

Liver and biliary tract disease

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This material covers diagnosis of most common liver and biliary tract disease and is an extension to a previous knowledge of physiology and pathophysiology of liver and gall bladder. If you are not familiar with this topic, make sure to study about liver structure and function, especially about metabolic liver functions, bilirubin metabolism, the role of liver enzymes, pathophysiology of liver failure, fibrosis and cirrhosis, first.

While there are many causes of liver disease (see the Annex at the end of this material), these disorders generally present clinically in a few distinct patterns. They are classified as *hepatocellular*, *cholestatic* (obstructive), or mixed. A diagnosis usually can be made accurately by careful elicitation of the patient's history, physical examination and application of basic laboratory tests. *Diagnostic imaging methods* also play a key role and with their improvement the need of invasive liver biopsy is reduced.

Liver diseases are an important topic to medical doctors of various specializations – if you become a general practitioner, choose to work in internal medicine or surgery, you are going to meet patients with these diseases on a daily routine. This material is an introduction to the clinically most important topics.

Diagnosis of liver disease

Laboratory tests

Bilirubin

Bilirubin, a breakdown product of heme-containing proteins, is found in blood in two fractions. *Unconjugated bilirubin* (indirect fraction) elevation is rarely due to a liver disease. It is seen primarily in hemolytic disorders and in a number of genetic conditions such as Crigler-Najjar and Gilbert's syndromes. Isolated unconjugated hyperbilirubinemia should prompt a workup for hemolysis, in the absence of hemolysis in an other-wise healthy patient it can be attributed to Gilbert's syndrome.

In contrast, *conjugated hyperbilirubinemia* (direct fraction) almost always implies liver or biliary tract disease. The rate-limiting step in bilirubin metabolism is not conjugation of bilirubin, but rather the transport of conjugated bilirubin into the bile canaliculi. Thus, elevation of the conjugated fraction may be seen in any type of liver disease including fulminant liver failure.

In most liver diseases, *both fractions of the bilirubin* tend to be elevated. Except in the presence of a purely unconjugated hyperbilirubinemia, fractionation of the bilirubin is rarely helpful in determining the cause of jaundice. Unconjugated bilirubin always binds to albumin in the serum and is not filtered by the kidney. Therefore, any bilirubin found in the urine is conjugated bilirubin; the presence of bilirubinuria implies the presence of liver disease.

Liver function tests

Serum biochemical tests (liver function tests) can be used to detect the presence of liver disease, distinguish among different types of disorders, evaluate the extent of liver damage and follow the response to treatment. Keep in mind that they lack sensitivity and specificity – they can be normal in patients with serious liver disease and abnormal in patients with disease that do not affect the liver at all. As always in medicine, you must consider the patient history and presentation when evaluating any laboratory results.

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The *aminotransferases* (transaminases) are sensitive indicators of *hepatocytes injury* and are helpful in recognizing acute hepatocellular diseases such as hepatitis. They are good indicators of hepatocellular damage, but not a good indicator of hepatic synthetic function. They include aspartate aminotransferase (AST), which is also found in many other tissues (cardiac and skeletal muscle, kidneys, brain and other) and alanin aminotransferase (ALT), which is found primarily in the liver and therefore is more specific.

The pattern of the aminotransferase elevation can be helpful diagnostically. In most acute hepatocellular disorders, the ALT is higher than or equal to the AST. Whereas the AST:ALT ratio is typically <1 in patients with chronic viral hepatitis and nonalcoholic fatty liver disease, and as cirrhosis develops, this ratio rises to >1 . An AST:ALT ratio $>2:1$ is suggestive, whereas a ratio $>3:1$ is highly suggestive, of alcoholic liver disease. A low level of ALT in the serum is due to an alcohol-induced deficiency of pyridoxal phosphate. The aminotransferases are usually not greatly elevated in obstructive jaundice. One notable exception occurs during the acute phase of biliary obstruction caused by the passage of a gallstone into the common bile duct. In this setting, the aminotransferases can briefly be extremely high. However, aminotransferase levels decrease quickly, and the biochemical tests rapidly evolve into those typical of cholestasis.

