HEPATOLOGY

Medicine

KKT

Contents

Jaundice and liver function tests

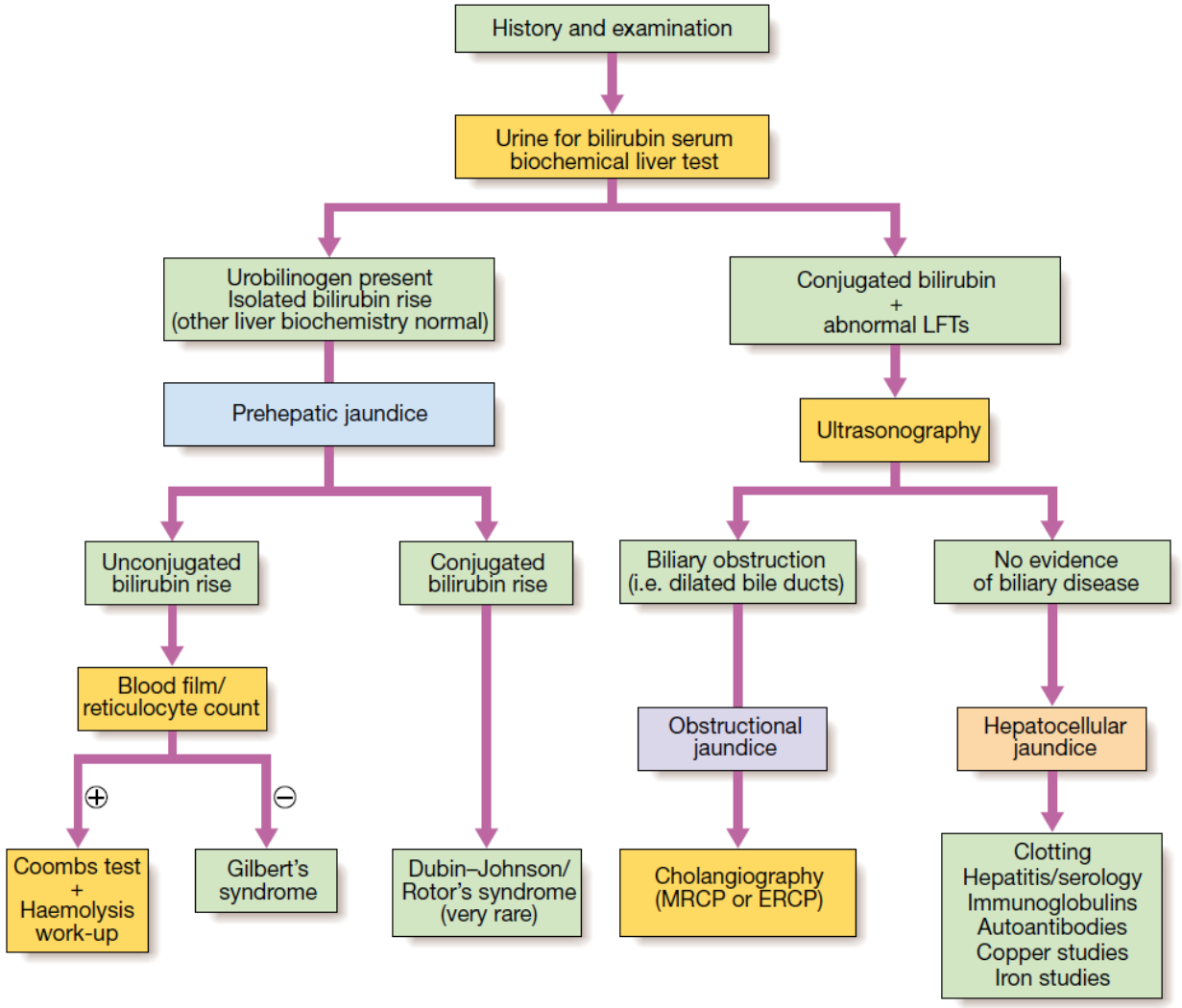


Fig. 23.14 Investigation of jaundice.

i 22.17 Congenital non-haemolytic hyperbilirubinaemia

Syndrome	Inheritance	Abnormality	Clinical features	Treatment
Unconjugated hyperbilirubinaemia				
Gilbert's	Can be autosomal recessive or dominant	↓Glucuronyl transferase ↓Bilirubin uptake	Mild jaundice, especially with fasting	None necessary
Crigler–Najjar:				
Type I	Autosomal recessive	Absent glucuronyl transferase	Rapid death in neonate (kernicterus)	
Type II	Autosomal recessive	↓↓Glucuronyl transferase	Presents in neonate	Phenobarbital, phototherapy or liver transplant
Conjugated hyperbilirubinaemia				
Dubin–Johnson	Autosomal recessive	↓Canalicular excretion of organic anions, including bilirubin Pigmentation of liver biopsy tissue	Mild jaundice	None necessary
Rotor's	Autosomal recessive	↓Bilirubin uptake ↓Intrahepatic binding	Mild jaundice	None necessary

22.2 'Hepatitic' and 'cholestatic'/'obstructive' liver function tests

Pattern	AST/ALT	GGT	ALP
Biliary obstruction	↑	↑↑	↑↑↑
Hepatitis	↑↑↑	↑	↑
Alcohol/enzyme-inducing drugs	N/↑	↑↑	N

N = normal; ↑ mild elevation (< twice normal); ↑↑ moderate elevation (2–5 times normal); ↑↑↑ marked elevation (>5 times normal).
(ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase)

23.3 Drugs that increase levels of GGT

- Barbiturates
- Carbamazepine
- Ethanol
- Griseofulvin
- Isoniazid
- Rifampicin
- Phenytoin

22.14 Common causes of elevated serum transaminases

Minor elevation (<100 U/L*)

- Chronic hepatitis C
- Chronic hepatitis B
- Haemochromatosis
- Fatty liver disease

Moderate elevation (100–300 U/L*)

As above plus:

- Alcoholic hepatitis
- Non-alcoholic steatohepatitis
- Autoimmune hepatitis
- Wilson's disease

Major elevation (>300 U/L*)

- Drugs (e.g. paracetamol)
- Acute viral hepatitis
- Autoimmune liver disease
- Ischaemic liver
- Toxins (e.g. *Amanita phalloides* poisoning)
- Flare of chronic hepatitis B

*These ranges are indicative but do not rigidly discriminate between different aetiologies.

22.15 Causes of cholestatic jaundice

Intrahepatic

- Primary biliary cholangitis
- Primary sclerosing cholangitis
- Alcohol
- Drugs
- Hepatic infiltrations (lymphoma, granuloma, amyloid, metastases)
- Cystic fibrosis
- Severe bacterial infections
- Pregnancy (p. 899)
- Inherited cholestatic liver disease, e.g. benign recurrent intrahepatic cholestasis
- Chronic right heart failure

Extrahepatic

- Carcinoma:
  - Ampullary
  - Pancreatic
  - Bile duct (cholangiocarcinoma)
  - Liver metastases
- Choledocholithiasis
- Parasitic infection
- Traumatic biliary strictures
- Chronic pancreatitis

22.18 Clinical features and complications of cholestatic jaundice

Cholestasis

Early features

- Jaundice
- Dark urine
- Pale stools
- Pruritus

Late features

- Malabsorption (vitamins A, D, E and K): weight loss, steatorrhoea, osteomalacia, bleeding tendency
- Xanthelasma and xanthomas

Cholangitis

- Fever
- Rigors
- Pain (if gallstones present)

Table 6.10 Examples of drug-induced jaundice

Haemolysis	• Antimalarials (eg dapsone)	
Hepatitis	• Paracetamol overdose (p844)	• Sodium valproate
	• Isoniazid, rifampicin, pyrazinamide	• Halothane
	• Monoamine oxidase inhibitors	• Statins
Cholestasis	• Flucloxacillin (may be weeks after Rx)	• Sulfonylureas
	• Fusidic acid, co-amoxiclav, nitrofurantoin	• Prochlorperazine
	• Steroids (anabolic; the Pill)	• Chlorpromazine

Cirrhosis of liver

- End-stage of chronic liver disease characterized by diffuse liver fibrosis, regenerating hepatocyte nodules and loss of normal liver architecture

- Causes
  - Alcohol (the most common cause in UK), NAFLD, autoimmune hepatitis
  - HBV (the most common cause worldwide), biliary cirrhosis (primary biliary cholangitis, secondary biliary cholangitis, primary sclerosing cholangitis, cystic fibrosis)
  - HCV, cardiac cirrhosis, cryptogenic cirrhosis
  - Drugs (methotrexate), drainage (Budd-Chiari syndrome)
  - Enzyme and metabolic disorders
    - α1-antitrypsin deficiency
    - Hemochromatosis, Wilson's disease

