بسم الله الرحمن الرحيم



Approach to Acute Hepatitis

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- INITIAL EVALUATION

- The initial evaluation of a patient with abnormal liver biochemical
- and function tests includes obtaining a history to identify potential risk
- factors for liver disease and performing a physical examination to look
- for clues to the etiology and for signs of chronic liver disease.
- Subsequent testing is determined based on the information .

- History
- hepatotoxins (including alcohol and medications),
- **Alcohol consumption is a common cause of liver** disease,
- significant alcohol consumption .

- We define significant alcohol consumption as an average consumption of >210 grams of alcohol per week in men or >140 grams of alcohol per week in women over at least a two-year period . A standard drink of 80-proof spirits) contains approximately 14 grams of alcohol.

- Patients should be asked about conditions that are associated with
- hepatobiliary disease, such as right-sided heart failure (congestive
- hepatopathy),
- diabetes mellitus, skin pigmentation, arthritis,hypogonadism and dilated cardiomyopathy (hemochromatosis),
- and obesity (nonalcoholic fatty liver disease),
- pregnancy (gallstones), inflammatory bowel disease (primary sclerosing cholangitis, gallstones),
- early onset emphysema (alpha-1 antitrypsin deficiency),
- celiac disease, and thyroid disease.

- Questioning about drug use should seek to identify all drugs used, the amounts ingested, and the durations of use. Drug use is not limited to prescription medications, but also includes over-the-counter medications, herbal and dietary supplements, and illicit drug use.

Features that suggest drug toxicity include lack of illness prior to ingesting the drug, clinical illness or biochemical abnormalities developing after beginning the drug, and improvement after the drug is withdrawn. If an immunologic reaction is suspected, the illness

- will generally recur upon reintroduction of the offending substance. However, rechallenge is not advised .

- Finally, patients should be questioned about occupational or recreational exposure to hepatotoxins (eg, mushroom picking). Examples of hepatitis due to exposures to hepatotoxins include industrial chemicals such as vinyl chloride and the mushrooms Amanita phalloides and Amanita verna, which contain a potent hepatotoxin (amatoxin).
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- The physical examination may suggest the presence of liver disease and may point to the underlying cause of the liver disease.
- Albumin: 3.3 to 5.0 ● g/dL (33 to 50 g/L)
- ● Alkaline phosphatase:
- • Male: 45 to 115 units/L
- • Female: 30 to 100 units/L

