

PART 1

HEPATOLOGY

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Approach to the Patient with Abnormal Liver Tests

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OVERALL BOTTOM LINE

- A detailed medical history is the single most important step in the evaluation of a patient with abnormal liver tests.
- Evaluation of liver enzyme elevation can be categorized into hepatocellular injury, cholestatic injury, or mixed injury based on patterns of relative elevation of different liver enzymes.
- Serum chemistries which are used to diagnose liver disease can be divided into laboratories which evaluate liver function (INR, albumin), those which primarily evaluate integrity of hepatocytes (AST, ALT) and those which predominantly assess abnormalities of bile ducts and bile flow (bilirubin, AP, GGT).
- The differential diagnosis of abnormal liver tests is broad and includes infectious (viral hepatitis), metabolic (NAFLD, Wilson disease, hemochromatosis, alpha-1 antitrypsin deficiency), toxin- and drug-induced (alcohol, herbal products), immunologic (autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, overlap syndromes), infiltrative, vascular and neoplastic diseases.
- Non-hepatic causes of elevated liver enzymes, such as congestive hepatopathy, shock liver, muscle diseases, thyroid disorders, celiac disease, or adrenal insufficiency must be excluded.

Section 1: Background

Definition of disease

Tests which are used to assess for liver injury and liver function

| | Normal function | Significance of abnormal value |
|-------------------------------|---|---|
| Tests of liver injury: | | |
| ALT, formerly SGOT | Catalyzes transfer of amino groups of alanine | Elevated in: <ul style="list-style-type: none">• Hepatocellular injury |
| AST, formerly SGPT | Catalyzes transfer of amino groups of L-aspartic acid | Elevated in: <ul style="list-style-type: none">• Hepatocellular injury• Myocyte injury (rhabdomyolysis, exercise, myocardial infarction) |

(Continued)

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| | Normal function | Significance of abnormal value |
|---------------------------------|--|--|
| AP | Enzyme found on canalicular membrane of hepatocytes, function unknown. Also found in bone, small intestine, placenta | Elevated in: <ul style="list-style-type: none">• Cholestatic liver disease of various etiology (biliary obstruction, biliary injury, drug induced)• Infiltrative diseases of the liver (sarcoidosis, amyloidosis)• Neoplastic diseases of the liver• Congestive hepatopathy• Bone disorders, normal bone growth, pregnancy |
| GGT | Found in cell membranes of many tissues (liver, kidney, pancreas, spleen) | Sensitive but non-specific indicator of hepatobiliary injury. An elevated GGT is not specific for alcohol use. Clinical utility is in differentiating origin of AP elevation (GGT elevated in liver disease, normal in bone disease) |
| Tests of liver function: | | |
| Total bilirubin | Normal breakdown product of heme | Elevated in biliary obstruction, disorders of bilirubin metabolism, hepatitis, cirrhosis and acute liver failure |
| Indirect bilirubin | Unconjugated form of bilirubin which is insoluble in plasma and converted to excretable conjugated form by hepatocytes | Elevated in: <ul style="list-style-type: none">• Increased heme breakdown (i.e. hemolysis)• Inherited disorders of bilirubin metabolism (Gilbert's disease) |
| Direct bilirubin | Conjugated form of bilirubin which is excreted by hepatocytes across canalicular membrane into bile | Elevated in: <ul style="list-style-type: none">• Obstruction of bile ducts• Impaired hepatocyte function (chronic liver disease, cirrhosis, liver failure)• Genetic syndromes (Rotor syndrome, Dubin-Johnson syndrome) |
| PT | Measurement of clotting time | Elevated in disease states causing impaired liver function and decreased hepatic production of clotting proteins (cirrhosis, acute liver failure) |
| Albumin | Protein synthesized by hepatocytes | Decreased in hepatocellular dysfunction/chronic liver disease |

- ALT and AST are enzymes found in hepatocytes. High serum levels reflect hepatocellular injury. AST is found in other cells including in the heart, skeletal muscle, brain and other organs. In contrast, ALT is found mostly in liver which makes it a more specific marker of liver injury compared with AST. Revised upper limits of ALT have been proposed (30 IU/L for men and 19 IU/L for women) after excluding individuals with probable NASH and hepatitis C from the “normal” population used to determine range limits.