The serum elevation of *alkaline phosphatase (ALP)* and *gamma-glutamyl transpeptidase (GGT)* are associated with cholestasis, as their blood levels rise with higher pressure in biliary ducts. Isolated GGT elevation is most often associated with increased alcohol intake.

The normal serum alkaline phosphatase consists of many distinct isoenzymes (found in the liver, bone, placenta, and, less commonly, in the small intestine). Alkaline phosphatase elevations greater than four times occur primarily in patients with cholestatic liver disorders, infiltrative liver diseases such as cancer and amyloidosis, and bone conditions characterized by rapid bone turnover. To specify the source of ALP elevation, ask the laboratory to determine specific isoenzymes.

Indicators of liver metabolic function

Albumin is the most important plasmatic protein and is synthesized exclusively by hepatocytes. It has a long half-life of 18-20 days, therefore it is not a good indicator of acute or mild hepatic dysfunction. Hypoalbuminemia is more common in chronic liver disorders such as cirrhosis and reflects severe liver damage. In patients with ascites, hypoalbuminemia does not necessarily mean severe liver damage, but is caused by increased volume of albumin distribution. Hypoalbuminemia is not specific for liver disease only but can be found in protein malnutrition, nephrotic syndrome, chronic infections and other.

The blood clotting factors are, with the exception of factor VIII, all made exclusively in hepatocytes. Their serum half-lives are much shorter (6h to 5days) which makes them a single best acute measure of hepatic synthetic function. They are used in diagnosis and assessing the prognosis of acute liver disease. Most useful is the *serum prothrombin time* (routinely evaluated as *INR*, international normalized ratio), which is also measured to evaluate warfarin therapy, and therefore is available in every laboratory. It may be elevated in hepatitis and cirrhosis as well as in disorders that lead to vitamin K deficiency such as obstructive jaundice or fat malabsorption of any kind. Because of coagulopathy, patients with high INR with acute liver failure are in a high risk of bleeding, especially if gastroesophageal varices develop.

Other laboratory findings

- *Immunoglobulins*: diffuse polyclonal increases in IgG levels are common in autoimmune hepatitis; increases >100% should alert the clinician to this possibility. Increases in the IgM levels are common in primary biliary cirrhosis, whereas increases in the IgA levels occur in alcoholic liver disease.
- *Ammonia* is produced by intestinal bacteria and the liver plays a role of detoxification by converting it to urea. It can be used for detecting encephalopathy or for monitoring hepatic synthetic function, but the correlation between the presence or severity of acute encephalopathy, hepatic function and elevation of blood ammonia, is very poor. Occasionally it can be useful for identifying occult liver disease in patients with altered mental status.
- *Creatinine* is elevated when hepatorenal syndromes develops and may mark a poor prognosis.
- *Glycaemia* – acute liver failure can be accompanied by symptomatic hypoglycaemia because of sudden cease of gluconeogenesis. Patients with cirrhosis are susceptible to hypoglycaemia as well and on the contrary hyperglycaemia can develop as well.
- *Ceruloplasmin* – low levels of ceruloplasmin are specific for Wilson's disease.
- *Specific antibodies and other*: see examples in the annex

History taking and physical examination

Obtaining clinical history should focus on the symptoms of liver disease, their characterization, patterns of onset, their dynamics and potential risk factors for liver disease. Keep in mind that patients with acute liver failure might not be in state to give you any information, you might have to ask patient family and friends some very sensitive questions.

Chronic alcohol or drug users are often not compliant enough to tell you the truth, and some of them can be easily agitated and act aggressively – always think about your and your staff's safety first. Also, patient's verbal or physical aggressivity should be understood as a symptom, not their personal characteristic – this view will make it easier for you to stay professional at all times and facilitate very harsh situations with patient's family. Maintaining social connection is an important key to dealing with any kind of addiction or severe disease and may have a life-or-death meaning for your patient.

