Classification and causes of jaundice or asymptomatic hyperbilirubinemia

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INTRODUCTION

The normal serum bilirubin concentration in children and adults is less than 1 mg/dL (17 micromol/liter), less than 5 percent of which is present in conjugated form. The measurement is usually made using diazo reagents and spectrophotometry. Conjugated bilirubin reacts rapidly ("directly") with the reagents. The measurement of unconjugated bilirubin requires the addition of an accelerator compound and is often referred to as indirect bilirubin. (See "Clinical aspects of serum bilirubin determination".)

Jaundice is often used interchangeably with hyperbilirubinemia. However, a careful clinical examination cannot detect jaundice until the serum bilirubin is greater than 2 mg/dL (34 micromol/liter), twice the normal upper limit. The yellow discoloration is best seen in the periphery of the ocular conjunctivae and in the oral mucous membranes (under the tongue, hard palate). Icterus may be the first or only sign of liver disease; thus, its evaluation is of critical importance.

This topic will review the causes of asymptomatic hyperbilirubinemia. The diagnostic approach to the patient with jaundice and the causes of hyperbilirubinemia presenting in the neonatal period are discussed separately. (See "Diagnostic approach to the adult with jaundice or asymptomatic hyperbilirubinemia" and "Unconjugated hyperbilirubinemia in neonates: Etiology and pathogenesis" and "Causes of cholestasis in neonates and young infants" and "Bilirubin metabolism".)

CLASSIFICATION

For clinical purposes, the predominant type of bile pigments in the plasma can be used to classify hyperbilirubinemia into two major categories (table 1).

- **Unconjugated hyperbilirubinemia** – Unconjugated hyperbilirubinemia is characterized by plasma elevation of predominantly unconjugated bilirubin due to the overproduction of bilirubin, impaired bilirubin uptake by the liver, or abnormalities of bilirubin conjugation.
- **Conjugated hyperbilirubinemia** – In patients with conjugated hyperbilirubinemia, both unconjugated and conjugated bilirubin levels increase. Conjugated hyperbilirubinemia may be due to hepatocellular diseases, impaired canalicular excretion, defective reuptake of conjugated bilirubin, or biliary obstruction.

DISORDERS ASSOCIATED WITH UNCONJUGATED HYPERBILIRUBINEMIA

Three basic pathophysiologic mechanisms, overproduction of bilirubin, reduced bilirubin uptake, and impaired bilirubin conjugation, are mainly responsible for unconjugated hyperbilirubinemia.

Overproduction of bilirubin — Bilirubin overproduction may result from excessive breakdown of heme derived from hemoglobin. Extravascular or intravascular hemolysis, extravasation of blood in tissues, or dyserythropoiesis are causes of enhanced heme catabolism.

- **Conditions associated with bilirubin overproduction**
  - **Hemolysis** – The reticuloendothelial cells of the spleen, bone marrow, and liver are responsible for the increased extravascular destruction of erythrocytes, which occurs in most hemolytic disorders. These phagocytic mononuclear cells are rich in heme oxygenase and biliverdin reductase activities and rapidly degrade heme to bilirubin (figure 1). (See "Bilirubin metabolism".)

    With intravascular hemolysis, bilirubin is predominantly formed in the liver and the kidneys. Hemoglobin released in the circulation is bound to haptoglobin; this complex is internalized and degraded by hepatocytes. However, circulating haptoglobin may be depleted with massive hemolysis. In these cases, unbound hemoglobin is converted to methemoglobin, from which heme is transferred to hemopexin or to albumin, forming methemalbumin. Heme-hemopexin and methemalbumin are internalized by hepatocytes, where heme is degraded to bilirubin. A significant fraction of free

methemoglobin is filtered by renal glomeruli after dissociation of the tetrameric globin to two dimers. Only the free (unbound) dimer is small enough to be filtered across the glomeruli. The heme moiety of filtered methemoglobin is largely degraded by tubular epithelial cells to bilirubin.

- **Dyserythropoiesis** – In a variety of diseases including megaloblastic and sideroblastic anemias, severe iron deficiency anemia, erythropoietic porphyria, erythroleukemia, lead poisoning, and a rare disorder of unknown pathogenesis termed primary shunt hyperbilirubinemia, the incorporation of hemoglobin into erythrocytes is defective [1,2]. This leads to the degradation of a large fraction of unincorporated hemoglobin heme.