- Clinical features
  - ❖ Features of chronic liver insufficiency
    - Features due to impaired synthesis
      - ↓clotting factor synthesis – skin bleeding, mucosal bleeding
      - ↓protein synthesis – leuconychia, muscle wasting
    - Features due to impaired storage – iron deficiency, folate deficiency
    - Features due to impaired excretion
      - ↓bile pigment excretion – mild jaundice
      - ↓bile salt excretion (in biliary cirrhosis) – ↓absorption of fat soluble vitamins
    - Features due to impaired metabolism
      - Impaired carbohydrate metabolism – hypoglycemia
      - Impaired fat metabolism – dyslipidemia
      - Circulatory changes
        - ➢ Systemic circulation – palmar erythema, spider nevi
        - ➢ Pulmonary circulation – cyanosis, clubbing
      - Impaired steroid metabolism – hyper-estrogenemia (sexual dysfunction)
        - ➢ Male – gynecomastia, testicular atrophy, impotence
        - ➢ Female – breast atrophy, menstrual disturbance
        - ➢ In both male and female – loss of libido, sparse axillary and pubic hair, infertility

Cirrhosis with hepatomegaly	Cirrhosis with small liver
▪ Early stage of cirrhosis ▪ HCC ▪ Alcoholic cirrhosis ▪ Hemochromatosis	▪ Viral hepatitis ▪ Autoimmune hepatitis

  - ❖ Micronodular cirrhosis (nodules < 3 mm in size) – alcoholic cirrhosis
  - ❖ Macronodular cirrhosis – viral hepatitis, biliary cirrhosis

- ❖ Features of complications
  - Portal hypertension
    - Ascites, spontaneous bacterial peritonitis (SBP)
    - Congestive splenomegaly, hypersplenism
    - Porto-systemic shunt – esophageal varices, rectal varices, caput medusa
    - Congestive gastropathy
  - Hepatic encephalopathy
  - Hepato-renal syndrome
  - Hepato-pulmonary syndrome – clubbing, cyanosis, platypnea, orthodeoxia
  - Porto-pulmonary hypertension
  - Liver failure – coagulopathy, encephalopathy
  - Hepatocellular carcinoma

- ❖ Features of etiology
  - Alcoholic cirrhosis – parotid swelling, florid spider nevi, gynecomastia
  - Hemochromatosis – bronze diabetes, hypogonadism
  - Wilson's disease – Keyser-Fleischer ring, chorea

- Severity assessment
  - ❖ Signs of decompensation – deep jaundice, ascites, variceal bleeding, hepatic encephalopathy

Box 7.3 Scoring systems in cirrhosis

(a) Modified Child's–Pugh classification

Score	1	2	3
Ascites	None	Mild	Moderate/severe
Encephalopathy	None	Mild	Marked
Bilirubin (μmol/L)	<34	34–50	>50
Albumin (g/L)	>35	28–35	<28
Prothrombin time (seconds over normal)	<4	4–6	>6

Add above scores for your patient for survival figures below

Grade (scores)	% survival		
	1 year	5 years	10 years
Child's A (< 7)	82	45	25
Child's B (7–9)	62	20	7
Child's C (10+)	42	20	0

(b) Model of end-stage liver disease (MELD)

$3.8 \times \text{LN}(\text{bilirubin in mg/dL}) + 9.6 \times \text{LN}(\text{creatinine in mg/dL}) + 11.2 \times \text{LN}(\text{INR}) + 6.4$

To convert:

- bilirubin from μmol/L to mg/dL divide by 17
- creatinine from μmol/L to mg/dL divide by 88.4

LN, natural logarithm; INR, international normalized ratio.
MELD scores (with no complications): 1-year survival 97% (score <10); 70% (score 30–40).

- ❖ Poor prognostic factors in cirrhosis
  - Child-Pugh scoring (Grade C)
    - Bilirubin > 3 mg/dl
    - Albumin < 28 g/L
    - PT > 6s prolonged
    - Ascites
    - Encephalopathy
  - Serum sodium < 125 mmol/L
  - Serum creatinine > 130 μmol/L

- Investigations
  - ❖ Investigations for diagnosis
    - USG (abdomen)/ CT (abdomen)
      - Features of cirrhosis
        - ➢ Diffuse liver fibrosis, regenerating hepatocyte nodules and loss of normal liver architecture, margin irregularity
      - Features of etiology
        - ➢ Budd-Chiari syndrome – hepatic vein thrombosis
        - ➢ Cardiac cirrhosis – hepatic vein dilatation
      - Features of complications
        - ➢ Portal hypertension – ascites, congestive splenomegaly, portal vein dilatation
        - ➢ Portal vein thrombus
        - ➢ HCC – SOL in liver
  - ❖ Investigations for severity assessment (Child-Pugh scoring)
  - ❖ Investigations for etiology
    - For alcoholic cirrhosis – macrocytosis, ↑GGT, AST:ALT > 2:1
    - For viral hepatitis – HBV, HCV serology
    - For hemochromatosis – transferrin saturation, ferritin, genetic study, liver biopsy
    - For Wilson's disease – serum copper, ceruloplasmin, urinary copper, liver biopsy
  - ❖ Investigations for complications
    - For chronic liver insufficiency
      - OSPT – prolonged, T&DP – ↓albumin
      - Impaired liver enzymes
    - For anemia – hemogram, blood film
    - For hypoglycemia – RBS
    - For portal hypertension
      - SBP – ascites fluid analysis
      - Esophageal varices – OGD scopy
    - For hepato-renal syndrome – urinalysis, creatinine
    - For HCC – AFP (α-fetoprotein), USG (abdomen) 6 monthly

22.28 Features of chronic liver failure

- Worsening synthetic liver function:
  - Prolonged prothrombin time
  - Low albumin
- Jaundice
- Portal hypertension
- Variceal bleeding
- Hepatic encephalopathy
- Ascites:
  - Spontaneous bacterial peritonitis
  - Hepatorenal failure

Causes of jaundice in a previously stable patient with cirrhosis

- Sepsis (esp. UTI, pneumonia, or peritonitis)
- Malignancy: eg hepatocellular carcinoma
- Alcohol; drugs (table 6.10)
- GI bleeding.

Signs of decompensation: Jaundice; ascites; UGI bleed; encephalopathy.

- Management
  - ❖ Removal of etiology
    - Abstinence of alcohol if alcoholic cirrhosis
    - Anti-viral therapy for HBV and HCV (e.g. tenofovir for HBV, sofosbuvir for HCV)
    - UDCA (urso-deoxycholic acid) for PBC and PSC
    - Stop or avoid hepatotoxic drugs, nephrotoxic drugs and sedatives
    - Desferrioxamine for hemochromatosis, D-penicillamine for Wilson's disease

i 22.53 Drugs to be avoided in cirrhosis

Drug	Problem	Toxicity
Non-steroidal anti-inflammatory drugs	Reduced renal blood flow Mucosal ulceration	Hepatorenal failure Bleeding varices
Angiotensin-converting enzyme inhibitors	Reduced renal blood flow	Hepatorenal failure
Codeine	Constipation	Hepatic encephalopathy
Narcotics	Constipation, drug accumulation	Hepatic encephalopathy
Anxiolytics	Drug accumulation	Hepatic encephalopathy

  - ❖ Supportive management
    - Nutrition
      - Adequate calories, vitamin B1 and glucose supplement
      - Normo-protein diet, BCAA, LOLA supplement
      - Multivitamin supplement, vitamin K supplement
  - ❖ Management of complications
    - For ascites
      - Salt and water restriction
      - Aldosterone antagonist (spironolactone) ± frusemide
      - Therapeutic paracentesis with IV albumin replacement
    - For SBP
      - Treatment with IV antibiotics (e.g. cefotaxime)
      - Secondary prophylaxis with oral quinolone
    - For prophylaxis of variceal bleeding
      - Propranolol to reduce portal pressure
      - Obliteration of esophageal varices by OGD scopy and banding
    - For hepatic encephalopathy
      - Removal of precipitating factors
      - Bowel sterilization
        - ➢ Oral lactulose
        - ➢ Oral rifaximin
    - For hepato-renal syndrome
      - Terlipressin + albumin infusion
  - ❖ Orthotopic liver transplant (according to MELD score)

Portal hypertension

- Portal venous pressure > 7 mmHg
- Clinical features and complications develop if portal venous pressure > 12 mmHg

- Causes of portal hypertension

Pre-hepatic, pre-sinusoidal	▪ Portal vein thrombosis
Intra-hepatic, pre-sinusoidal	▪ Schistosomiasis (most common cause worldwide) ▪ Congenital hepatic fibrosis ▪ Drugs (methotrexate), vinyl chloride ▪ Sarcoidosis
Intra-hepatic, sinusoidal	▪ Cirrhosis (most common cause in UK) ▪ Polycystic liver disease ▪ Nodular regenerative hyperplasia ▪ Liver metastases
Intra-hepatic, post-sinusoidal	▪ Veno-occlusive disease
Post-hepatic, post-sinusoidal	▪ Hepatic vein thrombosis (Budd-Chiari syndrome) ▪ IVC thrombosis
Cardiac cirrhosis	▪ Right ventricular failure ▪ Constrictive pericarditis ▪ Tricuspid regurgitation

