Training workshop on screening, diagnosis and treatment of hepatitis B and C

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Session 3

Causes, and symptoms and signs of liver injury

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Learning objectives

At the end of this session, participants should be familiar with

- Causes of hepatitis
- Signs and symptoms of liver disease
- Differences between
  - Acute hepatitis versus acute liver failure
  - Acute hepatitis versus chronic hepatitis
  - Chronic hepatitis versus cirrhosis
  - Compensated versus decompensated cirrhosis

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In this session we will learn about the causes of hepatitis, its signs and symptoms, and features that helps us in differentiating between the various clinical syndromes and stages of viral hepatitis.

Hepatitis

Hepatitis = *Hepat* + *itis*

Liver + inflammation

A wide variety of causes/factors can lead to liver inflammation

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Hepatitis means inflammation of the liver, which could be caused by a range of agents.

Hepatitis: Causes

A wide variety of causes

- Most often caused by **infection with a hepatotropic virus**
- Other causes
  - Alcohol
  - Drugs
  - Other infections
    - Viruses other than hepatitis viruses
    - Parasites (e.g. malaria)
    - Bacteria (e.g. typhoid)
  - Ischemia (reduced blood supply)
  - Autoimmune disorders

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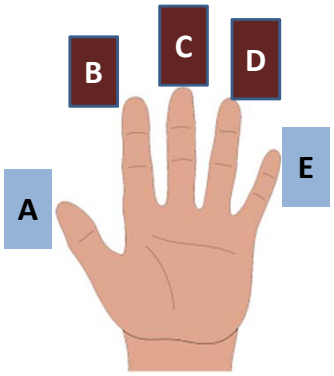
The liver can be injured by any number of agents but the major causes are viral infections (hepatitis viruses such as hepatitis C or B), toxins (alcohol) or drugs (antitubercular drugs – INH, rifampicin, pyrazinamide; antiepileptic drugs – phenytoin; paracetamol overdosing; etc.).

Hepatotropic viruses

- Hepatotropic viruses are viruses that selectively and preferentially infect and injure the liver
- At least five are currently known
  - Hepatitis A virus (HAV)
  - Hepatitis B virus (HBV)
  - Hepatitis C virus (HCV)
  - Hepatitis D virus (HDV)
  - Hepatitis E virus (HEV)



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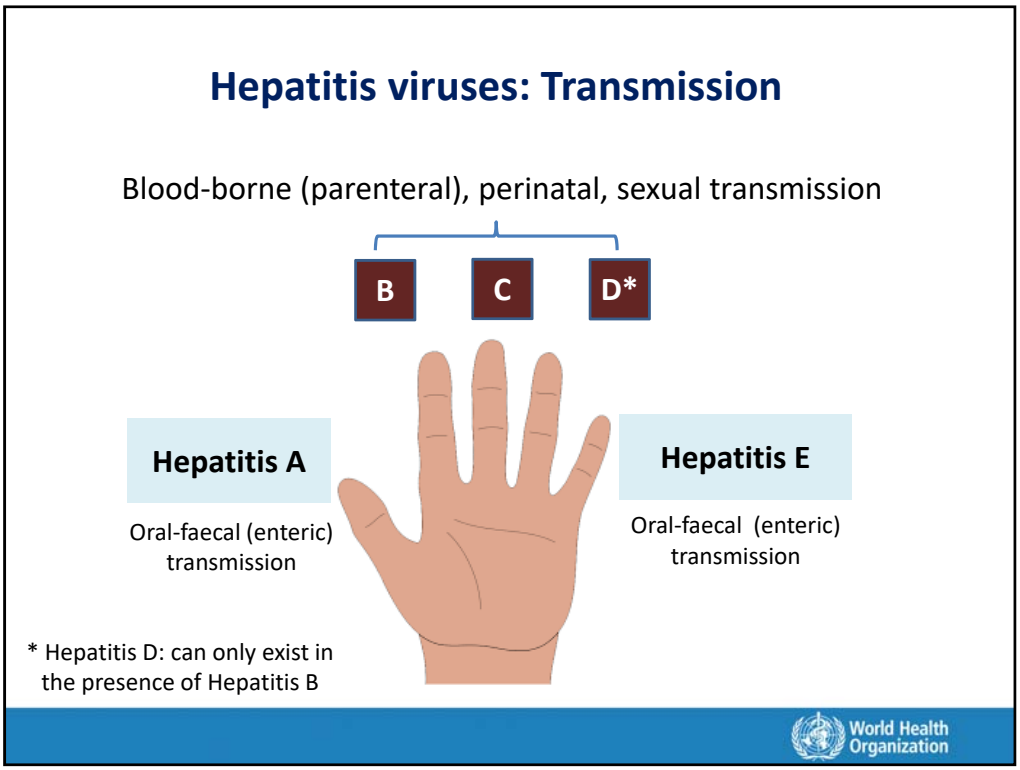
Viral hepatitis is most commonly caused by hepatotropic viruses. Hepatotropic viruses are so named because the liver is the primary site of infection for these viruses. These viruses may have limited involvement of the extrahepatic organs through an indirect mechanism.

Further, several non-hepatotropic viruses could also cause hepatitis such as dengue, cytomegalovirus, herpesvirus, varicella, etc.