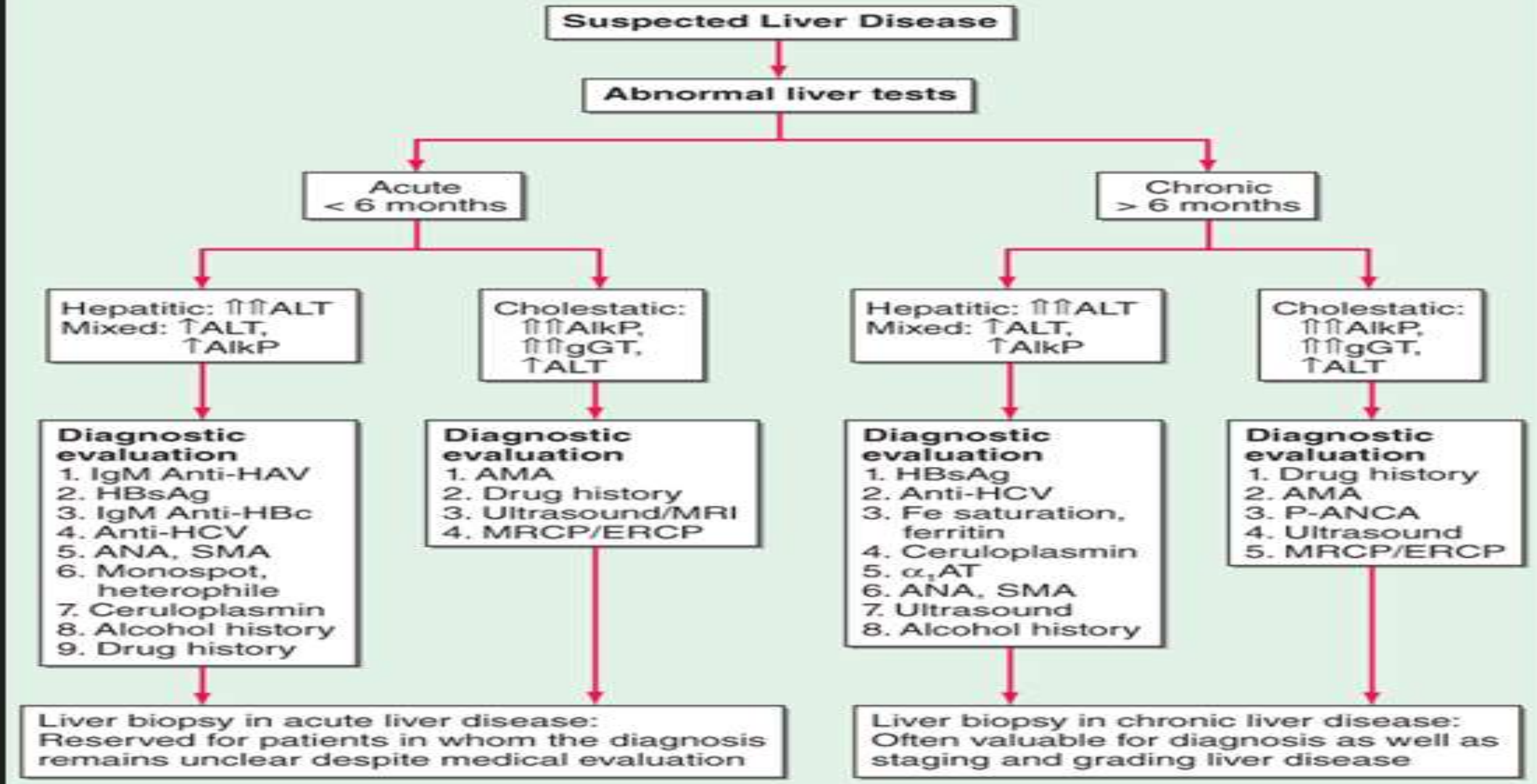
- ● Alanine aminotransferase (ALT):
- • Male: 29 to 33 units/L
- • Female: 19 to 25 units/L
- ● Aspartate aminotransferase (AST):
- • Male: 10 to 40 units/L
- • Female: 9 to 32 units/L
- ● Bilirubin, total: 0.0 to 1.0 mg/dL (0 to 17 micromol/L)
- ● Bilirubin, direct: 0.0 to 0.4 mg/dL (0 to 7 micromol/L)
- ● Gamma-glutamyl transpeptidase (GGT):
- • Male: 8 to 61 units/L
- • Female: 5 to 36 units/L
- ● Prothrombin time (PT): 11.0 to 13.7 seconds

- Acute viral hepatitis is a systemic infection affecting the liver predominantly. Almost all cases of acute viral hepatitis are caused by one of five viral agents:
- hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), the HBV-associated delta agent or hepatitis D virus (HDV), and hepatitis E virus (HEV).
- All these human hepatitis viruses are RNA viruses, except for hepatitis B, which is a DNA virus but replicates like a retrovirus. Although these agents can be distinguished by their molecular and antigenic properties, all types of viral hepatitis produce clinically similar illnesses.

- These range from asymptomatic and inapparent to fulminant and fatal acute infections common to all types,
- on the one hand, and from progressive chronic liver disease with cirrhosis and even hepatocellular carcinomasubclinical persistent infections to rapidly , common to the bloodborne types (HBV, HCV, and HDV), on the other.

- Risk factors for viral hepatitis include potential parenteral exposures (eg, intravenous drug use, blood transfusion prior to 1992), travel to areas endemic for hepatitis, and exposure to patients with jaundice.
- Hepatitis B and C are transmitted parenterally, whereas hepatitis A and E are transmitted from person to person via a fecal-oral route (often via contaminated food).
- Hepatitis E is uncommon in the United States, but it should be considered in patients who live in or have travelled to Asia, Africa, the Middle East, or Central America, and has been seen increasingly in Europe as a result of consumption of contaminated swine and game meat.

