retention of abnormally folded Z protein in the endoplasmic reticulum of hepatocytes
   B. Far fewer patients exhibit liver and lung disease associated with α1-ATD than estimated by population human genetic estimations, suggesting involvement of unidentified genetic and environmental factors and modifier genes in the development of tissue damage
   C. The pathogenesis of α1-ATD associated liver disease is not completely understood, with several possible theories proposed
      1. Accumulation of mutant protein in the endoplasmic reticulum, resulting in hepatotoxicity
      2. Autophagy, a cellular mechanism for disposal of accumulated proteins has been suggested to be defective in those with liver disease
      3. Other inherited traits for protein degradation and environmental factors (viral hepatitis, alcohol) may increase accumulation of the defective protein and result in increased liver injury
D. $\alpha$-1 ATD is associated with liver injury in other disease process. Several studies suggest that the PiMZ state may predispose to more severe liver injury in other hepatic disorders (HBV, HCV, alcoholic liver disease, cystic fibrosis and NAFLD)

E. Diagnosis is established by a serum $\alpha$-1 antitrypsin phenotype (Pi typing) or genotype
   1. Serum levels are generally significantly decreased in affected patients; however, $\alpha$-1 antitrypsin is an acute phase reactant and could be falsely elevated. Serum concentrations are rarely above 50–60 mg/dL in patients with PiZZ phenotype
   2. Liver histology demonstrates periodic acid-Schiff positive diastase-resistant globules in the endoplasmic reticulum of periportal hepatocytes, but should not be used for diagnosis, as some patients with PIMZ have this histology as well and this finding can be absent in young infants

V. Treatment and Screening
A. There are no specific therapies for $\alpha$-1 ATD–associated liver disease
B. Infants with cholestasis may benefit from fat-soluble vitamin supplements (vitamins A, D, E and K) and infant formula containing medium-chain triglyceride oil. In addition, ursodeoxycholic acid may increase bile flow and reduce liver injury associated with cholestasis, although there is no evidence of direct long-term benefit
C. Avoidance of cigarette smoking (including secondhand smoke) and environmental pollution exposure is mandatory in order to slow the progression of lung disease
D. Orthotopic liver transplantation (OLT) is the treatment for $\alpha$-1 ATD–associated end-stage liver disease and liver failure. The recipient assumes the donor Pi phenotype and is no longer at risk for emphysema
E. Screening is recommended for all relatives of patients with $\alpha$-1 ATD to identify PiZZ or PiSZ family members and is mandatory for siblings of affected patients. Newborn screening has not been instituted

Recommended Reading


Degenerative disease of the central nervous system associated with cirrhosis due to copper toxicity. Clinical manifestations vary between affected individuals, even within affected families. Children typically present with hepatic disease and neurologic disease is seen in later onset.

I. Overview
A. Also known as hepatolenticular degeneration
B. Rare autosomal-recessive disease of copper metabolism with a prevalence of 1:30,000
C. Abnormal gene (ATP7B) found in chromosome 13, encodes for a P-type ATPase expressed mainly in hepatocytes, which transports copper into bile and incorporates it into ceruloplasmin. Absent or reduced function of this protein leads to decreased hepatocellular excretion of copper into bile resulting in copper accumulation in the liver and decreased ceruloplasmin
D. As liver copper levels increase, it is released in the circulation and deposits in other organs, brain, kidneys and cornea

II. Clinical Features
A. Usually manifests as liver disease in children and teenagers; and as neuropsychiatric illness in adults
B. Classic 3 criteria: liver disease, decreased ceruloplasmin and Kaiser-Fleischer rings
C. Hepatic manifestations:
   1. Can be highly variable from asymptomatic with abnormal laboratories to acute liver failure
   2. Patients may present with hepatomegaly, signs of chronic liver disease and cirrhosis, splenomegaly, acute liver failure with Coombs-negative hemolytic anemia, coagulopathy unresponsive to parenteral vitamin K, gallstones, or histological findings of steatosis
   3. May be indistinguishable from autoimmune hepatitis. Patients with apparent autoimmune hepatitis that do not respond to therapy should be assessed for Wilson disease, because elevated serum immunoglobulins and nonspecific antibodies may be found in both conditions
D. Neurological manifestations:
   1. Usually onset 10–30 years of age
   2. Mainly affects the motor system, include changes in behavior, deterioration of schoolwork and handwriting, or inability to perform activities requiring good hand-eye coordination, tremor, lack of motor coordination, drooling, dysarthria, dystonia and spasticity. Due to pseudobulbar palsy, dysphagia may occur with risk of aspiration
   3. Other behavioral changes include depression, anxiety and even frank psychosis
   4. Sensory function and intelligence remain normal
E. Other manifestations: aminoaciduria and nephrolithiasis, skeletal abnormalities such as premature osteoporosis, spontaneous fractures, and arthritis, cardiomyopathy, EKG abnormalities, pancreatitis, hypoparathyroidism, and infertility or repeated miscarriages
F. Kaiser-Fleischer rings:
   1. Represent deposition of copper in Déçemet’s membrane of the cornea. It is seen only under slit-lamp examination
   2. Present in 50% of patients with liver disease and 95% of patients with neurological symptoms, but usually absent in children. Other eye manifestations are sunflower cataracts; represent deposits of copper in the lens. Both lesions usually disappear with treatment, if reappearance it suggests noncompliance with therapy
III. Diagnosis
A. Combination of clinical findings and biochemical testing
B. Laboratory findings:
   1. Aminotransferases are generally abnormal.
   2. Ceruloplasmin is usually low (<20 mg/dL) but can be normal or mildly elevated, since it is
      an acute phase reactant
   3. Serum copper: usually decreased or normal, elevated in acute liver failure
   4. Urinary copper excretion in 24 hours: >100 g, useful in diagnosis and monitoring of
      treatment
C. Hepatic copper concentration >250 g/g dry weight: it is the best biochemical evidence for Wilson
   Disease
D. Liver biopsy:
   1. Mild steatosis, glycogenated nuclei in hepatocytes and focal hepatocellular necrosis
   2. May have findings similar to autoimmune hepatitis
   3. With progression of the disease fibrosis and cirrhosis occur. Apoptosis of hepatocytes is
      a prominent feature with acute liver disease
   4. Electron microscopy reveals mitochondria of varying shapes and size with increased
      density of the matrix material, and numerous inclusions, including lipid and fine granular
      material that may correspond to copper. Increased intracristal space with dilatation of
      the tips of the cristae, creating a cystic appearance in absence of cholestasis, is consid-
      ered pathognomonic of WD
E. Brain radiological studies: CT or MRI show abnormalities in the basal ganglia
F. Genetic studies: molecular testing looking for haplotypes or polymorphisms of ATP7B gene.
   Useful in identifying affected first degree relatives.

IV. Treatment
A. Chelating agents:
   1. D-penicillamine
      a. Chelates copper and induces cupruria
      b. Needs supplementation with pyridoxine
      c. Side effects include fever, skin rash, lupus, lymphadenopathy, thrombocytopenia
         and nephrotoxicity
   2. Trientine
      a. Chelates copper and induces cupruria
      b. Safe during pregnancy
   3. Tetrathiomolybdate
      a. Blocks copper absorption
B. Zinc:
   1. Interferes with the uptake of copper from the gastrointestinal tract and induces
      enterocyte metallothionein that is an endogenous chelator
   2. It could be used alone or with a chelating agent
C. Antioxidants: Vitamin E may have a role in the treatment of WD
D. Dietary avoidance of food with high copper content:
   1. Shellfish, nuts, chocolate, mushrooms and organ meats
E. Liver transplant:
   1. Patients with fulminant liver failure, decompensated liver disease unresponsive to
      treatment, and patients with progressive neurological disease will benefit from liver
      transplantation

V. Monitoring
A. Serum copper and ceruloplasmin, hepatic transaminases, PT/INR, CBC, urinalysis and physical
   exam should be done at least every 6 months, especially for those on chelating therapy
B. A 24-hour urinary excretion of copper should be done at least once a year to monitor response
   and compliance with treatment
VI. Screening

A. Asymptomatic siblings and other first-degree relatives should be screened for the disease after age 3 or 4 years unless symptomatic before

1. History and physical examination, slit lamp examination, serum ceruloplasmin and copper concentration, hepatic transaminases and 24-hour urinary copper excretion should be performed
2. Liver biopsy is needed to confirm diagnosis
3. Alternative noninvasive approach is the genetic testing

Recommended Reading


I. Functions of peroxisomes include:
   A. Beta-oxidation of very long-chain fatty acids (VLCFA) and related substances
   B. Alpha-oxidation of 3-methyl fatty acids (e.g., phytanic acid)
   C. Biosynthesis of ether lipids, isoprenoids, cholesterol, and bile acids

II. General clinical features of peroxisomal disorder:
   A. Neurological – encephalopathy, hypotonia, seizures, deafness
   B. Skeletal – short limbs, calcific stippling, craniofacial abnormalities
   C. Ocular – retinopathy, cataract, blindness
   D. Hepatic – neonatal hepatitis, hepatomegaly, cholestasis, cirrhosis
   E. Lab testing includes:
      1. LFTs: abnormal ALT/AST with normal or elevated bilirubin
      2. Serum cholesterol: normal or low (in setting of cholestasis)
      3. Serum VLCFA: increased (C26 et al) with abnormal beta-oxidation of VLCFAs
      4. Serum pristanic acid: increased in disorders of beta-oxidation of VLCFAs
      5. Serum phytanic acid: increased in disorders of peroxisome biogenesis, Refsum disease
      6. Erythrocyte plasmalogens: decreased in disorders of ether lipid biosynthesis
      7. Bile acid intermediates (urine/serum): abnormal intermediates

