ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries

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Abstract

Clinicians are required to assess abnormal liver chemistries on a daily basis. The most common liver chemistries ordered are serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase and bilirubin. These tests should be termed liver chemistries or liver tests. Hepatocellular injury is defined as disproportionate elevation of AST and ALT levels compared with alkaline phosphatase levels. Cholestatic injury is defined as disproportionate elevation of alkaline phosphatase level as compared with AST and ALT levels. The majority of bilirubin circulates as unconjugated bilirubin and an elevated conjugated bilirubin implies hepatocellular disease or cholestasis. Multiple studies have demonstrated that the presence of an elevated ALT has been associated with increased liver-related mortality. A true healthy normal ALT level ranges from 29 to 33 IU/l for males, 19 to 25 IU/l for females and levels above this should be assessed. The degree of elevation of ALT and or AST in the clinical setting helps guide the evaluation. The evaluation of hepatocellular injury includes testing for viral hepatitis A, B, and C, assessment for nonalcoholic fatty liver disease and alcoholic liver disease, screening for hereditary hemochromatosis, autoimmune hepatitis, Wilson's disease, and alpha-1 antitrypsin deficiency. In addition, a history of prescribed and over-the-counter medicines should be sought. For the evaluation of an alkaline phosphatase elevation determined to be of hepatic origin, testing for primary biliary cholangitis and primary sclerosing cholangitis should be undertaken. Total bilirubin elevation can occur in either cholestatic or hepatocellular diseases. Elevated total serum bilirubin levels should be fractionated to direct and indirect bilirubin fractions and an elevated serum conjugated bilirubin implies hepatocellular disease or biliary obstruction in most settings. A liver biopsy may be considered when serologic testing and imaging fails to elucidate a diagnosis, to stage a condition, or when multiple diagnoses are possible.

Introduction

The authors were invited by the Board of Trustees and Practice Guidelines Committee of the American College of Gastroenterology to develop a practice guideline regarding the evaluation of abnormal liver chemistries. We used the following resources:

1. A formal review and literature search of the world literature on MEDLINE and EMBASE databases dealing with the evaluation of abnormal liver chemistries, studies that dealt with normal or reference range for alanine aminotransferase (ALT) levels and what thresholds trigger an evaluation for actionable liver disease. Studies detailing the relationship between ALT and nonalcoholic fatty liver disease, as well as studies assessing the significance of elevated liver chemistries on overall mortality and morbidity.
2. Guideline policies of the American College of Gastroenterology.
3. The experience of the authors and independent reviewers, as well as communication with senior hepatologists across the United States with regard to the threshold for evaluating abnormal liver chemistries.

These recommendations are intended for use by physicians and health care providers and suggest preferred approaches to the diagnoses and evaluation of those with abnormal liver tests (Table 1). These guidelines are intended to be flexible and should be adjusted as deemed appropriate when applied to individual patients. Recommendations are evidence-based where possible. On subjects lacking rigid scientific data, recommendations are made based on the consensus opinion of the authors. To more fully characterize the available evidence reporting the recommendations, the ACG Practice Guideline Committee has adopted the classification used by the grading of recommendation assessment, development, and evaluation workup with modifications. The strength of recommendations are classified as strong or conditional. The quality of evidence supporting strong or weak recommendations are designated by the following level is high, moderate low, or very low quality (1). This is a practice guideline rather than a review article.

Liver chemistries that are commonly ordered in comprehensive metabolic profiles are indirect markers of hepatobiliary disease. They are not true measures of hepatic function and thus are best referred to as liver chemistries or liver tests, and should not be referred to as liver function tests. True tests of liver function are not commonly performed but include measurement of hepatic substrates that are cleared by hepatic uptake, metabolism, or both processes (2). Because of the widespread use of the comprehensive metabolic profile testing that is done in routine practice to screen those who present for routine evaluation as well as those who are symptomatic and/or referred for elevation of abnormal liver chemistries, such abnormalities require a rational approach to interpretation. To date, there are no controlled trials that have been performed to determine the optimal approach to evaluate abnormal liver chemistries. This guideline has been developed to assist gastroenterologists and primary care providers in the interpretation of normal and abnormal liver chemistries as well as an approach to prioritize and evaluate those who present with abnormal liver chemistries.

Table 1. Recommendations	
1.	Before initiation of evaluation of abnormal liver chemistries, one should repeat the lab panel and/or perform a clarifying test (e.g., GGT if serum alkaline phosphate is elevated) to confirm that the liver chemistry is actually abnormal. (Strong recommendation, very low level of evidence).