- **Extravasation** – When blood is extravasated into tissues, or pleural or peritoneal cavities, erythrocytes are phagocytosed by tissue macrophages that degrade heme to biliverdin, resulting in the sequential green and yellow discoloration of the skin overlying a hematoma. The biliverdin is immediately reduced to unconjugated bilirubin by the enzyme biliverdin reductase and is released into the plasma.

- **Pattern of bilirubin elevation based on the presence of underlying liver disease**

  - **Patients without liver disease** – In hemolysis, unconjugated bilirubin production can increase up to 10-fold. The canalicular excretion of bilirubin is the rate-limiting step in bilirubin elimination since hepatic conjugating capacity normally exceeds maximum bilirubin production. These relationships account for two findings at a steady state of maximum bilirubin production in patients with normal hepatic function. First, the serum bilirubin concentration will not exceed 4 mg/dL (68 micromol/liter) in patients with normal liver function [3] and second, the proportion of conjugated bilirubin in plasma (approximately 3 to 5 percent of the total) remains normal [4]. However, hemolysis can lead to severe mixed conjugated and unconjugated hyperbilirubinemia in patients who have even mild hepatic disease.

  - **Patients with coexisting liver disease** – Most liver diseases affect canalicular excretion, resulting in the accumulation of both conjugated and unconjugated bilirubin in hepatocytes. In cholestatic states, the canalicular ATP-dependent organic anion pump, MRP2 (also termed ABCC2), is down-regulated. This may lead to upregulation of other forms of MRP, such as MRP3 (also termed ABCC3), in the contiguous membranes of the hepatocyte, resulting in active transport of unconjugated and conjugated bilirubin into the plasma [5,6]. Thus, plasma bilirubin accumulating in conditions resulting from a combination of bilirubin overload and liver disease is usually a mixture

of unconjugated and conjugated bilirubin. In cases where there is an inherited deficiency of conjugation (eg, Gilbert syndrome), hemolysis causes almost pure unconjugated hyperbilirubinemia. The rate-limiting step in these patients is bilirubin glucuronidation, rather than canalicular excretion. (See "Gilbert syndrome".)

Impaired hepatic bilirubin uptake — Impaired delivery of bilirubin to the liver and disorders of internalization of bilirubin by the hepatocyte result in reduced hepatic bilirubin uptake (figure 2).

- Medications (eg, rifamycin antibiotics, probenecid, flavaspidic acid, and bunamiodyl, a cholecystographic agent) can cause abnormal bilirubin uptake. The drug-induced defect usually resolves within 48 hours after discontinuation of the drug [7].

- Impaired bilirubin uptake at the sinusoidal surface of hepatocytes has been reported in some cases of Gilbert syndrome. (See "Gilbert syndrome".).

- Congestive heart failure or portosystemic shunts (spontaneously occurring collaterals in cirrhosis or surgical shunts) reduce hepatic blood flow and the delivery of bilirubin to hepatocytes, resulting in predominantly unconjugated hyperbilirubinemia. In some patients with cirrhosis, the direct contact of plasma with the hepatocytes may be compromised due to capillarization of the sinusoidal endothelial cells (loss of fenestrae), resulting in a further reduction in bilirubin uptake [8].

Impaired bilirubin conjugation — Reduced bilirubin conjugation as a result of a decreased or absent UDP-glucuronosyltransferase activity is found both in several acquired conditions and inherited diseases, such as Crigler-Najjar syndrome type I and II and Gilbert syndrome. (See "Gilbert syndrome" and "Crigler-Najjar syndrome".)

UGT activity toward bilirubin is modulated by various hormones. Hyperthyroidism and ethinyl estradiol, but not other oral contraceptives, inhibit bilirubin glucuronidation [9]. In comparison, the combination of progestational and estrogenic steroids results in increased enzyme activity. Bilirubin glucuronidation can also be inhibited by certain antibiotics (eg, novobiocin or gentamicin at serum concentrations exceeding therapeutic levels) and antiretroviral drugs (eg, atazanavir) [10]. Reduced bilirubin glucuronidation by liver tissue has been reported in chronic persistent hepatitis, advanced cirrhosis, and Wilson's disease.