III. Zellweger syndrome (cerebro-hepato-renal syndrome): autosomal recessive
   A. Clinical presentation:
      1. Usually identified as newborns with hypotonia, feed poorly, distinct facies (wide fontanelle, prominent forehead, midface hypoplasia, epicanthal folds), seizures and hepatic dysfunction.
      2. Older children: retinal dystrophy, sensorineural hearing loss, developmental delay with hypotonia and liver dysfunction
      3. Characteristic bony stippling (chondrodysplasia punctata) of the patella(e) and other long bones may occur
      4. Usually fatal in the first 2 years of life
   B. Liver has decreased production of normal bile acids and increase in abnormal di- and trihydroxy bile acids
   C. Liver ultrastructure reveals absence of peroxisomes, usually overall intact pericanalicular tight junctions with focal loss of integrity of pericanalicular tight junctions with dilation of the lateral spaces
   D. Diagnosis
      1. Elevated plasma very-long-chain fatty acid (VLCFA) levels
      2. Increased concentrations of phytanic acid, pristanic acid, and pipecolic acid in plasma and fibroblasts
      3. Reduced erythrocyte concentration of plasmalogen
      4. Mutations in 12 different PEX genes that encode peroxins (proteins required for normal peroxisome assembly) identified.
         a. Mutations in PEX1, the most common.
         b. Sequence analysis is available clinically for the following twelve genes: PEX1, PXMP3 (PEX2), PEX3, PEX5, PEX6, PEX10, PEX12, PEX13, PEX14, PEX16, PEX19 and PEX26
   E. Management
      1. Symptomatic therapy may include gastrostomy to provide adequate calories, vitamin supplementation, reduce exposure to phytanic acid and genetic counseling is very important
IV. Neonatal Adrenoleukodystrophy and Refsum Disease
A. Most have mutations in either the PEX1 or PEX6 genes that encode ATPases needed to import protein into peroxisomes.
B. Clinical courses are variable and may include developmental delays, hearing loss, vision impairment, liver dysfunction, episodes of hemorrhage and intracranial bleeding.
   1. Slowly progressive.
C. Liver disease is usually mild or absent
D. Neonatal Adrenoleukodystrophy
   1. Mid-face hypoplasia, adrenal insufficiency, behavioral problems
   2. Neurologic features include weakness, hypotonia, seizures, progressive visual and auditory dysfunction
   3. Labs—same biochemical abnormalities as seen in Zellweger syndrome
   4. Most children die by 5 years
E. Refsum Disease
   1. Least severe presentation: typically at 1–6 months with dysmorphic features, hypotonia, visual and auditory abnormalities, retinitis pigmentosa, polyneuropathy, cerebellar ataxia, deafness, anosmia, ichthyosis, skeletal and cardiac symptoms, normal IQ
   2. May not be diagnosed until later in life because of very mild features
   3. May present with vomiting, diarrhea and malabsorption
   4. Labs—same biochemical abnormalities as seen in Zellweger syndrome

V. Rhizomelic Chondrodysplasia Punctata
A. Clinical presentation includes proximal limb shortening, abnormal facies, small stature, microcephaly, contractures, spasticity, cataracts, ichthyosis
B. Diagnosis: decreased plasmalogens, increased phytanic acid, decreased pristanic acid
C. Therapy: restrict phytanic acid (benefit in some)

VI. α-Methyl-acyl-CoA Racemase Deficiency
A. Clinical presentation includes diarrhea, liver disease, retinitis pigmentosa, polyneuropathy, epilepsy
B. Diagnosis: elevated bile acid intermediates, elevated pristanic acid
C. Therapy: substitution of bile acids

Recommended Reading

I. Progressive Familial Intrahepatic Cholestasis

A. Epidemiology and Pathogenesis

1. Progressive Familial Intrahepatic Cholestasis (PFIC) was initially described as a clinical diagnosis based on the presence of hepatocellular cholestasis, low serum levels of gamma-glutamyl transferase (GGT) activity and autosomal-recessive inheritance recognized in an Amish kindred of Jacob Byler (known as Byler's disease).

2. Subsequently, patients were clinically divided into two distinct subtypes: low GGT-PFIC (PFIC-1 and PFIC-2) and high GGT-PFIC (PFIC-3).

B. PFIC has now become five separate diseases with specific gene defects and distinct clinical profiles. The specific genes involved in all subtypes of PFIC code for various bile canalicular transporters involved in bile export. We now identify the diseases by their gene defect, i.e., PFIC-1 as FIC1 disease (Table 1).

C. Clinical Features

1. There are many clinical similarities between the PFIC diseases. They are characterized by:
   a. Chronic cholestasis in early childhood which usually progresses to cirrhosis within the first decade of life. The average age at onset is 3 months.
      1) Pruritus is the dominant feature of cholestasis in the majority of patients.
   b. Growth failure, with more than 95% of patients having short stature (<5%), though their weight for height is often normal, giving a stocky appearance.
   c. Recurrent epistaxis in the absence of thrombocytopenia or coagulopathy and perennial asthma-like disease are common problems.
   d. These patients do not have xanthomas.
   e. These patients have severe fat-soluble vitamin deficiency.
   f. All have near normal serum cholesterol but markedly elevated levels of serum bile acids. Serum concentrations of alkaline phosphatase, aminotransferases, bilirubin and bile salts are similar to that seen in seen in several other cholestatic disorders.
   g. Hepatocellular and canalicular cholestasis with pseudoacinar transformation are the most uniform histologic findings. Giant cell transformation and ballooned hepatocytes are present. Portal to central bridging then develops in association with lacy lobular fibrosis, and eventually leads to cirrhosis.

Table 1. Gene Defects

<table>
<thead>
<tr>
<th>GGT</th>
<th>Gene</th>
<th>Locus</th>
<th>Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal</td>
<td>ATP8B1/FIC1</td>
<td>18q21-22</td>
<td>ATP-dependent amino-phospholipid transport</td>
</tr>
<tr>
<td>normal</td>
<td>ABCB11/BSEP</td>
<td>2q24</td>
<td>ATP-dependent bile-acid transporter</td>
</tr>
<tr>
<td>high</td>
<td>ABCB4/MDR3</td>
<td>7q21</td>
<td>ATP-dependent translocation of phosphatidylcholine</td>
</tr>
</tbody>
</table>

Karan McBride Emerick, MD
D. **Differences Between the PFIC Diseases**
   1. The laboratory findings in PFIC 1 and 2 are remarkable for the presence of low GGT, whereas, in PFIC-3, the GGT levels are considerably elevated.
   2. Examination with electron microscopy shows subtle differences between PFIC-1 and PFIC-2. Samples from patients with PFIC-1 show the retention of coarsely granular bile, so called Byler’s bile, in canalicular spaces and canalicular cholestasis, whereas PFIC-2 patients have amorphous or finely filamentous bile and neonatal hepatitis.
   3. Patients with PFIC-1 are more likely to have associated watery diarrhea, some of which is very severe.

E. **PFIC-1: FIC1 Disease**
   1. The gene for PFIC-1 (Byler’s disease) is FIC-1 and codes for an ATP-binding cassette (ABC), which functions in flipping a phosphatidylcholine molecule from the inner plasma membrane to the outer.
      a. The FIC-1 gene is present in liver, pancreas, intestine and lungs. Therefore, mutations in this gene lead to multisystemic disease.
   2. FIC-1 disease is therefore associated with progressive liver disease as well as intractable diarrhea, recurrent pancreatitis and, in some cases, hearing loss. Clinically, FIC-1 disease appears to have a later onset and slower course than the other two forms of PFIC.

F. **PFIC-2: BSEP Disease**
   1. PFIC-2 is caused by a defect in a gene named FIC-2, located at 2q24. The FIC-2 gene is an ABC bile salt transporter also called the bile salt export pump (BSEP).
      a. Lack of staining for BSEP protein by immunohistochemistry in the liver tissue from patients with gene defects in FIC-2 suggests that in the majority of PFIC-2 patients the gene defect is severe enough to produce no product/protein that can be inserted into the canalicular membrane.
   2. BSEP disease has been associated with cholangiocarcinoma and hepatocellular carcinoma in young children.

G. **PFIC-3 Multidrug Resistance gene-3 Deficient (MDR-3[-]) Disease**
   1. Patients with high serum GGT and familial intrahepatic cholestasis fit the category of so-called high GGT PFIC. PFIC-3 is due to mutations in an export pump of the ABC transporter family called multidrug resistance 3 (MDR-3) that is expressed on the canalicular membrane.
      a. The MDR3 gene has been mapped to 7q21. It functions in the translocation of phosphatidylcholine across the canalicular membrane and therefore in the excretion of phospholipid into bile.
      b. The mechanism of damage in MDR3 disease is likely to be due to the absence of phospholipid in bile, which then destabilizes micelles and promotes lithogenic bile with crystallized cholesterol. This lithogenic bile could produce the picture of small bile duct obstruction.
   2. Liver biopsies show expanded portal areas with proliferation of interlobular bile ducts plugged with bile, suggesting an obstructive disorder rather than a primary defect in bile formation.
   3. These patients have aggressive disease that progresses toward hepatic failure in the first few years of life.

H. **Benign Recurrent Intrahepatic Cholestasis (BRIC)**
   1. The condition benign recurrent cholestasis presents very similarly to PFIC with cholestasis, pruritus, low GGT and high serum bile acids. However, the hallmark of this condition is intermittent episodes of cholestasis, without progression to liver failure and later onset than PFIC.
   2. Patients are totally asymptomatic, both clinically and biochemically in between the episodes of cholestasis.
   3. BRIC shares the same locus with PFIC-1 (ATP8B1 mutation) and 2 (ABCB11 [BSEP]) but the mutations cause only partially impaired protein synthesis.
   4. The cholestasis episodes have been treated by temporary biliary diversion using nasobiliary tube drainage of bile during the episode with some success in relieving the pruritus.
I. Management/Treatment
1. Without intervention, PFIC is a progressive disease which results in cirrhosis. The disease does not typically respond to medical therapy, although ursodeoxycholic acid (20–30 mg/kg/day), is recommended in all forms of PFIC to enhance bile flow
2. Supplemental fat-soluble vitamins treatment is required to prevent deficiencies
3. A surgical treatment, biliary diversion, in which bile salts are diverted from the enterohepatic recirculation, may relieve pruritus and slow the progression of the disease. The diversion may be performed in two ways
   a. The first is called an ileal diversion, in which the small intestine is divided above the terminal ileum and reconnected to the proximal intestine at the cecum, thereby bypassing the receptors for bile acid reabsorption
   b. The second is called a partial external biliary diversion (PEBD), in which gallbladder bile is diverted out of the body by way of a conduit, fashioned from small intestine, connecting the gallbladder to the skin
   c. The end result of both procedures is a diversion of bile salts, with liver disease that improves in the majority of patients
4. Liver transplantation is indicated in patients with decompensated cirrhosis or failed diversion with mutilating pruritus

