Hepatitis

Inflammation of the liver with abnormal LFTs and various histological changes noted on biopsy. May be acute or chronic.

Acute Hepatitis

Features: Fever, liver tenderness, jaundice; may develop acute liver failure, ascites and hepatic encephalopathy.

Causes:

- Infection
  - Viral – Hep A, B(±D),C, E, G, CMV, HSV, yellow fever
  - Post-viral – Reye's syndrome
  - Non-viral – Leptospirosis, toxoplasmosis, coxiella burnetii (Q Fever), mycoplasma
- Drugs - see below
- Alcoholic
- Non-alcoholic steatohepatitis (NASH) – resembles alcoholic hepatitis but no history of alcohol abuse. F>M. Assoc with obesity & metabolic syndrome. Fatty infiltration (steatosis) on radiologic imaging. Biopsy shows hepatitis. May progress to cirrhosis.
- Poisons - amanita phalloides, paraquat, P, CCl_4 & other organic solvents
- Metabolic – Wilson's, alpha 1-antitrypsin deficiency, fatty change of pregnancy
- Autoimmune - >80% have Abs e.g. ANA and SMA, IgG; LKM-1; SLA/LP
- Ischaemic – shock, severe cardiac failure, Budd-Chiari

Drug-Induced Hepatitis & Liver Disease

Overview:

- Up to 25-50% of all cases of hepatitis:
- Acute hepatocellular damage:
  - dose-unrelated, e.g. **antituberculous drugs**, **halothane**, **anticonvulsants**
  - dose-related, e.g. **alcohol**, **paracetamol**, **amiodarone**, **methotrexate**
- Chronic active hepatitis, e.g. **isoniazid**, **nitrofurantoin**
- Cirrhosis, e.g. **alcohol**, **methotrexate**
- Hepatic tumours, e.g. **anabolic steroids**, **combined oral contraceptives**
- Intrahepatic cholestasis:
  - dose-unrelated, e.g. **carbimazole**, **erythromycin**, **phenothiazines**
  - dose-related, e.g. **anabolic steroids**, **azathioprine**, **oestrogens**
- Gallstones, e.g. **clofibrate**, **oestrogens**

Risk factors: Race (Afrocaribbeans & **isoniazid**), age, EtOH, liver disease, P450 enzyme genetics, malnourished

Pathogenesis:

- *Predictable or direct:* usually promptly follows an exposure to a new medication. Direct toxicity or a toxic metabolite, e.g. **paracetamol**.
- *Unpredictable or idiosyncratic:* may be related to immune hypersensitivity; rash, fever and eosinophilia are typically present. These reactions follow exposure by a few weeks e.g. **Augmentin**.
- Late (many months) onset idiosyncratic reactions are difficult to recognise and usually do not display features of hypersensitivity, e.g. **isoniazid**.

Clinical patterns:

- *Hepatitis:* elevated AST/ALT; e.g. **paracetamol** poisoning, **thiazolidinediones**, **statins**
- *Cholestasis:* elevated ALP; e.g. **chlorpromazine**, **erythromycin**, **oestrogens**
- *Mixed picture*: biliary canaliculi and hepatocytes damage: elevations in liver enzymes e.g. **Augmentin**

Investigations: LFTs, paracetamol level, viral serology, ANA, Cu & Fe levels, abdo USS/CT/MRI scan, liver biopsy.

Management: N-acetylcysteine for **paracetamol** poisoning. Supportive care or even transplant for liver failure.

Leptospirosis (Weil's Disease)

Spirochaete infection. Principal source of human infection is the rat but includes dogs & livestock. Contracted via contact with contaminated water, soil, or urine/tissues.

Epidemiology

- Most widespread zoonosis in the World
- Significant in Belize and Vietnam, eastern/southern Europe, Australia & New Zealand.
- Most often affects teenagers and adults and is more common in men.
- Risk factors include sewage workers, swimming in contaminated water, farmers, veterinarians, abattoir workers, rodent control workers, animal workers.

