Jaundice and Cholestasis

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Table of Contents

Preface .................................................. ii
Introduction ........................................... 1
Review of Hepatocellular Transport .................. 1
Extrahepatic Biliary Obstruction ..................... 1
Gilbert’s Syndrome .................................. 3
Postoperative Jaundice .............................. 4
Primary Biliary Cirrhosis .........................  5
Summary Points .................................. 6
Board Review Questions ............................ 8
Answers .......................................... 8
References ...................................... 8

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Preface

Board certification in gastroenterology and hepatology requires an understanding of all aspects of physiology, diagnosis, and therapy for gastrointestinal tract, liver, and pancreatic disorders. In addition to self-study of this discipline, candidates for board certification must have completed 2 years of fellowship, during which time the practical aspects of the diagnosis and treatment of gastroenterologic and hepatologic complications are learned through hands-on clinical investigation.

The Hospital Physician Gastroenterology Board Review Manual is a study guide intended to help candidates prepare for the written and oral components of this examination. The manual consists of quarterly publications that address the following areas:

- Acid peptic disease
- Acute appendicitis
- Aging and the gastrointestinal tract
- Basic biology
- Chronic cholestatic syndromes
- Cirrhosis and portal hypertension
- Diverticulosis coli
- Drug-induced and alcoholic liver disease
- Endoscopy of upper gastrointestinal hemorrhage
- Esophageal disorders
- Gallstones
- Gastrointestinal manifestations of AIDS
- Inflammatory bowel diseases and other diarrheal diseases
- Intestinal obstruction
- Irritable bowel syndromes
- Ischemic bowel disease
- Liver transplantation
- Malabsorption syndromes
- Nutritional support
- Pancreatic disease
- Small intestinal, colonic, and other tumors
- Viral and chronic hepatitis

Most of these topics are covered in the manual; however, some areas of interest are discussed in greater depth than others.

The manual presents clinical scenarios using a case-based format; questions and answers relating to the clinical presentation are provided. The editors believe that this question-and-answer format is an effective teaching tool and allows for adequate self-assessment. Each quarterly publication addresses only a few of the topics mentioned; board certification candidates should review the entire list of topics to be appropriately prepared for the examination. The Hospital Physician Gastroenterology Board Review Manual is prepared by the Series Editor and contributing authors and not in collaboration with the American Board of Internal Medicine, Gastroenterology/Hepatology.

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INTRODUCTION

One of the most important functions of the liver is bile formation. Disruptions in bile formation often become evident as cholestasis. Cholestasis is a condition in which there is impaired secretion of the numerous components of bile (which are normally removed from the portal circulation and transported into bile via hepatocytes, and secreted into the gut via the biliary system). Jaundice is a common presenting symptom of cholestasis. However, some conditions produce jaundice in the absence of cholestasis; jaundice is one of the most frequent (and typically the most obvious) presenting symptom of numerous diseases of the liver and biliary tract. Cholestasis can also be caused by numerous hepatobiliary diseases; it may be caused by diminished hepatic transport function (intrahepatic cholestasis) or by an anatomic obstruction to bile flow in the biliary system (extrahepatic cholestasis). This manual briefly describes mechanisms involved in the hepatocellular transport of substances into bile and uses case-based discussions to describe important steps in diagnosing the cause of jaundice and/or cholestasis in patients.

REVIEW OF HEPATOCELLULAR TRANSPORT

Jaundice, pruritus, and other symptoms and signs of cholestasis are caused by impaired elimination of numerous endogenous and pharmacologic substances, with a resultant increase in their serum levels. This impairment sometimes results from defects in the molecular mechanisms by which the liver transports these substances from the portal blood, across the hepatocyte, and into the biliary system. Over the past decade, many of these molecular mechanisms have been identified. Although a detailed discussion of these mechanisms is beyond the scope of this manual, a brief description of the uptake of these substances by the liver and their subsequent secretion into bile may be beneficial.

Figure 1 is a schematic representation of the general mechanisms involved in the hepatocellular uptake and secretion of the organic anions bilirubin (unconjugated) and bile salts. Each of these substances has distinct liver sinusoidal and canalicular transport proteins, which transport the compounds from the blood (sinusoidal proteins) into bile (canalicular proteins). These transport proteins are representative of other hepatic transport systems for other substrates. A reduction in the physiologic function of hepatic transport systems results in intrahepatic cholestasis.

