Author: Lawrence S Friedman, MD
Section Editor: Sanjiv Chopra, MD, MACP
Deputy Editor: Shilpa Grover, MD, MPH, AGAF

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INTRODUCTION

Abnormal liver biochemical and function tests are frequently detected in asymptomatic patients since many screening blood test panels routinely include them [1]. A population-based survey in the United States conducted between 1999 and 2002 estimated that an abnormal alanine aminotransferase (ALT) was present in 8.9 percent of respondents. Although the term "liver function tests" (LFTs) is used commonly, it is imprecise and potentially misleading since many of the tests reflecting the health of the liver are not direct measures of its function. Furthermore, the commonly used liver biochemical tests may be abnormal even in patients with a healthy liver.

This topic review will provide an overview on the evaluation of patients with abnormal liver biochemical and function tests. Our approach is largely consistent with the 2017 American College of Gastroenterology clinical guidelines on evaluation of abnormal liver biochemistries [2]. Other guidelines have also been published [3]. Detailed discussions of the individual tests and noninvasive assessment of liver fibrosis are presented separately. (See "Liver biochemical tests that detect injury to hepatocytes" and "Enzymatic measures of cholestasis (eg, alkaline phosphatase, 5'-nucleotidase, gamma-glutamyl transpeptidase)" and "Classification and causes of jaundice or asymptomatic hyperbilirubinemia" and "Tests of the liver's biosynthetic capacity (eg, albumin, coagulation factors, prothrombin time)" and "Noninvasive assessment of hepatic fibrosis: Overview of serologic and radiographic tests".)

COMMON LIVER BIOCHEMICAL AND FUNCTION TESTS

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase and bilirubin are biochemical markers of liver injury. Albumin, bilirubin, and prothrombin time are markers of hepatocellular function.

Elevations of liver enzymes often reflect damage to the liver or biliary obstruction, whereas an abnormal serum albumin or prothrombin time may be seen in the setting of impaired hepatic synthetic function. The serum bilirubin in part measures the liver's ability to detoxify metabolites and transport organic anions into bile.

Liver enzymes — Liver enzymes that are commonly measured in the serum include:

- Serum aminotransferases: alanine aminotransferase (ALT, formerly called SGPT) and aspartate aminotransferase (AST, formerly called SGOT)
- Alkaline phosphatase
- Gamma-glutamyl transpeptidase (GGT)
- 5'-nucleotidase
- Lactate dehydrogenase (LDH)

Aminotransferases — In adults, normal ALT levels range from 29 to 33 units/L for males and 19 to 25 units/L for females. Levels above these values should be assessed for underlying liver disease [2]. In children, median ALT levels range from 17 to 21 units/L in boys and 14 to 20 units/L in girls, with the 97th percentile (commonly used as a cutoff value) of 29 to 38 and 24 to 32 units/L, respectively [4].

The sensitivity and specificity of the serum aminotransferases (formerly transaminases), particularly serum ALT, for differentiating those with liver disease from those without liver disease depend on the cutoff values chosen to define an abnormal test. A population-based study from the US National Health and Nutrition Examination Survey examined patients with known hepatitis C virus infection (n = 259) and compared them with patients at low risk of liver injury (n = 3747) to determine optimal cutoff values for ALT [5]. The optimal cutoff for men was an ALT of 29 units/L and for women was an ALT of 22 units/L. (See "Liver biochemical tests that detect injury to hepatocytes", section on 'Serum aminotransferases'.)

AST is present in the liver and other organs including cardiac muscle, skeletal muscle, kidney, and brain. In children, levels decline with age, more so in girls than boys after age 11 [4]. ALT is present primarily in the liver, and thus is a more specific marker of hepatocellular cell injury. ALT levels correlate with the degree of abdominal adiposity [6], and at least two large studies have suggested that the cutoff values should be adjusted for sex and body mass index (but not age) [7,8]. However, most patients identified using the lower cutoff values have only mild liver disease or no identifiable cause of the abnormal laboratory values. Thus, the overall benefit of the proposed modifications is unclear since it would translate into a large increase in the absolute number of patients who would require evaluation for an uncertain clinical benefit [9].

Alkaline phosphatase — Serum alkaline phosphatase is derived predominantly from the liver and bones. An elevated alkaline phosphatase can be fractionated to determine if it originates from the liver or bones, although in practice a liver source is usually confirmed by the simultaneous elevation of other measures of cholestasis (eg, gamma-glutamyl transpeptidase). (See 'Confirming an elevated alkaline phosphatase is of hepatic origin' below.)

Other sources may also contribute to serum levels of alkaline phosphatase. Women in the third trimester of pregnancy, for example, have elevated serum alkaline phosphatase levels due to an influx into blood of placental alkaline phosphatase. Individuals with blood types O and B can have elevated serum alkaline phosphatase levels after eating a fatty meal due to an influx of intestinal alkaline phosphatase. Infants and toddlers occasionally display transient marked elevations of alkaline phosphatase in the absence of detectable bone or liver disease. Alkaline phosphatase elevations have been noted in patients with diabetes mellitus [10]. There are also reports of a benign familial occurrence of elevated serum alkaline phosphatase due to intestinal alkaline phosphatase. (See "Enzymatic measures of cholestasis (eg, alkaline phosphatase, 5'-nucleotidase, gamma-glutamyl transpeptidase)", section on 'Alkaline phosphatase' and "Transient hyperphosphatasemia of infancy and early childhood".)

Alkaline phosphatase levels also vary with age. Alkaline phosphatase levels are generally higher in children and adolescents because of physiologic osteoblastic activity. Levels may be up to three times higher than in healthy adults, with maximum levels in infancy and adolescence, coinciding with periods of maximum bone growth velocity (figure 1). Also, the normal serum alkaline phosphatase level gradually increases from age 40 to 65 years, particularly in women. The normal alkaline phosphatase level for an otherwise healthy 65-year-old woman is more than 50 percent higher than that for a healthy 30-year-old woman.

Gamma-glutamyl transpeptidase — GGT is found in hepatocytes and biliary epithelial cells, as well as in the kidney, seminal vesicles, pancreas, spleen, heart, and brain. In normal full-term neonates, serum GGT activity is six to seven times the upper limit of the adult reference range; levels then decline and reach low levels by five to seven months of age [11]. A gradual increase occurs in girls until age 10 and in boys through adolescence [4]. (See "Enzymatic measures of cholestasis (eg, alkaline phosphatase, 5'-nucleotidase, gamma-glutamyl transpeptidase)", section on 'Gamma-glutamyl transpeptidase'.)

