Jaundice and hepatic dysfunction frequently accompany a variety of bacterial infections. The relationship between sepsis and jaundice, particularly in a pediatric population, was reported as early as 1837. Jaundice may result either directly from bacterial products or as a consequence of the host’s response to infection. Frequently, both factors contribute to the development of jaundice. In addition, specific infections that target the liver may cause jaundice because of the liver injury associated with hepatic infection. Although jaundice may be an isolated abnormality, it is often associated with features of cholestasis. In critically ill patients, the development of jaundice and/or cholestasis complicates the clinical picture and poses a clinical challenge both in diagnostic evaluation and in management. In this article, we review the current concepts about the pathogenesis of jaundice and cholestasis with infection, their clinical presentation and diagnostic assessment, and the optimal management of these clinical problems.

**Epidemiologic Considerations**

Jaundice is a well-known complication of sepsis or extrabacterial infection. Sepsis and bacterial infection are responsible for up to 20% of cases of jaundice in patients of all ages in a community hospital setting. The incidence of jaundice in newborns and early infants varies between 20% and 60%. There are no data from large-scale prospective studies on the incidence of hyperbilirubinemia in adults with sepsis. Several small retrospective studies have reported widely varying numbers, from 0.6% to 54%. This variability probably reflects both the reporting bias and the populations of subjects studied (Table 1). Sepsis is more likely to manifest with jaundice in infants and children than in adults. In this population, males have a higher incidence of jaundice. However, in adults, no gender predilection has been reported.

Jaundice has been associated with infections caused by several organisms including aerobic and anaerobic gram-negative and gram-positive bacteria. Gram-negative bacteria cause most of these cases. The primary site of infection is most often intraabdominal, but infection of various other sites such as urinary tract infection, pneumonia, endocarditis, and meningitis have been associated with this complication. Other specific infections known to cause jaundice are infections of the hepatobiliary tree, clostridial infection, typhoid fever, and legionella.

Although jaundice can occur in isolation in patients with septicemia, it is frequently associated with other elements of cholestasis. Because the principal clinical manifestation of cholestasis is also jaundice, the published literature has primarily focused on the syndrome of jaundice, and the exact incidence of cholestasis with jaundice versus isolated jaundice remains unclear.

**Pathophysiology**

The pathogenesis of jaundice in systemic infections is multifactorial. The development of jaundice may occur from an aberration in the processing of bilirubin by hepatocytes or from other effects on the liver that lead to the accumulation of bilirubin in the body. Such processes include increased bilirubin load from hemoysis, hepatocellular injury, and cholestasis from the septic state and from various drugs used for the treatment of sepsis. The molecular and biochemical mechanisms by which jaundice develops in subjects with sepsis is best considered in the context of normal bilirubin metabolism.

**Normal Bilirubin Metabolism**

Bilirubin is the end product of the breakdown of the heme moiety of hemoproteins. In humans, 4 mg of bilirubin is formed daily from the degradation of hemoproteins, 80% of which is derived from hemoglobin. Unconjugated bilirubin is a highly hydrophobic molecule and circulates tightly but reversibly bound to albumin in...
plasma. Figure 1 shows normal bilirubin metabolism at the hepatocyte. Bilirubin dissociates from albumin at the sinusoidal, basolateral membranes of hepatocytes and is taken up inside in a carrier-mediated process that requires inorganic anions such as Cl\(^{-}\). Organic anion transport proteins (OATPs) are on the basolateral membranes of hepatocytes. Their role in bilirubin transport has still not been directly established, but bilirubin is a presumed substrate of OATPs.

Following uptake into a hepatocyte, bilirubin is bound by a group of cytosolic proteins (mainly glutathione S-transferases, GST) that prevent its efflux from the cell. Within a hepatocyte, bilirubin is conjugated to monoglucurononides and diglucurononides by the enzyme uridine diphosphate-glucuronosyltransferase. Conjugation of bilirubin converts it from a highly hydrophobic molecule to a relatively hydrophilic molecule that can be excreted into bile. Bilirubin glucurononides are excreted into bile against a steep concentration gradient by a canalicular membrane protein, the canalicular multispecific organic anion transporter (cMOAT), also commonly referred to as the multidrug-resistance-associated protein (MRP2). This process is the major driving force of bilirubin transport and is the rate-limiting step in bilirubin excretion by the liver.

