Enzymatic measures of cholestasis (eg, alkaline phosphatase, 5'-nucleotidase, gamma-glutamyl transpeptidase)

AUTHOR: Lawrence S Friedman, MD
SECTION EDITOR: Sanjiv Chopra, MD, MACP
DEPUTY EDITOR: Shilpa Grover, MD, MPH, AGAF

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Literature review current through: **Sep 2023.**
This topic last updated: **Jul 28, 2022.**

INTRODUCTION

A number of blood tests are available that reflect the condition of the liver [1-3]. The most common tests used in clinical practice include the serum aminotransferases, bilirubin, alkaline phosphatase, albumin, and prothrombin time. These tests are often referred to as "liver function tests," although this term is somewhat misleading since most do not accurately reflect how well the liver is functioning, and abnormal values can be caused by diseases unrelated to the liver. In addition, these tests may be normal in patients who have advanced liver disease.

Several specialized tests have also been developed (such as indocyanine green [ICG] clearance), which, although uncommonly used in clinical practice, can measure specific aspects of hepatic function.

Despite their limitations, liver biochemical and function tests have many applications in clinical medicine:

- They provide a noninvasive method to screen for the presence of liver disease. The serum aminotransferases, for example, are part of a panel of tests used to screen all blood donors in the United States for the presence of transmissible viruses.

- They can be used to measure the efficacy of treatments for liver disease (such as immunosuppressant agents for autoimmune hepatitis). (See "Management of autoimmune hepatitis".)

- They can be used to monitor the progression of a disease such as viral or alcohol-associated hepatitis.

- They can reflect the severity of liver disease, particularly in patients who have cirrhosis. As an example, the Child-Turcotte-Pugh score (Child-Pugh class), which incorporates the prothrombin time and serum bilirubin and albumin concentrations, can predict survival (table 1). Similarly, the Model for End-stage Liver Disease (MELD) score, based in part upon the serum bilirubin, is an accurate predictor of three-month mortality and is used routinely in determining the priority of patients awaiting liver transplantation. (See "Model for End-stage Liver Disease (MELD)".)

The pattern of abnormalities on these tests is more accurate than any of the individual tests. An elevation of serum aminotransferases indicates hepatocellular injury, while an elevation of alkaline phosphatase indicates cholestasis. Recognizing patterns that are consistent with specific diseases can prompt appropriate additional testing.

The liver biochemical and function tests that are used commonly in clinical practice and that are used occasionally for specific circumstances can be categorized as follows:

- Tests that detect injury to hepatocytes – Most of these tests measure the concentration of hepatic enzymes, such as the aminotransferases, in the circulation. These enzymes are normally intracellular but are released when hepatocytes are injured. (See "Liver biochemical tests that detect injury to hepatocytes".)

- Tests of the liver's capacity to transport organic anions and metabolize drugs – These tests measure the liver's ability to clear endogenous or exogenous substances from the circulation. The best studies include serum measurements of bilirubin, bile acids, caffeine, and lidocaine metabolites, a variety of breath tests, and clearance tests such as bromsulphalein (BSP) and ICG.

- Tests of the liver's biosynthetic capacity – The most commonly performed tests to assess the biosynthetic capacity of the liver are the serum albumin and the prothrombin time (which requires the presence of clotting factors produced in the liver). Other tests that have been used are the serum concentrations of lipoproteins, ceruloplasmin, ferritin, and alpha-1 antitrypsin.

- Tests that detect chronic inflammation in the liver, altered immunoregulation, or viral hepatitis — These tests include the immunoglobulins, hepatitis serologies, and specific autoantibodies. Most of these substances are proteins made by B lymphocytes, not by hepatocytes. However, some are quite specific for certain liver diseases, such as antimitochondrial antibodies in primary biliary cholangitis. (See "Clinical manifestations, diagnosis, and prognosis of primary biliary cholangitis".)

The liver contains thousands of enzymes, some of which are also present in serum in very low concentrations. Elevation of an enzyme activity in the serum primarily reflects release from damaged liver cells. Elevation of serum enzyme tests can be grouped into two categories:

- Enzymes that reflect generalized damage to hepatocytes
- Enzymes that reflect cholestasis

This topic review will discuss the serum tests that reflect cholestasis. The other categories of liver function tests and enzymes that reflect generalized damage to hepatocytes are discussed separately. (See "Liver biochemical tests that detect injury to hepatocytes".)

ALKALINE PHOSPHATASE

Alkaline phosphatase refers to a group of enzymes that catalyze the hydrolysis of a large number of organic phosphate esters at an alkaline pH optimum. Zinc is an important cofactor. Although alkaline phosphatase is found in many locations throughout the body, its precise function is not yet known [4]. It appears to have an active role in down-regulating the secretory activities of the intrahepatic biliary epithelium [5], and hydrolyzing phosphate esters to generate inorganic phosphate for uptake by various tissues [6]. Intestinal alkaline phosphatase detoxifies lipopolysaccharide and promotes commensal bacterial colonization of the intestine, tight junction integrity, and barrier function, and its absence is associated with increased intestinal inflammation, dysbiosis, bacterial translocation, and systemic inflammation [7,8]. Genetic mutations of the intestinal alkaline phosphatase gene are thought to contribute to some forms of chronic inflammatory diseases [8]. In bone, the enzyme is involved with calcification. At other sites, it may participate in transport processes.

At least three separate genes code for the different alkaline phosphatases that exist in multiple isoenzyme forms [9,10]. Most of the alkaline phosphatase isoenzymes of clinical interest are derived from the liver, bone, first trimester placenta, and kidneys, and are coded for by one gene. They are called tissue nonspecific alkaline phosphatase since they have the same immunologic properties and amino acid sequence. Although these alkaline phosphatase

isoenzymes catalyze the same reactions, they have different physicochemical properties, which are conferred by carbohydrate and lipid side chains added during posttranslational modification [4,10].

A second alkaline phosphatase gene codes for third trimester placental and intestinal alkaline phosphatase [9]. The third gene codes for a second type of intestinal alkaline phosphatase.

Alkaline phosphatase activity in serum is derived primarily from three sources: liver (more than 80 percent), bone, and in some patients the intestinal tract [4,11]. The intestinal contribution (about 10 to 20 percent) is of importance primarily in people with blood groups O and B who are secretors of the ABH red blood cell antigen [12]; it is enhanced by consumption of a fatty meal [13,14] and has limited clinical importance.