Signs and symptoms

- *Fatigue* is the most common symptom for chronic liver disease, described as lethargy, weakness, increased need for sleep, poor energy. Typically it arises after exercise, in the afternoon, and is not present after adequate rest – in the morning.
- *Nausea* and sometimes vomiting occurs with more severe liver disease. It may be provoked by food odor and eating fatty foods. Poor appetite with weight loss occurs in acute liver disease.
- *Right upper quadrant discomfort* or pain is most typical of gallbladder disease, liver abscess and sinusoidal obstruction syndrome, occasionally can be present in acute hepatitis. Hepatic tenderness is a discomfort or pain when the liver region is touched and is considered a very reliable physical finding.
- *Jaundice, icterus* is the hallmark symptom of liver disease and serves also as a marker of severity. At first patients report *darkening of the urine* (not in the case of unconjugated hyperbilirubinemia), *scleral icterus* is detectable later. Jaundice of the skin is not present with bilirubin levels < 40 µmol/L and the noticeability depends on the lightening of the room (natural light is the best) and a tone of the patient's skin. In dark-skinned individuals, examination of

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mucous membranes below the tongue can demonstrate jaundice. Icterus which is not accompanied by abdominal pain is a warning sign for a possible hepatocellular carcinoma.

- *Acholia* is a light colored stool, caused by absence of bile acids in intestine and accompanies severe cholestasis. It may be accompanied by diarrhoea or steatorrhea – presence of excess fat in feces.
- *Hepatomegaly* is not a highly reliable sign because of liver size variability and possibility of inaccurate physical examination. Significant hepatomegaly is typical of cirrhosis, sinusoidal obstruction syndrome, alcoholic hepatitis and infiltrative disorders.
- *Spider angiomata and palmar erythema* occur in both acute and chronic liver disease and are most prominent in patients with cirrhosis. They can develop in normal individuals during pregnancy.
- *Hepatic encephalopathy can be nonspecific* – change in personality and sleep patterns, irritability. Thereafter, *disorientation, confusion, stupor* and eventually *coma* may follow. It is a major criterion for diagnosis of fulminant hepatitis and indicates a poor prognosis. *Asterixis (flapping tremor)* is a specific sign of hepatic encephalopathy and means a tremor of the hand when the wrist is extended, sometimes said to resemble a bird flapping its wings.
- *Excitability and mania* may be present in acute liver failure.
- *Ascites and/or peripheral edema* are most often signs of advanced liver disease and hypoalbuminemia. Ascites is best evaluated by detecting shifting dullness by careful percussion, but always should be confirmed by ultrasound. With ascites, *hydrothorax* may develop as well.
- *Caput medusa* are prominent veins over the abdomen.
- *Splenomegaly*.
- *Muscle wasting* is found in chronic liver disease in general, although severe cachexia is more typical for metastatic liver disease or hepatocellular carcinoma.
- *Bruising* is an early sign of coagulopathy.
- *Hepatic fetor* is a slightly sweet, ammoniacal odor.
- *Kayser-Fleischer rings* found in Wilson disease are golden brown copper pigment deposits at the periphery of the cornea.
- *Dupuytren contracture and parotid enlargement* are signs of chronic alcoholism and alcoholic liver disease.

Risk factors

- Alcohol use
- Medication use
- Personal habits, diet, occupation
- Sexual activity
- Travel
- Exposure to jaundiced or other high-risk persons
- Injection drug use
- Recent surgery or transfusion of blood or blood products
- Family history of liver disease

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To indicate abuse or dependence on alcohol, you can use *CAGE questions set*, where one yes means a suspicion of an alcohol use problem, more than one is a strong indication:

- ✓ Have you ever felt you ought to cut down on your drinking?
- ✓ Have people annoyed you by criticizing your drinking?
- ✓ Have you ever felt guilty or bad about your drinking?
- ✓ Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (eye-opener)?

