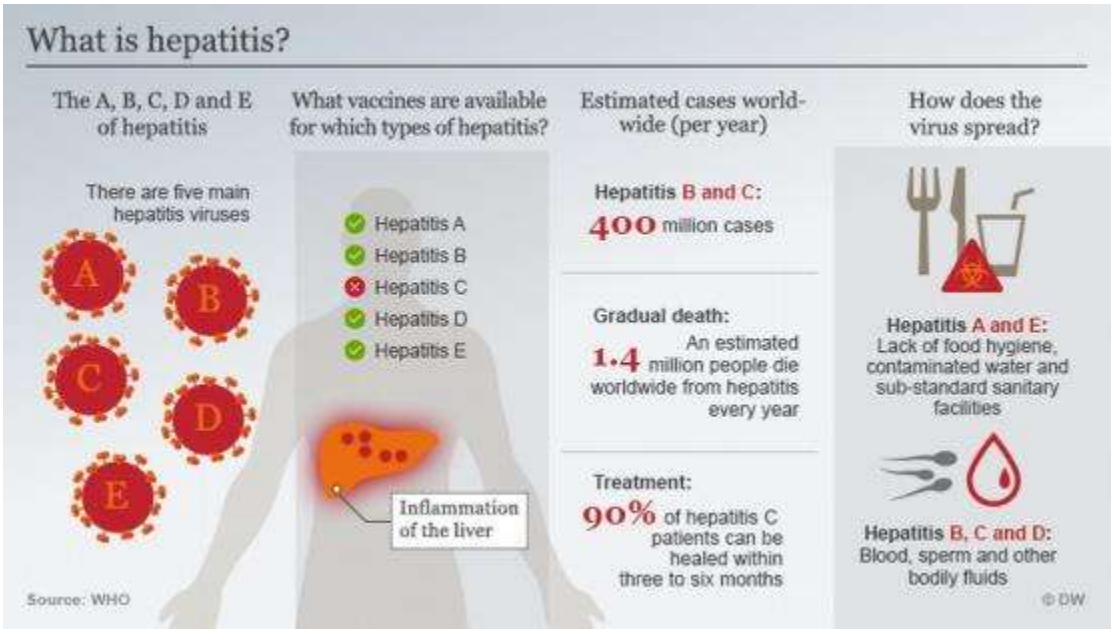
Hepatitis



Hepatitis

Signs and symptoms

- **Hepatitis** is inflammation of the liver tissue.
- Some people with hepatitis have no symptoms, whereas others develop yellow discoloration of the skin and whites of the eyes (jaundice), poor appetite, vomiting, tiredness, abdominal pain, and diarrhea.
- Hepatitis is *acute* if it resolves within six months, and *chronic* if it lasts longer than six months.
- Acute hepatitis can resolve on its own, progress to chronic hepatitis, or (rarely) result in acute liver failure.
- Chronic hepatitis may progress to scarring of the liver (cirrhosis), liver failure, and liver cancer.
- Hepatitis is most commonly caused by the viruse hepatitis A, B, C, D, and E.

Other causes include 1. **Heavy alcohol use,** 2. **Certain medications,** 3. **Toxins,** 4. **Other infections,** 5. **Autoimmune diseases,** 6. **Non-alcoholic steatohepatitis (NASH).**	

- Hepatitis A and E are mainly spread by contaminated food and water.

- Hepatitis B is mainly sexually transmitted, but may also be passed from mother to baby during pregnancy or childbirth and spread through infected blood.
- Hepatitis C is commonly spread through infected blood such as may occur during needle sharing by intravenous drug users.
- Hepatitis D can only infect people already infected with hepatitis B.
- Hepatitis A, B, and D are preventable with immunization.
- Medications may be used to treat chronic viral hepatitis.
- Antiviral medications are recommended in all with chronic hepatitis C, except those with conditions that limit their life expectancy.
- There is no specific treatment for NASH; however, physical activity, a healthy diet, and weight loss are recommended.
- Autoimmune hepatitis may be treated with medications to suppress the immune system.
- A liver transplant may be an option in both acute and chronic liver failure.

Worldwide in 2015,

- Hepatitis A occurred in about 114 million people,
- Chronic hepatitis B affected about 343 million people and
- Chronic hepatitis C about 142 million people.

In the United States,

- NASH (Non-alcoholic steatohepatitis) affects about 11 million people and
- Alcoholic hepatitis affects about 5 million people.
- Hepatitis results in more than a million deaths a year, most of which occur indirectly from liver scarring or liver cancer.
- In the United States, hepatitis A is estimated to occur in about 2,500 people a year and results in about 75 deaths.
- The word is derived from the Greek *hêpar* (ἧπαρ), meaning "liver", and *-itis* (-ῖτις), meaning "inflammation".

Contents

Signs and symptoms

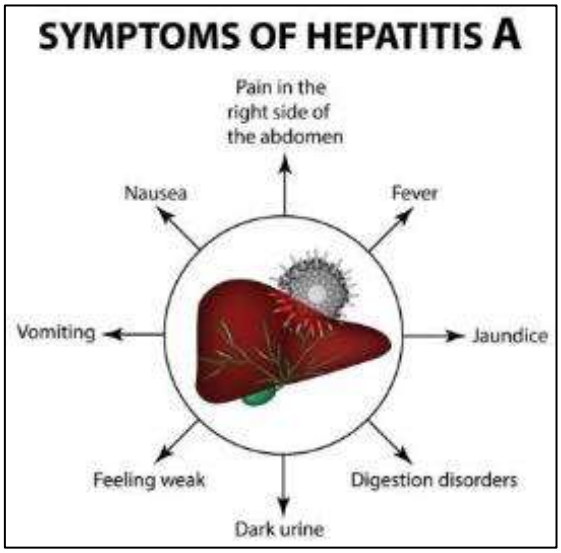
- Hepatitis has a broad spectrum of presentations that range from a complete lack of symptoms to severe liver failure.
- The acute form of hepatitis, generally caused by viral infection, is characterized by constitutional symptoms that are typically self-limiting.
- Chronic hepatitis presents similarly, but can manifest signs and symptoms specific to liver dysfunction with long-standing inflammation and damage to the organ.

