



**EDUCATIONAL OBJECTIVE:** Readers will consider when further evaluation of mildly abnormal liver enzyme levels is warranted

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# When and how to evaluate mildly elevated liver enzymes in apparently healthy patients

## ABSTRACT

Because 1% to 9% of people without symptoms have elevated liver enzymes, extensive evaluation of all abnormal test results would expose many patients to undue risks and expenses. On the other hand, failure to evaluate minor liver enzyme elevations could mean missing the early diagnosis of potentially treatable disorders. This review discusses likely causes of elevated aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase levels and provides algorithms for evaluating high liver enzyme values in apparently healthy patients in the primary care setting.

## KEY POINTS

Nonalcoholic fatty liver disease is the most common cause of asymptomatic elevated aminotransferase levels.

Suspect alcoholic liver disease when the aminotransferases are elevated and the aspartate aminotransferase level is two to three times higher than the alanine aminotransferase level, especially when gamma-glutamyl transferase levels are elevated.

If medications or alcohol is a suspected cause of elevated aminotransferase levels, remeasure the levels after 6 to 8 weeks of abstinence.

**I**N SEEMINGLY HEALTHY PATIENTS, abnormal liver enzyme levels challenge even the most experienced clinicians in deciding what further evaluation to pursue, if any. Automated laboratory testing has made serum liver enzyme levels very easy to obtain, leading to an increase in testing and also in the number of incidental abnormal findings. An estimated 1% to 9% of people who have no symptoms have high liver enzyme levels when screened with standard biochemistry panels.<sup>1,2</sup> A US survey<sup>2</sup> showed elevated alanine aminotransferase (ALT) in 8.9% of surveyed people from 1999 to 2002, an increase from previous reports.

An extensive evaluation can be costly, anxiety-provoking, and risky, especially if it leads to unnecessary invasive procedures such as liver biopsy or endoscopic retrograde cholangiopancreatography (ERCP). Not all people with a single, isolated, mildly elevated liver enzyme value have underlying liver disease, nor do they require an extensive evaluation. Factors to consider when deciding whether to evaluate include:

- The patient's overall health, including chronic illness
- The duration and pattern of enzyme elevation
- Patient characteristics such as age, a personal or family history of liver, lung, or neurologic disease, risk factors for viral hepatitis, amount of alcohol consumption, use of prescribed or over-the-counter drugs or dietary supplements
- The costs and risks associated with additional evaluation.

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TABLE 1

### Liver diseases and associated liver enzyme elevations

#### Hepatocellular diseases

(aminotransferase elevations predominate)

##### Common

Nonalcoholic fatty liver disease

Chronic viral hepatitis

Genetic hemochromatosis

(northern European ethnicity)

Alcoholic liver disease

Medication toxicity (see TABLE 2)

Autoimmune hepatitis

##### Less common

Wilson disease

Alpha-1-antitrypsin deficiency

#### Cholestatic diseases (alkaline phosphatase and gamma-glutamyl transferase elevations predominate)

##### Common

Primary biliary cirrhosis

Primary sclerosing cholangitis

Neoplasm

Biliary obstruction (gallstones, etc)

Drug hepatotoxicity

##### Less common

Autoimmune cholangiopathy

Sarcoidosis

**Nonalcoholic fatty liver disease may be the most common cause of mildly elevated liver enzymes in US patients**

This article reviews the most likely causes of elevated aminotransferase, alkaline phosphatase, and gamma-glutamyl transferase (GGT) levels. It also provides an algorithm for evaluating mildly abnormal liver enzyme values in apparently healthy people. Patients with signs of hepatic decompensation need a more concise and urgent evaluation.

#### ■ PATTERNS OF LIVER ENZYME ELEVATION

“Liver function test” is commonly used to describe liver enzyme measurements, but the term should be reserved for tests of the functional hepatic reserve—traditionally, the albumin level and the prothrombin time.<sup>3</sup>

On the other hand, elevated serum liver enzymes (aminotransferases, alkaline phosphatase, and GGT) can reflect abnormalities in liver cells or in the bile duct. For example, predominant elevation of aminotransfer-

ases typically indicates hepatocellular injury, whereas elevated alkaline phosphatase and GGT indicates cholestatic injury. Elevated alkaline phosphatase and aminotransferases can indicate a mixed pattern of injury.

#### High AST, ALT suggest liver cell damage

Both aspartate aminotransferase (AST) and ALT are normally present in serum at low levels, usually less than 30 to 40 U/L. Although the actual values may differ from laboratory to laboratory, normal serum levels are usually less than 40 U/L for AST and less than 50 U/L for ALT. On the other hand, some experts have suggested lowering the upper limit of normal because of the increasing rate of obesity and associated nonalcoholic fatty liver disease, which may not be detected using the traditional, higher normal values. Acceptance is growing for using ALT levels less than 40 U/L in men and less than 31 U/L in women, and AST levels less than 37 U/L in men and less than 31 U/L in women, as normal thresholds.