Diagnostic imaging and liver biopsy

Ultrasonography is the first diagnostic test to use in patients whose liver tests suggest cholestasis. It will confirm or exclude the presence of a dilated intrahepatic or extrahepatic biliary tree or identify gallstones and cholecystitis. It shows lesions within the liver and distinguishes between cystic and solid masses. US transient elastography provides an indirect assessment of fibrosis and cirrhosis and can eliminate the need of liver biopsy.

CT is also highly sensitive for detecting biliary duct dilation and can be the first-line option for investigating suspected obstructive jaundice. It is not a method of choice to detect gall stones. CT and MRI modifications can be used to quantify liver fat. MR elastography is more sensitive than US elastography.

ERCP and MRCP are a choice for visualization of the biliary tree. *ERCP (endoscopic retrograde cholangiopancreatography)* is an invasive method which also permits biopsy and provides several therapeutic options, such as sphincterotomy, stone extraction, placement of biliary catheters and stents. *MRCP (magnetic resonance cholangiopancreatography)* is a superior diagnostic method with several advantages – no need for contrast media and ionizing radiation, no risk of pancreatitis. It is useful in the diagnosis of bile duct obstruction and congenital biliary abnormalities. As it is non-invasive method, it also does not offer any therapeutic options.

Liver biopsy is a gold standard particularly in evaluating chronic liver disease. In selected instances, it is necessary for diagnosis, and in other cases is used for assessment of the severity and stage of liver damage, prognosis and monitoring response to treatment.

Diagnostic algorithms

Differential diagnosis of liver diseases can get complicated, especially if you consider the large number of possible diseases. It is important to proceed thoughtfully, considering the severity of problems when making diagnostic and therapeutic plan. It might be useful to follow algorithms such as these two shown below, to make sure you are proceeding in the best possible way.

Do not worry – you do not have to remember these algorithms by heart, you can easily find them in the time of need. Try going through all the pathways and try to understand their logic. Imagine making a plan for a patient with abnormal liver tests.

- How long do you think it would take to confirm obstruction of the bile duct? Or autoimmune hepatitis?