Moreover, the liver must also metabolize water-insoluble substances into water-soluble substances prior to their secretion into bile. Unconjugated bilirubin is the end product of heme degradation. Because unconjugated bilirubin is insoluble in water, it requires hepatic metabolism into a conjugated form (ie, bilirubin monoglucuronide or diglucuronide) by the endoplasmic reticulum enzyme, bilirubin uridine-diphosphate glucuronosyltransferase (UGT), before it can be secreted into bile. Conjugated bilirubin (a water-soluble substance) is secreted across the canalicular membrane. A disruption of either bilirubin metabolism (conjugation) or secretion can result in jaundice. Unconjugated (indirect) hyperbilirubinemia results from a disruption of bilirubin conjugation, whereas conjugated (direct) hyperbilirubinemia results from a disruption of bilirubin secretion.

Liver diseases frequently impair bilirubin secretion and result in clinical jaundice, the most easily “seen” manifestation of cholestasis. However, a clinician must remember that there may also be concomitant impairments of hepatic drug metabolism and secretion, as well as impairments regarding the excretion of endogenous toxins, which may be less easily “seen.”

EXTRAHEPATIC BILIARY OBSTRUCTION

CASE 1 PRESENTATION

Patient 1 is a 22-year-old woman with a 3-day history of acholic stools, dark urine, and painless jaundice. She had given birth 1 month ago to a boy who had neonatal jaundice; however, her son is now completely healthy. She had an uncomplicated pregnancy and delivery.

She denies experiencing any fevers, chills, pruritus, or abdominal pain. Physical examination findings are
unremarkable except for icteric sclera and jaundice. Her serum bilirubin level is 6.8 mg/dL; the direct (conjugated) bilirubin level is 6.0 mg/dL. Her alkaline phosphatase level is 675 U/L. Her alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels are 67 U/L and 54 U/L, respectively.

**DIFFERENTIAL DIAGNOSIS**

The causes of hyperbilirubinemia are listed in Table 1. Patient 1 has direct (conjugated) hyperbilirubinemia. The results of the initial laboratory evaluation, in which the serum bilirubin and alkaline phosphatase levels are elevated out of proportion to the aminotransferase levels, suggest that the cause of the jaundice is biliary in nature, rather than hepatocellular.

Obstructive, painless jaundice is frequently indicative of malignant disease; however, it can result from benign conditions, as well. Common malignancies that may cause biliary obstruction include cholangiocarcinoma, hepatocellular carcinoma or a hepatic metastasis, tumors of the pancreas or ampulla of Vater, and gastric or duodenal tumors. Additionally, extensive periportal lymphadenopathy caused by lymphomas or metastatic carcinoma can cause obstruction of the biliary tract.

Choledocholithiasis is a common, benign cause of biliary obstruction, and although it typically presents with abdominal pain, it may also present in the absence of pain. Patient 1 has no fever or evidence of infection, so it is unlikely that she has cholangitis, which would require more emergent intervention.

**DIAGNOSTIC EVALUATION**

The initial diagnostic evaluation of a patient with jaundice due to conjugated hyperbilirubinemia should involve a determination of whether or not there is biliary obstruction. An evaluation for biliary dilatation through abdominal ultrasonography, or alternatively through abdominal computed tomography (CT) scanning or magnetic resonance imaging (MRI), is indicated as an initial diagnostic test. Ultrasonography is sensitive for the evaluation of biliary dilatation and choledolithiasis. In addition, it can also be used to examine the hepatic parenchyma and other abdominal organs. The other radiologic imaging modalities are typically more effective.

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**Figure 1.** Schematic representation of the mechanisms involved in the hepatocellular transport of a bile salt and bilirubin from the portal blood into bile. The hydrophilic bile salt is taken up by the hepatocyte via the sinusoidal transport protein, sodium taurocholate cotransporting polypeptide (NTCP). It traverses the hepatocyte to the bile canalicular membrane, where it is secreted into bile by the ATP-dependent bile salt export pump (BSEP) transporter. Unconjugated bilirubin, which is not soluble in water, is bound to albumin in the perisinusoidal space and is taken up by the hepatocyte at the sinusoidal membrane via a mechanism that is not yet fully understood. It is subsequently conjugated (glucuronidated) by the endoplasmic reticulum (ER) enzyme, bilirubin uridine-diphosphate glucuronosyltransferase (bUGT), into its hydrophilic form, which enables it to be secreted into bile via the canalicular transporter multidrug resistance protein 2 (MRP2).

