Diagnostic approach to the adult with jaundice or asymptomatic hyperbilirubinemia

AUTHORS: Namita Roy-Chowdhury, PhD, FAASLD, Jayanta Roy-Chowdhury, MD, MRCP, AGAF, FAASLD
SECTION EDITOR: Sanjiv Chopra, MD, MACP
DEPUTY EDITOR: Shilpa Grover, MD, MPH, AGAF

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Sep 2023.**
This topic last updated: **Sep 12, 2023.**

INTRODUCTION

Jaundice and asymptomatic hyperbilirubinemia are common clinical problems that can be caused by a variety of disorders, including bilirubin overproduction, impaired bilirubin conjugation, biliary obstruction, and hepatic inflammation. (See "Classification and causes of jaundice or asymptomatic hyperbilirubinemia".)

This topic will provide an overview of the diagnostic approach to adults with jaundice or asymptomatic hyperbilirubinemia. The causes of jaundice and asymptomatic hyperbilirubinemia, detailed discussions of the specific testing used, and the evaluation of patients with other liver test abnormalities are discussed elsewhere. (See "Classification and causes of jaundice or asymptomatic hyperbilirubinemia" and "Approach to the patient with abnormal liver biochemical and function tests".)

TERMINOLOGY

For clinical purposes, serum bilirubin is fractionated to classify hyperbilirubinemia into one of two major categories (table 1) (see "Clinical aspects of serum bilirubin determination" and "Classification and causes of jaundice or asymptomatic hyperbilirubinemia"):

- **Unconjugated hyperbilirubinemia** – Unconjugated hyperbilirubinemia is characterized by plasma elevation of predominantly unconjugated (indirect) bilirubin. This may be 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 (direct) bilirubin are elevated. This may be due to hepatocellular disease, impaired canalicular excretion of bilirubin, or biliary obstruction.

EVALUATION

The diagnostic approach to the jaundiced patient begins with a careful history, physical examination, and initial laboratory studies [1]. A differential diagnosis is formulated based on those results and additional testing is performed to narrow the diagnostic possibilities.

Although the evaluation is usually not urgent, jaundice can reflect a medical emergency in a few situations. These include massive hemolysis (eg, due to *Clostridium perfringens* sepsis or falciparum malaria), ascending cholangitis, and fulminant hepatic failure. However, patients with these conditions are not asymptomatic. Expedient diagnosis and appropriate therapy can be life-saving in these settings.

History — Multiple clues to the etiology of a patient's hyperbilirubinemia can be obtained from the history information and should include the following (see "Approach to the patient with abnormal liver biochemical and function tests", section on 'History'):

- Use of medications, herbal medications, dietary supplements, and recreational drugs.

- Significant alcohol consumption (>210 grams of alcohol (15 drinks) per week in males, >140 grams of alcohol (10 drinks) per week in females.

- Hepatitis risk factors (eg, travel to endemic areas, blood transfusions prior to 1992, intravenous drug use).

- History of abdominal operations, including gallbladder surgery.

- History of inherited disorders, including liver diseases and hemolytic disorders.

- HIV status.

- Occupational or recreational exposure to toxic substances.

- Associated symptoms that should be elicited include:
  - Development/worsening of jaundice during times of stress is suggestive of Gilbert syndrome. (See "Gilbert syndrome".)
  - Fever, particularly when associated with chills or right upper quadrant pain and/or a history of prior biliary surgery, is suggestive of acute cholangitis.
  - Anorexia, malaise, and myalgias may suggest viral hepatitis.
  - Right upper quadrant pain suggests extrahepatic biliary obstruction.
  - Acholic stool (also termed clay-colored stool) refers to stool without the yellow-brown color, which is normally derived mainly from the bilirubin breakdown products, urobilin and stercobilin. Although rare, it can also be seen in the acute cholestatic phase of viral hepatitis and in prolonged near-complete common bile duct obstruction from cancer of the pancreatic head or the duodenal ampulla.