II. Alagille Syndrome
A. Epidemiology/Pathogenesis
1. Alagille syndrome (AGS) or arteriohepatic dysplasia, is an autosomal-dominant disorder
2. The traditional clinical diagnosis of AGS follows the guidelines of bile duct paucity plus 3 of 5 clinical criteria including cholestasis, cardiac murmur or heart disease, skeletal anomalies, ocular findings and characteristic facial features
3. Anomalies of the vascular system and abnormalities of the kidney and pancreas are also present in a significant number of AGS patients
4. The incidence of AGS believed to be at least 1:70,000 live births
5. Mutations in the JAG1 gene, which encodes a ligand in the Notch signaling pathway, cause AGS. JAG1 and the Notch signaling pathway are crucial for the development of the liver, bile ducts, heart, vasculature, kidneys and other organs affected in this multisystem disorder
   a. JAG1 mutations can be identified in up to 94% of patients who meet clinical criteria for AGS, 60% of which are de novo. The majority of the mutations (72%) are protein-truncating
   b. No genotype-phenotype correlation has been identified in AGS. There is tremendously clinical variability in individuals carrying the same JAG1 mutations
6. NOTCH2 mutations have also been identified in a small group of JAG1-negative individuals
B. Clinical Features
1. Hepatic manifestations of AGS
   a. Neonatal cholestasis is the most common clinical presentation of AGS
      1) Liver biopsy may be nondiagnostic in the neonatal period, due to evolution of bile duct paucity over time
   b. The chronic cholestatic liver disease in AGS causes significant pruritus, malabsorption and xanthomas
   c. Cholesterol levels may rise to the thousands, with the appearance of skin xanthomas at levels >500 mg/dL
   d. The pruritus in AGS can be extremely severe, interrupting sleep and daily activities, and may require multiple medical interventions or may respond to biliary diversion
   e. A minority of AGS patients develops progressive liver disease leading to cirrhosis and portal hypertension.
      1) It is estimated that 20%–40% of AGS patients will eventually require liver transplantation
2. **Cardiac manifestations**  
   a. Cardiac murmurs occur in 85%–98% of affected individuals  
      1) The most common abnormality is stenosis at some level in the pulmonary arterial tree  
   b. Up to 24% of patients may have structural heart disease, such as tetralogy of Fallot or ventricular septal defects  
   c. Mortality is dramatically higher in the group with structural heart disease compared to those without, with a predicted 20-year survival of only 40%  

3. **Skeletal manifestations**  
   a. Vertebral arch defects, the typical finding of butterfly vertebrae, is one of the least common features  
   b. Other minor skeletal abnormalities identified in AGS patients include a decreased interpedicular distance in the lumbar spine, and shortened distal phalanges in the hands  
   c. Risk of recurrent and poorly healing bone fractures in AGS patients is a significant source of morbidity in this population, and may be an indication for liver transplantation in severe cases  

4. **Ocular manifestations**  
   a. The most common ocular features of AGS are deepset hyperteloric eyes and bilateral posterior embryotoxon  
   b. Posterior embryotoxon is thought to represent a prominent thickened or hypertrophied Schwalbe's line that is anteriorly displaced, visible through a clear cornea as a sharply defined, concentric white line or opacity anterior to the limbus  
      1) Found in 90%–95% of patients with AGS, it is also found in parents of patients with AGS and in the normal population at a frequency between 8%–15%  

5. **Facial features**  
   a. Characteristic facial features are a highly penetrant manifestation of Alagille syndrome, identified in 70%–98% of patients  
   b. During childhood, the facies are typically described as triangular, with a broad forehead, deeply set eyes, a pointed chin and a straight nose with a bulbous tip  
   c. In adulthood, the facial appearance becomes less triangular, and the chin becomes more angular and prominent  

6. **Renal involvement in AGS**  
   a. Renal anomalies occur in 40%–50% of AGS patients, and renal involvement is now considered one of the major criteria for the diagnosis  
   b. Structural abnormalities include solitary kidney, ectopic kidney, bifid renal pelvis and multicystic or dysplastic kidneys  
   c. Functional abnormalities include renal tubular acidosis, neonatal renal insufficiency, nephronophthisis, lipidosis of the glomeruli and tubulointerstitial nephropathy  

7. **Vascular involvement in AGS**  
   a. Vascular anomalies in AGS involve the aorta, renal arteries and cerebral vessels  
   b. Intracranial vessel aneurysms, internal carotid artery aneurysms and moyamoya disease occur in up to 9% of AGS patients studied  
      1) Intracranial bleeding is a major cause of morbidity and mortality in the AGS population, accounting for 25% of the overall mortality  

8. **Growth**  
   a. Growth failure is multifactorial in etiology, including a genetic contribution, chronic cholestasis, fat malabsorption, congenital heart disease and limited oral intake
C. Management/Treatment

1. Adequate nutrition is crucial: a high-calorie diet with a high proportion of fat from medium-chain triglycerides is recommended in the neonatal period.
2. Ursodeoxycholic acid (20 mg/kg/day), is recommended to enhance bile flow.
3. Supplemental fat-soluble vitamins treatment is required to prevent deficiencies.
4. Biliary diversion may relieve pruritus and slow the progression of the disease.
5. Liver transplantation is indicated in patients with decompensated cirrhosis or failed diversion with mutilating pruritus.

Recommended Reading


I. Reye’s syndrome is an extremely rare, acute syndrome resulting in hepatic dysfunction and encephalopathy. The incidence is decreasing.

A. Epidemiology/Pathogenesis
   1. Typically occurs in the fall and winter, concurrent with influenza season
   2. Affects children at peak ages of 5–15 years
   3. Symptoms develop several days after the onset of a viral infection (influenza A/B or varicella)
      a. There is a strong association between use of aspirin during these illnesses and development of Reye syndrome
   4. Postulated to be a secondary mitochondrial hepatopathy, due to injury from a virus or drug that results in an acquired abnormality of mitochondrial respiration
   5. The incidence of Reye syndrome has decreased dramatically following aggressive public education warning against salicylate use in children

B. Clinical Features
   1. Affected children appear to be recovering from a viral illness and then develop persistent vomiting along with irritability and listlessness
      a. Encephalopathy progresses with evidence of cerebral edema
         1) Direct involvement of CNS mitochondria may be responsible for encephalopathy
      b. Hepatic dysfunction is universal if vomiting is present
         1) Markedly elevated aminotransferases, serum ammonia, but normal bilirubin
         2) Variable hypoglycemia
         3) Mild to moderate prolonged prothrombin time
      c. Liver biopsy
         1) Microvesicular steatosis without concurrent hepatic inflammation or necrosis
         2) On electron microscopy: characteristic swelling and pleomorphism of mitochondria
      d. Liver makes full recovery despite progressive and sometimes fatal cerebral edema

C. Management
   1. High mortality rate due to risk of cerebral herniation
      a. Management aimed at controlling cerebral edema while maintaining cerebral perfusion pressure, in a manner similar to patients with acute liver failure
   2. High morbidity rate if disorder is unrecognized and appropriate management is not initiated promptly

II. Reye Syndrome vs Fatty Acid Oxidation Defects
   A. Some patients diagnosed with Reye syndrome actually have a fatty acid oxidation defect (FAO), a primary mitochondrial hepatopathy
      1. The most commonly diagnosed FAO defects associated with Reye syndrome are medium and long-chain acyl coenzyme A dehydrogenase deficiencies
      2. All children diagnosed with Reye syndrome should be evaluated for FAO defects. Clinical clues may include:
         a. Recurrent Reye, family history of Reye or SIDS, or age <2 years
         b. Viral prodrome and vomiting universal in Reye and less common in FAO defects
         c. Low carnitine levels in FAO defects, not in Reye
      3. Histologically may appear similar, but electron microscopy will be different
Recommended Reading


Drug-induced liver injury is rare in children. Of all drug-related deaths, only 1/6 are due to acute liver failure. Antiepileptic and antineoplastic drugs are the most likely drugs to cause liver injury.

I. Hepatic Drug Metabolism
   A. Phase I → Activation: creates unstable and reactive metabolite, generally polar
      1. Cytochrome P450 enzymes perform most of phase I reactions
      2. Cytochrome P450 are monoxygenases, inducible and have overlapping substrate specificity
      3. Cytochromes P450 in the 1A, 2B, 2C, 2D, 2E and 3A subfamilies are important in human drug metabolism
   B. Phase II → Detoxification: transforms a hydrophobic chemical to a hydrophilic one for excretion in urine or bile
      1. Phase II enzymes include sulfotransferases, glucuronosyltransferases, epoxide hydrolase, acetyltransferases and glutathione S-transferases
   C. Polymorphisms in above enzymes can make individuals rapid or poor metabolizers

II. Classification of Drug-induced Liver Injury into three Types
   A. Intrinsic hepatotoxins: true poison, causes predictable injury in all persons in dose-dependent fashion
   B. Contingent hepatoxins: causes hepatotoxicity in susceptible individuals under unfavorable conditions (genetic or acquired)
   C. Immunoallergic responses: this includes drug hypersensitivity reaction, hepatic granulomatosis, autoantibodies and chronic active hepatitis

III. Overview of Drug Hepatotoxicity/Epidemiology
   A. Drug induced liver disease is rare in children
      1. Accounts for ~10% of acute hepatitis
   B. Most drug-induced liver disease is cytotoxic and targets hepatocytes
      1. Zonal hepatocellular necrosis suggests that toxic metabolites are involved in the pathogenesis of the hepatotoxicity
         a. Hepatocytes in zone 3 of the Rappaport acinus have the highest concentration of cytochromes P450
   C. Classification of drug hepatotoxicity by duration (classical 1993 definition)
      1. Hyperacute <7 days
      2. Acute 8–28
      3. Subacute 4–12 weeks
      4. Chronic >12 weeks
   D. Drug hepatotoxicity by clinical features (3 clinical and 2 systemic syndromes)
      1. Hepatic → elevated AST/ALT, symptoms of hepatitis
      2. Cholestatic → elevated bilirubin/GGT, jaundice
      3. Mixed → hepatic and cholestatic symptoms
      4. Drug hypersensitivity syndrome → fever, lymphadenopathy, eosinophilia, atypical lymphocytosis, inflammation of organ systems (Stevens–Johnson syndrome, renal dysfunction)
      5. Chronic active hepatitis → subacute or chronic course with fatigue, anorexia, presence of nonspecific autoantibodies, elevated serum immunoglobulin G, and variable systemic changes (rash, arthralgias)
IV. Selected Drugs Associated With Liver Injury

