Liver Function Tests and their Interpretation

Liver function tests (LFT) are a helpful screening tool, which are an effective modality to detect hepatic dysfunction. Since the liver performs a variety of functions, no single test is sufficient to provide complete estimate of function of liver. Often clinicians are faced with reports that do not tally with the clinical condition of the patient and they face difficulty in interpreting the LFT.

Liver has to perform different kinds of biochemical, synthetic and excretory functions, so no single biochemical test can detect the global functions of liver. All laboratories usually employ a battery of tests for initial detection and management of liver diseases and these tests are frequently termed 'Liver function tests', although they are of little value in assessing the liver function per se.

Moreover, the clinical history and physical examination play important role to interpret the functions. The role of specific disease markers, radiological imaging and liver biopsy can not be underestimated.

Uses

The various uses of Liver function tests include:
Screening: They are a non-invasive yet sensitive screening modality for liver dysfunction.
Pattern of disease: They are helpful to recognize the pattern of liver disease like differentiating between acute viral hepatitis and various cholestatic disorders or chronic liver disease.
Assess severity: They are helpful to assess the severity and predict the outcome of certain diseases like primary biliary cirrhosis.
Follow up: They are helpful in the follow up of certain liver diseases and also helpful in evaluating response to therapy like autoimmune hepatitis.

Limitations
Lack sensitivity: The LFT may be normal in certain liver diseases like cirrhosis, non cirrhotic portal fibrosis, congenital hepatic fibrosis, etc.
Lack specificity: They lack specificity and are not specific for any particular

disease. Serum albumin may be decreased in chronic disease and also in nephrotic syndrome. Aminotransferases may be raised in cardiac diseases and hepatic diseases.
Except for serum bile acids the LFT are not specific for liver diseases and all the parameters may be elevated for pathological processes outside the liver. Thus, LFT have certain advantages as well as limitations at the same time. Thus, it is important to view them keeping the clinical profile of the patient in mind.

Classification of liver function Tests

- Tests of the liver's capacity to transport organic anions and to metabolize drugs- Serum bilirubin, urine bilirubin, urobilinogen etc.

- Tests that detect injury to hepatocytes (serum enzyme tests) – Aminotransferases, alkaline phosphatase, ã glutamyl transpeptidase, 5 nucleotidase, leucine aminopeptidase *etc.*

- Tests of the Liver's biosynthetic capacity- Serum proteins, albumin, prealbumin, serum ceruloplasmin, procollagen III peptide, a 1 antitrypsin, alpha feto protein, and prothrombin time *etc.*

- Tests of the liver's capacity to transport organic anions and to metabolize drugs.

Clinical Significance of Liver Function Tests in Children

Normal	Basis of abnormality	Associated liver disease	Extrahepatic sources
Bilirubin 0-1mg/dl	Decreased hepatic clearance	*Mild elevations:* Liver diseases, physiological jaundice, inherited hyperbilirubinemias *Moderate elevations:* EHBA, IHBA, drugs, viral hepatitis, inherited hyperbilirubinemias	Hemolysis, ineffective erythropoiesis, hematoma, myoglobinemia
Aminotransferases ALT 10-55 U/L AST 10-40 U/L	Leakage from damaged tissues	*Marked elevations:* Hepatitis, autoimmune, toxic, neonatal hepatitis, ischemic AST/ALT >2 in CLD AST/ALT <1 acute hepatitis / injury	ALT specific for hepatocytic necrosis. AST for skeletal, cardiac, muscle, kidney, brain.

Alkaline phosphatase 45-115 U/L	Overproduction and leakage in blood	*Mild elevations:* Liver disease *Moderate elevations:* EHBA, IHBA, infiltrating disorders, granulomatous hepatitis	Bone diseases, placenta, intestine, tumour
g glutamyl transpeptidase 0-30 U/L	Overproduction and leakage in blood	Same as alkaline phosphatase, Raised in EHBA, PFIC	Kidney, spleen, pancreas, heart, lung, brain
5-nucleotidase 0-11 U/ml	Overproduction and leakage in blood	Same as alkaline phosphatase	Specific for liver
Prothrombin time 10-14sec	Decreased synthetic capacity	Acute/chronic liver disease-non responsive to Vit K EHBA/biliary obstruction-responsive to Vit K	Vit. K deficiency secondary to MAS, PEM, DIC
International normalized ratio 0.9-1.2	Decreased synthetic capacity	Same as PT	Same as PT
Serum albumin 3.5-5.5g/dl	Decreased synthesis	CLD, cirrhosis	Nephrotic syndrome, protein losing enteropathy, PEM, IBD, malignancy

Serum Bilirubin

Bilirubin is an endogenous anion derived from hemoglobin degradation from the RBC. The classification of bilirubin into direct and indirect bilirubin is based on the original van der Bergh method of measuring bilirubin. Bilirubin is altered by exposure to light so serum and plasma samples must be kept in dark before measurements are made. When the liver function tests are abnormal and the serum bilirubin levels more than 17μmol/L suggest underlying liver disease.

Types of bilirubin

i. Total bilirubin: This is measured as the amount, which reacts in 30 minutes after addition of alcohol. Normal range is 0.2-0.9 mg/dl (2-15μmol/L). It is slightly higher by 3-4 μmol/L in males as compared to females. It is this factor, which helps to diagnose Gilbert syndrome in males easily.

ii. Direct Bilirubin: This is the water-soluble fraction. This is measured by the reaction with diazotized sulfanilic acid in 1 minute and this gives estimation of conjugated bilirubin. Normal range 0.3mg/dl (5.1 μmol/ L)

iii. Indirect bilirubin: This fraction is calculated by the difference of the total

and direct bilirubin and is a measure of unconjugated fraction of bilirubin.