Physical examination — The physical examination may reveal a Courvoisier sign (a palpable gallbladder, caused by obstruction distal to the takeoff of the cystic duct by malignancy) or signs of chronic liver failure/portal hypertension such as ascites, splenomegaly, spider angiomata, and gynecomastia. Certain findings suggest specific diseases, such as hyperpigmentation in hemochromatosis, Kayser-Fleischer rings in Wilson disease, and xanthomas in primary biliary cholangitis [2]. (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Physical examination'.)

Initial laboratory tests and interpretation — Initial laboratory tests include measurements of the following:

- Serum total and unconjugated bilirubin
- Alkaline phosphatase
- Aminotransferases (aspartate aminotransferase [AST] and alanine aminotransferase [ALT])
- Prothrombin time/international normalized ratio (INR)
- Albumin

Assessment of patterns of elevation — Subsequent testing is guided by the predominant pattern of liver injury. Major patterns of injury and their characteristics include the following:

- **Cholestatic injury pattern**

- Disproportionate elevation in the alkaline phosphatase compared with the serum aminotransferases (eg, R value* ≤2)
- Serum bilirubin may be elevated
- Tests of synthetic function (eg, albumin, prothrombin time) may be abnormal

- **Hepatocellular injury pattern**
  - Disproportionate elevation (relative to the upper limit of normal [ULN]) in the serum aminotransferases (ALT and AST) compared with the alkaline phosphatase (eg, R value* ≥5)
  - Serum bilirubin may be elevated
  - Tests of synthetic function (eg, albumin, prothrombin time) may be abnormal
- **Isolated hyperbilirubinemia**
  - Elevated bilirubin level (total or direct) with normal serum aminotransferases and alkaline phosphatase

However, while liver tests provide a broad guideline for the initial distinction between the different causes of jaundice, exceptions do occur. As an example, viral hepatitis, which normally presents primarily with an elevation of serum aminotransferases, may present as a predominantly cholestatic syndrome with marked pruritus.

In patients with conjugated hyperbilirubinemia, the evaluation will be based on whether the abnormalities are likely due to biliary obstruction, intrahepatic cholestasis, hepatocellular injury, or an inherited condition (based on the presence of isolated conjugated hyperbilirubinemia).

Subsequent testing based on pattern of liver injury — Subsequent studies are guided based on findings from the history, physical examination, and initial laboratory tests. (See 'Initial laboratory tests and interpretation' above.)

Patients with hyperbilirubinemia and a cholestatic injury pattern — Elevation of the serum alkaline phosphatase out of proportion to the serum aminotransferases suggests biliary obstruction or intrahepatic cholestasis (algorithm 1). (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Elevated alkaline phosphatase'.)

Hepatic imaging for extrahepatic cholestasis — Testing in patients with elevated bilirubin and alkaline phosphatase of hepatic origin typically starts with right upper quadrant

ultrasonography to assess the hepatic parenchyma and bile ducts [3].

- The presence of biliary ductal dilatation on imaging suggests extrahepatic cholestasis. If ultrasonography shows biliary ductal dilatation without an apparent cause, advanced imaging with either magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) is obtained to confirm biliary ductal dilatation and determine the etiology. Endoscopic retrograde cholangiopancreatography (ERCP) is reserved for therapy to remove stones or stenting a stricture. (See "Choledocholithiasis: Clinical manifestations, diagnosis, and management", section on 'Additional imaging (MRCP or EUS)' and "Overview of endoscopic retrograde cholangiopancreatography (ERCP) in adults".)

- The absence of biliary ductal dilatation suggests intrahepatic cholestasis. (See 'Evaluation for intrahepatic cholestasis' below.)

Evaluation for intrahepatic cholestasis — In many cases, a possible cause of intrahepatic cholestasis can be identified based on the patient's history. If a likely source is identified, additional testing may not be required.

- **Discontinue culprit medications** – Any medications or supplements associated with cholestasis should be discontinued.