### Table 1. Reports of Jaundice and Sepsis

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>N</th>
<th>M/F</th>
<th>Age</th>
<th>TB/DB (mg %)</th>
<th>Alk Phos</th>
<th>ALT/AST</th>
<th>Agents of Infection</th>
<th>Bacteremia</th>
<th>Site of Infection</th>
<th>Deaths</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bernstein et al. (1962)</td>
<td>9</td>
<td>8/1</td>
<td>2-8 weeks</td>
<td>12-22/4-7</td>
<td></td>
<td></td>
<td>E. coli (5)</td>
<td>8</td>
<td>UTI (4)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Hall et al. (1963)</td>
<td>11</td>
<td>10/1</td>
<td>15-65 years</td>
<td>2-17/.4-14</td>
<td>5-21 (KA U/100 mL)</td>
<td></td>
<td>E. coli (18)</td>
<td>18</td>
<td>Urine (16)</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Hamilton et al. (1964)</td>
<td>24</td>
<td>13/11</td>
<td>&lt; 1 day-13 weeks</td>
<td>3-31/1-16</td>
<td></td>
<td></td>
<td>A. Aeruginosa (4)</td>
<td>4</td>
<td>Umbilicus (2)</td>
<td>1</td>
<td>Eye (1)</td>
</tr>
<tr>
<td>Kibukamusoke et al. (1964)</td>
<td>21</td>
<td>21/0</td>
<td>17-65 years</td>
<td>3-27</td>
<td>8-19 (KA U/100 mL)</td>
<td></td>
<td>E. coli (5)</td>
<td>8</td>
<td>Lungs (21)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Eley et al. (1965)</td>
<td>5</td>
<td>2/3</td>
<td>35-54 years</td>
<td>3-23/8-15</td>
<td>15-20 (KA U/100 mL)</td>
<td>16-34/24-88 (U/ml)</td>
<td>Str. pyogenes (2)</td>
<td>3</td>
<td>Intraabdominal (4)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Vermillion et al. (1969)</td>
<td>7</td>
<td>4/3</td>
<td>18-72 years</td>
<td>5-24/4-16</td>
<td>3-26 (mU/mL)</td>
<td>1-3 (IU/mL)</td>
<td>E. coli (3)</td>
<td>7</td>
<td>Lung (3)</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Miller et al. (1969)</td>
<td>9</td>
<td></td>
<td>1,2-2.5</td>
<td>1-2-2.5</td>
<td>7-50/1-37</td>
<td></td>
<td>E. coli (8)</td>
<td>19</td>
<td>Appendicitis (9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rooney et al. (1971)</td>
<td>22</td>
<td>19/3</td>
<td>1-3 weeks</td>
<td>1,2-2.5</td>
<td>7-50/1-37</td>
<td></td>
<td>Proteus (3)</td>
<td>19</td>
<td>UTI (9)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Miller et al. (1976)</td>
<td>30</td>
<td>15/15</td>
<td>15-27 years</td>
<td>2-20 (DB mean 6.78)</td>
<td>mean 128</td>
<td>mean 47.6</td>
<td>P. aeruginosa (2)</td>
<td>11</td>
<td>Soft tissue (4)</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Ng et al. (1971)</td>
<td>6</td>
<td>6/0</td>
<td>2-8 weeks</td>
<td>4-33/3-21</td>
<td>20-41 (KA U/100 mL)</td>
<td></td>
<td>Paracolon</td>
<td>4</td>
<td>UTI (6)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Borges et al. (1972)</td>
<td>13</td>
<td>8/5</td>
<td>3-31/2-14</td>
<td>28-300/50-920 (U/mL)</td>
<td></td>
<td></td>
<td>E. coli (5)</td>
<td>23</td>
<td>Lung (8)</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Franson et al. (1985)</td>
<td>23</td>
<td>10/13</td>
<td>25-77 years</td>
<td>2-24/2-14</td>
<td>56-1694</td>
<td>23-3300</td>
<td>Paracolon (1)</td>
<td>23</td>
<td>Abdominal cavity (5)</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>
Disorders of Bilirubin Metabolism During Systemic Infection

Various mechanisms can lead to hyperbilirubinemia alone during systemic infection (Table 2). These are discussed in detail in the following sections.

Increased Bilirubin Load/Hemolysis

The development of hemolysis causes an increased bilirubin load in septic individuals. In early studies, hemolysis was believed to be the principal mechanism of jaundice in sepsis. Using light microscopy, Tugswell et al. found excess iron-containing pigment in the liver of patients with pneumonia and noted ferritin containing lysosomes in Kupffer cells. This was believed to be compatible with hemolysis and secondary iron overload. Although hemolysis contributes to jaundice in sepsis, it is unlikely that it is the principal mechanism because the jaundice results from conjugated hyperbilirubinemia. Table 3 lists various mechanisms of hemolysis in the setting of sepsis.

Hemolysis may occur by multiple mechanisms in the setting of bacterial infection. These may be categorized as mechanisms of hemolysis (1) associated with normal red cells and (2) related to underlying red cell defects. The severe forms of many infections from gram-positive and gram-negative bacteria have been associated with hemolysis of normal red cells. Of these bacteria, *Clostridium perfringens* can give rise to severe, often fatal hemolysis in persons with normal red cells. This bacterium also produces proteolytic exotoxins that cause enzymatic dissolution of membrane proteins. Other infections that commonly cause hemolysis in normal red cells are malaria and babesiosis. *Escherichia coli* infection periodically may lead to hemolysis in persons with normal red cells. Aside from bacterial infection directly causing hemolysis, multiple drugs (e.g., penicillin, antimalarial medications, sulfa medications, or acetaminophen), hypersplenism from infection, portal hypertension, or neoplasm can increase the sequestration and phagocytosis of erythrocytes. Immunologically mediated hemolysis may be another mechanism by which hemolytic anemia occurs in normal RBCs of patients with sepsis. Overall, infections account for about 8% of cases of autoimmune hemolytic anemia (AHA) and for approximately 27% of such cases in children. Immunologically mediated hemolysis may develop by 3 mechanisms: antibody directed to red cell