Although ALT is present in several organs and in muscle, the highest levels are in the liver, which makes this enzyme a more specific indicator of liver injury. Both AST and ALT are released into the blood in greater amounts when hepatocytes are damaged.

#### Alkaline phosphatase suggests cholestasis

Alkaline phosphatase comes mostly from the liver and bone. In general, normal serum alkaline phosphatase levels in adults range between 20 and 120 U/L. When bone disease is excluded, an elevation suggests biliary obstruction, injury to the bile duct epithelium, or cholestasis. Additionally, there are rare cases of benign familial elevation of serum alkaline phosphatase, mainly of intestinal origin.

#### GGT is not specific

GGT is present in hepatocytes and biliary epithelial cells. The normal range is 0 U/L to 50 U/L in men, and 0 U/L to 35 U/L in women. GGT elevation is the most sensitive marker of hepatobiliary disease. However, its routine clinical use is not recommended, as it cannot by itself indicate a specific cause of liver disease, although measuring the GGT level can help determine a hepatic origin for an isolated elevation of alkaline phosphatase.

## ■ RISK FACTORS GUIDE THE WORKUP OF ELEVATED ENZYMES

Before beginning an extensive evaluation of an elevated liver enzyme, a brief review of liver diseases and how they are associated with specific liver enzyme elevations is useful (TABLE 1). This information and clinical data obtained from the history and physical examination provide important clues to guide further investigation.

### Chronic viral hepatitis

**Prevalence.** Hepatitis C virus infection affects an estimated 1.8% of the general population, but the rate is much higher in people with known risk factors (see below), and those with ALT levels greater than 40 U/L.

Hepatitis B virus infection is somewhat less common: between 0.2% and 0.9% of the general US population have positive results on tests for hepatitis B surface antigen. However, the prevalence of this antigen in the United States can be as high as 20% in patients who have emigrated from endemic areas of the world. The risk factors described below dramatically increase the prevalence of both viruses.

**Risk factors.** Risk factors include blood-product transfusions (especially before 1992), intravenous drug use, intranasal cocaine use, hemodialysis, organ transplantation, and birth in an endemic region. Although both viruses can be transmitted sexually, hepatitis B is more readily transmitted by this route than hepatitis C. Worldwide, transmission of hepatitis B virus usually occurs shortly after birth or at a young age.

**Comments.** Most patients with chronic viral hepatitis have no symptoms or only mild symptoms and minimally elevated ALT and AST levels, ie, two to five times higher than the upper limit of normal. Given the relatively high prevalence of hepatitis C, serologic testing for it should be done early in the evaluation of chronically elevated liver enzyme levels.<sup>4,5</sup>

### Hereditary hemochromatosis

**Prevalence.** The prevalence of the major HFE-gene mutations that cause hereditary hemochromatosis is 0.25% to 0.5% in people of

northern European descent. In northern Europe, about 1 person in 10 is heterozygous and 1 in 200 to 400 is homozygous for the mutated gene.

**Risk factors.** Northern European ancestry is the primary risk factor. In men, the onset of disease is usually in the third and fourth decades of life, while menses protects women until menopause. From 83% to 85% of people with clinically defined hemochromatosis are homozygous for the C282Y mutation in the HFE gene.

**Comments.** Hereditary hemochromatosis should be considered early in the evaluation of men of northern European descent. Patients usually have no symptoms until iron overload causes significant end-organ damage. Phlebotomy can be an effective treatment for this potentially fatal disease.<sup>6</sup>

### Alcoholic liver disease

**Risk factors.** The degree of alcohol-related liver disease depends on a variety of factors, including the volume and duration of alcohol ingestion, the type of liver disease, genetics, and the coexistence of viral hepatitis and obesity.

Alcohol-related liver disease can range from simple fatty liver to alcoholic hepatitis with or without cirrhosis. Cirrhosis develops in only 20% to 30% of patients who consume a substantial amount of alcohol, defined as more than a decade of 60 g/day to 80 g/day of alcohol in men and as little as 20 g/day in women. (A standard drink, ie, a 12-ounce beer, a 5-ounce glass of wine, or 1.5 ounces of distilled spirits, contains 12 g of alcohol.) Factors that potentiate alcohol's harmful effects include female sex, chronic viral hepatitis (especially hepatitis C), obesity, hereditary hemochromatosis, and use of drugs such as methotrexate (Trexall) and acetaminophen (Tylenol).

**Comments.** Although cirrhosis affects fewer than one-third of long-term heavy drinkers, early detection and treatment can potentially reduce morbidity and prevent early death. Alcoholic liver disease should be suspected in patients with elevated ALT and AST levels (if the AST level is two to three times higher than normal<sup>7</sup>) and with a history of excessive alcohol use.

