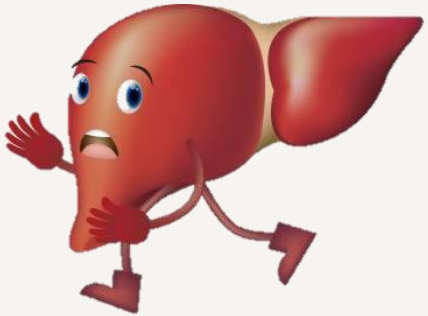
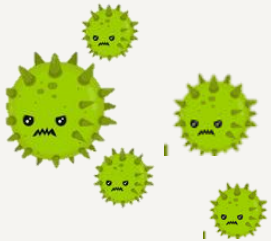
VIRAL HEPATITIS





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Introduction:

- Acute viral hepatitis is systemic infection affecting the liver predominantly
- Almost all cases of acute viral hepatitis are caused by one of the five viral agents:

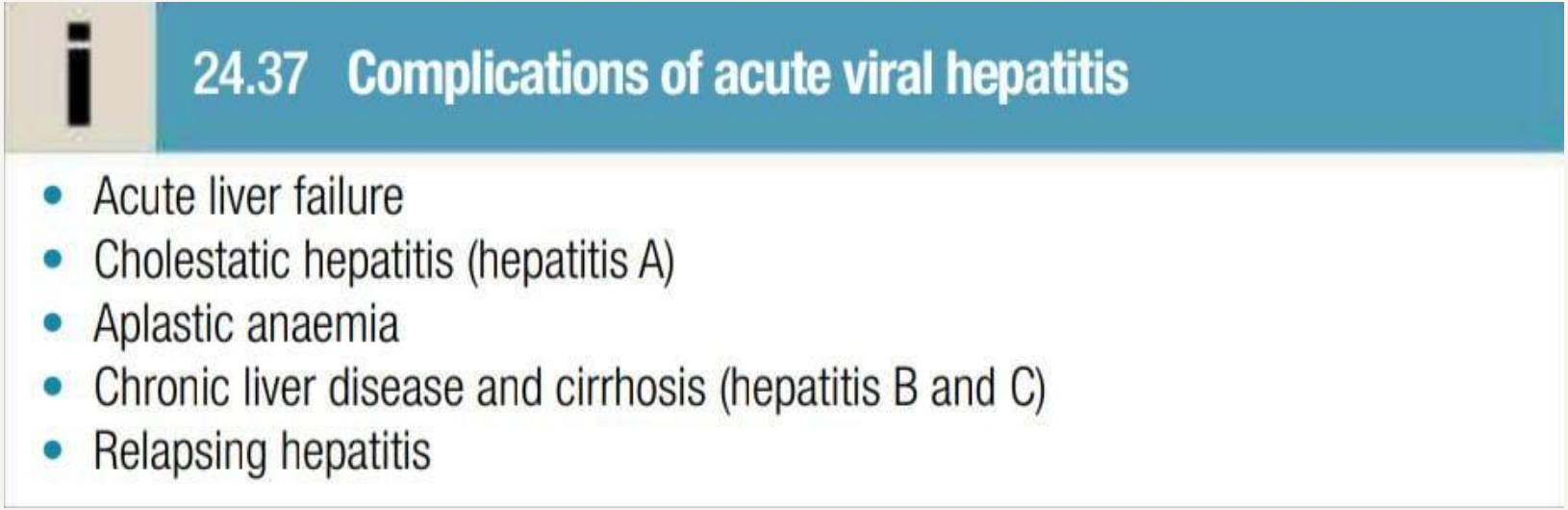
24.35 Causes of viral hepatitis

Common	
• Hepatitis A	• Hepatitis C
• Hepatitis B ± hepatitis D	• Hepatitis E
Less common	
• Cytomegalovirus	• Epstein–Barr virus
Rare	
• Herpes simplex	• Yellow fever

Clinical features:

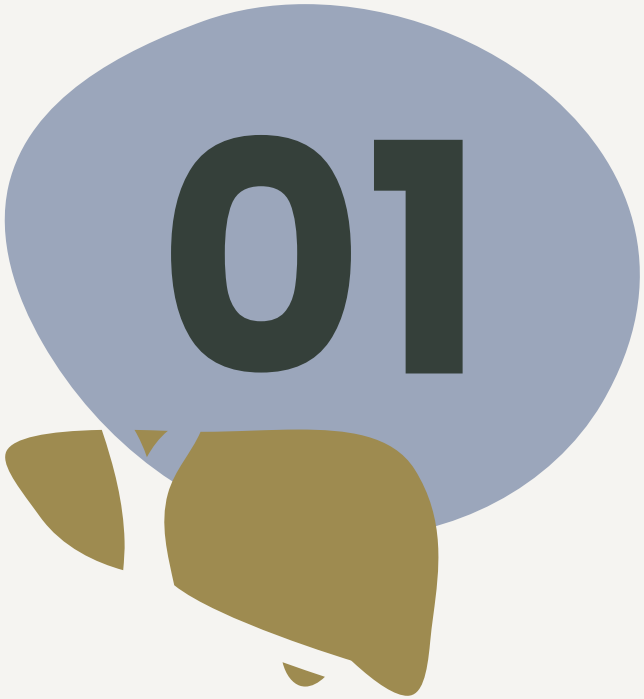
- A non-specific prodromal illness characterised by headache, myalgia, arthralgia, nausea and anorexia usually precedes the development of jaundice by a few days to 2 weeks.
- Vomiting and diarrhoea may follow and abdominal discomfort is common.
- Dark urine and pale stools may precede jaundice.
- There are usually few physical signs.
- The liver is often tender but only minimally enlarged.
- Occasionally, mild splenomegaly and cervical lymphadenopathy are seen (more frequent in children or those with EBV infection.)
- Symptoms rarely last longer than 3–6 weeks.

- Complications may occur but are rare.These may include:

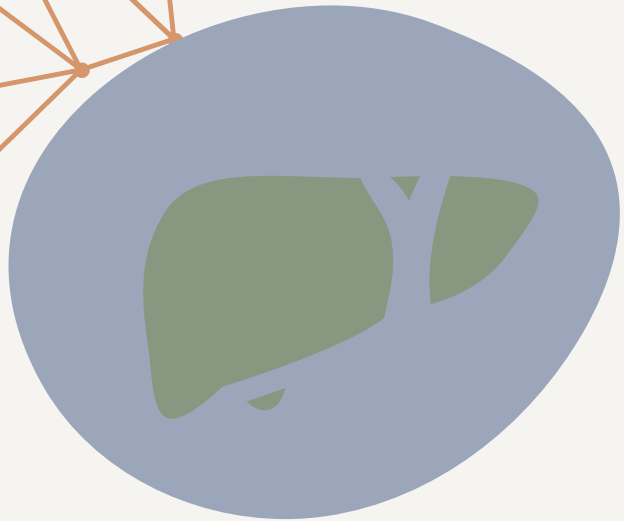


24.37 Complications of acute viral hepatitis

- Acute liver failure
- Cholestatic hepatitis (hepatitis A)
- Aplastic anaemia
- Chronic liver disease and cirrhosis (hepatitis B and C)
- Relapsing hepatitis



HEPATITIS A



HEPATITIS A

- Hepatitis A is the most common type of viral hepatitis
- Caused by hepatitis A virus (HAV)
- which is a nonenveloped, RNA virus belonging to the Picornavirus group.
- Overcrowding and poor sanitation facilitate the spread

Source of infections:

➔ acutely infected persons

Mode of spread:

- Feco-oral route
- In outbreaks, it spreads through water, milk, and shellfish.
- Virus replicates in the liver, is excreted in bile and then excreted in stool/feces of infected persons for about 2 weeks before the onset of symptoms.