DISORDERS ASSOCIATED WITH CONJUGATED HYPERBILIRUBINEMIA

Disorders with conjugated hyperbilirubinemia can be categorized according to their pathophysiology into those that are due to biliary obstruction (extrahepatic cholestasis), intrahepatic cholestasis, and hepatocellular injury (table 2 and table 3).

Cholestatic disorders — In disorders associated with cholestasis, both conjugated and unconjugated bilirubin accumulate in serum and patients have elevations in alkaline phosphatase. There is a disproportionate elevation in the alkaline phosphatase compared with the serum aminotransferases. Tests of synthetic function (eg, albumin, prothrombin time) may be abnormal. (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Patterns of liver test abnormalities'.)

Extrahepatic cholestasis/biliary obstruction — In biliary obstruction, both conjugated and unconjugated bilirubin accumulate in serum. Bilirubin may be transported back to the plasma via an MRP group of ATP-consuming pumps [6,11]. The serum concentrations of conjugated bilirubin and alkaline phosphatase can be used as markers for hepatobiliary obstruction. Obstruction of biliary flow causes retention of conjugated bilirubin within the hepatocytes, where reversal of glucuronidation may take place. The unconjugated bilirubin formed by this process may diffuse or be transported back into the plasma. (See "Bilirubin metabolism", section on 'Excretion of conjugated bilirubin'.)

Differential diagnosis of conjugated hyperbilirubinemia due to biliary obstruction varies with age (table 2). In adults, it includes cholelithiasis, intrinsic and extrinsic tumors, primary sclerosing cholangitis (PSC), parasitic infections, lymphoma, AIDS cholangiopathy, acute and chronic pancreatitis, and strictures after invasive procedures [12].

Intrahepatic cholestasis — A number of intrahepatic disorders can lead to jaundice and an elevated serum alkaline phosphatase (in relation to serum aminotransferases) (table 3). This presentation mimics that of biliary obstruction but the bile ducts are patent.

Inherited diseases — Elevated levels of conjugated bilirubin may occur in inherited diseases such as Dubin-Johnson syndrome, Rotor syndrome, progressive familial intrahepatic cholestasis (PFIC), benign recurrent intrahepatic cholestasis (BRIC), and low phospholipid-associated cholelithiasis (LPAC). BRIC is seen in adolescents and adults, while LPAC presents mainly in young adults. (See "Inherited disorders associated with conjugated hyperbilirubinemia".)

Disorders of fatty acid oxidation are characterized by episodes of metabolic decompensation, with hypoglycemia, liver dysfunction, and/or cardiomyopathy, triggered by fasting or intercurrent illness. These disorders may present at any age, from birth through adulthood.

(See "Metabolic myopathies caused by disorders of lipid and purine metabolism", section on 'Defects of beta-oxidation enzymes'.)

Inherited diseases that cause conjugated hyperbilirubinemia that present during the neonatal period include Alagille syndrome, cystic fibrosis, and disorders of carbohydrate, lipid, or bile acid metabolism. These diseases are discussed in detail separately. (See "Causes of cholestasis in neonates and young infants".)

Hepatitis

- Viral hepatitis – Viral hepatitis can present as a predominantly cholestatic syndrome with marked pruritus. Serologic evaluation is needed to distinguish this clinically from other causes of cholestasis.

- Alcoholic hepatitis – Cholestasis with fever and leukocytosis is often the distinctive sign of alcoholic hepatitis [13]. The diagnosis should be strongly considered in the jaundiced patient with ethanol dependency, especially if the ratio of serum aspartate aminotransferase (AST) to alanine aminotransferase (ALT) exceeds 2.0 with the values being below 500 international units/L. (See "Clinical manifestations and diagnosis of alcohol-associated fatty liver disease and cirrhosis".)

- Metabolic dysfunction-associated steatotic liver disease (MASLD) or MASLD-associated steatohepatitis (MASH) – Most patients with MASLD are asymptomatic, although some patients with MASH may complain of fatigue, malaise, and vague right upper abdominal discomfort [14]. A variety of conditions such as diabetes mellitus, morbid obesity, certain stomach and small bowel operations, and drugs can cause this disorder. (See "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults".)

Primary biliary cholangitis — Primary biliary cholangitis typically presents with a cholestatic picture, though evidence of hepatocellular injury also exists. (See "Clinical manifestations, diagnosis, and prognosis of primary biliary cholangitis".)