Circulating alkaline phosphatase appears to behave like other serum proteins [15]. Its half-life is seven days, and its clearance from serum is independent of the functional capacity of the liver or the patency of the bile ducts [15]. Its sites of degradation are unknown.

Mechanism of elevated concentration in hepatobiliary disorders — Increased serum alkaline phosphatase is derived from tissues whose metabolism is either functionally disturbed (the obstructed liver) or greatly stimulated (placenta in the third trimester of pregnancy and bone in growing children). The cause in hepatobiliary disease has been debated [16]. Two theories were proposed in the past: the damaged liver regurgitates hepatic alkaline phosphatase back into serum; and the damaged liver, particularly if due to obstructive jaundice, fails to excrete the alkaline phosphatase made in bone, the intestines, and the liver. This long-standing debate was resolved in favor of the regurgitation of liver alkaline phosphatase into serum. The data supporting this theory include the following:

- Only hepatic alkaline phosphatase is found in the serum of patients with liver disease, particularly cholestasis [17].
- The clearance rates of infused placental alkaline phosphatase are the same in patients with bile duct obstruction and healthy controls [15].
- In experimental bile duct obstruction in rats, the entire increase in serum alkaline phosphatase activity is due to the leakage of hepatic alkaline phosphatase into serum [18]. The increased serum activity is paralleled by a striking elevation in hepatic alkaline phosphatase activity and is not accounted for by biliary retention of alkaline phosphatase.

Thus, the elevation in serum alkaline phosphatase in hepatobiliary disease results from increased de novo synthesis in the liver followed by release into the circulation [19]. Retained

bile acids appear to play a central role in this process; they induce the synthesis of the enzyme and may cause it to leak into the circulation, perhaps by disruption of hepatic organelles and solubilization of phosphatase bound to such membranes [20].

The precise manner in which the alkaline phosphatase reaches the circulation is unclear. In some patients with cholestasis, small vesicles that contain many basolateral (sinusoidal) membrane enzymes still bound to these membranes, including alkaline phosphatase, have been found in serum [21].

Measurement — The most widely used procedure for determination of serum alkaline phosphatase activity involves measuring the release of p-nitrophenol or phosphate from p-nitrophenylphosphate under specified conditions. The results are expressed in international units (IU/L), which is the activity of alkaline phosphatase that releases 1 mmol of chromogen or Pi per minute. Other colorimetric and fluorescent strategies for determining alkaline phosphatase activity are under study [22].

Alkaline phosphatase isoenzymes can be determined using a variety of techniques. Although the isoenzymes can be separated by electrophoresis, bone and liver isoenzymes differ only slightly in electrophoretic mobility and often overlap if run on the electrophoretic systems used in most clinical laboratories. Separation using polyacrylamide gel slabs is the most reliable method and produces clear-cut separations of the liver, bone, intestinal, and placental isoenzymes. However, this method is not always available. Electrophoresis on cellulose acetate, with the addition of heat inactivation, may accomplish the same purpose [23].

A second method is based upon the observation that alkaline phosphatases from individual tissues differ in their susceptibility to inactivation by heat or 2 mol urea [24]. Placental alkaline phosphatase and an isoenzyme found in certain cancers, the Regan isoenzyme, are fully heat-stable after exposure to a temperature of 56°C for 15 minutes [25]. Thus, the finding of an elevated serum alkaline phosphatase concentration in a patient in whom all the excess activity is in a heat-stable fraction strongly suggests that the placenta or a tumor is the source of the elevated enzyme in serum. Unfortunately, in nonselected patients, this method has many limitations and is not recommended.

Because none of these methods is widely available, the most practical approach is to measure other enzymes whose elevation reflects liver disease. These include 5'- nucleotidase and gamma-glutamyl transpeptidase. (See '5'-Nucleotidase' below and 'Gamma-glutamyl transpeptidase' below.)

Clinical significance — The major value of the serum alkaline phosphatase in the diagnosis of liver disorders is in the recognition of cholestatic disease (table 2) [26]. However, an elevation

in the alkaline phosphatase concentration is a relatively common finding and does not always indicate the presence of hepatobiliary disease (algorithm 1). In addition, normal serum values of alkaline phosphatase vary based upon demographic and clinical circumstances:

- In the 15- to 50-year age group, mean serum alkaline phosphatase activity is somewhat higher in men than in women [27]. In comparison, in individuals over age 60, the enzyme activity of women equals or exceeds that of men [28].

- In children, serum alkaline phosphatase activity is considerably elevated in both sexes, correlates well with the rate of bone growth, and appears to be accounted for by the influx of enzyme from osteoid tissue [27,29]. Serum alkaline phosphatase in normal adolescent males may reach mean values three times greater than in normal adults without implying the presence of hepatobiliary disease (figure 1) [27,30-32]. Infants and young children occasionally display marked transient elevation of serum alkaline phosphatase activity in the absence of detectable liver or bone disease. (See "Transient hyperphosphatasemia of infancy and early childhood".)

- Patients older than 60 have somewhat higher values (up to 1.5 times normal) than younger adults [28,33]. The alkaline phosphatase is usually derived from the liver in older men and from bone in postmenopausal women [28].

- Enzyme activity in serum may double late in normal pregnancy, primarily because of an influx from the placenta [34]; higher values are rarely observed [35].

Identifying the source of the elevated isoenzyme is helpful if an elevated serum alkaline phosphatase is the only abnormal finding in an apparently healthy person or if the degree of elevation is higher than expected in the clinical setting. One series evaluated 317 patients in a university hospital for an increased serum alkaline phosphatase level: the source of elevation was the liver and bone in 80 and 18 percent, respectively [17]. The remaining patients had either a mixed or an intestinal source.

If alkaline phosphatase fractionation is not available, differentiation of the source of elevation can also be accomplished by obtaining additional enzyme tests. The best studied are the serum 5'-nucleotidase and gamma-glutamyl transpeptidase (GGT) concentrations (see below); one or the other can be obtained to evaluate an elevated alkaline phosphatase. An older test, leucine aminopeptidase, is no longer used. These enzyme tests are not elevated in bone disorders, and leucine aminopeptidase and possibly 5'-nucleotidase are not elevated in pregnancy.

Thus, an increased serum concentration of these enzymes in nonpregnant patients indicates that an elevated serum alkaline phosphatase is due at least in part to hepatobiliary disease.

However, a lack of increased serum 5'-nucleotidase in the presence of an elevated alkaline phosphatase level does **not** exclude liver disease because these enzymes do not necessarily increase in a parallel manner in early or modest hepatic injury [36]. (See "Approach to the patient with abnormal liver biochemical and function tests".)