The diazo method of bilirubin estimation is not very accurate especially in detecting low levels of bilirubin. Direct bilirubin over estimates bilirubin esters at low bilirubin levels and under estimates them at high concentration. Thus slight elevation of unconjugated bilirubin not detected, which is of value in detecting conditions like Gilbert syndrome.

A newer highly accurate method of estimation involves alkaline methanolysis of bilirubin followed by chloroform extraction of bilirubin methyl esters and later separation of these esters by chromatography and spectrophotometric determination at 430 nm.

Diagnostic value of bilirubin levels: Bilirubin in body is a careful balance between production and removal of the pigment in body. Hyperbilirubinemia seen in acute viral hepatitis is directly proportional to the degree of histological injury of hepatocytes and the longer course of the disease.

Hyperbilirubinemia: It results from overproduction / impaired uptake, conjugation or excretion / regurgitation of unconjugated or conjugated bilirubin from hepatocytes to bile ducts. Approach to jaundice in neonatal period is given in Fig 1.

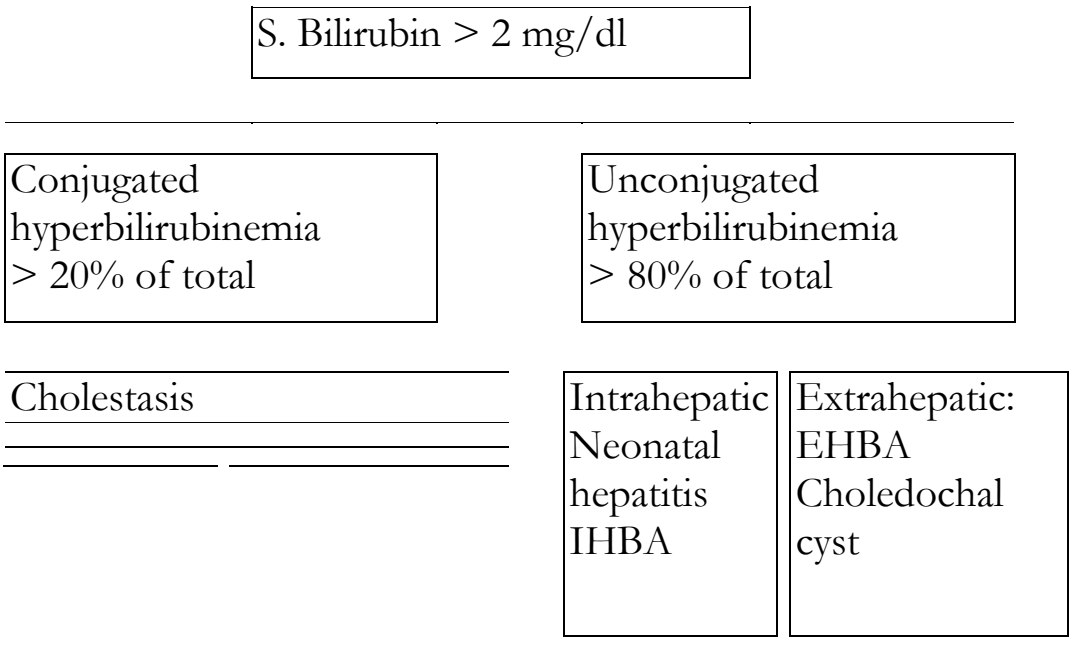


Fig.1. Algorithm to Approach Hyperbilirubinemia in Neonatal Period

Increased unconjugated bilirubin: This results from overproduction /impaired uptake, conjugation
Increased conjugated bilirubin: Impaired intra-hepatic excretion / regurgitation of unconjugated or conjugated bilirubin from hepatocytes of bile ducts.

Serum bilirubin could be lowered by drugs like salicylates, sulphonamides, free fatty acids which displace bilirubin from its attachment to plasma albumin. On the contrary it could be elevated if the serum albumin increases and the bilirubin may shift from tissue sites to circulation.

Prognostic value of bilirubin levels

Bilirubin may be of prognostic value in conditions like fulminant hepatic failure where deep jaundice is associated with increased mortality.

Hyperbilirubinemia and Hemolysis

Bilirubin itself is not soluble in water and is bound to albumin and thus does not appear in urine. Hemolysis with overproduction of bilirubin and concomitant reduced GFR causes decreased excretion and can lead to high bilirubin levels. Bilirubin levels in excess of 25 mg/ dl may be seen in hemolysis in association with liver disease.
Other causes of extreme hyperbilirubinemia include severe parenchymal disease, septicemia and renal failure.

Urine Bilirubin

The presence of urine bilirubin indicates hepatobiliary disease. Unconjugated bilirubin is tightly bound to albumin and is not filtered by the glomerulus and thus not present in urine. Measurable amounts of conjugated bilirubin in serum are found only in hepatobiliary disease.
Because the renal threshold for conjugated bilirubin is low and the laboratory methods can detect low levels of bilirubin in urine so conjugated bilirubin may be found in urine when the serum bilirubin levels are normal. This is the case in early acute viral hepatitis.

Urobilinogen

An increase in the urobilinogen in urine is a sensitive indicator of hepatocellular dysfunction. It is a good indication of alcoholic liver damage, well compensated cirrhosis or malignant disease of the liver. In viral hepatitis it appears early in urine. It is markedly increased in hemolysis. In cholestatic jaundice urobilinogen disappears from urine. It may be intermittently present in case of gallstones.

Tests that detect injury to hepatocytes (serum enzyme tests):

The liver contains thousands of enzymes and these enzymes have no function and behave as serum proteins.