A. Acetaminophen
1. Leading drug-related cause of acute liver failure
2. Doses > 350 mg/kg likely to develop severe liver toxicity
   a. Acute Ingestion → Minimum toxic dose 150 mg/kg or >12 g in 24 hours
   b. Chronic Ingestion → Minimum toxic 150–175 mg/kg over 2–4 days
3. Histopathology
   a. Hepatocellular necrosis in a zonal, centrilobular pattern with minimal inflammatory infiltrate
4. Clinical Course
   a. Stage 1 (<24 hours): nausea, vomiting, diaphoresis, pallor, lethargy followed by an asymptomatic interval
   b. Stage 2 (24–72 hours): jaundice, abnormal transaminases, coagulopathy
   c. Stage 3 (72–96 hours): peak LFT abnormalities, can progress to hepatic failure
   d. Stage 4 (4–14 days): recovery phase → resolution of symptoms and labs
5. Treatment
   a. N-acetylcysteine → acts by providing substrate to make more glutathione to minimize toxic intermediate of acetaminophen
      1) Most effective if given within 10 hours of ingestion
      2) Two regimens → 72-hour regimen of oral vs 20-hour intravenous
   b. Good prognosis if after 48 hours of treatment, PT and LFTs are all normal

B. Antiepileptic Drugs
1. Usually presents with hepatitis with a drug hypersensitivity reaction
   a. Primarily with phenobarbital, phenytoin, carbamazepine
2. Phenobarbital
   a. Can lead to fulminant hepatitis characterized by jaundice within 8 weeks of starting medication, generalized rash, fever and eosinophilia
3. Phenytoin
   a. Fever, rash, lymphadenopathy, eosinophilia, atypical lymphocytosis
   b. Histopathology → spotty necrosis of hepatocytes, cholestasis in severe cases, occasional granulomas
   c. Treat with corticosteroids in severe cases
4. Carbamazepine
   a. Hepatotoxicity is rare
      1) Children → hepatitis with drug hypersensitivity reaction
      2) Adults → can see ductopenia
5. Valproic Acid
   a. Two different types of hepatotoxicity
      1) Dose-responsive effect that resolves with stopping drug
      2) Progressive liver failure that starts with hepatitis-like prodrome
         a) Malaise, anorexia, nausea, vomiting
      3) Can lead to coagulopathy and hypoglycemia (sign of poor prognosis)
   b. Histopathology → hepatocellular necrosis, microvesicular fat

C. Anti-neoplastic Drugs
1. Commonly see asymptomatic elevation of aminotransferases with no other evidence of severe liver toxicity
   a. Drugs: 6-mercaptopurine, cis-platinum, cytosine arabinoside, dacarbazine, nitrosoureas
2. Veno-occlusive disease
   a. Acute onset of tender hepatomegaly, ascites, jaundice, elevated transaminases
   b. Drugs: 6-thioguanine, busulfan, cytosine arabinoside, dactinomycin, dacarbazine
3. L-asparaginase
   a. Associated with severe steatosis, fibrosis, hepatocellular necrosis
D. Immunosuppressant Drugs
   1. Azathioprine
      a. Histopathology → centrilobular hepatocyte ballooning, canalicular cholestasis, endothelial cell damage
   2. Methotrexate
      a. Histopathology → hepatic (periportal) fibrosis, macrovesicular steatosis

E. Antibiotics
   1. Tetracyclines (minocycline)
      a. Histopathology → features of chronic active hepatitis
         1) Chronic inflammatory cell infiltrate (plasma cells), interface hepatitis, bridging necrosis and fibrosis
      b. Clinical course can lead to hepatic failure without discontinuation of drug
         1) Can result in autoimmune hepatitis and may need treatment

V. Other Patterns of Injury
   A. Steatohepatitis
      1. Steatosis, lobular inflammation, fibrosis, hepatocellular ballooning
      2. Drugs: amiodarone, irinotecan
   B. Hepatic vein thrombosis
      1. Presents clinically as Budd-Chiari syndrome
      2. Drugs: oral contraceptives, dacarbazine
   C. Granulomatous hepatitis
      1. Present in portal tracts or parenchyma, lack of necrosis
      2. Drugs: isoniazid, penicillin, phenytoin, diazepam, carbamazepine
   D. Stellate cell lipidosis
      1. Hepatic stellate cells are modified fibroblasts that store lipids and vitamin A
      2. Drugs: retinoids (isotretinoin, etretinate) → due to hypervitaminosis A
   E. Ground glass cytoplasmic inclusions
      1. Ground glass change in cytoplasm (pale eosinophilic cytoplasmic inclusions) reflects hypertrophy of smooth endoplasmic reticulum
      2. Drugs: diazepam, insulin, steroids, tacrolimus, mycophenolate mofetil
   F. Lipofusion pigment deposits
      1. Lysosomal pigment in centrizonal hepatocytes
      2. Drugs: phenothiazine, phenacetin
   G. Drug-related neoplasms
      1. Oral contraceptives associated primarily with hepatic adenomas, but also with focal nodular hyperplasia and hepatocellular carcinoma
      2. Anabolic steroids associated with hepatic adenoma

Recommended Reading


60-3. Other Acquired Liver Diseases—Iron Storage Disorders

Nitika Arora Gupta, MD

I. There are many disorders that can lead to iron overload. The primary forms include hereditary hemochromatosis, neonatal hemochromatosis, aceruloplasminemia, atransferemia and heavy-chain ferritin disease. The secondary forms are primarily transfusion associated.

II. Hereditary Hemochromatosis
   A. Autosomal-recessive disorder of iron overload
      1. Occurs secondary to reduced synthesis or activity of hepcidin, which downregulates iron entry into the bloodstream
   B. Predominant mutation is in the HFE gene, which regulates hepcidin synthesis
      1. Identified mutations in HFE gene include: C282 Y mutation (a change from cysteine to tyrosine at position 282) and H63D (a change from histidine to aspartate at position 63)
   C. Majority of patients with classic hereditary hemochromatosis are homozygous for C282Y mutation, with 5% compound heterozygous (C282Y/H63D)
   D. Clinical Features/Presentation
      1. C282Y homozygosity present in 1 of 200–400 Caucasians of North European descent
      2. Rare in African Americans, Asians and Pacific Islanders
      3. Although increased iron absorption begins in childhood, clinical symptoms typically do not occur until adulthood
         a. Most pediatric patients are asymptomatic, but may be diagnosed based on clinical or family risk factors
      4. Common symptoms include: chronic liver disease (elevated liver tests, fibrosis, cirrhosis), skin pigmentation, arthritis, cardiac problems (heart failure, arrhythmias, cardiomyopathy), diabetes, gonadal dysfunction
         a. Classic presentation of bronze skin, diabetes and joint inflammation rarely seen because of early screening
         b. Most common presentation is fatigue, malaise, arthralgias and hepatomegaly
      5. Spectrum of the disease ranges from mild (genetic predisposition with a mildly elevated serum transferrin saturation) to iron overload without symptoms (2–5 gs of iron), overt iron overload (>5 gs of iron) with early symptoms of fatigue and joint pains and the severe form leading to organ damage
      6. Heterozygotes generally do not have clinically important iron overload
   E. Diagnosis and Screening
      1. In adults, serum transferrin saturation >45% in men and >42% in premenopausal women warrants further investigation
         a. Elevated serum ferritin indicates iron accumulation
         b. Consider genetic testing
      2. Although asymptomatic, many affected children will have an elevated transferrin saturation, but normal ferritin
      3. Indications for liver biopsy include elevated liver tests, hepatomegaly or serum ferritin >1,000, which allows for evaluation of fibrosis and other concurrent diseases
         a. Liver biopsy will show increased Prussian blue staining and total hepatic iron index (calculated by iron concentration (in μmol/grams of liver) ÷ age (in years))
      4. MRI of the abdomen can be used to quantify hepatic iron stores
      5. Other disorders associated with iron overload should be excluded, such as alcoholic and nonalcoholic liver disease, cystic fibrosis, porphyria cutanea tarda and chronic viral hepatitis
F. **Treatment:** Goal is to reduce total body iron stores and prevent reaccumulation
   1. Iron depletion: weekly phlebotomy of roughly 1 unit of blood over 1–2 years, until ferritin <50 and transferrin saturation is <30%
   2. Maintenance therapy: phlebotomy 2–4 times per year to maintain ferritin between 50–100.
   3. In symptomatic children: weekly phlebotomy of 5–8 cc/kg until ferritin <300, then 2–4 times per year

G. **Management of Children With an Affected Parent**
   1. Genotype affected parent and spouse
   2. If both have at least one mutation, then genotype children
   3. If child has positive genotype: annual fasting transferrin saturation and serum ferritin
   4. Initiate phlebotomy when abnormal

III. Neonatal Hemochromatosis

A. **Introduction**
   1. The most common identified cause of acute liver failure in the neonate
   2. Associated with hepatic and extrahepatic deposition of iron (such as in the thyroid, pancreas, heart and salivary glands) without involvement of the reticuloendothelial system
   3. Proposed theories of pathogenesis are: 1) Fetal alloimmune disorder; 2) Primary disorder of fetoplacental iron handling
   4. Unrelated to hereditary or juvenile hemochromatosis
   5. Extremely rare in first pregnancies, but late fetal loss in sibships is common

B. **Clinical Presentation**
   1. Liver failure within hours of life, with hypoglycemia, coagulopathy and edema
   2. Illness develops in utero, with resultant intrauterine growth retardation, oligohydramnios, placental edema or stillbirth

C. **Diagnosis**
   1. Laboratory studies:
      a. Serum aminotransferases disproportionately low considering degree of hepatic dysfunction.
      b. Hypersaturation of transferrin, with hypotransferrinemia.
      c. Hyperferritinemia (>800 n/mL)
      d. Elevated alphofetaprotein (100,000–600,000 ng/mL)
   2. Magnetic resonance imaging of the abdomen for evidence of extrahepatic deposition of iron in the pancreas and myocardium.
   3. Buccal biopsy of the lip to show deposition of iron in the minor salivary glands is diagnostic
   4. Liver biopsy is neither required nor advisable for diagnosis because of severe coagulopathy. If performed, it shows evidence of giant cell transformation, siderosis, bile ductular proliferation and fibrosis, nodular regeneration, cirrhosis and massive loss of hepatocytes

D. **Management**
   1. Consider transfer to liver transplant center
   2. Supportive regimen for acute liver failure
   3. Antioxidant cocktail is commonly used, but controversial and consists of N-acetyl cysteine, selenium, prostaglandin E and alpha tocopherol
   4. Exchange transfusion or IVIG may be beneficial
   5. Liver transplantation should be considered
Recommended Reading


Non-alcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in childhood and adolescence.