Drugs and toxins — Drug-induced cholestasis can occur in a dose-related fashion (eg, alkylated steroids such as methyltestosterone and ethinyl estradiol) or as an idiosyncratic or allergic reaction in a minority of subjects (eg, chlorpromazine). Drugs and toxins causing hepatocellular injury may eventually present as a predominantly cholestatic syndrome [15].

Certain plants used in "natural" medicines (eg, Jamaican bush tea) contain pyrrolizidine alkaloids, which may cause veno-occlusive disease of the liver [16,17] (see "Hepatotoxicity due

to herbal medications and dietary supplements").

Arsenic can cause cholestasis. It has recently gained increased attention because of its contamination of ground water in various parts of the world [18]. In addition to the well-known skin lesions, arsenic-contaminated drinking water has been associated with hepatic fibrosis and portal hypertension, usually without the formation of cirrhotic nodules.

Parenteral nutrition — Steatosis, lipidosis, and cholestasis are frequently encountered in patients receiving parenteral nutrition. This complication usually requires at least two to three weeks of therapy for the development of cholestasis [19]. The underlying illness, preexisting liver disease, hepatotoxic drugs, and the parenteral nutrition itself all may contribute to the cholestasis.

Parenteral nutrition promotes bacterial overgrowth in the small intestine, which in turn favors conditions well known to induce cholestasis such as translocation of intestinal endotoxins into the portal system [20], bacterial sepsis [21], and the formation of secondary bile acids (eg, lithocholic acid). Other contributing factors to cholestasis include biliary sludge, which occurs in all patients after six weeks of total parenteral nutrition (TPN), and hepatotoxic factors such as tryptophan degradation products and aluminum contaminants.

Sepsis and low perfusion states — Bacterial sepsis is very often accompanied by cholestasis. Multiple factors including hypotension, drugs, and bacterial endotoxins are responsible for the jaundice in these patients [22-24]. On the other hand, hyperbilirubinemia can promote bacterial sepsis by increasing intestinal wall permeability and altering mucosal immunity [25]. Signs of cholestasis can also be found in other low perfusion states of the liver (heart failure, hypotension) and hypoxemia that is not profound enough to produce hepatic necrosis.

Infiltrative disorders — Infiltrative processes of the liver (eg, amyloidosis, lymphoma, sarcoidosis, tuberculosis) can precipitate intrahepatic cholestasis. Paraneoplastic syndromes associated with malignancy can induce a reversible form of cholestasis (Stauffer syndrome) [26]. It has most commonly been described in association with renal cell carcinoma, though it has also been reported in patients with malignant lymphoproliferative diseases, gynecologic malignancies, and prostate cancer [27,28].

Intrahepatic cholestasis of pregnancy — Pruritus, usually occurring in the third trimester of pregnancy but sometimes earlier, typically heralds cholestasis, which may evolve into frank jaundice [29] and may be associated with an increased frequency of stillbirths and prematurity [30]. All the pathologic changes disappear following delivery (see "Intrahepatic cholestasis of pregnancy"). It is of crucial importance to distinguish this entity from other

potentially lethal liver disorders in pregnancy such as acute fatty liver and the HELLP (Hemolysis, Elevated Liver enzymes and Low Platelets) syndrome. (See "Acute fatty liver of pregnancy".)

Other conditions associated with cholestasis

- **Postoperative jaundice** – Jaundice occurs commonly in postoperative patients and is usually multifactorial in origin. Serum unconjugated bilirubin levels may increase because of blood transfusions, hematoma resorption, and hemolysis after heart surgery. Other contributing factors include sepsis, TPN, the administration of hepatotoxic drugs during surgery (such as halothane) [31], postoperative hypoxia, hypotension, or a newly acquired viral hepatitis [32]. Concomitant renal failure will exaggerate the hyperbilirubinemia. Surgery also can exacerbate a preexisting hemolytic disease or unmask an underlying genetic disorder (eg, Gilbert syndrome or glucose-6-phosphate dehydrogenase deficiency). (See "Approach to the patient with postoperative jaundice".)

- **Organ transplantation** – Intrahepatic cholestasis is common in transplant recipients (especially bone marrow and liver). These patients often require TPN and receive multiple potentially hepatotoxic drugs including immunosuppressive agents, which increase the susceptibility to infection. In addition to the skin and intestinal epithelium, other target sites of graft-versus-host disease in bone marrow transplants include the small interlobular bile ducts. The resulting inflammation and destruction lead to cholestasis. Intensive pretransplantation radiation and chemotherapy predisposes to the development of veno-occlusive disease of the liver, with cholestasis and liver failure.