Evaluation of Abnormal Liver Tests

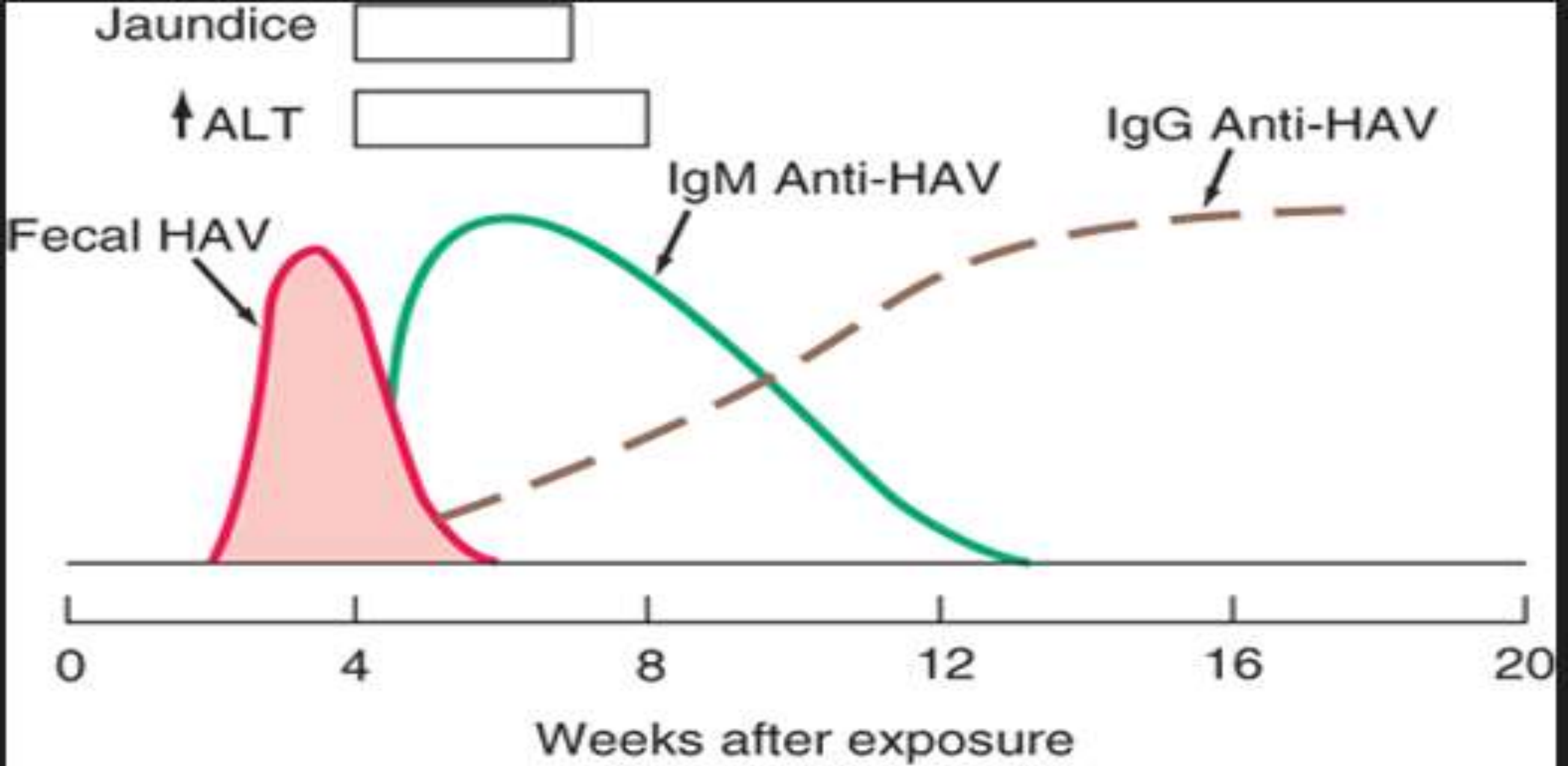


Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

- Hepatitis A has an incubation period of ~4 weeks.
- Its replication is limited to the liver, but the virus is present in the liver, bile, stools, and blood during the late incubation period and acute preicteric/presymptomatic phase of illness.

- Despite slightly longer persistence of virus in the liver, fecal shedding, viremia, and infectivity diminish rapidly once jaundice becomes apparent. HAV can be cultivated reproducibly in vitro.

- Antibodies to HAV (anti-HAV) can be detected during acute illness when serum aminotransferase activity is elevated and fecal HAV shedding is still occurring. This early antibody response is predominantly of the IgM class and persists for several (~3) months, rarely for 6–12 months.
- During convalescence, however, anti-HAV of the IgG class becomes the predominant antibody . Therefore, the diagnosis of hepatitis A is made during acute illness by demonstrating anti-HAV of the IgM class.
- After acute illness, anti-HAV of the IgG class remains detectable indefinitely, and patients with serum anti-HAV are immune to reinfection. Neutralizing antibody activity parallels the appearance of anti-HAV, and the IgG anti-HAV present in immune globulin accounts for the protection it affords against HAV infection.