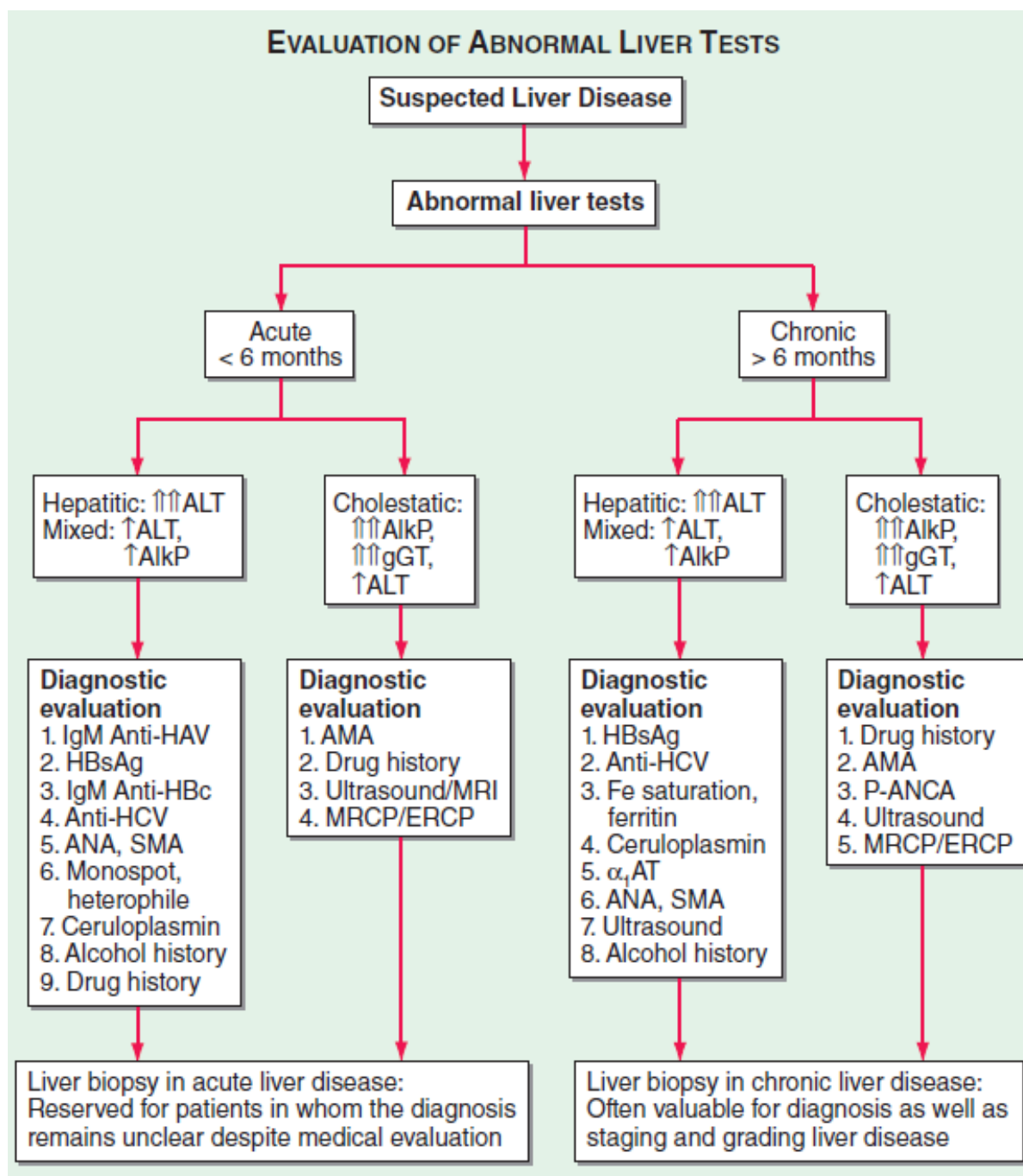


Figure 1 Algorithm for evaluation of abnormal liver tests (Source: *Harrison's principles of Internal medicine, 20th Edition*); α₁ AT, α₁ antitrypsin; AMA; antimitochondrial antibody; ANA, antinuclear antibody; anti-HBc, antibody to hepatitis B core (antigen); ERCP, endoscopic retrograde cholangiopancreatography; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; MRCP, magnetic resonance cholangiopancreatography; P-ANCA, peripheral antineutrophil cytoplasmic antibody; SMA, smooth-muscle antibody.

