Viral Hepatitis

Rami Dwairi, MD

Hepatitis A

- Hepatitis A is the most common type of viral hepatitis occurring world-wide, often in epidemics
- Spread of infection is mainly by the feco-oral route and arises from the ingestion of contaminated food or water
- Overcrowding and poor sanitation facilitate spread
- There is no carrier state
- HAV is a picornavirus, that replicates in the liver, is excreted in bile and is then excreted in the feces of infected persons for about 2 weeks before the onset of clinical illness and for up to 7 days after
- The disease is maximally infectious just before the onset of jaundice
- HAV particles can be demonstrated in the feces by electron microscopy

Clinical Features

- The viremia causes the patient to feel unwell with nonspecific symptoms that include nausea, anorexia and a distaste for cigarettes
- Many recover at this stage and remain anicteric
- After 1 or 2 weeks some patients become jaundiced and symptoms often improve
- As the jaundice deepens, the urine becomes dark and the stools pale owing to intrahepatic cholestasis
- The liver is moderately enlarged and the spleen is palpable in about 10% of patients
- Occasionally, tender lymphadenopathy is seen, with a transient rash in some cases
- Thereafter the jaundice lessens and in the majority of cases the illness is over within 3–6 weeks
- Extrahepatic complications are rare but include arthritis, vasculitis, myocarditis and renal failure
- Rarely the disease may be very severe with fulminant hepatitis, coma and death

Investigations

- Prodromal stage: serum bilirubin is usually normal but there is bilirubinuria and increased urinary urobilinogen
- A raised serum AST or ALT, which can sometimes be very high, precedes the jaundice
- Icteric stage: Serum AST reaches a maximum 1–2 days after the appearance of jaundice, and may rise above 500 IU/L
- Serum ALP is usually less than 300 IU/L and after the jaundice has subsided, the aminotransferases may remain elevated for a few weeks and occasionally for up to 6 months.
- There is leucopenia with a relative lymphocytosis. Very rarely there is hemolytic anemia or an associated aplastic anemia
- The prothrombin time (PT) is prolonged in severe cases
- The erythrocyte sedimentation rate (ESR) is raised
- Viral markers: IgG antibodies to HAV are common in the general population over the age of 50 years, but an anti-HAV IgM means an acute infection
- Further tests are not necessary in the presence of an IgM antibody, but liver biochemistry must be followed to establish a return to normal levels

Course and Treatment

- The prognosis is excellent, with most patients making a complete recovery
- The mortality in young adults is 0.1% but it increases with age. Death is due to fulminant hepatic necrosis
- Occasionally a more severe jaundice with cholestasis will run a prolonged course of 7–20 weeks and is called cholestatic viral hepatitis
- Patients may complain of debility for several months following resolution of the symptoms and biochemical parameters. This is known as the post-hepatitis syndrome
- Treatment is by reassurance. HAV hepatitis never progresses to chronic liver disease
- There is no specific treatment, and rest and dietary measures are unhelpful. Admission to hospital is not usually necessary

Prevention and Prophylaxis

- Control of hepatitis depends on good hygiene.
- **Active immunization:** An inactivated HAV vaccine is given to people travelling frequently to endemic areas, patients with chronic liver disease, people with hemophilia, and workers in frequent contact with hepatitis cases (e.g. in residential institutions for patients with learning difficulties)
- Community outbreaks can be interrupted by vaccination. A single dose produces antibodies that persist for at least 1 year, with immunity lasting beyond 10 years
- **Passive immunization:** Normal human immunoglobulin is used if exposure to HAV is < 2 weeks
- HAV vaccine should also be given

Hepatitis B

- Hepatitis B is one of the most common causes of chronic liver disease and hepatocellular carcinoma worldwide. Approximately 250 million people have chronic HBV infection.
- There is large regional variation, with the highest rates seen in the Western Pacific and African regions
- Vertical transmission from mother to child in utero, during parturition or soon after birth, is the usual means of transmission world-wide. This is related to the HBV replicative state of the mother (90% HbeAg +ve, 30% HbeAg –ve). HBV is not transmitted by breast feeding
- In endemic areas, vertical transmission from mother to child in the perinatal period is the most common cause of infection and carries the highest risk of ongoing chronic infection (90%–95%).
- HBV spread also occurs by the intravenous route (e.g. by contaminated needles used by drug users, tattooists or acupuncturists)
- The virus can be found in semen and saliva and can be transmitted sexually