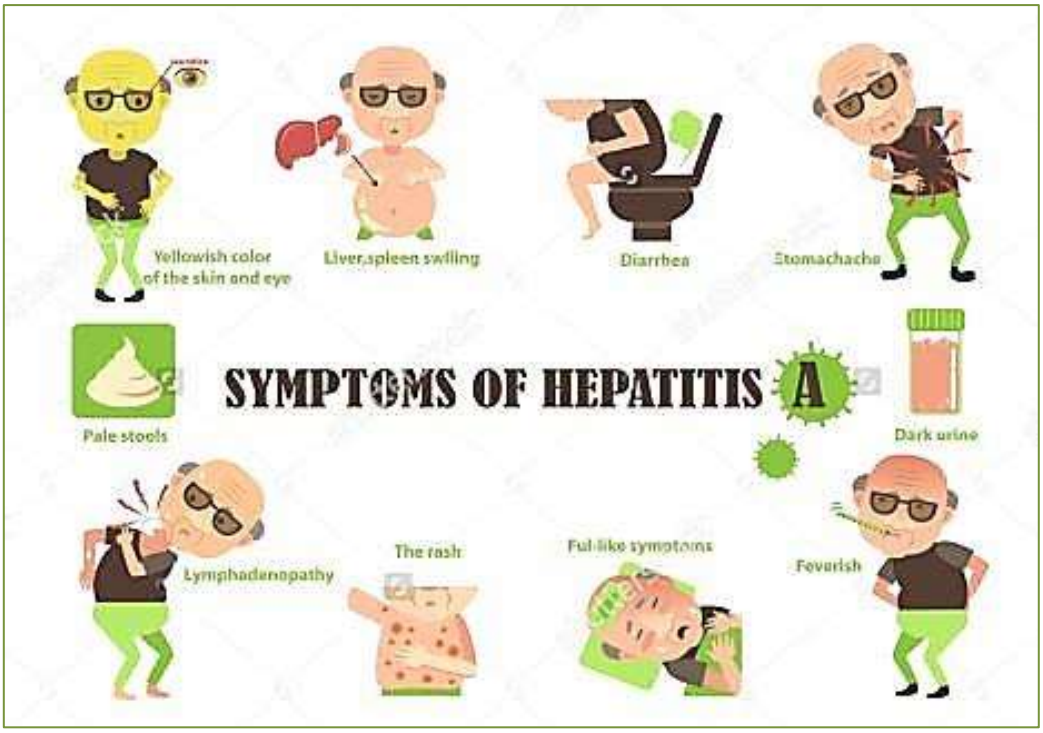
Acute hepatitis

Acute viral hepatitis follows three distinct phases:

1. **The initial prodromal phase** (preceding symptoms) involves non-specific and flu-like symptoms common to many acute viral infections.
   These include
   1. Fatigue,
   2. nausea,
   3. vomiting,
   4. Poor appetite,
   5. Joint pain, and
   6. Headaches.
   7. Fever, when present, is most common in cases of hepatitis A and E.

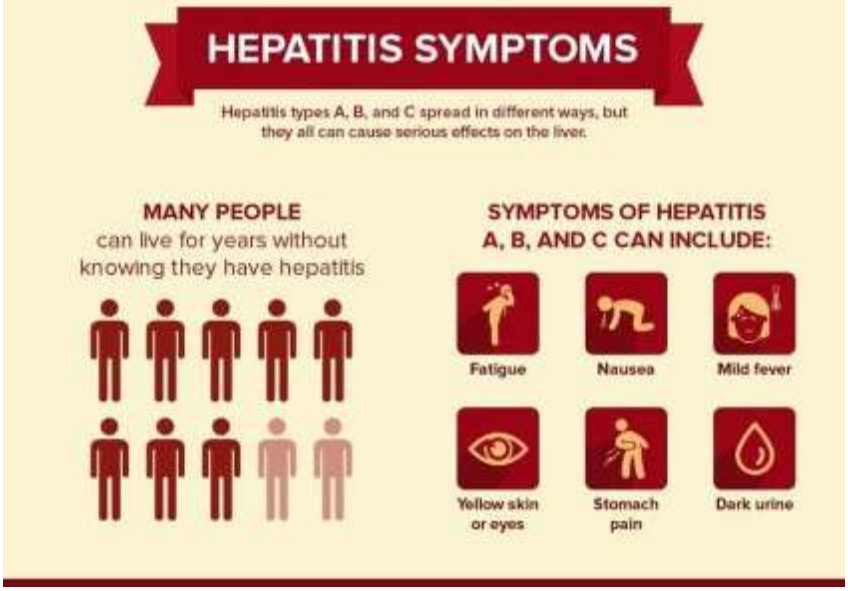
   Late in this phase, people can experience **liver-specific symptoms**, including
   1. Choluria (dark urine) and
   2. Clay-colored stools.





2. **Yellowing of the skin** and whites of the eyes follow the prodrome after about 1–2 weeks and can last for up to 4 weeks.
   The non-specific symptoms seen in the prodromal typically resolve by this time, but people will develop an enlarged liver and right upper abdominal pain or discomfort.
   10–20% of people will also experience an enlarged spleen, while some people will also experience a mild **unintentional weight loss**.
3. **The recovery phase** is characterized by resolution of the clinical symptoms of hepatitis with persistent elevations in liver lab values and potentially a persistently enlarged liver.
   All cases of hepatitis A and E are expected to fully resolve after 1–2 months. Most hepatitis B cases are also self-limiting and will resolve in 3–4 months. Few cases of hepatitis C will resolve completely.

- Both drug-induced hepatitis and autoimmune hepatitis can present very similarly to acute viral hepatitis, with slight variations in symptoms depending on the cause.
- Cases of drug-induced hepatitis can manifest with systemic signs of an allergic reaction including
  - **Rash,**
  - **Fever,**
  - **Serositis (inflammation of membranes lining certain organs),**
  - **Elevated eosinophils (a type of white blood cell), and**
  - **Suppression of bone marrow activity.**

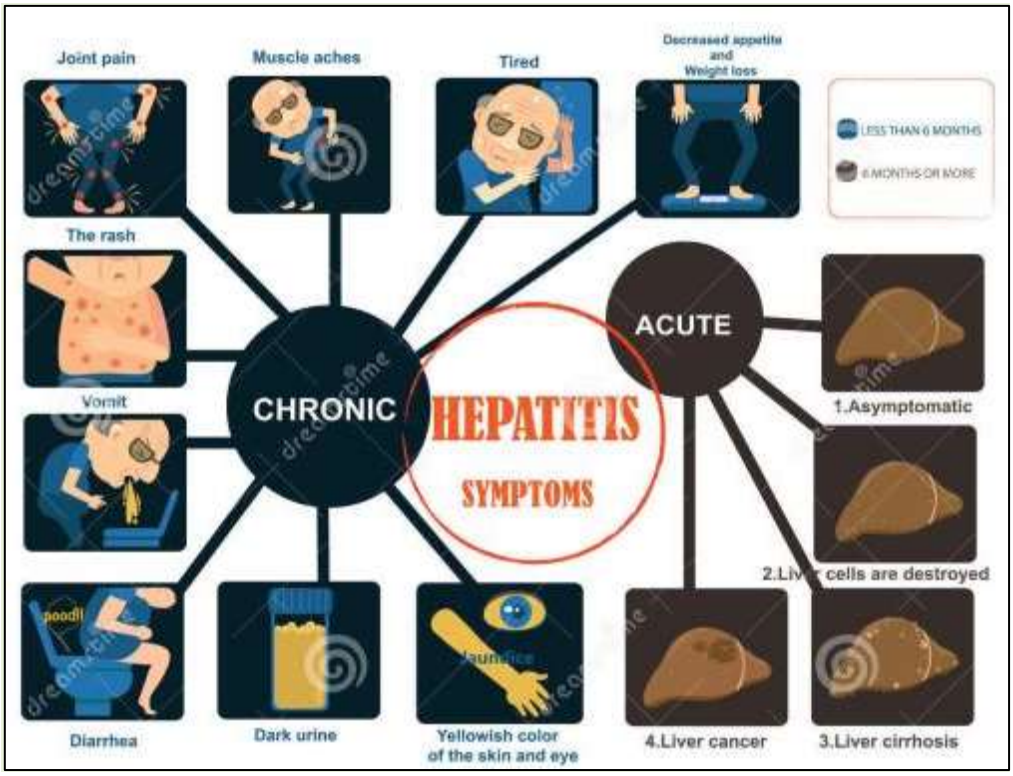


Fulminant hepatitis

- Fulminant hepatitis, or massive hepatic cell death, is a rare and life-threatening complication of acute hepatitis that can occur in cases of hepatitis B, D, and E, in addition to drug-induced and autoimmune hepatitis.
- The complication more frequently occurs in instances of hepatitis B and D co-infection at a rate of 2–20% and in pregnant women with hepatitis E, at rate of 15–20% of cases.
- In addition to the signs of acute hepatitis, people can also demonstrate signs of
    - Coagulopathy (abnormal coagulation studies with easy bruising and bleeding) and
    - Encephalopathy (confusion, disorientation, and sleepiness).
    - Mortality due to fulminant hepatitis is typically the result of various complications **including**:
        - Cerebral edema,
        - Gastrointestinal bleeding,
        - Sepsis,
        - Respiratory failure, or
        - Kidney failure.