Marked elevation — Approximately 75 percent of patients with prolonged cholestasis have serum alkaline phosphatase values increased to four times the upper limit of normal or more. Elevations of this magnitude can occur in a variety of diseases associated with extrahepatic or intrahepatic obstruction (table 2), and the extent of the elevation does not distinguish between the two:

- Obstructive jaundice due to cancer.
- Bile duct stones.
- Sclerosing cholangitis (primary or secondary).
- Bile duct stricture.
- Drug and toxins associated with cholestasis.
- Primary biliary cholangitis.
- Liver allograft rejection.
- Ischemic cholangiopathy [37].
- Infectious hepatobiliary diseases seen in patients with AIDS (eg, cytomegalovirus or microsporidiosis and tuberculosis with hepatic involvement).
- Infiltrative liver disease (eg, sarcoidosis, tuberculosis, metastatic malignancy, amyloidosis).
- Familial cholestatic syndromes.
- Alcohol-associated hepatitis (rarely) [38].

Moderate elevation — Lesser increases in alkaline phosphates activity, up to four times the upper limit of normal, are nonspecific and occur in all types of liver disease, including viral hepatitis, chronic hepatitis, cirrhosis, infiltrative diseases of the liver, and congestive heart failure (table 2) [3,14,16,39]. Elevations in hepatic alkaline phosphatase of this magnitude can also occur in disorders that do not directly involve the liver, such as Hodgkin lymphoma, myeloid metaplasia, intra-abdominal infections, and osteomyelitis [17].

A two- to fourfold elevation in serum alkaline phosphatase levels has been described in several members of a family who had no evidence of bone or liver disease [40]. The elevation appeared to be transmitted as an autosomal dominant trait, but the site of the excess alkaline phosphatase could not be determined.

Isolated or disproportionate elevation — Isolated elevations of hepatic alkaline phosphatase or disproportionate elevation compared with other tests, such as the serum aminotransferases

and bilirubin, can occur in a number of circumstances including:

- Partial bile duct obstruction due to gallstones or tumor. The mechanism is unknown but probably represents local areas of bile duct obstruction with induced synthesis of hepatic alkaline phosphatase and leakage of the alkaline phosphatase into the serum.
- Early in the course of some cholestatic liver diseases such as primary sclerosing cholangitis, primary biliary cholangitis, and IgG4-associated cholangitis.
- Infiltrative diseases such as amyloidosis, sarcoidosis, hepatic abscesses, tuberculosis, and metastatic carcinoma.
- Ischemic cholangiopathy.
- Extrahepatic diseases such as myeloid metaplasia, peritonitis, diabetes mellitus, subacute thyroiditis, uncomplicated gastric ulcer, and sepsis. The increase in alkaline phosphatase in these disorders is thought to be related to hepatic dysfunction despite the absence of overt liver disease [41]. Vitamin D deficiency has been associated with an isolated elevation of the alkaline phosphatase level [1].
- Extrahepatic tumors, including osteosarcomas; lung, gastric, head and neck, renal cell, ovarian, and uterine cancers; and Hodgkin lymphoma, that secrete alkaline phosphatase (often a form known as the Regan isoenzyme) or cause leakage of hepatic alkaline phosphatase into serum by an unknown mechanism [17,42]. Renal cell carcinoma may also be complicated by non-metastatic cholestatic hepatitis, sometimes termed Stauffer's syndrome [43].
- Certain drugs such as phenytoin.
- Infants and young children occasionally display marked transient elevation of serum alkaline phosphatase activity in the absence of detectable liver or bone disease. The hyperphosphatasemia typically includes elevations in both bone and liver isoenzymes, and appears to be caused by delayed clearance of the enzyme. The clinical presentation and evaluation of an infant or child with this finding is discussed separately. (See "Transient hyperphosphatasemia of infancy and early childhood".)

Subnormal values — Extremely low serum alkaline phosphatase concentrations can be seen in patients with acute liver failure due to Wilson disease complicated by hemolysis [44,45]. (See "Wilson disease: Clinical manifestations, diagnosis, and natural history".)

Low values can also occur in patients with hypothyroidism, pernicious anemia, zinc deficiency, congenital hypophosphatemia, and certain types of progressive familial intrahepatic cholestasis in children.

Non-hepatic alkaline phosphatase — As noted above, bone is the most likely source of isolated plasma alkaline phosphatase that is not of liver origin (in nonpregnant patients). 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. If the etiology is unclear, referral to an endocrinologist for evaluation is often the next step. 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 in adults", section on 'Diagnostic and etiologic evaluation'.)

Intestinal alkaline phosphatase has multiple biological functions [6,46]. As noted above, elevated levels in serum are usually of no clinical importance. They are most often found postprandially after a fatty meal and tend to run in families, suggesting that there may be a genetic basis [47]. Because elevation is nonspecific, it should not prompt evaluation for a particular intestinal disorder. Normalization of the level while fasting can provide reassurance that its origin is intestinal.

5'-NUCLEOTIDASE

5'-Nucleotidase is found in the liver, intestine, brain, heart, blood vessels, and endocrine pancreas [48]. 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.

Similar to alkaline phosphatase, 5'-nucleotidase has a subcellular location in hepatocytes [49]. It is bound to bile canalicular and sinusoidal membranes [50] and must be solubilized, perhaps via the detergent action of bile acids, to gain access to the circulation. In experimental bile duct obstruction in rats, bile acid concentrations rapidly reach levels sufficient to disrupt plasma membranes and solubilize the enzyme [51]. The same phenomenon may occur in hepatobiliary disorders in which there is any degree of cholestasis [49].

Measurement — Serum 5'-nucleotidase activity is most commonly assayed by measuring the release of inorganic phosphate using 5'-phosphate as a substrate [52]. A unit of 5'-nucleotidase activity is designated as equivalent to that amount of enzyme that liberates 1 mg of phosphate per 100 mL of serum per hour (1 mg/dL per hour). These units are analogous to the old Bodansky units of alkaline phosphatase activity [53]. The presence of alkaline phosphatase in serum complicates the assay because it also hydrolyzes the 5'-nucleotide substrates, and corrections must be made for its activity.

In most series of normal adults, the serum 5'-nucleotidase concentration ranges from 0.3 to 3.2 Bodansky units and is not clearly influenced by gender or race [54,55]. Values are substantially lower in children than in adults, rise gradually in adolescence, and reach a plateau after age 50 [56].