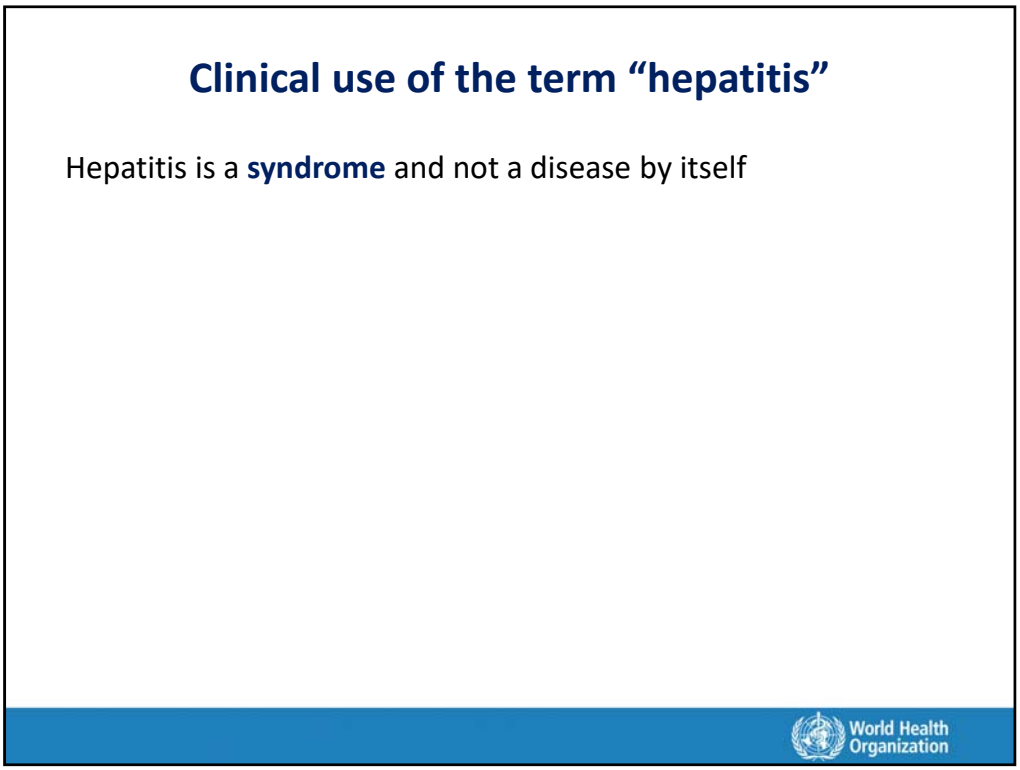
There are five known hepatotropic viruses: HAV, HBV, HCV, HDV and HEV.



The five hepatotropic virus could be clubbed into two groups based upon certain similarities among them:

(A) enterically transmitted viruses, which include HAV and HEV. HAV primarily affects children whereas HEV primarily affects adults; both these viruses cause acute hepatitis, which recovers completely without causing any longstanding chronic hepatitis. HEV can occasionally cause chronic hepatitis in the immunocompromised population, in particular, in European countries; HAV is not reported to cause chronic hepatitis.

(B) parenterally transmitted viruses, which include HBV, HDV and HCV. The most common parenteral routes of transmission include transfusion of contaminated blood, use of unsafe injections or needles, transmission from a pregnant woman to her baby, and unsafe sex.



Hepatitis is a syndrome and not a disease. A syndrome is characterized by a group of signs and symptoms that could have several causes. Here, hepatitis syndrome is characterized by prodromal symptoms, jaundice, raised liver enzymes, hepatomegaly, among other symptoms, regardless of the virus that has caused it.

Clinical use of the term “hepatitis”

Hepatitis is a **syndrome** and not a disease by itself

Syndrome

A set of symptoms and signs that often occur together and are often associated with a particular disease or group of diseases

e.g. Common cold syndrome
Acute gastroenteritis

Two distinct presentations

Acute hepatitis / acute liver failure

Chronic hepatitis / cirrhosis

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In an analogy, we can compare hepatitis to pneumonia, which is also a syndrome and could be caused by any number of pathogens; similarly, in the surgical area, bowel obstruction is a syndrome characterized by pain abdomen and vomiting but it could have several causes such as tuberculosis, malrotation, stricture, etc.

Hepatotropic viruses could have two syndromic presentations: first, acute hepatitis, which could occasionally progress to acute liver failure; and chronic hepatitis, which could progress to liver cirrhosis.

Hepatotropic viruses: Transmission

Virus	Route		
HAV	**Faecal–oral**		
HBV	Parenteral		
HCV	Parenteral		
HDV	Parenteral		
HEV	**Faecal–oral**		

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This table summarizes the routes of transmission and the clinical syndrome caused by the two groups of hepatotropic viruses.

Hepatotropic viruses: Acute vs chronic infection

Virus	Route	Acute infection	
HAV	**Fecal-oral**	**+++**	
HBV	Parenteral	++	
HCV	Parenteral	+	
HDV	Parenteral	+ (co-infection)	
HEV	**Fecal-oral**	**++**	

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Hepatotropic viruses: Acute vs chronic infection

Virus	Route	Acute infection	Chronic infection
HAV	**Faecal–oral**	**+++**	**No**
HBV	Parenteral	++	+++
HCV	Parenteral	+	+++
HDV	Parenteral	+ (coinfection)	++ (superinfection)
HEV	**Faecal–oral**	**++**	**No, (except in a few immunosuppressed persons)**