- Clinical features
  - Splenomegaly (cardinal finding)
  - Ascites (except in pre-sinusoidal causes)
  - Porto-systemic shunting
    - Esophageal varices (at distal esophagus near gastro-esophageal junction)
    - Rectal varices
    - Caput medusae
    - Venous hum (Cruveilhier-Baumgarten syndrome)
  - Portal hypertensive gastropathy (congestive gastropathy)

- Complications – hypersplenism, iron deficiency anemia, renal failure, hepatic encephalopathy

- Investigations
  - Wedged hepatic venous pressure (WHVP)
  - USG (abdomen)
    - Portal vein dilatation, splenomegaly, ascites
    - Hepatic vein dilatation in post-hepatic and cardiac causes
  - OGD scopy for gastroesophageal varices (the most useful investigation)
  - Hemogram – thrombocytopenia

Ascites

- Abnormal collection of fluid in the peritoneal cavity

- Investigation (ascites fluid analysis)
  - Color
    - Clear, straw-colored – uncomplicated ascites in cirrhosis
    - Bloody – malignancy, trauma
    - Greenish yellow – biliary communication
    - Milky white (chyle) – lymphatic obstruction
    - Cloudy, turbid – bacterial peritonitis

  - Biochemistry
    - Serum-ascites albumin gradient (SAAG)

↑SAAG (>11g/L) (portal hypertension cause)	↓SAAG (<11g/L) (non-portal hypertension cause)
▪ Cirrhosis, polycystic liver disease, liver metastases ▪ Veno-occlusive disease ▪ Budd-Chiari syndrome, IVC thrombosis ▪ Cardiac cirrhosis (TR, constrictive pericarditis, right ventricular failure)	▪ Peritoneal TB ▪ Peritoneal malignancy (malignant ascites) ▪ Pancreatitis (pancreatic ascites) ▪ Hypothyroid (myxedema ascites) ▪ Meig's syndrome (ovarian ascites) ▪ Nephrotic syndrome (nephrogenic ascites)

    - Glucose – low in peritoneal TB, malignancy
    - Triglyceride – high in chylous ascites
    - Amylase – high in pancreatic ascites
    - LDH – high in bacterial peritonitis, malignancy

  - Microscopy
    - Neutrophils > 250 x 10^6/L – bacterial peritonitis
    - Lymphocytes – high in peritoneal TB, malignancy
    - Malignant cells – malignancy

  - Microbiology – Gram stain; AFB stain (if TB suspect)

- Management of ascites in cirrhosis
  - Bed rest
  - Salt and water restriction
    - Salt restriction in all patients with ascites
    - Water restriction if sodium < 125mmol/l
  - Diuretics – spironolactone (up to 400 mg/day) ± frusemide (up to 160 mg/day)
  - Therapeutic paracentesis
    - Large-volume paracentesis (to dryness) with IV albumin replacement (6-8g/L of ascites removed) (100 ml of 20% human albumin solution for every 3L of ascites drained)
  - TIPSS – if the patient requires frequent large-volume paracentesis + reasonable liver function

Spontaneous bacterial peritonitis (SBP)

- Portal hypertension → congestive gastroenteropathy → bacterial translocation → septicemia → SBP

- Causal organisms
  - Enteric bacteria
    - E. coli (the most common cause)
    - *Klebsiella,* enterococci

    - ❖ In SBP, single organism is isolated.
    - ❖ If multiple organisms are isolated, suspect bowel perforation.

- Clinical features
  - Fever, abdominal pain (may be absent in 1/3 of cases)
  - Suspect SBP in any patient with ascites who deteriorates suddenly

- Investigations
  - Ascites fluid analysis
    - Color – cloudy, turbid
    - Microscopy – neutrophils > 250 x 10^6/L
    - Microbiology – Gram stain, culture and sensitivity
  - Blood culture

- Management (IV antibiotics for 5 days)
  - Cefotaxime
  - Piperacillin-tazobactam
  - Metronidazole (if recent instrumentation)

- Risk of recurrence – 70% in a year
- Mortality – 10-15%

- Prophylaxis
  - Oral quinolone (e.g. norfloxacin)
    - until ascites disappears
    - until liver transplant
    - until death
  - Secondary prophylaxis in all patients with history of SBP
  - Primary prophylaxis in patients with ascites if ascites albumin < 10g/L

- SBP can precipitate hepatic encephalopathy and hepato-renal syndrome.

Hepatic encephalopathy

- Neuropsychiatric syndrome caused by liver disease

- Pathophysiology
  - CNS inhibition by neurotoxins, ammonia and false neurotransmitters
  - Due to liver failure + porto-systemic shunting of blood

- Clinical features
  - Acute HE
    - Poor arithmetic; constructional apraxia
    - Altered behavior/mood; sleep disturbance (reversal of sleep pattern)
    - Confusion (time, place, person)
    - Decorticate or decerebrate posture
    - Bilateral extensor plantar response
    - Flapping tremor; fetor hepaticus

i 22.25 Factors precipitating hepatic encephalopathy

- Drugs (especially sedatives, antidepressants)
- Dehydration (including diuretics, paracentesis)
- Portosystemic shunting
- Infection
- Hypokalaemia
- Constipation
- ↑Protein load (including gastrointestinal bleeding)

  - Grading of acute HE

Hepatic encephalopathy: letting loose some false neurotransmitters

As the liver fails, nitrogenous waste (as ammonia) builds up in the circulation and passes to the brain, where astrocytes clear it (by processes involving the conversion of glutamate to glutamine). This excess glutamine causes an osmotic imbalance and a shift of fluid into these cells—hence cerebral oedema. Grading:

I Altered mood/behaviour; sleep disturbance (eg reversed sleep pattern); dyspraxia ('Please copy this 5-pointed star'); poor arithmetic. No liver flap.

II Increasing drowsiness, confusion, slurred speech ± liver flap, inappropriate behaviour/personality change (ask the family—don't be too tactful).

III Incoherent; restless; liver flap; stupor.

IV Coma.

►What else could be clouding consciousness? Hypoglycaemia; sepsis; trauma; postictal.

  - Chronic HE
    - Dementia
    - Parkinsonian syndrome
    - Cerebellar syndrome
    - Spastic paraplegia

- Investigations
  - EEG – slowing of α-wave; development of δ-wave
  - Arterial ammonia level – increased

- Management
  - ❖ Removal of precipitating factors

  - ❖ Bowel sterilization
    - Oral lactulose
      - Mechanism of action
        - ➢ ↓Colonic pH → ↓ammonia absorption
        - ➢ Osmotic laxative
      - Dose – 30-50ml 8hrly
      - Target – 2-4 soft stool/day
      - Alternative – lactitol (more palatable; less explosive action on bowel function)

    - Oral antibiotics
      - Rifaximin (non-absorbable oral antibiotics to reduce pathogenic GI bacteria)
      - Neomycin (avoid long-term use due to nephrotoxicity)

  - ❖ For cerebral edema
    - Nurse in 20° head-up tilt position (if stable)
    - IV 20% mannitol

  - ❖ Liver transplant – for chronic/refractory HE

Hepato-renal syndrome

- Pre-renal AKI due to renal vasoconstriction and splanchnic vasodilation

- Clinical features
  - Cirrhosis + ascites + pre-renal AKI unresponsive to fluid therapy (diagnosis of exclusion)
  - Precipitating factors for HRS – hypovolemia, sepsis, drugs (e.g. NSAID)
  - Prognosis
    - Type 1 HRS – median survival < 2weeks
    - Type 2 HRS – median survival ~ 6 months

- Investigations
  - ↑Creatinine (urea should not be used to assess HRS)
  - ↓Urine sodium, ↑urine osmolality
  - Renal biopsy – normal

- Management
  - Terlipressin + albumin infusion
  - Hemodialysis should not be used routinely
  - Liver transplant

Acute variceal bleeding

- Gastro-esophageal varices
  - Submucosal venous dilatation secondary to ↑portal pressure
  - Approximately 90% of patients with cirrhosis will develop gastro-esophageal varices over 10yrs, but only one-third of these will bleed.
  - High risk of bleeding – large varices, ↑portal pressure, red signs at endoscopy (red wale marks, cherry-red spots, hemocystic spots, diffuse erythema), severe liver disease
  - Overall 6-week mortality from variceal hemorrhage is 15-25%, reaching 50% in Child grade C.

- Primary prophylaxis of acute variceal bleeding
  - Patients with cirrhosis and significant varices that have not bled should be prescribed non-selective beta blockers (oral propranolol, nadolol or carvedilol).
  - This reduces the chance of upper GI bleeding by about 50% and overall mortality by about 20%.
  - If contraindicated, variceal banding is an option.