Clinical significance — Elevations in serum 5'-nucleotidase are seen in the same types of hepatobiliary diseases associated with an increased serum alkaline phosphatase. Most studies suggest that serum alkaline phosphatase and 5'-nucleotidase are equally valuable in demonstrating biliary obstruction or hepatic infiltrative and space-occupying lesions [55,57]. Although values of the two enzymes are generally correlated, the concentrations may not rise proportionately in individual patients [54,58]. Thus, in selected patients, one enzyme may be elevated and the other normal.

Conflicting data have been reported for serum 5'-nucleotidase activity during normal pregnancy [59,60]. In contrast, most studies show that serum 5'-nucleotidase does not rise in bone disease, [61] and in the few instances in which an increase was observed, it was of low magnitude [58].

Thus, the major value of the 5'-nucleotidase assay is its specificity for hepatobiliary disease. An increased serum 5'-nucleotidase concentration in a nonpregnant person suggests that a concomitantly increased serum alkaline phosphatase is of hepatic origin. However, because of the occasional dissociation between the two enzymes, a normal serum 5'-nucleotidase does not rule out the liver as the source of an elevated serum alkaline phosphatase.

GAMMA-GLUTAMYL TRANSPEPTIDASE

Gamma-glutamyl transpeptidase (GGT) catalyzes the transfer of the gamma-glutamyl group from gamma-glutamyl peptides such as glutathione to other peptides and to L-amino acids. GGT is present in cell membranes in many tissues, including the kidneys, pancreas, liver, spleen, heart, brain, and seminal vesicles [62]. It is thought to play a role in amino acid transport [63].

Measurement — Enzyme activity is most commonly assayed using gamma-L-glutamyl-r-nitroanilide as a substrate [64]. The liberated product, (chromogen r-nitroaniline) can be measured spectrophotometrically.

Clinical significance — GGT is present in the serum of healthy individuals. The normal range is 0 to 30 IU/L (0 to 0.5 mkat/L). Most studies have found values to be comparable in men and women [65,66], although some reports have noted higher values in men [67]. Values within the normal range have been reported to correlate with overall and cardiovascular mortality [68]. Newborn infants have serum GGT activity six to seven times the upper limit of the adult reference range; levels decline and reach adult levels by five to seven months of age [69]. Serum enzyme activity does not rise during the course of normal pregnancy [66].

Elevated serum activity is found in diseases of the liver, biliary tract, and pancreas, and reflects the same spectrum of hepatobiliary disease as alkaline phosphatase, 5'-nucleotidase, and leucine aminopeptidase. Serum GGT and alkaline phosphatase correlate reasonably well. There are conflicting data as to whether serum GGT has better sensitivity for hepatobiliary disease than alkaline phosphatase or leucine aminopeptidase [66,70].

As with serum 5'-nucleotidase, the major clinical value of serum GGT is in conferring organ specificity to an elevated value for alkaline phosphatase, since GGT activity is not increased in patients with bone disease [66]. However, an elevation in serum GGT is not completely specific for hepatobiliary disease. High serum GGT values are found in people who take medicines such as barbiturates or phenytoin [71] or ingest large quantities of alcohol [72] even when values for other serum enzyme tests and serum bilirubin are normal. In these settings, there is no correlation between the serum GGT and alkaline phosphatase [62]. Rarely, an isolated high serum GGT level occurs in families on a genetic basis [73].

An isolated elevation in serum GGT or a GGT elevation out of proportion to that of other enzymes (such as the alkaline phosphatase and alanine aminotransferase) may be an indicator of alcohol abuse or alcoholic liver disease [74]. The reasons for this are not well understood. Although hepatic microsomal GGT may be induced by alcohol [75], neither elevated serum GGT nor a history or recent alcohol ingestion correlates with hepatic GGT activity in patients with biopsy-proven alcohol-associated liver disease [76,77]. In vitro studies suggest an alternative mechanism: alcohol may cause the leakage of GGT from hepatocytes [75].

Aside from its value in conferring liver specificity to an elevated serum alkaline phosphatase level and its possible use in identifying patients with alcohol abuse, serum GGT offers no advantage over aminotransferases and alkaline phosphatase. In one prospective study that included 1040 nonselected inpatients, 13 percent had an elevated serum GGT activity; only 32

percent of them had hepatobiliary disease [78]. In the remaining patients, the elevated serum GGT may have been due to alcohol ingestion or medications, which caused a temporary rise in levels but without liver disease.

SUMMARY AND RECOMMENDATIONS

- **Alkaline phosphatase function and sources** – Alkaline phosphatase refers to a group of enzymes that catalyze the hydrolysis of a large number of organic phosphate esters at an alkaline pH optimum. Although alkaline phosphatase is found in many locations throughout the body, its precise function is not fully understood. Alkaline phosphatase activity in serum is derived primarily from three sources: liver (more than 80 percent), bone, and in some patients, the intestinal tract. (See 'Mechanism of elevated concentration in hepatobiliary disorders' above.)

- **Causes of alkaline phosphatase elevation** – The major value of serum alkaline phosphatase in the diagnosis of liver disorders is in the recognition of cholestatic disease (table 2). However, an elevation in the alkaline phosphatase concentration is a relatively common finding and does not always indicate the presence of hepatobiliary disease. The degree of elevation does not distinguish intra- from extra-hepatic cholestasis (algorithm 1). (See 'Clinical significance' above and "Approach to the patient with abnormal liver biochemical and function tests", section on 'Elevated serum aminotransferases'.)

- **Role of 5'-nucleotidase measurement** – Elevations in serum 5'-nucleotidase are seen in the same types of hepatobiliary diseases associated with an increased serum alkaline phosphatase. The value of the 5'-nucleotidase assay is its specificity for hepatobiliary disease. An increased serum 5'-nucleotidase concentration in a nonpregnant person suggests that a concomitantly increased serum alkaline phosphatase is of hepatic origin. However, because of the occasional dissociation between the two enzymes, a normal serum 5'-nucleotidase does not rule out the liver as the source of an elevated serum alkaline phosphatase. (See '5'-Nucleotidase' above.)

- **Cause of gamma-glutamyl transpeptidase elevation** – Elevated serum levels of gamma-glutamyl transpeptidase (GGT) are found in diseases of the liver, biliary tract, and pancreas, and reflect the same spectrum of hepatobiliary disease as alkaline phosphatase, 5'-nucleotidase, and leucine aminopeptidase. Serum GGT and alkaline phosphatase correlate reasonably well. There are conflicting data as to whether serum GGT has better sensitivity for hepatobiliary disease than alkaline phosphatase or leucine aminopeptidase.