  Signs of cholestasis after orthotopic liver transplantation may reflect preservation injury of the donor organ, an operative complication (bile leak, stricture) [33], and chronic allograft rejection ("vanishing bile duct syndrome"). In addition, cholestasis is occasionally the sole indicator of acute transplant rejection.

- **End-stage liver disease** – With chronic hepatocellular injury, the biochemical profile changes over time as the liver injury progresses to cirrhosis and liver failure. The elevation of liver enzymes, a marker of active liver injury, becomes less prominent or even disappears. The primary manifestations at this time result from impaired hepatic protein synthesis (eg, hypoalbuminemia and a prolonged prothrombin time) and impaired excretory function, leading to jaundice. The hallmarks of end-stage liver disease and cirrhosis, regardless of its etiology, include jaundice with an elevation of both conjugated and unconjugated bilirubin as well as portal hypertension and decreased hepatic synthetic function.

Hepatocellular injury — Hepatocellular injury is typically characterized by the release of intracellular proteins and small molecules into the plasma. Thus, in contrast to cholestatic syndromes, the elevations in serum conjugated and unconjugated bilirubin and bile salts are accompanied by elevations in the serum concentrations of hepatocellular enzymes, such as AST and ALT. Disorders frequently associated with hepatocellular jaundice are listed in the table (table 4). However, many of these conditions can also present with cholestatic syndromes.

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or email these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Jaundice in adults (The Basics)" and "Patient education: Gilbert syndrome (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Classification of hyperbilirubinemia** – Based on the predominant type of bile pigments in the plasma, hyperbilirubinemia is classified into two major categories: conjugated and unconjugated (table 1). Unconjugated hyperbilirubinemia is characterized by plasma elevation of predominantly unconjugated bilirubin due to the overproduction of bilirubin, impaired bilirubin uptake by the liver, or abnormalities of bilirubin conjugation. In patients with conjugated hyperbilirubinemia, **both** unconjugated and conjugated bilirubin levels increase. (See "Diagnostic approach to the adult with jaundice or asymptomatic hyperbilirubinemia".)

- **Mechanisms for unconjugated hyperbilirubinemia** – Three basic pathophysiologic mechanisms, overproduction of bilirubin, reduced bilirubin uptake, and impaired bilirubin

conjugation, are mainly responsible for unconjugated hyperbilirubinemia. Bilirubin overproduction may result from excessive breakdown of heme derived from hemoglobin. Extravascular or intravascular hemolysis, extravasation of blood in tissues, or dyserythropoiesis are causes of enhanced heme catabolism. (See 'Disorders associated with unconjugated hyperbilirubinemia' above.)

- **Causes of conjugated hyperbilirubinemia** – Disorders with conjugated hyperbilirubinemia can be categorized according to their pathophysiology as those due to biliary obstruction (extrahepatic cholestasis), intrahepatic cholestasis, or hepatocellular injury.

  In cholestatic disorders, both conjugated and unconjugated bilirubin accumulate in serum and patients have elevations in alkaline phosphatase. In patients with hepatocellular causes of hyperbilirubinemia, elevations in serum conjugated and unconjugated bilirubin and bile salts are accompanied by elevations in the serum concentrations of hepatocellular enzymes, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

  The differential diagnosis of extrahepatic and intrahepatic hyperbilirubinemia is summarized in the tables (table 2 and table 3). (See 'Disorders associated with conjugated hyperbilirubinemia' above.)

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Topic 3615 Version 32.0

GRAPHICS

Classification of jaundice according to type of bile pigment and mechanism

Unconjugated hyperbilirubinemia
Increased bilirubin production*
Extravascular hemolysis
Extravasation of blood into tissues
Intravascular hemolysis
Dyserythropoiesis
Wilson disease
Impaired hepatic bilirubin uptake
Heart failure
Portosystemic shunts
Some patients with Gilbert syndrome
Certain drugs¶ – Rifampin, probenecid, flavaspadic acid, bunamiodyl
Impaired bilirubin conjugation
Crigler-Najjar syndrome types I and II
Gilbert syndrome
Neonates
Hyperthyroidism
Ethinyl estradiol
Liver diseases – Chronic hepatitis, advanced cirrhosis
Conjugated hyperbilirubinemia
Defect of canalicular organic anion transport
Dubin-Johnson syndrome
Defect of sinusoidal reuptake of conjugated bilirubin
Rotor syndrome