I. Overview/Epidemiology
   A. NAFLD encompasses a spectrum of liver pathology:
      1. Isolated steatosis or macrovesicular fat accumulation within hepatocytes, without inflammation
      2. Non-alcoholic steatohepatitis (NASH), fat accumulation associated with inflammation and/or evidence of cellular injury
      3. Cirrhosis
   B. Natural history and progression of disease in children remains undetermined
   C. NAFLD in children and adults predisposes to Type 2 diabetes, hypertension and dyslipidemia
   D. True prevalence of NAFLD is difficult to assess, as liver biopsy needed for definitive diagnosis, although an autopsy study demonstrated a 9.6% overall prevalence of NAFLD in children ages 2–19.
   E. Factors associated with increased risk of NAFLD:
      1. Obesity
      2. Male sex
      3. Older age
      4. Hispanic ethnicity
      5. Asian race (especially those of Chinese or Filipino descent)
   F. ~10% of NAFLD patients are of healthy weight

II. Pathogenesis
   A. Pathophysiology of NAFLD thought to be multifactorial
   B. Hyperinsulinemia and hepatic insulin resistance important in development of fatty liver
   C. Two-hit hypothesis is a commonly agreed-upon theory of pathophysiology:
      1. 1st hit: insulin resistance → leads to hepatic steatosis
      2. 2nd hit: oxidative injury required for progression to necroinflammatory steatohepatitis
   D. Obesity, especially increased visceral adiposity, is correlated with dyslipidemia and increased insulin resistance.
      1. Visceral adiposity with increased risk of steatosis given presence of increased free fatty acids (FFA) in combination with anatomical ease of transport of FFAs directly to portal vein for conversion to triglycerides (TG) in liver
      2. Presence of obesity in NAFLD patients increases risk of development of fibrosis three-fold as opposed to nonobese NAFLD patients
      3. Adolescent males more likely to develop NAFLD secondary to greater degree of insulin resistance in adolescents compared to children and adults; estrogen may be protective against progression of steatosis to NASH
   E. Insulin resistance a key pathophysiological component in NAFLD
      1. Enhances peripheral lipolysis, increases TG synthesis and increases hepatic uptake of fatty acids leading to an overall increase in hepatic FFA accumulation
      2. Associated with decreased beta oxidation of FFAs, impairment of apolipoprotein B and decreased TG secretion → net excess of hepatic TG storage
   F. Steatosis: increased quantities of FFA contribute to a cycle of deteriorating function and hepatotoxicity by downregulating beta-oxidation and activating proinflammatory pathways
G. Oxidative injury (second hit) sources:
   1. Hepatic iron (reactive oxygen species (ROS) produced in reduction of Fe$^{3+}$ → Fe$^{2+}$)
   2. Antioxidant deficiency
   3. Hypoxia
   4. Intestinal bacteria

H. Increased amounts of ROS → lipid peroxidation, inflammation, hepatocellular apoptosis and fibrosis
   1. ROS induces expression of proinflammatory cytokines: TGF-β, TNF-α, Fas ligands

III. Diagnosis
   A. Average age of presentation: 10–14 years
   B. Clinically, most children asymptomatic, though some may complain of vague abdominal pain in the RUQ
      1. Acanthosis nigricans found in >50% of patients with NAFLD
   C. Initial screening labs: CBC, AST/ALT, GGT, lipids and fasting glucose, insulin
      1. Lab findings that may indicate NAFLD: elevated serum aminotransferases with ALT > AST, elevated GGT and alkaline phosphatase, low HDL and elevated fasting triglycerides
   D. Family history important in terms of viral hepatitis, autoimmune diseases, which may be risk factors
   E. Imaging: hepatic ultrasound and MRI
      1. Ultrasound is readily available and inexpensive, but this is balanced by a lack of sensitivity to milder degrees of steatosis, operator dependence, and inability to adequately quantify the degree of steatosis, fibrosis or inflammation
      2. MRI is more sensitive, but concurrently more expensive
   F. Liver biopsy and histological examination of the liver required for definitive diagnosis
      1. For diagnosis, at least 5% of hepatocytes must contain macrovesicular fat
      2. Two distinct histological subtypes of NASH found in children:
         a. Type 1 NASH: steatosis with ballooning degeneration of hepatocytes and perisinusoidal fibrosis
         b. Type 2 NASH: steatosis with portal inflammation and/or portal fibrosis without evidence of ballooning degeneration
      3. Type 1 NASH is consistent with the typical adult pattern
      4. Type 2 NASH unique to children
      5. Children with type 2 NASH generally younger and more severely obese than those with type 1 NASH
         a. Males and Asian or Native Americans more likely to have type 2 NASH
         b. Type 2 NASH more often associated with severe (bridging) fibrosis

IV. Differential Diagnosis
   A. Infections: hepatitis B and hepatitis C
   B. Autoimmune disease: autoimmune hepatitis, insulin-dependent diabetes mellitus
   C. Wilson’s disease
   D. Alpha-1-antitrypsin deficiency
   E. Drug-induced liver injury: prednisone, amiodarone, tetracycline, valproate, methotrexate
   F. Chronic use of total parenteral nutrition (TPN)
   G. Nutritional deficiencies: refeeding syndrome, rapid weight loss, starvation
   H. Following bypass surgeries

V. Treatment/Management
   A. Weight loss through lifestyle modification
      1. Nutritional goals:
         a. Eliminated foods high in saturated fats, trans fats and simple sugars
         2. Increased aerobic exercise
         3. Decreasing sedentary behaviors
   B. Amount of weight loss required to induce a significant change in NAFLD unknown
   C. Pharmacological treatments still undergoing trials, no definitive evidence to support their use
      1. Metformin has been utilized in trials to increase insulin sensitivity and decrease hepatic glucose production.
      2. Vitamin E trial recently completed, with goal of slowing progression of simple steatosis to NASH
Recommended Reading


60-5. Acute Graft vs Host Disease and Veno-occlusive Disease

Preeti Viswanathan, MD
Debora Kogan-Liberman, MD

I. Veno-occlusive Disease

A. Clinical syndrome characterized by jaundice, painful hepatomegaly and fluid retention

B. Among the spectrum of organ injury syndromes that occurs after high-dose chemotherapy (alkylating agents) used for hematopoietic stem cell transplant (HSCT)
   1. Typically occurs by day 35 post-HSCT, although can occur later

C. May also occur with other toxins including alcohol, radiation, terbinafine, oral contraceptives, azathioprine, herbal teas made with pyrrolozidine alkaloids and solid organ transplantation, including liver and kidney

D. Pathogenesis
   1. Initial injury occurs to sinusoidal endothelial cells
   2. Hepatic Zone 3 involved, where there is both a high concentration of cytochrome P450 and glutathione S transferase
      a. Cytochrome P450 enzymes metabolize chemotherapeutic agents, e.g., cyclophosphamide
      b. Glutathione is needed to detoxify metabolites. Depletion of glutathione may play a role in sinusoidal injury and leads to hepatic necrosis
   3. Dilation of sinusoids and ongoing hepatic necrosis lead to collagen deposition in the sinusoids and venules, sclerosis of venular walls and fibrosis of venular lumens
   4. Activated stellate cells secrete plasminogen activator inhibitor type 1 and other vasoactive mediators
   5. The coagulation cascade is activated by endothelial injury, with resultant low antithrombin, and protein C and consumption of Factor VII and platelets

E. Histology
   1. Injury to hepatic venules is first histological change
   2. Subendothelial edema, red cell extravasations and fibrin deposition also occur

F. Risk factors
   1. Pretransplant factors include: female gender, prior radiation, preexisting liver disease, elevated transaminases, exposure to amphotericin B, vancomycin, acyclovir
   2. Post-transplantation factors include: high-dose conditioning regimens, allogenic transplantation, HLA mismatch, use of Busulfan for conditioning, use of cyclophosphamide, GVHD prophylaxis

G. Diagnosis
   1. Mainly clinical
   2. Criteria for diagnosis include the development, prior to day 30, of jaundice, hepatomegaly with right upper quadrant pain, ascites or unexplained weight gain
   3. CT and ultrasound with Doppler may be useful in excluding Budd-Chiari and constrictive pericarditis
   4. Transvenous liver biopsy (percutaneous is contraindicated due to risk of bleeding) and measurement of hepatic venous pressure gradient (HVPG) remain gold standard of pathologic diagnosis. HVPG represents the gradient between pressures in the portal vein and the intraabdominal portion of inferior vena cava. A gradient of >10 mmHg has 91% specificity for VOD
H. Prognostic factors
   1. Rates of bilirubin rise and weight gain are significantly higher in those with severe disease
   2. Hepatic venous pressure gradient >20 mmHg—poor prognosis
   3. Multiorgan failure is a key indicator of poor prognosis—these patients die of renal or cardiac failure rather than hepatic insufficiency.
I. Treatment
   1. Defibrotide: an adenosine receptor agonist. It has local antithrombotic effect, without systemic anticoagulant properties. Appears to modulate endothelial cell injury without enhancing systemic bleeding, and protects sinusoidal epithelium without compromising the antitumor effects of cytotoxic therapy
   2. TIPS—likely not of long-term benefit and not shown to change the course of VOD
   3. Transplant—limited by patient’s clinical status, especially presence of multiorgan failure, and finding suitable liver graft