Hepatitis B virus (HBV)

- The complete infective virion or is a 42 nm particle comprising an inner core surrounded by an outer envelope of surface protein (HBsAg)
- This surface coat is produced in excess by the infected hepatocytes and can exist separately from the whole virion in serum and body fluid
- The core or nucleocapsid is formed of core protein (HBcAg) containing incompletely double-stranded circular DNA and DNA polymerase/reverse transcriptase
- Hepatitis B e antigen (HBeAg) is part of the core antigen that is detectable in the blood and can be used as an indicator of viral replication

- Once hepatitis B infection has been present for more than 6 months, spontaneous clearance is uncommon.
- Most patients with chronic hepatitis B are asymptomatic and develop complications, such as cirrhosis and hepatocellular carcinoma, only after many years.
- Fibrosis accumulates during periods of liver injury (the ‘hepatitis’ phases) and results in cirrhosis in 15%–20% of patients with chronic HBV over 5–20 years

Investigation

Acute infection

- HBsAg appears in the blood from about 6 weeks to 3 months after an acute infection and then disappears
- HBeAg rises early and usually declines rapidly
- Anti-HBs appears late and indicates immunity
- Anti-HBc is the first antibody to appear and high titers of IgM anti-HBc suggest an acute and continuing viral replication. It persists for many months. IgM anti-HBc may be the only serological indicator of recent HBV infection in a period when HBsAg has disappeared and anti-HBs is not detectable in the serum
- Anti-HBe appears after the anti-HBc and its appearance relates to a decreased infectivity

Development of chronic hepatitis

- HBsAg persists beyond 6 months and indicates a chronic infection or carrier state
- HBeAg persists and correlates with increased severity and infectivity and the development of chronic liver disease
- HBV DNA suggests continual viral replication

Table 7.7 Significance of viral markers in hepatitis B

Antigens	
HBsAg	Acute or chronic infection
HBeAg	Acute hepatitis B Persistence implies: continued infectious state development of chronicity increased severity of disease
HBV DNA	Implies viral replication Found in serum and liver
Antibodies	
Anti-HBs	Immunity to HBV; previous exposure; vaccination
Anti-HBe	Seroconversion
Anti-HBc	
IgM	Acute hepatitis B (high titre) Chronic hepatitis B (low titre)
IgG	Past exposure to hepatitis B (HBsAg-negative)

Passive and active immunization

- Vaccination is universally available in most developed countries as well as countries with high endemicity
- Groups at high risk are: all healthcare personnel; members of emergency and rescue teams; morticians; children in high-risk areas; people with hemophilia; patients in some psychiatric units; patients with chronic kidney disease on dialysis units; long-term travellers; intravenous drug users
- Combined prophylaxis (i.e. vaccination and immunoglobulin) should be given to: staff with accidental needle-stick injury; all newborn babies of HBsAg-positive mothers; regular sexual partners of HBsAg-positive patients, who have been found to be HBV-negative
- For adults a dose of 500 IU of specific hepatitis B immunoglobulin (HBIG) is given and the vaccine (i.m) is given at another site

Active immunization

- This is with a recombinant vaccine produced by insertion of a plasmid containing the gene of HBsAg into a yeast
- Dosage regimen includes three injections (at 0, 1 and 6 months) are given into the deltoid muscle; this gives short-term protection in over 90% of patients
- People who are over 50 years of age or clinically ill or immunocompromised have a poor antibody response; more frequent and larger doses are required

- Treatment is aimed at suppressing viral replication to prevent disease progression to cirrhosis or hepatocellular carcinoma.
- The goals of treatment are therefore HBeAg seroconversion, reduction in HBV-DNA and normalisation of the LFTs.
- Only a proportion (10%–40%) of patients with chronic hepatitis B will require treatment. This is usually targeted at those in the 'hepatitis' phases with high viral load and accompanying liver injury, either in terms of necroinflammation (raised ALT) or established fibrosis (on biopsy or raised liver stiffness on transient elastography).
- All patients with cirrhosis should be treated to prevent decompensation.
- Treatment may also be initiated during pregnancy in the absence of liver injury to prevent mother-to-child transmission