Aminotransferases

Enzymes that detect Hepatocellular Necrosis

The aminotransferases are the most frequently utilized and specific indicators of hepatocellular necrosis. These enzymes- aspartate aminotransferase (AST, formerly serum glutamate oxaloacetic transaminase -SGOT) and Alanine amino transferase (ALT, formerly serum glutamic pyruvate transaminase-SGPT) catalyze the transfer of the á amino acids of aspartate and Alanine respectively to the á keto group of ketoglutaric acid. ALT is primarily localized to the liver but the AST is present in a wide variety of tissues like the heart, skeletal muscle, kidney, brain and liver.

AST: Alanine + a ketoglutarate = oxaloacetate + glutamate
ALT: Alanine + a ketoglutarate = pyruvate + glutamate

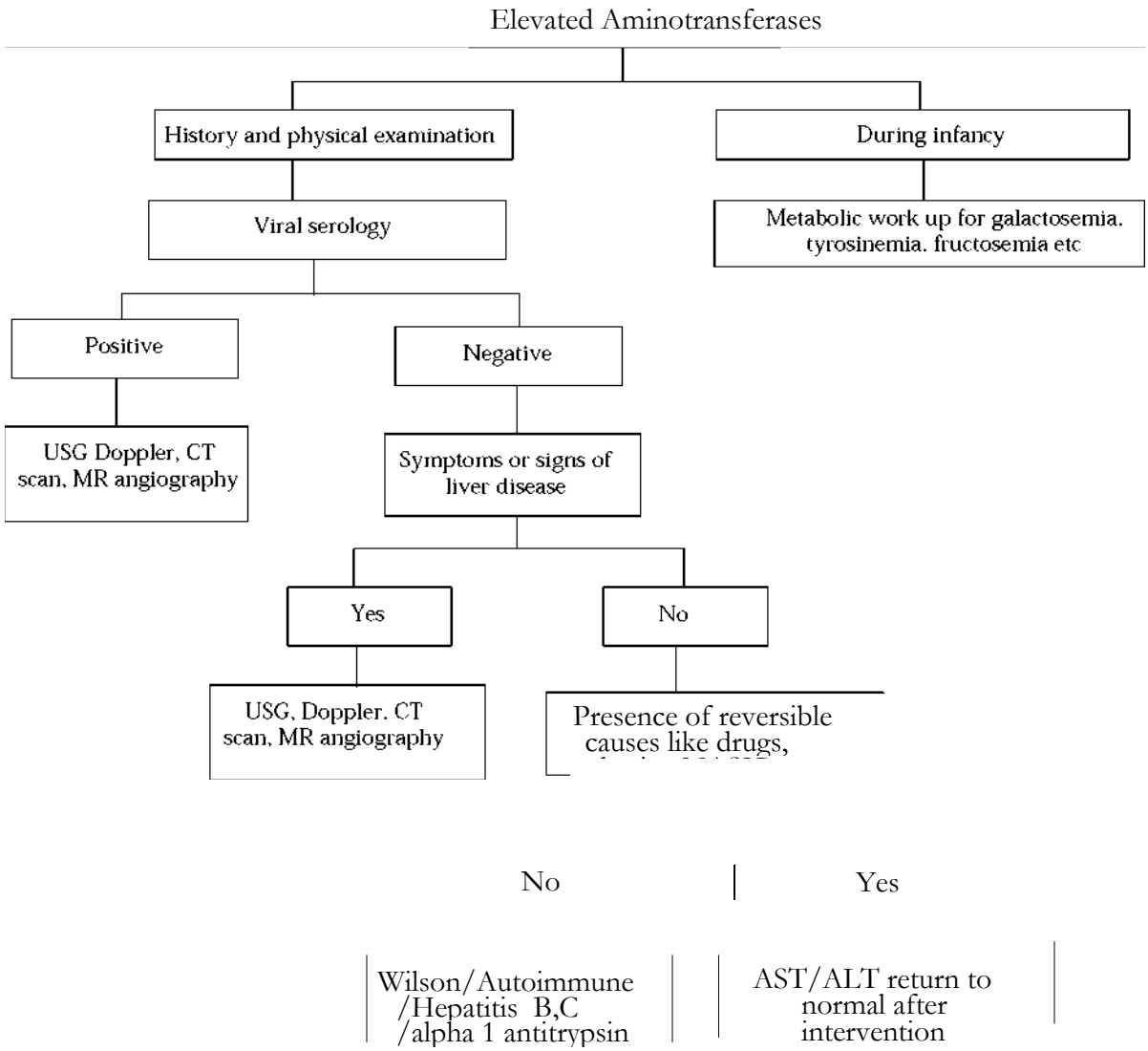
Whereas the AST is present in both the mitochondria and cytosol of hepatocytes, ALT is localized to the cytosol. The cytosolic and mitochondrial forms of AST are true isoenzymes and immunologically distinct. About 80% of AST activity in human liver is contributed by the mitochondrial isoenzyme, whereas most of the circulating AST activity in normal people is derived from the cytosolic isoenzyme.

Algorithm to approach mild and sustained rise of aminotransferases is given in

Fig. 2.

Large increases in mitochondrial AST occur in serum after extensive tissue necrosis. Because of this, assay of mitochondrial AST have been advocated in myocardial infarction. Mitochondrial AST is also increased in chronic liver disease.

Their activity in serum at any moment reflects the relative rate at which they enter and leave circulation. Of the numerous methods used for measuring their levels, the most specific method couples the formation of pyruvate and oxaloacetate- the products of the aminotransferase reactions to their enzymatic reduction to lactate and malate. Virtually no aminotransferases are present in the urine or bile and hepatic sinusoids are the primary site for their clearance.