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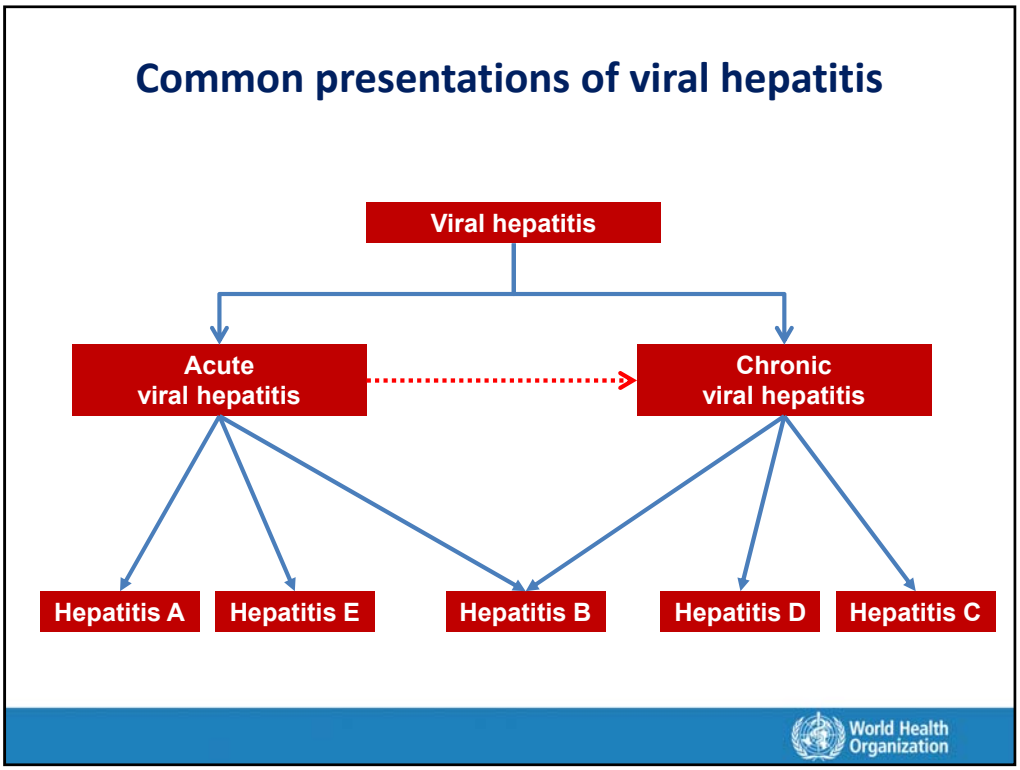

Please note a small difference here from what we have learned so far. HBV can cause acute hepatitis as well as chronic hepatitis. This is because the syndromic presentation of HBV infection is determined by the age of the host at which virus exposure occurred.

Among children, HBV infection frequently progresses to chronic hepatitis whereas in adults it presents as acute hepatitis. We will learn more about it in due course.

Acute hepatitis

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Acute viral hepatitis

- Inflammation of the liver due to a recent infection with a hepatotropic virus
- Usually short duration (days to weeks)

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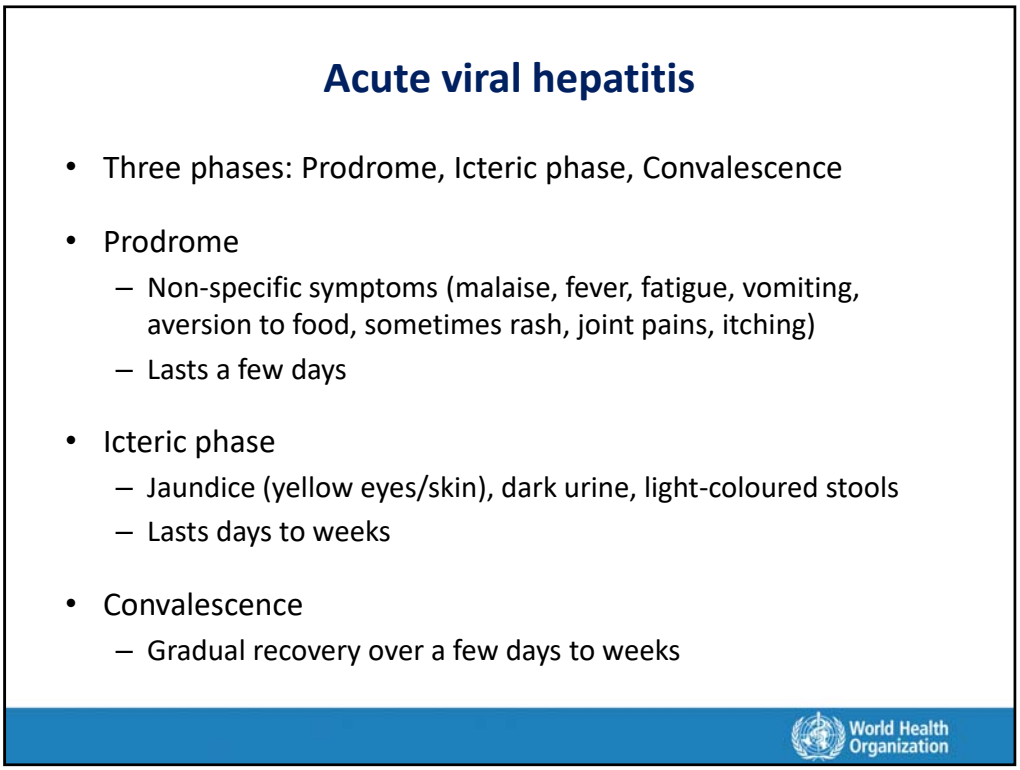
Acute hepatitis implies a recently acquired infection. Acute hepatitis is marked by sudden and massive death of the hepatocytes over a short period of time and is characterized by all the five components of inflammation. Clinically we find liver enlargement (tumor); tenderness on palpation (dolor); jaundice with or without coagulopathy/encephalopathy (loss of function).