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2 Hospital Physician Board Review Manual
than ultrasonography for evaluating a patient for pancreatic and other abdominal masses and may be preferred for the initial radiologic evaluation if malignant obstruction is suspected.

Recent data have shown that MRI/magnetic resonance imaging cholangiopancreatography (MRCP) is highly effective for diagnosing biliary obstructive diseases, as well as primary sclerosing cholangitis, although it is slightly less sensitive than endoscopic retrograde cholangiopancreatography (ERCP). Moreover, MRI/MRCP may be more cost-effective than invasive cholangiography in the diagnostic setting, mainly because MRI/MRCP has a lower complication rate. However, if there is a high clinical suspicion of extrahepatic obstruction, ERCP or percutaneous transhepatic cholangiography (PTC) should be performed. Surgical intervention (with possible intraoperative cholangiography) may be required for definitive therapy but is often not performed prior to nonsurgical cholangiography. The obvious advantage of performing ERCP or PTC rather than MRI/MRCP if there is a high clinical suspicion of biliary obstruction is that ERCP and PTC are useful both diagnostically and therapeutically. Common bile duct stones can be removed, biliary obstruction can be alleviated with stenting, and biopsy specimens and brushings can be obtained for histopathologic evaluation, to confirm the presence of malignant disease.

CONTINUED CLINICAL COURSE OF PATIENT 1

Patient 1 undergoes an ultrasonographic evaluation, which shows cholelithiasis and intrahepatic and extrahepatic biliary dilatation. She subsequently undergoes diagnostic and therapeutic ERCP for confirmation and treatment of choledocholithiasis (Figure 2).

GILBERT’S SYNDROME

CASE 2 PRESENTATION

Patient 2 is a 23-year-old man presenting to his internist for a routine health examination. He has no significant prior medical history. He is currently taking no medications, drinks minimal amounts of alcoholic beverages, and has no risk factors for the acquisition of viral hepatitis.

Physical examination findings are entirely unremarkable. Serum liver chemistry tests indicate a bilirubin level of 2.4 mg/dL, with normal serum ALT, AST, and alkaline phosphatase levels. When his physician notifies him of the test results, the patient recalls that he had yellow eyes on 2 occasions during his teens—during both times he also had flu-like symptoms.

DIFFERENTIAL DIAGNOSIS

There are several hepatic and biliary diseases that could be causing patient 2’s hyperbilirubinemia. However, many of the causes of hyperbilirubinemia (Table 1) can be easily eliminated with respect to patient 2 (eg, medications, sepsis, total parenteral nutrition [TPN], pregnancy, neonatal jaundice, congenital syndromes). His history of intermittent jaundice over the past decade; the unremarkable physical examination findings; normal ALT, AST, and alkaline phosphatase levels; and the asymptomatic nature of the mild hyperbilirubinemia make cirrhosis and obstructive causes secondary to abdominal malignancies less likely to be responsible for the elevated serum bilirubin. The patient’s presentation is mostly consistent with Gilbert’s syndrome, which is highly prevalent in the general population.

FURTHER EVALUATION OF PATIENT 2

A further evaluation of patient 2 should involve a determination of whether the hyperbilirubinemia is unconjugated (indirect) or conjugated (direct). In a healthy individual with mild unconjugated hyperbilirubinemia (serum total bilirubin concentration, < 4 mg/dL) and otherwise normal serum liver chemistry test results, the diagnosis of Gilbert’s syndrome is highly likely.