**Studies suggest that fatty liver, due to alcohol or nonalcoholic steatohepatitis, is the major cause of mildly elevated aminotransferases**

TABLE 2

**Hepatotoxicity of selected drugs****Hepatocellular abnormalities**

Acetaminophen (Tylenol)—acute hepatitis  
 Allopurinol (Zyloprim)—granuloma  
 Azathioprine (Imuran)—veno-occlusive disease, nodular regenerative hyperplasia  
 Diclofenac (Voltaren) and other nonsteroidal anti-inflammatory drugs  
 Hydralazine (Apresoline)—granuloma  
 Isoniazid  
 Methotrexate—fibrosis  
 Methyldopa (Aldomet)  
 Nitrofurantoin (Furadantin, Macrobid)—autoimmune-like disease  
 Quinidine—granuloma  
 Statins

**Cholestatic abnormalities**

Amoxicillin-clavulanate (Augmentin) and other penicillin derivatives  
 Anabolic steroids  
 Captopril (Capoten)  
 Chlorpromazine (Thorazine)  
 Erythromycin estolate  
 Estrogens  
 Oral contraceptives  
 Phenytoin (Dilantin)—mononucleosis-like syndrome  
 Carbamazepine (Tegretol)  
 Sulfa drugs

**Drug-induced fatty liver**

(with or without hepatocellular abnormalities)  
 Amiodarone (Cordarone)—phospholipidosis  
 Corticosteroids  
 Tetracycline  
 Valproic acid (Depakote)

**Nonalcoholic fatty liver disease**

**Prevalence.** Nonalcoholic fatty liver disease is a spectrum that ranges from simple steatosis to nonalcoholic steatohepatitis to cirrhosis. Its prevalence in the general US population is about 25%, but is much higher in groups at risk, such as patients with type 2 diabetes (50% to 60%), and morbidly obese patients undergoing bariatric surgery (90% to 95%).

On the other hand, the prevalence of the potentially progressive form of nonalcoholic fatty liver disease, ie, nonalcoholic steatohepatitis, is estimated to be 3% to 5%.

Nonalcoholic fatty liver disease is perhaps the most common cause of mildly elevated liver enzymes in the United States.

**Risk factors.** The major risk factors for nonalcoholic fatty liver disease are the components of the metabolic syndrome—ie, abdominal obesity, diabetes (insulin resistance), hyperlipidemia, and hypertension—and the use of certain medications (TABLE 2).

**Comments.** Nonalcoholic steatohepatitis and steatonecrosis describe a potentially progressive form of nonalcoholic fatty liver disease. Although these disorders are histologically indistinguishable from alcohol-induced liver disease, their mechanism is related to insulin resistance, abnormalities of lipid metabolism, increased hepatic lipid peroxidation, activated fibrocytes, and abnormal patterns of adipokine and cytokine production related to visceral obesity. Results from a few natural history studies suggest that simple steatosis has a benign course, whereas nonalcoholic steatohepatitis can progress to cirrhosis in 10% to 20% of patients.<sup>8</sup>

Treatment of diabetes, obesity, hypertension, and hyperlipidemia has potential benefit and should be undertaken regardless of liver test abnormalities in any patient with underlying nonalcoholic fatty liver disease.

**Autoimmune hepatitis**

**Prevalence.** The prevalence of autoimmune hepatitis varies, depending on geographic location and on the extent of viral hepatitis in the community. In Hong Kong, only 1% of all people with chronic hepatitis have autoimmune hepatitis. By contrast, in Germany and Austria, 34% and 62% of patients with chronic hepatitis may have autoimmune hepatitis.<sup>9</sup> In North America, the prevalence of autoimmune hepatitis in patients with chronic liver disease is estimated to be 11% to 23%, and the incidence is about 0.68 per 100,000 individuals per year. In addition to underlying genetic differences, detection bias can explain the variability in prevalence rates.

**Risk factors.** Autoimmune hepatitis occurs predominantly in women and can be associated with other autoimmune disorders.

**Comments.** The diagnosis of autoimmune hepatitis is suggested by exclusion of viral causes of chronic hepatitis, by pathologic

**Hepatobiliary diseases and several bone conditions can cause a moderately to markedly elevated alkaline phosphatase level**

findings, and by the presence of autoimmune markers such as antinuclear antibody, smooth muscle antibody, and liver-kidney microsomal antibody. Hypergammaglobulinemia is present in most patients, and serum protein electrophoresis may be helpful as part of the initial evaluation of autoimmune hepatitis.

Liver biopsy is usually needed to confirm the diagnosis and to stage the extent of fibrosis. The International Autoimmune Hepatitis Group Scoring System is based on clinical, laboratory, and pathologic data and can be very helpful in establishing the diagnosis.