Chronic hepatitis

- Acute cases of hepatitis are seen to be resolved well within a six-month period.
- When hepatitis is continued for more than six months it is termed chronic hepatitis.
- Chronic hepatitis is often asymptomatic early in its course and is detected only by liver laboratory studies for screening purposes or to evaluate non-specific symptoms.
- As the inflammation progresses, patients can develop constitutional symptoms similar to acute hepatitis, including fatigue, nausea, vomiting, poor appetite, and joint pain.
- Jaundice can occur as well, but much later in the disease process and is typically a sign of advanced disease.



- Chronic hepatitis interferes with hormonal functions of the liver which can result in
  - **Acne,**
  - **Hirsutism (abnormal hair growth), and**
  - **Amenorrhea (lack of menstrual period) in women**.
- Extensive damage and scarring of the liver over time defines cirrhosis, a condition in which the liver's ability to function is permanently impeded.
- This results in
  - **Jaundice,**
  - **Weight loss,**
  - **Coagulopathy,**
  - **Ascites (abdominal fluid collection), and**
  - **Peripheral edema (leg swelling).**
- Cirrhosis can lead to other life-threatening complications such as
  - **Hepatic encephalopathy,**
  - **Esophageal varices,**
  - **Hepatorenal syndrome, and**
  - **Liver cancer**.

Causes of Hepatitis

Causes of hepatitis can be divided into the following major categories:

1. **Infectious,**
2. **Metabolic,**
3. **Ischemic,**
4. **Autoimmune,**
5. **Genetic, and**
6. **Other.**

Infectious agents include

1. Viruses,
2. Bacteria, and
3. Parasites.

Metabolic causes include

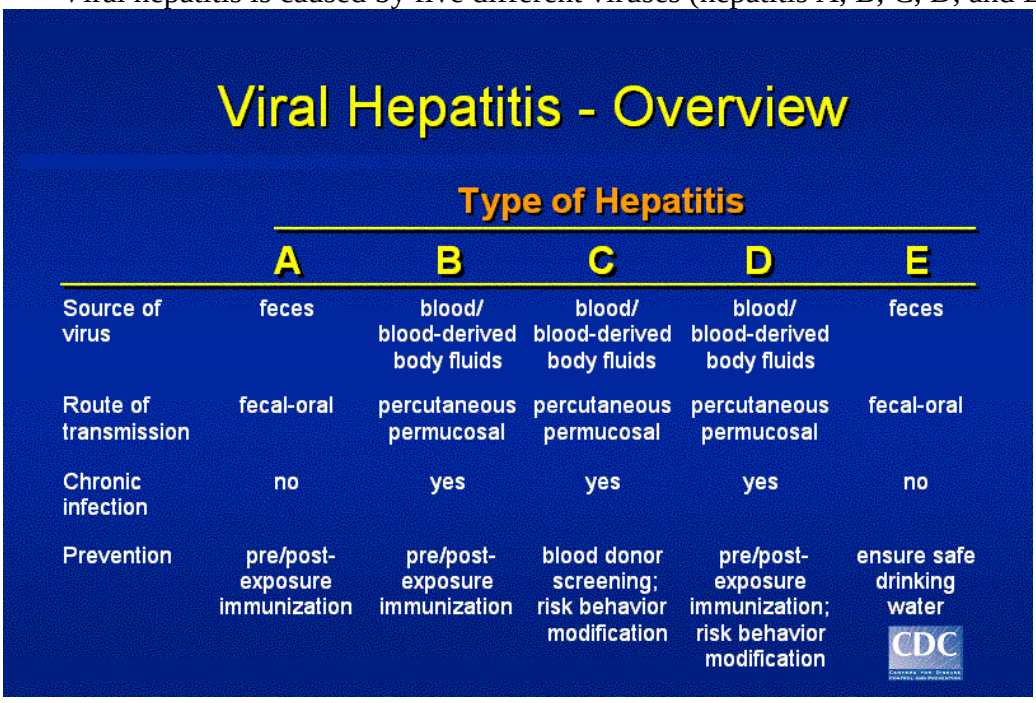
1. Prescription medications,
2. Toxins (most notably alcohol), and
3. Non-alcoholic fatty liver disease.

Autoimmune and genetic causes of hepatitis involve genetic predispositions and tend to affect characteristic populations.

Infectious

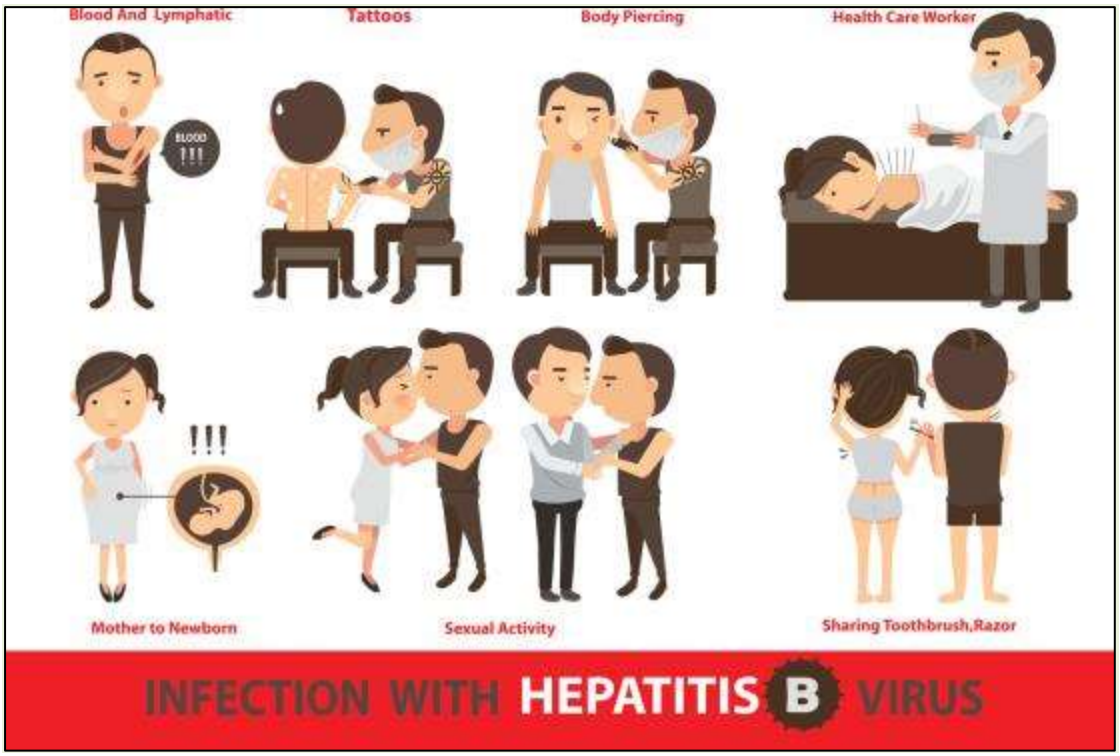
Viral hepatitis

- Viral hepatitis is the most common type of hepatitis worldwide.
- Viral hepatitis is caused by five different viruses (hepatitis A, B, C, D, and E).