5'-nucleotidase — 5'-nucleotidase is found in the liver, intestine, brain, heart, blood vessels, and endocrine pancreas, but it is only released into serum by hepatobiliary tissue. Although its physiologic function is unknown, 5'-nucleotidase specifically catalyzes hydrolysis of nucleotides such as adenosine 5'-phosphate and inosine 5'-phosphate, in which the phosphate is attached to

the 5 position of the pentose moiety. (See "Enzymatic measures of cholestasis (eg, alkaline phosphatase, 5'-nucleotidase, gamma-glutamyl transpeptidase)", section on '5'-Nucleotidase'.)

Lactate dehydrogenase — LDH is a cytoplasmic enzyme present in tissues throughout the body (table 1). Five isoenzyme forms of LDH are present in serum and can be separated by various electrophoretic techniques. The slowest migrating band predominates in the liver [12,13]. This test is not as sensitive as the serum aminotransferases in liver disease and has poor diagnostic specificity, even when isoenzyme analysis is used. It is more useful as a marker of hemolysis. It can be used in practice to distinguish ischemic hepatitis from viral hepatitis and was used in the past as a marker of myocardial infarction [12]. (See "Biomarkers of myocardial injury other than troponin".)

Function tests — Tests of hepatic synthetic function include:

- Serum albumin
- Prothrombin time/international normalized ratio

Reference ranges — Liver test reference ranges will vary from laboratory to laboratory. Interpretation of a specific abnormal result should be based on the reference range reported for that result. As an example, one hospital's normal reference ranges for adults are as follows [14]:

- Albumin: 3.3 to 5.0 g/dL (33 to 50 g/L)
- Alkaline phosphatase:
  - Male: 45 to 115 units/L
  - Female: 30 to 100 units/L
- Alanine aminotransferase (ALT):
  - Male: 29 to 33 units/L
  - Female: 19 to 25 units/L
- Aspartate aminotransferase (AST):
  - Male: 10 to 40 units/L
  - Female: 9 to 32 units/L
- Bilirubin, total: 0.0 to 1.0 mg/dL (0 to 17 micromol/L)
- Bilirubin, direct: 0.0 to 0.4 mg/dL (0 to 7 micromol/L)
- Gamma-glutamyl transpeptidase (GGT):

- Male: 8 to 61 units/L
- Female: 5 to 36 units/L

- Prothrombin time (PT): 11.0 to 13.7 seconds

However, guidelines suggest that the optimal cutoff for ALT should be lower than the upper limits used by many laboratories (ie, it should be 33 units/L for men and 25 units/L for women) [2]. (See 'Aminotransferases' above.)

INITIAL EVALUATION

The initial evaluation of a patient with abnormal liver biochemical and function tests includes obtaining a history to identify potential risk factors for liver disease and performing a physical examination to look for clues to the etiology and for signs of chronic liver disease. Subsequent testing is determined based on the information gathered from the history and physical examination as well as the pattern of test abnormalities. (See 'Patterns of liver test abnormalities' below.)

History — A thorough medical history is central to the evaluation of a patient with abnormal liver tests. The history should determine if the patient has had exposure to any potential hepatotoxins (including alcohol and medications), is at risk for viral hepatitis, has other disorders that are associated with liver disease, or has symptoms that may be related to the liver disease or a possible predisposing condition.

Alcohol consumption is a common cause of liver disease, although obtaining an accurate history can be difficult. Several definitions have been proposed for what constitutes significant alcohol consumption [15]. We define significant alcohol consumption as an average consumption of >210 grams of alcohol per week in men or >140 grams of alcohol per week in women over at least a two-year period, a definition that is consistent with a 2012 joint guideline from the American Gastroenterological Association, the American Association for the Study of Liver Diseases, and the American College of Gastroenterology [16,17]. A standard drink (360 mL [12 oz] of beer, 150 mL [5 oz] of wine, or 45 mL [1.5 oz] of 80-proof spirits) contains approximately 14 grams of alcohol. (See "Clinical manifestations and diagnosis of alcohol-associated fatty liver disease and cirrhosis", section on 'Diagnosis'.)

Questioning about drug use should seek to identify all drugs used, the amounts ingested, and the durations of use. Drug use is not limited to prescription medications, but also includes over-the-counter medications, herbal and dietary supplements, and illicit drug use. Features that suggest drug toxicity include lack of illness prior to ingesting the drug, clinical illness or biochemical abnormalities developing after beginning the drug, and improvement after the drug is withdrawn. If

an immunologic reaction is suspected, the illness will generally recur upon reintroduction of the offending substance. However, rechallenge is not advised. (See "Drug-induced liver injury" and "Hepatotoxicity due to herbal medications and dietary supplements".)

Risk factors for viral hepatitis include potential parenteral exposures (eg, intravenous drug use, blood transfusion prior to 1992), travel to areas endemic for hepatitis, and exposure to patients with jaundice. Hepatitis B and C are transmitted parenterally, whereas hepatitis A and E are transmitted from person to person via a fecal-oral route (often via contaminated food). Hepatitis E is uncommon in the United States, but it should be considered in patients who live in or have travelled to Asia, Africa, the Middle East, or Central America, and has been seen increasingly in Europe as a result of consumption of contaminated swine and game meat. (See "Epidemiology, transmission, and prevention of hepatitis B virus infection" and "Epidemiology and transmission of hepatitis C virus infection" and "Hepatitis A virus infection in adults: Epidemiology, clinical manifestations, and diagnosis" and "Hepatitis E virus infection".)

Patients should be asked about conditions that are associated with hepatobiliary disease, such as right-sided heart failure (congestive hepatopathy), diabetes mellitus, skin pigmentation, arthritis, hypogonadism and dilated cardiomyopathy (hemochromatosis), and obesity (nonalcoholic fatty liver disease), pregnancy (gallstones), inflammatory bowel disease (primary sclerosing cholangitis, gallstones), early onset emphysema (alpha-1 antitrypsin deficiency), celiac disease, and thyroid disease. (See "Congestive hepatopathy" and "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults", section on 'Association with other disorders' and "Gallstones: Epidemiology, risk factors and prevention", section on 'Risk factors' and "Clinical manifestations and diagnosis of hereditary hemochromatosis".)

Finally, patients should be questioned about occupational or recreational exposure to hepatotoxins (eg, mushroom picking). Examples of hepatitis due to exposures to hepatotoxins include industrial chemicals such as vinyl chloride and the mushrooms *Amanita phalloides* and *Amanita verna*, which contain a potent hepatotoxin (amatoxin). (See "Amatoxin-containing mushroom poisoning (eg, Amanita phalloides): Clinical manifestations, diagnosis, and treatment".)

Physical examination — The physical examination may suggest the presence of liver disease and may point to the underlying cause of the liver disease.

- Temporal and proximal muscle wasting suggest longstanding disease.
- Stigmata of liver disease include spider nevi, palmar erythema, gynecomastia, and caput medusae.
- Ascites or hepatic encephalopathy may be seen in patients with decompensated cirrhosis.