Presentation

- Incubation period is usually 7-14 days (range from 2-25 days). Onset is usually abrupt.
- Infection may be anicteric (self-limiting) or icteric leptospirosis (Weil's disease).
- Often mild with flu-like symptoms, but may cause pneumonitis, arthritis, orchitis, cholecystitis, myocarditis, coronary arteritis, aortitis, aseptic meningitis and uveitis.
- Approximately 10% become jaundiced (with hepatocellular necrosis) and have a severe and rapidly progressive form of the disease with liver failure and renal failure.
- The jaundice appears during days 5-9 of illness and lasts ~1 month. The degree of jaundice itself is not prognostic but leptospirosis without jaundice is rarely fatal.
- Purpura, petechiae, epistaxis, minor haemoptysis and other signs of bleeding are common.
- Other symptoms include fever, vomiting, abdominal pain, hepatomegaly, skin rashes, conjunctival haemorrhage, uveitis. There is often a severe headache, retro-orbital pain, and photophobia. (aseptic meningitis). A severe myalgia (lower back, and legs) is common.
- Resp sympts vary from cough, SOB, and haemoptysis to ARDS and massive haemorrhage.
- Leptospiral nephropathy is usual, sometimes → life threatening renal failure.

Differential Diagnosis

Possible alternative diagnoses to consider will include viral hepatitis, meningitis, influenza, malaria, typhoid fever, yellow fever, relapsing fever, scrub typhus, Dengue fever, Legionnaire's disease and Toxic shock syndrome.

Investigations

- Bloods: LFT (↑Bili, ↑AST&ALT), ↑INR, FBC (↓Hb, ↑WCC, ↓plts), renal impairment, ↑CK (rhabdo), coags (↑PT)
- MSU usually shows sediment and proteinuria.
- CXR: may be normal or show patchy shadowing in alveolar haemorrhage.
- Dx based on serology (paired), either using microscopic slide agglutination test or ELISA

Management

- Oral **doxycycline** or **amoxicillin** (Jarisch-Herxheimer reaction possible).
- Intravenous **penicillin G** or **chloramphenicol** for severely ill patients
- Supportive care and treatment of the hypotension, haemorrhage, RF and liver failure
- **Vitamin K** should be administered for hypoprothrombinaemia
- Immunity to leptospirosis is incomplete and so avoid re-exposure if possible

Complications

- Spontaneous abortion
- Acute renal failure
- Thrombocytopenia
- Liver failure
- GI haemorrhage
- Pulm. Haemorrhage, ARDS
- Rhabdomyolysis
- Uveitis, chorioretinits
- Sudden & profound ↓BP
- CVA, SAH
- Kawasaki disease
- Erythema nodosum
- Myocarditis
- CCF (rare)
- Non-specific ECG changes

Prognosis

- Usually self-limiting. Most cases without jaundice recover spontaneously.
- Liver and renal dysfunction are usually reversible, with resolution over 1-2 months
- Leptospirosis with jaundice is fatal in 5-15%. Mortality is increased in the elderly.
- Death is often caused by GI and pulmonary haemorrhage, renal failure and ARDS

Prevention

- Reduce contact with infected animals & urine. Avoid ponds, lakes, and sources known to be contaminated.
- Immunization of animals with Leptospira vaccines
- **Doxycycline** prophylaxis for high-risk water sports activities or workers if flooding in known endemic areas

Viral Hepatitis

Introduction: Responsible for ~50% of all cases of acute hepatitis. Hep viruses A-E, CMV, EBV, adenovirus and, rarely, herpes simplex virus and others. A recently discovered DNA virus, SEN-V, is apparently responsible for cases of post-transfusion hepatitis.

Epidemiology: Hepatitis A-E account for about ≥95% of cases of acute viral hepatitis and concern the rest of this article.

Modes of transmission.