Table 2. Mechanisms of Hyperbilirubinemia in Sepsis

<table>
<thead>
<tr>
<th>1. Hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. In normal red cells</td>
</tr>
<tr>
<td>b. In RBCs with red cell enzyme defects (G6PD)</td>
</tr>
<tr>
<td>c. Pathologic changes to RBCs secondary to infection</td>
</tr>
<tr>
<td>d. Drug-induced hemolysis</td>
</tr>
<tr>
<td>2. Hepatic dysfunction</td>
</tr>
<tr>
<td>a. Decreased bilirubin uptake</td>
</tr>
<tr>
<td>b. Decreased canalicular transport</td>
</tr>
<tr>
<td>c. Decreased clearance of conjugated bilirubin</td>
</tr>
<tr>
<td>d. Hepatic ischemia</td>
</tr>
<tr>
<td>i. Hypotension</td>
</tr>
<tr>
<td>ii. Prolonged Hypoxia</td>
</tr>
<tr>
<td>e. Hepatocellular injury (mild reactive hepatitis to overt hepatocellular necrosis)</td>
</tr>
<tr>
<td>3. Cholestasis</td>
</tr>
</tbody>
</table>

Table 3. Mechanisms of Hemolysis in Sepsis

<table>
<thead>
<tr>
<th>1. Normal RBCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Infections directly causing hemolysis (e.g., <em>Clostridium perfringens</em>)</td>
</tr>
<tr>
<td>b. Immunologically mediated red cell injury</td>
</tr>
<tr>
<td>1. Cold agglutinin–associated hemolytic anemia</td>
</tr>
<tr>
<td>a. <em>Mycoplasma pneumoniae</em></td>
</tr>
<tr>
<td>b. <em>Legionella</em></td>
</tr>
<tr>
<td>2. Paroxysmal cold hemoglobinuria</td>
</tr>
<tr>
<td>c. Drug-induced hemolysis</td>
</tr>
<tr>
<td>d. Transfusion reactions</td>
</tr>
<tr>
<td>e. Hypersplenism</td>
</tr>
<tr>
<td>2. Underlying red blood cell defects</td>
</tr>
<tr>
<td>a. Inherited enzyme deficiency</td>
</tr>
<tr>
<td>b. Sickle cell disease</td>
</tr>
<tr>
<td>c. Hemoglobinopathies</td>
</tr>
</tbody>
</table>

Fig. 1. Normal bilirubin metabolism. Bilirubin dissociates from albumin at the sinusoidal surface of the hepatocyte and is taken up by the hepatocyte. Inside the hepatocyte, bilirubin is bound by a group of cytosolic proteins that prevent its efflux from the cell. Bilirubin is then conjugated to monoglucuronides and diglucuronides by the enzyme uridine diphosphate-glucuronosyltransferase. Bilirubin glucuronides are excreted into bile against a steep concentration gradient by a canalicular membrane protein termed canalicular multispecific organic anion transporter (cMOAT), also commonly referred to as the multidrug-resistance-associated protein (MRP2). This process is the major driving force of bilirubin transport and is the rate-limiting step in bilirubin excretion by the liver.
antigens (IgM or IgG mediated), antigen/antibody complexes, or polyagglutination. IgM antibodies give rise to intravascular hemolysis, and IgG antibodies give rise to extravascular hemolysis.

Several pathogens, for example, *Mycoplasma pneumoniae* and *Legionella* may cause “cold agglutinin”–associated hemolytic anemia. The cold agglutinins, which are often IgMs, bind to red cells at low temperatures, fix complement, and cause intravascular hemolysis. On the other hand, IgG antibodies, for example, Donath-Landsteiner antibodies in paroxysmal cold hemoglobinuria, often cause extravascular hemolysis. This condition has been associated with upper respiratory tract infections and a variety of infections that normally do not lead to sepsis syndrome, for example, syphilis, varicella, Epstein-Barr, measles, and mumps. Hemolysis and jaundice from paroxysmal cold hemoglobinuria may be severe in cold weather.

In individuals with underlying red cell defects, the threshold for hemolysis is often lower than in normal individuals. A common defect associated with an increased propensity for hemolysis in a variety of circumstances including sepsis is glucose-6-phosphate dehydrogenase (G-6-PD) deficiency. Many types of infections as well as antibiotics can cause hemolytic anemia in patients with this deficiency. G-6-PD is required for regeneration of nicotinamide adenine dinucleotide dehydrogenase (NADPH), which is essential for reducing the amount of oxygen radicals. In the absence of G-6-PD, red cell NADPH stores are diminished, thereby lowering the threshold for oxidant-stress-mediated cell injury. Sepsis is often associated with oxidant stress, and this may induce hemolysis, particularly in those with a lowered threshold for oxidant-mediated injury.

Microangiopathic hemolytic anemias may be triggered by a variety of infections such as *Shigella*, *Campylobacter*, and *Aspergillus*. Disseminated intravascular coagulation (DIC) may also cause hemolysis with infections; up to 60% of all cases of DIC have been attributed to infections, with many bacterial, viral, fungal, and parasitic pathogens implicated.

Drugs are a major cause of hemolysis in patients with sepsis (Table 4). This occurs through a variety of mechanisms, an apparently major one of which is increased oxidant stress. Finally, hemolysis of nonviable erythrocytes may occur during massive blood transfusions, resorption of large hematomas, or trauma. These additional factors are commonly encountered in patients with sepsis in the ICU.