Table 1. Causes of Conjugated and Unconjugated Hyperbilirubinemia

<table>
<thead>
<tr>
<th>Conjugated hyperbilirubinemia</th>
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<tbody>
<tr>
<td>Bile duct obstruction</td>
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<tr>
<td>Medications/toxins</td>
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<tr>
<td>Hepatitis or cirrhosis</td>
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<tr>
<td>Cholestatic liver diseases</td>
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<tr>
<td>Sepsis or infection</td>
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<tr>
<td>Total parenteral nutrition</td>
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<tr>
<td>Intrahepatic cholestasis of pregnancy</td>
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<tr>
<td>Benign recurrent cholestasis</td>
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<tr>
<td>Postoperative jaundice</td>
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<tr>
<td>Dubin-Johnson syndrome</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Unconjugated hyperbilirubinemia</th>
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<tr>
<td>Gilbert’s syndrome</td>
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<tr>
<td>Increased heme breakdown</td>
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<tr>
<td>Neonatal jaundice</td>
</tr>
<tr>
<td>Crigler-Najjar syndrome</td>
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CHARACTERISTICS OF GILBERT’S SYNDROME

Gilbert’s syndrome is a benign, unconjugated hyperbilirubinemia occurring in approximately 5% of the normal population. It is caused, at least in part, by a genetic polymorphism in the TATA box of the promoter region of the gene that encodes for bilirubin UGT,7,8 the hepatic enzyme that converts unconjugated bilirubin into a conjugated, water-soluble form so that it can be secreted into bile for eventual elimination through the gut (Figure 1). This enzyme is first expressed during the neonatal period and continues to be expressed throughout adulthood. It is usually functional even when there is severe liver disease. However, in patients with Gilbert’s syndrome, there is a reduced expression of this enzyme.

Although this genetic variant is usually of no clinical significance, it may predispose patients to drug-induced hyperbilirubinemia, which may potentially result in discontinuation of necessary medical therapy.10 In addition, indirect hyperbilirubinemia caused by Gilbert’s syndrome may result in extensive and costly medical evaluations if clinicians are not aware of this highly prevalent and generally benign genetic variant.

Although fasting or modified diets, nicotinic acid administration tests, and molecular analysis of the bilirubin UGT gene can be used to diagnosis this entity,10–12 these measures are not routinely required. A complete inventory of a patient’s prescription, herbal, and over-the-counter medications is required to exclude medication-induced causes of hyperbilirubinemia. Occult hemolysis should be excluded by using standard laboratory tests (eg, hemoglobin concentration, reticulocyte count, haptoglobin level, peripheral blood smear), and one should confirm the presence of normal serum aminotransferase and alkaline phosphatase levels. With these measures, a presumptive diagnosis of Gilbert’s syndrome can be made and the provocative tests cited above are thus not routinely required.

POSTOPERATIVE JAUNDICE

CASE 3 PRESENTATION

Patient 3 is a 28-year-old man who was in excellent health until 10 days ago when he fractured his femur and experienced severe head and abdominal trauma in a motor vehicle accident. On the day of the accident, he was brought to the emergency room in a comatose condition and underwent an exploratory laparotomy, which revealed a ruptured spleen. A splenectomy was performed. In addition, he underwent orthopedic and neurosurgical procedures and has remained comatose and on mechanic ventilation due to severe pneumonia.

After the exploratory laparotomy, he developed progressive hyperbilirubinemia. He has had the hyperbilirubinemia for the past 10 days. He is unable to give a history secondary to his head trauma, but his medical history as provided by his sister is unremarkable. However, she notes that he consumed large amounts of alcohol on a daily basis before the accident.

He is receiving TPN and multiple medications including anticonvulsants. Following his splenectomy, he experienced postoperative bleeding, which was treated conservatively with blood transfusions. He is intubated and comatose and has a fever (temperature, 102.5°F [39.2°C]). His physical examination is notable for multiple ecchymosis, but with no stigmata of chronic liver disease. His serum total bilirubin level is 16 mg/dL; his direct bilirubin level is 12.8 mg/dL. Alkaline phosphatase, ALT, and AST levels are slightly elevated—they are less than 1 and 1/2 times normal. His serum liver chemistry test results were normal at the time of admission.

PATHOGENESIS OF POSTOPERATIVE JAUNDICE

Patient 3 presents with a syndrome often termed postoperative jaundice.13 Postoperative jaundice resolves in most patients without specific intervention, when the patient clinically improves. However, some patients have causative factors that can be potentially life threatening.

Factors that contribute to the clinical picture of postoperative jaundice include varying degrees of bilirubin overproduction; hepatocellular injury and hypoxemia;...
intrahepatic cholestasis from drugs, infection, or TPN; and biliary obstruction. Because bilirubin is the breakdown product of heme, blood transfusions with (1) hemolysis, (2) disseminated intravascular coagulation, or (3) resorption of large hematomas can increase bilirubin production. Hypoxemia and perioperative or postoperative hypotension predispose the liver to ischemic injury. Multiple medications can cause either hepatotoxicity or cholestasis in the absence of hepatic injury by altering the function of hepatic transport proteins; TPN and sepsis also cause intrahepatic cholestasis, likely via the same mechanisms. Finally, biliary obstruction and bile leaks (secondary to trauma or iatrogenic injury) raise serum bilirubin levels by preventing its secretion into the gut.