The major clinical value of serum GGT is in conferring organ specificity to an elevated value for alkaline phosphatase, since GGT activity is not increased in patients with bone disease. However, an elevation in serum GGT is not specific for hepatobiliary disease. (See 'Gamma-glutamyl transpeptidase' above.)

REFERENCES

1. Newsome PN, Cramb R, Davison SM, et al. Guidelines on the management of abnormal liver blood tests. Gut 2018; 67:6.
2. Schreiner AD, Rockey DC. Evaluation of abnormal liver tests in the adult asymptomatic patient. Curr Opin Gastroenterol 2018; 34:272.
3. Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. Am J Gastroenterol 2017; 112:18.
4. Kaplan MM. Alkaline phosphatase. Gastroenterology 1972; 62:452.
5. Alvaro D, Benedetti A, Marucci L, et al. The function of alkaline phosphatase in the liver: regulation of intrahepatic biliary epithelium secretory activities in the rat. Hepatology 2000; 32:174.
6. Bates JM, Akerlund J, Mittge E, Guillemin K. Intestinal alkaline phosphatase detoxifies lipopolysaccharide and prevents inflammation in zebrafish in response to the gut microbiota. Cell Host Microbe 2007; 2:371.
7. Fawley J, Gourlay DM. Intestinal alkaline phosphatase: a summary of its role in clinical disease. J Surg Res 2016; 202:225.
8. Lallès JP. Recent advances in intestinal alkaline phosphatase, inflammation, and nutrition. Nutr Rev 2019; 77:710.
9. Sussman HH. Structural analysis of human alkaline phosphatase. In: Human alkaline phosp hatase, Stigbrand T, Fisher WH (Eds), Alan R Liss, New York 1984. p.87.
10. Lowe D, John S.. StatPearls, StatPearls Publishing, Treasure Island (FL) 2020.
11. Kaplan MM. Alkaline phosphatase. N Engl J Med 1972; 286:200.
12. Cho SR, Lim YA, Lee WG. Unusually high alkaline phosphatase due to intestinal isoenzyme in a healthy adult. Clin Chem Lab Med 2005; 43:1274.
13. BAMFORD KF, HARRIS H, LUFFMAN JE, et al. SERUM-ALKALINE-PHOSPHATASE AND THE ABO BLOOD-GROUPS. Lancet 1965; 1:530.

14. Posen S. Alkaline phosphatase. Ann Intern Med 1967; 67:183.
15. Clubb JS, Neale FC, Posen S. The behavior of infused human placental alkaline phosphatase in human subjects. J Lab Clin Med 1965; 66:493.
16. GUTMAN AB. Serum alkaline phosphatase activity in diseases of the skeletal and hepatobiliary systems. A consideration of the current status. Am J Med 1959; 27:875.
17. Brensilver HL, Kaplan MM. Significance of elevated liver alkaline phosphatase in serum. Gastroenterology 1975; 68:1556.
18. Kaplan MM, Righetti A. Induction of rat liver alkaline phosphatase: the mechanism of the serum elevation in bile duct obstruction. J Clin Invest 1970; 49:508.
19. Kaplan MM. Serum alkaline phosphatase--another piece is added to the puzzle. Hepatology 1986; 6:526.
20. Hatoff DE, Hardison WG. Induced synthesis of alkaline phosphatase by bile acids in rat liver cell culture. Gastroenterology 1979; 77:1062.
21. De Broe ME, Borgers M, Wieme RJ. The separation and characterization of liver plasma membrane fragments circulating in the blood of patients with cholestasis. Clin Chim Acta 1975; 59:369.
22. Niu X, Ye K, Wang L, et al. A review on emerging principles and strategies for colorimetric and fluorescent detection of alkaline phosphatase activity. Anal Chim Acta 2019; 1086:29.
23. POSEN S, NEALE FC, CLUBB JS. HEAT INACTIVATION IN THE STUDY OF HUMAN ALKALINE PHOSPHATASES. Ann Intern Med 1965; 62:1234.
24. Bahr M, Wilkinson JH. Urea as a selective inhibitor of human tissue alkaline phosphatases. Clin Chim Acta 1967; 17:367.
25. ARIAS IM, WOLFSON S, LUCEY JF, MCKAY RJ Jr. TRANSIENT FAMILIAL NEONATAL HYPERBILIRUBINEMIA. J Clin Invest 1965; 44:1442.
26. Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. N Engl J Med 2000; 342:1266.
27. CLARK LC Jr, BECK E. Plasma alkaline phosphatase activity; normative data for growing children. J Pediatr 1950; 36:335.
28. Kuwana T, Sugita O, Yakata M. Reference limits of bone and liver alkaline phosphatase isoenzymes in the serum of healthy subjects according to age and sex as determined by wheat germ lectin affinity electrophoresis. Clin Chim Acta 1988; 173:273.
29. Kattwinkel J, Taussig LM, Statland BE, Verter JI. The effects of age on alkaline phosphatase and other serologic liver function tests in normal subjects and patients with cystic fibrosis. J

Pediatr 1973; 82:234.