### Hepatocyte Dysfunction as a Cause of Hyperbilirubinemia

In addition to increased bilirubin load, decreased bilirubin uptake, intrahepatic processing, and canalicular excretion are also important mechanisms of jaundice associated with infection. This is supported by the mainly conjugated hyperbilirubinemia that occurs in sepsis. Many studies have examined the effects of sepsis on the function of organic anion transporters in the liver. Tetra-bromosulphophthalein (BSP) is taken up by hepatocytes by the sodium-independent transport system, the basolateral OATP. Bilirubin is a presumed substrate for this transporter system. Hepatic uptake of BSP is reported to be markedly lower in lipopolysaccharide (LPS)-treated animals. BSP, glutathione, and sulfolithocholyltaurine (SLCT) are excreted at the canalicular membrane through MRP2. There is also a decrease in canalicular transport of glutathione and SLCT, suggesting decreased MRP2 activity. Roelofsen et al. studied the transport of bilirubin in a rat model of sepsis. In this study, LPS was injected into rats intravenously to induce endotoxemia. The transport of bilirubin and another organic acid, taurocholate, were studied 18 hours after the infusion. Sinusoidal uptake, hepatic content, and canalicular excretion of bilirubin were all decreased in endotoxemic rats compared to in control animals. Also, a 50% decrease in steady-state elimination of bilirubin was observed in livers exposed to endotoxin.

It is unlikely that bilirubin conjugation is substantially affected by sepsis because more than 60% of the bilirubin in blood is conjugated. Also, when endotoxin was administered to rats, the clearance of conjugated bilirubin decreased to the same degree that unconjugated bilirubin did, suggesting that the conjugation of bilirubin was not contributing to the impairment in bilirubin clearance. This is further supported by the finding that the degree of bilirubin conjugation in livers exposed to endotoxin was not substantially different from normal controls.

### Decreased Bile Flow

Cholestasis is the predominant mechanism by which jaundice develops in sepsis. Extrahepatic cholestasis is

<table>
<thead>
<tr>
<th>Table 4. Antibiotics Associated with Hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune Complex Mediated</strong></td>
</tr>
<tr>
<td>Quinine</td>
</tr>
<tr>
<td><strong>Autoantibody Medicated</strong></td>
</tr>
<tr>
<td>Sulfonamides</td>
</tr>
<tr>
<td>Penicillin</td>
</tr>
<tr>
<td>Cephalosporins</td>
</tr>
<tr>
<td>Indinivir</td>
</tr>
<tr>
<td><strong>Hemolysis in G6PD</strong></td>
</tr>
<tr>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>Phenazopyridine</td>
</tr>
<tr>
<td>Primaquine</td>
</tr>
<tr>
<td>Sulfonamides</td>
</tr>
</tbody>
</table>
caused by obstruction of the hepatic or common bile duct and directly impedes the flow of bile. This can result from a primary infection such as cholangitis or can become secondarily infected. Partial biliary obstruction and obstruction as a result of choledolithiasis are more commonly complicated by infection of the biliary tree, which could further lead to decreased bile flow.

Sepsis-Associated Cholestasis

Normal Bile Acid Flow

Before elaborating on the potential mechanisms of cholestasis in sepsis, it is important to understand the steps in the formation of bile (Fig. 2). Bile is formed by the inflow of water along osmotic gradients produced by secretion of bile salts into hepatic canaliculi. Bile salts are the principal solute secreted into this space, and bile flow is mainly driven by the osmotic forces generated by the secretion of bile salts into hepatic canaliculi. This is also known as bile-salt-dependent bile flow, whereas the generation of bile from osmotic forces related to other solutes is known as bile-salt-independent flow.

Bile salts are derived from *de novo* synthesis in the liver and from reabsorption of bile salts from the intestine. Bile acids are transported to the liver following intestinal absorption. They are taken up by hepatocytes via transport proteins on the basolateral (sinusoidal) membranes. The principal mediator of this basolateral transport of bile acids is the Na-K-ATPase pump, which is ATP dependent and maintains an inwardly directed sodium gradient. It is an integral component of the basolateral membrane, and Na-K-ATPase pumps are found throughout the hepatic lobule. Sodium-dependent taurocholate cotransporter (NTCP) is the principal transporter in the uptake of conjugated bile salts from plasma into hepatocytes. This highly efficient pathway results in a high first-pass clearance of bile salts. The unconjugated bile salt cholate, organic ion sulfochromophthalein (BSP), and other lipophilic compounds are primarily transported from plasma into hepatocytes by sodium-independent transport systems such as organic anion transport proteins OATP 1, OATP 2, and OATP 3.

Bile acids are transported from the basolateral membrane to the canalicular membrane by cytosolic transporter proteins. Transcytotic transport occurs by 2 main methods: (1) binding to cytosolic proteins and diffusion to apical domains (mainly conjugated primary and secondary bile acids) and (2) vesicular transcytosis. The passage of bile salts into the biliary canaliculus is the rate-limiting step in bile formation, which is ATP dependent. Conjugated bile salts are excreted into bile through the BSEP. The multiple drug resistance 1 (MDR1) transporter is responsible for transporting hydrophobic organic cations across the canalicular membrane. The tight junctions between hepatocytes provide a barrier to bile salts, inhibiting the regurgitation of formed bile into the space of Disse.

Mechanisms and Mediators of Cholestasis Associated with Infections

The liver has a central role in the regulation of host defenses. It serves as a source of inflammatory mediators and is a major site of the removal of bacteria and endotoxins from systemic circulation. Kupffer cells (KCs) of the liver make up 80%-90% of the fixed-tissue macrophages of the reticuloendothelial system (RES) and represent terminally differentiated macrophages. KCs take up bacteria, particles, and endotoxins (LPS) and are stimulated to release a wide range of products implicated in liver injury, such as tumor necrosis factor, interleukin 1 and interleukin 6, superoxides, lysosomal enzymes, procoagulants, and platelet-activating factor.