- **Laboratory tests** – There are numerous possible causes of intrahepatic cholestasis, including primary biliary cholangitis, primary sclerosing cholangitis, viral hepatitis, intrahepatic cholestasis of pregnancy, benign postoperative cholestasis, and infiltrative disease. The testing should be informed by the patient's history and risk factors. Typically, the evaluation starts with testing for primary biliary cholangitis along with any other conditions for which the patient is at increased risk due to history or possible exposure (eg, testing for primary sclerosing cholangitis in a patient with ulcerative colitis, obtaining serum bile acids in a woman who is pregnant).

  - Primary biliary cholangitis: Antimitochondrial antibody
  - Primary sclerosing cholangitis: MRCP
  - Hepatitis A virus: Immunoglobulin M (IgM) antihepatitis A
  - Hepatitis B virus: Hepatitis B surface antigen, IgM antihepatitis core antigen, antibody to hepatitis B surface antigen
  - Hepatitis C virus: Antihepatitis C antibody, hepatitis C viral RNA
  - Hepatitis E virus: Hepatitis E virus antibodies
  - Cytomegalovirus (CMV): Anti-CMV antibodies, CMV antigen
  - Epstein-Barr virus: Heterophile antibody
    Intrahepatic cholestasis of pregnancy: Serum pregnancy test, serum bile acids

Patients with unexplained cholestasis despite serologic evaluation and imaging, should be referred to a hepatologist for further evaluation and consideration of a liver biopsy to rule out infiltrative disease.

Patients with isolated hyperbilirubinemia — If the alkaline phosphatase and aminotransferases are normal, hyperbilirubinemia is likely not due to hepatic injury or biliary tract disease. Further evaluation is based on the type of hyperbilirubinemia [4]. (See 'Terminology' above.)

Isolated unconjugated hyperbilirubinemia — The initial evaluation of a patient with isolated unconjugated hyperbilirubinemia includes an assessment for hemolytic anemia and discontinuation of medications (eg, rifampin and probenecid) that impair hepatic uptake of bilirubin (algorithm 2). In a patient with a history consistent with Gilbert syndrome (persistent unconjugated hyperbilirubinemia <4 mg/dL, no evidence of hemolysis and normal plasma aminotransferases and alkaline phosphatase concentrations with development of jaundice during times of stress), additional testing is not required. However, patients with unconjugated bilirubin levels ≥4 mg/dL or abnormal aminotransferases should be referred to a hepatologist for further evaluation and consideration of a liver biopsy. (See "Diagnosis of hemolytic anemia in adults" and "Gilbert syndrome" and "Crigler-Najjar syndrome".)

Isolated conjugated hyperbilirubinemia — Conjugated hyperbilirubinemia without other routine liver test abnormalities is found in two rare inherited conditions: Dubin-Johnson syndrome and Rotor syndrome. Dubin-Johnson syndrome and Rotor syndrome should be suspected in patients with mild hyperbilirubinemia (with a conjugated fraction of approximately 50 percent) in the absence of other abnormalities of standard liver biochemical tests. Differentiating between these syndromes is possible but clinically unnecessary due to their benign nature. (See "Inherited disorders associated with conjugated hyperbilirubinemia".)

Patients with hyperbilirubinemia and a hepatocellular injury pattern — A predominant elevation of serum aminotransferase activity suggests that jaundice is caused by intrinsic hepatocellular disease (table 2). The evaluation is based on the degree and pattern of aminotransferase elevation and is discussed in detail separately. (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Laboratory tests'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Abnormal liver

biochemical tests".)

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 e-mail 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)")

SUMMARY AND RECOMMENDATIONS

- **Classification of hyperbilirubinemia** – For clinical purposes, serum bilirubin is fractionated to classify hyperbilirubinemia into one of two major categories: unconjugated (indirect) hyperbilirubinemia and conjugated (direct) hyperbilirubinemia. Unconjugated hyperbilirubinemia is characterized by plasma elevation of predominantly unconjugated (indirect) bilirubin. This may be 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 (direct) bilirubin are elevated. This may be due to hepatocellular disease, impaired canalicular excretion of bilirubin, or biliary obstruction. (See 'Terminology' above.)