- Normal ALT serum levels have a high negative predictive value (>90%) in excluding a clinically significant liver disease.
- GGT is present in decreasing quantities in the kidneys, liver, pancreas and intestine. It is a sensitive indicator of hepatobiliary disease, but lacks specificity. GGT levels are increased in cholestatic liver diseases, NAFLD, space-occupying liver lesions and venous hepatic congestion. GGT may be induced by many drugs and alcohol.
 - GGT is not a marker of alcoholic liver disease.
 - ▶ Decreasing enzyme activities during abstinence from alcohol are diagnostically more helpful than the presence of an elevated GGT per se.
 - Normal GGT levels have a high negative predictive value (>90%) in excluding hepatobiliary disease.
 - An isolated elevation of GGT should not lead to an exhaustive work-up for liver disease.
- Liver AP is a sensitive indicator of cholestasis of various etiologies, but AP does not discriminate between intra- and extrahepatic cholestasis. Elevation in 5'-nucleotidase, GGT and liver isoenzyme fractionation of AP can be used to confirm hepatic origin of AP.
- Mild elevations of serum AP levels may be found in viral hepatitis, drug induced, granulomatous and neoplastic liver disease.
- Bilirubin is formed from breakdown of heme. It is carried bound to albumin to hepatocytes where UGT1A1 (bilirubin-UDP-glucuronosyltransferase) conjugates bilirubin. The conjugated bilirubin is then exported through a transporter into bile canaliculi and excreted through bile ducts. Transport of bilirubin through the canalicular membrane into the canaliculus is the rate limiting step ("bottle neck") of bilirubin excretion. Causes of hyperbilirubinemia include excess heme breakdown, disorders of conjugation and bilirubin transport, hepatocellular damage and obstruction of bile ducts.
 - Increases in conjugated bilirubin are highly specific for hepatobiliary disease.

Disease classification

| Enzyme patterns of liver injury | |
|--|---------------------------|
| Enzyme pattern | ALT:AP ratio ^a |
| Hepatocellular | ≥5 |
| Cholestatic | ≤2 |
| Mixed | >2 to <5 |
| ^a All enzymes expressed as multiples of ULN | |

Etiology

See "Definition of disease."

Pathology/pathogenesis

See "Definition of disease."

Section 2: Prevention

Not applicable for this topic.

Section 3: Diagnosis

BOTTOM LINE/CLINICAL PEARLS

- A detailed history is the key to the correct interpretation of abnormal liver tests. History taking should include information including alcohol use, recent use of acetaminophen, herbal products or other medications, and risk factors for viral hepatitis transmission.
- Physical examination should include assessment for jaundice and encephalopathy which can indicate acute liver failure in a patient with no prior history of underlying liver disease. Stigmata of cirrhosis (spider angiomas, ascites, muscle wasting, Dupuytren's contracture, splenomegaly) should be noted on physical examination.
- Elevated INR and bilirubin in a patient with encephalopathy and no underlying liver disease indicates acute liver failure and should prompt consideration of referral to a transplant center.
- Further laboratory investigations and imaging to diagnose the cause of elevated liver tests should be driven by clinical history and the pattern of liver test elevation (see Table: Enzyme patterns of liver injury and algorithms shown in Algorithm 1.1 and Algorithm 1.2).

- Viral and metabolic causes (i.e. hemochromatosis and Wilson disease) can be diagnosed with confirmatory laboratory tests. However, alcoholic liver disease, NASH and DILI rely on careful history taking and clinical diagnosis. Herbal preparations can be overlooked as a cause of hepatotoxicity unless an accurate history is obtained. Causes of elevated tests that are unique to pregnancy are discussed at the end of the chapter and in a separate chapter.