- Hepatitis A and hepatitis E behave similarly: they are both transmitted by the fecal–oral route, are more common in developing countries, and are ***self-limiting illnesses that do not lead to chronic hepatitis.***
- Hepatitis B, hepatitis C, and hepatitis D are transmitted when blood or mucous membranes are exposed to **infected blood and body fluids**, such as

- **Semen &**
- **Vaginal secretions.**
- **Saliva and**
- **Breastmilk.**

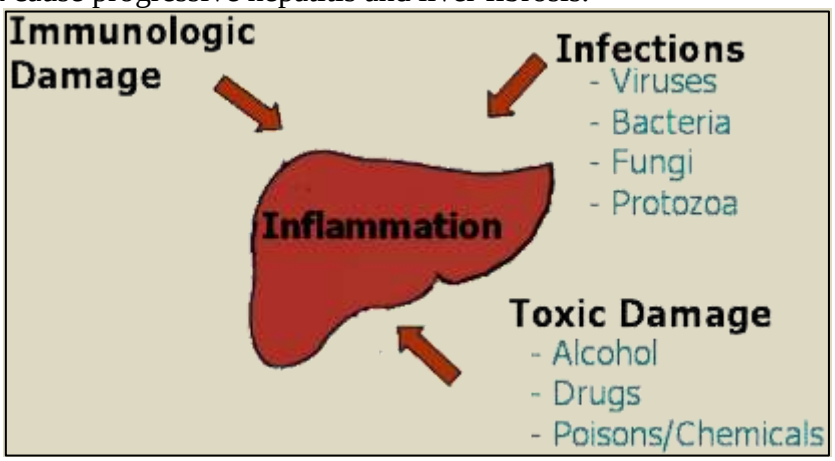


- However, kissing, sharing utensils, and breastfeeding do not lead to transmission unless these fluids are introduced into **open sores or cuts**.
- ***Hepatitis B and C can present either acutely or chronically***.
- Hepatitis D is a defective virus that requires hepatitis B to replicate and is only found with hepatitis B co-infection.
- In adults, hepatitis B infection is most commonly self-limiting, with less than **5% progressing to chronic state**, and **20 to 30% of those chronically infected developing cirrhosis or liver cancer.**
  - ***(5% → chronic & 1-2% cirrhosis & cancer)***
- However, infection in infants and children frequently leads to chronic infection.
- Unlike hepatitis B, **most cases of hepatitis C lead to chronic infection**.
- Hepatitis C is the second most common cause of cirrhosis in the US (second to alcoholic hepatitis).
- In the 1970s and 1980s, blood transfusions were a major factor in spreading hepatitis C virus.
- Since widespread screening of blood products for hepatitis C began in 1992, the risk of acquiring hepatitis C from a blood transfusion has decreased from approximately 10% in the 1970s to 1 in 2 million currently.
  - (10:100) →($1:2x10^6$ =1:2000000)

Parasitic hepatitis

Ecchinococcus granulosus

- Parasites can also infect the liver and activate the immune response, resulting in symptoms of acute hepatitis with increased serum IgE (though chronic hepatitis is possible with chronic infections).
- **Of the protozoans,**
  - Trypanosoma cruzi,
  - Leishmania species, and
  - The malaria-causing Plasmodium species all can cause liver inflammation.
  - Another protozoan, Entamoeba histolytica, causes hepatitis with distinct liver abscesses.
- **Of the worms**, the cestode Ecchinococcus granulosus, also known as the dog tapeworm, infects the liver and forms characteristic hepatic hydatid cysts.
- The liver flukes Fasciola hepatica and Clonorchis sinensis live in the bile ducts and cause progressive hepatitis and liver fibrosis.



Bacterial hepatitis

- Bacterial infection of the liver commonly results in
  - **Pyogenic liver abscesses,**
  - **Acute hepatitis, or**
  - **Granulomatous (or chronic) liver disease.**[31]
- Pyogenic abscesses commonly involve enteric bacteria such as *Escherichia coli* and *Klebsiella pneumoniae* and are composed of multiple bacteria up to 50% of the time.
- ***Acute hepatitis is caused by***
  - *Neisseria meningitidis*,

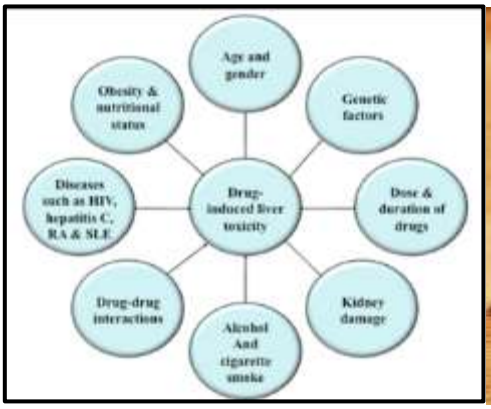
- *Neisseria gonorrhoeae*,
- *Bartonella henselae*,
- *Borrelia burgdorferi*,
- Salmonella species,
- Brucella species and
- Campylobacter species.[31]

- ***Chronic or granulomatous hepatitis is seen with infection from***
  - Mycobacteria species,
  - *Tropheryma whipplei*,
  - *Treponema pallidum*,
  - *Coxiella burnetii*, and
  - Rickettsia species.

Metabolic

Alcoholic hepatitis

- Excessive alcohol consumption is a significant cause of hepatitis and is the most common cause of cirrhosis in the U.S.
- Alcoholic hepatitis is within the spectrum of alcoholic liver disease.
- This ranges in order of severity and reversibility from
  - **Alcoholic steatosis (least severe, most reversible),**
  - **Alcoholic hepatitis,**
  - **Cirrhosis, and**
  - **Liver cancer (most severe, least reversible).**
- Hepatitis usually develops ***over years-long exposure to alcohol,*** occurring in 10 to 20% of alcoholics.
- The most important risk factors for the development of alcoholic hepatitis are **quantity and duration of alcohol intake**.
- Long-term alcohol intake in excess of 80 grams of alcohol a day in men and 40 grams a day in women is associated with development of alcoholic hepatitis (1 beer or 4 ounces of wine is equivalent to 12g of alcohol).
- Alcoholic hepatitis can vary from
  - Asymptomatic hepatomegaly (enlarged liver) to
  - Symptoms of acute or chronic hepatitis to
  - Liver failure.