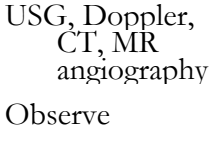


Fig.2. Algorithm to Approach Mild but Sustained Rise of Aminotransferases

Severe, Moderate, and Mild, elevations of Aminotransferases

Severe (> 20 times, 1000 U/L): The AST and ALT levels are increased to some extent in almost all liver diseases. The highest elevations occur in severe viral hepatitis; drug or toxin induced hepatic necrosis and circulatory shock. Although enzyme levels may reflect the extent of hepatocellular necrosis they do not correlate with eventual outcome. In fact declining AST and ALT may indicate either recovery of poor prognosis in fulminant hepatic failure.4, 5

Moderate (3-20 times): The AST and ALT are moderately elevated in acute hepatitis, neonatal hepatitis, chronic hepatitis, autoimmune hepatitis, drug induced hepatitis, alcoholic hepatitis and acute biliary tract obstructions. The ALT is usually more frequently increased as compared to AST except in chronic liver disease. In uncomplicated acute viral hepatitis, the very high initial levels approach normal levels within 5 weeks of onset of illness and normal levels are obtained in 8 weeks in 75% of cases.

Mild (1-3 times): These elevations are usually seen in sepsis induced neonatal hepatitis, extrahepatic biliary atresia (EHBA), fatty liver, cirrhosis, non alcoholic steato hepatitis (NASH), drug toxicity, myositis, duchenne muscular dystrophy and even after vigorous exercise.

For reasons, which are not, understood AST levels appear disproportionately low in patients with Wilson disease.

One third to one half of healthy individuals with an isolated elevation of ALT on repeated testing has been found to be normal.

AST: ALT ratio

The ratio of AST to ALT is of use in Wilson disease, CLD and alcoholic liver disease and a ratio of more than 2 is usually observed. The lack of ALT rise is probably due to pyridoxine deficiency. In NASH the ratio is less than one in the absence of fibrosis on liver biopsy.
In viral hepatitis the ratio is usually less than one. The ratio invariably rises to more than one as cirrhosis develops possibly because of reduced plasma clearance of AST secondary to impaired function of sinusoidal cells.

ALT exceeds AST in toxic hepatitis, viral hepatitis, chronic active hepatitis and cholestatic hepatitis.
Mitochondrial AST: Total AST ratio: This ratio is characteristically elevated in alcoholic liver disease. Abstinence from alcohol improves this ratio. It is also seen to be high in Wilson's disease.

Falsely low aminotransferase levels: They have been seen in patients on long term hemodialysis probably secondary to either dialysate or pyridoxine deficiency. Low levels have also been seen in uremia.
Other enzymes tests of hepatocellular necrosis
None of these tests have proved to be useful in practice than the aminotransferases. These include glutamate dehydrogenase, isocitrate dehydrogenase, lactate dehydrogenase and sorbitol dehydrogenase.

Alkaline Phosphatase

Enzymes that detect cholestasis

Alkaline phosphatases are a family of zinc metaloenzymes, with a serine at the active center; they release inorganic phosphate from various organic orthophosphates and are present in nearly all tissues. In liver, alkaline phosphatase is found histochemically in the microvilli of bile canaliculi and on the sinusoidal surface of hepatocytes. Alkaline phosphatase from the liver, bone and kidney are thought to be from the same gene but that from intestine and placenta are derived from different genes.5 Approach to elevated alkaline phosphatase is given in Fig. 3.
In liver two distinct forms of alkaline phosphatase are also found but their precise roles are unknown. In healthy people most circulating alkaline phosphatase originates from liver or bone.17
The internationally recommended reference method uses p- nitro-phenol phosphate as substrate, in al alkaline buffer. Fresh unhemolysed serum is the specimen of choice for the estimation. Heparinized plasma may also be used. The test should not be done on plasma if citrate, oxalate or EDTA were used as anticoagulants; they form a complex with zinc and the alkaline phosphatase, causing irreversible enzyme inactivation.
Average values of alkaline phosphatase vary with age and are relatively high in childhood and puberty and lower in middle age and higher again in old age. Males usually have higher values as compared to females. The levels correlate