Treatment of autoimmune hepatitis with immunosuppression is effective. Most patients may need long-term maintenance treatment.

### Wilson disease

**Prevalence.** The estimated prevalence of Wilson disease is 1 in 40,000 to 1 in 100,000. It has been reported in most populations worldwide.

**Risk factors.** Anyone under age 40 with abnormal liver enzyme levels (including mild elevations) should be evaluated for Wilson disease, even in the absence of neurologic or ocular findings. However, such routine screening is rarely helpful in patients over age 50. Genetic testing is of limited value because of the large number of potential mutations of the ATP7B gene, the gene responsible for Wilson disease. However, if a person is known to have Wilson disease, genetic screening of family members is useful.

**Comments.** Effective therapy is available (ie, D-penicillamine, trientine, zinc). For Wilson disease, alpha-1-antitrypsin deficiency, and genetic hemochromatosis, establishing the diagnosis is not only important to the individual patient; it also may prompt the screening of asymptomatic members of the proband's family.<sup>10-12</sup>

### Alpha-1-antitrypsin deficiency

**Prevalence.** Alpha-1-antitrypsin deficiency is present in 1 of every 1,600 to 1,800 live births.<sup>11</sup>

**Risk factors.** Patients with emphysema or with a young sibling with liver failure should undergo an investigation for alpha-1-antitrypsin deficiency, consisting of a measurement of the alpha-1-antitrypsin level and an assess-

ment for the PiZZ genotype (the most severe form, because homozygous for the abnormal Z allele).

**Comments.** Although alpha-1-antitrypsin deficiency is a common cause of liver disease in the very young, it is important to remember that a small number of these patients develop end-stage liver disease in adulthood. Liver transplantation is the only effective treatment for end-stage liver disease associated with alpha-1-antitrypsin deficiency.

### Primary biliary cirrhosis

**Prevalence.** In one study of urban-dwelling women in northeast England, the prevalence of primary biliary cirrhosis was estimated at 0.10%.<sup>13</sup>

**Risk factors.** Like autoimmune hepatitis, primary biliary cirrhosis mainly affects women and can be associated with other autoimmune disorders.

**Comments.** A cholestatic pattern of injury is predominant in primary biliary cirrhosis. Treatment of primary biliary cirrhosis with the cytoprotective agent ursodeoxycholic acid improves liver enzyme levels, may lead to histologic improvement and increased survival, and may also delay the need for liver transplantation.<sup>9,13</sup>

### Drug- and toxin-related liver diseases

Nonsteroidal anti-inflammatory drugs and penicillin-derived antibiotics are the drugs that most commonly cause abnormal serum liver enzyme levels. The mechanisms of drug-induced liver disease include induction of hepatic enzymes (antiepileptic drugs), allergic reactions, autoimmunity (nitrofurantoin [Furadantin, Macrobid]), idiosyncratic reactions, and veno-occlusive injury.<sup>14</sup> Drugs that are potentially hepatotoxic are listed in TABLE 2 and are classified as causing hepatocellular damage, cholestatic damage, or steatosis.

## ■ MILD ENZYME ELEVATIONS AS INDICATORS OF SPECIFIC DISEASES

Mildly elevated liver enzymes are common and potentially important, yet very few well-designed prospective studies have addressed the issue of what should be done once they are identified. Most current data are from

**Extensive workup of an isolated GGT elevation in an apparently healthy patient is not warranted**

small retrospective studies that lack accurate information on the important causes of liver diseases such as hepatitis C and nonalcoholic steatohepatitis.

Despite these shortcomings, the literature delineates the three patterns of mild liver enzyme elevations discussed earlier: hepatocellular injury pattern (elevated ALT or AST), cholestatic pattern (elevated alkaline phosphatase or GGT, or both), and mixed pattern (elevation of ALT, AST, and alkaline phosphatase). The following paragraphs focus on the causes of elevation of specific liver enzymes.

### ■ AMINOTRANSFERASE ELEVATION

#### Causes

Aminotransferases are commonly used markers of hepatocyte injury. AST is present in blood cells and many tissues, including liver, muscle, brain, pancreas, and lung. ALT is a cytosolic enzyme found primarily in hepatocytes, making it a more specific indicator of liver disease.

Acute viral hepatitis, toxins, and liver ischemia can markedly raise serum aminotransferase levels (often into the thousands of units per liter). On the other hand, these enzymes are only mildly elevated ( $< 300$  U/L) in nonalcoholic steatohepatitis, chronic hepatitis, cholestatic liver conditions, drug-induced hepatotoxicity, and liver tumors.

Because AST is a mitochondrial enzyme and is affected by alcohol ingestion, an AST level more than twice that of the ALT suggests hepatic damage due to alcohol.