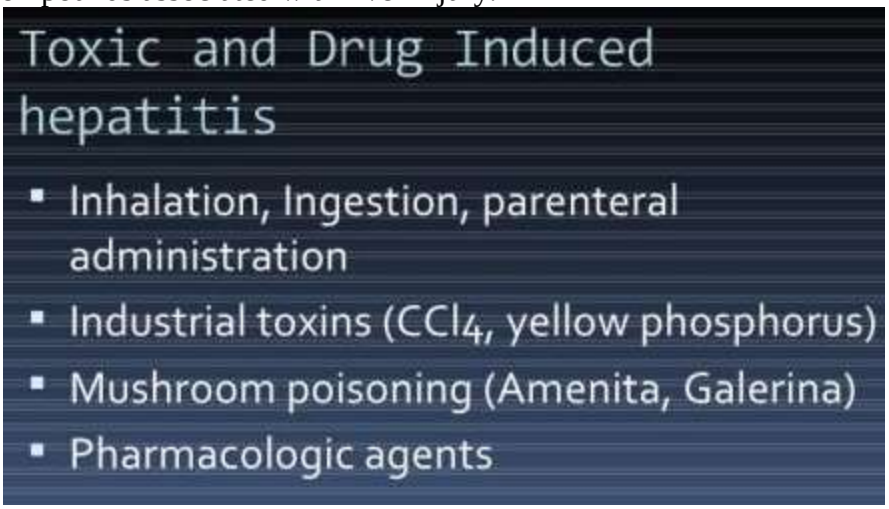
Toxic and drug-induced hepatitis

- Many chemical agents, including
  - **Medications,**

    - **Industrial toxins, and**
    - **Herbal and dietary supplements**,
- Can cause hepatitis.
- The spectrum of drug-induced liver injury varies from
    - **Acute hepatitis to**
    - **Chronic hepatitis to**
    - **Acute liver failure**.
- Toxins and medications can cause liver injury through a variety of mechanisms, including
    - **Direct cell damage,**
    - **Disruption of cell metabolism, and**
    - **Causing structural changes.**
- Some drugs such as paracetamol exhibit **predictable dose-dependent liver** damage while others such as isoniazid cause idiosyncratic and unpredictable reactions that vary among individuals.
- There are wide variations in the mechanisms of liver injury and latency period from exposure to development of clinical illness.
- Many types of drugs can cause liver injury, including
    - the analgesic paracetamol;
- **Antibiotics such as**
    - Isoniazid,
    - Nitrofurantoin,
    - Amoxicillin-clavulanate,
    - Erythromycin, and
    - Trimethoprim-sulfamethoxazole;
- **Anticonvulsants such as**
    - valproate and
    - phenytoin;
- **Cholesterol-lowering statins;**
    - **Steroids such as**
    - **Oral contraceptives and**
    - **Anabolic steroids**; and
- **Highly active anti-retroviral therapy used in the treatment of HIV/AIDS.**
- Of these,

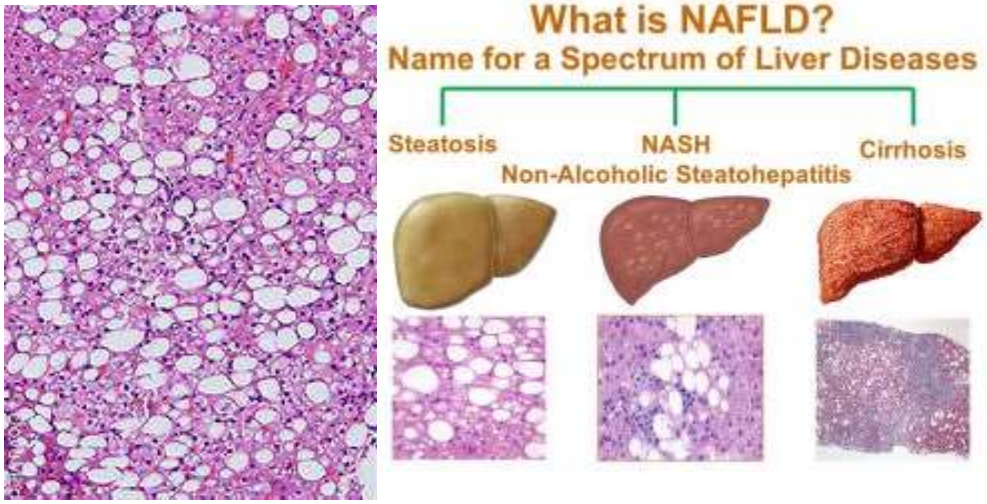
- Amoxicillin-**clavulanate** is the most common cause of drug-induced liver injury, and
- Paracetamol toxicity the most common cause of **acute liver failure** in the United States and Europe.

- **Herbal remedies and dietary supplements** are another important cause of hepatitis; these are the most common causes of drug-induced hepatitis in Korea.
- The United-States-based Drug Induced Liver Injury Network linked more than 16% of cases of hepatotoxicity to herbal and dietary supplements.
- In the United States, herbal and dietary supplements – unlike pharmaceutical drugs – are unregulated by the Food and Drug Administration.
- However, the National Institutes of Health maintains the LiverTox database for consumers to track all known prescription and non-prescription compounds associated with liver injury.



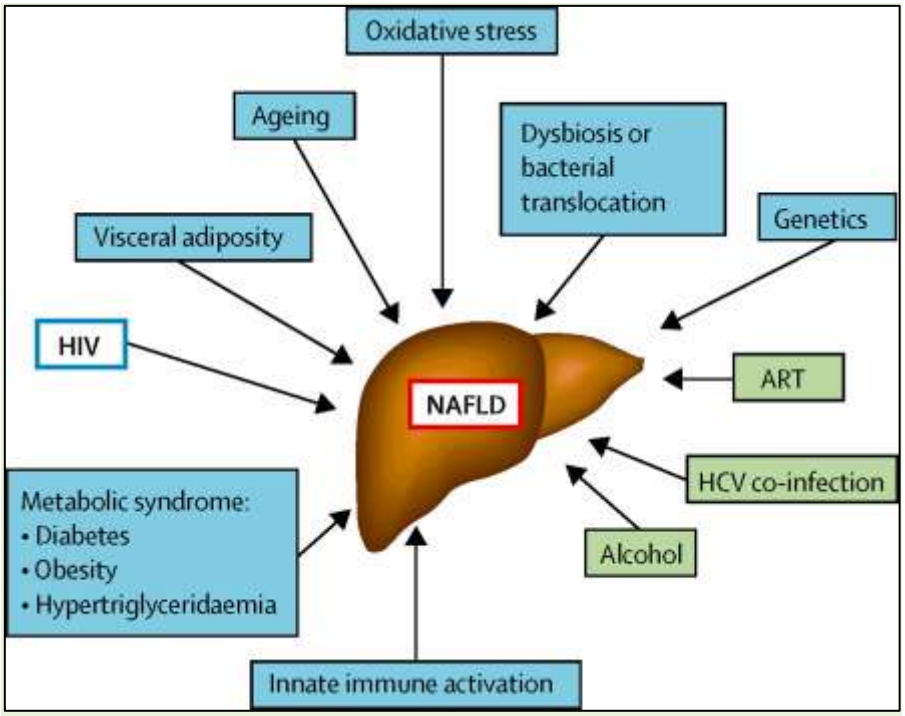
- **Exposure to other hepatotoxins can occur accidentally** or intentionally through ingestion, inhalation, and skin absorption.
- **The industrial toxin** carbon tetrachloride and the wild mushroom Amanita phalloides are other known hepatotoxins.