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition: www.accessmedicine.com
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- Laboratory tests — The pattern of liver test abnormalities may suggest that the underlying cause of the patient's liver disease is primarily the result of hepatocyte injury (elevated aminotransferases) or cholestasis (elevated alkaline phosphatase).
- ALT is a more specific marker of hepatic injury as compared with AST.
- Patterns of liver test abnormalities — Liver test abnormalities can often be grouped into one of several patterns: the abnormalities may be acute, subacute, or chronic based on
- whether they have been present for less than six weeks (acute), six weeks to six months (subacute), or more than six months (chronic). Based on the pattern of elevation, liver test abnormalities may be grouped as hepatocellular, cholestatic, or isolated hyperbilirubinemia.

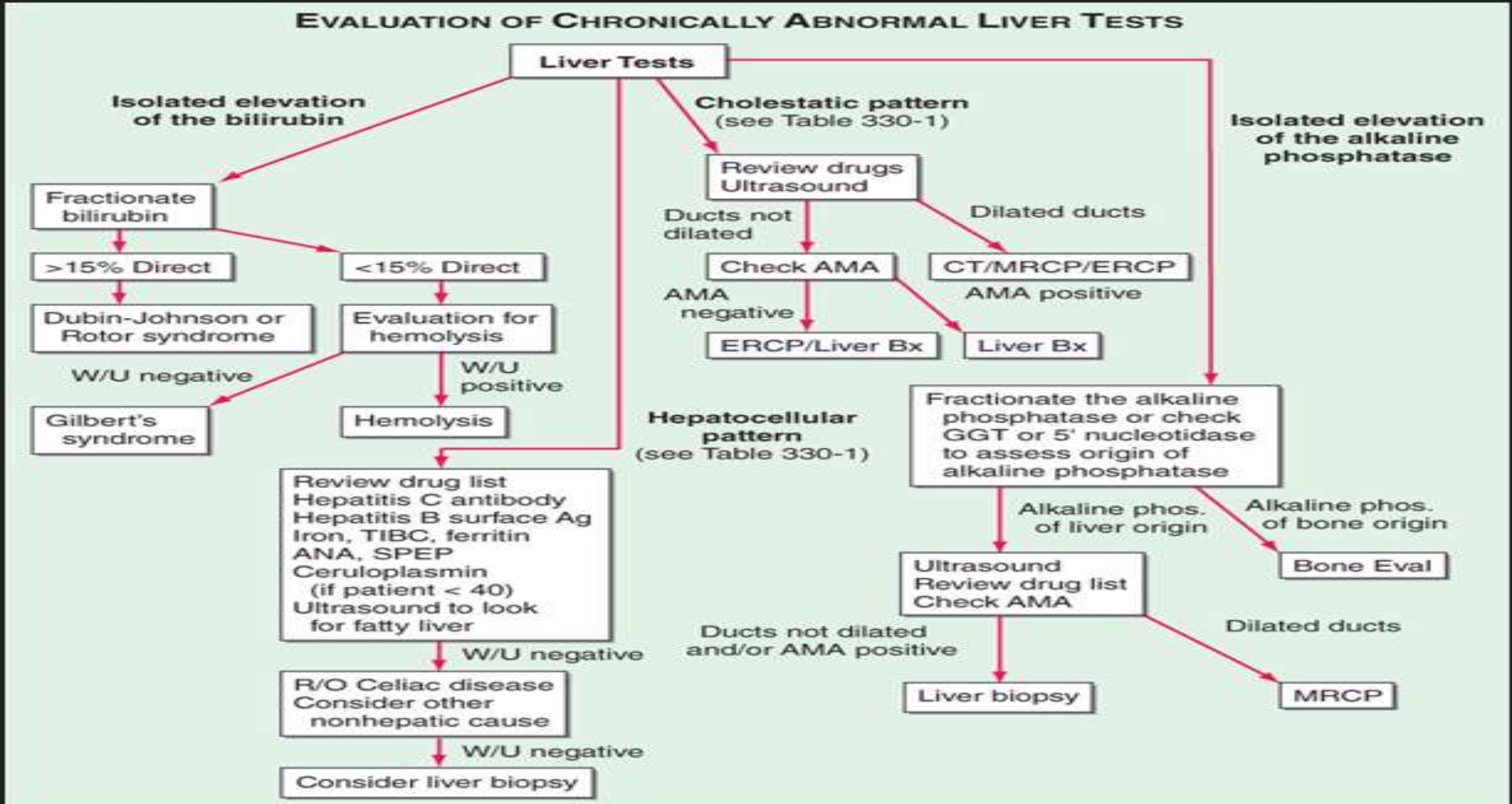
- The R value (also known as the R factor) can be used to help determine the likely type of liver injury (hepatocellular versus cholestatic) in patients with elevated aminotransferases and alkaline phosphatase.
- R value = (ALT ÷ ULN ALT) / (alkaline phosphatase ÷ ULN alkaline phosphatase)
- The R value is interpreted as follows:
- Because the serum bilirubin can be prominently elevated in both hepatocellular and cholestatic conditions, it is not helpful in differentiating between the two.
- Common hepatocellular diseases associated with an elevated bilirubin and jaundice include viral and toxic hepatitis (including drugs, herbal therapies, and alcohol) and end-stage cirrhosis from any cause .