2.	Testing for chronic hepatitis C is conducted with anti-HCV and confirmation is performed with HCV-RNA by nucleic acid testing. Risk factors for hepatitis C include history of intranasal or intravenous drug use, tattoos, body piercings, blood transfusions, high risk sexual conduct, and those born between 1945 and 1965. Testing for acute hepatitis C is with anti-HCV and HCV RNA by nucleic acid testing. (Strong recommendation, very low level of evidence).
3.	Testing for chronic hepatitis B is conducted with HBsAg testing. Testing for acute hepatitis B is with HBsAg and IgM anti-HBc. The following groups are at highest risk: persons born in endemic or hyperendemic areas (HBsAg prevalence >2%), men who have sex with men, persons who have ever used injection drugs, dialysis patients, HIV-infected individuals, pregnant women, and family members, household members, and sexual contacts of HBV-infected persons. (Strong recommendation, very low level of evidence).
4.	Testing for acute Hepatitis A (IgM HAV) should occur in patients presenting with acute hepatitis and possible fecal-oral exposure. Testing for acute hepatitis E (IgM HEV) should also be considered in those returning from endemic areas and whose tests for acute hepatitis A, B, and C are negative. (Strong recommendation, very low level of evidence).
5.	Patients with elevated BMI and other features of metabolic syndrome including diabetes mellitus, overweight or obesity, hyperlipidemia, or hypertension with mild elevations of ALT should undergo screening for NAFLD with ultrasound. (Strong recommendation, very low level of evidence).
6.	Women consuming more than 140 g per week or men consuming more than 210 g per week who present with AST>ALT should be considered at risk for alcoholic liver disease and should be counseled for alcohol cessation. (Strong recommendation, very low level of evidence).
7.	All patients with abnormal liver chemistries in the absence of acute hepatitis should undergo testing for hereditary hemochromatosis with an iron level, transferrin saturation, and serum ferritin. HFE gene mutation analysis should be performed in patients with transferrin saturation ≥45% and/or elevated serum ferritin. (Strong recommendation, very low level of evidence).
8.	Patients with abnormal AST and ALT levels, particularly patients with other autoimmune conditions, should undergo testing for autoimmune liver disease including ANA, ASMA, and globulin level. (Strong recommendation, very low level of evidence).
9.	Patients with persistently elevated AST and ALT levels, especially patients <55 years of age, should undergo screening for Wilson's disease with serum ceruloplasmin testing. In the setting of low ceruloplasmin, confirmatory testing with 24-h urinary copper and slit-lamp eye examination to identify pathognomonic Kayser–Fleischer rings should occur. (Strong recommendation, very low level of evidence).
10.	Patients with persistently elevated AST or ALT should undergo screening for alpha-1 anti-trypsin (A1AT) deficiency with alpha-1 anti-trypsin phenotype. (Strong recommendation, very low level of evidence).
11.	Physicians should ask patients with abnormal liver chemistries about prescribed and over-the-counter medications, non-prescribed complementary or alternative medicines, and dietary or herbal supplements which may be associated with DILI. (Strong recommendation, very low level of evidence).

12.	A liver biopsy may be considered when serologic testing and imaging fails to elucidate a diagnosis, to stage a condition, or when multiple diagnoses are possible. (Strong recommendation, very low level of evidence).
13.	An elevation of alkaline phosphatase should be confirmed with an elevation in GGT. Given its lack of specificity for liver disease, GGT should not be used as a screening test for underlying liver disease in the absence of other abnormal liver chemistries. (Strong recommendation, very low level of evidence).
14.	Patients with alkaline phosphatase elevation with or without elevation of bilirubin should undergo testing for PBC (formerly named primary biliary cirrhosis) with testing for anti-mitochondrial antibody. (Strong recommendation, very low level of evidence).
15	Patients with alkaline phosphatase elevation with or without elevation of bilirubin should undergo testing for PSC with MR cholangiography or ERCP in conjunction with IgG4. (Strong recommendation, very low level of evidence).
16	In those with ALT and/or AST levels <5X ULN, the history and laboratory testing should assess for viral hepatitis B and C, alcoholic and NAFLD, hemochromatosis, Wilson's disease, alpha-1-anti-trypsin deficiency, autoimmune hepatitis and consider drugs/supplement related injury. (Strong recommendation, very low level of evidence).
17	In those with ALT and/or AST levels 5–15X ULN, evaluation should also assess for acute hepatitis A, B, and C in addition to all etiologies for AST/ALT elevation less than 5x ULN. (Strong recommendation, very low level of evidence).
18	In those with ALT and/or AST levels >15X ULN, or massive elevation ALT of >10,000 IU/l, evaluation should also assess for acetaminophen toxicity and ischemic hepatopathy (shock liver). (Strong recommendation, very low level of evidence).
19	A patient presenting with acute hepatitis with an elevated prothrombin time, and/or encephalopathy requires immediate referral to liver specialist. (Strong recommendation, very low level of evidence).