- Management of acute variceal bleeding
  - ❖ Immediate management if shocked
    - Airway – protect airway and keep NBM (to prevent aspiration)
    - Breathing – high-flow oxygen if hypoxia
    - Circulation – IV access with 2 short large-bore cannulae
    - Urgent investigations – FBC, U&E, LFT, glucose, clotting screen, cross-match 4-6units

    - Fluid resuscitation
      - Rapid infusion of IV crystalloid and/or colloid to restore intravascular volume
      - If deteriorating despite fluid resuscitation, give group O Rh-ive blood until cross-match

    - Blood component therapy
      - Transfuse if significant Hb drop (<7g/dl)
      - Correct clotting abnormalities (vitamin K, FFP, platelets)

    - Monitoring
      - Insert urinary catheter; consider CVP line (aim CVP >5cmH_2O)
      - Monitor vital signs (BP, PR, CVP) at least hourly until stable
      - Organize CXR, ECG, and check ABG.

  - ❖ Focused assessment
    - For variceal bleeding suspect – known varices, known liver disease or alcohol excess, features of chronic liver insufficiency and portal hypertension
    - Past history of peptic ulcer; drug history (NSAID, anti-platelet, anti-coagulant)
    - Previous history of upper GI bleeding and endoscopy findings
    - Other comorbid conditions

- Supportive management
  - Prophylactic antibiotics (oral ciprofloxacin or IV cephalosporin or piperacillin/tazobactam) to reduce incidence of sepsis and SBP
  - Prophylactic PPI (in patients undergoing successful endoscopic hemostasis) to reduce the risk of secondary bleeding from banding-induced ulceration and to prevent peptic ulcers
  - Phosphate enema and/or lactulose to prevent hepatic encephalopathy

- Pharmacological reduction of portal venous pressure
  - Terlipressin
    - Synthetic vasopressin analogue that reduces portal blood flow (mortality benefit)
    - 2mg IV 4 times daily until bleeding stops, then 1mg IV 4 times daily for up to 72hrs
    - Caution in patients with severe IHD or peripheral vascular disease
    - Alternative: octreotide (somatostatin analogue)

- Urgent upper GI endoscopy
  - This should be carried out after adequate resuscitation, ideally within 24hrs
  - Advantages of endoscopy
    - Confirms diagnosis and assesses severity of esophageal varices
    - Can find other sources of bleeding
    - Can give endoscopic therapies for hemostasis
      - Stops variceal bleeding in 80% of patients and can be repeated if bleeding recurs
      - Endoscopic variceal ligation (EVL) (banding) – fewer side-effects than sclerotherapy
      - Injection sclerotherapy – risk of esophageal perforation and stricture
      - For gastric fundal varices, injection of thrombin or cyanoacrylate glue is the best treatment (banding is less effective)

- Balloon tamponade (using four-lumen Sengstaken-Blakemore tube)
  - Is used if endoscopic therapy has failed or if there is exsanguinating hemorrhage
  - Hemostasis is achieved in up to 90% (is only a bridge to more definitive therapy)
  - It should be deflated for about 10mins every 3hrs to avoid esophageal mucosal damage
  - Complications – aspiration pneumonia, esophageal rupture, mucosal ulceration
  - Alternative: self-expanding removable esophageal stents for esophageal varices (not gastric)

- Management of acute rebleed (usually due to ulceration or slippage of a ligation band)
  - Rebleeding occurs in approximately 15-20% within 5 days
  - Repeat endoscopy and endoscopic therapy should be given.
  - If hemostasis cannot be achieved, TIPSS will be necessary.

- TIPSS (Transjugular intrahepatic portosystemic stent shunt)
  - Placement of a stent between portal vein and hepatic vein within the liver under radiological control via internal jugular vein to reduce portal pressure
  - TIPSS is associated with less rebleeding than endoscopic therapy (no survival benefit)
  - Complications – hepatic encephalopathy; contraindications – portal vein thrombosis

- Emergency surgery
  - Acute portosystemic shunt surgery (only in patients with good liver function)
  - Esophageal transection and ligation of feeding vessels to varices

- Secondary prevention of variceal bleeding
  - After a first variceal bleed, 60% rebleed within 1yr.
  - Non-selective beta-blockade (oral propranolol or carvedilol)
    - Portal inflow is reduced by ↓cardiac output (β_1) and by splanchnic vasoconstriction (β_2)
    - Reducing pulse rate by 25% decreases portal pressure.
    - Significant reduction in HVPG below 12mmHg confers very low rates of rebleeding.
  - Repeated sessions of endoscopic banding at 2wkly intervals until varices are obliterated.
  - TIPSS may be considered for resistant varices
  - Surgery
    - Surgical portosystemic shunting – if TIPSS is not available
    - Devascularization procedures including esophageal transection – when there is splanchnic venous thrombosis
    - Liver transplantation – is the best option when there is poor liver function

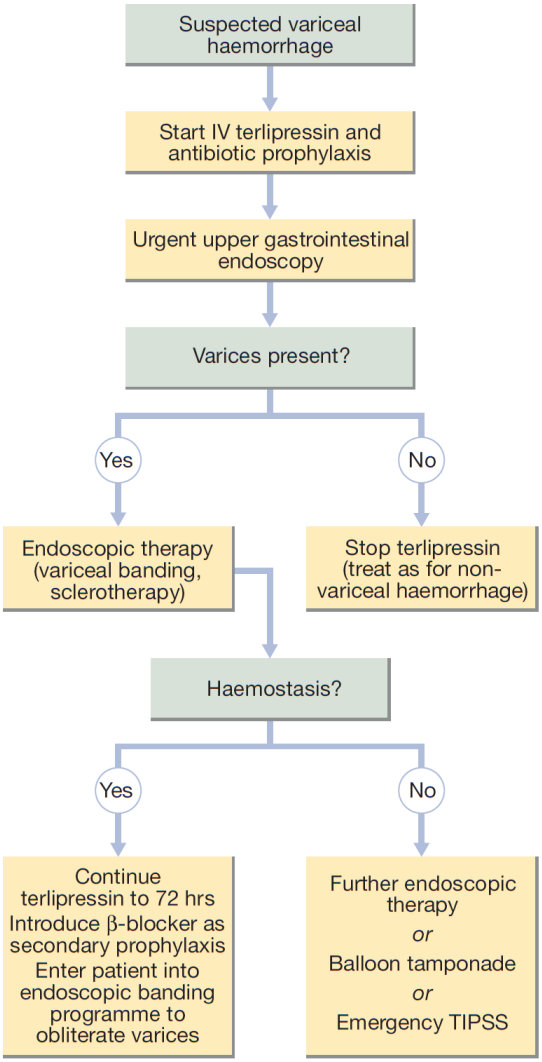


Fig. 22.21 Management of acute bleeding from oesophageal varices. (TIPSS = transjugular intrahepatic portosystemic stent shunt)

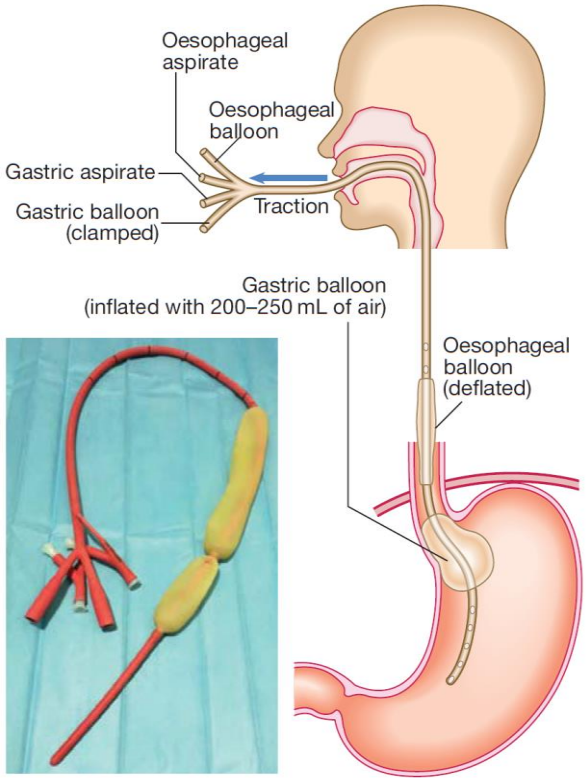


Fig. 22.22 Sengstaken–Blakemore tube.