Clinical features:

Phase 1: Incubation period

- 30 days(15-45 days)

Phase 2: Symptomatic preicteric phase

- Lasts for 1-2 weeks before onset of jaundice.
- Prodromal symptoms- anorexia, nausea, vomiting, poor appetite, fatigue, malaise, headache, etc...
- Low-grade fever-more in hepatitis A and E than in hepatitis B or
- Upper vague abdominal pain due to stretching of liver capsule..Dark urine and clay-colored stools

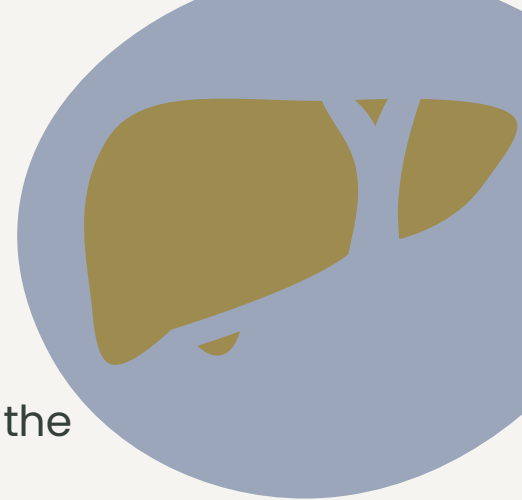
Phase 3: Symptomatic icteric phase

- With the onset of clinical jaundice, the prodromal symptoms usually diminish.
- Liver becomes enlarged and tender.
- Pruritus may develop due to bile salt retention
- Splenomegaly and cervical
- Dark urine and pale stool

Phase 4: Recovery (convalescence) phase

- Symptoms disappear, appetite improves, jaundice decreases, stools and urine normal, and liver size decreases.
- Duration is variable, 2-12 weeks.
- It is more prolonged in acute hepatitis B and C.
- Complete clinical and biochemical recovery within 1-2 months in A and E and 3-4 months in B and C.

Investigations :



- Against HAV infected people make an antibody to this antigen (**anti-HAV**).
- Anti-HAV is important in diagnosis, as HAV is present in the blood only transiently during the incubation period.
- Excretion in the stools occurs for only 7–14 days after the onset of the clinical illness and the virus cannot be grown readily.
- Anti-HAV of the IgM type, indicating a primary immune response, and is present in the blood from the onset of the clinical illness and is diagnostic of an acute HAV infection.
- Anti-HAV of the IgG type is of no diagnostic value, and this antibody persists for years after infection - **marker of previous HAV infection.**

Management

- ✓ Maintain good hygiene and improve social conditions.
- ✓ HAV is resistant to chlorination but is killed by boiling water for 10 minutes.
- ✓ Active immunization: formaldehyde-inactivated HAV vaccine (contains the single HAV antigen) above the age of 2 years. It probably provides lifelong immunity
- ✓ Passive immunization: Normal human immunoglobulin [0.02 mL/kg intramuscularly (IM)].
- ✓ Immediate protection by immune serum globulin if given soon after exposure to the virus.
- ✓ There is no role for antiviral drugs in the therapy of HAV infection.

HEPATITIS B

Hepatitis B Virus

- A core containing DNA and a DNA polymerase enzyme surrounded a surface protein.
- The virus and the surface protein known as the hepatitis B surface antigen, HBsAg, circulates in the blood and assembles within the hepatocytes
- Hepatic damage occurs due to the immune-mediated clearance of the infected hepatocytes
- Most common cause of chronic liver disease and hepatocellular carcinoma
- Hepatitis B can cause acute and chronic infection
- Chronic hepatitis can lead to cirrhosis or hepatocellular carcinoma, usually after decades of infection

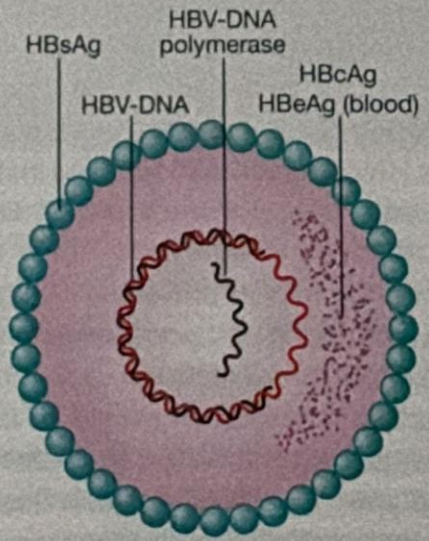


Fig. 24.25 Schematic diagram of the hepatitis B virus. Hepatitis B surface antigen (HBsAg) is a protein that makes up part of the viral envelope. Hepatitis B core antigen (HBcAg) is a protein that makes up the capsid or core part of the virus (found in the liver but not in blood). Hepatitis B e antigen (HBeAg) is part of the HBcAg that can be found in the blood and indicates infectivity. (HBV = hepatitis B virus)