ALT, alanine aminotransferase; ANA, anti-nuclear antibody; ASMA, anti-smooth antibody; AST, aspartate aminotransferase; BMI, body mass index; DILI, drug-induced liver injury; GGT, gamma-glutamyl transferase; HAV, hepatitis A virus; HBc, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HEV, hepatitis E virus; HFE, hereditary hemochromatosis; IgM, immunoglobulin M; MR, magnetic resonance; NAFLD, non-alcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; ULN, upper limit of normal.

What are Truly Normal Liver Chemistry Tests?

Summary statements

1. A true healthy normal ALT level in prospectively-studied populations without identifiable risk factors for liver disease ranges from 29-33 IU/L for males and 19-25 IU/L for females, and levels above this should be assessed by physicians.
2. Elevated ALT or AST above the upper limit of normal (ULN) in a population without identifiable risk factors is associated with increased liver-related mortality.
3. There is a linear relationship between ALT level and body mass index (BMI) that should be assessed by physicians.
4. A normal ALT level may not exclude significant liver disease.
5. ALT levels are higher in males than females.
6. AST and ALT ULN ranges can vary between different labs.
7. Clinicians may rely on local lab ULN ranges for alkaline phosphatase and bilirubin.

Clinical Assessment of the Patient with Abnormal Liver Chemistries

Summary statements

Clinical assessment of the patient with elevated liver tests should begin with a thorough history and physical examination.

1. History should include risk factors for underlying liver disease, associated medical conditions, use of alcohol, and use of medications including over-the-counter products and herbal supplements.
2. Physical examination should assess for stigmata of chronic liver disease, as well as signs or symptoms pointing to a specific liver disease etiology.

Patterns of Liver Chemistry Test Elevations

Summary statements

1. Hepatocellular injury is defined as disproportionate elevation of AST and ALT levels as compared to the alkaline phosphatase level.
2. Cholestatic injury is defined as disproportionate elevation in alkaline phosphatase level as compared to AST and ALT levels.
3. Mixed pattern of injury is defined as elevation of both alkaline phosphatase and AST/ALT levels.
4. Isolated hyperbilirubinemia is defined as elevation of bilirubin with normal alkaline phosphatase and AST/ALT levels.
5. The *R* ratio is calculated by the formula R = (ALT value ÷ ALT ULN) ÷ (alkaline phosphatase value ÷ alkaline phosphatase ULN) with an *R* ratio of > 5 defined as hepatocellular injury, < 2 cholestatic injury, and 2-5 mixed pattern.

Approach to Evaluation for Those with Elevated AST and ALT

Summary statements

1. A borderline AST and/or ALT elevation is defined as < 2X ULN, a mild AST and/or ALT elevation as 2-5X ULN, moderate AST and/or ALT elevation 5-15X ULN, severe AST and/or ALT elevation >15X ULN, and massive AST and/or ALT > 10,000 IU/L.
2. Fulminant hepatic failure (FHF) or acute liver failure (ALF), defined as the rapid development of acute liver injury with severe impairment of the synthetic function as manifested by prolonged prothrombin time and hepatic encephalopathy in a patient without obvious, previous liver disease requires immediate evaluation regardless of ALT level.

Evaluation of Alkaline Phosphatase Level

Recommendation

1. (Table 5 and Figure 4) Right upper quadrant ultrasound should be performed in the setting of an elevation of alkaline phosphatase; if normal, evaluation for intrahepatic causes should be considered, including PBC, PSC, and drug- induced liver injury. (Strong recommendation, very low level of evidence).

Evaluation of Total Bilirubin Level

Summary statements

1. (Table 6 and Figure 5) Elevated serum total bilirubin levels should be fractionated to direct and indirect bilirubin.
2. An elevated serum conjugated bilirubin implies hepatocellular disease or biliary obstruction in most settings.