- Isolated hyperbilirubinemia: As the term implies, patients with isolated hyperbilirubinemia have an elevated bilirubin level with normal serum aminotransferases and alkaline phosphatase
- ● ≥5: Hepatocellular injury
- ● >2 to <5: Mixed pattern
- ● ≤2: Cholestatic injury
- ● Alcoholic fatty liver disease: AST <8 times the upper limit of normal; ALT <5 times the upper limit of normal.
- ● Nonalcoholic fatty liver disease: AST and ALT <4 times the upper limit of normal.
- ● Acute viral hepatitis or toxin-related hepatitis with jaundice: AST and ALT >25 times the upper limit of normal.

- Ischemic hepatitis (ischemic hepatopathy, shock liver, hypoxic hepatitis): AST and ALT >50 times the upper limit of normal (in addition the lactate dehydrogenase is often markedly elevated).

- ● Chronic hepatitis C virus infection: Wide variability, typically normal to less than twice the upper limit of normal, rarely more than 10 times the upper limit of normal.
- Chronic hepatitis B virus infection: Levels vary; the AST and ALT may be normal in inactive carriers, whereas most patients with chronic hepatitis B have mild to moderate elevations (approximately twice the upper limit of normal); with exacerbations, levels are more than 10 times the upper limit of normal.

Evaluation of Chronically Abnormal Liver Tests



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

- TREATMENT: Acute Viral Hepatitis

- Most persons with acute hepatitis (especially hepatitis A, B, and E) recover spontaneously and do not require specific antiviral therapy.

- PROPHYLAXIS
- Because application of therapy for acute viral hepatitis is limited and because antiviral therapy for chronic viral hepatitis is cumbersome, costly, and not effective in all patients , emphasis is placed on prevention through immunization.
- The prophylactic approach differs for each of the types of viral hepatitis. In the past, immunoprophylaxis relied exclusively on passive immunization with antibody-containing globulin preparations purified by cold ethanol fractionation from the plasma of hundreds of normal donors.
- Currently, for hepatitis A, B, and E, active immunization with vaccines is the preferable approach to prevention.

- Hepatitis A
- Both passive immunization with IG and active immunization with killed vaccines are available.
- All preparations of IG contain anti-HAV concentrations sufficient to be protective. When administered before exposure or during the early incubation period, IG is effective in preventing clinically apparent hepatitis A.
- For postexposure prophylaxis of intimate contacts (household, sexual, institutional) of persons with hepatitis A, the administration of 0.02 mL/kg is recommended as early after exposure as possible; it may be effective even when administered as late as 2 weeks after exposure.

- Prophylaxis is not necessary for those who have already received hepatitis A vaccine, for casual contacts (office, factory, school, or hospital), for most elderly persons, who are very likely to be immune, or for those known to have anti-HAV in their serum.
- In day care centers, recognition of hepatitis A in children or staff should provide a stimulus for immunoprophylaxis in the center and in the children's family members.
- By the time most common-source outbreaks of hepatitis A are recognized, it is usually too late in the incubation period for IG to be effective; however, prophylaxis may limit the frequency of secondary cases.

- For travelers to tropical countries, developing countries, and other areas outside standard tourist routes, IG prophylaxis had been recommended before a vaccine became available.
- When such travel lasted <3 months, 0.02 mL/kg was given; for longer travel or residence in these areas, a dose of 0.06 mL/kg every 4–6 months was recommended.
- Administration of plasma-derived globulin is safe; all contemporary lots of IG are subjected to viral inactivation steps and must be free of HCV RNA as determined by PCR testing.
- Administration of IM lots of IG has not been associated with transmission of HBV, HCV, or HIV.