- Dupuytren's contractures, parotid gland enlargement, and testicular atrophy are commonly seen in advanced alcoholic cirrhosis and occasionally in other types of cirrhosis.
- An enlarged left supraclavicular node (Virchow's node) or periumbilical nodule (Sister Mary Joseph's nodule) suggest an abdominal malignancy.
- Increased jugular venous pressure, a sign of right-sided heart failure, suggests hepatic congestion.
- A right pleural effusion, in the absence of clinically apparent ascites, may be seen in advanced cirrhosis.
- Neurologic and psychiatric signs and symptoms may be seen in patients with Wilson disease.

The abdominal examination should focus on the size and consistency of the liver, the size of the spleen (a palpable spleen is two to threefold enlarged), and an assessment for ascites (usually by determining whether there is a fluid wave, shifting dullness, or bulging of the flanks). Patients with cirrhosis may have an enlarged left lobe of the liver (which can be felt below the xiphoid) and an enlarged spleen (which is most easily appreciated with the patient in the right lateral decubitus position).

A grossly enlarged, hard, nodular liver or an obvious abdominal mass suggests malignancy. An enlarged, tender liver could be due to viral or alcoholic hepatitis or, less often, an acutely congested liver secondary to right-sided heart failure or Budd-Chiari syndrome [18]. Severe right upper quadrant tenderness with a positive Murphy's sign (respiratory arrest on inspiration while pressing on the right upper quadrant) suggests cholecystitis or, occasionally, ascending cholangitis. Ascites in the presence of jaundice suggests either cirrhosis or malignancy with peritoneal spread.

Laboratory tests — The pattern of liver test abnormalities may suggest that the underlying cause of the patient's liver disease is primarily the result of hepatocyte injury (elevated aminotransferases) or cholestasis (elevated alkaline phosphatase). In addition, the magnitude of the liver test abnormalities and the ratio of the aspartate aminotransferase (AST) to alanine aminotransferase (ALT) may make certain diagnoses more or less likely. ALT is a more specific marker of hepatic injury as compared with AST.

Patterns of liver test abnormalities — Liver test abnormalities can often be grouped into one of several patterns: the abnormalities may be acute, subacute, or chronic based on whether they have been present for less than six weeks (acute), six weeks to six months (subacute), or more than six months (chronic). Based on the pattern of elevation, liver test abnormalities may be grouped as hepatocellular, cholestatic, or isolated hyperbilirubinemia.

- Hepatocellular pattern:
  - Disproportionate elevation in the serum aminotransferases compared with the alkaline phosphatase
  - Serum bilirubin may be elevated
  - Tests of synthetic function may be abnormal
- Cholestatic pattern:
  - Disproportionate elevation in the alkaline phosphatase compared with the serum aminotransferases
  - Serum bilirubin may be elevated
  - Tests of synthetic function may be abnormal
- Isolated hyperbilirubinemia: As the term implies, patients with isolated hyperbilirubinemia have an elevated bilirubin level with normal serum aminotransferases and alkaline phosphatase

The R value (also known as the R factor) can be used to help determine the likely type of liver injury (hepatocellular versus cholestatic) in patients with elevated aminotransferases and alkaline phosphatase.

R value = (ALT ÷ ULN ALT) / (alkaline phosphatase ÷ ULN alkaline phosphatase)

The R value is interpreted as follows:

- ≥5: Hepatocellular injury
- >2 to <5: Mixed pattern
- ≤2: Cholestatic injury

Because the serum bilirubin can be prominently elevated in both hepatocellular and cholestatic conditions, it is not helpful in differentiating between the two. Common hepatocellular diseases associated with an elevated bilirubin and jaundice include viral and toxic hepatitis (including drugs, herbal therapies, and alcohol) and end-stage cirrhosis from any cause (table 2).

If both the serum aminotransferases and alkaline phosphatase are elevated, the liver test abnormalities are characterized by the predominant abnormality (eg, if the serum aminotransferases are 10 times the upper limit of normal and the alkaline phosphatase is twice the upper limit of normal, the liver test abnormalities would be characterized as primarily hepatocellular). However, making this distinction is not always possible. The degree of aminotransferase elevation can occasionally help in differentiating between hepatocellular and cholestatic processes. While ALT

and AST values less than eight times the upper limit of normal may be seen in either hepatocellular or cholestatic liver disease, values 25 times the upper limit of normal or higher are seen primarily in hepatocellular diseases.

Abnormal tests of synthetic function may be seen with both hepatocellular injury and cholestasis. A low albumin suggests a chronic process, such as cirrhosis or cancer, while a normal albumin suggests a more acute process, such as viral hepatitis or choledocholithiasis. A prolonged prothrombin time indicates either vitamin K deficiency due to prolonged jaundice and intestinal malabsorption of vitamin K or significant hepatocellular dysfunction. The failure of the prothrombin time to correct with parenteral administration of vitamin K suggests severe hepatocellular injury. (See "Tests of the liver's biosynthetic capacity (eg, albumin, coagulation factors, prothrombin time)".)

AST to ALT ratio — Most causes of hepatocellular injury are associated with a serum AST level that is lower than the ALT. An AST to ALT ratio of 2:1 or greater is suggestive of alcoholic liver disease, particularly in the setting of an elevated gamma-glutamyl transpeptidase [19]. In a study of 271 patients with biopsy-confirmed liver disease, more than 90 percent of the patients in whom the AST to ALT ratio was two or greater had alcoholic liver disease [20]. The percentage increased to greater than 96 percent when the ratio was greater than three. In addition, 70 percent of the patients with known alcoholic liver disease had an AST to ALT ratio greater than two. (See "Clinical manifestations and diagnosis of alcohol-associated fatty liver disease and cirrhosis", section on 'Liver test abnormalities'.)

However, the AST to ALT ratio is occasionally elevated in an alcoholic liver disease pattern in patients with nonalcoholic steatohepatitis, and it is frequently elevated (although not greater than two) in patients with hepatitis C who have developed cirrhosis. In addition, patients with Wilson disease or cirrhosis due to viral hepatitis may have an AST that is greater than the ALT, although in patients with cirrhosis the ratio typically is not greater than two. (See "Wilson disease: Clinical manifestations, diagnosis, and natural history", section on 'Hepatic disease'.)

Magnitude of AST and ALT elevations — The magnitude of AST and ALT elevations varies depending on the cause of the hepatocellular injury [21-24]. While values may vary in individual patients, the following are typical AST and ALT patterns:

- Alcoholic fatty liver disease: AST <8 times the upper limit of normal; ALT <5 times the upper limit of normal.
- Nonalcoholic fatty liver disease: AST and ALT <4 times the upper limit of normal.

- Acute viral hepatitis or toxin-related hepatitis with jaundice: AST and ALT >25 times the upper limit of normal.

- Ischemic hepatitis (ischemic hepatopathy, shock liver, hypoxic hepatitis): AST and ALT >50 times the upper limit of normal (in addition the lactate dehydrogenase is often markedly elevated).