Hepatic injury without biliary obstruction may accompany systemic infection in adults with pneumococcal pneumonia, streptococcal bacteremia, salmonella infec-
tions (especially typhoid fever), and Escherichia coli bacteremia. This can range from mild reactive hepatitis to overt hepatocellular necrosis that it, has been shown, usually resolves when the bacteremia is appropriately treated. Hepatocellular injury is not considered a frequent occurrence during extrahepatic bacterial infection. Most studies that reviewed liver histology in hyperbilirubinemia or hepatic abnormalities in bacterial infection have noted very mild to no inflammation (see Table 1). The mechanism of hepatic injury depends on the underlying infection, yet most likely there is an unspecified toxin elaborated by the offending bacteria that ultimately leads to hepatocellular injury.

Ischemic liver damage may occur as a consequence of hypotension or prolonged hypoxia in sepsis. Hepatic blood flow is depressed in sepsis and nutrient blood flow to the liver is reduced, which can lead to Kupffer cell dysfunction and hepatocellular alteration. The lack of oxygen, mainly to the centrilobular cells and later from delivery of oxygen-derived free radicals from reperfusion, leads to hepatocellular damage and thus may result in centrilobular necrosis of the liver. Mediation of hepatocellular injury via necrosis and/or apoptosis has been attributed to nitric oxide (NO). This was demonstrated in septic animal models when inhibition of NO production gave rise to reductions in both hepatocyte necrosis and apoptosis.

The underlying state of endotoxemia and the products released in response to infection appear to play a key role in the pathophysiology of the cholestasis of sepsis. Various effects of this state on the liver that lead to cholestasis are listed in Table 5. Decreased hepatocellular function has been demonstrated to occur early after the onset of sepsis despite increased cardiac output and hepatic perfusion. This suggests that the hepatocellular dysfunction in sepsis may be associated with the release of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) or interleukin 6 (IL-6). Various investigations have confirmed the central role of endotoxemia in the genesis of cholestasis associated with sepsis. Direct invasion of the liver by bacteria is not a major cause of cholestasis or hepatic injury in most cases of septicemia. Several studies have shown a quantitative reduction in bile flow within the isolated perfused livers of rats following LPS or cytokine administration.

TNF-α is a cytokine released by macrophages, endothelial cells, and Kupffer cells and is the primary mediator of the systemic effects of endotoxins. TNF-α has been implicated in endotoxin-induced cholestasis by the finding that immunization with anti-TNF-α antibodies blocked endotoxin-associated reduction in bile flow and bile salt excretion. LPS, TNF-α, and interleukins 1β and 6 all have been shown to mediate these effects, giving rise to cholestasis in the liver. Procoagulants released by activated Kupffer cells induce microvascular thrombosis and have been postulated to cause circulatory disturbance, which, in turn, could contribute to endotoxin-induced hepatic injury.

**Abnormalities in Bile Acid Formation and Flow**

Endotoxemia does not affect bile acid synthesis, cytosolic bile acid transport, or the permeability of tight junctions. LPS and cytokines appear to mainly affect hepatocyte uptake and excretion of bile acids. Table 5 lists various steps in bile acid transport that possibly are affected in sepsis, thus giving rise to cholestasis. Endotoxemia decreases the basolateral and canalicular transport of bile acids (cholate, taurocholate, and chenodeoxycholate) and organic anions (BSP and the taurine conjugate of sulfolithocholate). It is also postulated that LPS may stimulate degradation of membrane proteins as well.

Several studies have observed endotoxin-induced inhibition of basolateral membrane Na-K-ATPase activity. Endotoxin may cause decreased function of Na-gradient dependent transporters at the basolateral membrane such as the NTCP. It has also been observed that endotoxin affects membrane fluidity; this may be the mechanism involved in reducing Na-K-ATPase activity after endotoxin administration. TNF-α and IL-1β modulate gene expression of transporters NTCP and BSEP at both the transcriptional and the posttranscriptional levels. In a study by Green et al., 16 hours after intraperitoneal administration of LPS, both protein expression and functional activity of NTCPs were reduced by more than 90%.

Impaired hepatocyte transport function has also been detected at the canalicular level. Cholyltaurine (CT) and chenodeoxycholyltaurine (CDCT) are substrates for canalicular bile acid transporters. ATP-dependent CT and CDCT transport was markedly decreased in a rat sepsis model. This appears to result from down-regulation of transporters at the canalicular membrane.

**Table 5. Mechanisms of Cholestasis of Sepsis**

<table>
<thead>
<tr>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased basolateral transport of bile acids</td>
</tr>
<tr>
<td>Inhibition of basolateral membrane Na-K-ATPase activity</td>
</tr>
<tr>
<td>Decreased basolateral membrane fluidity</td>
</tr>
<tr>
<td>Down-regulation of transporters</td>
</tr>
<tr>
<td>Decreased NTCP function</td>
</tr>
<tr>
<td>Decreased canalicular transport of bile acids</td>
</tr>
<tr>
<td>Down-regulation of transporters</td>
</tr>
<tr>
<td>Decreased BSEP function</td>
</tr>
<tr>
<td>Decreased MRP2 function</td>
</tr>
</tbody>
</table>

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of GSH and, to a lesser extent, of HCO3−. The main evidence for this is the inhibition of biliary excretion of GSH and, to a lesser extent, of HCO3− after LPS administration. Maximum reduction in bile acid flow occurs 12-18 hours after endotoxin and/or cytokine administration.