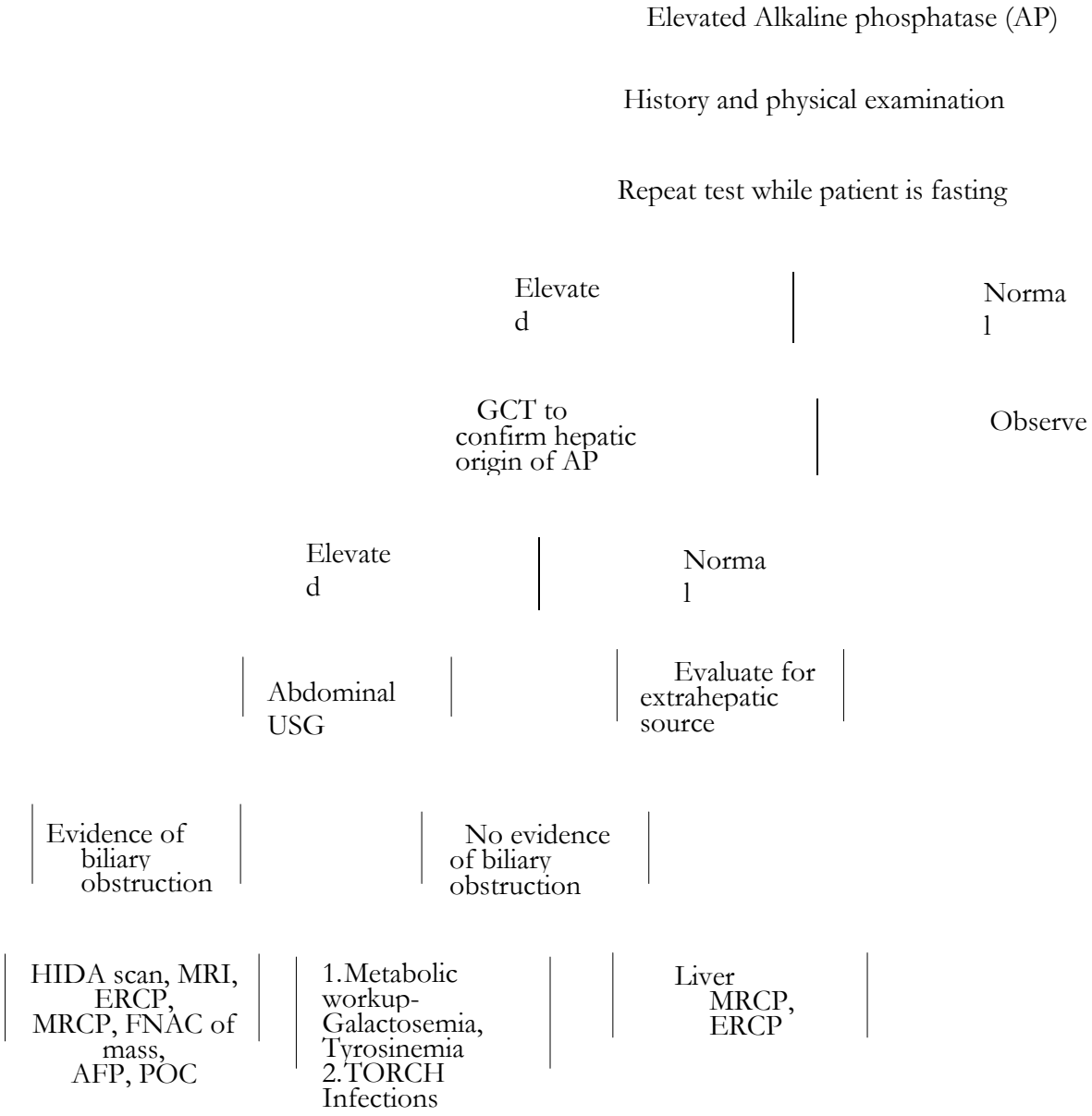
with person's weight and inversely with the height of person.
Not uncommonly isolated elevated levels of alkaline phosphatase in otherwise healthy persons return to normal on follow up.

Highest levels of alkaline phosphatase occur in cholestatic disorders. Elevations occur as a result of both intra-hepatic and extrahepatic obstruction to bile flow and the degree of elevation does not help to distinguish between the two. Alkaline phosphatase levels are likely to be very high in EHBA.
The mechanism by which alkaline phosphatase reaches the circulation is uncertain; leakage from the bile canaliculi into hepatic sinusoids may result from leaky tight junctions. and the other hypothesis is that the damaged liver fails to excrete alkaline phosphatase made in bone, intestine and liver..
In acute viral hepatitis, alkaline phosphatase is usually either normal or moderately increased. Hepatitis A may present a cholestatic picture with marked and prolonged itching and elevation of alkaline phosphatase. Tumours may secrete alkaline phosphatase into plasma and there are tumour specific isoenzymes such as Regan, Nagao and Kasahara isoenzymes.

Elevated serum levels of intestinal alkaline phosphatase have been found in patients with cirrhosis, particularly those with blood group type O, and may be associated specifically with intra-hepatic disease as opposed to extrahepatic obstruction.
Hepatic and bony metastasis can also cause elevated levels of alkaline phosphatase. Other diseases like infiltrative liver diseases, abscesses, granulomatous liver disease and amyloidosis may also cause a rise in alkaline phosphatase. Mildly elevated levels of alkaline phosphatase may be seen in cirrhosis and hepatitis of congestive cardiac failure.

Low levels of alkaline phosphatase occur in hypothyroidism, pernicious anemia, zinc deficiency and congenital hypophosphatasia. Wilson's disease complicated by hemolysis and FHF may also have very low levels of alkaline phosphatase. Ratio of alkaline phosphatase and bilirubin is low in fulminant Wilson disease. This might be the result of replacement of cofactor zinc by copper and subsequent inactivation of alkaline phosphatase. Regardless of the cause of acute hepatic failure a low ratio of alkaline phosphatase to bilirubin is associated with a poor prognosis.
Drugs like cimetidine, frusemide, phenobarbitone and phenytoin may increase levels of alkaline phosphatase.