Acute liver failure

- Liver failure – development of coagulopathy (INR >1.5) and encephalopathy

22.8 Classification of acute liver failure

Type	Time: jaundice to encephalopathy	Cerebral oedema	Common causes
Hyperacute	<7 days	Common	Viral, paracetamol
Acute	8–28 days	Common	Cryptogenic, drugs
Subacute	29 days to 12 weeks	Uncommon	Cryptogenic, drugs

- Causes of acute liver failure

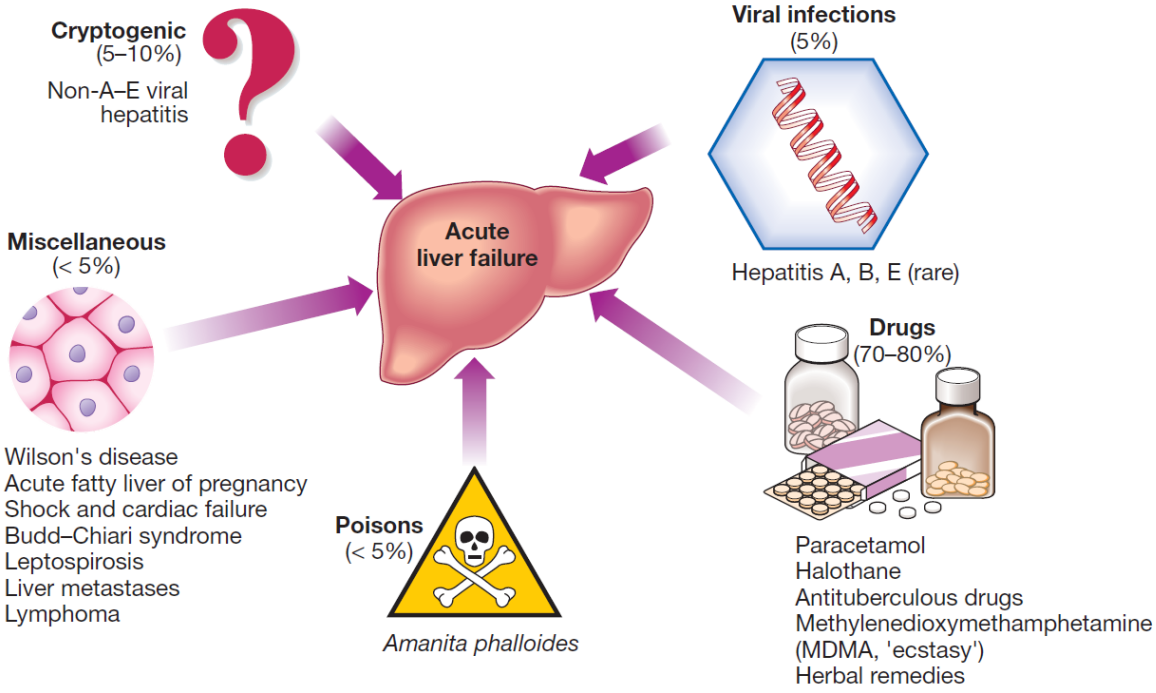


Fig. 22.13 Causes of acute liver failure in the UK. The relative frequency of the different causes varies according to geographical area.

- Clinical features
  - Features of hepatic encephalopathy and cerebral edema
  - Jaundice; liver is usually of normal size and later becomes smaller
  - Hepatomegaly in the presence of a sudden onset of ascites suggests Budd-Chiari syndrome.
  - Splenomegaly is uncommon and never prominent.

- Complications of acute liver failure

22.13 Complications of acute liver failure

- Encephalopathy and cerebral oedema
- Hypoglycaemia
- Metabolic acidosis
- Infection (bacterial, fungal)
- Renal failure
- Multi-organ failure (hypotension and respiratory failure)

- Investigations
  - Liver function tests – ↑PT (factor V level can be used instead of PT), ↑bilirubin, normal albumin
  - Liver enzymes – ALT, AST, ALP, ɣ-GT

22.10 Investigations to determine the cause of acute liver failure

- Toxicology screen of blood and urine
- HBsAg, IgM anti-HBc
- IgM anti-HAV
- Anti-HEV, HCV, cytomegalovirus, herpes simplex, Epstein–Barr virus
- Caeruloplasmin, serum copper, urinary copper, slit-lamp eye examination
- Autoantibodies: ANA, ASMA, LKM, SLA
- Immunoglobulins
- Ultrasound of liver and Doppler of hepatic veins

(ANA = antinuclear antibody; anti-HBc = antibody to hepatitis B core antigen; ASMA = anti-smooth muscle antibody; HAV = hepatitis A virus; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HEV = hepatitis E virus; IgM = immunoglobulin M; LKM = liver–kidney microsomal antibody; SLA = soluble liver antigen)

- Management (in HDU/ICU)
  - Management of complications – encephalopathy, cerebral edema, hypoglycemia and sepsis
  - Management of underlying cause – e.g. N-acetylcysteine for paracetamol overdose

King's College Hospital criteria in acute liver failure

Paracetamol-induced liver failure

- Arterial pH <7.3 24h after ingestion.

Or all of the following:

- Prothrombin time (PT) >100s
- Creatinine >300μmol/L
- Grade III or IV encephalopathy.

Non-paracetamol liver failure

- PT >100s.

Or 3 out of 5 of the following:

1. Drug-induced liver failure
2. Age <10 or >40yrs old
3. >1wk from 1st jaundice to encephalopathy
4. PT >50s
5. Bilirubin ≥300μmol/L.

Fulfilling these criteria predicts poor outcome in acute liver failure and should prompt consideration for transplantation (p277).

Reproduced from O'Grady J *et al.* 'Early indicators of prognosis in fulminant hepatic failure.' *Gastroenterology*, 97(2):439–45, 1989 with permission from Elsevier.

Viral hepatitis

- Causes of viral hepatitis

22.33 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

- Features of the main hepatitis viruses

22.34 Features of the main hepatitis viruses

	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Virus					
Group	Enterovirus	Hepadnavirus	Flavivirus	Incomplete virus	Calicivirus
Nucleic acid	RNA	DNA	RNA	RNA	RNA
Size (diameter)	27 nm	42 nm	30–38 nm	35 nm	27 nm
Incubation (weeks)	2–4	4–20	2–26	6–9	3–8
Spread*					
Faeces	Yes	No	No	No	Yes
Blood	Uncommon	Yes	Yes	Yes	No
Saliva	Yes	Yes	Yes	Unknown	Unknown
Sexual	Uncommon	Yes	Uncommon	Yes	Unknown
Vertical	No	Yes	Uncommon	Yes	No
Chronic infection	No	Yes	Yes	Yes	No (except immune-compromised)
Prevention					
Active	Vaccine	Vaccine	No	Prevented by hepatitis B vaccination	No
Passive	Immune serum globulin	Hyperimmune serum globulin	No		No

*All body fluids are potentially infectious, although some (e.g. urine) are less infectious than others.

Acute viral hepatitis

- Clinical features
  - ❖ Icteric hepatitis
    - Prodromal (pre-icteric) phase
      - Flu-like symptoms – fever, malaise, headache, myalgia, arthralgia
      - GI symptoms – anorexia, nausea, vomiting, RUQ abdominal pain, diarrhea
      - Serum sickness-like symptoms – rash, arthritis
    - Icteric phase
      - Jaundice, tender hepatomegaly
      - Cholestasis if obstruction to bile canaliculi
        - Deep jaundice, clay colored stool, high colored urine, pruritus
      - Splenomegaly, cervical lymphadenopathy (in some)
    - Convalescent phase
      - Resolution of clinical symptoms and biochemical abnormalities
      - ↑Appetite, ↓GI symptoms
      - ↓Jaundice, ↓hepatomegaly, stool color and urine color – normal
  - ❖ Anicteric hepatitis (more common than icteric hepatitis) (especially in HAV and HCV infection)
    - Hepatitis without jaundice
      - Known contact with a definite case
      - Non-specific GI symptoms or malaise
      - Biochemical evidence of hepatic dysfunction

- Complications
  - Post-hepatitis syndrome
  - Persistent hyperbilirubinemia in Gilbert syndrome

22.35 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

- Investigations
  - Liver function test
    - OSPT – prolonged; albumin – normal; serum bilirubin – raised
  - Liver enzymes
    - ALT, AST – typically between 200 and 2000 U/L
    - ALP, GGT – raised (if cholestasis +)
  - Hepatitis serology
  - Hemogram (normal WBC count with relative lymphocytosis), U&E

- Management
  - ❖ Most individuals do not need hospital care.

  - ❖ No specific treatment
  - ❖ Supportive management
    - Nutrition
      - High calorie diet; good protein diet
      - Light diet with fruit juice and glucose
    - Hydration
      - Proper hydration (oral or parenteral) for optimal fluid and electrolyte balance
      - IV fluid and glucose if vomiting is severe
    - Fever control – tepid sponging
    - Avoid hepatotoxic drugs, nephrotoxic drugs and sedatives
    - Alcohol should not be taken during the acute illness.
    - Elective surgery should be avoided as there is a risk of post-operative liver failure.

  - ❖ Prevention and treatment of acute liver failure
    - For hepatic encephalopathy – bowel sterilization (lactulose, rifaximin), IV mannitol
    - To prevent GI bleeding – PPI or H2 blocker

  - ❖ Liver transplantation is very rarely indicated for acute viral hepatitis.