Hepatocellular/mixed elevation of liver tests

- The diagnostic approach to aminotransferase or mixed aminotransferase/cholestatic liver test elevation is shown in Algorithm 1.1 and selection of testing is largely driven by the clinical presentation and the degree of AST and ALT elevation. Aminotransferase elevation above 10 times the ULN reflects severe acute injury and is observed in shock liver, toxic- or drug-induced injury, acetaminophen toxicity, and acute viral hepatitis A, B (\pm D) and E. A detailed history eliciting recent toxin or drug exposure, or a recent period of hypotension is important in making the diagnosis. An acetaminophen level may be helpful for confirmation of suspected acetaminophen injury.
- Acute liver injury in the setting of suspected recent viral hepatitis exposure (hepatitis B, C and A) should prompt specific testing (HBV core IgM, HBV DNA, HCV RNA, hepatitis A IgM) due to absence of antibodies in the window phase of acute infection. Failure to send the proper tests can result in a missed or delayed diagnosis.
- Lesser degrees (up to $5 \times$ ULN) of aminotransferase elevation can be caused by chronic viral hepatitis, alcoholic hepatitis, autoimmune hepatitis, Wilson disease, hemochromatosis, Budd–Chiari syndrome, and infiltrative diseases. Serologic testing is available for autoimmune hepatitis, Wilson disease, hemochromatosis and alpha-1 antitrypsin deficiency whereas diagnosis of alcoholic hepatitis, NASH and drug-induced liver injury relies on careful history taking.
- Alcoholic hepatitis often causes elevations of AST and ALT in a 2:1 ratio. This is because patients with alcoholic liver disease are deficient in pyridoxal 5'-phosphate, which is required for synthesis of ALT more so than AST. Additional features of alcoholic hepatitis include leukocytosis, fever and jaundice.
- NASH, the most common cause of abnormal liver tests in the developed world, is diagnosed after excluding other causes of elevated liver tests and after taking a history to exclude excess

alcohol use (20 g/day in women, 40 g/day in men). Diagnosis is supported by a history of metabolic syndrome and can be confirmed with liver biopsy and/or imaging demonstrating steatosis. Cirrhosis in the absence of steatosis can develop as a late complication of NASH.

- DILI is diagnosed based on a history of exposure and after excluding other causes of liver enzyme elevation. Often the diagnosis is made by observing normalization of liver tests after discontinuation of a drug. A liver biopsy may be helpful in certain instances of specific pathologic findings seen with certain drugs (i.e. pseudoalcoholic hepatitis with amiodarone, sinusoidal obstructive syndrome with chemotherapeutic agents, nodular regenerative hyperplasia with azathioprine).
- Budd–Chiari syndrome, primary and secondary malignancies, and infiltrative diseases such as amyloidosis can cause elevated liver tests and are diagnosed through imaging and/or liver biopsy. Sarcoidosis may cause liver enlargement and is associated with AP elevation; diagnosis is confirmed with a liver biopsy demonstrating non-caseating granulomas.

| Laboratory features of selected conditions leading to elevated liver enzymes | |
|--|--|
| Differential diagnosis | Features |
| Shock liver | AST and ALT in the thousands range, peak rise 2–3 days following hypotensive injury, prompt decline after restoration of blood flow |
| Alcoholic hepatitis | AST:ALT ratio > 2:1, jaundice, elevated GGT, leukocytosis |
| NASH | ALT > AST, elevated GGT, history of obesity or metabolic syndrome, alcohol intake < 20–40 g/day |
| Wilson disease | AP disproportionately low compared with other liver tests, AST:ALT ratio > 4:1 (fulminant Wilson disease), unconjugated hyperbilirubinemia/hemolysis |
| Acute liver failure from HSV | Bilirubin disproportionately normal compared with other liver tests |

Cholestatic elevation of liver tests

- AP, a canalicular enzyme, and GGT, found in hepatocytes and biliary epithelial cells, are elevated in instances of biliary obstruction and hepatocellular injury and can help distinguish liver-related causes of hyperbilirubinemia from non-liver related causes.
- The diagnostic approach to hyperbilirubinemia starts with assessing whether the conjugated (direct) or unconjugated (indirect) form of bilirubin predominates. Causes of predominantly unconjugated hyperbilirubinemia are hemolysis, disorders of bilirubin metabolism and drug-induced impairment of conjugation and transport. Isolated indirect hyperbilirubinemia in the absence of aminotransferase or AP elevation should prompt an investigation for hemolysis. If hemolysis is ruled out, the differential diagnosis includes drug-induced causes and Gilbert's syndrome. Gilbert's syndrome is a benign condition due to a congenital mutation in UGT1A1 and is characterized by asymptomatic isolated indirect hyperbilirubinemia. Drugs that can cause an isolated indirect hyperbilirubinemia include indinavir and atazanavir (competitively inhibit UGT1A1) and drugs such as rifampin, chloramphenicol and gentamicin which affect uptake of bilirubin by hepatocytes.
- Conjugated hyperbilirubinemia can result from obstruction of bile ducts. Abdominal imaging starting with ultrasound to assess for biliary dilation is essential. Causes of biliary obstruction include choledocholithiasis, cholangiocarcinoma and tumors involving the head of the pancreas. Imaging which shows dilated bile ducts may prompt further diagnostic studies including

ERCP or EUS (EUS is the most sensitive method in the diagnosis of common bile duct stones). Absence of biliary dilation does not rule out the presence of bile duct stone(s).