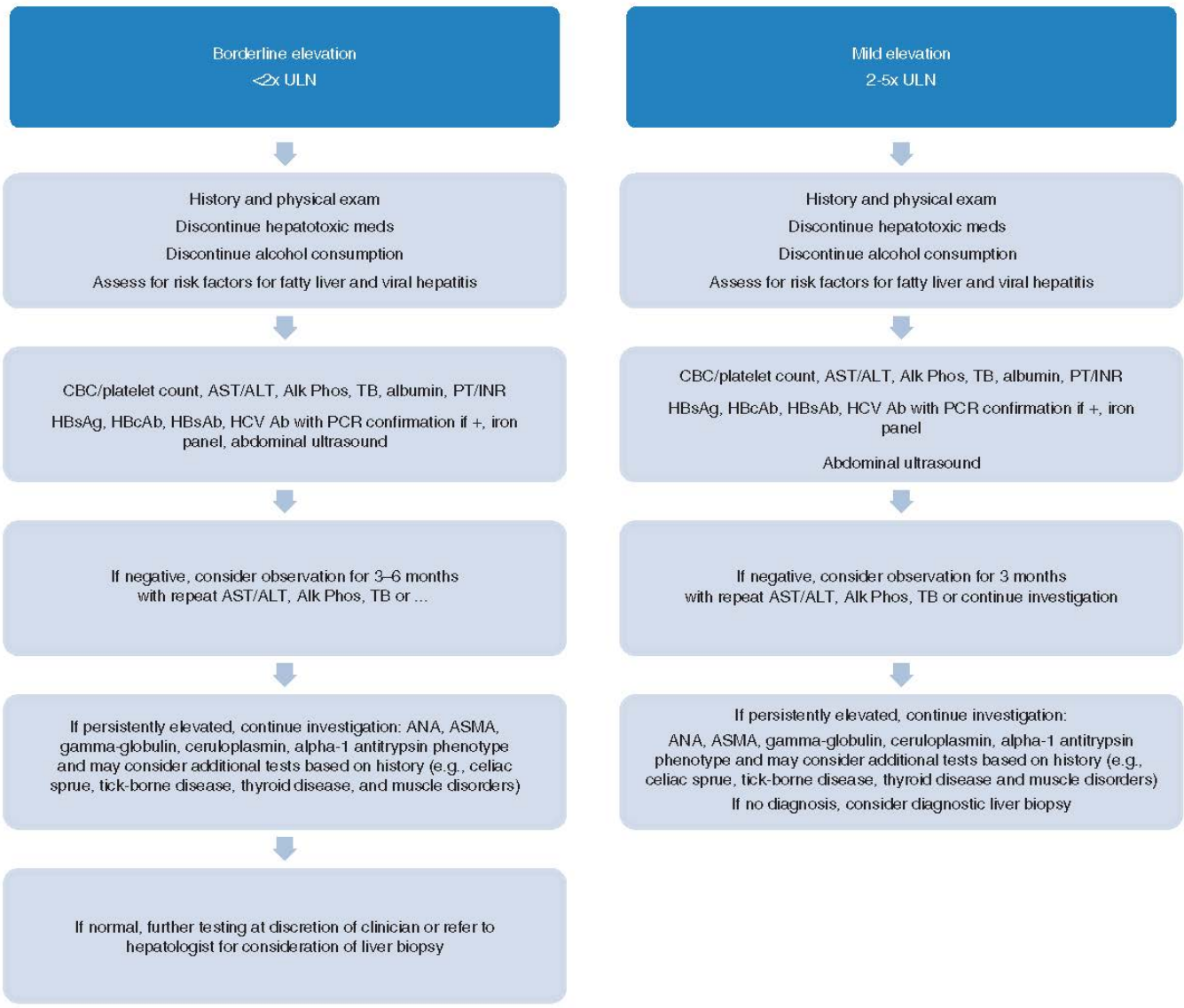

Figure 1. Algorithm for evaluation of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) level. HCV, hepatitis C virus.