Risk factors of acquisition of hepatitis B infection

Vertical transmission (90-95%)

- Hepatitis B surface antigen (HBsAg)-positive mother

Horizontal transmission

- Intravenous drug use
- Infected unscreened blood products
- Needle stick injury
- Sharing toothbrush/ razor
- Tattoos/acupuncture needles
- Sexual transmission
- Close living quarters/playground play as a toddler (may contribute to
- high rate of horizontal transmission in Africa)

INVESTIGATIONS

Serology

- HBV antigens and their antibodies are important in identifying the stage of HBV infection
- Direct assessment of viral load by polymerase chain reaction (PCR) for HBV DNA

Hepatitis B surface antigen (HBsAg)

- Indicates active infection
- A negative test makes HBV infection very unlikely
- In acute liver failure from hepatitis B, the liver damage is mediated by viral clearance so HBsAg is negative, but there will be presence of hepatitis B core IgM.
- In resolving acute infection antibody to HBsAg (anti-HBs) usually appears after about 3–6 months and persists for many years or permanently

Hepatitis B core antigen (HBcAg)

- HBcAg is not found in the blood, but antibody to it (anti-HBc) appears early in the illness and rapidly reaches a high titre.
- Anti-HBc is initially of IgM type, with IgG antibody appearing later.

Hepatitis B e antigen (HBeAg)

- HBeAg is a part of core antigen and can be used as an indicator of viral replication
- Loss of HBeAg and development of anti-Hbe antibody indicates a partial immune control of virus

Viral load and genotype

- HBV-DNA can be measured by PCR in the blood.
- Viral loads are usually highest in HBeAg- positive infection, making this the most infectious phase
- Measurement of viral load is important in detecting flares of HBeAg negative hepatitis and in monitoring antiviral therapy

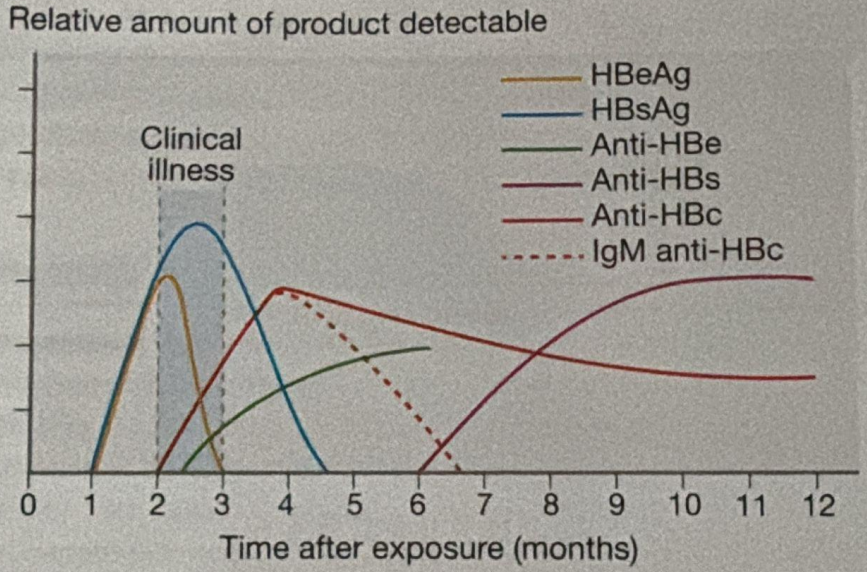


Fig. 24.27 Serological responses to hepatitis B virus infection. (anti-HBc = antibody to hepatitis B core antigen; anti-HBe = antibody to HBeAg; anti-HBs = antibody to HBsAg; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; IgM = immunoglobulin M)