Typically, acute viral hepatitis has three phases: prodromal, icteric and convalescent. The prodromal phase consists of a variable mixture of marked anorexia, fever, generalized body ache, joint pains, headache, myalgia, malaise, nausea and vomiting. A few patients may also have skin rash or lymphadenopathy. Anorexia is often the most remarkable symptom. This phase usually lasts for 5–7 days and ends with the onset of jaundice. During the prodrome, serum transaminases are elevated, with their level usually exceeding 3 times the upper limit of normal (ULN) and often being >10-fold. In all forms of viral hepatitis, this phase is associated with the potential for transmission of infection and the viruses can be detected in various body fluids, depending upon the particular agent. The icteric phase is marked by clinical jaundice. It usually lasts a few (often 2–4 but longer at times) weeks, and is followed by lowering of serum bilirubin. Abdominal examination reveals mid- and right upper quadrant tenderness, mild tender hepatomegaly, and occasionally mild splenomegaly and mild ascites.

In the convalescent phase, jaundice recedes, all other symptoms improve and organomegaly regresses. Some cases with acute viral hepatitis, particularly those due to HAV and HEV infection, may have a prolonged phase of cholestasis with intractable pruritus, that may continue for few months.

Differential diagnosis of acute viral hepatitis

- Many other diseases can have symptoms similar to acute viral hepatitis
- Systemic infections
  - Malaria
  - Dengue
  - Leptospirosis
- Drug-induced liver injury
- Biliary obstruction

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In tropical countries, where systemic infections are much more common, we need to differentiate these from acute viral hepatitis. It is very important because most of these infections as well as viral hepatitis occur during the same period of the year and a few of them have specific and effective treatment.

Further, drug use is very common in developing countries, in particular, antitubercular drugs, which could cause drug-induced liver injury (DILI) and will need timely identification and drug discontinuation. Similarly, obstructive jaundice is also common and needs to be identified.

Examination

- Jaundice of variable degree
- Slight enlargement of the liver, usually soft, may be mildly tender
- No or mild splenomegaly
- No abdominal mass
- No ascites (in some, mild ascites may be present)

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Acute hepatitis is characterized by soft, mildly tender hepatomegaly; normal-size spleen or mild, soft, non-tender splenomegaly; no ascites or presence of mild ascites in occasional patients.

Indicators of acute viral hepatitis in a jaundiced patient

- Prodromal features, especially loss of appetite
- Seasonal occurrence
- Epidemiological setting – outbreak
- Presence of risk factors
- Relatively minor nature of fever, abdominal pain, etc.
- Sudden onset of conjugated hyperbilirubinaemia
- Marked elevation of ALT/AST (usually >10-fold upper limit; often much more, even up to 150 times)

Note: Do not forget to ask about intake of hepatoxic drugs

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Marked loss of appetite is the most prominent prodromal feature. It is known that during viral hepatitis, smokers develop an aversion to smoking as well. Cases caused by the waterborne hepatotropic viruses (HAV and HEV) predominantly occur during either the hot summer months (because of scarcity of safe drinking water and poor hygiene) or in the post rainy season, when the risk of faecal contamination of drinking water is the maximum.

During travel, the risk of exposure to contaminated food and water is increased, which could transmit HEV/HAV. Because their median incubation period is usually in the range of 4–8 weeks, we should ask for the history 1–2 months before the onset of symptoms.

Investigations

- Liver function tests
  - Serum bilirubin
  - Liver enzymes: ALT, AST, Alkaline phosphatase
  - Prothrombin time (INR)
- Viral serology
  - IgM anti-HAV
  - IgM anti-HEV
  - HBsAg -> IgM anti-HBc
  - Anti-HCV and/or HCV RNA
- Ultrasound may help to distinguish from biliary obstruction

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During the laboratory work-up of acute hepatitis, we need to have liver function tests; prothrombin time with INR; ultrasound (USG) abdomen if biliary obstruction or other pathology such as liver abscess is suspected. To diagnose if hepatitis virus are the cause of acute hepatitis, we need IgM testing for HAV, HEV and screening for HbsAg and anti-HCV.

If HBsAg is positive, then IgM anti-HBc should be done to confirm. If anti-HBc IgM is positive, this could be acute HBV or flare up of chronic HBV infection. In the early phase of acute HCV, anti-HCV may be negative, thus, HCV RNA is the optimal test. Patients who are acutely infected with hepatitis C virus typically develop abnormal laboratory findings in the following order: detectable HCV RNA, followed by elevation in ALT, and then HCV antibody.

Treatment of acute viral hepatitis

- No dietary restrictions
  - Dietary restrictions do not change the outcomes
  - However, often leads to malnutrition

- Only supportive measures to relieve symptoms
- No need for “bed rest” or marked restriction of physical activity
- Hepatoprotective drugs have no role
- Antiviral drugs have no role
- Usual infection-control precautions may be used, but no need for isolation of cases

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Most patients with acute viral hepatitis improve with supportive symptomatic treatment, and specific medical treatment is neither indicated nor available. Dietary restrictions and enforced bed rest have NO role in the treatment of acute viral hepatitis. The former merely serves to undermine the patient’s nutritional status.

There is no specific therapy for acute HAV and HEV. Acute HBV does not need any therapy though some data suggest that antiviral drugs may be useful in patients with severe acute viral hepatitis or acute liver failure due to HBV infection.