- If no biliary obstruction is seen on imaging and choledocholithiasis is excluded, PSC and PBC should be considered. PSC is diagnosed by MRCP or ERCP showing beading of intrahepatic ducts caused by periductal fibrosis. Small duct PSC may not show abnormalities on gross imaging and may require a liver biopsy for diagnosis. PBC usually affects women and is associated with positive antimitochondrial antibodies (M2) and elevated IgM levels. A liver biopsy is helpful for diagnosis and staging. Inherited causes of conjugated hyperbilirubinemia are Dubin–Johnson syndrome (caused by a mutation in the canalicular transporter of bilirubin) and Rotor syndrome. Both have a benign course and can be differentiated by liver biopsy findings.

Typical presentation

- Patients with elevated liver tests due to acute liver failure may present with jaundice, encephalopathy or non-specific symptoms such as fatigue, nausea, or abdominal pain from hepatomegaly. Prompt recognition and diagnosis of acute liver failure with timely referral to a transplant center can be lifesaving.
- In contrast to acute liver failure, most patients with chronic liver disease are asymptomatic. Abnormal laboratory results in patients with chronic liver disease are often detected after blood tests during routine visits or during investigation of unrelated symptoms. Patients with later stages of cirrhosis may present with symptoms of hepatic decompensation such as ascites, encephalopathy, variceal bleeding or jaundice.

Clinical diagnosis

History

- History should include:
 - Alcohol use.
 - Recent use of medications, including herbal products.
 - Family history of liver disease (hemochromatosis, Wilson disease, alpha-1 antitrypsin deficiency).
 - Duration of jaundice (new onset jaundice in a patient with no underlying liver disease suggests acute liver failure).
 - Risk factors for viral hepatitis transmission (needle drug use, unprotected intercourse, tattoos, blood transfusions, hemodialysis).

Physical examination

Pertinent components of physical examination assessment include:

- Neurologic examination to assess for asterix and/or encephalopathy (acute liver failure), stigmata of cirrhosis (spider angiomas, splenomegaly, ascites, muscle wasting).
- Presence of ascites (Budd–Chiari syndrome, cirrhosis).

Laboratory diagnosis

List of diagnostic tests

- Specific further tests which can aid in diagnosis:
 - Acetaminophen toxicity – acetaminophen level.
 - Hepatitis B – hepatitis B surface antigen, HBV DNA, HBV core IgM (acute infection and some cases of reactivation).

- Hepatitis C – HCV antibody, HCV RNA.
- Hepatitis A – hepatitis A IgM (positive in acute infection).
- Hepatitis Delta – hepatitis Delta antibody (in a patient with underlying hepatitis B).
- Hepatitis E – hepatitis E antibody (travel to endemic areas, pregnancy, immunosuppression).
- Autoimmune hepatitis – ANA, ASMA, anti-LKM, SLA/LP, IgG.
- PBC – AMA (M2), IgM.
- Wilson disease – ceruloplasmin, 24 hour urine copper, slit lamp examination to assess for Kayser–Fleischer rings.
- Hemochromatosis – iron studies, HFE gene mutation analysis (C282Y, H63D).
- Alpha-1 antitrypsin deficiency – alpha-1 antitrypsin phenotype
- A liver biopsy may be useful in making or confirming a diagnosis of autoimmune hepatitis, PBC, small duct PSC, Wilson disease, drug-induced liver injury, and alcoholic/non-alcoholic steatohepatitis. Infiltrative diseases such as sarcoidosis, amyloidosis and lymphoma may require liver biopsy for diagnosis.

List of imaging techniques

- Diagnoses which can be made by imaging:
 - Budd–Chiari syndrome – hepatic vein thrombosis on ultrasound, CT, MRI or venogram.
- PSC – MRCP (ERCP) showing beaded ducts.
- Biliary obstruction due to stones, stricture, cholangiocarcinoma, or pancreatic head neoplasm – MRI/MRCP, EUS, ERCP.
- Infiltrative diseases of the liver (sarcoidosis, malignancies) – ultrasound, CT, MRI.
- Non-alcoholic fatty liver disease – ultrasound, CT or MRI may show evidence of hepatic steatosis.

Diagnostic algorithm

See Algorithms 1.1 and 1.2 which outline the diagnostic approach to hepatocellular/mixed versus cholestatic liver test elevations.