24.39 The five phases of chronic hepatitis B virus (HBV) infection

Phase	HBsAg	HBeAg	Viral load	ALT	Histology	Notes
HBeAg positive chronic infection	+	+	+++ ($>10^7$ IU/ml)	Normal	Normal/minimal necroinflammation	Prolonged in perinatally infected individuals; may be short or absent if infected as an adult. High viral load and so very infectious. Previously known as 'immune-tolerant'
HBeAg-positive chronic hepatitis	+	+	++ (10^4–10^7 IU/ml)	Raised	Moderate/severe necroinflammation	May last weeks or years. Risk of cirrhosis or HCC if prolonged. Previously known as 'immune-reactive'
HBeAg-negative chronic infection	+	–	+/– (<2000 IU/ml)	Normal	Normal/minimal necroinflammation	Low risk of cirrhosis or HCC in majority. Previously known as 'inactive carrier'.
HBeAg-negative chronic hepatitis	+	–	Fluctuating +/++ (>2000 IU/ml)	Raised/ fluctuating	Moderate/severe necroinflammation	May represent late immune reactivation or presence of 'pre-core mutant' HBV. High risk of cirrhosis or HCC
HBsAg-negative phase	–	–	–/±	Normal	Normal	Ultrasensitive techniques may detect low-level HBV DNA even after HBsAg loss

(HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma)

Management of chronic hepatitis B

- Ideal goal of therapy would be to achieve long term viral clearance with loss of HBsAg, but this is rarely achieved by current therapy.
- Treatment is aimed at suppressing viral replication to prevent disease progression
- The goals of treatment are HBeAg seroconversion, reduction in HBV-DNA and normalisation of the LFTs.
- Indication of treatment is the high viral load accompanying liver injury
- Treatment may be initiated during pregnancy in the absence of liver injury to prevent mother-to-child transmission

Direct-acting nucleoside/nucleotide antiviral agents

- ❖ Inhibits the reverse transcription of pre-genomic RNA to HBV-DNA by HBV-DNA polymerase
- ❖ Do not directly affect the covalently closed circular DNA (cccDNA) template for viral replication
- ❖ So relapse is common if treatment is withdrawn.
- ❖ One major concern is the selection of antiviral-resistant mutations with long-term treatment.

***Lamivudine*:** long-term therapy is often complicated by the development of HBV-DNA polymerase mutants (e.g. the 'YMDD variant'), which lead to viral resistance.

- Occurs in half of the patient after 3 years of treatment and is characterized by rise in viral load
- Now, seldom used for treatment but may be used to prevent reactivation

***Entecavir and tenofovir*:** Monotherapy with entecavir or tenofovir is more effective than lamivudine in reducing viral load in HBeAg-positive and HBeAg-negative chronic hepatitis.

- Antiviral resistance - only in 1–2% after 3 years of entecavir drug exposure.
- Monotherapy is contraindicated in HIV-positive patients, as it may lead to HIV antiviral drug resistance

***Pegylated interferon-alfa (PEG-IFN)* :** augments host immune response

- This is most effective in patients with a low viral load and serum transaminases greater than twice the upper limit of normal
- Contraindicated in the presence of cirrhosis, as it may cause rise in serum transaminase and precipitate liver failure

***Liver transplantation*:** required in patients with advanced liver disease or HCC

- The use of nucleoside/nucleotide analogues post transplant has made recurrent disease due to graft re-infection very uncommon.