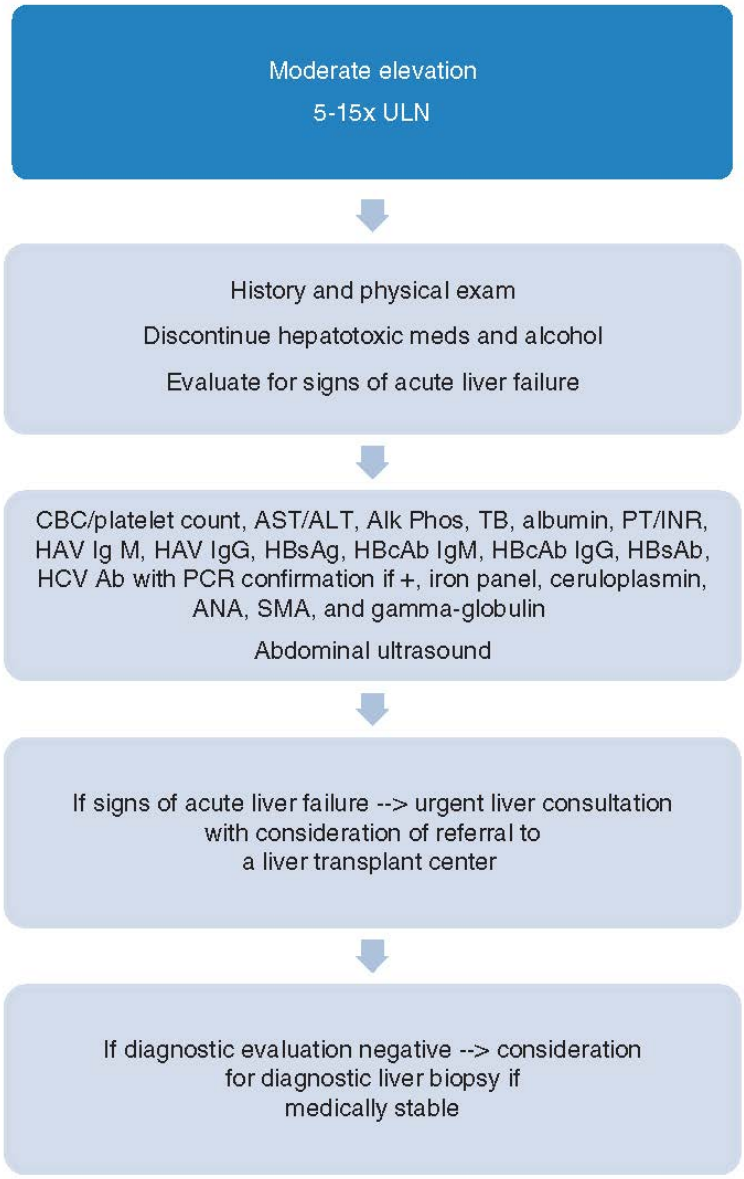

Figure 2. Evaluation of moderate elevation of aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels. HCV, hepatitis C virus.