Conjugated hyperbilirubinemia (continued)
Extrahepatic cholestasis (biliary obstruction)
Choledocholithiasis
Intrinsic and extrinsic tumors (eg, cholangiocarcinoma, pancreatic cancer)
Primary sclerosing cholangitis
AIDS cholangiopathy
Acute and chronic pancreatitis
Strictures after invasive procedures
Certain parasitic infections (eg, *Ascaris lumbricoides*, liver flukes)
Intrahepatic cholestasis
Viral hepatitis
Alcohol-associated hepatitis
Non-alcohol-associated steatohepatitis
Chronic hepatitis
Primary biliary cholangitis
Drugs and toxins (eg, alkylated steroids, chlorpromazine, herbal medications [eg, Jamaican bush tea], arsenic)
Sepsis and hypoperfusion states
Infiltrative diseases (eg, amyloidosis, lymphoma, sarcoidosis, tuberculosis)
Total parenteral nutrition
Postoperative cholestasis
Following organ transplantation
Hepatic crisis in sickle cell disease
Pregnancy

End-stage liver disease

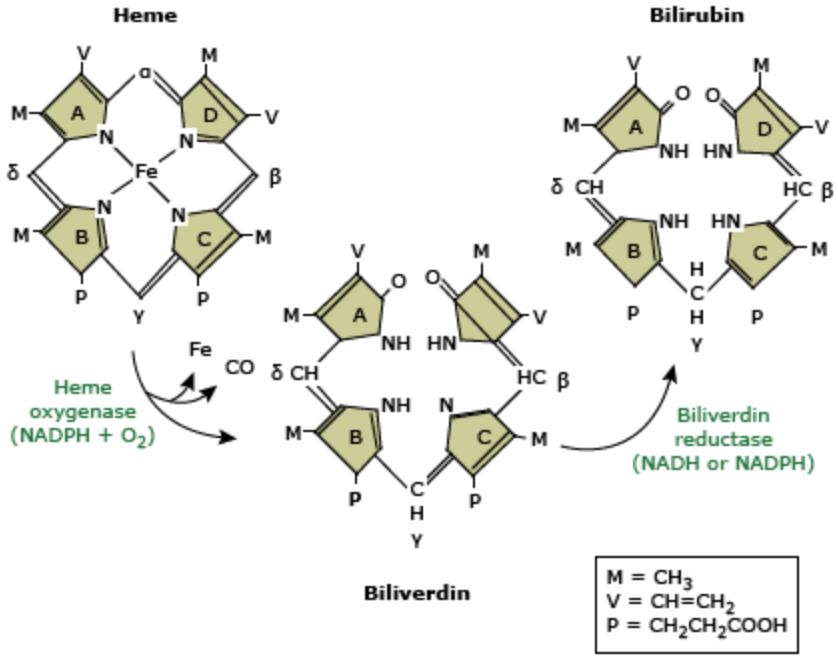
AIDS: acquired immunodeficiency syndrome.

* Serum bilirubin concentration is usually less than 4 mg/dL (68 mmol/L) in the absence of underlying liver disease.

¶ The hyperbilirubinemia induced by drugs usually resolves within 48 hours after the drug is discontinued.