II. Graft vs Host Disease
   A. Incidence of graft vs host disease (GVHD) is directly related to HLA disparity
   B. Generally, there are three requirements for development of GVHD
      1. Graft must contain immunologically competent cells (T cells)
      2. Recipient must express antigens that are not present in the donor
      3. Recipient must be incapable of mounting an effective response to eliminate the transplanted cells
   C. Allogenic HSCT is the most common setting for the development of GVHD, in which recipients receive immunoablative chemotherapy or radiation before hematopoietic stem cell infusion containing T cells. However, it can occur with transfer of any tissue containing T cells (blood products, solid organs)
   D. Two types: acute and chronic. Previously classified based on timeframe of occurrence (before and after 100 days from transplantation), now classified based on constellation of symptoms, including an overlap syndrome where features of acute and chronic GVHD may be present

III. Acute GVHD
   A. Exaggerated response of normal inflammatory mechanisms that involves donor T cells and multiple innate and adaptive cells and mediators
   B. Clinical features:
      1. The three main organs involved in acute GVHD are the skin, liver and GI tract
      2. The extent of involvement of the three principal target organs determines the overall severity of acute GVHD. The overall grades are defined as I (mild), II (moderate) and III (severe)
      3. Skin is generally the first and most commonly affected organ, generally coinciding with donor cell engraftment
         a. Characterized by an erythematous, maculopapular rash that is often pruritic, with blisters and ulcerations in severe cases
      4. Liver GVHD initially presents with jaundice or an increase in alkaline phosphatase
         a. May be difficult to distinguish from other causes of jaundice posttransplant (drug toxicity, VOD, infections, parenteral nutrition–associated cholestasis), and a biopsy is often required
         b. Histology demonstrates endothelialitis, lymphocytic infiltration of the portal areas, pericholangitis and bile duct destruction
      5. GI tract involvement may present with nausea, vomiting, anorexia, abdominal pain or diarrhea
         a. Gastric involvement causes postprandial vomiting that is not always preceded by nausea
         b. The diarrhea of GVHD is secretory
         c. Mucosal ulcerations may cause GI bleeding and is a predictor of poor outcome
         d. Histological features include patchy ulcerations, apoptotic bodies, crypt abscesses and loss and flattening of epithelial surface
Table 1. Acute GVHD Grading Criteria

<table>
<thead>
<tr>
<th>Stage</th>
<th>Skin</th>
<th>Liver (Bilirubin)</th>
<th>GI Tract (Stool Output/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No GVHD rash</td>
<td>&lt;2 mg/dL</td>
<td>Adult: &lt;500 mL/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Child: &lt;10 mL kg/d</td>
</tr>
<tr>
<td>1</td>
<td>Maculopapular rash 25% BSA</td>
<td>2-3 mg/dL</td>
<td>Adult: 500-999 mL/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Child: 10-19.9 mL/kg/d or persistent</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nausea, vomiting, or anorexia, with a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>postive upper GI biopsy</td>
</tr>
<tr>
<td>2</td>
<td>Maculopapular rash 25%-50% BSA</td>
<td>3.1-6 mg/dL</td>
<td>Adult: 1000-1500 mL/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Child: 20-30 mL/kg/d</td>
</tr>
<tr>
<td>3</td>
<td>Maculopapular rash &gt;50% BSA</td>
<td>6.1-15 mg/dL</td>
<td>Adult: &gt;1500 mL/d</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Child: &gt;30 mL/kg/d</td>
</tr>
<tr>
<td>4</td>
<td>Generalized erythroderma with bullous</td>
<td>&gt;15 mg/dL</td>
<td>Severe abdominal pain with or</td>
</tr>
<tr>
<td></td>
<td>formation</td>
<td></td>
<td>without ileus</td>
</tr>
</tbody>
</table>


IV. Chronic GVHD
A. Major cause of late non-relapse death following allogenic HSCT  
B. It is associated with decreased quality of life and impaired physical and functional status  
C. Can occur between 6–18 months after transplant with median time at diagnosis of 4.5 months  
D. It is a complex multisystem disorder that involves many organ systems, characterized by immune dysregulation, immunodeficiency, impaired organ function and decreased survival  
E. The clinical manifestations are similar to autoimmune diseases, suggesting a similar pathophysiology  
1. Mainly involves skin, eyes, oral cavity, GI tract, liver and lungs, but unlike acute GVHD, can involve any other organs  
2. Clinical manifestations may be inflammatory (rash, mucositis, diarrhea) or fibrotic and sclerotic (lichen planus, bronchiolitis obliterans, sick syndrome, esophageal strictures)  
3. Increased levels of nonspecific auto (vs allo) antibodies have been described, including ANA, antiSMA, antineutrophil antibody, antiplatelet antibody  
F. One of the most important risk factors is severity of previous acute GVHD

V. Treatment
A. Prevention is an important component  
B. Most widely used acute GVHD prophylaxis is a combination of calcineurin inhibitor and methotrexate  
1. Calcineurin inhibitors impede the function of cytoplasmic enzyme calcineurin, which is critical to the activation of T cells  
2. The most important predictor of long-term survival in patients with acute GVHD is the primary response to the first line of treatment  
3. Mild skin GVHD can be treated with topical corticosteroids, more severe skin or visceral GVHD requires systemic corticosteroids, typically starting at 1–2 mg/kg/day. Gradual dose reduction is attempted after 7 days or more of high-dose corticosteroids  
4. Nonabsorbable corticosteroids like oral budesonide are also commonly used for GI GVHD  
C. Steroid-refractory GVHD is defined as disease progression or lack of response following 3–7 days of systemic therapy with corticosteroids and a calcineurin inhibitor  
D. No effective prophylaxis regimen exists for chronic GVHD  
E. Definitive treatment of chronic GVHD in pediatrics is highly variable. The general approach is high-dose corticosteroid plus calcineurin inhibitor, with gradual steroid taper to lowest allowable dose to prevent GVHD flare  
1. The mean duration of therapy for chronic GVHD is 3 years  
2. Approximately 90% of patients who ultimately respond do so within 3 months.  
F. Extracorporeal photopheresis is increasingly used in the management of acute and chronic GVHD to minimize steroid exposure. Response rate varies from 52%–83%
VI. VOD vs GVHD

A. May be difficult to distinguish between the two entities, as well as other cause of jaundice posttransplant
   1. Absence of fluid retention and weight helps distinguish VOD from GVHD
   2. Hyperacute GVHD can be confused with VOD
      a. As GVHD progresses, alkaline phosphatase levels increase (unusual in VOD)
      b. When ascites, pleural effusions, renal failure and sepsis are present, VOD is by far the most common cause
      c. The histological hallmark of GVHD-induced cellular injury is apoptosis with lymphoid infiltration. In VOD, inflammatory cells are absent and hepatocyte necrosis is seen.

Recommended Reading


I. The liver is often involved in systemic disease as an innocent bystander. Elevated transaminases may be the first sign of systemic disease. Rheumatologic diseases in particular have systemic involvement, with 43% of patients demonstrating transient liver transaminase abnormalities. In a small percentage, these abnormalities are persistent and most often represent coexisting primary liver disease (i.e., autoimmune hepatitis, NAFLD, viral hepatitis or primary biliary cirrhosis) or medication-related liver toxicity.

II. Cardiac Diseases
A. Constrictive Pericarditis, Pulmonary atresia, Tetralogy of Fallot, and s/p Fontan for single ventricle heart diseases.
   1. Liver abnormality: hepatic congestion
   2. Pathophysiology: increased right atrial and ventricular pressures cause sinusoidal engorgement, which leads to modest elevations in transaminases. May sometimes see unconjugated hyperbilirubinemia. Alkaline phosphatase is usually normal
   3. Histopathology:
      - Gross appearance- 'nutmeg liver - red central area (due to sinusoidal congestion and bleeding into atrophic regions surrounding enlarged hepatic veins) intermixed with a yellow area of either normal or fatty liver.
      - Microscopic appearance- sinusoidal dilation around the central vein, engorged with erythrocytes, no inflammation.
      - Congestive hepatopathy. Liver tissue showing sinusoidal dilatation and congestion in the perivenular zone.


4. Clinical Features
   a. Early tender hepatomegaly
   b. Late hypoalbuminemia with PLE, ascites, cirrhosis and portal hypertension
   c. Diagnosis: If constrictive pericarditis, cardiac catherization may be necessary

5. Differential for hepatic congestion: Budd-Chiari syndrome, veno-occlusive disease, tuberculous pericarditis

6. Management: diuretics, treatment of underlying heart disease
III. Autoimmune/Connective Tissue Diseases
   A. Systemic Lupus Erythematosus (SLE) SLE is a multisystem immune-mediated disease. Liver involvement can be difficult to differentiate from autoimmune hepatitis.
      1. Liver abnormality: variable fatty liver, chronic active hepatitis, liver failure, Budd-Chiari syndrome, nodular regenerative hyperplasia (NRH), hepatic infarction
      2. Pathophysiology:
         a. Fatty liver likely related to corticosteroid therapy
         b. Budd Chiari syndrome – antiphospholipid antibodies lead to hepatic venous thromboembolism causing obstruction, portal hypertension, cirrhosis and subsequent ascites
         c. Nodular Regenerative Hyperplasia (NRH) – antiphospholipid antibodies lead to focal ischemia induced liver injury, and subsequent liver regeneration to maintain liver functional capacity. Majority with NRH are asymptomatic, but NRH may lead to noncirrhotic portal hypertension with ascites and variceal bleeding
      3. Histopathology: variable
         a. Hepatic steatosis: micro- and macrovesicular fat in hepatocytes
         b. Chronic active hepatitis/lupus hepatitis, nonspecific lymphocytic infiltration of periportal areas

Figure 2.
Liver biopsy in a SLE patient showing active interface hepatitis with prominent plasmacytic infiltrates. This is consistent with lupus hepatitis (H&E 200X)