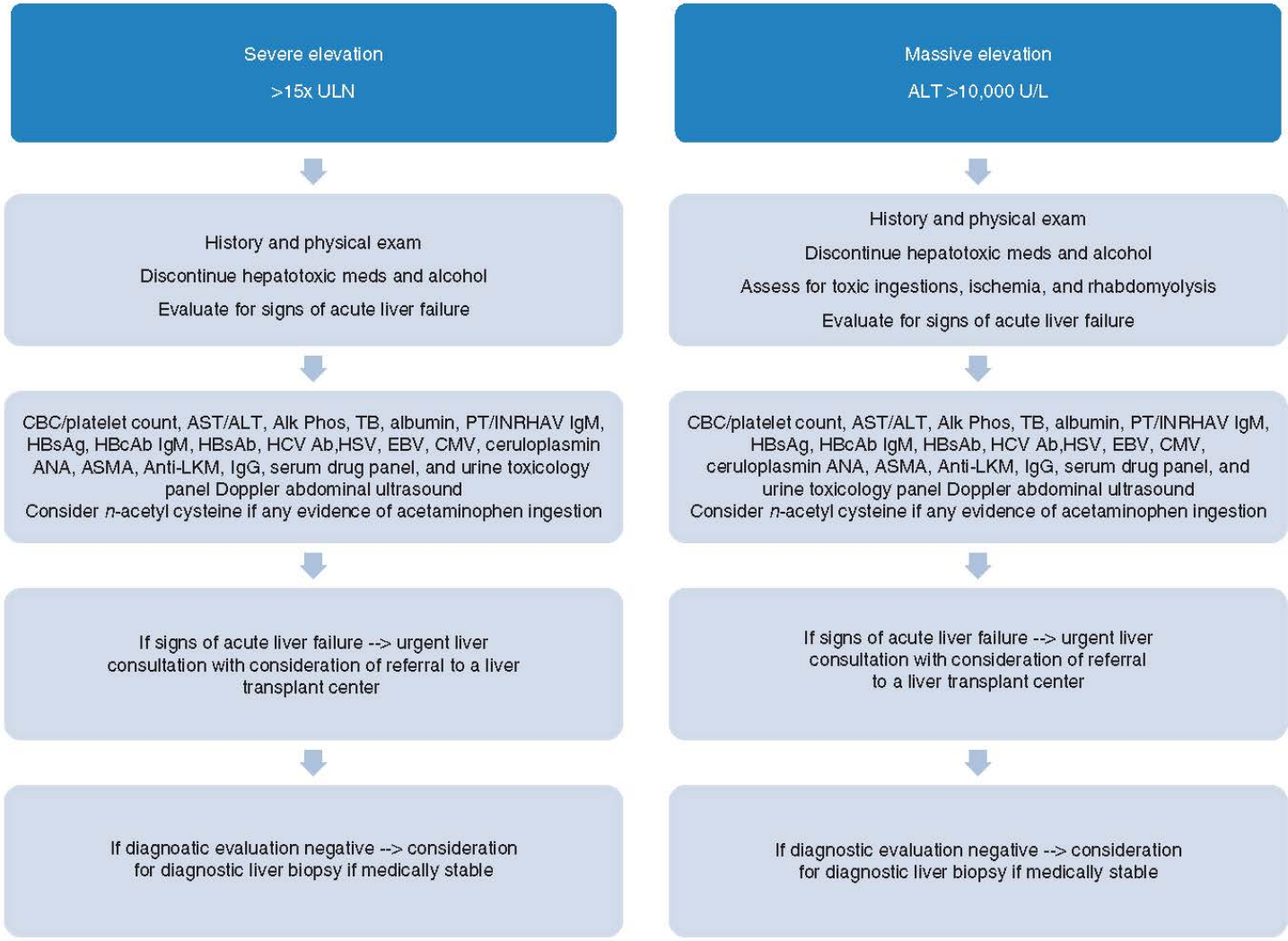

Figure 3. Evaluation of severe elevation of aspartate aminotransferase (AST) and or alanine aminotransferase (ALT) levels. HCV, hepatitis C virus.

Table 4. Causes of elevated AST and ALT
Hepatic (generally AST>ALT)
Alcoholic liver disease
Cirrhosis (of any etiology)
Ischemic hepatitis
Congestive hepatopathy
Acute Budd-Chiari syndrome
Hepatic artery damage/thrombosis/occlusion
TPN
Hepatic (generally ALT>AST)
NAFLD
Steatosis
NASH
Chronic viral hepatitis
Acute viral hepatitis
Medications and drug-induced liver injury
Prescription medications
Herbal products and supplements
Over-the-counter agents
Toxic hepatitis (amanita exposure)
Hemochromatosis
Autoimmune hepatitis
Wilson's disease
Alpha-1-antitrypsin deficiency
Celiac disease
Acute bile duct obstruction
Liver trauma
Post-liver surgery
Veno-occlusive disease/sinusoidal obstruction syndrome
Diffuse infiltration of the liver with cancer
HELLP syndrome
Acute fatty liver of pregnancy
Sepsis
Hemophagocytic lymphohistiocytosis

Table 4. Causes of elevated AST and ALT (continued)
Non-hepatic
Skeletal muscle damage/rhabdomyolysis
Cardiac muscle damage
Thyroid disease
Macro-AST
Strenuous exercise
Heat stroke
Hemolysis
Adrenal insufficiency
ALT, alanine aminotransferase; AST, aspartate aminotransferase; HELLP, hemolysis, elevated liver tests, low platelets; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; TPN, total parenteral nutrition.

Table 5. Causes of elevated alkaline phosphatase
Hepatobiliary
Bile duct obstruction
Choledocholithiasis
Malignant obstruction
Bile duct flukes
Bile duct stricture
Ductopenia
AIDS cholangiopathy
Cholestatic liver diseases
Primary biliary cirrhosis
PSC
Medications and drug-induced liver injury
Infiltrative diseases of the liver
Sarcoid
Granulomatous hepatitis
Tuberculosis
Amyloid
Metastatic cancer
Lymphoma

Table 5. Causes of elevated alkaline phosphatase (continued)
Hepatobiliary (continued)
Hepatic abscess
Hepatocellular carcinoma
Viral hepatitis
Cirrhosis
Vanishing bile duct syndrome
Ischemic cholangiopathy
Benign recurrent cholestasis
Sarcoidosis
Alcoholic liver disease
Intrahepatic cholestasis of pregnancy
Benign post-operative jaundice
ICU jaundice or multifactorial jaundice
TPN
Liver allograft rejection
Acute alcoholic hepatitis
Sickle cell liver crisis
Sepsis
Congestive heart failure
Hemophagocytic lymphohistiocytosis
Non-hepatic
Bone disease
Osteomalacia
Paget's disease
Primary bony malignancy
Bony metastases
Hyperthyroidism
Hyerparathyroidism
Pregnancy (third trimester)
Chronic renal failure
Lymphoma
Extra-hepatic malignancy
Congestive heart failure
Childhood growth

Table 5. Causes of elevated alkaline phosphatase (continued)
Non-hepatic (continued)
Infection
Inflammation
Influx of alkaline phosphatase after a fatty meal
Blood type O and B
Myeloid metaplasia
Peritonitis
Diabetes mellitus
Gastric ulcer
Increasing age, especially women
PSC, primary sclerosing cholangitis; TPN, total parenteral nutrition.