Acute viral hepatitis

- Severity and duration of illness can vary widely
- Acute viral hepatitis (HAV, HBV and HEV) often milder in children than in adults
- Some patients develop a serious form of disease:

  "acute liver failure"

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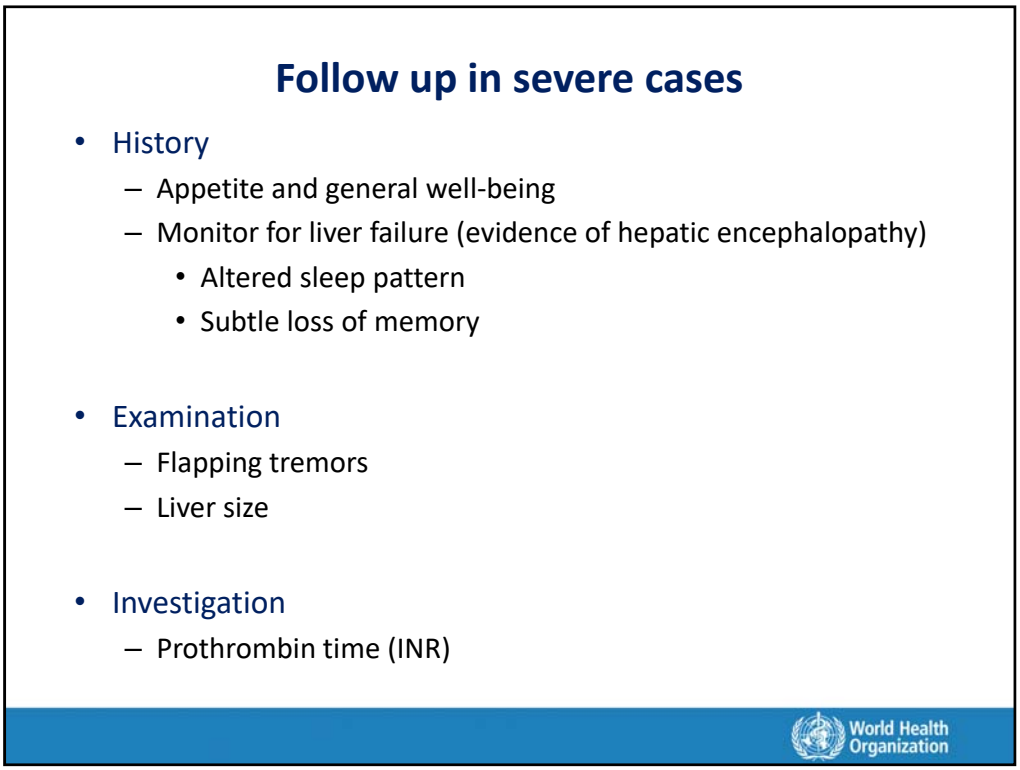
The severity of illness due to acute viral hepatitis is very variable. In general, it is milder among children than adults. The reason for this difference in disease severity is not well understood. Very occasionally, patients with acute viral hepatitis may progress to acute liver failure.



Patients with acute viral hepatitis are at risk, though very small, of progression to acute liver failure. Hence, all acute hepatitis patients should be monitored for the early features of acute liver failure. On clinical examination, presence of an altered sleep pattern and flapping tremors are the early signs of liver failure.

The only laboratory test that indicates liver failure is prothrombin time (International Normalized Ratio, INR). Hence, during follow up for acute viral hepatitis, INR must be repeated as and when required.

Acute liver failure (ALF)

ALF is defined as

- jaundice
- no pre-existing chronic liver disease
- hepatic encephalopathy
- prolonged prothrombin time (INR>1.5)

ALF to be managed in the intensive care unit (ICU) with support for

- invasive vital monitoring
- organ replacement therapy
- liver transplantation

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Acute liver failure is characterized by additional features of hepatic encephalopathy and prolonged INR. Though there is no specific drug treatment for ALF, early detection is useful so that the patient can be shifted early to an intensive care unit where an organ support system may be in place and liver transplantation, if needed, could be done.

Approach to acute viral hepatitis with HBsAg

A patient with acute viral hepatitis who has HBsAg +ve may have:

Acute hepatitis B

IgM anti-HBc +ve

Acute hepatitis A or E with pre-existing chronic hepatitis B

IgM anti-HAV +ve or

IgM anti-HAV +ve

Hepatitis B reactivation (have features of chronic liver disease)

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Sometimes patients with chronic HBV infection may present with acute viral hepatitis-like features. This happens because of the HBV virus reactivation. HBV reactivation could be suspected in the presence of radiological or laboratory markers of chronic liver disease, cirrhosis or portal hypertension.

Acute hepatitis B

- Not uncommon
- Consider risk factors: may help identify the source and help prevent acquisition of other infections
- When in older children and adults, follow-up testing at 6 months
  - 95% will clear the virus in 6–12 months
- Antiviral drugs do not have much role

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HBV has a unique pattern of clinical illness, which is primarily determined by the age of the host at the time of exposure. There is an inverse relationship between the risk of developing acute hepatitis and its progression to chronic infection and the age of the host. Infections during infancy remain asymptomatic and carry more than 90% chance of progressing to chronic infection. Up to the age of 5 years, about 20% develop chronic infection.

After the age of 5 years and particularly in adults, more than 90% develop acute hepatitis (usually mild symptoms, with some people having severe symptoms). Most adults clear the virus within six months and recover fully.

Acute hepatitis in pregnancy

- Consider HEV as the main cause in endemic areas
- HEV infection in pregnancy carries a higher risk of
  - clinical disease
  - acute liver failure
  - maternal complications and death
  - adverse fetal outcome
- Needs close monitoring and may need hospitalization

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Pregnant women, in particular those in their third trimester of gestation, are prone to developing acute HEV infection. Acute HEV in pregnant women frequently develop acute liver failure (about 20–25%) with high rates of maternal and fetal mortality.