30. Salz JL, Daum F, Cohen MI. Serum alkaline phosphatase activity during adolescence. J Pediatr 1973; 82:536.
31. Loh TP, Metz MP. Trends and physiology of common serum biochemistries in children aged 0-18 years. Pathology 2015; 47:452.
32. Zierk J, Arzideh F, Haeckel R, et al. Pediatric reference intervals for alkaline phosphatase. Clin Chem Lab Med 2017; 55:102.
33. HEINO AE, JOKIPII SG. Serum alkaline phosphatase levels in the aged. Ann Med Intern Fenn 1962; 51:105.
34. Birkett DJ, Done J, Neale FC, Posen S. Serum alkaline phosphatase in pregnancy; an immunological study. Br Med J 1966; 1:1210.
35. Stanley Z, Vignes K, Marcum M. Extreme elevations of alkaline phosphatase in pregnancy: A case report. Case Rep Womens Health 2020; 27:e00214.
36. Connell MD, Dinwoodie AJ. Diagnostic use of serum alkaline phosphatase isoenzymes and 5-nucleotidase. Clin Chim Acta 1970; 30:235.
37. Laurent L, Lemaitre C, Minello A, et al. Cholangiopathy in critically ill patients surviving beyond the intensive care period: a multicentre survey in liver units. Aliment Pharmacol Ther 2017; 46:1070.
38. Perrillo RP, Griffin R, DeSchryver-Kecskemeti K, et al. Alcoholic liver disease presenting with marked elevation of serum alkaline phosphatase. A combined clinical and pathological study. Am J Dig Dis 1978; 23:1061.
39. Boyde TRC, Latner AL. Starch gel electrophoresis of transaminase in human tissue extracts and serum. Biochem J 1961; 82:52.
40. Wilson JW. Inherited elevation of alkaline phosphatase activity in the absence of disease. N Engl J Med 1979; 301:983.
41. Dalovisio JR, Blonde L, Cortez LM, Pankey GA. Subacute thyroiditis with increased serum alkaline phosphatase. Ann Intern Med 1978; 88:505.
42. Fishman WH. Immunologic and biochemical approaches to alkaline phosphatase isoenzyme analysis: the Regan isoenzyme. Ann N Y Acad Sci 1969; 166:745.
43. Gremida A, Al-Taee A, Alcorn J, McCarthy D. Hepatic Dysfunction in Renal Cell Carcinoma: Not What You Think? Dig Dis Sci 2017; 62:2298.
44. Shaver WA, Bhatt H, Combes B. Low serum alkaline phosphatase activity in Wilson's disease. Hepatology 1986; 6:859.

45. Berman DH, Leventhal RI, Gavaler JS, et al. Clinical differentiation of fulminant Wilsonian hepatitis from other causes of hepatic failure. Gastroenterology 1991; 100:1129.
46. Lallès JP. Intestinal alkaline phosphatase: multiple biological roles in maintenance of intestinal homeostasis and modulation by diet. Nutr Rev 2010; 68:323.
47. Siraganian PA, Mulvihill JJ, Mulivor RA, Miller RW. Benign familial hyperphosphatasemia. JAMA 1989; 261:1310.
48. Goldberg DM. 5'nucleotidase: recent advances in cell biology, methodology and clinical significance. Digestion 1973; 8:87.
49. Righetti A, Kaplan MM. Disparate responses of serum and hepatic alkaline phosphatase and 5' nucleotidase to bile duct obstruction in the rat. Gastroenterology 1972; 62:1034.
50. Song CS, Kappas A, Bodansky O. 5'-nucleotidase of plasma membranes of the rat liver: studies on subcellular distribution. Ann N Y Acad Sci 1969; 166:565.
51. Schlaeger R, Haux P, Kattermann R. Studies on the mechanism of the increase in serum alkaline phosphatase activity in cholestasis: significance of the hepatic bile acid concentration for the leakage of alkaline phosphatase from rat liver. Enzyme 1982; 28:3.
52. Campbell DM. Determination of 5'-nucleotidase in blood serum. Biochem J 1962; 82:348.
53. YOUNG II. Serum 5-nucleotidase; characterization and evaluation in disease states. Ann N Y Acad Sci 1958; 75:357.
54. BARDAWILL C, CHANG C. SERUM LACTIC DEHYDROGENASE, LEUCINE AMINOPEPTIDASE AND 5-NUCLEOTIDASE ACTIVITIES: OBSERVATION IN PATIENTS WITH CARCINOMA OF THE PANCREAS AND HEPATOBILIARY DISEASE. Can Med Assoc J 1963; 89:755.
55. Hill PG, Sammons HG. An assessment of 5'-nucleotidase as a liver-function test. Q J Med 1967; 36:457.
56. Belfield A, Goldberg DM. Normal ranges and diagnostic value of serum 5'nucleotidase and alkaline phosphatase activities in infancy. Arch Dis Child 1971; 46:842.
57. KOWLESSAR OD, HAEFFNER LJ, RILEY EM, SLEISENGER MH. Comparative study of serum leucine aminopeptidase, 5-nucleotidase and non-specific alkaline phosphatase in diseases affecting the pancreas, hepatobiliary tree and bone. Am J Med 1961; 31:231.
58. Eschar J, Rudzki C, Zimmerman HJ. Serum levels of 5'-nucleotidase in disease. Am J Clin Pathol 1967; 47:598.
59. Kater RM, Mistilis SP. Obstetric cholestasis and pruritus of pregnancy. Med J Aust 1967; 1:638.
60. Seitanidis B, Moss DW. Serum alkaline phosphatase and 5'-nucleotidase levels during

normal pregnancy. Clin Chim Acta 1969; 25:183.

61. HUNTON DB, BOLLMAN JL, HOFFMAN HN 2nd. The plasma removal on indocyanine green and sulfobromophthalein: effect of dosage and blocking agents. J Clin Invest 1961; 40:1648.
62. Goldberg DM. Structural, functional, and clinical aspects of gamma-glutamyltransferase. CRC Crit Rev Clin Lab Sci 1980; 12:1.
63. Meister A. The gamma-glutamyl cycle. Diseases associated with specific enzyme deficiencies. Ann Intern Med 1974; 81:247.
64. Szasz G. A kinetic photometric method for serum gamma-glutamyl transpeptidase. Clin Chem 1969; 15:124.
65. ARONSEN KF, HANSON A, NOSSLIN B. THE VALUE OF GAMMA-GLUTAMYL TRANSPEPTIDASE IN DIFFERENTIATING VIRAL HEPATITIS FROM OBSTRUCTIVE JAUNDICE. A STATISTICAL COMPARISON WITH ALKALINE PHOSPHATASE. Acta Chir Scand 1965; 130:92.
66. Lum G, Gambino SR. Serum gamma-glutamyl transpeptidase activity as an indicator of disease of liver, pancreas, or bone. Clin Chem 1972; 18:358.
67. RUTTENBURG AM, GOLDBARG JA, PINEDA EP. SERUM GAMMA-GLUTAMYL TRANSPEPTIDASE ACTIVITY IN HEPATOBILIARY PANCREATIC DISEASE. Gastroenterology 1963; 45:43.
68. Wang J, Zhang D, Huang R, et al. Gamma-glutamyltransferase and risk of cardiovascular mortality: A dose-response meta-analysis of prospective cohort studies. PLoS One 2017; 12:e0172631.
69. Cabrera-Abreu JC, Green A. Gamma-glutamyltransferase: value of its measurement in paediatrics. Ann Clin Biochem 2002; 39:22.
70. Betro MG, Oon RC, Edwards JB. Gamma-glutamyl transpeptidase in diseases of the liver and bone. Am J Clin Pathol 1973; 60:672.
71. Rosalki SB, Tarlow D, Rau D. Plasma gamma-glutamyl transpeptidase elevation in patients receiving enzyme-inducing drugs. Lancet 1971; 2:376.
72. Lamy J, Baglin MC, Ferrant JP, Weill J. [Decrease in serum gamma-glutamyltranspeptidase following abstention from alcohol]. Clin Chim Acta 1974; 56:169.
73. De Grandi A, Franzini M, Rosipal Š, et al. Highly Elevated Plasma γ-Glutamyltransferase Elevations: A Trait Caused by γ-Glutamyltransferase 1 Transmembrane Mutations. Hepatology 2020; 71:1124.
74. Kaplan MM, et al. Biochemical basis for serum enzyme abnormalities in alcoholic liver disea se. In: Early identification of alcohol abuse, Research Monograph No. 17, Chang NC, Chan N M (Eds), NIAAA, 1985. p.186.