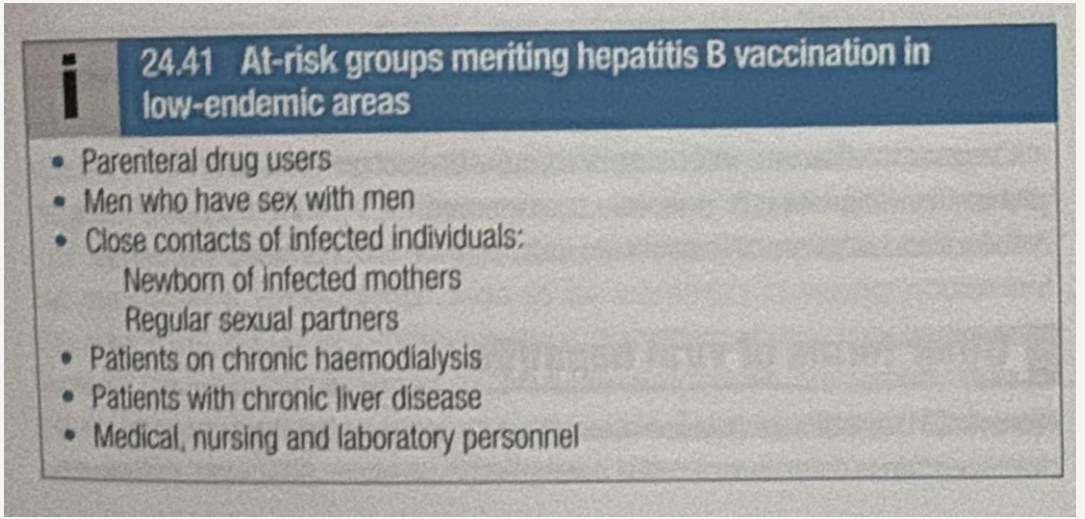
***Hepatocellular carcinoma risk* :** Chronic HBV infection is associated with an increased risk of HCC even in the absence of cirrhosis.

- Risk increases with age, male sex, smoking, diabetes, family history and high viral loads
- Scoring systems like REACH-B and PAGE-B helps to identify high-risk non-cirrhotic patients who may benefit from HCC screening

Prevention

- ✓ Individuals are most infectious when high levels of HBV-DNA are present in the blood, in HBeAg positive infection phase.

✓A recombinant hepatitis B vaccine containing HBsAg is available (Engerix) and is capable of producing active immunisation in 95% of normal individuals. The vaccine should be offered to those at special risk of infection who are not already immune.



i 24.41 At-risk groups meriting hepatitis B vaccination in low-endemic areas

- Parenteral drug users
- Men who have sex with men
- Close contacts of infected individuals:
  - Newborn of infected mothers
  - Regular sexual partners
- Patients on chronic haemodialysis
- Patients with chronic liver disease
- Medical, nursing and laboratory personnel

PREVENTION Cont…

✓The vaccine is ineffective in those already infected by HBV.

✓ Infection can also be prevented or minimised by the intramuscular injection of specific hepatitis B immunoglobulin (HBIg) prepared from blood containing anti-HBs.

✓ Neonates born to hepatitis B-infected mothers should be immunised at birth and given immunoglobulin.

Co-infection with HIV

- Around 10% of HIV-infected population has concurrent HBV
- Co-infection increases morbidity and mortality
- There are greater levels of HBV viremia, faster progression to chronic infection and greater risk of cirrhosis and HCC
- The immunosuppression that is seen in HIV infection can lead to loss of anti-HBs antibodies, reactivation of infection and a poorer antibody response to HBV vaccination
- Several nucleoside analogues have dual antiviral activity and some regimens have been associated with emergence of drug resistance.
- Antiviral therapy should be considered for co-infected pregnant women, using drugs with dual activity, e.g. tenofovir with emtricitabine or lamivudine

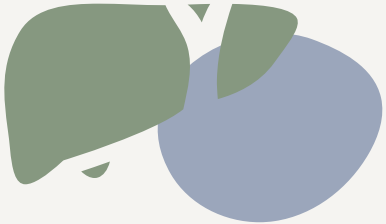
HEPATITIS C

HEPATITIS C

- **Etiological agent :** small, enveloped, single-stranded RNA virus belonging to the family Flaviviridae.
- Previously called bloodborne non-A, non-B hepatitis.
- HCV has six genotypes and in India, most prevalent is **HCV3**

Mode of spread:

- ✓ parenteral route – mainly (transfusion of blood and blood products, and in drug addicts)
- ✓ Sexual contact (low chances of transmission)“
- ✓ Perinatal/vertical transmission
- ✓ Not transmitted by breastfeeding