Viral hepatitis type	A	B	C	D	E
Faecal-oral	+ + +	-	-	-	+ + +
Parenteral transmission e.g. transfusion, shared needles	+	+ + +	+ + +	+ +	-
Sexual transmission	-	+ + +	(+)	+ +	-
Perinatal transmission	-	+ + +	+	+	-

Presentation

Acute infection: nausea and vomiting, myalgia, fatigue/malaise, RUQ pain, altered sense of smell or taste, coryza, photophobia, headache and diarrhoea (may have pale stools and dark urine). Often no signs unless jaundice develops. Hepatomegaly (10%), splenomegaly (5%), and LN (5%).
Chronic infection: About 90% of neonates and 5% of adults with acute hepatitis B, and up to 85% of cases of acute hepatitis C will evolve to chronic hepatitis. See below.

Investigations

FBC, U&E, LFT, INR, serology. USS/CT/MRI to assess presence of cirrhosis/other causes.

Differential diagnosis of any hepatitis

Acute: Drugs, toxins, alcohol, infectious mononucleosis, CMV, Q fever, leptospirosis, syphilis, malaria, yellow fever, obstructive jaundice.
Chronic: Alcohol, drugs, autoimmune hepatitis, Wilson's disease.

Hepatitis A

May occur in outbreaks in institutions; common in travellers. Most infections pass unnoticed in childhood. It is a small, unenveloped, symmetrical RNA virus (picornavirus).
Clinical features: 2-6 weeks' incubation and a prodrome of anorexia, nausea, joint pain, and fever, precede the jaundice. Tender hepatomegaly, splenomegaly, and lymphadenopathy may occur. 15% have prolonged or relapsing illness for 6-9 months.
Investigations: Serum transaminases rise 22-40 days after exposure. Anti-HAV antibodies rise from 25 days: IgM signifies recent infection, and IgG remains detectable for life.
Treatment: Supportive. Recovery takes ~4wks. Avoid alcohol until LFTs normal. Admit patients with severe systemic upset or intractable vomiting for rehydration and observation.
Prevention:
Infective 2w before & 1w after onset of jaundice.
After infection immunity is probably life-long.
Good hygiene and sanitation, avoidance of tap water in high risk areas. Safe sex.
Immunisation:

- Passive: Normal human immunoglobulin gives <3 months' immunity to those at risk (e.g. travellers; all household contacts) and during incubation.
- Active: Inactivated protein derived from HAV. 2 doses 6mo apart gives 10yr immunity

Prognosis:
Usually self-limiting (rarely fulminant). No carrier state or chronic liver disease.