4. Clinical features of SLE are variable, but typically involve skin, joints, kidneys, cardiovascular, CNS and hematologic systems. Other organs, including the liver, may be involved
5. Clinical hepatic features: elevated transaminases, cholestasis, pruritis, ascites, non-specific increased immunoglobulin subclasses, acute liver failure (rare)
   a. Liver laboratory tests are abnormal at some point in disease course in up to 50% of patients
   b. Hepatomegaly is found in up to 2/3 of patients
   c. Few patients have primary liver disease; however, a Japanese registry did demonstrate chronic hepatitis in 2.4%, cirrhosis 1.1%, and liver fibrosis in 1%.
6. Liver disease is also seen in 10% of neonatal SLE with three patterns
   a. Liver failure at birth or in utero
   b. Transient hyperbilirubinemia
   c. Transient elevate aminotransferases
7. Diagnosis: see American College of Rheumatology diagnostic criteria
   a. Lupus-related liver disease may resemble AIH. ANA may be seen in both, but antismooth muscle and antimitochondrial antibodies (AMA) are rare in SLE. Antiribosomal P protein antibodies are present in SLE
   b. Liver biopsy not very useful in diagnosis due to wide range of nonspecific findings. Biopsy may provide useful prognostic information, e.g., extensive necrosis or fibrosis portends poor prognosis
c. SLE is the attributable cause of approximately 20% of liver abnormalities
d. Liver biopsy with mild lobular inflammation without piecemeal necrosis
e. Degree of liver enzyme elevation correlates with disease activity and improves with steroid treatment

8. Management: treat the underlying SLE with NSAIDs, steroids, azathioprine
   Liver disease in SLE may be associated with inflammation in other organs — fibrosing alveolitis, pericarditis, autoimmune gut disease

B. Juvenile Rheumatoid Arthritis (JRA)
   JRA is an autoimmune disorder characterized by particular joint inflammation. Extraarticular involvement can include the lungs, heart, liver and blood.
   1. Liver involvement is variable with abnormal liver tests reported in 5%–77% of patients
      a. Elevated alkaline phosphatase and gamma glutamyl transferase (GGT) is the most common liver finding
      b. Levels are a reflection of disease activity and correlate with elevated ESR
   2. Liver involvement may also be due to therapy
      a. Salicylates are currently used less often, but can be hepatotoxic
      b. Methotrexate may cause elevated transaminases, and less frequently, hepatic fibrosis
   3. Liver biopsy demonstrates a nonspecific periportal collection of inflammatory cells and Kupffer cell hyperplasia.
   4. Felty's syndrome (long-standing JRA with splenomegaly and leukopenia) is associated with hepatomegaly and elevated transaminases. The liver injury is due to obliteration of portal venules resulting in portal hypertension

C. Sjogren's—autoimmune disorder mainly affecting salivary and lacrimal glands
   1. Liver abnormality: chronic nonsuppurative cholangitis
   2. Histopathology: inflammation and/or abnormal connective tissue confined to the portal areas
   3. Clinical features:
      a. Keratoconjunctivitis, xerostomia, salivary gland inflammation and often Raynaud's phenomenon, achlorhydria, alopecia and splenomegaly
      b. In children, Sjogren's syndrome typically accompanies another connective tissue disease
      c. In children with JRA and Sjogren's syndrome, 40% will have subclinical liver disease
      d. Children with antimitochondrial antibodies may develop liver injury that resembles primary biliary cirrhosis
      e. Elevated alkaline phosphatase, AST and ALT
      f. Positive antimitochondrial antibody (AMA) titers are also seen and are associated with histopathologic abnormalities similar to those seen in stage I PBC
      g. Liver histopathology is present even when transaminases are normal
   4. Diagnosis: AMA is a sensitive indicator of underlying liver pathology
   5. Management: geared toward treatment of the other disease manifestations

D. Ankylosing Spondylitis (AS)
   Ankylosing spondylitis is an inflammatory arthropathy of the sacroiliac joints and the spine.
   1. Clinical presentation involves back pain and worsening spinal stiffness
   2. Laboratory findings may include elevated alkaline phosphatase
      a. Gel electrophoresis can be used to identify liver or bone etiology
      b. 5-nucleotidase (5-NT) and GGT typically increase in parallel if liver is source
      c. Increases correlate with elevation in ESR and respond to disease treatment
IV. Granulomatous Diseases

A. The liver is a common associated site for various granulomatous diseases. Granulomas are a discrete aggregate of specialized immune cells which fuse to form large epithelioid multinucleated giant cells which are surrounded by fibroblasts and lymphocytes (see section on Granulomatous Liver Disease).

Figure 3. A large hyalinized granuloma in a well-established case of sarcoidosis (hematoxylin-eosin, original magnification x 4). Note the lack of cellular debris in the areas of hyalinization (inset; hematoxylin-eosin, original magnification x 40). This lack of cellular debris is one of the useful features in differentiating hyalinization (pseudonecrosis) from true necrosis. (B) A truly necrotic granuloma in a patient who had positive acid-fast bacilli (AFB) staining (hematoxylin-eosin, original magnification x 10). Note the ample cellular debris in the necrotic region. Adapted from Lagana SM, Moreira RK, Lefkowitch JH. Hepatic Granulomas: Pathogenesis and Differential Diagnosis. Clin Liver Dis. 2010;14:605-617.

B. Sarcoidosis
   1. Systemic granulomatous disease, unknown etiology.
      a. Liver abnormality: non-caseating epithelioid granulomas (see section on Granulomatous Liver Disease)

C. Chronic Granulomatous Disease
   1. Primary immunodeficiency, incidence 1/200,000, X-linked recessive, occasionally autosomal-recessive.
   2. Liver abnormality: liver abscesses; ascites (see section on Immunodeficiency States)

V. Endocrine Diseases

A. Type I polyglandular autoimmune syndrome (Hypoparathyroidism, adrenal insufficiency, mucocutaneous candidiasis)/APECED (autoimmune polyendocrinopathy- candidiasis-ectodermal dysplasia).
B. Liver abnormality: chronic active hepatitis (15%–18%) (see section on Autoimmune Enteropathy)
VI. Renal Diseases
   A. Infantile Polycystic Disease
   B. Liver abnormality: congenital hepatic fibrosis (see section on Congenital Hepatic Fibrosis)

![Image]

Figure 4. Congenital hepatic fibrosis and ARPKD in a newborn girl. The bile ducts (arrows) are concentrated at the edge of the portal triad. Normally, bile ducts are found in the center of portal triads. In congenital hepatic fibrosis, bile ducts are tortuous, dilated with irregular contours and are in the periphery of portal triads (PV portal vein; H&E, original magnification×200). Adapted from Veigel MC, Prescott-Focht J, Rodriguez MG, Zinati R, Shao L, Moore CAW, Lowe LH. Fibropolycystic liver disease in children. Pediatr Radiol. 2009;39:317-327.

VII. Hematologic Diseases
   A. Hemophagocytic Lymphohistiocytosis (HLH)
      1. Liver abnormality: acute liver failure
      2. Etiologies: sporadic, viral (EBV, parvo, B19, echovirus), familial (autosomal-recessive, occasionally X-linked)
      3. Pathophysiology:
         a. Macrophages (including Kupffer cells) become excessively activated and phagocytose neighboring cells (e.g., RBCs and WBCs) secrete inflammatory cytokines
         b. Patients have NK cell function defect that results in overexpression of proinflammatory cytokines; 80% with primary immune defect
         c. Familial forms are heterogeneous, but all demonstrate mutations in intracellular killing (i.e. granzyme)
   B. Histopathology: Erythrophagocytosis in liver or bone marrow; in familial HLH atypical lymphocytes or histiocytes are seen in CSF.
   C. Clinical Features:
      1. Fever, cytopenia, lymphadenopathy, and liver dysfunction including hepatosplenomegaly, ascites, jaundice, fulminant hepatic failure with coagulopathy; mortality 75%
      2. Clinical features may also involve skin infiltrates, respiratory failure and CNS involvement
   D. Diagnosis
      1. Laboratory finding include hypofibrogenemia, hyperferitinemia, elevated triglycerides and serum lactate dehydrogenase in addition to cytopenia
      2. Liver or bone marrow biopsy showing erythrophagocytosis
   E. Management:
      1. Supportive care for liver failure
      2. Cytotoxic therapy with etoposide
      3. Methylprednisolone and methotrexate (yields remission in 1/3)
      4. Allogeneic BMT or SCT in high-risk populations (age <2 years or familial pattern)

VIII. Oncologic Diseases
   A. Post-HSCT (Hematopoietic stem cell transplant)
   B. Graft versus Host Disease (GVHD)
      1. Systemic immunologically mediated reaction of immune competent donor cells against the recipient's HLA. Involves skin, gut, lung, eye, pancreas and liver (40% of cases).
         Acute: 100 days or less s/p HSCT. Chronic: >100 days s/p HSCT.
      2. Liver abnormality: small bile duct damage (see section on GVHD vs VOD)
C. Veno-occlusive Disease (VOD) or Sinusoidal Obstructive Syndrome (SOS)
   3. Liver abnormality: hepatic congestion, portal hypertension (see section on GVHD vs VOD)
D. Hepatobiliary infections (see section on Viral Hepatitis and Bacterial and Parasitic Infections)

IX. Multisystemic disorders
   A. Sepsis
      1. Liver abnormality: liver failure
      2. Histopathology: hyperplasia in the reticuloendothelial system; fatty change
      3. Clinical features:
         a. Early: jaundice, hepatomegaly, nonspecific elevation in transaminases
         b. Late: coagulopathy due to liver failure or DIC
      4. Diagnosis: ultrasound to identify abscess, fluid collections or an obstructed biliary tree
due to sludge. Most common ultrasound finding is an echo-bright liver
      5. Management: treat sepsis; supportive care for the liver failure

   B. Hypoxia/ischemia
      1. Liver abnormality: diffuse hepatic injury
      2. Pathophysiology: occurs after interruption of hepatic blood supply due to hypotensive
episode, coronary bypass surgery if bypass time >2 hours, sickle cell hepatic sequestration
   crisis, hepatic artery or portal vein thrombosis.
      3. Histopathology:
         a. Hepatocyte necrosis and a variable degree of architectural collapse in zone 3
            (around the central vein, i.e., furthest from arterial blood supply)
         b. If severe and prolonged ischemia, necrosis may extend to mid-zonal
            hepatocytes
      4. Clinical features: transaminases rise 24–48 hours post-op. Range may be >10,000.
         Transaminases return to normal within 1–2 weeks. LDH also significantly elevated.
         Bilirubin rises after aminotransferases begin to decline. Normal to slightly impaired liver
         synthetic function
      5. Diagnosis: clinical presentation consistent with hypoxia/ischemia
      6. Management: correction of circulatory disturbance

X. Kawasaki syndrome
   A. Kawasaki syndrome is an autoimmune vasculitis typically affecting heart, skin, lymph nodes and
   mucus membranes.
      1. Gallbladder hydrops and hepatobiliary dysfunction have been reported
      2. Hepatomegaly is seen in 14% and liver laboratory studies are abnormal in 30%
      3. Liver pathology demonstrates portal inflammation, vasculitis, sinusoidal infiltrates,
         Kupffer cell hyperplasia and congestive changes presumed to be from cardiac disease

Recommended Reading


Pediatric liver transplantation has an increasing number of indications. Recent advances in preoperative care, posttransplant care and immunosuppression have improved survival.