- Chronic hepatitis C virus infection: Wide variability, typically normal to less than twice the upper limit of normal, rarely more than 10 times the upper limit of normal.

- Chronic hepatitis B virus infection: Levels vary; the AST and ALT may be normal in inactive carriers, whereas most patients with chronic hepatitis B have mild to moderate elevations (approximately twice the upper limit of normal); with exacerbations, levels are more than 10 times the upper limit of normal.

Other laboratory abnormalities — Patients with Wilson disease may have a Coombs-negative hemolytic anemia, a ratio of alkaline phosphatase (units/L) to total bilirubin (mg/dL) of less than two, or a normal/subnormal alkaline phosphatase. Patients with acute liver failure due to Wilson disease often have an AST to ALT ratio greater than 2.2 and an alkaline phosphatase to total bilirubin ratio less than 4. (See "Wilson disease: Clinical manifestations, diagnosis, and natural history", section on 'Hepatic disease'.)

ELEVATED SERUM AMINOTRANSFERASES

In the setting of hepatocyte damage, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are released from hepatocytes, leading to increased serum levels. The differential diagnosis for elevated serum aminotransferases is broad and includes viral hepatitis, hepatotoxicity from drugs or toxins, alcoholic liver disease, ischemic hepatitis, and malignant infiltration. The evaluation should take into account the patient's risk factors for liver disease as well as findings from the physical examination that may point to a particular diagnosis. (See 'History' above and 'Physical examination' above.)

Acute liver failure — Acute liver failure is characterized by acute hepatocellular injury with liver tests typically more than 10 times the upper limit of normal, hepatic encephalopathy, and a prolonged prothrombin time (international normalized ratio greater than or equal to 1.5). The evaluation of patients with acute liver failure is discussed in detail elsewhere. (See "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis", section on 'Diagnosis'.)

Marked elevation without liver failure — Patients with marked or severe elevations in their aminotransferase levels (approximately 15 times the upper limit of normal or higher) often have acute hepatitis, although in some cases, there may be underlying chronic liver disease (eg, Wilson disease or an acute exacerbation of hepatitis B virus). Massive elevations in aminotransferases (>5,000 U/L) are usually due to ischemic or drug-induced hepatitis. Other causes of massive elevations in AST include rhabdomyolysis and heat stroke.

Differential diagnosis — Marked elevations in serum aminotransferase levels may be seen with:

- Acetaminophen (paracetamol) toxicity
- Idiosyncratic drug reactions
- Acute viral hepatitis (hepatitis A, B, C, D, E; herpes simplex virus; varicella zoster virus; Epstein-Barr virus; cytomegalovirus [CMV]); other viral infections; or an acute exacerbation of chronic viral hepatitis (hepatitis B)
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson disease
- Ischemic hepatitis
- Budd-Chiari syndrome
- Sinusoidal obstruction syndrome (veno-occlusive disease)
- HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome and occasionally acute fatty liver of pregnancy
- Malignant infiltration (most often breast cancer, small cell lung cancer, lymphoma, melanoma, or myeloma)
- Partial hepatectomy
- Toxin exposure, including mushroom poisoning
- Sepsis
- Heat stroke
- Muscle disorders (acquired muscle disorders [eg, polymyositis], seizures, and heavy exercise [eg, long distance running])

Evaluation of markedly elevated aminotransferases — For patients with marked elevations of serum aminotransferases, we obtain the following laboratory tests:

- Acetaminophen level
- Toxicology screen
- Acute viral hepatitis serologies

- IgM anti-hepatitis A virus.
- Hepatitis B surface antigen (HBsAg), IgM anti-hepatitis B core antigen (anti-HBc), antibody to HBsAg.
- Anti-hepatitis C virus antibody (HCV), hepatitis C viral RNA.
- In some cases (based on patient history and risk factors): anti-herpes simplex virus antibodies, anti-varicella zoster antibodies, anti-CMV antibodies, CMV antigen, and, for Epstein-Barr virus, heterophile antibody.

- Serum pregnancy test in women of childbearing potential who are not already known to be pregnant
- Autoimmune markers (antinuclear antibodies, anti-smooth muscle antibodies, anti-liver/kidney microsomal antibodies type 1, IgG)
- Transabdominal ultrasonography with Doppler imaging to look for evidence of vascular occlusion (eg, Budd-Chiari syndrome)

Additional tests that are indicated in specific circumstances include:

- Ceruloplasmin level and urinary copper quantitation in patients suspected of having Wilson disease. (See "Wilson disease: Clinical manifestations, diagnosis, and natural history", section on 'When to consider Wilson disease' and "Wilson disease: Clinical manifestations, diagnosis, and natural history", section on 'Diagnosis'.)
- Hepatitis D virus antibodies in patients with acute or chronic hepatitis B. (See "Diagnosis of hepatitis D virus infection", section on 'Diagnosis of HDV infection'.)
- Hepatitis E virus antibodies in patients who live in or travel to areas endemic for hepatitis E, such as Asia, Africa, the Middle East, and Central America, or in patients who are pregnant (because of the high rates of acute liver failure in pregnant women with hepatitis E). Additionally, cases of hepatitis E in the absence of foreign travel have been reported increasingly in developed countries [25,26] and in some cases of suspected drug-induced liver disease [27], and it is reasonable to test for antibodies to hepatitis E virus if no other cause for the elevated aminotransferases is found. (See "Hepatitis E virus infection", section on 'Diagnosis'.)
- Urinalysis to look for proteinuria in women who are pregnant. (See "Preeclampsia: Clinical features and diagnosis", section on 'Definitions/diagnostic criteria'.)

- Serum creatinine kinase or aldolase in patients with risk factors for or symptoms of muscle disorders.

If the above testing is negative, we typically proceed with a liver biopsy if the acute elevation of the serum aminotransferases fails to resolve or decline, or if the patient appears to be developing acute liver failure. If the elevation is less than five times the upper limit of normal and the patient appears well, we may follow the patient expectantly, checking liver tests every three to six months.

Mild to moderate elevation — Mild to moderate elevations of the serum aminotransferases (less than 15 times the upper limit of normal) are often seen with chronic liver disease, although transient elevations may also be seen in patients with mild hepatic insults (eg, intake of nontoxic doses of acetaminophen).