Clinical Syndromes

The jaundice of sepsis is usually cholestatic and can occur within a few days of the onset of bacteremia and may even appear before other clinical features of the underlying infection become apparent. In the absence of intraabdominal infection, abdominal pain is rare. Similarly, pruritus is not a major manifestation of cholestasis associated with infection. Hepatomegaly occurs about half the time. Conjugated hyperbilirubinemia occurs in the range of 2-10 mg/dL is often seen, although rarely higher levels can be seen. This is particularly true in those with postoperative jaundice who also are septic and on TPN. Serum alkaline phosphatase is usually elevated but rarely more than 2-3 times above the upper limit of normal. Serum aminotransferase is generally only modestly elevated (Table 6).

Specific Clinical Scenarios of Infection and Jaundice

Biliary Tract Disease. Obstruction or infection of the hepatobiliary tree should be considered a potential cause of jaundice, especially when a patient presents with right upper quadrant pain, jaundice, and fever. Cholangitis most commonly occurs secondary to obstruction of the biliary tract with a gallstone or after biliary intervention. Less commonly, cholangitis may occur after obstruction from a tumor of the ampulla, bile duct, or pancreas. Laboratory results will show leukocytosis, conjugated hyperbilirubinemia, and elevation of alkaline phosphatase disproportionate to transaminasemia. Acute cholangitis has a more severe course than jaundice associated with extrahepatic infections.

Liver Abscess and Pylephlebitis. Biliary tract disease is the most common condition associated with liver abscess. This includes infection (cholangitis) that may occur secondary to choledocholithiasis, biliary stricture, or malignancy. Another potential cause of pyogenic abscess is spread through the portal vein from an intraabdominal primary site to the liver. Almost a third of liver abscesses are cryptogenic. Patients present with fever, chills, and weight loss. Abdominal complaints most often are vague or absent. Up to two thirds of patients have hepatomegaly. Alkaline phosphatase levels are invariably elevated, with less frequent elevation of bilirubin and aminotransferases. Optimal treatment includes prompt diagnosis, percutaneous or surgical drainage of the abscess, and broad-spectrum enteric antibiotic coverage. Prognosis depends on prompt recognition and treatment, with a cure rate ranging from 80% to 100%.

ICU Setting. A patient presenting with jaundice in the ICU is a frequently encountered problem. Infections, hemodynamic instability, renal insufficiency, hepatotoxic drugs, multiple blood transfusions, and/or TPN administration are some of the potential causes of jaundice, which usually presents 1-2 weeks after onset of the initiating event. Jaundice under these circumstances is usually of a cholestatic type, with mainly conjugated hyperbilirubinemia and only slightly elevated AST and ALT. When there is no obvious biliary obstruction; underlying systemic infection is highly likely. Sepsis is the most common etiology of jaundice and cholestasis in the ICU. This is especially true in patients who are in an ICU due to trauma. In a retrospective study by Boekhorst et al., the development of jaundice in the ICU was shown to have a poor prognosis. This could be a result of a delay in diagnosis of the instigating factor. If the underlying process is detected and adequately treated in a timely fashion, the prognosis is usually good.

Gram-Negative Bacterial Infections. Cholestasis is a known complication of gram-negative bacterial infection, especially in infants. This syndrome is more frequent in the neonatal period and may account for as much as a third of the cases of neonatal jaundice. Most cases of sepsis associated with cholestatic jaundice have evidence of gram-negative bacteremia, with Escherichia coli being the more common pathogen. Pyelonephritis, peritonitis, appendicitis, diverticulitis, pneumonia, and meningitis are types of infections observed to cause jaundice. The urinary tract is the most common site of infection associated with this syndrome, especially in the neonatal period. Liver histology shows intrahepatic cholestasis with Kupffer cell hyperplasia and little or no evidence of cellular necrosis. Aside from cholestasis, liver histology reveals an almost normal hepatic parenchyma. The manifestations of the underlying infection usually dominate the presentation. Jaundice and cholestasis are usually reversible and subside completely after resolution of the infection.

Pneumonia. The male-to-female ratio of patients who develop jaundice with pneumococcal pneumonia is.

<table>
<thead>
<tr>
<th>Table 6: Liver Test Abnormalities in Sepsis</th>
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<tr>
<td>• Conjugated hyperbilirubinemia: total bilirubin ranging from 2 to 10 mg/dL</td>
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<tr>
<td>• Elevated alkaline phosphatase: rarely more than 2-3 times upper limit of normal</td>
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<tr>
<td>• Mild elevation of aminotransferases</td>
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10 to 1. Most investigators think that pneumonia-associated jaundice is a result of hepatocellular damage. Many patients with pneumonia, with or without jaundice, have abnormalities suggestive of hepatocellular damage. Hepatic necrosis has more commonly been identified in liver biopsies of patients with pneumonia. Liver histology consistently shows patchy necrosis and dilated biliary canaliculi with bilirubinostasis. The prognosis is good after complete resolution of the infection.

**Clostridium perfringens.** *Clostridium perfringens* is a commonly isolated clostridial species that can cause a wide spectrum of clinical manifestations, from transient bacteremia to massive red blood cell hemolysis, shock, and death. Clostridial hemolysis has been described as a rare complication of septic abortion, gall bladder disease, and surgical procedures. Severe bacteremia may result in massive hemolysis, hemoglobinuria, shock, and death. *Clostridium perfringens* produces a large variety of toxins and virulence factors. The alpha toxin, a lecithinase, is capable of hydrolyzing sphingomyelin and lecithin to phosphoryl choline and diglyceride. Lysolecithins are capable of hydrolyzing sphingomyelin and lecithin to phosphoryl choline and diglyceride. Lysolecithins released from cell membranes also act as hemolysins. Lysolecithins also produce RBC membrane failure, which accounts for the profound or fatal hemolytic anemia in clostridial sepsis. Striking hemoglobinemia and hemoglobinuria are seen in this condition, and the high plasma hemoglobin level may produce marked dissociation between blood hemoglobin and hematocrit levels. Acute renal failure and hepatic failure usually develop. The prognosis in this clinical setting is very poor, with more than half the patients dying even with proper and extensive treatment. Therapy consists of high-dose penicillin and surgical debridement.