Graphic 55607 Version 13.0

Bilirubin synthesis

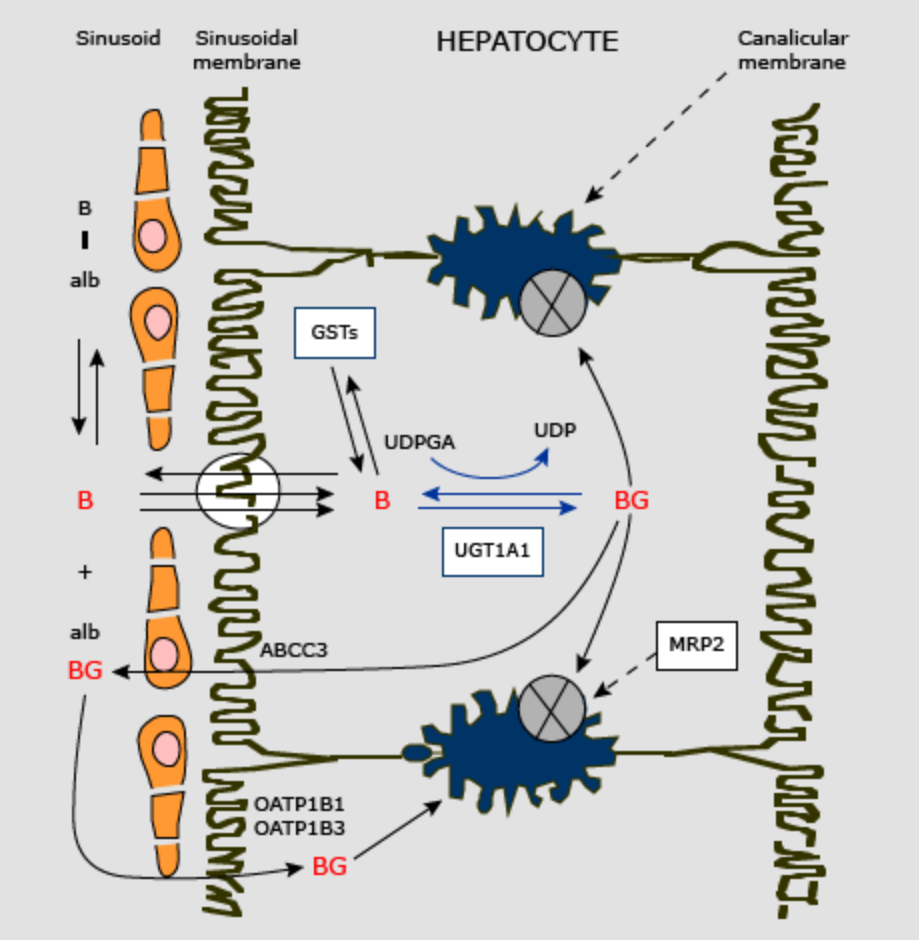


Conversion of heme to biliverdin and then bilirubin. Heme ring-opening at the alpha-carbon bridge of heme is catalyzed by heme oxygenase, resulting in the formation of biliverdin. This is followed by reduction of biliverdin to bilirubin in a reaction catalyzed by biliverdin reductase.

NADH: reduced nicotinamide adenine dinucleotide; NADPH: reduced nicotinamide adenine dinucleotide phosphate.

Graphic 65197 Version 2.0

Bilirubin throughput in hepatocytes



Schematic representation of the steps involved in bilirubin (B) throughput in hepatocytes: transport to the liver (primarily as albumin-bound bilirubin), uptake at the sinusoidal membrane, intracellular binding, conjugation (glucuronidation), and canalicular excretion. Sinusoidal bilirubin uptake requires inorganic anions such as chloride and is thought to be mediated by carrier proteins. Within the hepatocyte, bilirubin binds to glutathione S-transferases (GSTs). GST-binding reduces the efflux of the internalized bilirubin, thereby increasing the net uptake. GSTs also bind bilirubin glucuronides (BG) prior to excretion. Bilirubin also enters hepatocytes by passive diffusion. Glucuronidation of bilirubin is mediated by a family of enzymes, termed uridine diphosphoglucuronosyltransferase (UGT), the most important of which is bilirubin-UGT-1 (UGT1A1). Conjugated bilirubin is secreted actively across the bile canalicular membrane of the hepatocyte against a concentration gradient that may reach 1:1000. The canalicular multidrug resistance protein 2 (MRP2) appears to be the most important for the canalicular secretion of bilirubin. A portion of the conjugated bilirubin is transported into the sinusoidal blood via the ATP hydrolysis-couple pump, ABCC3, to undergo

reuptake via OATP1B1 and OATP1B3 by hepatocytes downstream to the sinusoidal blood flow.

UDP: uridine diphosphate; UDPGA: uridine 5'-diphosphoglucuronic acid; ABCC3: ATP-binding cassette subfamily C number 3; OATP1B1: organic anion-transporting polypeptide 1B1; OATP1B3: organic anion-transporting polypeptide 1B3.