Differential diagnosis — Conditions associated with mild to moderate serum aminotransferase elevations include (table 3):

- Medication use
- Chronic viral hepatitis (hepatitis B, C, D)
- Alcoholic liver disease
- Hemochromatosis
- Nonalcoholic fatty liver disease
- Autoimmune hepatitis
- Wilson disease
- Alpha-1 antitrypsin deficiency
- Congestive hepatopathy
- Adult bile ductopenia
- Malignant infiltration (most often breast cancer, small cell lung cancer, lymphoma, melanoma, or myeloma)
- Muscle disorders (eg, subclinical inborn errors of muscle metabolism)
- Thyroid disorders
- Celiac disease
- Adrenal insufficiency
- Anorexia nervosa
- Macro-AST (moderate elevations in plasma AST levels due to the presence AST-immunoglobulin complexes, usually IgG) [28]

Evaluation of mildly or moderately elevated aminotransferases — The initial evaluation of patients with mildly to moderately elevated serum aminotransferases includes testing for chronic viral hepatitis, hemochromatosis, and nonalcoholic fatty liver disease (table 4). The majority of

patients in whom the diagnosis remains unclear after obtaining a history and laboratory testing will have alcoholic liver disease, steatosis, or steatohepatitis [29,30], and an initial evaluation directed toward likely causes of serum aminotransferase elevations can be cost-saving [29-32].

We typically start the evaluation with the following:

- Hepatitis B: HBsAg, antibody to HBsAg, anti-HBc. (See "Hepatitis B virus: Screening and diagnosis".)
- Hepatitis C: Anti-HCV. (See "Screening and diagnosis of chronic hepatitis C virus infection".)
- Hemochromatosis: Serum iron and total iron binding capacity (TIBC) with calculation of transferrin saturation (serum iron/TIBC). A transferrin saturation greater than 45 percent warrants obtaining a serum ferritin. Ferritin is less useful as an initial test because it is an acute phase reactant and therefore less specific than the transferrin saturation. A serum ferritin concentration of greater than 400 ng/mL (900 pmol/L) in men and 300 ng/mL (675 pmol/L) in women further supports (but does not confirm) the diagnosis of hemochromatosis. (See "Approach to the patient with suspected iron overload", section on 'Diagnosis'.)
- Nonalcoholic fatty liver disease: The initial evaluation to identify the presence of fatty infiltration of the liver is radiologic imaging, usually ultrasonography, or possibly computed tomography (CT) or magnetic resonance imaging (MRI). Ultrasonography has a lower sensitivity than CT or MRI but is less expensive. (See "Epidemiology, clinical features, and diagnosis of nonalcoholic fatty liver disease in adults".)

In a patient with a history of significant alcohol consumption, we generally do not obtain additional testing if the above tests are negative. For patients with liver test elevations less than five times the upper limit of normal, we typically recheck the liver tests in three to six months and only pursue the above workup if they remain elevated [2]. (See 'History' above.)

If the initial evaluation fails to identify a likely source of the aminotransferase elevation, we test for the following:

- Autoimmune hepatitis: Antinuclear antibodies, anti-smooth muscle antibodies, and anti-liver/kidney microsomal antibodies, IgG (see "Overview of autoimmune hepatitis", section on 'Diagnostic evaluation').
- Wilson disease: Serum ceruloplasmin, evaluation for Kaiser-Fleisher rings, (see "Wilson disease: Clinical manifestations, diagnosis, and natural history", section on 'Initial evaluation').

- Alpha-1 antitrypsin deficiency: Serum alpha-1 antitrypsin level; if indicated, alpha-1 antitrypsin phenotyping (see "Clinical manifestations, diagnosis, and natural history of alpha-1 antitrypsin deficiency", section on 'Evaluation and diagnosis').

- Thyroid disorders: Thyroid-stimulating hormone, free T4 concentration, free T3 concentration (see "Diagnosis of and screening for hypothyroidism in nonpregnant adults" and "Diagnosis of hyperthyroidism").

- Celiac disease: Antibody screening with serum tissue transglutaminase antibodies [33] (see "Diagnosis of celiac disease in adults").

If the source of the liver test abnormalities is still unclear, we test for the following:

- Adrenal insufficiency (in patients with symptoms associated with adrenal insufficiency, such as chronic malaise, anorexia, or weight loss): 8 AM serum cortisol and plasma corticotropin (ACTH), and a high-dose ACTH stimulation test (see "Clinical manifestations of adrenal insufficiency in adults" and "Diagnosis of adrenal insufficiency in adults").

- Muscle disorders (in patients with symptoms such exercise intolerance, muscle pain, or muscle weakness): Creatinine kinase or aldolase (see "Inborn errors of metabolism: Epidemiology, pathogenesis, and clinical features", section on 'Clinical manifestations').

A liver biopsy is often considered in patients in whom all of the above testing has been unrevealing [34]. However, in some settings, the best course may be expectant observation.

We suggest expectant observation in patients in whom the ALT and AST levels are less than five times the upper limit of normal and no chronic liver condition has been identified by the above noninvasive testing [2]. We use a conservative estimate for the upper limit of normal for aminotransferases (approximately 33 units/L for men and 25 units/L for women). In such patients, we will follow their liver biochemical and function tests every six months. This approach was supported by a preliminary study in which expectant clinical follow-up was found to be the most cost-effective strategy for managing asymptomatic patients with negative viral, metabolic, and autoimmune markers and chronically elevated aminotransferases [35]. A second small study also found that biopsy results rarely affected the management of such patients [36].

We suggest a liver biopsy in patients in whom the ALT and AST are persistently greater than twice the upper limit of normal, particularly if noninvasive testing suggests that advanced liver fibrosis is unlikely [34]. Occasionally, the biopsy will provide an unsuspected diagnosis or lead to a change in management [30]. In most cases, however, the biopsy proves reassuring to the patient and clinician

by confirming that there is no evidence of serious or advanced liver disease. (See "Noninvasive assessment of hepatic fibrosis: Overview of serologic and radiographic tests".)

ELEVATED ALKALINE PHOSPHATASE

Cholestasis may develop in the setting of extrahepatic or intrahepatic biliary obstruction (table 5). In patients with cholestasis, the alkaline phosphatase is typically elevated to at least four times the upper limit of normal. The magnitude of the serum alkaline phosphatase elevation does not distinguish extrahepatic cholestasis from intrahepatic cholestasis. Lesser degrees of elevation are nonspecific and may be seen in many other types of liver disease, such as viral hepatitis, infiltrative diseases of the liver, and congestive hepatopathy. The gamma-glutamyl transpeptidase (GGT) may also be elevated in the setting of cholestasis. However, elevated levels of serum GGT have been reported in a wide variety of other conditions. Patients with a predominantly cholestatic pattern typically undergo a right upper quadrant ultrasound to further characterize the cholestasis as intrahepatic or extrahepatic; the latter is suggested by biliary tract dilatation.

Confirming an elevated alkaline phosphatase is of hepatic origin — If a patient has an isolated elevation of the alkaline phosphatase, the first step in the evaluation is to confirm it is of hepatic origin, since alkaline phosphatase can come from other sources, such as bone and placenta (algorithm 1). If, however, there are abnormalities in other liver chemistries or markers of hepatic function, particularly an elevated bilirubin, confirmation is typically not required.