Non-alcoholic fatty liver disease



- Non-alcoholic hepatitis is within the spectrum of non-alcoholic liver disease (NALD), which ranges in severity and reversibility from
  - **Non-alcoholic fatty liver disease (NAFLD) to**
  - **Non-alcoholic steatohepatitis (NASH) to**
  - **Cirrhosis to**
  - **Liver cancer,**
- Similar to the spectrum of alcoholic liver disease.
- Non-alcoholic liver disease occurs in people with little or no history of alcohol use, and is instead strongly associated with
  - **Metabolic syndrome,**
  - **Obesity,**
  - **Insulin resistance and**
  - **Diabetes, and**
  - **Hypertriglyceridemia.**

- Over time, non-alcoholic fatty liver disease can progress to non-alcoholic steatohepatitis, which additionally involves liver cell death, liver inflammation and possible fibrosis.
- **Factors accelerating progression from NAFLD to NASH are**
  - **Obesity,**
  - **Older age,**
  - **Non-African American ethnicity,**
  - **Female gender,**
  - **Diabetes mellitus,**
  - **Hypertension,**
  - **Higher ALT or AST level,**
  - **Higher AST/ALT ratio,**
  - **Low platelet count, and an**
  - **Ultrasound steatosis score.**



- In the early stages (as with NAFLD and early NASH), most patients are asymptomatic or have mild right upper quadrant pain, and diagnosis is suspected on the basis of abnormal liver function tests.
- As the disease progresses, symptoms typical of chronic hepatitis may develop.
- While imaging can show fatty liver, only liver biopsy can demonstrate inflammation and fibrosis characteristic of NASH.
- **9 to 25%** of patients with NASH develop cirrhosis.
- NASH is recognized as the third most common cause of liver disease in the United States.

Autoimmune

- Autoimmune hepatitis is a chronic disease caused by **an abnormal immune response against liver cells.**
- The disease is thought to have a genetic predisposition as it is associated with certain human leukocyte cytoplasmic antigens involved in the immune response. Anti-Neutrophils Cytoplasmic Antigen
    - (cANCA & pANCA
- As in other autoimmune diseases, circulating auto-antibodies may be present & are helpful in diagnosis.
- Auto-antibodies found in patients with autoimmune hepatitis include the
    - **Sensitive but less specific anti-nuclear antibody (ANA),**
    - **Smooth muscle antibody (SMA), and**
    - **Atypical perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA).**
- Other autoantibodies that are less common but more specific to autoimmune hepatitis are
    - The antibodies against liver kidney microsome 1 **(LKM1)** and
    - Soluble liver antigen **(SLA).**
- Autoimmune hepatitis **can also be triggered by drugs (such** as
    - Nitrofurantoin,
    - Hydralazine, and
    - Methyldopa),
    - After liver transplant, or
    - By viruses (such as hepatitis A, Epstein-Barr virus, or measles).
- Autoimmune hepatitis can present anywhere within the spectrum from asymptomatic to acute or chronic hepatitis to fulminant liver failure.
- Patients are asymptomatic 25–35% of the time, and the diagnosis is suspected on the basis of abnormal liver function tests.
- Up to 40% of cases present with signs and symptoms of acute hepatitis.

- As with other autoimmune diseases, autoimmune hepatitis usually affects **young women** (though it can affect patients of either sex of any age), and patients can exhibit classic signs and symptoms of autoimmunity such as
    - **Fatigue,**
    - **Anemia,**
    - **Anorexia,**
    - **Amenorrhea,**

    - **Acne,**
    - **Arthritis,**
    - **Pleurisy,**
    - **Thyroiditis,**
    - **Ulcerative colitis,**
    - **Nephritis, and**
    - **Maculopapular rash.**
- Autoimmune hepatitis increases the risk for cirrhosis, and the risk for liver cancer is increased by about 1% for each year of the disease.
- Many people with autoimmune hepatitis have other autoimmune diseases.
- Autoimmune hepatitis is distinct from the other autoimmune diseases of the liver:
- Primary biliary cirrhosis (autoimmune cholangitis) and
- Primary sclerosing cholangitis.
- However, all of these diseases can lead to scarring, fibrosis, and cirrhosis of the liver.

Genetic

- Genetic causes of hepatitis include
    - **Alpha-1-antitrypsin deficiency,**
    - **Hemochromatosis, and**
    - **Wilson's disease.**
- In alpha-1-antitrypsin deficiency, a co-dominant mutation in the gene for alpha-1-antitrypsin results in the abnormal accumulation of the mutant AAT protein within liver cells, leading to liver disease.
- Hemochromatosis and Wilson's disease are both autosomal recessive diseases involving abnormal storage of minerals.
- In hemochromatosis, **excess amounts of iron** accumulate in multiple body sites, including the liver, which can lead to cirrhosis.
- In Wilson's disease, **excess amounts of copper** accumulate in the liver and brain, causing cirrhosis and dementia.
- When the liver is involved, alpha-1-antitrypsin deficiency and Wilson's disease tend to present as hepatitis in the neonatal period or in childhood.
- Hemochromatosis typically presents in adulthood, with the onset of clinical disease usually after age 50.

Ischemic hepatitis

- Ischemic hepatitis (also known as **shock liver**) results from reduced blood flow to the liver as in
    - **Shock,**
    - **Heart failure, or**
    - **Vascular insufficiency.**
- The condition is most often associated with heart failure but can also be caused by shock or sepsis.
- Blood testing of a person with ischemic hepatitis will show very high levels of transaminase enzymes (AST and ALT).
- The condition usually resolves if the underlying cause is treated successfully.
- Ischemic hepatitis rarely causes permanent liver damage.