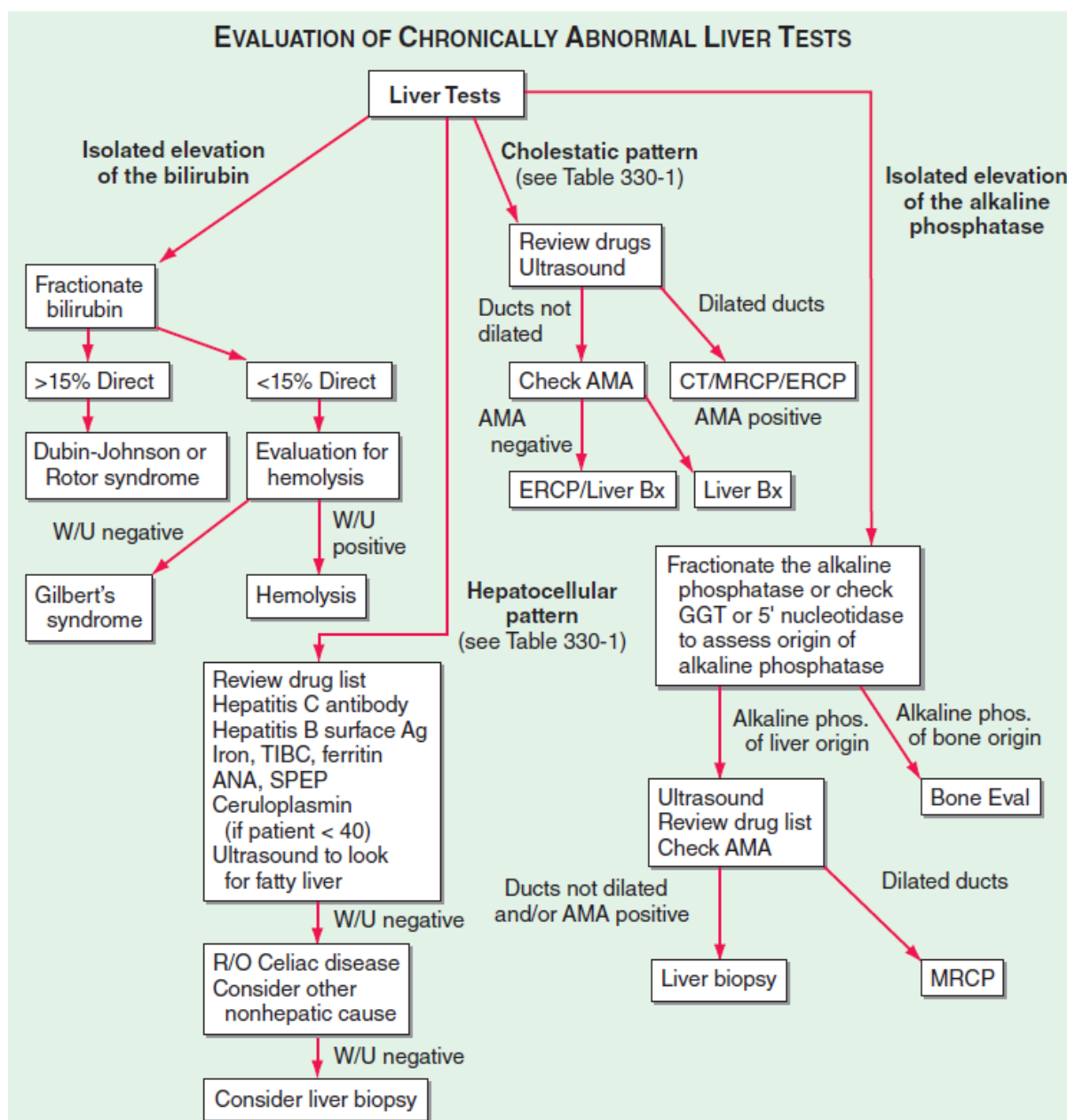


Figure 2 Algorithm for the evaluation of chronically abnormal liver tests. (Source: *Harrison's principles of Internal medicine, 20th Edition*); AMA, antimitochondrial antibody; ANA, antinuclear antibody; Bx, biopsy; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; GGT, gama-glutamyl transpeptidase; MRCP, magnetic resonance cholangiopancreatography; R/O, rule out; SPEP, serum protein electrophoresis; TIBC, total iron-binding capacity; W/U, workup.

Acute liver failure

Acute liver failure is a syndrome that occurs in hepatocyte destruction from various causes. It is defined by *coagulopathy* and any degree of *encephalopathy* in patients without cirrhosis.

Depending on the disease progression it can be classified as:

- a) *fulminant* – onset within 7 days, with often brain oedema
- b) *acute* – 28 days,
- c) *subacute* – 24 weeks, often accompanied by ascites and portal hypertension.

Acute liver failure can be caused by any hepatocytes damaging processes. The most common etiology is *paracetamol intoxication* either in suicidal attempts (doses over 10 grams), or by unintentional paracetamol overdose, which occurs more often in chronic alcohol abusers (doses from 4 grams and more).

— Can you name any other drugs that induce liver damage?

Clinical presentation of acute liver failure is a variation of manifesting coagulopathy, icterus, hypoglycaemia and encephalopathy. The presentation is often accompanied by metabolic acidosis, hypotension and gastrointestinal bleeding.