I. General Indications for Liver Transplantation in Children

A. Cholestatic Liver Diseases: leading to chronic liver disease with complications secondary to hepatic decompensation
   1. Most common indication for pediatric liver transplant (54%)
   2. Biliary atresia, Alagille syndrome, progressive familial intrahepatic cholestasis (PFIC), primary sclerosing cholangitis

B. Chronic Non-cholestatic Liver Diseases
   1. Chronic hepatitis B and C, autoimmune hepatitis

C. Metabolic Diseases
   1. Primary liver diseases: Alpha-1-antitrypsin deficiency, tyrosinemia, glycogen storage disease, cystic fibrosis, Wilson’s disease
   2. Primary non-liver disease: Urea cycle defects, primary hyperoxaluria, organic acidemias, bile acid synthesis defects

D. Acute Liver Failure
   1. 11% of pediatric liver transplants
   2. Indeterminate etiology in up to 49% of pediatric patients with ALF
   3. Consider drugs, toxins, acetaminophen, viral etiologies
   4. Outcome after liver transplantation is not as good as with chronic liver disease

E. Liver Tumors
   1. Hepatoblastoma is the most common primary liver tumor in children
      a. If complete resection is not possible, liver transplantation is performed when maximum benefit of chemotherapy has been obtained
      b. Children presenting with metastatic hepatoblastoma with lung metastases that clear with chemotherapy have favorable outcomes as well
      c. Outcomes following liver transplantation for this indication are comparable to transplantation for other diagnoses
      d. Ideal transplant candidates include children with tumors that are completely confined to the liver, but which are unresectable, despite a definite response to chemotherapy
   2. Hepatocellular carcinoma is rare in children

F. Cirrhosis not otherwise specified, despite complete evaluation
   1. Cirrhosis is an indication for liver transplantation when there is evidence of functional hepatic decompensation (coagulopathy, ascites, frequent or massive gastrointestinal hemorrhage, malnutrition and growth failure, and frequent severe bacterial infections)

G. Miscellaneous: congenital hepatic fibrosis, Caroli’s disease, TPN-related cirrhosis, neonatal hemochromatosis, nonalcoholic steatohepatitis

II. Contraindications to Transplant

A. Absolute contraindications
   1. Extrahepatic malignancy
   2. Uncontrolled sepsis
   3. AIDS
   4. Irreversible and severe brain injury
   5. Uncorrectable congenital anomalies affecting major organs (e.g., severe cardiac disease or pulmonary hypertension)

B. Relative contraindications
   1. Progressive extrahepatic disease
   2. Substance abuse
III. Referral to a Transplant Center
   A. Ideally as soon as the patient is identified as having a condition that will require transplantation
      1. Patients with chronic liver disease, including infants with biliary atresia who remain jaundiced post-Kasai procedure
      2. Patients with metabolic disease poorly controlled by medication, and patients with cirrhosis for any reason
      3. Early referral allows the transplant center to have a maximum input into the pretransplant management strategy
         a. Aggressive ascites treatment
         b. Variceal bleeding management
         c. Management of hepatorenal syndrome
         d. Aggressive nutritional management: fat-soluble vitamins, supplemental enteral or parental nutrition
         e. Immunizations

IV. The MELD/PELD Scoring System
   A. Designed to prioritize patients by acuity of illness rather than waiting time
   B. The MELD score (Model for End-Stage Liver Disease) and the PELD score (Pediatric End-Stage Liver Disease) are disease severity scales that are predictive of the risk of dying from liver disease within 3 months for patients who are listed for transplant
   C. The MELD score incorporates a patient’s bilirubin, INR and creatinine levels with a mathematical equation. A score from 6 to 40 is calculated
   D. A PELD score is calculated for pediatric patients who are less than 12 years of age and incorporates a patient’s bilirubin, INR, albumin, growth failure and age

V. Postoperative Complications
   A. Primary Non-function (PNF): 5%
      1. Characterized by encephalopathy, coagulopathy, minimal bile output, and progressive renal and multisystem failure with increasing serum lactate level and rapidly rising liver enzymes
      2. Histologic evidence of hepatocyte necrosis in the absence of any vascular complication
      3. Donor risk factors include prolonged cold ischemia time, unstable donor, high level of steatosis in the liver allograft, older donor, high serum sodium level in the donor and recovered organ from DCD (donation after cardiac death/non-heartbeating) donors
   B. Hepatic Artery Thrombosis (HAT): 4%–6% in children
      1. Presents with markedly escalating transaminases and coagulopathy
      2. Urgent retransplantation is necessary
      3. May present as biliary leak, as hepatic artery is sole blood supply for biliary system
      4. Late HAT: multiple biliary strictures, late complication
      5. Diagnosis: Doppler ultrasonography or arteriography used to confirm HAT
   C. Portal Vein Stenosis/Thrombosis
      1. May present as recurrent variceal bleeding, enlarging spleen/liver, ascites or liver allograft dysfunction
      2. Doppler ultrasound may be diagnostic or may require venogram
      3. Treatment: surgical intervention in the early posttransplantation period for portal vein thrombosis. In the late posttransplant period, portal vein angioplasty ± stenting
   D. Biliary Complications (Biliary Leak and Biliary Obstruction): 10%–30%
      1. Range from early anastomotic leak to late stricture and obstruction, both in the extrahepatic or intrahepatic biliary system
      2. Biochemical abnormalities with elevation of bilirubin and canalicular enzymes (alkaline phosphatase and gamma-glutamyltransferase) are not specific, these indicators of biliary obstruction are also seen in ischemic graft injury, rejection, recurrent HCV and sepsis
      3. Bile leaks tend usually within 1–2 weeks of transplant and result from a technically poor anastomosis or a thrombosed hepatic artery
         a. Immediate exploration is required to control or repair the leak
      4. Strictures at the anastomosis may occur months to years after transplantation
         a. ERCP and/or Percutaneous transhepatic cholangiogram (PTC) with dilatation and stenting are the usual first-line treatment
         b. Surgical revision reserved for lesions refractory to interventional approaches
VI. Rejection

A. Acute Rejection: 20%–50% of patients within the first 3 months post-transplant
   1. Clinical manifestations: fever, graft enlargement and tenderness, and reduced bile flow
   2. First manifestation however is elevation of AST and/or ALT
   3. Diagnosis requires histological confirmation with liver biopsy
      a. Classical biopsy findings include: 1) portal inflammation, 2) bile duct damage
         and 3) venular endothelialitis.

B. Chronic Rejection
   1. Histologically: loss of small bile ducts and an obliterator vasculopathy affecting large
      and medium-size arteries
   2. Bile duct loss is generally considered to be the most important diagnostic feature, the
      term ductopenic rejection is widely used as an alternative to chronic rejection
   3. Clinically characterized by progressive jaundice accompanied by progressive rise in GGT,
      alkaline phosphatase and bilirubin
   4. Most cases are due to medication noncompliance

VII. Infection

A. Early Infections (0–30 Days):
   1. Usually caused by either bacteria or yeast
   2. Bacterial infections are most often caused by Gram-negative organisms, enterococci or
      staphylococci
   3. Re-exploration of the abdomen is associated with increased risk for fungal infections

B. Intermediate Period (31–180 Days):
   1. Donor-related infections (peak incidence of CMV infection especially in seronegative
      recipients receiving seropositive donor organs)
   2. Reactivated viruses (EBV-associated PTLD)
   3. Opportunistic infections (PCP)

C. Late Infections (>180 Days):
   1. Recurrent bacterial cholangitis and PTLD
   2. Use of CMV prophylaxis may delay the onset of this infection to the late period

VIII. Immunosuppressive Therapy (see section on Immunosuppressive and Transplant Therapy)

A. Corticosteroids: Inhibit the synthesis of cytokines, such as IL-2 and interferon-γ → reduction in
   the proliferation of lymphocytes and the migration and activity of neutrophils

B. Calcineurin Inhibitors (CNI): Bind to intracellular proteins called immunophilins.
   The immunophilin-drug complex inhibits the activity of calcineurin → blocks the transcription of
   IL-2 which regulates the proliferative T-cell response
   1. Side effects include nephrotoxicity, neurotoxicity, hypertension, hyperglycemia/diabetes
      (more with tacrolimus) and dyslipidemia
   2. Tacrolimus and cyclosporine

C. Mycophenolate Mofetil: Inhibits the enzyme inosine monophosphate dehydrogenase, which is
   essential for purine synthesis → arrested lymphocytes replication. Side effects include GI symp-
   toms and bone marrow suppression.

D. Sirolimus: A macrolide antibiotic that blocks T-cell activation by way of IL-2R post-receptor
   signal transduction. Used as a rescue treatment in chronic rejection and CNI toxicity. A common
   side effect is dyslipidemia

IX. Post-Transplant Lymphoproliferative Disorder (PTLD)

A. Broad range of lymphoproliferative disorders that result from primary EBV infection in the setting
   of immunosuppressive therapy

B. Most frequent tumor in children following OLT and usually occurs in the first 2 years after
   transplantation

C. Risk factors
   1. High total immunosuppression load
   2. EBV-naive recipient
   3. Intensity of active viral load

D. Clinical presentation may include fever, lymphadenopathy, tonsillar enlargement, anemia,
   splenomegaly or masses
E. Treatment options depend on the presence of architectural distortion on lymph node, tissue or tonsil biopsy and includes:
   1. Immediate decrease or withdrawal of immunosuppression, taking into account the increased risk of rejection
   2. Anti-CD20 monoclonal antibody, rituximab, if the tumor expresses the B-cell marker CD20
   3. Severe cases: the combination of cyclophosphamide + prednisone + rituximab

X. Long-term Outcomes
   A. 1-year patient survival around 85%–90%
   B. 5-year patient survival around 75%–80%
   C. Common non-immune complications of immunosuppressive therapy include chronic kidney disease, hypertension, hyperglycemia and dyslipidemia

Recommended Reading