EVALUATION AND MANAGEMENT

The diagnostic evaluation must be focused on determining whether there are any causes of jaundice present that require medical or surgical intervention. Also, an evaluation of the prothrombin time (PT) is essential, because elevations of the PT and the presence of encephalopathy (which cannot be assessed with regard to patient 3 owing to his comatose condition) are the most important predictors of hepatic failure.14,15

Patient 3 had extensive abdominal trauma and abdominal surgery, and thus, an evaluation to exclude an injury to the bile duct, causing a bile leak, or biliary obstruction should be performed. An abdominal CT scan (or potentially MRI or ultrasonography) could be performed to rule out biliary dilatation, fluid collections consistent with bilomas, intra-abdominal hematomas, abscesses, or other fluid collections. If bile duct injury is evident, a diagnostic and potentially therapeutic ERCP is warranted (although surgical repair may also be required on occasion). If the hyperbilirubinemia is less severe, hepato-iminodiacetic acid (HIDA) scans can be used to reveal bile leaks but are not frequently required.

Also, it is important to evaluate for potentially treatable medical causes of intrahepatic cholestasis. Considering that TPN can cause cholestasis, enteric feedings should be instituted if possible. Many anticonvulsant and other drugs cause hepatotoxicity and cholestasis; all unnecessary medications should be discontinued, or alternative medications should be instituted. Because sepsis and occult infections (including abscesses) can cause intrahepatic cholestasis, efforts should be made to diagnose and treat infections promptly. In addition, resorption of hematomas and hemolysis from blood transfusions (or other causes) also increase bilirubin production. However, blood transfusions are typically prescribed only if clinically indicated, and hematomas obviously do not require evacuation because of hyperbilirubinemia.

PRIMARY BILIARY CIRRHOSIS

CASE 4 PRESENTATION

Patient 4 is a 42-year-old woman with a 2-month history of generalized pruritus. She also has a 10-year history of irritable bowel syndrome (IBS); she has 4 to 6 loose bowel movements per day and occasional constipation. She has been undergoing thyroid replacement therapy for 6 years owing to hypothyroidism. For the past 2 months, she has noted generalized pruritus without a rash, which is now making it difficult for her to sleep. She is referred from her internist, who ordered serum liver chemistry tests, which revealed an alkaline phosphatase level of 987 U/L, bilirubin of 0.9 mg/dL, ALT of 111 U/L, and AST of 88 U/L. Her physical examination is notable for extensive excoriations but otherwise yields unremarkable findings. Her internist recently reviewed her medical records and noted that she had an isolated, elevated alkaline phosphatase level of 2 times normal on routine blood screening 2 years ago.

DIFFERENTIAL DIAGNOSIS

The fact that the ALT and AST levels are elevated strongly suggests that the elevation of the alkaline phosphatase level is of hepatic origin. The differential diagnosis of an elevated alkaline phosphatase level of hepatic origin is listed in Table 2. In order to confirm that an elevated alkaline phosphatase level is of hepatic origin (as opposed to originating from bone, the gut, or, in pregnant women, the placenta), one can measure the serum γ-glutamyltransferase or 5′-nucleotidase level or fractionate the alkaline phosphatase for isoenzyme determination.

Patient 4’s pruritus is likely associated with cholestasis, although the pruritogenic substance remains unclear. Given the patient’s age and gender, one should have a high suspicion for primary biliary cirrhosis. The chronic diarrhea that has been diagnosed as IBS could potentially be caused by inflammatory bowel disease. If so, this would raise the clinical suspicion of primary sclerosing cholangitis, although this disease is more prevalent in males. Similarly, primary biliary cirrhosis is associated with celiac sprue, which can also cause malabsorption and diarrhea.