- **Historical clues** – Multiple clues to the etiology of hyperbilirubinemia can be obtained from the history (see 'History' above):

  - Use of medications, herbal medications, dietary supplements, and recreational drugs
  - Significant alcohol consumption (>210 grams of alcohol (15 drinks) per week in males, >140 grams of alcohol (10 drinks) per week in females

- Hepatitis risk factors (eg, travel to endemic areas, blood transfusions prior to 1992, intravenous drug use)
- History of abdominal operations, including gallbladder surgery
- History of inherited disorders, including liver diseases and hemolytic disorders
- HIV status
- Occupational or recreational exposure to toxic substances
- Associated symptoms (eg, fever, right upper quadrant pain, myalgias)

- **Laboratory evaluation** – Initial laboratory tests include measurements of serum total and unconjugated bilirubin, alkaline phosphatase, aminotransferases (aspartate aminotransferase and alanine aminotransferase), prothrombin time/international normalized ratio, and albumin. Subsequent testing is guided by the predominant pattern of liver injury. (See 'Initial laboratory tests and interpretation' above.)

- **Additional testing to determine etiology of hyperbilirubinemia based on pattern of liver tests**

  - **Conjugated hyperbilirubinemia and elevated alkaline phosphatase** – Elevation of the serum alkaline phosphatase out of proportion to the serum aminotransferases suggests biliary obstruction or intrahepatic cholestasis. Testing in patients with elevated bilirubin and alkaline phosphatase of hepatic origin typically starts with right upper quadrant ultrasonography to assess the hepatic parenchyma and bile ducts (algorithm 1). The absence of biliary ductal dilatation suggests intrahepatic cholestasis. (See 'Patients with hyperbilirubinemia and a cholestatic injury pattern' above.)

  - **Conjugated hyperbilirubinemia and hepatocellular injury** – A predominant elevation of serum aminotransferase activity suggests that jaundice is caused by intrinsic hepatocellular disease (table 2). The evaluation is based on the degree and pattern of aminotransferase elevation and is discussed in detail separately. (See "Approach to the patient with abnormal liver biochemical and function tests", section on 'Elevated serum aminotransferases'.)

  - **Isolated unconjugated hyperbilirubinemia** – The evaluation of unconjugated hyperbilirubinemia typically involves evaluation for hemolytic anemia, drugs that impair hepatic uptake of bilirubin, and Gilbert syndrome (algorithm 2). However, patients with unconjugated bilirubin levels ≥4 mg/dL or abnormal aminotransferases should be referred to a hepatologist for further evaluation and consideration of a liver biopsy. (See 'Isolated unconjugated hyperbilirubinemia' above.)

- **Isolated conjugated hyperbilirubinemia** – Conjugated hyperbilirubinemia without other routine liver test abnormalities is found in two rare inherited conditions: Dubin-Johnson syndrome and Rotor syndrome. Normal levels of serum alkaline phosphatase and gamma-glutamyl transpeptidase help distinguish these conditions from disorders associated with biliary obstruction. (See 'Isolated conjugated hyperbilirubinemia' above.)

REFERENCES

1. Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. Am J Gastroenterol 2017; 112:18.
2. Roberts EA, Schilsky ML. Current and Emerging Issues in Wilson's Disease. N Engl J Med 2023; 389:922.
3. Saini S. Imaging of the hepatobiliary tract. N Engl J Med 1997; 336:1889.
4. Newsome PN, Cramb R, Davison SM, et al. Guidelines on the management of abnormal liver blood tests. Gut 2018; 67:6.