Fig. 3. Algorithm to evaluate Marked Rise of Alkaline Phosphatase



g Glutamyl Transpeptidase

g Glutamyl transpeptidase(GGT) is a membrane bound glycoprotein which catalyses the transfer of g glutamyl group to other peptides, amino acids and water.
Large amounts are found in the kidneys, pancreas, liver, intestine and prostate. The gene for g glutamyl transpeptidase is on chromosome 22. The levels of ã glutamyl transpeptidase are high in neonates and infants up to 1 yr and also increase after 60 yr of life. Men have higher values. Children more than 4 yr old have serum values of normal adults. The normal range is 0-30IU/L
In acute viral hepatitis the levels of g glutamyl transpeptidase may reach its peak in the second or third wk of illness and in some patients they remain elevated for 6 weeks. In EHBA GGT is markedly elevated.
Often clinicians are faced with a dilemma when they see elevated alkaline phosphatase levels and are unable to differentiate between liver diseases and bony disorders and in such situations measurement of g glutamyl transferase helps as it is raised only in cholestatic disorders and not in bone diseases.
In liver disease g glutamyl transpeptidase activity correlates well with alkaline phosphatase levels but rarely the g glutamyl transpeptidase levels may be normal in intra hepatic cholestasis like in some familial intra-hepatic cholestasis.
Other conditions causing elevated levels of g glutamyl transpeptidase include uncomplicated diabetes mellitus, acute pancreatitis and myocardial infarction. Drugs like phenobarbitone, phenytoin, paracetamol, tricyclic antidepressants may increase the levels of g glutamyl transpeptidase.
Non-hepatic causes of increased levels of the enzyme include anorexia nervosa, Gullian barre syndrome, hyperthyroidism, obesity and dystrophica myotonica..
As a diagnostic test the primary usefulness of g glutamyl transpeptidase is limited to the exclusion of bone disease, as g glutamyl transpeptidase is not found in bone.
These are the other enzymes that are not routinely estimated to

detect cholestasis.
5 Nucleotidase
Leucine aminopeptidase.

Serum Proteins

Tests of the Liver's biosynthetic capacity

The liver is the major source of most the serum proteins. The parenchymal cells are responsible for synthesis of albumin, fibrinogen and other coagulation factors and most of the a and b globulins.

Albumin: Albumin is quantitatively the most important protein in plasma synthesized by the liver and is a useful indicator of hepatic function. Because the half life of albumin in serum is as long as 20 days, the serum albumin level is not a reliable indicator of hepatic protein synthesis in acute liver disease. Albumin synthesis is affected not only in liver disease but also by nutritional status, hormonal balance and osmotic pressure. Liver is the only site of synthesis of albumin.
The serum levels are typically depressed in patients with cirrhosis and ascites. In patients with or without ascites, the serum albumin level correlates with prognosis. In addition the rate of albumin synthesis has been shown to correlate with the Child- Turcotte or Child- Pugh score.
Normal serum values range from 3.5g/dl to 4.5 g/dl. The average adult has approximately 300 to 500 g of albumin. The serum levels at any time reflect its rate of synthesis, degradation and volume of distribution.
Corticosteroids and thyroid hormone stimulate albumin synthesis by increasing the concentration of albumin mRNA and tRNA in hepatocytes.
The serum albumin levels tend to be normal in diseases like acute viral hepatitis, drug related hepatotoxicity and obstructive jaundice. Albumin levels below 3g/dl in hepatitis should raise the suspicion of chronic liver disease like cirrhosis which usually reflects decreased

albumin synthesis. In ascites there may be normal synthesis but the levels may appear reduced because of increased volume of distribution.
Hypoalbuminemia is not specific for liver disease and may occur in protein malnutrition, nephrotic syndrome and chronic protein losing enteropathies.

Prealbumin
The serum prealbumin level is 0.2- 0.3 g/L. these levels fall in liver disease presumably due to reduced synthesis. Because of its short half life, changes may precede alteration in serum albumin. Determination of prealbumin has been considered particularly useful in drug-induced hepatotoxicity.

Serum Ceruloplasmin
Normal plasma levels are 0.2-0.4g/L. It is synthesized in the liver and is an acute phase protein. The plasma concentration rises in infections, rheumatoid arthritis, pregnancy, non Wilson liver disease and obstructive jaundice.
This is an important diagnostic marker in Wilson disease, in which the plasma level is usually low. Low levels may also be seen in neonates, Menke's disease, kwashiorkor, marasmus, protein losing enteropathy, copper deficiency and aceruloplasminemia.
Procollagen III Peptide
The serum concentration of this peptide appears to increase not only with hepatic fibrosis but also with inflammation and necrosis. Serial measurement of procollagen III may be helpful in the follow up of chronic liver disease.
alpha 1 Antitrypsin
a 1 antitrypsin is a glycoprotein synthesized by the liver and is an inhibitor of serine proteinases, especially elastase. Its normal concentration is 1- 1.6g/L. it is an acute phase protein, serum levels increase with inflammatory disorders, pregnancy and after oral contraceptive pills (OCP).
The various alleles coded are M,F,S,Z and null forms. PiZZ homozygotes are associated with neonatal hepatitis. Cirrhosis in

adults has been found with ZZ, MZ, SZ and FZ phenotypes.
Liver disease is usually seen with deficiency of a 1 antitrypsin, an inherited disorder. Deficiency should be confirmed by quantitative measurement.

alpha Feto Protein

This protein, the principal one in fetal plasma in early gestation is subsequently present at very low levels. (<25mg/L) It is increased in hepatocellular carcinoma (HCC)and more than 90% of such patients have raised levels. Raised values are also found in other liver diseases like chronic hepatitis, in regeneration phase of acute hepatitis and in hepatic metastasis. This is also raised in adenomas associated with tyropsinemia.
alpha feto protein elevation is less frequent when HCC arises in non cirrhotic liver. Serial determination is of value in cirrhotic patients and rise in the values should raise the suspicion of HCC.