Subacute liver failure has less specific symptoms – subicterus, fatigue, nausea and hepatic tenderness. Crucial sign to confirm liver failure is encephalopathy.

Liver failure is often complicated by multiorgan failure, infections and sepsis or acid-base disbalance.

Treatment

Treatment of acute liver failure requires placement on intensive care unit and cooperation with hepatologist and other specialists. Severe state leads to metabolic disruption and multiorgan failure and the treatment is symptomatic. The state requires careful monitoring and adjustments of vital functions, acid-base balance, electrolytes and glycaemia. For severe coagulopathy it might be necessary to transfuse plasma and coagulation factors, vitamin K, to avoid bleeding complications and DIC (disseminated intravascular coagulation).

Renal failure is a frequent complication, leading to hemodialysis. To prevent further damage, avoid nephrotoxic drugs. To cure sepsis, cefalosporines of the 3rd generation in combination with vancomycin are recommended. Fungal infections are also frequent.

There is only one causal treatment of liver failure: liver transplantation. Find more information about it here: <https://transplantsurgery.ucsf.edu/conditions--procedures/liver-transplant.aspx>

Paracetamol intoxication

Lethal dose of paracetamol is 13-25 grams, acute liver failure may individually develop even in lower doses. In alcohol abusers or people with present liver disease even dose of 4 grams and more may cause liver failure.

Paracetamol is the most common cause of drug-induced liver failure.

— Can you name any other hepatotoxic drugs and chemicals?

Cirrhosis

Cirrhosis is a condition defined by histopathology and has a variety of clinical manifestations and complications, some of which can be life-threatening.

Cirrhosis may be caused by:

- Alcoholism
- chronic viral hepatitis B or C
- autoimmune hepatitis
- nonalcoholic steatohepatitis
- biliary cirrhosis (PBC, PSC)
- cardiac cirrhosis
- metabolic liver disease (diabetes mellitus, hemochromatosis, Wilson's disease...)

Major complications of cirrhosis are:

- Portal hypertension
- Hepatorenal syndrome type 1 and type 2
- Hepatic encephalopathy
- Ascites
- Hepatopulmonary syndrome
- Portopulmonary hypertension
- Malnutrition
- Coagulopathy
- Hematologic abnormalities - anemia, hemolysis, thrombocytopenia, neutropenia
- Bone disease – osteopenia, osteoporosis, osteomalacia

Portal hypertension may lead to gastroesophageal varices, gastropathy, splenomegaly, ascites or spontaneous bacterial peritonitis. Majority of patients with cirrhosis develop varices in their lifetimes, and are in a high risk of bleeding, especially if coagulopathy, thrombocytopenia or ascites is present. It is common to screen cirrhotics with endoscopy, perform varices ligation if needed and treat portal hypertension with non-selective betablockers (karvedilol) and diuretics (furosemide, spironolactone). TIPS is also a possibility: a transjugular intrahepatic portosystemic shunt is a tract created within the liver using x-ray guidance to connect the higher-pressure portal vein and the lower-pressure hepatic vein, which relieves portal hypertension.

Hepatorenal syndrome (HRS) is a functional renal failure without renal pathology. It occurs in 10% of patients with advanced cirrhosis or acute liver failure. It is caused by poorly understood renal vasoconstriction. Type 1 HRS is characterized by a progressive loss of renal function and significant reduction in creatinine clearance within 1-2 weeks of presentation. It is associated with a very poor prognosis. Type 2 HRS is fairly stable and associated with a better outcome than type 1 HRS, although both types have a poor prognosis unless transplant can be achieved in a short time.

Prognosis

Current standard method for determining prognosis is MELD (Model for End stage Liver Disease)

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The MELD Score predicts three-month survival in patients (age 12+) with liver cirrhosis. Scores range from 6 to 40, with higher scores correlating with increased severity of liver dysfunction and higher three-month mortality. It is preferable to use the calculator to calculate the MELD.

Try it out here and see what facts and values does it evaluate:

<https://www.mdcalc.com/calc/10437/model-end-stage-liver-disease-meld> .