Potential pitfalls/common errors made regarding diagnosis of disease

Errors made in evaluating patients with elevated liver enzymes

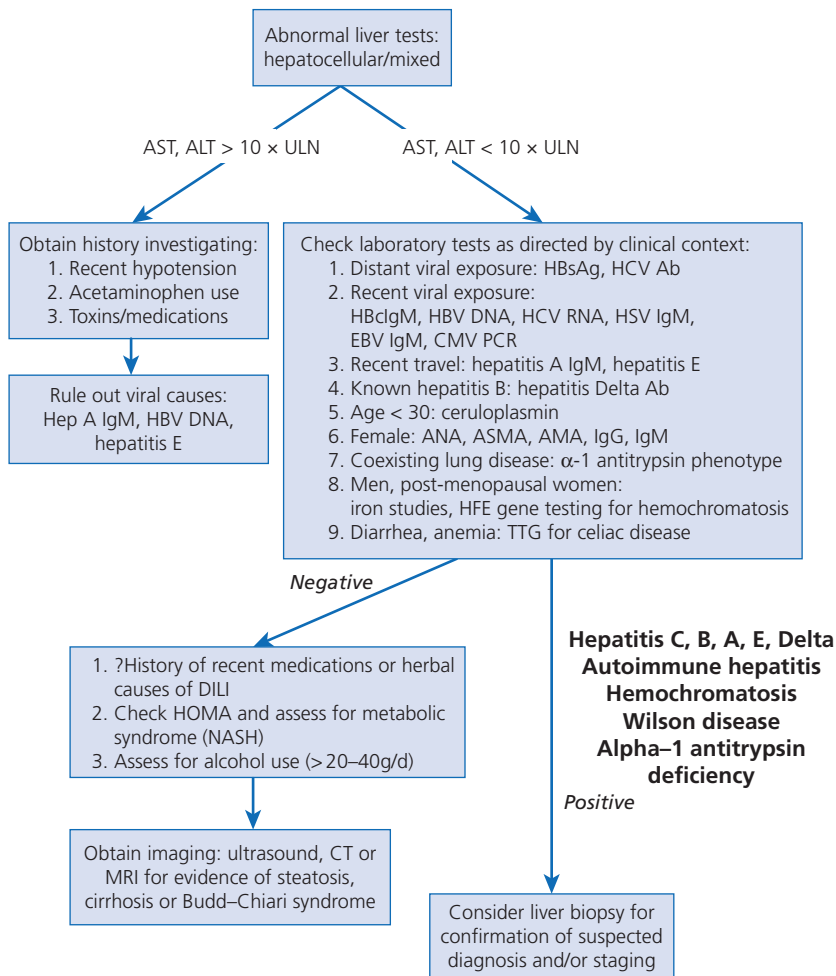
- Inadequate history.
- Haphazard use of a wide net of assorted tests instead of a directed approach guided by the history and the clinical context.
- Failure to consider extrahepatic causes for elevated liver enzymes.
 - AP can be elevated in bone diseases, celiac disease or pregnancy.
 - Isolated elevations in bilirubin (predominantly indirect) can be due to hemolysis.
 - AST can be elevated in muscle injury (as seen following strenuous exercise or in the setting of rhabdomyolysis or myocardial infarction). CK and aldolase are elevated in muscle injury.
- To initiate an exhaustive investigation for liver disease based on an isolated elevation of GGT

Section 4: Treatment

When to hospitalize

- Acute liver failure, defined as coagulopathy (INR > 1.5, encephalopathy, and new onset jaundice within 8 weeks of presentation in a patient with no underlying liver disease should prompt hospitalization and transfer to a liver transplant center.

Algorithm 1.1 Diagnostic algorithm for evaluation of hepatocellular/mixed liver enzyme elevation