Of note, aminotransferase elevation can also be due to nonhepatic causes. For example, muscle necrosis can result in mild elevation of these enzymes, especially AST, and an elevated creatine kinase can help confirm that the source is muscle tissue.

Undiagnosed celiac disease has been associated with abnormal liver enzyme levels when all other causes have been ruled out, but the mechanism is not yet understood. In this situation, ALT and AST levels typically return to normal with a gluten-free diet.<sup>15</sup>

#### Studies of mild aminotransferase elevations

Only a few studies have documented the results of a thorough evaluation of patients with

mildly elevated aminotransferase levels:

**Hultcrantz et al**<sup>1</sup> performed a full evaluation, including liver biopsy, in 149 consecutive patients with chronic, asymptomatic, mild elevations of AST or ALT. Of these patients, 63% had “fatty liver,” 20% had “chronic hepatitis,” and 17% had miscellaneous diagnoses. Whether patients in the “chronic hepatitis” group had hepatitis C was not determined because serologic testing was not available at the time.

**Friedman et al**<sup>16</sup> studied 100 healthy blood donors with elevated ALT levels and found that in 33% of patients the elevation occurred once, in 36% it was intermittent, and in 28% it was persistent. In this series, 45% of patients had no diagnosis, 22% were obese (presumed to have nonalcoholic steatohepatitis), 5% had alcoholic liver disease, 3% had “resolving hepatitis,” 1% had hemochromatosis, and 1% had “cytomegalovirus hepatitis.”<sup>16</sup> Although the patients underwent a complete history, physical examination, and serologic testing, liver biopsy was not done to confirm the clinical diagnosis.

**Hay et al**<sup>17</sup> described 47 patients with chronically elevated aminotransferases (three to eight times higher than normal levels) who underwent full evaluation and liver biopsy and who had no clinical symptoms of alcoholic, viral, or drug-induced liver disease. A diagnosis of steatohepatitis was given in 10 patients, another 34 were diagnosed with “chronic hepatitis,” and 3 had miscellaneous diagnoses. Of patients with chronic hepatitis, 16 had evidence of cirrhosis on biopsy, and 18 tested positive for at least one autoimmune marker (antinuclear antibody or smooth muscle antibody).

**Daniel et al**<sup>18</sup> performed biopsy in 81 of 1,124 asymptomatic and symptomatic patients with chronically elevated aminotransferases in whom a cause was not identified via noninvasive studies. Liver biopsy showed that 67 (83%) of the 81 patients had steatosis or steatohepatitis, while 8 (10%) had normal histologic findings. Of note, 6 patients had underlying fibrosis or cirrhosis and some degree of fatty infiltration.

Together, these studies suggest that fatty liver, resulting either from alcohol use or from nonalcoholic fatty liver disease, is the major cause of mildly elevated aminotransferases.

**An AST level more than twice the ALT suggests the damage is due to alcohol**

Two major drawbacks of the earlier studies include the lack of data on the hepatitis C serologic status of patients with the diagnosis of “chronic hepatitis” and the lack of a uniform approach to the pathologic diagnosis of non-alcoholic steatohepatitis. With serologic testing for hepatitis C virus infection now widely available, it is possible that a substantial portion of patients with “chronic hepatitis” can further be classified as having chronic hepatitis C infection.

### Workup of aminotransferase elevations

**FIGURE 1** shows an algorithm for evaluating patients with elevated aminotransferase levels on an initial examination. The first step is to confirm the abnormality by repeating the blood test. If an enzyme elevation is confirmed, further investigation is warranted. A directed history and physical examination can provide crucial clues in the preliminary workup. The history may disclose risk factors for:

- Viral hepatitis (intravenous drug use, intranasal cocaine use, native of an endemic area of the world, unsafe sexual activity, blood product transfusions)
- Nonalcoholic fatty liver disease (components of the metabolic syndrome, including visceral obesity)
- Alcoholic liver disease (smaller amounts are needed to cause liver disease in women)
- Medication exposure (prescription, over-the-counter, and herbal medications)
- Genetic liver disorders (family history of liver disease)
- Possible coexisting disease (diabetes and obesity in nonalcoholic steatohepatitis, neurologic disorders in Wilson disease, emphysema in alpha-1-antitrypsin deficiency, thyroid disease in autoimmune hepatitis and primary biliary cirrhosis, and diabetes and impotence in genetic hemochromatosis).

Although the physical signs of chronic liver disease (eg, spider angiomas, palmar erythema, caput medusae, and gynecomastia) are nonspecific and are usually observed in advanced liver disease, some physical findings suggest potential causes (eg, Kayser-Fleischer rings on slit-lamp examination for Wilson disease, hypertrophy of the second and third metacarpophalangeal joints for

hemochromatosis). Iron studies for middle-aged men, autoimmune markers for women, and screening for Wilson disease in young patients are helpful when the clinical information points to one of these entities as a potential diagnosis.