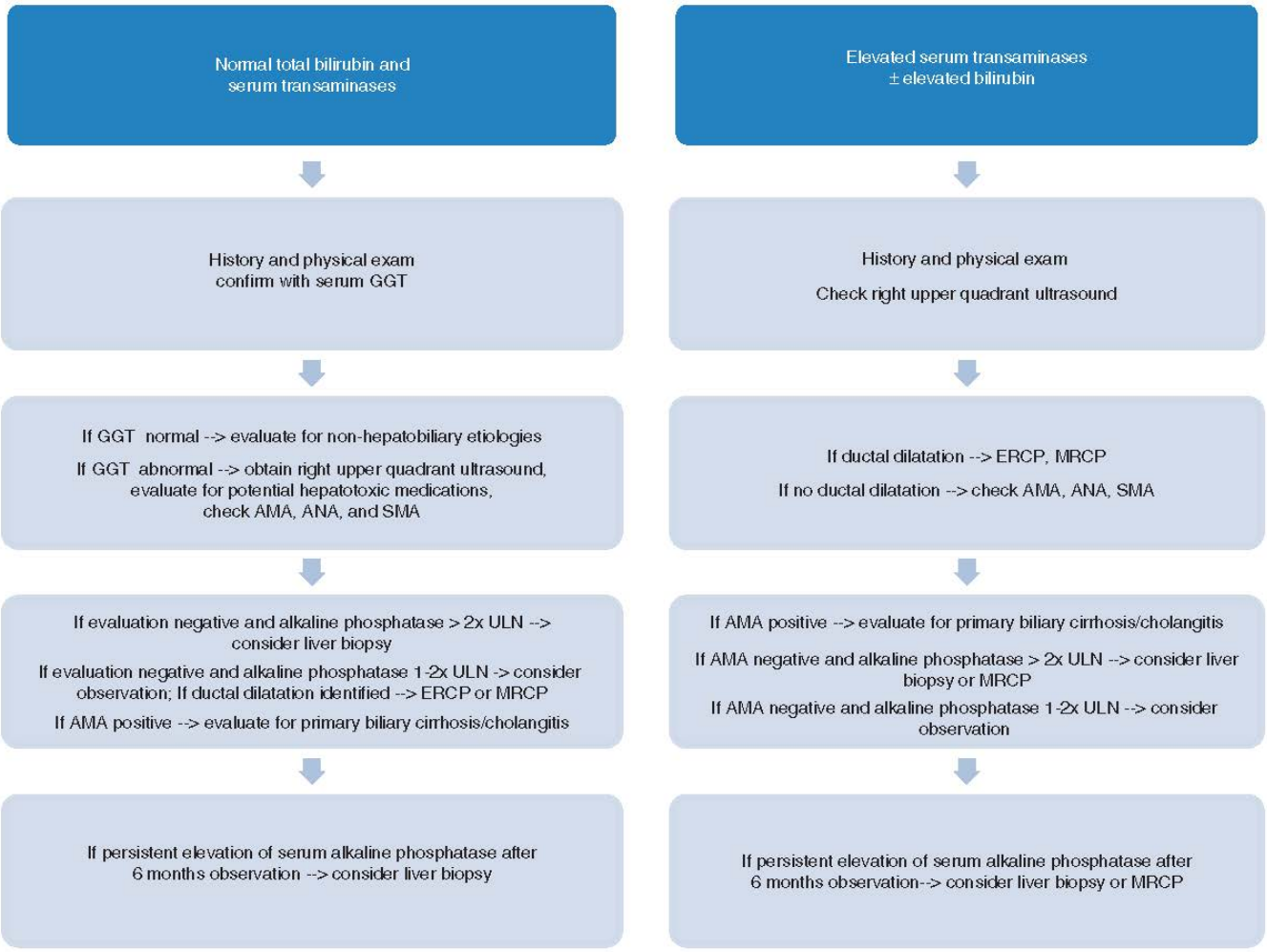

Figure 4. Algorithm for evaluation of elevated serum alkaline phosphatase.

Table 6. Causes of elevated bilirubin
Elevated unconjugated bilirubin
Gilbert's syndrome
Crigler-Najjar syndrome
Hemolysis (intravascular and extravascular)
Ineffective erythropoiesis
Resorption of large hematomas
Neonatal jaundice
Hyperthyroidism
Medications
Post-blood transfusion
Elevated conjugated hyperbilirubinemia
Bile duct obstruction
Choledocholithiasis
Malignant obstruction
Bile duct flukes
Bile duct stricture
AIDS cholangiopathy
Viral hepatitis
Toxic hepatitis
Medications or drug-induced liver injury
Acute alcoholic hepatitis
Ischemic hepatitis
Cirrhosis
Primary biliary cirrhosis
PSC
Infiltrative diseases of the liver
Sarcoid
Granulomatous hepatitis
Tuberculosis
Metastatic cancer
Lymphoma
Hepatocellular carcinoma
Wilson disease (especially fulminant Wilson's disease)
Autoimmune hepatitis
Ischemic hepatitis

Table 6. Causes of elevated bilirubin (continued)
Elevated conjugated hyperbilirubinemia (continued)
Congestive hepatopathy
Sepsis
TPN
Intrahepatic cholestasis of pregnancy
Benign post-operative jaundice
ICU or multifactorial jaundice
Benign recurrent cholestasis
Vanishing bile duct syndrome
Ductopenia
Dubin-Johnson syndrome
Rotor syndrome
Sickle cell liver crisis
Hemophagocytic lymphohistiocytosis
PSC, primary sclerosing cholangitis; TPN, total parenteral nutrition.