Acute viral hepatitis: Summary

In a patient with acute viral hepatitis, important considerations include the following:

- Make a diagnosis; exclude other causes of jaundice
- Identify cases with acute liver failure
- Monitor severe cases for progression to acute liver failure
  - using prothrombin time (INR)
- Most patients improve spontaneously over days to weeks
  - Dietary changes and drugs have very little role
  - Reassurance and symptomatic treatment, if needed, are the most important

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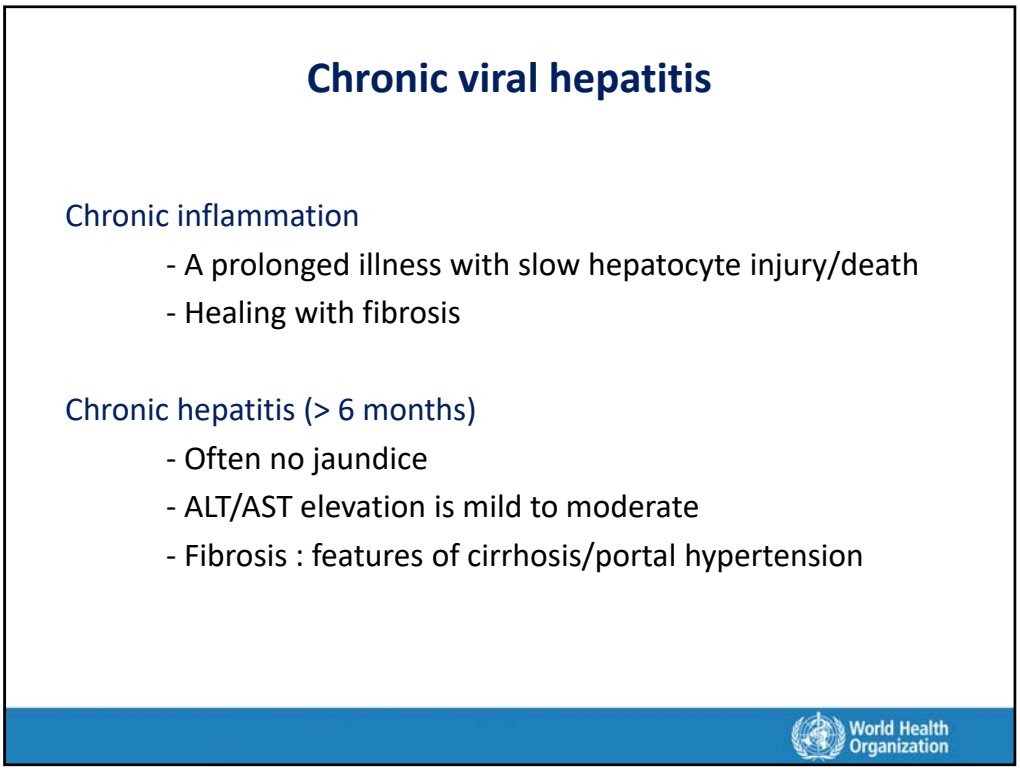
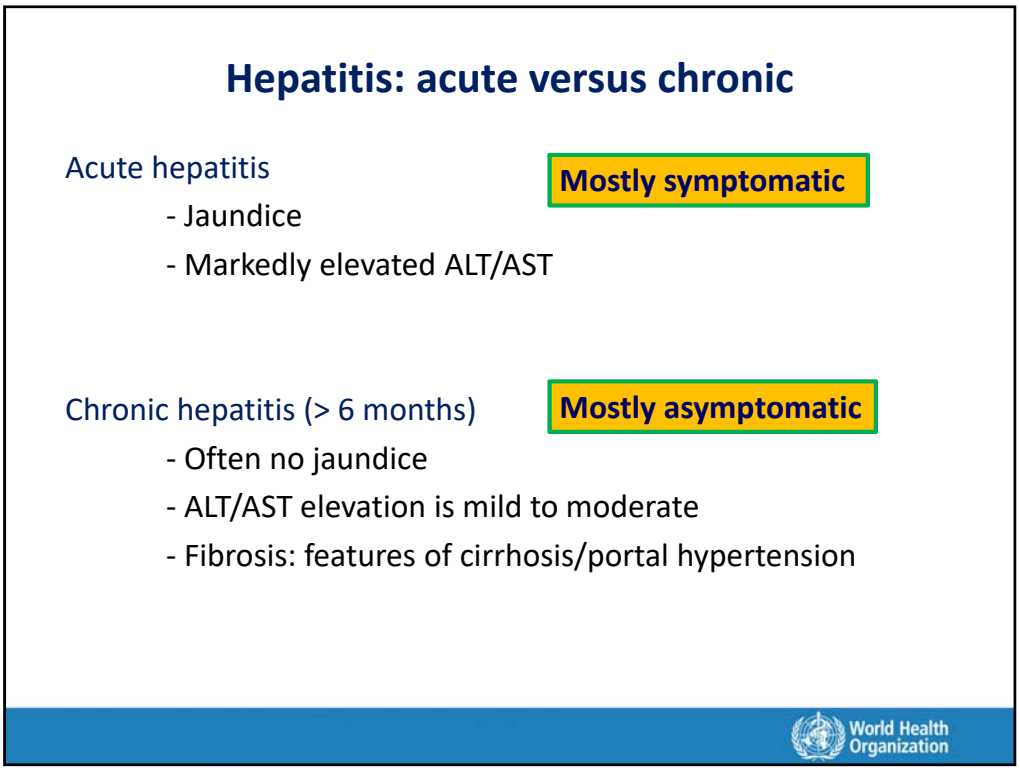


Chronic hepatitis is characterized by slow but longstanding injury, which leads to an ongoing process of cell death and healing. Healing in chronic hepatitis is in the form of fibrosis.