To confirm that an isolated elevation in the alkaline phosphatase is coming from the liver, a GGT level or serum 5'-nucleotidase level should be obtained. These tests are usually elevated in parallel with the alkaline phosphatase in liver disorders but are not increased in bone disorders. An elevated serum alkaline phosphatase with a normal GGT or 5'-nucleotidase should prompt an evaluation for bone diseases.

An elevated bone alkaline phosphatase is indicative of high bone turnover, which may be caused by several disorders including healing fractures, osteomalacia, hyperparathyroidism, hyperthyroidism, Paget disease of bone, osteogenic sarcoma, and bone metastases. We generally refer such patients to an endocrinologist for evaluation. Initial testing may include measurement of serum calcium, parathyroid hormone, 25-hydroxy vitamin D, and imaging with bone scintigraphy. (See "Bone physiology and biochemical markers of bone turnover", section on 'Markers of bone turnover' and "Clinical manifestations and diagnosis of Paget disease of bone", section on 'Clinical manifestations' and "Clinical manifestations, diagnosis, and treatment of osteomalacia", section on 'Diagnosis'.)

Differential diagnosis — If the alkaline phosphatase elevation is isolated (ie, the other routine liver biochemical test levels are normal), is confirmed to be of hepatic origin, and persists over time, chronic cholestatic or infiltrative liver diseases should be considered (table 5). The most common causes include partial bile duct obstruction, primary biliary cholangitis (PBC), primary sclerosing cholangitis, and certain drugs, such as androgenic steroids and phenytoin. Infiltrative diseases include sarcoidosis, other granulomatous diseases, amyloidosis, and, less often, unsuspected cancer that is metastatic to the liver.

Acute or chronic elevation of the alkaline phosphatase in conjunction with other liver biochemical abnormalities may be due to extrahepatic causes (eg, bile duct stones, primary sclerosing cholangitis, malignant biliary obstruction) or intrahepatic causes (eg, PBC, primary sclerosing cholangitis, infiltrative disease). (See 'Extrahepatic cholestasis' below and 'Intrahepatic cholestasis' below.)

Rarely, an elevated alkaline phosphatase level is seen because of the presence of macro-alkaline phosphatase. Macro-alkaline phosphatase is due to the formation of complexes of alkaline phosphatase with immunoglobulins, which have reduced renal clearance compared with unbound alkaline phosphatase [37]. The clinical significance of these complexes is uncertain.

Evaluation of elevated alkaline phosphatase — Testing in patients with an elevated alkaline phosphatase of hepatic origin typically starts with right upper quadrant ultrasonography to assess the hepatic parenchyma and bile ducts.

The presence of biliary dilatation on ultrasonography suggests extrahepatic cholestasis, whereas the absence of biliary dilatation suggests intrahepatic cholestasis. However, ultrasonography may fail to show ductal dilatation in the setting of extrahepatic cholestasis in patients with partial obstruction of the bile duct or in patients with cirrhosis or primary sclerosing cholangitis, in which scarring prevents the intrahepatic ducts from dilating.

The subsequent evaluation depends on whether ultrasonography suggests extrahepatic cholestasis or intrahepatic cholestasis. (See 'Extrahepatic cholestasis' below and 'Intrahepatic cholestasis' below.)

Extrahepatic cholestasis — Although ultrasonography may indicate extrahepatic cholestasis, it rarely identifies the site or cause of obstruction. The distal bile duct is a particularly difficult area to visualize by ultrasonography because of overlying bowel gas. Potential causes of extrahepatic cholestasis include (table 5):

- Choledocholithiasis (the most common cause) (see "Choledocholithiasis: Clinical manifestations, diagnosis, and management", section on 'Transabdominal ultrasound' and

"Choledocholithiasis: Clinical manifestations, diagnosis, and management", section on 'Additional imaging (MRCP or EUS)').

- Malignant obstruction (pancreas, gallbladder, ampulla, bile duct cancer, or metastasis to perihilar lymph nodes) (see "Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer", section on 'Diagnostic approach' and "Gallbladder cancer: Epidemiology, risk factors, clinical features, and diagnosis", section on 'Diagnostic evaluation' and "Ampullary carcinoma: Epidemiology, clinical manifestations, diagnosis and staging", section on 'Diagnosis and staging' and "Clinical manifestations and diagnosis of cholangiocarcinoma").

- Primary sclerosing cholangitis with an extrahepatic bile duct stricture (see "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis", section on 'Diagnosis').

- Chronic pancreatitis (including autoimmune pancreatitis) with stricturing of the distal bile duct (see "Overview of the complications of chronic pancreatitis", section on 'Biliary obstruction').

- AIDS cholangiopathy (see "AIDS cholangiopathy", section on 'Clinical suspicion and diagnosis').

If ultrasonography suggests obstruction due to a stone or malignancy, or if the onset of the cholestasis was acute, endoscopic retrograde cholangiopancreatography (ERCP) should be carried out to confirm the diagnosis and facilitate biliary drainage. If the cholestasis is chronic or ultrasonography shows biliary dilatation without an apparent cause or in patients who are at high risk for ERCP, magnetic resonance cholangiopancreatography (MRCP) or computed tomography (CT) should be obtained. In some cases, endoscopic ultrasonography may help identify an obstruction. ERCP can then be performed if there is evidence of an obstructing stone, stricture, or malignancy. If the results of ERCP or MRCP are negative for biliary tract disease, liver biopsy should be considered. (See "Endoscopic retrograde cholangiopancreatography: Indications, patient preparation, and complications", section on 'Indications for ERCP'.)

Intrahepatic cholestasis — There are numerous possible causes of intrahepatic cholestasis (table 5), including drug toxicity, PBC, primary sclerosing cholangitis, viral hepatitis, cholestasis of pregnancy, benign postoperative cholestasis, infiltrative diseases, and total parenteral nutrition. In many cases, a possible cause can be identified based on the patient's history. If drug-induced cholestasis is suspected, elimination of the offending drug usually leads to resolution of cholestasis, although it may take months. If no cause is identified, additional testing is required.

In patients with intrahepatic cholestasis, antimitochondrial antibodies (AMA), antinuclear antibodies, and antismooth muscle antibodies should be checked. If present, AMA are highly suggestive of PBC, and a liver biopsy may be considered to confirm the diagnosis. (See "Clinical manifestations,

diagnosis, and prognosis of primary biliary cholangitis (primary biliary cirrhosis)", section on 'Diagnosis'.)

If AMA are absent, additional testing includes:

- MRCP to look for evidence of primary sclerosing cholangitis (see "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis", section on 'Diagnosis').
- Testing for hepatitis A, B, C, and E (see 'Elevated serum aminotransferases' above).
- Testing for Epstein-Barr virus and cytomegalovirus (see "Infectious mononucleosis", section on 'Diagnosis' and "Overview of diagnostic tests for cytomegalovirus infection").
- Pregnancy testing in women of child bearing potential who are not known to be pregnant (see "Intrahepatic cholestasis of pregnancy", section on 'Diagnosis').