**Leptospirosis.** Leptospirosis is a zoonanthroponosis transmitted among animals and occasionally from animals to humans. In the incubation period, the leptospira organisms disseminate to different organs, especially the liver, kidneys, muscles, and lungs. Experimental data suggest that after the leptospira gain access to the bloodstream, they concentrate in the liver, where they reproduce. There are two classical forms of presentation of leptospirosis, the icteric and anicteric forms. The icteric form is the less common. A severe presentation of the disease, occurring in only 5% to 10% of all leptospiral infections, is known as Weil’s disease. This is associated with high fever, severe hepatic function impairment, intense jaundice, renal insufficiency, hemorrhagic diathesis, and cardiovascular compromise. Although serum bilirubin may be extremely high, serum aminotransferases and alkaline phosphatase are only slightly to moderately elevated. The mortality rate for this presentation is high.

**Typhoid Fever.** Typhoid fever, also known as enteric fever, is an acute systemic illness caused by *Salmonella typhi*. Typhoid fever is an infection that not only causes jaundice but also induces liver injury. Hepatomegaly occurs in about 30% of patients, and jaundice occurs in about a third of patients with hepatomegaly. Alkaline phosphatase is usually 2-3 times the normal level, and serum aminotransferases rarely are more than 5 times the upper limits of normal. Rarely, ALT values may be markedly elevated. The diagnosis is made by (1) isolating salmonellae from the blood or stool and (2) observing a rise in the titer of the Widal reaction during the course of the illness. The etiology of the hepatic damage in typhoid fever is believed to be secondary to the effect of endotoxin. Previous studies have demonstrated that injection of *Salmonella typhi* endotoxin produces focal hepatic necrosis. Other studies have suggested that liver injury may occur by local release of cytokotins or local inflammatory reactions within reticuloendothelial cells. Cholangitis and biliary stasis are apparently not important in the pathogenesis of hepatic lesions. The histology of the livers of patients with typhoid fever shows focal cell necrosis with mononuclear cell infiltration and marked Kupffer cell hyperplasia with mild cholestasis. Typhoid nodules, aggregations of Kupffer cells, are characteristic of typhoid fever and are randomly distributed throughout the hepatic lobule. Follow-up liver biopsies have shown complete resolution within 2 weeks after control of infection.

**Natural History**

The presence of jaundice and sepsis or the degree of its severity does not seem to influence survival or predict the overall prognosis of the patient. The overall prognosis depends on the underlying infection. There usually is complete resolution of hepatic dysfunction and cholestasis if the underlying condition is adequately treated, yet the outcome may be guarded if detection and treatment are delayed. Certain causes of jaundice in a critically ill patient such as acalculous cholecystitis and ascending cholangitis have a very poor prognosis.

**Histology**

The most prominent finding in sepsis is intrahepatic cholestasis. Histologically, bile is found in the bile canaliculi and in hepatocyte cytoplasm (Fig. 3A,C). Bile backflow into the perisinusoidal spaces may lead to bile uptake by Kupffer cells. There may also be some cholestasis-related parenchymal changes including feathery degeneration of the hepatocyte cytoplasm. Apoptosis when present appears as rounded bile-tinged apoptotic bodies in the
hepatic lobule. An increased amount of smooth endoplasmic reticulum as a result of cholestasis may lead to hepatocytes having a ground-glass appearance.

**Evaluation of Jaundice in an Infected Patient.** The guiding principles in the evaluation of a given patient are consideration of (1) the differential diagnosis, (2) specific diagnoses likely to have negatively affect the patient if missed, and (3) therapeutic options available when a diagnosis can be made. Table 7 outlines the recommended steps for evaluating a patient at risk for sepsis of jaundice. The outcome of sepsis-associated jaundice is linked to effective treatment of the sepsis. When jaundice develops in a patient with an established diagnosis of infection, the possibility of sepsis-related jaundice is obvious. On the other hand, a high index of suspicion is often necessary to diagnose this condition when jaundice is the presenting manifestation of infection. The presence of hyperbilirubinemia and abnormal hepatic parameters may draw attention from assessing a more serious underlying disease process and lead to an unnecessary search for hepatic or biliary disease. However, if a septic source is not known, the possibility of hepatic or biliary infection as the cause of jaundice should also be considered. There are many specific entities that require special attention.

Given the common causes of jaundice and the different circumstances in which it is encountered, a thorough, systematic approach should be carried out to evaluate the cause (Table 7). Table 8 lists various etiologies in the differential diagnosis in this setting. The type of jaundice, that is, unconjugated versus conjugated and isolated hyperbilirubinemia versus jaundice with liver enzyme abnormalities, provides valuable clues that should guide further workups. Unconjugated hyperbilirubinemia should initiate a search for hemolysis and potential causes of hemolysis. On the other hand, with a predominantly cholestatic jaundice, it is imperative to exclude a potentially treatable hepatobiliary cause of sepsis and jaundice. Imaging studies to evaluate the hepatobiliary tract are extremely valuable for this purpose. Sonography is relatively inexpensive and can be performed at the bedside of critically sick patients. Also, Doppler sonography can exclude vascular occlusion as a cause of jaundice. However, sonography is not sensitive enough to pick up small abscesses, and a CT scan should be performed when a hepatic abscess is suspected.