Conventionally, if hepatitis continues for >6 months, it is labelled as chronic hepatitis.

In contrast to acute viral hepatitis, chronic hepatitis is characterized by absence of jaundice, mild-to-moderate elevation of serum levels of liver enzymes, with or without features of cirrhosis or portal hypertension.



Because of prodromal symptoms and clinical jaundice, patients with acute hepatitis come to the physician on their own. In contrast, chronic hepatitis remains silent for decades before becoming symptomatic, hence physicians need to suspect and actively search for it.

Chronic viral hepatitis

- May be entirely asymptomatic
- May manifest as a variable combination of
  - Jaundice
  - Hepatomegaly/small liver
  - Elevated serum transaminases (ALT, AST)
- If liver injury marked
  - Features of liver failure
- If injury prolonged (chronic)
  - Features of portal hypertension

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The majority of patients with chronic hepatitis are asymptomatic and are accidentally identified when screened for some other reason such as presurgical work-up, pre-visa screening, antenatal screening, etc. In the later stages of fibrosis, the patient may present with various combinations of jaundice, deranged liver function tests or features of portal hypertension.

Symptoms of chronic liver disease or cirrhosis

- General malaise, easy fatiguability
- Anorexia, nausea, vomiting
- Weight loss
- Low grade fever
- Abdominal fullness
- Abdominal pain (in upper abdomen – right or midline)

None of the symptoms are specific or pathognomonic

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Chronic liver disease (CLD) has no specific feature. The features of CLD are common non-specific features. The features of decompensation such as ascites, bleeding, encephalopathy appear at a very late stage of the disease.

Features of liver failure

Several functions

Glycogenesis & gluconeogenesis

Poor glycogen store	> hypoglycaemia
	> hyperglycaemia
Poor gluconeogenesis	> hypoglycaemia

Excretory function

Bile pigment	
Impaired excretion	> jaundice

Synthetic function

Albumin	> hypoalbuminaemia>edema/ascites
Coagulation factors	> prolonged prothrombin time (INR)

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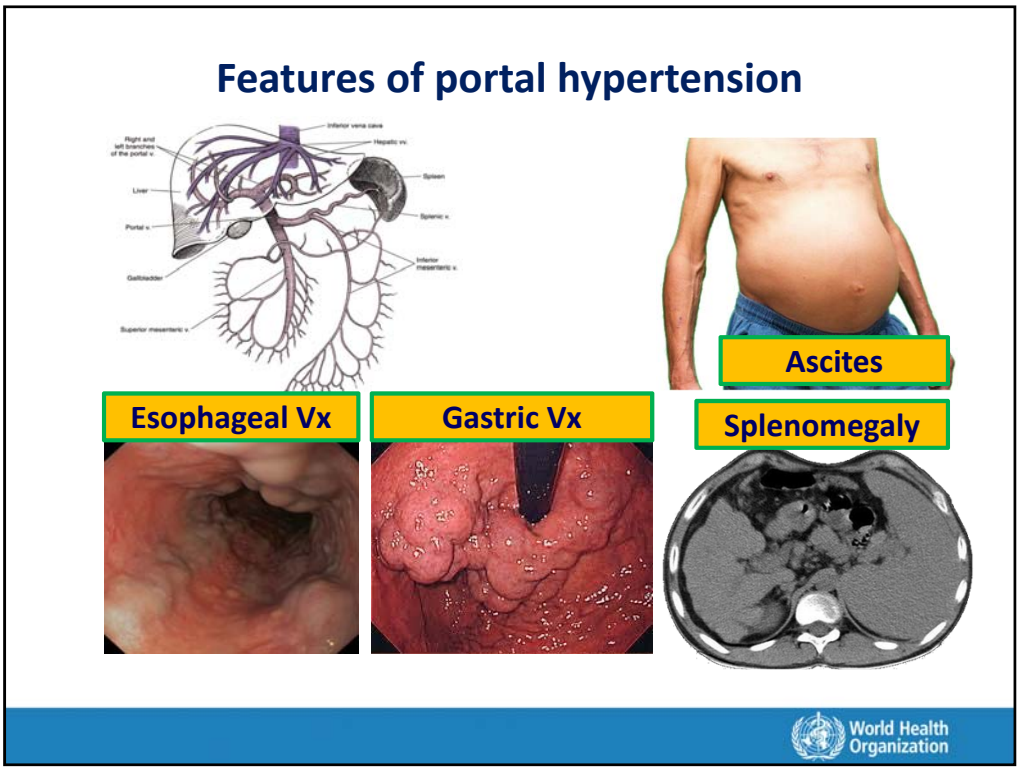
There are three major functions of the liver: glucose metabolism, which maintains the blood glucose within an acceptable range; excretion of waste substances from body in the bile; and synthesis of important body proteins such as albumin and coagulation factors. Impaired glucose metabolism results in postprandial hyperglycaemia and hypoglycaemia after fasting. Impaired excretion of bilirubin results in jaundice. Impaired clearance of toxic wastes may lead to unconsciousness. Albumin is the main protein that maintains the oncotic pressure of the blood and keeps the body vascular volume maintained. If albumin not synthesized then fluid will move out from the blood vessels to spaces such as the peritoneal cavity and pleural cavities. It results in ascites and pleural effusion. Impaired synthesis of coagulation factors will lead to bleeding manifestations.