75. Barouki R, Chobert MN, Finidori J, et al. Ethanol effects in a rat hepatoma cell line: induction of gamma-glutamyltransferase. Hepatology 1983; 3:323.

76. Ivanov E, Adjarov D, Etarska M, et al. Elevated liver gamma-glutamyl transferase in chronic alcoholics. Enzyme 1980; 25:304.

77. Selinger MJ, Matloff DS, Kaplan MM. gamma-Glutamyl transpeptidase activity in liver disease: serum elevation is independent of hepatic GGTP activity. Clin Chim Acta 1982; 125:283.

78. Burrows S, Feldman W, McBride F. Serum gamma-glutamyl transpeptidase. Evaluation in screening of hospitalized patients. Am J Clin Pathol 1975; 64:311.

Topic 3612 Version 27.0

GRAPHICS

Child-Pugh classification of severity of cirrhosis

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/L)	2 to 3 mg/dL (34.2 to 51.3 micromol/L)	>3 mg/dL (>51.3 micromol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
Prothrombin time (seconds over control) or	<4	4 to 6	>6
INR	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the serum concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total Child-Turcotte-Pugh score of 5 to 6 is considered Child-Pugh class A (well-compensated disease), 7 to 9 is class B (significant functional compromise), and 10 to 15 is class C (decompensated disease). These classes correlate with one- and two-year patient survival: class A: 100 and 85%; class B: 80 and 60%; and class C: 45 and 35%.

INR: international normalized ratio.

Graphic 78401 Version 15.0

Causes of an elevated alkaline phosphatase

Marked elevation (≥4 times the upper limit of normal)*	**Extrahepatic biliary obstruction¶**
	Choledocholithiasis (most common) ▪ Uncomplicated ▪ Complicated (biliary pancreatitis, acute cholangitis)
	Malignant obstruction ▪ Pancreas ▪ Gallbladder ▪ Ampulla of Vater ▪ Bile duct ▪ Metastasis to perihilar lymph nodes
	Biliary strictures ▪ Primary sclerosing cholangitis with extrahepatic bile duct stricture ▪ Complications after invasive procedures ▪ Chronic pancreatitis with stricturing of distal bile duct ▪ Biliary anastomotic stricture following liver transplantation
	Infections ▪ AIDS cholangiopathy ▪ *Ascaris lumbricoides* ▪ Liver flukes
	Intrahepatic cholestasis
	Drug and toxins associated with cholestasis[Δ]
	Primary biliary cholangitis[Δ]
	Primary sclerosing cholangitis[Δ]
	Intrahepatic cholestasis of pregnancy
	Benign postoperative cholestasis
	Total parenteral nutrition
	Infiltrative diseases[Δ] ▪ Amyloidosis ▪ Lymphoma ▪ Sarcoidosis ▪ Tuberculosis ▪ Hepatic abscess
	Metastatic carcinoma to the liver[Δ]

	Liver allograft rejection
	Other cholangiopathies (eg, IgG4 cholangiopathy, ischemic cholangiopathy, COVID-19)
	Alcohol-associated hepatitis
	Sickle cell disease (hepatic crisis)
	Nonhepatic causes◇
	Transient hyperphosphatemia of infancy and childhood
Moderate elevation (<4 times upper limit normal)	**Hepatic causes**
	Nonspecific, seen with all types of liver disease including: ▪ Hepatitis: viral, chronic, alcoholic ▪ Cirrhosis ▪ Infiltrative diseases of the liver ▪ Hypoperfusion states: sepsis, heart failure
	Nonhepatic causes◇
	Physiologic (children and adolescents)
	Third trimester of pregnancy
	Influx of intestinal alkaline phosphatase after eating a fatty meal (individuals with blood type O or B)
	High bone turnover ▪ Growth ▪ Healing fractures ▪ Osteomalacia ▪ Paget disease of bone ▪ Osteogenic sarcoma, bone metastasis ▪ Hyperparathyroidism ▪ Hyperthyroidism
	Extrahepatic disease ▪ Myeloid metaplasia ▪ Peritonitis ▪ Diabetes mellitus ▪ Subacute thyroiditis ▪ Gastric ulcer (uncomplicated) ▪ Extrahepatic tumors • Osteosarcoma • Lung • Gastric • Head and neck

	• Renal cell • Ovarian • Uterine • Hodgkin lymphoma

* The alkaline phosphatase value may vary and be <4 times the upper limit of normal at times (eg, early in the disease process).