Antiviral agents

- Interferon, lamivudine, adefovir, entecavir and tenofovir are the most commonly used drugs
- Pegylated interferon-alfa (PEG-IFN) acts by augmenting the host immune response. This is most effective in patients with a pre-treatment low viral load and serum transaminases greater than twice the upper limit of normal.
- Treatment is for a finite period (typically around 1 year), and is associated with higher rates of HBsAg and HBeAg seroconversion than nucleoside/nucleotide agents but with greater side-effects.
- Interferon is contraindicated in the presence of cirrhosis, as it may cause a rise in serum transaminases and precipitate liver failure..
- Side-effects of treatment are many, with an acute flu-like illness occurring 6–8 hours after the first injection. This usually disappears after subsequent injections, but malaise, headaches and myalgia are common and depression, reversible hair loss and bone marrow depression and infection may occur. The platelet count should be monitored

- Lamivudine
- Although initially effective, long-term therapy is often complicated by the development of HBV-DNA polymerase mutants (e.g. the 'YMDD variant'), which lead to viral resistance.
- These occur in around half of patients after 3 years and are characterized by a rise in viral load during treatment.
- Outside resource-limited settings, this agent is now seldom used for the treatment of HBV but may be used to prevent reactivation in patients with past HBV infection if they are undergoing treatment which suppresses the immunity

- Entecavir and Tenofovir
- Monotherapy with entecavir or tenofovir is substantially more effective than lamivudine in reducing viral load in HBeAg positive and HBeAg-negative chronic hepatitis.
- Antiviral resistance mutations occur very rarely, in < 1% after 5 years of entecavir and with no evidence of resistance after 8 years of tenofovir.
- Both drugs have action against human immunodeficiency virus (HIV) and so their use as monotherapy is contraindicated in HIV-positive patients, as it may lead to HIV antiviral drug resistance.
- Current Euroean guidelines advise that the other nucleoside/nucleotide antivirals should not be used as first-line monotherapy due to the induction of viral mutations, unless entecavir or tenofovir are not available or appropriate

HEPATITIS D

- This is caused by the hepatitis D virus (HDV or delta virus) which is an incomplete RNA particle enclosed in a shell of HBsAg
- It is unable to replicate on its own but is activated by the presence of HBV. It is particularly seen in intravenous drug users but can affect all risk groups for HBV infection
- Hepatitis D viral infection can occur either as a co-infection with HBV or as a superinfection in an HBsAg-positive patient
- Co-infection of HDV and HBV is clinically indistinguishable from an acute icteric HBV infection, but a biphasic rise of serum aminotransferases may be seen
- Diagnosis is confirmed by finding serum IgM anti-HDV in the presence of IgM anti-HBc. IgM anti-delta appears at 1 week and disappears by 5–6 weeks (occasionally 12 weeks) when serum IgG antidelta is seen. The HDV RNA is an early marker of infection
- Superinfection results in an acute flare-up of previously stable chronic HBV infection. A rise in serum AST or ALT may be the only indication of infection
- Diagnosis is by finding HDV RNA or serum IgM anti-HDV at the same time as IgG anti-HBc
- Fulminant hepatitis can follow both types of infection but is more common after co-infection. HDV RNA in the serum and liver can be measured and is found in acute and chronic HDV infection

Hepatitis C

- This is caused by an RNA flavivirus.
- Acute symptomatic infection with hepatitis C is rare. Most individuals are unaware of when they became infected and are identified only when they develop chronic liver disease.
- Around 70% of individuals exposed to the virus become chronically infected and late spontaneous viral clearance is rare. It is estimated that around 70 million individuals have chronic hepatitis C worldwide, with the highest prevalence in the Eastern Mediterranean region.
- There is no active or passive protection against hepatitis C virus
- The virus is transmitted by blood and blood products and was common in people with hemophilia treated before screening of blood products was introduced
- The incidence in intravenous drug users is high (50–60%)
- The low rate of hepatitis C (HCV) infection in high-risk groups – such as homosexual men, prostitutes and attendees at STI clinics – suggests a limited role for sexual transmission
- Vertical transmission can occur, but is rare
- In 20% of cases the exact mode of transmission is unknown
- There is a rapid change in envelope proteins, making it difficult to develop a vaccine