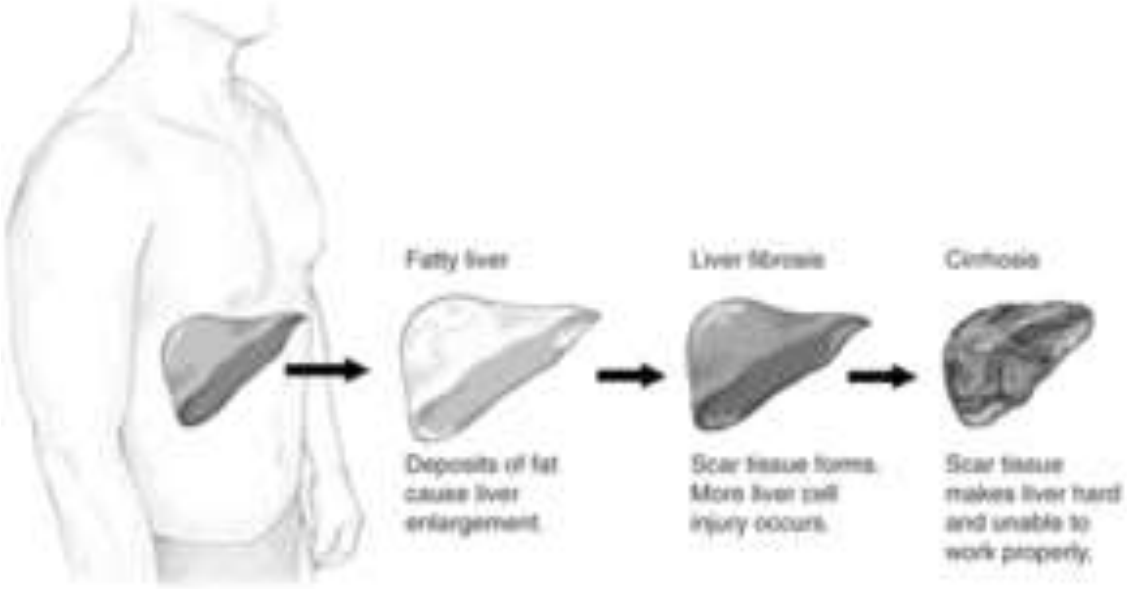
Other

Neonatal hepatitis

- Hepatitis can also occur in neonates and is attributable to a variety of causes, some of which are not typically seen in adults.
- Congenital or perinatal infection with the
  - **Hepatitis viruses,**
  - **Toxoplasma,**
  - **Rubella,**
  - **Cytomegalovirus, and**
  - **Syphilis can cause neonatal hepatitis.**
- **Structural abnormalities** such as
  - **Biliary atresia and**
  - **Choledochal cysts can lead to**
  - **Cholestatic liver injury** leading to neonatal hepatitis.
- **Metabolic diseases** such as
  - **Glycogen storage disorders and**
  - **Lysosomal storage disorders are also** implicated.
- Neonatal hepatitis can be **idiopathic**, and in such cases, biopsy often shows large multinucleated cells in the liver tissue.
- This disease is termed giant cell hepatitis and may be associated with viral infection, autoimmune disorders, and drug toxicity.

Mechanism of liver injury

- The specific mechanism varies and depends on the underlying cause of the hepatitis. Generally, there is an
- ***Initial insult that causes*** →
- ***Liver injury and activation of an inflammatory response,***
- ***This can become chronic, leading to progressive fibrosis and cirrhosis.***



Viral hepatitis

Stages of liver disease

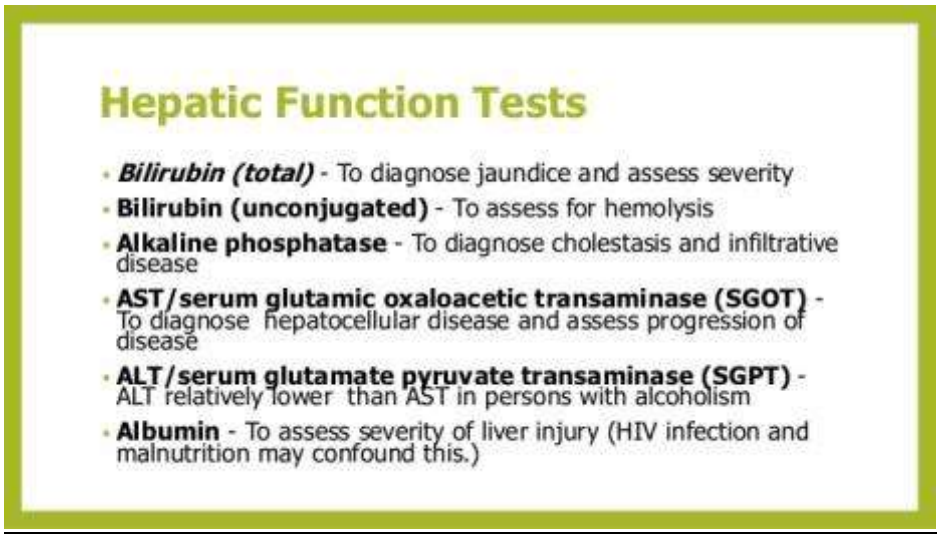
- The pathway by which hepatic viruses cause viral hepatitis is best understood in the case of hepatitis B and C.
- The viruses do not directly cause apoptosis (cell death).
- Rather, infection of liver cells activates the innate and adaptive arms of the immune system leading to an inflammatory response which causes cellular damage and death.
- Depending on the
    - **Strength of the immune response, the**
    - **Types of immune cells involved and the**
    - **Ability of the virus to evade the body's defense,**
- Infection can either lead to
    - **Clearance (acute disease) or**
    - **Persistence (chronic disease) of the virus.**
- The chronic presence of the virus within liver cells results in multiple waves of inflammation, injury and wound healing that over time lead to scarring or fibrosis and culminate in hepatocellular carcinoma.
- Individuals with an impaired immune response are at greater risk of developing chronic infection.
- Natural killer cells are the primary drivers of the initial innate response and create a cytokine environment that results in the recruitment of CD4 T-helper and CD8 cytotoxic T-cells.
- Type I interferons are the cytokines that drive the antiviral response.
- In chronic Hepatitis B and C, natural killer cell function is impaired.

Steatohepatitis

- Steatohepatitis is seen in both alcoholic and non-alcoholic liver disease and is the culmination of a cascade of events that began with injury.
- In the case of non-alcoholic steatohepatitis, this cascade is initiated by changes in metabolism associated with obesity, insulin resistance, and lipid dysregulation.
- In alcoholic hepatitis, chronic excess alcohol use is the culprit.

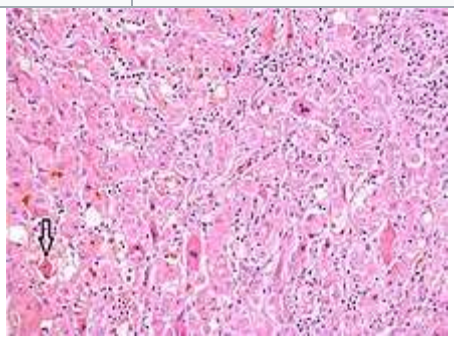
- Though the inciting event may differ, the progression of events is similar and begins with accumulation of free fatty acids (FFA) and their breakdown products in the liver cells in a process called steatosis.
- This initially reversible process overwhelms the hepatocyte's ability to maintain lipid homeostasis leading to a toxic effect as fat molecules accumulate and are broken down in the setting of an oxidative stress response.
- Over time, this abnormal lipid deposition triggers the → immune system via →toll-like receptor 4 (TLR4) resulting in the production of inflammatory cytokines such as TNF that cause liver cell injury and death.
- These events mark the transition to steatohepatitis and in the setting of chronic injury, fibrosis eventually develops setting up events that lead to cirrhosis and hepatocellular carcinoma.
- Microscopically, changes that can be seen include
    - **Steatosis with large and swollen hepatocytes (ballooning),**
    - **Evidence of cellular injury and cell death (apoptosis, necrosis),**
    - **Evidence of inflammation in particular in zone 3 of the liver,**
    - **Variable degrees of fibrosis and Mallory bodies.**

Diagnosis



Most elevated aminotransferase	Cause
ALT	Chronic hepatitis B, C, and D
	Nonalcoholic liver disease
	Acute viral hepatitis
	Medications/toxins
	Autoimmune hepatitis
	Wilson's disease
	Alpha-1-antitrypsin deficiency

	Hemochromatosis
	Ischemic hepatitis (severe elevation up to thousands)
AST	Alcoholic liver disease
	Cirrhosis