If the above tests are negative and the alkaline phosphatase is persistently more than two times the upper limit of normal for more than six months, we obtain a liver biopsy. A liver biopsy may reveal evidence of an infiltrative disease (eg, sarcoidosis, malignancy) or other causes of cholestasis, such as vanishing bile duct syndrome and idiopathic adulthood bile ductopenia.

If the alkaline phosphatase is less than two times the upper limit of normal, all of the other liver biochemical tests are normal, and the patient is asymptomatic, we suggest observation alone, since further testing is unlikely to influence management [36].

ISOLATED GAMMA-GLUTAMYL TRANSPEPTIDASE (GGT) ELEVATION

Elevated levels of serum GGT have been reported in a wide variety of clinical conditions, including pancreatic disease, myocardial infarction, renal failure, chronic obstructive pulmonary disease, diabetes mellitus, and alcoholism. High serum GGT values are also found in patients taking medications such as phenytoin and barbiturates. GGT is sensitive for detecting hepatobiliary disease, but its usefulness is limited by its lack of specificity.

An elevated GGT with otherwise normal liver biochemical tests (including a normal alkaline phosphatase) should not lead to an exhaustive work-up for liver disease. We suggest GGT only be used to evaluate elevations of other serum enzyme tests (eg, to confirm the liver origin of an elevated alkaline phosphatase or to support a suspicion of alcohol abuse in a patient with an elevated AST and an AST to ALT ratio of greater than 2:1). (See "Enzymatic measures of cholestasis (eg, alkaline phosphatase, 5'-nucleotidase, gamma-glutamyl transpeptidase)".)

ISOLATED HYPERBILIRUBINEMIA

The initial step in evaluating a patient with an isolated elevated hyperbilirubinemia is to fractionate the bilirubin to determine whether the hyperbilirubinemia is predominantly conjugated (direct hyperbilirubinemia) or unconjugated (indirect hyperbilirubinemia). An increase in unconjugated bilirubin in serum results from overproduction, impairment of uptake, or impaired conjugation of bilirubin. An increase in conjugated bilirubin is due to decreased excretion into the bile ductules or leakage of the pigment from hepatocytes into serum. (See "Clinical aspects of serum bilirubin determination" and "Diagnostic approach to the adult with jaundice or asymptomatic hyperbilirubinemia".)

Unconjugated (indirect) hyperbilirubinemia — Unconjugated hyperbilirubinemia may be observed in a number of disorders (table 6). These can be divided into disorders associated with bilirubin overproduction (such as hemolysis and ineffective erythropoiesis) and disorders related to impaired hepatic uptake or conjugation of bilirubin (such as Gilbert disease, Crigler-Najjar syndrome, and the effects of certain drugs). The evaluation typically involves evaluation for hemolytic anemia as well as obtaining a history to determine if the patient has Gilbert syndrome. In a patient with a history consistent with Gilbert syndrome (eg, the development of jaundice during times of stress or fasting), normal serum aminotransferase and alkaline phosphatase levels and mild unconjugated hyperbilirubinemia (<4 mg/dL), additional testing is not required [2]. Genetic testing can confirm the diagnosis in settings where there is diagnostic confusion. In patients with persistent or worsening unexplained unconjugated hyperbilirubinemia, symptomatic hyperbilirubinemia, or abnormal aminotransferases, a liver biopsy should be performed. (See "Gilbert syndrome and unconjugated hyperbilirubinemia due to bilirubin overproduction", section on 'Diagnosis'.)

Hemolysis — Hemolysis can usually be detected by examining the peripheral blood smear or obtaining a reticulocyte count and serum haptoglobin. Hemolytic disorders that cause excessive heme production may be either inherited or acquired. Inherited disorders include spherocytosis, sickle cell disease, and deficiency of a red cell enzyme, such as pyruvate kinase or glucose-6-phosphate dehydrogenase. In these conditions, the serum bilirubin rarely exceeds 5 mg/dL (86 micromol/L). Higher levels may occur when there is coexistent renal or hepatocellular dysfunction or acute hemolysis. (See "Diagnosis of hemolytic anemia in adults".)

Acquired hemolytic disorders include microangiopathic hemolytic anemia (eg, hemolytic-uremic syndrome), paroxysmal nocturnal hemoglobinuria, and immune hemolysis. Ineffective erythropoiesis occurs in cobalamin, folate, and iron deficiencies.

Impaired hepatic uptake or conjugation — Impaired hepatic uptake or conjugation of bilirubin should be considered in the absence of hemolysis. This is most commonly caused by certain drugs (including rifampin and probenecid) that diminish hepatic uptake of bilirubin or by Gilbert syndrome (a common genetic disorder associated with unconjugated hyperbilirubinemia). Much less commonly, indirect hyperbilirubinemia can be caused by two other genetic disorders: Crigler-Najjar syndrome types I and II.

- Studies in Western populations have estimated that Gilbert syndrome affects approximately 3 to 7 percent of the population, with White males predominating over females by a ratio of 2 to 7:1 [38]. Impaired conjugation of bilirubin is due to reduced bilirubin uridine diphosphate (UDP) glucuronosyltransferase activity. Affected patients have mild unconjugated hyperbilirubinemia with serum levels almost always less than 6 mg/dL (103 micromol/L). The serum levels may fluctuate, and jaundice is often identified only during periods of illness or fasting. In an otherwise healthy adult with mildly elevated unconjugated hyperbilirubinemia and no evidence of hemolysis, the presumptive diagnosis of Gilbert syndrome can be made without further testing. (See "Gilbert syndrome and unconjugated hyperbilirubinemia due to bilirubin overproduction".)

- Crigler Najjar type I is an exceptionally rare condition found in neonates and is characterized by severe jaundice (bilirubin >20 mg/dL [342 micromol/L]) and neurologic impairment due to kernicterus. Crigler-Najjar type II is more common than type I. Patients live into adulthood with serum bilirubin levels that range from 6 to 25 mg/dL (103 to 428 micromol/L). Bilirubin UDP glucuronosyltransferase activity is typically present but greatly reduced. Bilirubin UDP glucuronosyltransferase activity can be induced by the administration of phenobarbital, which can reduce serum bilirubin levels in these patients. (See "Crigler-Najjar syndrome".)

Conjugated (direct) hyperbilirubinemia — An isolated elevation in conjugated bilirubin 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 direct-reacting fraction of approximately 50 percent) in the absence of other abnormalities of standard liver biochemical tests. Normal levels of serum alkaline phosphatase and GGT help to distinguish these conditions from disorders associated with biliary obstruction. Differentiating between these syndromes is possible but clinically unnecessary due to their benign nature. In children, other inherited disorders caused by mutations in one of a variety of bile salt transporters may need to be considered [39]. (See "Inherited disorders associated with conjugated hyperbilirubinemia".)