If medication or alcohol is a suspected cause, aminotransferase levels should be repeated after 6 to 8 weeks of abstinence. If nonalcoholic steatohepatitis is suspected, testing should be repeated after treating the potential risk factor (eg, obesity, diabetes, hyperlipidemia), but the levels may remain elevated for a period of time. An imaging study (ultrasonography, computed tomography, or magnetic resonance imaging) may be helpful; eg, abdominal ultrasonography may show increased hepatic echogenicity, suggesting increased fatty infiltration, in addition to excluding most hepatic tumors.

If the clinical data obtained from the history or physical examination raise clinical suspicion for a particular disease, a disease-specific marker (**FIGURE 1** and **FIGURE 2**) can further support the potential diagnosis. Note that liver biopsy can help establish the diagnosis for many liver disorders and is the best method currently available to establish cirrhosis, with important prognostic implications.<sup>19</sup>

If the history and physical do not suggest a specific condition, serologic testing for hepatitis C should be done. If negative, other testing can be helpful (iron studies in men, autoimmune markers in women, ceruloplasmin and slit-lamp examination in young patients). If the preliminary workup remains negative and the aminotransferase levels remain elevated for 6 months (ie, chronic elevation), liver biopsy may establish the diagnosis. Features in the biopsy specimens may further confirm the diagnosis: eg, globules positive on periodic acid-Schiff testing in alpha-1-antitrypsin deficiency; hepatic iron index for hemochromatosis; hepatic copper content for Wilson disease.