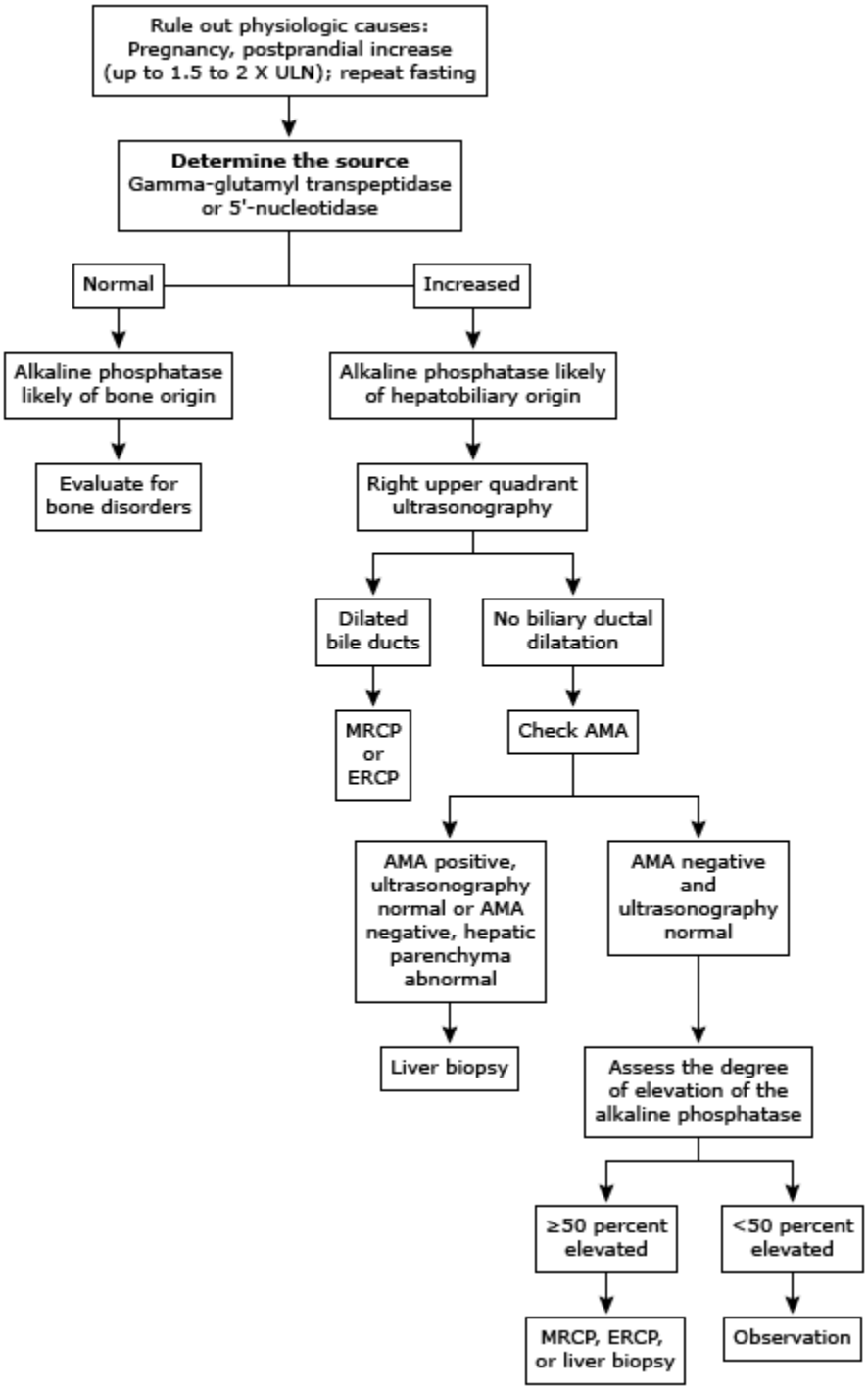
¶ May cause an isolated elevation in hepatic alkaline phosphatase if partial obstruction.

Δ May cause an isolated elevation in hepatic alkaline phosphatase.

◇ Alkaline phosphatase may be derived from several sites including the liver, bone, third trimester placenta, intestine, and kidneys. An elevation in alkaline phosphatase with a normal gamma-glutamyl transpeptidase or 5'-nucleotidase suggests a nonhepatic source of alkaline phosphatase.

Graphic 99099 Version 8.0

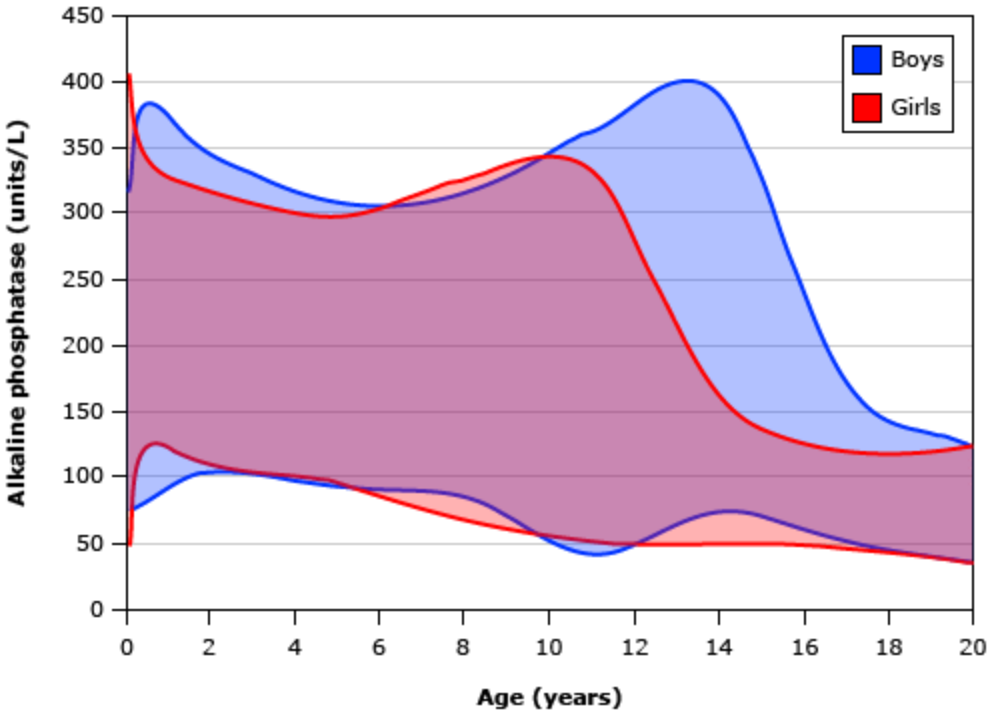
Evaluation of elevated serum alkaline phosphatase



AMA: antimitochondrial antibodies; ERCP: endoscopic retrograde cholangiopancreatography; MRCP: magnetic resonance cholangiopancreatography; ULN: upper limit of normal.

Graphic 78223 Version 7.0

Reference range for serum alkaline phosphatase activity in children and adolescents



Normal ranges for serum alkaline phosphatase activity for boys (blue) and girls (red).

Data from: NIH Clinical reference laboratory, available at: www.cc.nih.gov/ccc/pedweb/pedsstaff/pedlab.html.

Graphic 56695 Version 3.0

Contributor Disclosures

Lawrence S Friedman, MD Other Financial Interest: Elsevier [Gastroenterology]; McGraw-Hill [Gastroenterology]; Wiley [Gastroenterology]. All of the relevant financial relationships listed have been mitigated. **Sanjiv Chopra, MD, MACP** No relevant financial relationship(s) with ineligible companies to disclose. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

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

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