- Formalin-inactivated vaccines made from strains of HAV attenuated in tissue culture have been shown to be safe, immunogenic, and effective in preventing hepatitis A.
- Hepatitis A vaccines are approved for use in persons who are at least 1 year old and appear to provide adequate protection beginning 4 weeks after a primary inoculation.
- If it can be given within 4 weeks of an expected exposure, such as by travel to an endemic area, hepatitis A vaccine is the preferred approach to preexposure immunoprophylaxis.
- If travel is more imminent, IG (0.02 mL/kg) should be administered at a different injection site, along with the first dose of vaccine.

- Other populations whose recognized risk of hepatitis A is increased should be vaccinated, including
- men who have sex with men, injection drug users, persons with clotting disorders who require frequent administration of clotting-factor concentrates, persons traveling from the United States to countries with high or intermediate hepatitis A endemicity, postexposure prophylaxis for contacts of persons with hepatitis A, and household members and other close contacts of adopted children arriving from countries with high and moderate hepatitis A endemicity.

- Acute liver failure is characterized by acute liver injury, hepatic encephalopathy, and an elevated prothrombin time/international normalized ratio (INR).

It has also been referred to as as fulminant hepatic failure, acute hepatic necrosis, fulminant hepatic necrosis, and fulminant hepatitis.

Untreated, the prognosis is poor, so timely recognition and management of patients with acute liver failure is crucial . Whenever possible, patients with acute liver failure should be managed in an intensive care unit at a liver transplantation center.

- DEFINITIONS — Acute liver failure refers to the development of severe acute liver injury with encephalopathy and impaired synthetic function (INR of ≥1.5) in a patient without cirrhosis or preexisting liver disease . While the time course that differentiates acute liver failure from chronic liver failure varies among reports, a commonly used cutoff is an illness duration of <26 weeks.

- Acute liver failure may also be diagnosed in patients with previously undiagnosed Wilson disease, vertically acquired hepatitis B virus, or autoimmune hepatitis, in whom underlying cirrhosis may be present, provided the disease has been recognized for <26 weeks. On the other hand, patients with acute severe alcoholic hepatitis, even if recognized for <26 weeks, are considered to have acute-on-chronic liver failure since most have a long history of heavy drinking. The approach to such patients is discussed elsewhere.

- Acute liver failure can be subcategorized based upon how long the patient has been ill and various cutoffs have been used. We classify acute liver failure as hyperacute (<7 days), acute (7 to 21 days), or subacute (>21 days and <26 weeks). In patients with hyperacute or acute liver failure, cerebral edema is common, whereas it is rare in subacute liver failure.

- On the other hand, renal failure and portal hypertension are more frequently observed in patients with subacute liver failure. These subcategories have been associated with prognosis, but the associations reflect the underlying causes, which are the true determinants of prognosis.

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- As an example, patients with hyperacute liver failure tend to have a better prognosis than those with subacute liver failure.
- The better prognosis is related to the fact that these patients often have acetaminophen toxicity or ischemic hepatopathy, diagnoses associated with a better prognosis than many of the disorders that may result in subacute liver failure, such as Wilson disease

Mnemonic for causes of acute liver failure: The ABCs

Mnemonic for causes of acute liver failure: The ABCs

A	Acetaminophen, hepatitis A, autoimmune hepatitis, *Amanita phalloides* (mushroom poisoning), adenovirus
B	Hepatitis B, Budd-Chiari syndrome
C	Cryptogenic, hepatitis C, CMV
D	Hepatitis D, drugs and toxins
E	Hepatitis E, EBV
F	Fatty infiltration - acute fatty liver of pregnancy, Reye's syndrome
G	Genetic - Wilson disease
H	Hypoperfusion (ischemic hepatitis, SOS, sepsis), HELLP syndrome, HSV, heat stroke, hepatectomy, hemophagocytic lymphohistiocytosis
I	Infiltration by tumor

CMV: cytomegalovirus; EBV: Epstein-Barr virus; SOS: sinusoidal obstruction syndrome (veno-occlusive disease); HELLP: hemolysis, elevated liver enzymes, low platelets; HSV: herpes simplex virus.