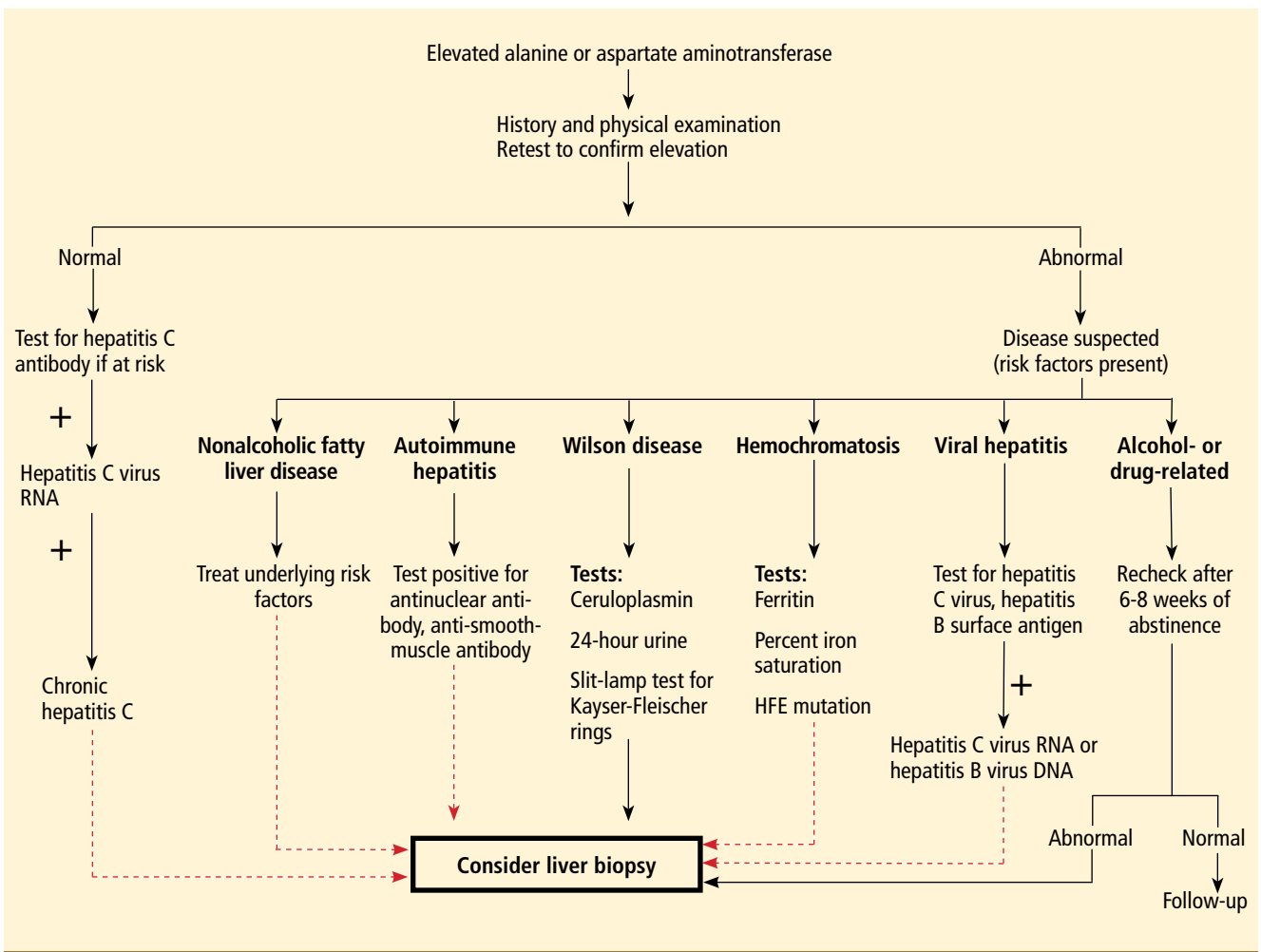
### ■ ALKALINE PHOSPHATASE ELEVATION

#### Causes

Alkaline phosphatase is active in many organs, mainly the liver and bones, but is also found in the small bowel, kidneys, and placenta. Diseases of the hepatobiliary system

**If a drug or alcohol is the suspected cause, retest AST and ALT after 6 to 8 weeks of abstinence**

## MILDLY ELEVATED LIVER ENZYMES



**FIGURE 1.** Algorithm for the evaluation of elevated aminotransferase levels. Black arrows indicate the diagnostic pathway, and red arrows indicate the steps in staging the liver disease.

can cause moderate to marked elevations of alkaline phosphatase. Conditions with bone involvement, such as Paget disease of the bone, sarcoma, metastatic disease, hyperparathyroidism, and rickets, can raise alkaline phosphatase levels. Elevated GGT in conjunction with elevated alkaline phosphatase usually points to hepatobiliary injury. Clinically, isoenzyme fractionation of alkaline phosphatase may help distinguish the source of the elevation, but this is often not needed if the GGT is also elevated.

Hepatobiliary causes of alkaline phosphatase elevation can be divided into four categories:

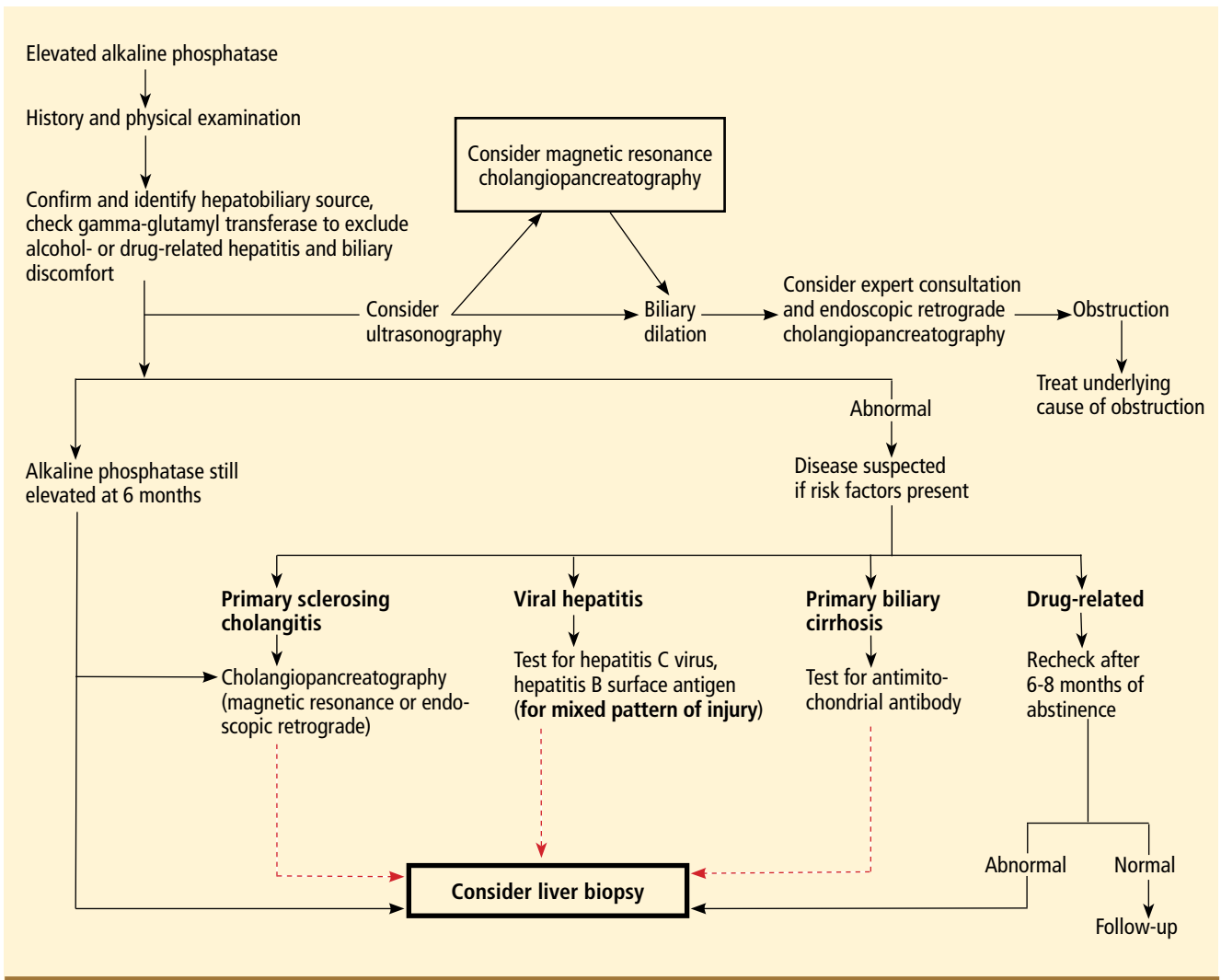
- Chronic inflammation involving the bile ducts (eg, as in primary biliary cirrhosis