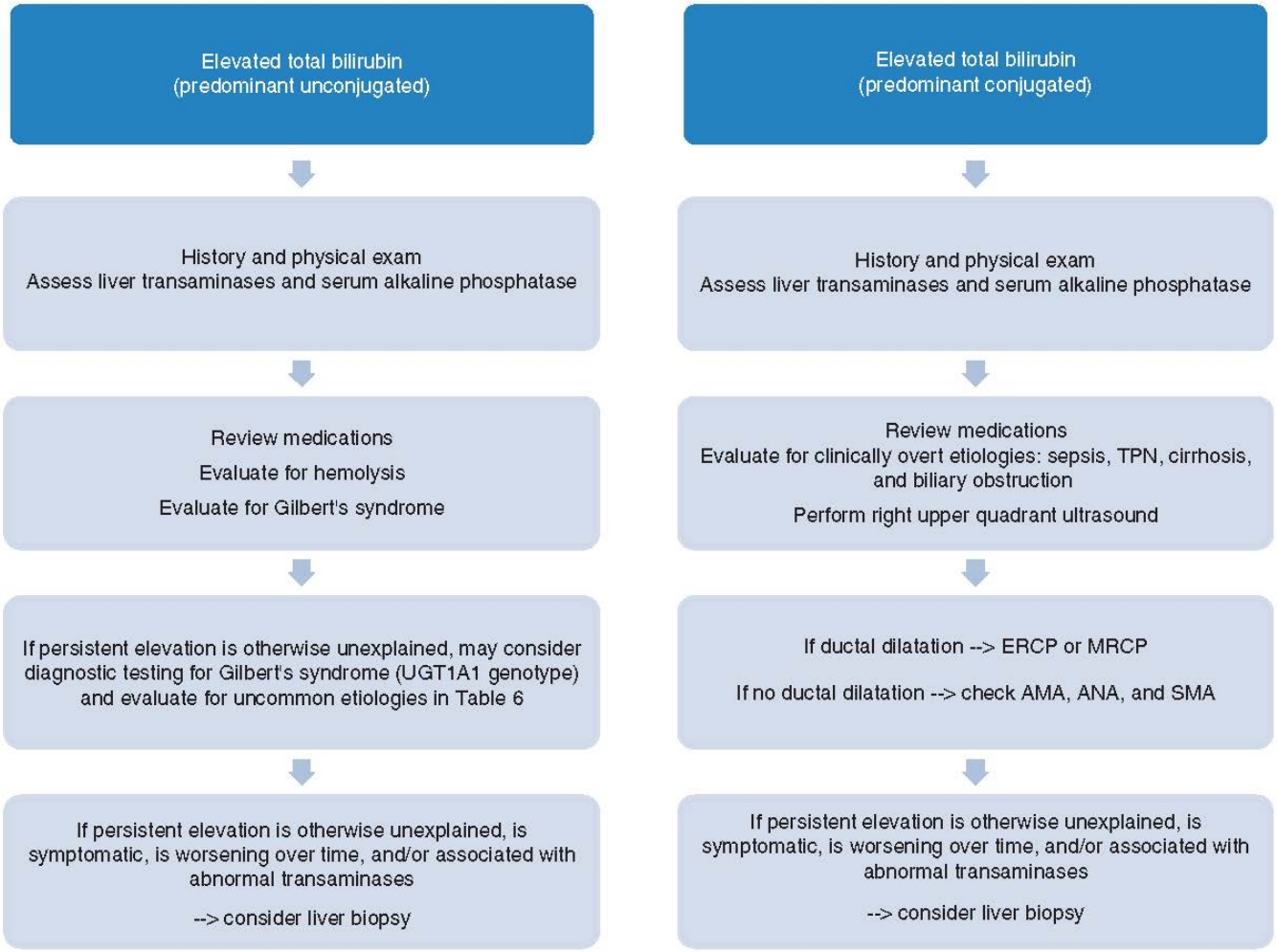

Figure 5. Algorithm for evaluation of elevated serum total bilirubin.