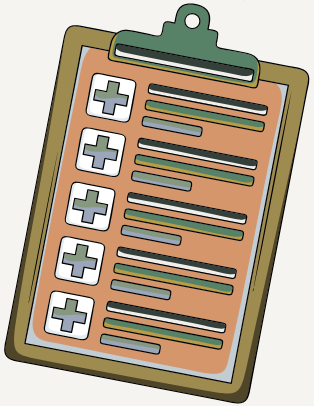


Risk factors

22.40 Risk factors for the acquisition of chronic hepatitis C infection

- Intravenous drug misuse (95% of new cases in the UK)
- Unscreened blood products
- Vertical transmission (3% risk)
- Needlestick injury (3% risk)
- Iatrogenic parenteral transmission (e.g. contaminated vaccination needles)
- Sharing toothbrushes/razors

Investigations



- Serology and virology
  - HCV antibody in the serum
  - HCV RNA detectable in all patients
- LFT
  - Normal or show fluctuating serum transaminases between 50 and 200 U/L
- Histology
  - Liver biopsy - shows features of chronic hepatitis, with lymphoid follicles in the portal tracts, and fatty change.
- Fibrosis assessment
  - Transient elastography, blood biomarkers and non-invasive fibrosis scoring systems

Management

- ✓ There are four main classes of DAA, which are defined according to their mechanism of action .
- ✓ These compounds are targeted to specific steps in the hepatitis C viral life cycle to disrupt viral replication
- ✓ These drugs are now frequently combined into single pill combinations hat can be taken once daily for8-12 weeks

Management of acute hepatitis B

- Full spontaneous recovery occurs in 95% of adults following acute HBV infection. Remaining <5% develop a chronic infection
- Treatment is supportive with monitoring for acute liver failure
- Antiviral therapy is considered when there is severe liver injury with coagulopathy
- Recovery from acute infection occurs within 6 months.

22.41 Direct-acting antiviral agents for hepatitis C

Drug class	Therapeutic target	Selected drugs
Protease inhibitors (PIs)	Non-structural viral protein NS3/4A (protease that cleaves the HCV polyprotein)	Telaprevir Boceprevir Simeprevir Paritaprevir Grazoprevir
Nucleoside polymerase inhibitors (NPIs)	Non-structural viral protein NS5B (RNA-dependent RNA polymerase needed for viral replication)	Sofosbuvir
Non-nucleoside polymerase inhibitors (NNPIs)	Non-structural viral protein NS5B (RNA-dependent RNA polymerase needed for viral replication)	Dasabuvir
NS5A replication complex inhibitors	Non-structural viral protein NS5A (assembly of viral replication complex)	Daclatasvir Velpatasvir Ledipasvir Ombitasvir Elbasvir
Host-targeting antiviral drugs (HTAs)	Cyclophilin (pharmacological inhibitor targets host cell functions involved in the HCV life cycle)	Alisporivir

(HCV = hepatitis C virus)

04

HEPATITIS D

Hepatitis D (Delta virus)

- The hepatitis D virus (HDV) is an RNA-defective virus that has no independent existence; it requires HBV for replication and has the same sources and modes of spread.
- It can infect individuals simultaneously with HBV or can superinfect chronic carriers
- Simultaneous infections give rise to acute hepatitis
- Chronic infection with HBV and HDV can also occur, and this frequently causes rapidly progressive chronic hepatitis and eventually cirrhosis.
- It is endemic in parts transmission is mainly by close personal contact and occasionally by vertical transmission from mothers who also carry HBV.
- In non-endemic areas, transmission is mainly a consequence of parenteral drug misuse.

INVESTIGATIONS

- HDV contains a single antigen to which infected individuals make an antibody (anti-HDV).
- Diagnosis depends on detecting anti-HDV.
- This antibody generally disappears within 2 months.
- Super-infection of patients with chronic HBV infection leads to the production of high titres of anti-HDV, initially IgM and later IgG.

MANAGEMENT

Effective management of hepatitis B prevents hepatitis D.

05

HEPATITIS E

HEPATITIS E

- **Etiology:**
➢ Hepatitis E virus (HEV) is an unenveloped, single-stranded RNA virus in the Hepevirus genus.
➢ Viral particles are 32-34 nm in diameter
➢ Hepatitis E occurs primarily in young to middle-aged adults.
- **Source of infection:**
➢ HEV is a zoonotic disease with animal reservoirs, such as monkeys, cats, pigs, rodents, and dogs.
➢ Virions are shed in stool during the acute illness.
- **Mode of transmission:** An enterically transmitted, waterborne infection. It is common after contamination of water supplies such as after monsoon flooding.
- **Incubation period:** 14-60 days (mean, 5-6 weeks).