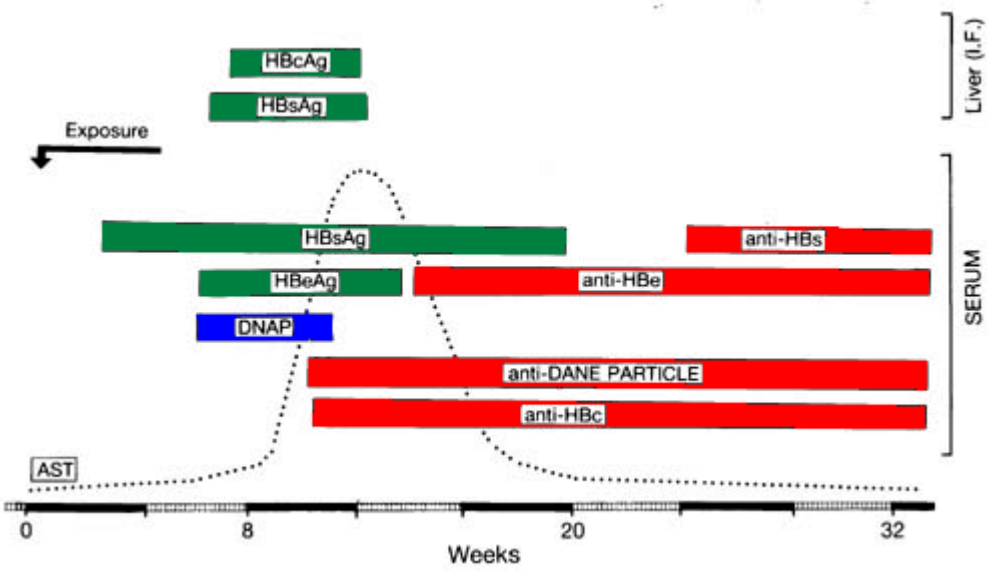
Hepatitis B

Double-stranded DNA virus (hepadnaviridae family). Endemic in the human population and hyperendemic in many parts of the world (Far East, Africa and the Mediterranean). Chronicity is dependent mostly upon age at exposure – 90% of children infected aged <1 will become carriers, compared with ~5% in adults. Hence low risk of cirrhosis/liver Ca.

Risk factors: unsafe sex, blood products (particularly if pooled, e.g. pre-recombinant Factor VIII for haemophiliacs), needlestick injury/surgical transmission in healthcare workers, recreational intravenous drug use, haemodialysis. Endemic in tropics and Mediterranean area.

Clinical features: As HAV, with 1-6mo incubation. Signs and symptoms less common in children, 30% cases may have none. Urticaria and arthralgia may occur.

Serological Markers for HBV Infection:



	Incubation	Acute	Carrier	Recovery	Vaccinated
LFT's	Normal	↑↑↑	↑	Normal	Normal
HBsAg	+	+	+		
HBeAg	+	+	±		
Anti-HBs		?+		+	+
Anti-HBe			±		
Anti-HBc IgM		+	±		
Anti-HBc IgG		+	+	+	

NB: Dane particles are HBV virions. DNAP = DNA polymerase. HBsAg (surface antigen) is present from 1–6mo after exposure. Persistence of HBsAg for >6mo defines carrier status. Occurs in 5–10%. HBeAg implies high infectivity; usually present for 6-12wk after acute illness. Antibodies to HBcAg (core antigen, i.e. anti-HBc) imply past infection. Antibodies to HBsAg (ie anti-HBs) alone implies vaccination.

Immunisation

- Passive: specific antiHBV Ig given to non-immune contacts after high-risk exposure.
- Active: recombinant vaccine of HBsAg grown in yeast cells (avoid if allergic to yeast).

Treatment:

- Post-exposure: e.g. needle-stick injury or unprotected sex with source.
- Acute phase: Supportive. It is not known whether anti-viral agents have any effect in the acute phase of hepatitis B. Avoid alcohol.
- Chronic phase: **Interferon alfa**, **lamivudine** and **adefovir dipivoxil** (latter two are synthetic nucleotide analogues) can have severe side effects. Immunize sexual contacts.

Complications: Fulminant hepatic failure (rare), relapse, prolonged cholestasis, chronic hepatitis (<5%, unless neonatal where>90%), cirrhosis, hepatocellular carcinoma, GN, cryoglobulinaemia.

Hepatitis C

Single stranded enveloped RNA flaviviridae with a narrow host range (humans and chimpanzees). 6 major genotypes and >90 subtypes. Transmission similar to HBV and the major cause of post-transfusion hepatitis. >50% develop chronic infection and ~25% cirrhosis and 15% of these → hepatic Ca. Incubation period of acute HCV is usually between 6-12wks, with specific antibody usually present by 3 months from infection, but may be delayed up to 6 months.
Risk Factors associated with more rapid progression to severe liver disease are: >40yrs when infected, alcohol consumption, M, co-infection with HIV or hepatitis B, Immunosuppression.

Clinical Features

Acute: ~80% asymptomatic. 20-30% have elevated bilirubin or deranged liver enzymes; and 20-30% have nonspecific symptoms such as anorexia, lethargy or abdominal pain.
Chronic: Asymptomatic persistently elevated or fluctuating LFTs.