FURTHER EVALUATION OF PATIENT 4

In the evaluation of patient 4, biliary obstruction needs to be excluded. If an ultrasonographic evaluation yields unremarkable findings, a test for antimitochondrial antibody (AMA) should be performed; it is positive in

Jaundice and Cholestasis
at least 90% of patients with primary biliary cirrhosis. This diagnosis can be confirmed (even in patients with negative AMA test results) with a liver biopsy. However, if the AMA test result is negative, the clinician should consider imaging the biliary system (especially in male patients) with either ERCP or MRCP. Although a liver biopsy may be useful for staging primary sclerosing cholangitis, ERCP and MRCP are the diagnostic procedures of choice because these procedures can be used to observe the large bile ducts.

Patient 4 had a normal colonoscopy 1 year ago; this fact makes inflammatory bowel disease less likely. She is not taking any new medications and has no evidence of systemic disease. Nonetheless, in the presence of a chronically elevated hepatic alkaline phosphatase level, a liver biopsy should strongly be considered.

Patient 4 has an AMA titer of 1:2560. The micrograph of the specimen obtained during the liver biopsy, which confirmed the diagnosis of primary biliary cirrhosis, is shown in Figure 3A. (Figure 3B is the micrograph of a liver biopsy specimen obtained from a patient with primary sclerosing cholangitis, shown for comparison.)

**SYMPTOMS AND SIGNS OF PRIMARY BILIARY CIRRHOSIS**

Patients with primary biliary cirrhosis may develop fatigue, pruritus, fat-soluble vitamin deficiencies, osteoporosis, skin xanthomata, complications of portal hypertension, or liver failure. Severe osteoporosis is common in patients with primary biliary cirrhosis, and although the metabolism of vitamin D is normal, malabsorption of calcium and vitamin D may occur. Fat-soluble vitamin malabsorption may necessitate supplementation with vitamins A, D, E, and K. The serum cholesterol may be extremely high in patients with primary biliary cirrhosis, causing skin xanthomas and xanthelasmas; however, retrospective studies do not suggest an increase in atherosclerotic heart disease associated with primary biliary cirrhosis. However, many other diseases, including thyroid disease, Sjögren’s syndrome, Raynaud’s phenomenon, and celiac sprue, are associated with primary biliary cirrhosis.

**TREATMENT OF PRIMARY BILIARY CIRRHOSIS**

Ursodeoxycholic acid (UDCA) at a dosage of 12 to 15 mg/kg daily is recommended for the treatment of primary biliary cirrhosis. Although UDCA appears to slow the progression of primary biliary cirrhosis, it does not lead to a complete resolution of the disease. Thus, primary biliary cirrhosis will continue to progress to end-stage liver disease. The most reliable determinants of the prognosis of primary biliary cirrhosis are the serum bilirubin level and the Mayo risk score. In end-stage liver disease, liver transplantation is indicated. Immunosuppressive therapies have not been shown to prolong survival and should be regarded as investigational or unproven at the current time.

**TREATMENT OF CHOLESTATIC PRURITUS**

The pruritus associated with cholestatic liver disease can be treated with UDCA or with oral anion-exchange resins such as cholestyramine. Cholestyramine should not be taken within 4 hours of taking UDCA. Antihistamines and topical therapies may also have some efficacy in treating the itching. Rifampicin has been shown to decrease the pruritus; naloxone, naltrexone, ultraviolet light exposure, and plasmapheresis have also been used for refractory patients.

**SUMMARY POINTS**

- Cholestasis is a condition in which there is impaired secretion of the numerous components of bile (which are normally removed from the portal circulation and transported into bile via hepatocytes, and secreted into the gut via the biliary system).
- Cholestasis may be caused by diminished hepatic transport function (intrahepatic cholestasis) or by an anatomic obstruction to bile flow in the biliary system (extrahepatic cholestasis).
• The liver must metabolize water-insoluble substances into water-soluble substances prior to their secretion into bile.
• A disruption of either bilirubin metabolism (conjugation) or secretion can result in jaundice.
• Obstructive, painless jaundice is frequently indicative of malignant disease; however, it can result from benign conditions, as well.
• Ultrasonography is sensitive for the evaluation of biliary dilatation and cholelithiasis; MRI, MRI/MRCP, ERCP, or PTC may be preferred for the initial radiologic evaluation if malignant obstruction is suspected.
• Gilbert’s syndrome is a benign, unconjugated hyperbilirubinemia occurring in approximately 5% of the normal population.
• Factors that contribute to the clinical picture of postoperative jaundice include varying degrees of bilirubin overproduction; hepatocellular injury and hypoxemia; intrahepatic cholestasis from drugs, infection, or TPN; and biliary obstruction.
• Patients with primary biliary cirrhosis may develop fatigue, pruritus, fat-soluble vitamin deficiencies, osteoporosis, skin xanthomata, complications of portal hypertension, or liver failure.
• The most reliable determinants of the prognosis of primary biliary cirrhosis are the serum bilirubin level and the Mayo risk score; in end-stage liver disease, liver transplantation is indicated.