and primary sclerosing cholangitis)

- Infiltrative process (eg, neoplasm, tuberculosis, sarcoidosis)
- Cholestatic disorders (eg, drug hepatotoxicity)
- Biliary obstruction (eg, in neoplasia or cholelithiasis).

Only a few studies have investigated the significance of a mild, isolated elevation of alkaline phosphatase. Lieberman and Phillips<sup>20</sup> evaluated 87 patients and found that the abnormality resolved completely in less than 3 months in 28 patients, and resolved in 3 to 12 months in another 17 patients. Of the other 42 patients, 24 did not undergo further evaluation because they had significant coexisting disease. Of the remaining 18 patients, 5 had





**FIGURE 2.** Algorithm for the evaluation of elevated alkaline phosphatase levels. Black arrows indicate the diagnostic pathway, and red arrows indicate the steps in staging the liver disease.

phenytoin-related hepatotoxicity, 3 had congestive heart failure, 3 had metabolic bone disease, 2 had hepatobiliary disease, and 1 had metastatic bone disease; in 4 patients, no explanation was determined. Follow-up was 1.5 to 3 years.

### Workup of alkaline phosphatase elevation

An isolated elevated alkaline phosphatase level should always be confirmed and a hepatic origin suspected if the GGT level is also elevated (FIGURE 2).

A history of recent drug exposure usually points to drug hepatotoxicity as the source of this abnormality. Similarly, other informa-

tion from the history can point to a potential underlying pathologic process causing the rise in alkaline phosphatase. For example, a history of ulcerative colitis suggests primary sclerosing cholangitis, and a history of previous cancer or sarcoidosis suggests liver involvement.

As part of the initial evaluation, an imaging study (eg, ultrasonography) can exclude biliary obstruction or suggest an infiltrative process.

If a drug is the suspected cause, the alkaline phosphatase level should be repeated after the patient has abstained from the drug for 6 to 8 weeks. If the initial examination

suggests a specific disease, disease-specific markers (eg, antimitochondrial antibody for primary biliary cirrhosis, or viral serology) can confirm the suspected diagnosis. If the disease-specific markers are negative and the alkaline phosphatase level does not return to normal, further studies should be considered, including liver biopsy and endoscopic retrograde cholangiopancreatography or magnetic resonance cholangiopancreatography. Given the invasive nature of biopsy and pancreatography, an expert consultation should be done before ordering these tests.

### ■ GGT ELEVATION

GGT is a membrane enzyme that is a marker of hepatobiliary disease. Elevations usually parallel the elevation of alkaline phosphatase, confirming a hepatic source for the latter. GGT is the most sensitive marker of biliary tract disease but is not very specific. Alcohol and drugs (eg, phenytoin, phenobarbital) induce GGT. In one study,<sup>21</sup> GGT was elevated in 52% of patients

without known liver disease. The GGT level can be used to monitor abstinence from alcohol in patients with alcoholic liver disease.<sup>21</sup>

### Workup of GGT elevation

Because GGT lacks specificity as a marker and is highly inducible, an extensive evaluation of an isolated GGT elevation in an otherwise asymptomatic patient is not warranted.

### ■ WHEN TO CONSULT

Many of the evaluations discussed in this paper and elsewhere<sup>22–27</sup> can be carried out by primary care providers following a systematic approach. Input from a gastroenterologist or hepatologist can be valuable if the initial workup fails to establish the diagnosis, as well as in assuring that the most effective therapy for a specific disease is initiated. Reassurance, patient education, and a systematic approach for evaluating these abnormalities can identify most treatable causes of liver disease in the most cost-effective and efficient manner. ■

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