Viral hepatitis A

- Virus type – RNA virus, picornavirus
- Mode of transmission – fecal-oral route; saliva, blood, sex
- Incubation period – 2-6wks
- Period of infectivity – 2 weeks before and after the onset of symptoms

- Clinical course
  - Acute hepatitis, acute liver failure (0.1%)
  - Cholestatic hepatitis in some cases
  - No carrier state nor chronic hepatitis

- Investigations
  - Anti-HAV antibody – IgM is diagnostic; IgG indicates past exposure and immunity
  - ALT/AST – significantly raised

- Treatment – supportive
- Prevention
  - Active immunization – killed vaccine (especially for travelers)
  - Passive immunization – HAIG for post-exposure prophylaxis if < 2wks of exposure

Viral hepatitis B

- Virus type – DNA virus, hepadna virus (incubation period >6wks)

22.36 Source of hepatitis B infection and risk of chronic infection

Horizontal transmission (10%)

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

Vertical transmission (90%)

- Hepatitis B surface antigen (HBsAg)-positive mother

- Clinical course
  - 65% – subclinical infection
  - 25% – acute hepatitis (acute liver failure in 1%)
  - 1-10% – chronic hepatitis cirrhosis or HCC

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

Phase	HBsAg	HBeAg	Anti-HBe Ab	Viral load	ALT	Histology	Notes
'Immune-tolerant' phase	+	+	–	+++	Normal/ low	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
'Immune-reactive' HBeAg-positive chronic hepatitis phase	+	+	–	++	Raised	Moderate/severe necroinflammation	May last weeks or years. High risk of cirrhosis or HCC if prolonged. Increased chance of spontaneous loss of HBeAg with seroconversion to anti-HBe antibody-positive state
'Inactive carrier' phase	+	–	+	–/+	Normal	Normal/minimal necroinflammation	Low risk of cirrhosis or HCC in majority
HBeAg-negative chronic hepatitis phase	+	–	+	Fluctuating +/++	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 even after HBsAg loss

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

- Investigations
  - HBV serology

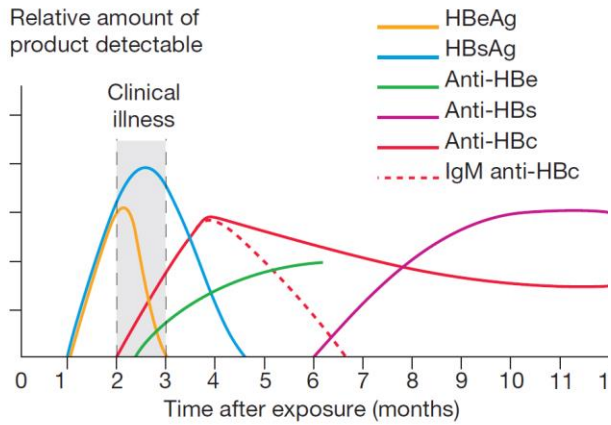


Fig. 23.25 Serological responses to hepatitis B virus infection (HBeAg = hepatitis B e antigen; anti-HBe = antibody to HBeAg; HBsAg = hepatitis B surface antigen; anti-HBs = antibody to HBsAg; anti-HBc = antibody to hepatitis B core antigen)

23.42 How to interpret the serological tests of acute hepatitis B virus infection

Interpretation	HBsAg	Anti-HBc IgM	Anti-HBc IgG	Anti-HBs
Incubation period	+	+	–	–
Acute hepatitis				
Early	+	+	–	–
Established	+	+	+	–
Established (occasional)	–	+	+	–
Convalescence				
(3–6 months)	–	±	+	±
(6–9 months)	–	–	+	+
Post-infection	–	–	+	±
Immunisation without infection	–	–	–	+

+ Positive; – negative; ± present at low titre or absent.

HBsAg	Marker of infection	▪ HBsAg persists > 6mths – chronic infection ▪ HBsAg can be negative in window period, in acute liver failure and in HBsAg negative chronic hepatitis
HBeAg	Marker of viral replication	▪ HBeAg can be negative in pre-core mutant chronic hepatitis (HBeAg negative chronic hepatitis) despite high viral load
IgM anti-HBc Ab	Marker of acute infection	▪ High titer in acute hepatitis B ▪ Low titer in chronic hepatitis B ▪ Can be found in window period
IgG anti-HBc Ab	Marker of exposure	▪ Can be found in window period
Anti-HBe Ab	Marker of seroconversion	▪ Reflects ↓viral replication except in pre-core mutant
Anti-HBs Ab	Marker of immunity	▪ Reflects viral eradication

  - Viral load (HBV DNA PCR)
  - ALT/AST – significantly raised in acute flare
  - Liver biopsy – to assess degree of liver damage

- Treatment
  - ❖ Acute hepatitis – supportive
  - ❖ Chronic hepatitis
    - Indications for antiviral therapy
      - High viral load + active hepatitis
        - ➢ High viral load – assess by HBsAg, HBeAg and viral load
        - ➢ Active hepatitis – assess by ALT/AST and liver biopsy
      - Cirrhosis

    - Antiviral therapy
      - PEG-IFN-α
        - ➢ Route – weekly subcutaneous injection
        - ➢ Mechanism of action – booster immune system for viral clearance
        - ➢ Disadvantages – flu-like symptoms, depression, auto-immune thyroiditis
        - ➢ Contraindications – cirrhosis, auto-immune hepatitis, severe depression

      - Oral direct acting nucleoside/nucleotide antiviral agents
        - ➢ Drugs – lamivudine, adefovir, tenofovir, entecavir
        - ➢ Mechanism of action – inhibit viral reverse transcriptase to suppress viral replication
        - ➢ Disadvantages
          - ✓ Lamivudine and adefovir have high risk of resistance
          - ✓ Tenofovir – nephrotoxicity

    - Treatment target – HBeAg seroconversion; reduction in HBV DNA; normalization of LFTs

- Prevention

Vaccinating to prevent hepatitis B (and associated complications)

Use hepatitis B vaccine 1mL into deltoid; repeat at 1 & 6 months (child: 0.5mL × 3 into the anterolateral thigh). *Indications:* Everyone (WHO advice, even in areas of 'low' endemicity—in 2014 this meant that 82% of the world's children received protection against HBV). This contrasts with the approach in eg the UK and USA of targeting at-risk groups (p278). The immunocompromised and others may need further doses. Serology helps time boosters and finds non-responders (correlates with older age, smoking, and ♂ sex). ►*Know your own antibody level!*

Table 6.15 Post-immunization anti-HBs titres and actions

Anti-HBs (IU/L)	Actions and comments (advice differs in some areas)
>1000	Good level of immunity; retest in ~4yrs.
100–1000	Good level of immunity; if level approaches 100, retest in 1yr.
<100	Inadequate; give booster and retest.
<10	Non-responder; give another set of 3 vaccinations. Retest; if <10 get consent to check hepatitis B status: HBsAg +ve means chronic infection; anti-HB core +ve represents past infection and immunity. If a non-responder is deemed susceptible to HBV, and has recently come in contact with risky bodily fluids, offer 2 doses of anti-hep B immunoglobulin.

NB: protection begins some weeks after dose 1, so it won't work if exposure is recent; here, specific antihepatitis B immunoglobulin is best if not already immunized.

Viral hepatitis C

- Virus type – RNA virus, flavivirus (incubation period >6wks)

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

- Clinical course
  - 20% recovery
  - 80% carrier/chronic hepatitis cirrhosis HCC
  - 20% of chronic hepatitis in 20 years develop cirrhosis
  - No acute hepatitis nor acute liver failure

- Investigations
  - Anti-HCV antibody; if positive, proceed HCV RNA PCR to confirm active HCV infection
  - HCV genotyping (there are 6 genotypes) (most common genotypes in Myanmar – 3, 6, 1)
    - No effect on liver damage
    - Differs in treatment response
      - Genotype 1 and 4 have poor treatment response
      - Genotype 2 and 3 have good treatment response
  - ALT/AST – usually normal (poor predictor of liver fibrosis)
  - Liver biopsy – to stage degree of liver fibrosis

- Treatment
  - Conventional therapy – PEG-IFN-α ± ribavirin (SE: hemolytic anemia)
  - Newer antiviral therapies – e.g. sofosbuvir, dasabuvir

- Treatment target – to achieve cure (sustained virological response (SVR) where viral load is undetectable 6 months after cessation of therapy)

- Prevention – no active nor passive immunization for HCV

- Extra-hepatic manifestations
  - Cryoglobulinemia (Raynaud phenomenon + mononeuritis multiplex + nephritis)
  - Porphyria cutanea tarda (blisters on face and dorsum of hand with photosensitivity)
  - MCGN (mesagniocapillary glomerulonephritis) (nephritis-nephrotic syndrome)
  - Diabetes (diabetogenic hepatitis)

Viral hepatitis D

- Virus type – RNA-defective virus, delta virus
- Mode of transmission – same as HBV

- Pattern of infection
  - HDV requires HBV for viral replication.
  - Co-infection – where HBV and HDV infection occur simultaneously
  - Super-infection – where HDV infection occurs in chronic HBV carriers