Topic 3620 Version 29.0

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

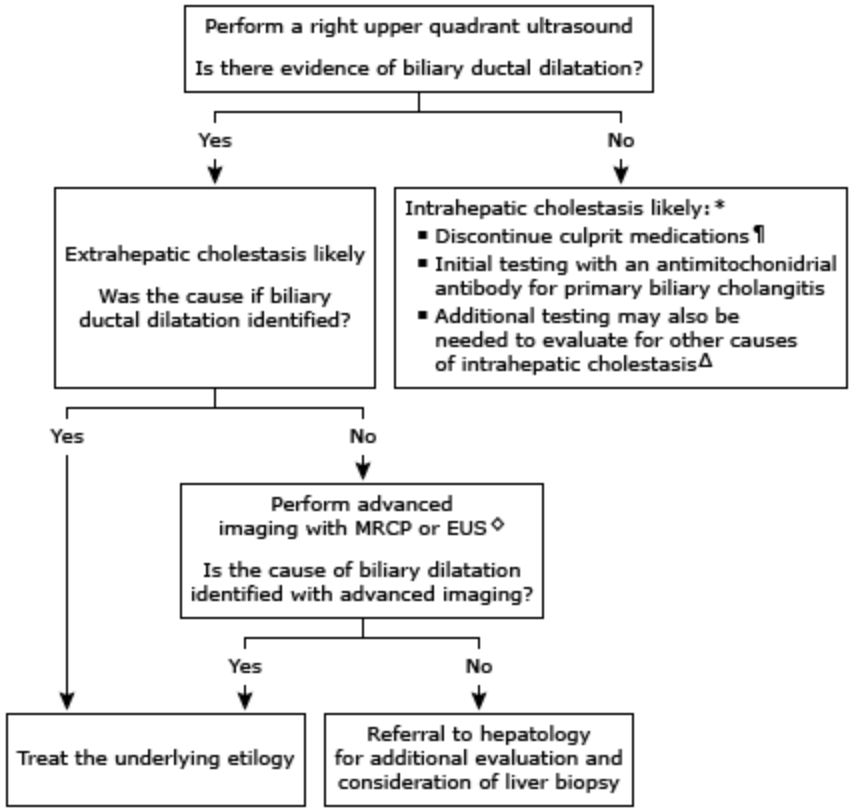
AIDS: acquired immunodeficiency syndrome.

* 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

Approach to the evaluation of an asymptomatic adult with elevated alkaline phosphatase and hyperbilirubinemia



EUS: endoscopic ultrasound; MRCP: magnetic resonance cholangiopancreatogram; ERCP: endoscopic retrograde cholangiopancreatography; CMV: cytomegalovirus; EBV: Epstein-Barr virus.

* Causes for intrahepatic cholestasis include drug toxicity, primary biliary cholangitis, primary sclerosing cholangitis, viral hepatitis, intrahepatic cholestasis of pregnancy, benign postoperative cholestasis, infiltrative diseases, total parenteral nutrition.

¶ If drug-induced cholestasis is suspected, elimination of the offending drug usually leads to resolution of cholestasis, although it may take months. The National Institutes of Health maintains a searchable database of drugs, herbal medications, and dietary supplements that have been associated with liver injury.