- Histopathology of acute hepatitis with
  - **Lobular disarray and**
  - **Associated lymphocytic inflammation,**
  - **Acidophil body formation (arrow) and**
  - **Bilirubin stasis.**
- ***Diagnosis of hepatitis is made on the basis of some or all of the following:***
  - **A person's signs and symptoms,**
  - **Medical history including sexual and substance use history,**
  - **Blood tests,**
  - **Imaging, and**
  - **Liver biopsy.**
- In general, for viral hepatitis and other acute causes of hepatitis, the person's blood tests and clinical picture are sufficient for diagnosis.
- For other causes of hepatitis, especially chronic causes, blood tests may not be useful.
- In this case, liver biopsy is the gold standard for establishing the diagnosis:
- Histopathologic analysis is able to reveal the precise extent and pattern of inflammation and fibrosis.
- However, liver biopsy is typically not the initial diagnostic test because it is invasive and is associated with a **small but significant risk of bleeding** that is increased in people with liver injury and cirrhosis.
- **Blood testing includes**
  - **Liver enzymes,**
  - **Serology (i.e. For autoantibodies),**
  - **Nucleic acid testing (i.e. For hepatitis virus DNA/RNA),**
  - **Blood chemistry, and**
  - **Complete blood count.**
  - **Characteristic patterns of liver enzyme abnormalities can point to certain causes or stages of hepatitis.**
- Generally, AST and ALT are elevated in most cases of hepatitis regardless of whether the person shows any symptoms.
- ***However,***
  - ***The degree of elevation***
    - ***(i.e. Levels in the hundreds vs. In the thousands),***

    - ***The predominance for AST vs. ALT elevation, and***
    - ***The ratio between AST and ALT are informative of the diagnosis.***
- Ultrasound, CT, and MRI can all identify steatosis (fatty changes) of the liver tissue and nodularity of the liver surface suggestive of cirrhosis.
- CT and especially MRI are able to provide a higher level of detail, allowing visualization and characterize such structures as vessels and tumors within the liver.
- Unlike steatosis and cirrhosis, no imaging test is able to detect liver inflammation (i.e. hepatitis) or fibrosis.
- Liver biopsy ***is the only definitive diagnostic test*** that is able to assess inflammation and fibrosis of the liver.[29]

Viral hepatitis

- Viral hepatitis is primarily diagnosed through blood tests for levels of
- Viral antigens (such as
- The hepatitis B surface or core antigen),
    - Anti-viral antibodies (such as the anti-hepatitis B surface antibody or anti-hepatitis A antibody), or
    - Viral DNA/RNA.
- In early infection (i.e. within 1 week), IgM antibodies are found in the blood.
- In late infection and after recovery, IgG antibodies are present and remain in the body for up to years.
- Therefore, when a patient is positive for IgG antibody but negative for IgM antibody, he is considered immune from the virus via either prior infection and recovery or prior vaccination.
- In the case of hepatitis B, blood tests exist for multiple virus antigens (which are different components of the virion particle) and antibodies.
- The combination of antigen and antibody positivity can provide information about the stage of infection (acute or chronic), the degree of viral replication, and the infectivity of the virus.

Alcoholic versus non-alcoholic

- The most apparent distinguishing factor between:
- Alcoholic steatohepatitis (ASH) and nonalcoholic steatohepatitis (NASH) is a history of alcohol use or abuse.
- Thus, in patients who have no or negligible alcohol use, the diagnosis is unlikely to be alcoholic hepatitis.
- However, in those who use alcohol, the diagnosis may just as likely be alcoholic or nonalcoholic hepatitis especially if there is concurrent obesity, diabetes, and metabolic syndrome.
- In this case, alcoholic and nonalcoholic hepatitis can be distinguished by the **pattern of liver enzyme abnormalities**;
- Specifically, in alcoholic steatohepatitis **AST > ALT** with ratio of **AST:ALT >2:1**
- While in nonalcoholic steatohepatitis ALT>AST with ratio of **ALT: AST >1.5:1.**
- Of note, liver biopsy shows identical findings in patients with ASH and NASH, specifically,

    - **The presence of polymorphonuclear infiltration, hepatocyte necrosis and apoptosis in the form of ballooning degeneration,**
    - **Mallory bodies, and**
    - **Fibrosis around veins and sinuses.**

Screening for viral hepatitis

- The purpose of screening for viral hepatitis is to identify people infected with the disease as early as possible, even before symptoms and transaminase elevations may be present.
- This allows for early treatment, which can both prevent disease progression and decrease the likelihood of transmission to others.

Hepatitis A

- **Hepatitis A** causes an acute illness that does not progress to chronic liver disease.
- Therefore, the role of screening is to assess immune status in people who are at high risk of contracting the virus, as well as in people with known liver disease for whom hepatitis A infection could lead to liver failure.
- People in these groups who are not already immune can receive the hepatitis A vaccine.
- Those at high risk and in need of screening include:
    - **People with poor sanitary habits such as not washing hands after using the restroom or changing diapers**
    - **People who do not have access to clean water**
    - **People in close contact (either living with or having sexual contact) with someone who has hepatitis A**
    - **People who use illegal drugs**
    - **People with liver disease**
    - **People traveling to an area with endemic hepatitis A**
    - The presence of anti-hepatitis A IgG in the blood indicates past infection with the virus or prior vaccination.

Hepatitis B

The CDC, WHO, USPSTF, and ACOG recommend routine hepatitis B screening for certain high-risk populations.

Specifically, these populations include people who are:

- ***Born in countries where the prevalence of hepatitis B is high (defined as ≥2% of the population), whether or not they have been vaccinated***
- ***Born in the United States whose parents are from countries where the prevalence of hepatitis B is very high (defined as ≥8% of the population), and who were not vaccinated***
- ***HIV positive***
- ***Intravenous drug users***
- ***Men who have sex with men***
- ***In close contact with (i.e. live or have sex with) people known to have hepatitis B***
- ***Pregnant***
- ***Beginning immunosuppressive or cytotoxic therapy***
- ***Found to have elevated liver enzymes without a known cause***
- ***Blood, organ, or tissue donors***
- ***Incarcerated***
- ***On hemodialysis***

- Screening consists of a blood test that detects hepatitis B surface antigen (HBsAg).
- If HBsAg is present, a second test – usually done on the same blood sample – that detects the antibody for the hepatitis B core antigen (anti-HBcAg) can differentiate between acute and chronic infection.
- People who are high-risk whose blood tests negative for HBsAg can receive the hepatitis B vaccine to prevent future infection.

Hepatitis C

The CDC, WHO, USPSTF, AASLD, and ACOG recommend screening people at high risk for hepatitis C infection.

These populations include people who are:

- ***Intravenous drug users (past or current)***
- ***Intranasal illicit drug users***
- ***HIV-positive***
- ***Men who have sex with men***
- ***Incarcerated, or who have been in the past***
- ***On long-term hemodialysis, or who have been in the past***
- ***Recipients of tattoos in an "unregulated setting"***
- ***Recipients of blood products or organs prior to 1992 in the United States***
- ***Adults in the United States born between 1945-1965***
- ***Born to HCV-positive mothers***
- ***Pregnant, and engaging in high-risk behaviors***
- ***Workers in a healthcare setting who have had a needle-stick injury***
- ***Blood or organ donors.***
- ***Sex workers***

For people in the groups above whose exposure is ongoing, screening should be "periodic," though according to the USPSTF, research has not defined the optimal screening interval.

- The AASLD recommends screening men who have sex with men who are HIV-positive annually.
- People born in the US between years 1945-1965 should be screened once (unless they have other exposure risks).
- Screening consists of a blood test that detects anti-hepatitis C virus antibody. If anti-hepatitis C virus antibody is present, a confirmatory test to detect HCV RNA indicates chronic disease.