- Clinical course
  - HDV infection may cause spontaneous recovery of both HBV and HDV infection, or may cause rapid progression to cirrhosis.
  - Acute hepatitis, acute liver failure
  - Chronic hepatitis, cirrhosis, HCC

- Investigations – anti-HDV antibody
- Treatment and prevention – same as HBV

Viral hepatitis E

- Virus type – RNA virus, calcivirus
- Mode of transmission – fecal-oral route
- Incubation period – 2-6wks

- Clinical features
  - Acute hepatitis, acute liver failure (1-2%)
  - High mortality in pregnancy (20% develop acute liver failure)
  - No carrier nor chronic state

- Investigations
  - Anti-HEV antibody
  - ALT/AST – significantly raised

- Treatment – supportive
- Prevention – no active nor passive immunization

Alcoholic liver disease

- Risk factors
  - Amount of alcohol – 30g/day of ethanol confers risk of developing alcoholic liver disease.
  - Drinking pattern – continuous drinkers can have liver damage more likely than intermittent or binge drinkers. (chance for liver to recover)
  - Gender – women have higher blood alcohol level than men after consuming same amount of alcohol. (↓volume of distribution of alcohol)
  - Genetics – alcoholism is more concordant in monozygotic twins than dizygotic twins.
  - Nutrition – obesity increase liver-related mortality by over fivefold in heavy drinkers.

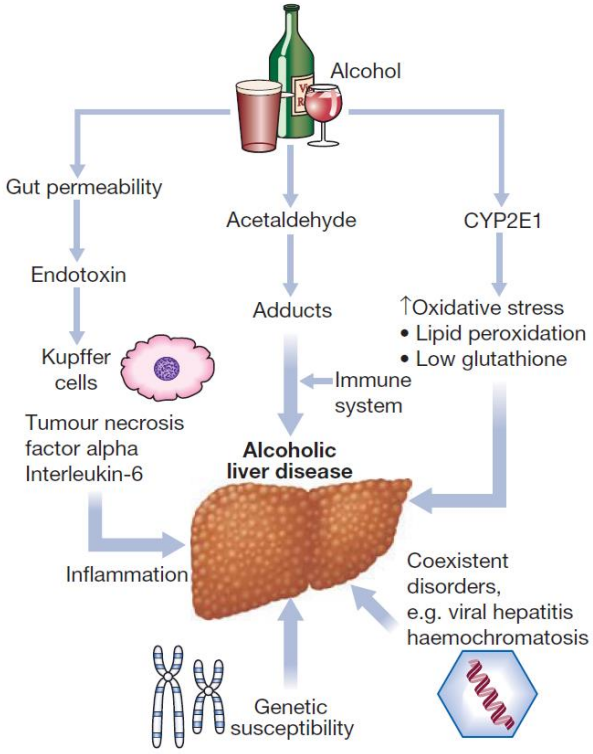


Fig. 22.29 Factors involved in the pathogenesis of alcoholic liver disease.

i 22.46 Clinical syndromes of alcoholic liver disease

Fatty liver	
• Asymptomatic abnormal liver biochemistry	• Normal/large liver
Alcoholic hepatitis	
• Jaundice • Malnutrition • Hepatomegaly	• Features of portal hypertension (e.g. ascites, encephalopathy)
Cirrhosis	
• Stigmata of chronic liver disease • Ascites/varices/ encephalopathy	• Large, normal or small liver • Hepatocellular carcinoma

i 22.45 Pathological features of alcoholic liver disease

• Alcoholic hepatitis: Lipogranuloma Neutrophil infiltration Mallory's hyaline Pericellular fibrosis	• Macrovesicular steatosis • Fibrosis and cirrhosis • Central hyaline sclerosis

- Investigations
  - To establish alcohol misuse – macrocytosis in the absence of anemia, ↑ɣ-GT, AST:ALT > 2:1
  - For fatty liver – incidental finding on USG (abdomen)
  - For alcoholic hepatitis
    - Discriminant function (DF) (Maddrey score)
      - DF = [4.6 x Increase in PT (sec)] + Bilirubin (mg/dl)
      - A value over 32 implies severe liver disease with a poor prognosis.
    - Blood film – neutrophil leukocytosis, ↓platelet
    - Liver biopsy – neutrophil infiltration, Mallory hyaline, macrovesicular steatosis

22.47 How to assess prognosis using the Glasgow alcoholic hepatitis score

Score	1	2	3
Age	<50	>50	
White cell count ($\times 10^9$/L)	<15	>15	
Urea (mmol/L *(BUN mg/dl)*)	<5 *(14)*	>5 *(14)*	
PT ratio	<1.5	1.5–2.0	>2.0
Bilirubin (μmol/L *(mg/dL)*)	<125 *(7.4)*	125–250 *(7.4–14.8)*	>250 *(14.8)*
A score of ≥9 is associated with a 40% 28-day survival, compared to 80% for patients with a score of <9.			

(BUN = blood urea nitrogen; PT = prothrombin time)

Box 34.23 Lille score for alcoholic hepatitis

(*Calculator at* http://www.lillemodel.com)

R = 3.19 – (0.101 × age in years) + (0.147 × albumin on admission in g/L) + (0.0165 × change in bilirubin level from day 0 to day 7 in μmol/L) – (0.206 × renal insufficiency [0 if absent, 1 if present][a]) – (0.0065 × bilirubin day 0 in μmol/L) – (0.0096 × INR)

Score = EXP(–R)/[1+EXP(–R)]

A score of <0.16 indicates a 96% chance of survival at 28 days; ≥0.56 indicates a 55% chance of survival at 28 days.

[a]Creatinine >115 μmol/L. INR, international normalized ratio.

- Management of alcoholic hepatitis
  - Stop alcohol drinking
  - For withdrawal symptoms – oral chlordiazepoxide or IM lorazepam

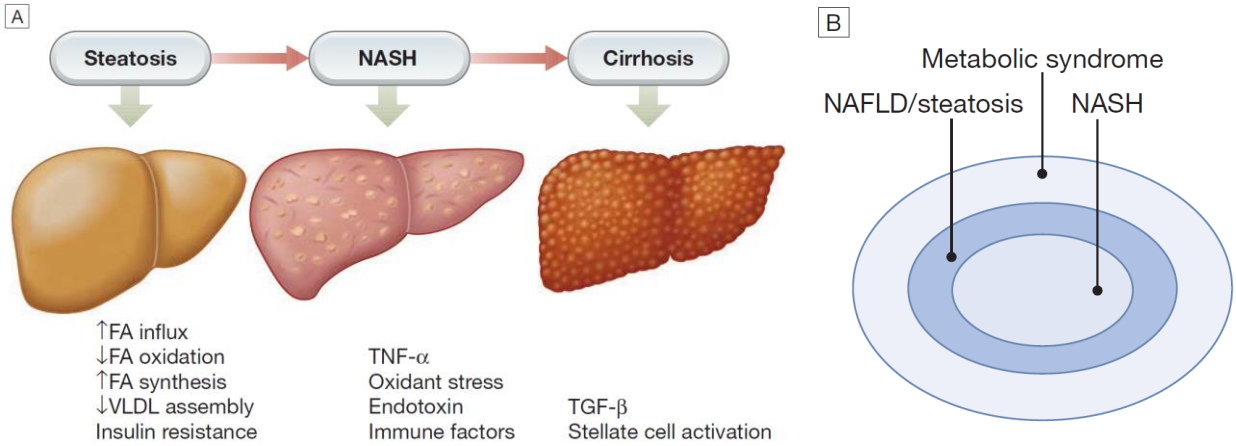
  - Nutrition
    - Optimize nutrition (35-40kcal/kg/day non-protein energy)
    - Give >1.2g/kg/day of protein which prevents encephalopathy, sepsis, and some deaths.
    - Vitamins: Vitamin K 10mg/day IV for 3d. Thiamine 100mg/day PO

  - If Maddrey score > 32 and encephalopathy, consider prednisolone (CI: sepsis, variceal bleeding
    - If Lille score >0.45, it indicates poor response to steroids which can therefore be stopped.
    - Alternative – pentoxifylline (weak anti-TNF agent with vasodilatory properties)

- Prognosis
  - Fatty liver usually disappears after 3 months of alcohol abstinence.
  - Severe alcoholic hepatitis confers mortality x 50% at 30d.
  - Alcoholic cirrhosis confers 5-year survival of 60%, and if decompensated, 35%.