Investigations

- FBC, LFT, GGT, Glucose, INR, serum ferritin (to exclude haemochromatosis), autoantibodies/immunoglobulins, hepatitis B serology and USS liver.
- Anti-HCV Ab ELISA screening test (sensitivity ≥97% but cannot distinguish acute, chronic or resolved infection). Positives should get HCV RNA PCR.
- Liver biopsy
- Quantitative measurement of HCV RNA serum concs and HCV genotype are recommended

Associated Diseases

In patients with HCV infection, there is also an increased risk of developing the following:

- DM
- Sjogren's Syndrome
- Essential mixed cryoglobulinemia
- Polyarteritis nodosa
- Autoimmune hepatitis
- Thyroiditis
- Membranous glomerulonephritis
- Porphyria cutanea tarda
- Lichen planus
- Idiopathic thrombocytopenic purpura

Management

- Refer for counselling and review by hepatologist.
- They should not donate blood, organs, tissues or semen.
- Abstinence from alcohol is advisable.
- If cirrhosis enrol in surveillance programmes for hepatocellular carcinoma
- **Peginterferon alfa-2a** (or **alfa-2b**) and **ribavirin** can be prescribed if >18yrs and elevated LFTs, or those who have had a liver transplant.

Complications

- Cirrhosis develops in almost 20% of patients over a period of 20 to 30 years.
- Patients who develop cirrhosis are at increased risk of hepatocellular carcinoma. Between 1-5% of those infected with hepatitis C will develop primary liver cancer.

Prognosis

- The natural history is slowly progressive. 90% will progress to chronic liver disease (median time to cirrhosis is 28-32 years).
- Co-infection with both hepatitis B and alcohol seem to have an additional effect.

Prevention

- No vaccine is currently available.
- Patients and at risk groups should be counselled to minimise transmission.

Hepatitis D

Unusual, circular ssRNA virus. Reqs HBV for replication. Co-infection with Hepatitis B, or as a superinfection (more likely to have more severe disease) in those with carrier or existing chronic Hepatitis B. More important cause of acute and severe chronic liver damage in some parts of the world (Mediterranean, Eastern Europe, Middle East, Africa, and S. America).

Clinical features: Co-infection: increased risk of fulminant hepatic failure. Superinfection: progression to cirrhosis believed more common.

Tests: Anti-HDV antibody.

Treatment: **Interferon-alfa** has limited success.

Prevention: As per HBV

Hepatitis E

Non-enveloped, ssRNA calicivirus – it is similar to HAV in transmission and clinical features with no apparent risk of chronic liver disease. In some areas it is the commonest viral cause of hepatitis in adults and older children, causing major epidemics in the Indian subcontinent, Central and South-East Asia, the Middle East, and parts of Africa. Mortality if pregnant may be up to 20%. Intrauterine infection (± stillbirth) is common

Incubation: 2-9 weeks.

Diagnosis: serology.

Prognosis: Usually self-limiting.

Prevention: Good hygiene and sanitation, avoidance of tap water in high risk areas (most outbreaks associated with contaminated drinking water). Gammaglobulin is ineffective, no vaccine currently available.

Hepatitis G viruses

Originally identified in the blood of a surgeon (GB) with jaundice. Two distinct viruses were identified initially when tamarind monkeys were inoculated with the serum of this patient (GBV-A and GBV-B). The third virus, GBV-C, was later isolated from a human specimen. All three are members of the ssRNA flaviviridae and share significant homology with HCV. Evidence now suggests this virus is not hepatotropic and doesn't have a role in either acute or chronic liver disease, although there may be an association with aplastic anaemia (controversial).

Hepatitis TT

First described in 1997 - TT being the initials of a patient in Japan with post-transfusion hepatitis. It is an unenveloped ssDNA virus, which was described in the sera of 3/5 patients with biopsy proven non-A to G post-transfusion hepatitis. It may be a cause of chronic hepatitis, although studies have failed to demonstrate a pathogenic role.

Chronic Hepatitis

Definition:

Inflammatory disease of the liver lasting for >6mo. The histological differentiation between chronic persistent hepatitis (no cell necrosis) and chronic active hepatitis (cell necrosis) does not correlate with prognosis and is therefore now much less used.