- **Outcome of Infection:**
  - ➢ HEV infection is responsible for more than 30-60% of cases of sporadic acute hepatitis (clinically very similar to hepatitis A) in India.
  - ➢ It produces self-limiting acute hepatitis.
  - ➢ It does not cause chronic liver disease.
  - ➢ High mortality rate (about 20%) among pregnant women.
- **Diagnosis:** based on detection of anti-HEV IgM antibodies but it is possible to measure HEV RNA or capsid antigen in the blood and stool (especially immunocompromised patients).
- **Management:**
  - ➢ Good sanitation and hygiene similar to hepatitis A.
  - ➢ Vaccines have been developed and used in China.

SEVER ACUTE COMPLICATIONS

- • Fulminant Hepatitis: A rare, life-threatening condition presenting with massive hepatic necrosis and hepatic encephalopathy within 8 weeks of illness.
- ◦ Particularly high mortality (10–20%) in pregnant women with Hepatitis E (HEV).
- ◦ High risk in Hepatitis D (HDV) co-infections or superinfections.
- ◦ Progression to deep coma carries a mortality rate exceeding 80% (risks include cerebral edema, GI bleeding, sepsis, and organ failure).
- • Cholestasis: Hepatitis A (HAV) can sometimes cause severe cholestasis that mimics biliary obstruction.

CHRONIC AND EXTRAHEPATIC COMPLICATIONS

- • Cirrhosis: Chronic hepatitis B leads to cirrhosis in 25–40% of cases. Chronic hepatitis C causes cirrhosis in 20–25% of cases after ~20 years.
- ◦ Cirrhosis complications include ascites, variceal bleeding, and coagulopathy.
- • Hepatocellular Carcinoma (Liver Cancer): Chronic HBV and HCV infections significantly increase the risk of developing liver cancer.
- • Extrahepatic Manifestations (Systemic):
- ◦ Hepatitis B: Arthritis, glomerulonephritis, polyarteritis nodosa–like vasculitis.
- ◦ Hepatitis C: Cryoglobulinemia, porphyria cutanea tarda, lymphocytic sialadenitis

DIFFERENTIAL DIAGNOSIS

- (When evaluating a patient with acute liver injury, consider these non-viral causes)
- • Drug-Induced Liver Injury (DILI): Acetaminophen toxicity, prescription medications, or herbal supplements.
- • Alcoholic Hepatitis: Acute liver inflammation caused by heavy or prolonged alcohol use.
- • Autoimmune Hepatitis: The body's immune system attacks liver cells.
- • Ischemic Hepatitis ("Shock Liver"): Hypoperfusion to the liver due to heart failure, sepsis, or severe hypotension.
- • Biliary Tract Disease: Choledocholithiasis (gallstones), cholangitis, or other obstructive jaundice.
- • Other Viral Infections: Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), or Herpes Simplex Virus (HSV).

DIFFERENTIATING THE DIAGNOSES

- **Viral Hepatitis:** Confirmed via specific viral serologies (e.g., HBsAg, anti-HCV, IgM anti-HAV). AST and ALT are typically elevated in the thousands during acute phases.
- **Drug-Induced (DILI):** Diagnosed via careful patient history of recent ingestions and medication timelines.
- **Alcoholic Hepatitis:** The AST to ALT ratio is classically > 2:1, whereas viral hepatitis usually has an ALT higher than or equal to AST.
- **Autoimmune Hepatitis:** Identified by the presence of autoantibodies (ANA, ASMA, LKM-1) and elevated IgG levels.
- **Ischemic Hepatitis:** Characterized by a rapid, massive spike in transaminases followed by a rapid decline, coupled with a history of a hypotensive event.
- **Biliary Obstruction:** Shows a disproportionate elevation of Alkaline Phosphatase and Bilirubin compared to ALT/AST. Confirmed via imaging (ultrasound showing dilated ducts).

- REFERENCE : DAVIDSON’S Principles and Practice of Medicine

THANK YOU