**Table 7. Evaluation of Patient at Risk for Sepsis with Jaundice**

1. Assess the type of jaundice
   * Conjugated versus Unconjugated
     - Unconjugated—initiate a search for hemolysis
     - Conjugated
       * Search for a hepatobiliary cause
         - Imaging studies
         - US (with or without Doppler)
         - CT
   * Isolated jaundice versus jaundice associated with liver enzyme elevation
2. Full workup to evaluate for infection
   * Complete blood count with differential
   * Urine analysis
     - Blood
     - Urine
     - Sputum
     - Catheter tips
     - Drains
     - Other potential sources of infection
   * Imaging
     - CXR
     - Further imaging of potential sites of infection (rule out abscess, hepatobiliary disease, etc.)
   * Empiric antibiotic coverage: in selected cases, hepatic parameters may improve within a couple of weeks if they were secondary to infection alone

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Fig. 3. Liver biopsies of subjects with cholestasis showing (A) bile plugs (black arrows), (B) pericholangitis, and (C) intrahepatic inspissated bile in a subject with TPN-induced cholestasis.
In patients at risk for sepsis who develop jaundice without other features of infection, blood cultures, urine cultures, and a chest X-ray should be obtained as a minimum workup to exclude sepsis. Also, cultures should be sent from intravascular catheter tips, drains, or any other source of potential infection. If an obvious cause is still not apparent, further aggressive evaluation for underlying infection or iatrogenic causes should be sought. There are no controlled data that either validate or refute giving empiric antibiotic coverage to all patients with jaundice who have not yet shown other features of infection. Frequently, empiric antibiotic coverage with a broad-spectrum antibiotic is given to those who are likely to be unable to tolerate sepsis. Hepatic parameters, which usually improve within 1-2 weeks of therapy for the underlying infection, should be followed closely.

Hepatocellular jaundice is diagnosed when hyperbilirubinemia is accompanied by high AST and ALT levels and only modest or no elevation of alkaline phosphatase. This is usually a result of ischemia, toxins, viral infection, or iatrogenic injury. Hepatitis viral serology tests should be done. A Tylenol level may be obtained if this drug has been used to treat fever associated with infection. Typically, ALT levels are markedly elevated in such patients. The passage of biliary sludge may sometimes be associated with a rapid rise in AST that declines just as rapidly after passage of the sludge. A hepatobiliary sonogram can be used to confirm the presence of sludge. A liver biopsy does not usually aid in management of this situation.

**Management**

The most important part of management is early diagnosis and treatment of infection (Table 9). Other additional steps in management follow.

**Correction of Fluid and Electrolyte Imbalances.** Initial management should always include aggressive intravascular volume repletion and vasopressive agents if needed to maintain adequate mean arterial blood pressure for organ perfusion.

**Treatment of Infection.** The only effective treatment of cholestasis of sepsis is the appropriate management of the underlying infection. Appropriate antibiotic therapy should be initiated as soon as possible. Septic foci should be removed or drained. A delay in the diagnosis of infection and the initiation of antibiotic therapy significantly worsens the prognosis.

**Enteral Feeding.** Enteral feeding may help to resolve cholestasis. Healthy individuals show a decreased serum bilirubin with continuous enteral feeding. In infants, cholestasis resolves when enteral feeding is introduced.

**Ursodeoxycholic Acid.** Ursodeoxycholic acid can potentially improve bile flow and bilirubin levels in TPN-AC- and drug-induced cholestasis. Currently, the clinical evidence is insufficient to support the use of ursodeoxycholic acid to treat cholestasis from these causes.

**Glycine Administration.** Glycine serum concentrations are decreased in sepsis. At a cellular level, glycine decreases the influx of calcium into Kupffer cells, thereby reducing the release of TNF. This reduction in TNF may play a beneficial role in treatment of sepsis-associated cholestasis and hepatocellular dysfunction. Yang et al. demonstrated a beneficial effect of glycine on hepatocyte function and integrity in sepsis. After administration of this nonessential amino acid early after onset of polymicrobial sepsis in an animal model, hepatocellular function markedly improved and the mortality rate decreased from 50% to 0% 10 days after the onset of sepsis.

**Nitric Oxide Donor Administration.** Nitric oxide (NO) is a paracrine-acting gas enzymatically synthesized from l-arginine. Cholestasis and endotoxemia have been
shown to cause hepatocyte apoptosis through caspase-mediated pathways. In vitro studies show that NO donors attenuate hepatic apoptosis via interruption of mitochondrial apoptotic signaling through S-nitrosylation of caspases.74,75 Brown et al. showed that NO has a hepato-protective effect against this liver injury.76 They showed that providing NO by administering molsidomine (a NO donor) resulted in improved survival in septic rat models and decreased liver injury and hepatocyte apoptosis.76

**N-Acetyl-l-Cysteine.** N-acetyl-l-cysteine (NAC) has been used as a free-radical scavenger, working either as a direct scavenger or by increasing intracellular stores of glutathione. Prior administration of NAC allowed an improved cardiac index and lower maximal TNF levels in endotoxemic dogs compared to controls in a study by Zhang et al.77

### References