Aetiology

- Chronic Hepatitis B, Hepatitis C or Hepatitis D infection
- Autoimmune hepatitis
- Alcoholic liver disease
- Sarcoidosis
- Drug induced hepatitis, e.g. isoniazid, methyldopa, nitrofurantoin, etc
- Metabolic, e.g. Wilson's disease, alpha-1 antitrypsin deficiency, haemochromatosis

Autoimmune hepatitis

- Unknown cause, but often autoantibodies (e.g. ANA, anti-smooth muscle Ab, antimitochondrial Ab, antiphospholipid Ab) & assoc with other autoimmune diseases.
- Autoimmune hepatitis is associated with HLA types A1, B8, DR3 and Dw3.
- Autoimmune hepatitis is a heterogeneous disorder
    - Type 1: Anti Smooth Muscle, ANA and/or Antiactin
    - Type 2: Anti-LKM, P-450 IID6 or Synthetic core motif peptides 254-271
    - Type 3: Soluble liver-kidney antigen, Cytokeratins 8 and 18

Epidemiology

- Most commonly aged 20-50 years. Incidence 0.1-2/100,000 of Type 1 autoimmune hepatitis in Northern Europeans. Type 2 is more frequent in Southern Europeans.
- Autoimmune hepatitis is more common in women.
- 60% have other autoimmune diseases as well e.g. autoimmune haemolytic anaemia, ITP, coeliacs, Hasimoto's, Graves' disease, RA, systemic sclerosis, uveitis.

Presentation

- Acute hepatitis.
- Chronic features: Fatigue, upper abdominal discomfort, hepatomegaly, jaundice, splenomegaly and hypersplenism, ascites, pruritus, anorexia, muscle pains, arthralgia, spider naevi, non-specific skin rashes, hirsutism, weight loss.
- Cirrhosis

Investigations

- Full blood count & clotting studies
- Renal function and electrolytes
- LFTs
- Hepatitis B and C serology
- Autoantibodies: antinuclear antibodies, smooth muscle antibodies, anti-mitochondrial antibodies.
- Alpha-1 antitrypsin
- Caeruloplasmin, copper
- Iron studies
- Ultrasound, CT scan or MRI
- Liver biopsy

Management

Supportive management will depend on general and hepatic clinical status.

Autoimmune Hepatitis

- First line treatment is combination **prednisolone** and **azathioprine**. (60% respond but 80% of those responding to treatment will relapse when treatment is stopped).
- Other drugs, including **Cyclosporin A**, are used for those who don't respond to these.

Chronic Hepatitis B

- **Lamivudine** is an option for the initial Rx. Also used in decompensated liver disease.
- **Peginterferon alfa-2a** can be used as first Rx for adults over **interferon alfa**. Both are effective in less than 50% treated & relapse is frequent.
- **Adefovir dipivoxil** may be effective in lamivudine, peginterferon alfa-2a or interferon alfa resistant chronic hepatitis B or where these drugs can't be tolerated.
- **Entecavir** is effective in patients resistant to lamivudine.
- **Tenofovir** in combination with either **emtricitabine** or **lamivudine** may be used with other antiretrovirals in patients who require treatment for both HIV and chronic hepatitis B.

Chronic Hepatitis C

- **Peginterferon alfa** ± **ribavirin** may be used for treating moderate to severe chronic hepatitis C in patients aged over 18 years:
- Liver transplantation: 5-year survival rates reported at ≥90% or more.

Complications

- Cirrhosis (in ~20% of Chronic HBV/HCV) ± hepatocellular carcinoma
- Hepatic failure
- Portal hypertension
- Osteoporosis.

Prognosis

- The ten year survival for patients with chronic active hepatitis is now ~ 85%.
- Cirrhosis on initial liver biopsy indicates a poor prognosis.

Prevention

- Hepatitis B prevention, Hepatitis C prevention.