Graphic 52393 Version 5.0

Differential diagnosis of cholestatic jaundice: Extrahepatic

Cholangiopathies and other disorders involving bile ducts
Cholelithiasis
Biliary strictures after invasive procedure
Cholangiocellular carcinoma
Primary sclerosing cholangitis
AIDS cholangiopathy
CMV
Cryptosporidium sp
HIV
Choledochal cyst
Sphincter of Oddi dysfunction
Parasitic infections
Ascaris lumricoides
Histiocytosis X

Extrinsic causes
Pancreatitis (acute and chronic)
Pancreatic carcinoma
Portal adenopathy
Metastases
Tuberculosis
Periampullary carcinoma
Periampullary diverticulum
Mirizzi's syndrome

CMV: cytomegalovirus; HIV: human immunodeficiency virus.

Graphic 73409 Version 2.0

Differential diagnosis of cholestatic jaundice: Intrahepatic

Acute hepatocellular
Viral hepatitis
Alcohol-associated fatty liver and/or hepatitis
Non-alcoholic steatohepatitis
Drugs
Chronic hepatocellular
Primary sclerosing cholangitis
Primary biliary cholangitis
Drugs
Hepatitis (viral, alcohol, autoimmune)
Cirrhosis of any cause
Multifactorial
Total parental nutrition
Systemic infection
Postoperative
Sickle cell disease/crisis
Organ transplantation (rejection; graft-versus-host disease; venoocclusive disease)

Miscellaneous
Hypotension/hypoxemia/HF
Budd-Chiari syndrome
Parasitic infection (Clonorchis sinensis; Fasciola hepatica)
Idiopathic adulthood ductopenia
Other cholangiopathies (IgG4 cholangiopathy; ischemic cholangiopathy; COVID-19)
Inherited/endocrine
Benign recurrent intrahepatic cholestasis (BRIC)
Progressive familial intrahepatic cholestasis (PFIC)
Low phospholipid-associated cholestasis (LPAC)
Thyrotoxicosis
Alagille syndrome
Disorders of carbohydrate, lipid, or bile acid metabolism
Caroli's disease
Pregnancy
Protoporphyria
Infiltrative/granulomatous
Amyloidosis
Lymphoma*
Sarcoidosis
Tuberculosis

* Rarely patients with lymphoma may have hyperbilirubinemia (direct) in the absence of tumor involvement of the liver or extrahepatic obstruction.

Graphic 71068 Version 5.0

Differential diagnosis of hepatocellular jaundice

Neoplasms
Hepatocellular carcinoma
Cholangio carcinoma
Metastases (bronchogenic, GI tract, breast, GU tract)
Lymphoma
Hemangioendothelioma
Hepatoblastoma
Metabolic/hereditary
Wilson disease
Alpha-1 antitrypsin deficiency
Hemochromatosis
Porphyrias
Congenital hepatic fibrosis
Fibropolycystic disease
Systemic
Acute ischemia
Severe heart failure
Tricuspid insufficiency
Constrictive pericarditis
Budd-Chiari syndrome
Venoocclusive disease
Telangiectasias
Sarcoidosis
Amyloidosis
Miscellaneous
Secondary biliary cirrhosis
Cryptogenic cirrhosis

Infections
Viral
Hepatitis viruses
Herpes viruses
"Hemorrhagic" viruses: yellow fever, Ebola, Marburg, Lassa
Adenoviruses, enteroviruses, etc
Bacterial
Tuberculosis, leptospirosis, syphilis, pyogenic abscess, *Brucella*, *Rickettsia*, *Tropheryma whippeli*, *Rochalimea*
Parasitic
Helminths: *Ascaris*, *Fasciola*, *Clonorchis*, schistosomiasis, echinococcosis
Protozoa: amebiasis, plasmodia, babesiosis, toxoplasmosis, leishmaniasis
Fungal
Candida, *Blastomyces*, *Coccidioides*, *Histoplasma*, *Cryptococcus*
Toxic/immunologic
Medications (allergic, idiosyncratic)
Alcohol
Chlorinated hydrocarbons (carbon tetrachloride, chloroform)
Amanita phalloides toxin
Aflatoxin B1
Vitamin A
Pyrrolizidine alkaloids
Arsenic
Phosphorous
Autoimmune hepatitis
Primary biliary cholangitis

Primary sclerosing cholangitis
Overlap syndrome
Autoimmune cholangiopathy
Nonalcoholic steatohepatitis

GI: gastrointestinal; GU: genitourinary.

Graphic 66083 Version 2.0

Contributor Disclosures

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Conflict of interest policy

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