Prothrombin Time (PT)

Clotting is the end result of a complex series of enzymatic reactions that involve at least 13 factors. The liver is the major site of synthesis of 11 blood coagulation proteins: fibrinogen, prothrombin, labile factor, stable factor, christmas factor, stuart power factor, prekallikrein and high molecular wt kininogen.
Most of these are present in excess and abnormalities of coagulation only result when there is substantial impairment in the ability of the liver to synthesize these factors.
The standard method to assess is the one stage prothrombin time of quick, which evaluate the extrinsic coagulation pathway.
The results of this test may be expressed in sec or as a ratio of the plasma prothrombin time to control plasma time. Normal control usually is in the range of 9-11 seconds. A prolongation of more than 2 seconds is considered abnormal.
The prolonged PT is not specific for liver diseases and is seen in various deficiencies of coagulation factors, DIC, and ingestion of certain drugs.
In acute and chronic hepatocellular disease the PT may serve as a prognostic indicator. In acute hepatocellular disease worsening of PT

suggests an increased likelihood of acute hepatic failure. The PT is a predictor of outcome in cases of acetaminophen over dosage and acute alcoholic hepatitis. Prolongation of PT is also suggestive of poor long-term outcome in chronic liver disease.
If the PT returns to normal or improves by at least 30% within 24 hr of a single parenteral injection of vitamin K1 (5-10 mg), it may be surmised that parenchymal function is good and that hypo-vitaminosis K was responsible for the original prolongation of PT. Patients with parenchymal disease by contrast will show only minimal improvement. Most patients with extra hepatic obstruction like EHBA would respond promptly to a single injection of vitamin K1.
The PT is particularly important in the management of patients with liver disease. It is important to perform before procedures like liver biopsy and kidney biopsy and it permits an assessment of the tendency to bleed. In many centers the International normalized ratio (INR) is done in place of PT.
To assess the severity of liver disease the Child Pugh scoring was in use and proved very good to predict the outcome of the disease. Now with the upsurge of liver transplantation the model for end stage liver disease (MELD) and pediatric end stage liver disease (PELD) scoring system is being followed to prioritize the transplant surgery.
Because of the shortcomings of the biochemical liver function tests, the quantitative function tests are used and are shown to be very sensitive but their utility in pediatric age group is limited
A single liver function test is of little value in screening for liver disease as many serious liver diseases may be associated with normal levels and abnormal levels might be found in asymptomatic healthy individuals. The use of battery of liver function tests, however constitutes a highly sensitive procedure. The number of false negatives must be reduced by this technique. The use of battery of liver tests is also associated with high specificity especially when more than one test is abnormal. The pattern of enzyme abnormality, interpreted inthe context of the patient's characteristics, can aid in directing the subsequent diagnostic work-up. Awareness of the prevalence of determined liver disease in specific populations and of

possible hepatic involvement during systemic illnesses or drug therapies may help the clinician identify the cause of alterations efficiently.

Interpreting abnormal liver function tests

Interpreting abnormal liver function tests and trying to diagnose any underlying liver disease is a common scenario in Primary Care. Abnormal liver function tests may be asymptomatic, and are often inadequately investigated - which may miss an early opportunity of identifying and treating chronic liver disease.[1]The primary problem may be the liver, or the abnormal results can be secondary to other problems elsewhere in the body.

Alternatively there may be nothing wrong with the liver at all! Traditionally 'normal' values are defined as being within ± 2 standard deviations meaning that 2.5% of a healthy population will have liver function tests outside the normal range. However, as liver disease is frequently asymptomatic, such a 'healthy' population may have significant numbers of people with undiagnosed liver disease, and thus this argument should not be used as an excuse for inadequate investigation.

Common liver investigations

Liver function tests (LFTs) are readily available and are often included as a baseline investigation for a large number of different presentations. They usually consist of:

- Bilirubin:
    - Bilirubin is derived from the breakdown of heme in the red blood cells within the reticuloendothelial system.
    - The unconjugated bilirubin then binds albumin and is taken up by the liver.
    - In the liver it is conjugated which then makes it water soluble and thus allows it to be excreted into the urine.

    - Normally total serum bilirubin is measured; however the unconjugated and conjugated portions can be determined by measures of the fractions of indirect bilirubin and direct bilirubin respectively.
- Albumin - sensitive marker of hepatic function, but not useful in the acute stages as has a long half life (20 days).
- Total Protein
- Transferase - usually *either* Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST), rarely does a laboratory routinely provide both:
    - These enzymes normally reside inside cells (in cytoplasm) so raised levels usually represent hepatocellular damage. ALT is more specific to the liver, as AST is also found in cardiac and skeletal muscle and red blood cells.
    - Very high levels (>1000 IU/l) suggest drug induced hepatitis (e.g. paracetamol), acute viral hepatitis (A or B) , ischemic or rarely autoimmune hepatitis.
    - The ratio of AST to ALT can give some extra clues as to the cause:
      In chronic liver disease ALT > AST, once cirrhosis established AST > ALT. The extremes of the ratio of AST: ALT can also be helpful: >2 suggests alcoholic liver disease, and a ratio of <1.0 suggests non-alcoholic liver disease.
- Gamma-glutamyl transferase (GGT) - also related to the bile ducts. Typically elevated in cholestasis (with elevated ALP), but if ALP normal suggests induction of hepatic metabolic enzymes (e.g. alcohol or enzyme inducing drugs).
- Alkaline phosphatase (ALP) - comes mainly from the cells lining bile ducts but also in bone. Marked elevation is typical of cholestasis (often with elevated GGT) or bone disorders (usually normal GGT). Isoenzymes analysis may help identify source. It is physiologically increased when there is increased bone turnover (e.g. adolescence) and is elevated in the third trimester (produced by the placenta).

When basic liver function tests are abnormal, ensure a full history and examination is performed.