There is an older model called Child-Pugh score. Some physicians still use it, but MELD has a better prognostic value.

Resources

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Annex --- Overview of liver diseases

Disease	Main diagnostic tests or findings
Inherited hyperbilirubinemia	
Gilbert syndrome	mild unconjugated hyperbilirubinemia
Crigler-Najjar syndrome, types I and II	unconjugated hyperbilirubinemia
Dubin-Johnson syndrome	conjugated hyperbilirubinemia
Rotor syndrome	conjugated hyperbilirubinemia
Viral hepatitis	
Hepatitis A	Anti-HAV IgM
Hepatitis B - acute	HBsAg and anti-HBc IgM
Hepatitis B - chronic	HBsAg and HBeAg and/or HBV DNA
Hepatitis C	Anti-HCV and HCV RNA
Hepatitis D	HBsAg and anti-HDV
Hepatitis E	Anti-HEV IgM and HEV RNA
Others (Epstein-Barr virus [mononucleosis] herpesvirus, cytomegalovirus, adenovirus)	
Cryptogenic hepatitis	
Immune and autoimmune liver diseases	
Primary biliary cholangitis	Mitochondrial antibody, elevated IgM levels, and compatible histology
Autoimmune hepatitis	ANA or SMA, elevated IgG levels, and compatible histology
Sclerosing cholangitis	P-ANCA, cholangiography
Graft-versus-host disease	
Allograft rejection	
Genetic liver diseases	
α 1 antitrypsin deficiency	Reduced α 1 antitrypsin levels, phenotype PiZZ or PiSZ
Hemochromatosis	Elevated iron saturation and serum ferritin; genetic testing for HFE gene mutations
Wilson disease	Decreased serum ceruloplasmin and increased urinary copper; increased hepatic copper level
Benign recurrent intrahepatic cholestasis	history of pruritus attacks
Progressive familial intrahepatic cholestasis, types I-III	
Others (galactosemia, tyrosinemia, cystic fibrosis, Niemann-Pick-disease, Gaucher's disease)	
Alcoholic liver disease	History of excessive alcohol intake and compatible histology
Acute fatty liver	
Acute alcoholic hepatitis	
Laënnec cirrhosis	
Nonalcoholic fatty liver	Ultrasound or CT evidence of fatty liver and/or compatible histology
Steatosis	
Steatohepatitis	
Acute fatty liver of pregnancy	
Liver involvement in systemic diseases	
Sarcoidosis	

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	Amyloidosis	
	Glycogen storage diseases	
	Celiac disease	
	Tuberculosis	
	Mycobacterium avium-intracellulare	
	infection	
Cholestatic syndromes		hyperbilirubineamia, elevated liver tests
	Benign postoperative cholestasis	
	Jaundice of sepsis	
	Total parenteral-nutrition–induced jaundice	
	Cholestasis of pregnancy	
	Cholangitis and cholecystitis	
	Extrahepatic biliary obstruction (stone, stricture, cancer)	
	Biliary atresia	
	Caroli disease	
	Cryptosporidiosis	
Drug-induced liver disease		History of drug ingestion
	Hepatocellular patterns (isoniazid, acetaminophen)	very high aminotransferases
	Cholestatic patterns (methyltestosterone)	high ALP, GMT
	Mixed patterns (sulfonamides, phenytoin)	
	Micro- and macrovesicular steatosis (methotrexate, fialuridine)	
Vascular injury		
	Sinusoidal obstruction syndrome	
	Budd-Chiari syndrome	
	Ischemic hepatitis	
	Passive congestion	
	Portal vein thrombosis	
	Nodular regenerative hyperplasia	
Mass lesions		
	Hepatocellular carcinoma	Elevated α -fetoprotein level (to >500 ng/mL); ultrasound or CT image of mass
	Cholangiocarcinoma	
	Adenoma	
	Focal nodular hyperplasia	
	Metastatic tumors	
	Abscess	
	Cysts	
	Hemangioma	