Patients with both conditions present with asymptomatic jaundice, typically in the second decade of life. The defect in Dubin-Johnson syndrome is altered hepatocyte excretion of bilirubin into the bile

ducts, while Rotor syndrome is due to defective hepatic reuptake of bilirubin by hepatocytes [40].

ISOLATED ABNORMALITIES OF TESTS OF SYNTHETIC FUNCTION

Abnormalities in tests of liver synthetic function, such as the prothrombin time and serum albumin level, are often seen in patients with chronic liver disease in conjunction with other liver test abnormalities. These patients should be evaluated according to the predominant pattern of liver test abnormalities. (See 'Patterns of liver test abnormalities' above.)

However, isolated abnormalities in the prothrombin time or albumin are typically due to causes other than liver disease. The evaluation of these abnormalities is discussed elsewhere. (See "Clinical use of coagulation tests", section on 'Prothrombin time (PT) and INR' and "Overview of heavy proteinuria and the nephrotic syndrome" and "Protein-losing gastroenteropathy" and "Malnutrition in children in resource-limited countries: Clinical assessment".)

WHEN TO REFER TO A SPECIALIST

Referral to a gastroenterologist or hepatologist should be considered for patients with unexplained, persistent liver biochemical test elevations (≥2 times the upper limit of normal for aminotransferases or 1.5 times the upper limit of normal for alkaline phosphatase) and for patients who are being considered for liver biopsy. We use a conservative estimate for the upper limit of normal for aminotransferases (approximately 30 units/L for men and 20 units/L for women) since the higher limits reported by many laboratories likely underestimate the degree of aminotransferase elevation. (See 'Aminotransferases' above.)

If the liver tests normalize or remain mildly elevated (<2 times the upper limit of normal for aminotransferases or less than 1.5 times the upper limit of normal for alkaline phosphatase), expectant management is reasonable in most cases. In such patients, we would follow their liver biochemical and function tests every six months. It is reasonable to refer such patients to a gastroenterologist or hepatologist if the liver biochemical tests remain elevated without a clear explanation, if they subsequently increase, or if otherwise warranted by the specific features of the case.

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 topics (see "Patient education: Toxic hepatitis (The Basics)")

SUMMARY AND RECOMMENDATIONS

- Blood tests commonly obtained to evaluate the health of the liver include liver enzyme levels (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, gamma-glutamyl transpeptidase), tests of hepatic synthetic function (albumin, prothrombin time/international normalized ratio [INR]), and the serum bilirubin level. (See 'Common liver biochemical and function tests' above.)

  The initial evaluation of a patient with abnormal liver biochemical and function tests includes obtaining a history to identify potential risk factors for liver disease and performing a physical examination to look for clues to the etiology and for signs of chronic liver disease. Subsequent testing is determined based on the information gathered from the history and physical examination as well as the pattern of liver test abnormalities (table 4 and algorithm 1). (See 'Initial evaluation' above.)

- Liver biochemical test abnormalities can often be grouped into one of several patterns: hepatocellular, cholestatic, or isolated hyperbilirubinemia. Patients with a hepatocellular process generally have a disproportionate elevation in the serum aminotransferases compared with the alkaline phosphatase, while those with a cholestatic process have the opposite findings. The serum bilirubin can be prominently elevated in both hepatocellular and cholestatic conditions and therefore is not necessarily helpful in differentiating between the two. Abnormal

tests of synthetic function may be seen with both hepatocellular injury and cholestasis. (See 'Patterns of liver test abnormalities' above.)

- In the setting of hepatocyte damage, ALT and AST are released from hepatocytes, leading to increased serum levels. The differential diagnosis for elevated serum aminotransferases is broad and includes viral hepatitis, hepatotoxicity from drugs or toxins, alcoholic liver disease, hepatic ischemia, and malignant infiltration. The evaluation should take into account the patient's risk factors for liver disease as well as findings from the physical examination that may point to a particular diagnosis. The evaluation often involves testing for viral hepatitis and autoimmune disease (table 4). Occasionally, a liver biopsy may be required. (See 'Elevated serum aminotransferases' above.)

- Cholestasis may develop in the setting of extrahepatic or intrahepatic biliary obstruction (table 5). In patients with cholestasis, the alkaline phosphatase is typically elevated to at least four times the upper limit of normal. Lesser degrees of elevation are nonspecific and may be seen in many other types of liver disease, such as viral hepatitis, infiltrative diseases of the liver, and congestive hepatopathy. Patients with a predominantly cholestatic pattern typically undergo right upper quadrant ultrasonography to further characterize the cholestasis as intrahepatic or extrahepatic. (See 'Elevated alkaline phosphatase' above.)

  The presence of biliary dilatation on ultrasonography suggests extrahepatic cholestasis which may be due to gallstones, strictures, or malignancy. The absence of biliary dilatation suggests intrahepatic cholestasis. There are numerous possible causes of intrahepatic cholestasis (table 5), including drug toxicity, primary biliary cholangitis, primary sclerosing cholangitis, viral hepatitis, cholestasis of pregnancy, benign postoperative cholestasis, infiltrative diseases, and total parenteral nutrition. Subsequent testing to identify the underlying cause may include checking antimitochondrial antibodies, magnetic resonance cholangiopancreatography, computed tomography, endoscopic ultrasonography, and/or endoscopic retrograde cholangiopancreatography (algorithm 1). (See 'Evaluation of elevated alkaline phosphatase' above.)

- The evaluation of isolated hyperbilirubinemia begins with determining whether the hyperbilirubinemia is predominantly conjugated (direct hyperbilirubinemia) or unconjugated (indirect hyperbilirubinemia). An increase in unconjugated bilirubin in serum results from overproduction, impairment of uptake, or impaired conjugation of bilirubin. The evaluation of unconjugated hyperbilirubinemia typically involves evaluation for hemolytic anemia as well as obtaining a history to determine if the patient has Gilbert syndrome. In a patient with a history consistent with Gilbert syndrome (eg, the development of jaundice during times of stress or fasting), normal serum aminotransferase and alkaline phosphatase levels, and mild

unconjugated hyperbilirubinemia (<4 mg/dL), additional testing is not required. (See 'Isolated hyperbilirubinemia' above and 'Unconjugated (indirect) hyperbilirubinemia' above.)

An isolated elevation in conjugated bilirubin is found in two rare inherited conditions: Dubin-Johnson syndrome and Rotor syndrome, as well as other genetic bile transport disorders in children. Dubin-Johnson syndrome and Rotor syndrome should be suspected in patients with mild hyperbilirubinemia (with a direct-reacting fraction of approximately 50 percent) in the absence of other abnormalities of standard liver biochemical tests. Normal levels of serum alkaline phosphatase and GGT help to distinguish these conditions from disorders associated with biliary obstruction. Differentiating between these syndromes is possible but clinically unnecessary due to their benign nature. (See 'Conjugated (direct) hyperbilirubinemia' above.)

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