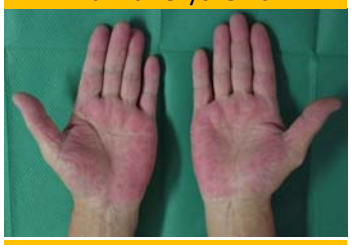


Vasculature proximal to liver gets congested, which is known as portal hypertension. Portal hypertension results in appearance of varices, splenomegaly, ascites, etc. Portal hypertension results in collateral formation at various places. The newly formed collateral vessels manifest as esophageal varices or gastric varices.

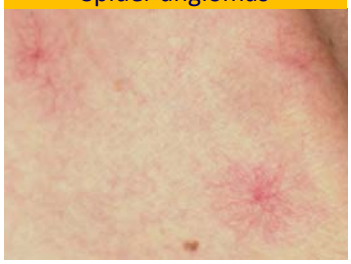
Other signs

- Dark skin pigmentation
- Palmar erythema
- Vascular spider
- Xanthoma
- Subcutaneous bleed
- Gynaecomastia

Palmar erythema



Spider angiomas



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These are a few features which are found in patients with liver cirrhosis. These features helps in early suspicion of cirrhosis by a simple clinical examination.

Cirrhosis

An advanced stage of liver disease characterized by

- extensive hepatic fibrosis
- alteration of liver architecture
- disrupted hepatic circulation
- liver nodularity

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Chronic hepatitis versus cirrhosis

- No distinct cut-off to differentiate the two conditions
- Cirrhosis may be discernible with the following:
  - Firm liver, with nodular margin
  - Features of portal hypertension
    - Splenomegaly (non-tender, firm)
    - Pancytopenia, specially low platelet (<100,000/µL)
    - Esophageal/Gastric varices
    - Non-invasive indicators such as APRI index >2.0

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As we know, liver fibrosis in chronic hepatitis is a continuous process and the severity of fibrosis extends from F1 to F4. Fibrosis stage F4 is also called cirrhosis.

Clinically, cirrhosis is characterized by the presence of a small, hard liver, which has a nodular surface and irregular margins. In addition, patients with cirrhosis also have features of portal hypertension.

Compensated versus decompensated cirrhosis

- A person with cirrhosis initially continues to function normally because of a large reserve capacity in liver function
- At some stage, this “compensation” fails and cirrhosis starts to affect body function and threatens survival: “decompensation”
- Decompensated cirrhosis is characterized by
  features of portal hypertension
  plus
  features of liver failure

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Cirrhosis has two stages: compensated and decompensated. A person with cirrhosis initially continues to function normally because of a large reserve capacity in liver function

At some stage, this “compensation” fails, and cirrhosis starts to affect body functions and threatens survival: “decompensation”

Decompensated cirrhosis is characterized by features of portal hypertension plus features of liver failure.

Decompensated cirrhosis

Usually defined as presence of one of the following features:

- Ascites
- Hepatic encephalopathy
- Total bilirubin >2.5 x ULN* + prolonged prothrombin time (>3 second prolongation or INR** >1.5)
- Variceal bleed

* Upper limit of normal

** International normalized ratio

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Decompensation is defined by the presence of any of the four features as described above. Even if the ascites resolves, a patient will still be considered as decompensated.

Summary: Chronic viral hepatitis

- Chronic viral hepatitis may be entirely asymptomatic or have only non-specific manifestations, despite significant liver injury or even cirrhosis
- Increasing liver injury may lead to signs and symptoms related to
  - portal hypertension
  - liver failure
- Development of “decompensated” liver disease is associated with a marked worsening of clinical outcomes, including the risk of liver-related death

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Hepatitis A virus

- A small RNA virus
- Faecal–oral route of transmission
- Endemic/epidemic in resource-constrained settings
- Most common cause of acute viral hepatitis in children
- Majority of infections are subclinical
- Self-limiting acute hepatitis in the majority
- Acute liver failure in a few
- Lifelong immunity following natural infection
- Effective vaccine is widely available

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Hepatitis B virus

- Circular DNA genome
- Parenteral transmission:
  - Contaminated blood
  - Unsafe injections
  - Unprotected sex, mother-to-child
- Risk of developing chronic infection depends upon the age of the person
- Self-resolving acute hepatitis in adults
- Chronic infection continues throughout life in the majority
- Chronic infection >chronic hepatitis >cirrhosis >liver cancer
- Highly effective vaccine is available

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Hepatitis C virus

- Genome is made up of RNA
- Parenteral transmission: use of contaminated blood/sharp instruments, unprotected sex, pregnant mother to child
- Low risk for sexual and mother-to-child transmission
- Acute infection goes unnoticed
- Majority (70%) of infected persons develop chronic infection
- Chronic infection >chronic hepatitis >cirrhosis >liver cancer
- Chronic infection can easily be treated now
- No vaccine is available

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Hepatitis D virus

- An incomplete RNA virus
- Can cause infection in the presence of hepatitis B virus infection
- People with chronic HBV infection are at risk for acquiring HDV infection
- Parenteral transmission
- Oral drugs effective against HBV are ineffective against HDV
- Treated with pegylated interferon
- Hepatitis B vaccination prevents against HBV infection

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Hepatitis E virus

- A small RNA virus
- Endemic/epidemic in resource-constrained settings, especially among adults
- Most common cause of acute viral hepatitis in adults
- Faecal–oral route of transmission
- Majority of infections are subclinical
- Self-limiting acute hepatitis in majority
- Acute liver failure in a few
- Lifelong immunity following natural infection
- Effective vaccine is available in China

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