- If hepatitis C infection is left untreated, progression from chronic hepatitis to cirrhosis may occur, with 20% developing cirrhosis over 20 years.
- Risk factors for progression include male gender, immunosuppression (such as co-infection with HIV), prothrombotic states and heavy alcohol misuse.
- Once cirrhosis is present, 2%–5% per year will develop primary hepatocellular carcinoma, although this rate falls by around 75% following successful antiviral therapy
- Extrahepatic manifestations are seen, including arthritis, glomerulonephritis associated with cryoglobulinemia, and porphyria cutanea tarda
- HCV RNA can be detected from 1 to 8 weeks after infection. Anti-HCV tests are usually positive 8 weeks from infection

Chronic Hepatitis C

- Patients with chronic hepatitis C infection are usually asymptomatic, the disease being discovered only following a routine biochemical test when mild elevations in the aminotransferases (usually ALT) are noticed (50%)
- The elevation in ALT may be minimal and fluctuating and some patients have a persistently normal ALT (25%), the disease being detected by checking HCV antibodies
- Severe chronic hepatitis (25%) and even cirrhosis can be present with only minimal elevation in aminotransferases, but progression is very uncommon in those with a persistently normal ALT
- Fatigue is the commonest symptom with sometimes nausea, anorexia and weight loss, which do not correlate with disease activity

Diagnosis

- This is made by finding HCV antibody in the serum
- HCV RNA should be assayed using quantitative HCV-RNA PCR
- Liver biopsy is indicated if treatment is being considered
- The changes on liver biopsy are highly variable. Sometimes only minimal inflammation is detected, but in most cases the features of chronic hepatitis are present

Direct-Acting Antiviral Agents

- Novel DAAs against hepatitis C include compounds that target the HCV protease, the HCV NS5A protein, and the HCV polymerase. These drugs inhibit HCV replication by interfering with the respective step in the HCV life cycle
- Eexamples include simeprevir, sofosbuvir, faldaprevir, boceprevir, and telaprevir
- Used in different combinations with each other and with ribavirin and interferon

- Older treatments included combination therapy with pegylated interferon and ribavirin for 6-12 months
- Ribavirin is usually well tolerated but side-effects include a dose-related hemolysis, pruritus and nasal congestion
- Pregnancy should be avoided as ribavirin is teratogenic

Hepatitis E

- It is enterally transmitted, usually by contaminated water, with 30% of dogs, pigs and rodents carrying the virus
- Epidemics have been seen in many developing countries
- It has a mortality from fulminant hepatic failure of 1–2%, which rises to 20% in pregnant women
- There is no carrier state and it does not progress to chronic liver disease
- An ELISA for IgG and IgM anti-HEV is available for diagnosis
- HEV RNA can be detected in the serum or stools by PCR
- Prevention and control depend on good sanitation and hygiene
- A vaccine has been developed

ACUTE HEPATITIS DUE TO OTHER INFECTIOUS AGENTS

Abnormal liver biochemistry is frequently found in a number of acute infections. The abnormalities are usually mild and have no clinical significance

- **Infectious mononucleosis**. This is due to the Epstein–Barr (EB) virus. Mild jaundice associated with minor abnormalities of liver biochemistry is extremely common, but clinical hepatitis is rare. Treatment is supportive
- **Cytomegalovirus** . This can cause acute hepatitis, particularly in a patient with an impaired immune response. The virus may be isolated from the urine. Liver biopsy shows intranuclear inclusions and giant cells
- **Yellow fever**. This viral infection is carried by the mosquito Aedes aegypti and can cause acute hepatic necrosis. There is no specific treatment.
- **Herpes simplex** . Very occasionally causes a generalized acute infection, particularly in the immunosuppressed patient, and occasionally in pregnancy. Aminotransferases are usually massively elevated. Liver biopsy shows extensive necrosis. Aciclovir is used for treatment
- **Toxoplasmosis**. This produces a clinical picture similar to that of infectious mononucleosis, with abnormal liver biochemistry

Thank You