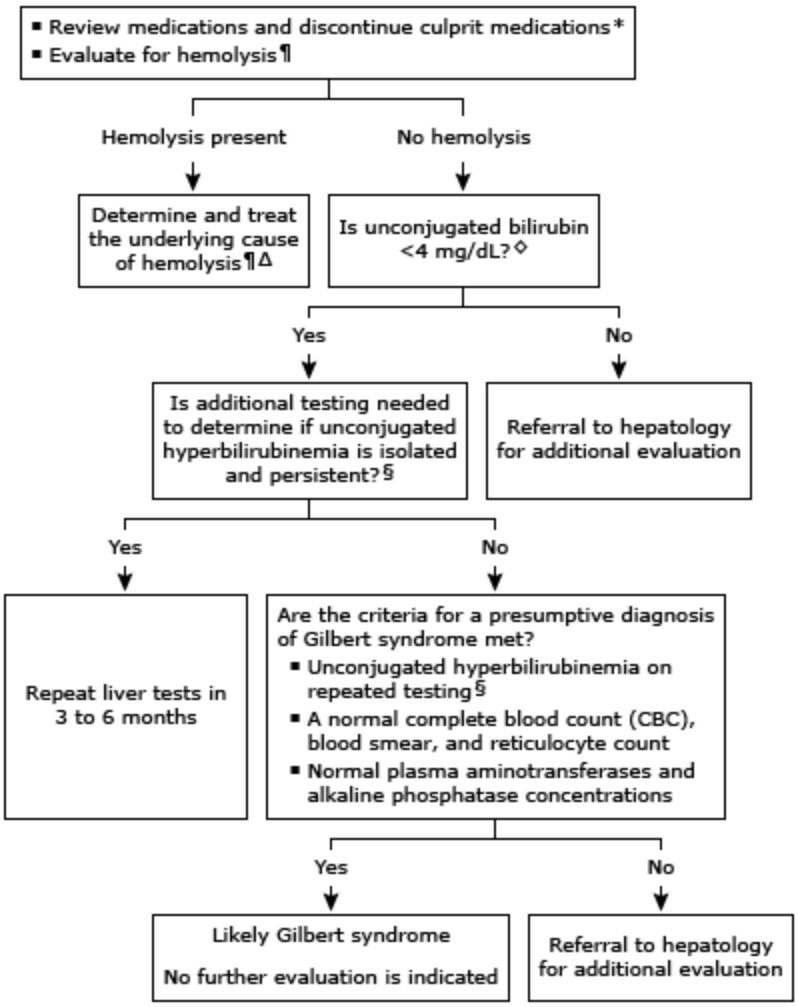
Δ The extent of testing should be informed by the patient's history and risk factors. Evaluation may include serologies for viral etiologies (hepatitis A, B, C, E, CMV, EBV) and exclusion of intrahepatic cholestasis of pregnancy (serum pregnancy test and serum bile acids) and MRCP for primary sclerosing cholangitis. Patients with unexplained cholestasis despite serologic evaluation

and imaging should be referred to a hepatologist for further evaluation and consideration of a liver biopsy to rule out infiltrative disease.

◇ Typically, either MRCP or EUS is obtained to confirm biliary ductal dilatation. ERCP is an option if needed to facilitate management (eg, to remove a common bile duct stone).

Graphic 141797 Version 1.0

Approach to the evaluation of an adult with isolated unconjugated hyperbilirubinemia



LDH: lactate dehydrogenase; RBC: red blood cell.

* The National Institutes of Health maintains a searchable database of drugs, herbal medications, and dietary supplements that have been associated with liver injury. The hyperbilirubinemia induced by drugs or supplements usually resolves within 48 hours after the drug is discontinued.

¶ Laboratory studies that support the diagnosis of hemolysis include low hemoglobin level, an increased reticulocyte count and signs of RBC destruction (increased LDH or low haptoglobin). Evaluation of a peripheral smear can confirm the presence and determine cause of hemolytic anemia. Refer to UpToDate topics on hemolytic anemia.

Δ Patients with hemolysis may also have Gilbert syndrome. This should be suspected in the presence of severe hyperbilirubinemia compared with the degree of hemolysis.

◇ Serum bilirubin levels fluctuate in patients with Gilbert syndrome. They are usually less than 3 mg/dL (51.3 micromol/L) and can be normal. Certain associated pathologic conditions or physiologic events can increase the plasma bilirubin concentrations to higher values, but usually less than 6 mg/dL (102.6 micromol/L).

§ If repeat testing has not been performed to confirm persistent isolated unconjugated hyperbilirubinemia (over at least 3 months), liver tests should repeated.

Graphic 141804 Version 1.0

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

Namita Roy-Chowdhury, PhD, FAASLD No relevant financial relationship(s) with ineligible companies to disclose. **Jayanta Roy-Chowdhury, MD, MRCP, AGAF, FAASLD** No relevant financial relationship(s) with ineligible companies to disclose. **Sanjiv Chopra, MD, MACP** No relevant financial relationship(s) with ineligible companies to disclose. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

→