Figure 3. (A) High-power view of a liver biopsy specimen of a patient with primary biliary cirrhosis, showing the portal triad; there is a monocytic infiltrate and bile duct destruction. (B) High-power view of a liver biopsy specimen of a patient with primary sclerosing cholangitis, also showing the portal triad; there is concentric fibrosis of the portal area, and an “onion skin” appearance. Although a liver biopsy specimen may have characteristic findings and may be useful for staging the disease, primary sclerosing cholangitis should be diagnosed via cholangiography.
BOARD REVIEW QUESTIONS

Choose the single best answer for each question.

1. A 60-year-old man presents with a 1-month history of painless jaundice, generalized pruritus, choluria, and acholic stools. His serum total bilirubin level is 20 mg/dL. His alkaline phosphatase level is 1500 U/L, and his alanine aminotransferase level is 35 U/L. A sonogram and CT scan confirm the presence of extrahepatic ductal dilatation and a pancreatic mass. There is no evidence of liver involvement, but the CT scan shows portal vein invasion, precluding surgical extirpation. The patient undergoes ERCP with stenting of the obstructed duct and is being prepared for chemotherapy and irradiation therapy. However, his bilirubin level 1 week later is still 15 mg/dL. Which of the following is the most likely explanation for his continued high bilirubin level?
   A) Intrahepatic metastasis  
   B) Stent has occluded  
   C) Drug toxicity  
   D) Normal catabolic processes of albumin  
   E) Previously unknown Gilbert’s syndrome

2. A 24-year-old man develops severe nausea, vomiting, diarrhea, and fever (temperature, 102°F). He is seen in the emergency room, is found to have scleral icterus, and is admitted with a presumptive diagnosis of acute viral hepatitis, probably hepatitis A. His blood studies show a total bilirubin level of 4.0 mg/dL, but his alkaline phosphatase and aminotransferase levels are normal. Which of the following is the most likely explanation for this patient’s illness?
   A) Dubin-Johnson syndrome  
   B) Gilbert’s syndrome  
   C) Extrahepatic biliary obstruction  
   D) Acetaminophen toxicity  
   E) Viral hepatitis

3. A clinician evaluates a patient in the ward who is receiving postoperative total parenteral nutrition and notes that there has been a rise in the patient’s alkaline phosphatase, and serum bilirubin levels. The patient weighs 70 kg and is receiving 100 g of fat (lipid emulsion), 100 g of protein, and 3000 kcal per day intravenously. Which of the following is the most appropriate recommendation regarding this patient’s feeding regimen?
   A) Increase the fat component and the protein component  
   B) Decrease the fat component and the total calories

ANSWERS

1. The answer is D. When there has been an elevated bilirubin level for several weeks, the bilirubin becomes covalently bound to albumin; thus, the decline in the bilirubin level would be related to the catabolism of serum albumin. Albumin kinetic studies have shown that in healthy subjects serum albumin has a long half-life (in the range of 20 days) and in patients who are acutely ill serum albumin has a shorter half-life (in the range of 10 days). It is not unusual for the bilirubin level to decline slowly in such patients as the one presented in question 1.

2. The answer is B. The patient probably has Gilbert’s syndrome, and the jaundice is probably brought out by his fever and fasting—both of which accentuate the indirect hyperbilirubinemia. His urine should show no increase in bilirubin, as the direct-reacting bilirubin level should be normal.

3. The answer is B. Studies of cholestasis in patients receiving total parenteral nutrition have shown that fat administered in excess of 1 g/kg body weight per day, and calories in excess of 40 kcal/kg per day expose a patient to the risk of liver disease. The amount of fat and calories the patient is being administered should be decreased. The protein component is satisfactory (approximately 1.4 g/kg per day).

REFERENCES