Some drugs, herbal products, and toxins associated with acute liver failure

Some drugs, herbal products, and toxins associated with acute liver failure

Abacavir
Acetaminophen (paracetamol)
Alcohol
Allopurinol
Amiodarone
Amoxicillin
Aspirin
Carbamazepine
Carbon tetrachloride
Ciprofloxacin
Cocaine
Comfrey
Dapsone
Didanosine

Dideoxyinosine

Disulfiram

Doxycycline

Efavirenz

Gemtuzumab

Gold

Greater celandine

Halothane

He Shou Wu

Herbalife®

Hydroxycut®

Isoflurane

Isoniazid

Itraconazole

Kava Kava

Ketoconazole

Labetalol

LipoKinetix®

Ma Huang

MDMA (Ecstasy)
Methamphetamine
Monoamine oxidase inhibitors
Methyldopa
Nicotinic acid
Nitrofurantoin
Nonsteroidal anti-inflammatory drugs
Phenprocoumon
Phenytoin
Poison mushrooms (*Amanita phalloides*)
Propylthiouracil
Pyrazinamide
Rifampin
Senecio
Statins
Sulfonamides
Terbinafine
Tetracycline

Tricyclic antidepressants
Valproic acid

- Viral hepatitis
- — Several viruses have been associated with acute liver failure, including hepatitis A, B, C, D, and E. In addition, acute liver failure can be seen with herpes simplex virus (HSV), varicella zoster virus, Epstein-Barr virus, adenovirus, and cytomegalovirus .

- Acute liver failure is estimated to develop in 0.35 percent of patients with hepatitis A and in 0.1 to 0.5 percent of patients with acute hepatitis B .

- CLINICAL MANIFESTATIONS — By definition, patients with acute liver failure have severe acute liver injury (demonstrated by liver test abnormalities) with signs of hepatic encephalopathy and a prolonged prothrombin time (INR ≥1.5). Other clinical manifestations may include jaundice, hepatomegaly, and right upper quadrant tenderness.
- Symptoms — Many of the initial symptoms in patients with acute liver failure are nonspecific . They include:

- ●Fatigue/malaise

- ●Lethargy

- ●Anorexia

- ●Nausea and/or vomiting
- ●Right upper quadrant pain
- ●Pruritus
- ●Jaundice
- ●Abdominal distension from ascites
- As the liver failure progresses, patients who were initially anicteric may develop jaundice, and those with subtle mental status changes (eg, lethargy, difficulty sleeping) may become confused or eventually comatose.

- Physical examination findings

- Neurologic examination
- — The presence of hepatic encephalopathy is one of the defining characteristics of acute liver failure.
- Findings in patients with hepatic encephalopathy are variable, ranging from changes in behavior to coma. Hepatic encephalopathy is graded from I to IV

- ●Grade I: Changes in behavior, mild confusion, slurred speech, disordered sleep, including sleep reversal
- ●Grade II: Lethargy, moderate confusion

- .
- ●Grade III: Marked confusion (stupor), incoherent speech, sleeping but wakes with stimulation
- ●Grade IV: Coma, unresponsive to pain
- Patients with grade I encephalopathy may have mild asterixis, whereas pronounced asterixis is typically seen in patients with grade II or III encephalopathy
- .Asterixis is typically absent in patients with grade IV encephalopathy, who instead may demonstrate decorticate or decerebrate posturing .

- Cerebral edema may develop in patients with acute liver failure leading to increased intracranial pressure
- Cerebral edema is uncommon in patients with grade I or II encephalopathy, but it is present in 25 to 35 percent of those with grade III encephalopathy and in approximately 75 percent of those with grade IV encephalopathy.
- Pupillary changes are one sign of increased intracranial pressure. The pupils may progress from having a normal response (typical with grade I encephalopathy), to being hyperresponsive (grade II to III encephalopathy), to being slowly responsive (grade III to IV encephalopathy).
- As the coma worsens, the pupils may become fixed and dilated (a sign typically associated with brainstem herniation).

- Other clinical features of increased intracranial pressure can include systemic hypertension, bradycardia, respiratory depression (Cushing's triad), seizures, and abnormal brainstem reflexes (eg, oculocephalic reflex, corneal reflex, jaw reflex, cough response to tracheobronchial suctioning).
- Seizure activity in patients with acute liver failure is common but may be difficult to detect if patients are intubated and receiving paralytics.
- In the control arm of one trial, 7 of 22 patients (32 percent) had subclinical seizure activity detected by electroencephalogram

- Other physical examination findings — Other findings on physical examination in patients with acute liver failure may include:

●Jaundice, which is a common finding in patients with acute liver failure but may be absent early in the course of acetaminophen poisoning or herpes simplex virus (HSV) infection