Non-alcoholic fatty liver disease

- Commonest liver disorder in Western industrialized countries (prevalence ≈ 20%)
- NAFLD represents ↑fat in hepatocytes (steatosis) visualized, e.g. on ultrasound, that cannot be attributed to other causes (most commonly alcohol so consider NAFLD if drink <18 units/week in male, <9 units/week in female).
- Hepatic manifestation of metabolic syndrome
- Risk factors for progression – older age, obesity, DM, hyperlipidemia



- Investigations
  - Biochemical tests – modest elevation of ALT and AST, NAFLD fibrosis score
  - Imaging – USG (abdomen), elastography
  - Liver biopsy – steatosis, hepatocellular injury and inflammation with zone 3 distribution, Mallory-Denk bodies, perisinusoidal fibrosis

- Treatment
  - Control obesity – lifestyle advice, orlistat, bariatric surgery
  - Control insulin resistance and dyslipidemia – metformin, pioglitazone, fibrate
  - Control cardiovascular risk (commonest cause of death)
  - Avoid alcohol consumption
  - No drug is of proven benefit though vitamin E may improve histology in fibrosis.

- Follow-up
  - Monitor for complications (NASH, cirrhosis, DM).
  - If cirrhotic, screen for HCC with ultrasound ± AFP twice-yearly.

Autoimmune hepatitis

- Inflammatory liver disease of unknown cause characterized by abnormal T cell function and autoantibodies directed against hepatocyte surface antigens
- Strong association with other autoimmune diseases and hypergammaglobulinemia especially IgG
- Liver biopsy – mononuclear infiltrate of portal and periportal areas

Table 6.12 Classifying autoimmune hepatitis: types I–II

I	Seen in 80%. Typical patient: ♀<40yrs. Antismooth muscle antibodies (ASMA) +ve in 80%. Antinuclear antibody (ANA) +ve in 10%. ↑IgG in 97%. Good response to immunosuppression in 80%. 25% have cirrhosis at presentation.
II	Commoner in Europe than USA. More often seen in children, and more commonly progresses to cirrhosis and less treatable. Typically anti-liver/kidney microsomal type 1 (LKM1) antibodies +ve. ASMA and ANA −ve.

- Treatment – steroid; liver transplant if treatment failure or decompensated cirrhosis

Primary biliary cholangitis

- Chronic autoimmune granulomatous inflammation of interlobular bile ducts
- Risk factors – middle aged women, positive family history, smoking
- Clinical features and complications
  - Pruritus
  - Malabsorption of fat-soluble vitamins – osteomalacia, coagulopathy
  - Xanthelesma, xantomata
  - Jaundice, skin pigmentation, hepatosplenomegaly, portal hypertension
- Investigations
  - Liver enzymes – cholestatic pattern; impaired LFT (↑bilirubin, ↑PT, ↓albumin)
  - Anti-mitochondrial antibody (AMA) M2 subtype (positive in 98%), ↑IgM
  - USG (abdomen) – to exclude extrahepatic cholestasis
  - Liver biopsy – granuloma around bile ducts
- Treatment
  - For pruritus – colestyramine, naltrexone, rifampicin
  - Osteoporosis prevention – calcium and vitamin D supplement; bisphosphonate if osteoporosis
  - Fat-soluble vitamin prophylaxis
  - High-dose ursodeoxycholic acid (UDCA) (improves survival and delays transplant)
  - Liver transplant – for end-stage liver disease or intractable pruritus

Primary sclerosing cholangitis

- Diffuse inflammation and fibrosis of entire biliary tree (intrahepatic and extrahepatic bile ducts)
- Risk factors – young men, inflammatory bowel disease (especially ulcerative colitis)
- Clinical features – pruritus, fatigue, chronic liver insufficiency
- Cancers – bile duct, gallbladder, liver and colon cancers are more common
- Investigations
  - Liver enzymes – cholestatic pattern; impaired LFT
  - AMA negative; ANA, SMA and ANCA may be positive
  - ERCP or MRCP – generalized beading appearance of biliary tree (stricture and dilatation)
  - Liver biopsy – periductal onion skin fibrosis and inflammation, obliterative cholangitis
- Treatment
  - Colestyramine for pruritus; antibiotics (e.g. ciprofloxacin) for bacterial cholangitis
  - UDCA may improve LFT but have no survival benefit.
  - Liver transplant – for end-stage liver disease

Budd-Chiari syndrome

- Thrombosis of larger hepatic veins and sometimes inferior vena cava
- Risk factors – pregnancy and COC pills, thrombophilia, obstruction due to tumor
- Clinical features
  - Acute venous occlusion
    - Rapid development of upper abdominal pain, marked ascites and occasionally acute liver failure
    - Hepatomegaly, frequently with liver tenderness, is almost always present.
  - Gradual venous occlusion causes chronic liver insufficiency and cirrhosis.
- Investigations
  - LFTs – variable depending on presentation
  - Doppler ultrasound – hepatic vein thrombosis and reversed flow in portal vein
  - CT (abdomen) – thrombosis of hepatic vein and IVC, enlargement of caudate lobe
  - Investigations for underlying cause – e.g. thrombophilia screen
- Treatment
  - For suspected recent thrombosis – thrombolysis with streptokinase followed by heparin and oral anticoagulation
  - For more extensive venous obstruction – TIPSS followed by anticoagulation
  - For progressive liver failure – liver transplant and life-long anticoagulation

α1-antitrypsin deficiency

- Inherited disorder affecting lung and liver
- Clinical features
  - Chief genetic cause of liver disease in children – cirrhosis, cholestatic jaundice
  - Emphysema in adults (particularly in smokers) – lower lobe panacinar emphysema
- Investigations
  - Serum α1-antitrypsin level ↓
  - Phenotyping by electrophoresis – PiZZ type has the highest risk
  - Liver biopsy – PAS positive, diastase-resistant globules
  - Lung function tests – obstructive pattern if emphysema
- Treatment
  - Smoking cessation
  - α1-antitrypsin may be given to prevent COPD exacerbations
  - Liver transplant – for decompensated cirrhosis

Hereditary hemochromatosis

- Autosomal recessive disorder of iron metabolism in which ↑intestinal iron absorption leads to iron deposition and damage of severe organs
- Genetics – HFE gene mutation (C282Y mutation, H63D mutation)
- Middle-aged men are more frequently and severely affected than women, in whom the disease tends to present ~10yrs later (menstrual blood loss is protective).
- Clinical features
  - Skin pigmentation, arthralgia and knee pseuodgout
  - Chronic liver insufficiency, hepatomegaly, dilated cardiomyopathy
  - Endocrinopathies – DM (bronze diabetes), hypogonadism
- Investigations
  - Iron study – ↑ferritin; ↑transferrin saturation >45%
  - LFT; Liver biopsy – hepatic iron index >1.9 suggests HH.
  - HFE genotyping
  - Investigations for complications – cardiac assessment, hormonal assays
- Treatment – venesection; desferrioxamine if intolerant of venesection; avoid iron-rich food
- Screening of 1st degree relatives of patient by genetic testing

Wilson disease

- Autosomal recessive disorder of copper excretion with excess deposition in liver and CNS
- Clinical features
  - Liver disease (children)
    - Episodes of acute hepatitis, sometimes recurrent
    - Fulminant liver failure (with massive hemolysis and renal tubulopathy)
    - Chronic hepatitis and cirrhosis
  - Neurological disease (young adults)
    - Extrapyramidal features (Parkinsonism, tremor, choreoathetosis, dystonia)
    - Dysarthria, dysphagia, ataxia/clumsiness, dementia
  - Kayser-Fleischer rings (almost always present in neurological Wilson disease)
- Investigations
  - Copper study – ↓serum ceruloplasmin, ↑free serum copper, ↑24hr urine copper excretion
  - LFT; liver biopsy – ↑hepatic copper; MRI (brain)
  - Genetic testing
- Treatment – lifelong penicillamine; avoid copper-rich food
- Screening of 1st degree relatives of patient

Hepatocellular carcinoma

- Causes – HBV (leading cause worldwide), HCV, cirrhosis, aflatoxin, anabolic steroids
- Clinical features (male:female ≈ 3)
  - Fatigue, ↓appetite, ↓weight, RUQ pain, jaundice, ascites
  - Deterioration of liver function in patients with underlying cirrhosis, with signs of decompensation (worsening jaundice, ascites, encephalopathy or variceal hemorrhage)
  - Hepatomegaly (hard and irregular), upward enlargement of liver, liver bruit
- Investigations – 3-phase CT (delayed washout of contrast in a suspect mass); AFP, USG, biopsy
- Curative treatment (for early stage)
  - Liver resection if solitary tumor <3cm
  - Liver transplant if solitary tumor <5cm or three tumors <3cm
  - Percutaneous therapy – RFA (radiofrequency ablation), PEI (percutaneous ethanol injection)
- Palliative treatment
  - TACE (trans-arterial chemo-embolization) with Gelfoam and doxorubicin
  - Sorafenib (multikinase inhibitor with activity against Raf, VEGF and PDGF)
  - Best supportive care for terminal stage
- Fibrolamellar hepatocellular carcinoma (rare variant of HCC)
  - Young adults (M=F), in the absence of HBV and cirrhosis; large tumor at presentation
  - Normal AFP; biopsy – malignant hepatocytes surrounded by dense fibrous stroma
  - Treatment of choice is surgical resection; better prognosis