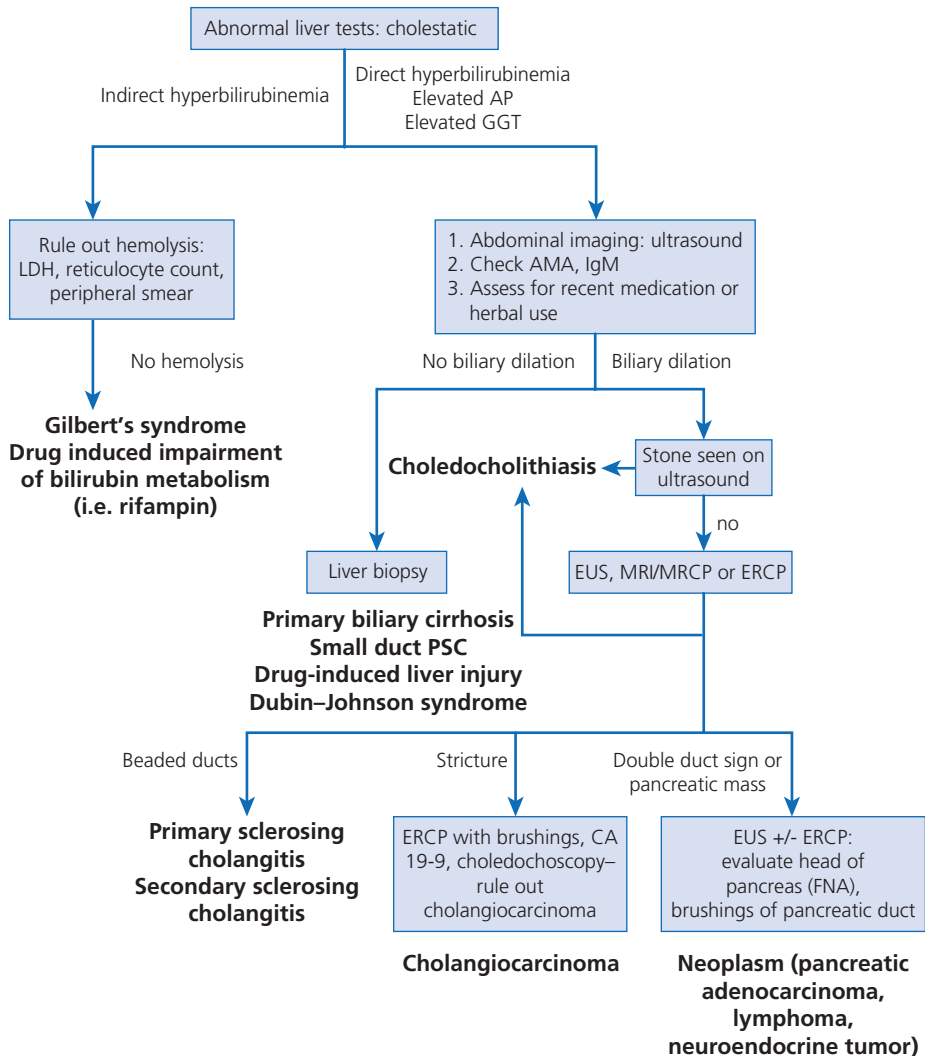
Section 5: Special Populations

Pregnancy

Abnormal liver tests during pregnancy (see also Chapter 25)

- Hyperemesis gravidarum occurs during the first trimester and is characterized by intractable vomiting along with elevated liver tests in 50% of cases. Management is supportive care including intravenous fluids to correct volume depletion.
- Intrahepatic cholestasis of pregnancy is characterized by pruritis during the second half of pregnancy. Jaundice occurs in 10–20% of cases and aminotransferase elevation can be mild to 10–20 times normal.
- Pre-eclampsia occurs during the third trimester and is diagnosed by the triad of hypertension, edema and proteinuria. Liver tests can be elevated up to 10–20-fold.

Algorithm 1.2 Diagnostic algorithm for investigation of cholestatic liver test elevation



- HELLP syndrome is defined by hemolysis, elevated liver tests and low platelets. It usually occurs in the third trimester but can also occur post-partum.
- Acute fatty liver of pregnancy occurs in the third trimester and can present as abnormal liver tests with elevated aminotransferases (up to 500 IU/L) and bilirubin (up to 5 mg/dL). Liver biopsy shows microvesicular fatty infiltration. However, coagulopathy in the setting of acute liver failure may preclude biopsy. Cases can progress to acute liver failure, therefore INR assessment is critical in timely management.

Section 6: Prognosis

Not applicable for this topic.

Section 7: Reading List

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Section 8: Guidelines
National society guidelines

| Guideline title | Guideline source | Date |
|--|---|------|
| American Gastroenterological Association Medical Position Statement: Evaluation of liver chemistry tests | American Gastroenterological Association (AGA) http://download.journals.elsevierhealth.com/pdfs/journals/0016-5085/PIIS0016508502002408.pdf | 2002 |

Section 9: Evidence

Not applicable for this topic.

Section 10: Images

Not applicable for this topic.

Additional material for this chapter can be found online at:
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This includes case studies and multiple choice questions