History and examination of a patient with abnormal LFTs

Full history - Include:

- Recent travel
- Transfusions
- Drugs including paracetamol overdose and herbal remedies
- Tattoos
- Unprotected sexual intercourse
- Drug history (including herbal remedies)
- Alcohol
- Occupation
- Diabetes Mellitus, obesity, hyperlipidemia (all associated with fatty liver disease)
- Family history

Full examination - Look especially for:

- Stigmata of chronic liver disease e.g. icteric skin and mucous membranes, palmar erythema, bruising, spider naevi, gynaecomastia.
- Hepatomegaly
- Splenomegaly
- Ascites
- Obesity (associated with a fatty liver).
- Any clues to underlying cause e.g. lymphadenopathy
- Features suggestive of hepatic encephalopathy

Further tests will also be needed to try to find out the underlying cause:

- The other transaminase - i.e. ensure you have both ALT and AST results. The ratio of AST to ALT may be useful for

distinguishing fatty liver due to alcoholic and non-alcoholic etiologies.
- Prothrombin (INR) - sensitive marker of hepatic synthetic function
- Viral serology e.g. hepatitis B and C, CMV, EBV and possibly HIV
- Autoantibody screen e.g. anti-mitochondrial antibody, anti-smooth muscle antibody and anti-nuclear antibody
- Immunoglobulins (if not available, raised immunoglobulins may be suggested by a raised globulin fraction (total protein minus albumin))
- Serum ferritin and transferrin saturation
- α fetoprotein
- Copper / ceruloplasmin
- α 1 antitrypsin

Imaging: ultrasound is non-invasive and helpful to detect structural abnormalities.

How to approach abnormal liver function tests

Consider drug toxicity in all cases**.**

Once results are obtained determine which of the following scenarios they fit in to:

- **Rise in bilirubin alone** - need to know if unconjugated hyperbilirubinemia or conjugated hyperbilirubinemia. Usually due to defects of hepatic excretion. It can be detected by measuring the direct bilirubin component of the total bilirubin (> 50% confirms the presence of conjugated hyperbilirubinemia).

  Unconjugated -

  - Haemolysis - Check reticulocyte count, blood film, haptoglobins, LDH and may need direct Coomb's test.

- Drugs
- Gilbert's syndrome
- Crigler-Najjar syndrome

Conjugated -

- Dubin-Johnson syndrome
- Rotor syndrome
- Chronic liver disease, (usually associated with other liver function test abnormalities)

- **Obstructive picture or cholestasis** - rise in ALP and GGT more than AST and ALT. This may be intra-hepatic or extrahepatic (bilirubin will also be raised).
  - *Intrahepatic* -
    - primary biliary cirrhosis
    - drugs
  - *Extrahepatic* -
    - Gallstone in common bile duct
    - Head of pancreas neoplasm
    - Drugs e.g. erythromycin, tricyclic antidepressants, flucloxacillin, oral contraceptive pill and anabolic steroids
    - Cardiac failure - improves with treatment
    - Primary biliary cirrhosis - commoner in women and first sign is a rise in ALP
    - Primary sclerosing cholangitis
    - Neoplasm - primary (rarely) and secondaries
    - Familial (benign)
- **Hepatitic picture** Rise in AST and ALT more than ALP and GGT:
  - Alcohol - fatty infiltration and acute alcoholic hepatitis (usually associated with markedly deranged liver function).
  - Cirrhosis of any cause - alcohol being one of the commonest.

- Medications e.g. Phenytoin, carbamazepine, isoniazid, statins, methotrexate, paracetamol overdose, amiodarone. (Transaminase may be >1000 IU/l).
- Chronic hepatitis B and C.
- Acute viral hepatitis e.g. hepatitis A, B and C and CMV infection.
- Autoimmune hepatitis.
- Neoplasms - primary or secondaries.
- Haemochromatosis.
- Metabolic - Glycogen storage disorders, Wilson's disease.
- Ischaemic liver injury e.g. severe hypotension
- Fatty liver disease (mild elevation in transaminases <100 IU/l).
- Non-hepatic causes: Coeliac disease, haemolysis and hyperthyroidism.

- **Isolated rise in individual enzymes** e.g. ALP and GGT:
  - Isolated rise in GGT:
    - This is most commonly due to alcohol abuse, or enzyme inducing drugs.
    - An isolated rise can occur even if no major liver disease.
    - The rise is not related to the amount of alcohol intake.
    - Also many heavy alcohol users may have normal GGT.
    - Stopping alcohol for 4 weeks should rectify the abnormality.
  - Isolated rise in ALP:
    - Third trimester of pregnancy (comes from the placenta - a normal finding)
    - If isolated rise in ALP consider other sources e.g. bone or kidney
      In the elderly consider:
      - Fractures
      - Paget's disease of bone
      - Osteomalacia

- Bony metastases

ALP is not usually raised in myeloma or osteoporosis (without a fracture).

Occasionally the liver enzymes e.g. ALP, GGT, AST or ALT may all be similarly elevated making it difficult to determine whether it is a cholestatic or hepatitic picture.

Management plan

Any liver abnormalities with evidence of hepatic dysfunction e.g. low albumin, raised INR should be referred to a specialist.

1. *If slightly abnormal rise in liver function tests (i.e. less than twice upper limit of normal):*
    - Repeat liver function tests in 6 months time.
    - If you suspect the cause to be alcohol related then inform the patient and ask them to abstain and repeat the tests.
    - Other lifestyle changes may help e.g. good Diabetic control and weight loss.
    - If still abnormal perform further tests e.g. viral serology or ultrasonography.
    - If remain abnormal for longer than six months then consider referral to a specialist.
    - If the patient is unwell despite slightly abnormal LFT's then they may need to be referred more urgently.
2. *Very abnormal liver function tests (i.e. more than twice upper limit of abnormal):*
    - Organise further blood tests and imaging.
    - Refer to out-patients - if you suspect the cause may be malignancy then an urgent cancer referral should be made.

Consider urgent referral for hospital admission if patient unwell, for example

- Severe jaundice

- Severe ascites
- Encephalopathy
- Septic

Otherwise out-patient referrals for anyone less ill if indicated - but try to determine cause.