●Vesicular skin lesions suggestive of HSV (present in 30 to 50 percent of patients with acute liver failure due to HSV)

●Fever in patients with HSV (reported in 82 percent of patients in one review)

●Right upper quadrant tenderness and hepatomegaly

●Ascites

●Signs of intravascular volume depletion, such as orthostatic hypotension

- — Laboratory test abnormalities typically seen in patients with acute liver failure include:

●Prolonged prothrombin time, resulting in an INR ≥1.5 (this finding is part of the definition of acute liver failure and thus must be present); hemostasis when measured by thromboelastography is normal

●Elevated aminotransferase levels (often markedly elevated).

●Elevated bilirubin level.

●Low platelet count (≤150,000/mm3), but this is variable and has been associated with portal hypertension.

- Decreasing aminotransferase levels may indicate spontaneous recovery but could also signal worsening of the liver failure with loss of hepatocyte mass.

- In patients who are improving, the bilirubin and prothrombin time/INR will decline,
- whereas in those with worsening liver failure, the bilirubin and prothrombin time/INR will continue to rise.
- Elevations in bilirubin with associated jaundice can take weeks to months to resolve.

- Because of the prognostic importance of the prothrombin time/INR, it is recommended that products such as plasma only be used when there is a clear indication. In addition, despite an abnormal INR, patients may not be hypocoagulable.
- In a study of 20 patients with acute liver failure, thromboelastography suggested a hypocoagulable state in 20 percent, normal coagulation in 45 percent, and a hypercoagulable state in 35 percent

- Other laboratory findings that may be seen in patients with acute liver failure include :

- Hemolytic anemia
- Elevated serum creatinine and blood urea nitrogen
- Elevated amylase and lipase
- Hypoglycemia
- Hypophosphatemia
- Hypomagnesemia
- Hypokalemia
- Acidosis or alkalosis
- Elevated ammonia level
- Elevated lactate dehydrogenase (LDH) level

- Acute kidney injury complicates acute liver failure in approximately 30 to 70 percent of patients .
- The frequency of renal injury is higher (up to 75 percent) for etiologies of acute liver failure that are known to independently damage the kidneys, such as acetaminophen intoxication .
- In one series of 1604 patients with acute liver failure, some degree of acute kidney injury developed in 70 percent of the patients, with 30 percent receiving renal replacement therapy .

- Laboratory findings associated with specific diagnoses — Laboratory test findings often vary depending upon the specific cause of acute liver failure. Patterns seen on laboratory testing may suggest a diagnosis, but additional history, laboratory and imaging testing is required prior to making a diagnosis. These patterns should not be used to rule in or rule out a given diagnosis.
- Some patterns that may be seen include :

- ●Acetaminophen – Very high aminotransferase levels (>3500 international units/L), low bilirubin, high INR

- ●Ischemic hepatic injury – Very high aminotransferase levels (25 to 250 times the upper limit of normal), elevated serum LDH levels

- ●Hepatitis B virus – Aminotransferase levels of to 1000 to 2000 international units/L are common, alanine aminotransferase (ALT) level that is higher than the aspartate aminotransferase (AST) level
- ●Wilson disease – Coombs-negative hemolytic anemia, aminotransferase levels <2000 international units/L, AST to ALT ratio of >2, normal or markedly subnormal alkaline phosphatase (<40 international units/L), alkaline phosphatase (international units/L) to total bilirubin (mg/dL) ratio <4, rapidly progressive renal failure, low uric acid levels (see "Wilson disease:

- ●Acute fatty liver of pregnancy/HELLP syndrome – Aminotransferase levels <1000 international units/L, elevated bilirubin, low platelet count (see "HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)" and "Acute fatty liver of pregnancy")

- ●Herpes simplex virus – Markedly elevated aminotransferases, leukopenia, low bilirubin

- ●Reye syndrome, valproate toxicity, or tetracycline toxicity – Minor to moderate elevations in aminotransferase and bilirubin levels

- Empiric therapy is often started along with the diagnostic workup if a particular cause is likely based upon history or examination findings.
- This is especially true in patients with suspected acetaminophen-associated acute liver failure since the treatment, N-acetylcysteine (NAC), significantly improves outcomes if started early and has few side effects.
- NAC has also been used for patients with non-acetaminophen Induced liver failure.
- Once the cause of the liver failure is confirmed, therapy can be adjusted as needed.


THANK YOU
FOR YOUR
ATTENTION