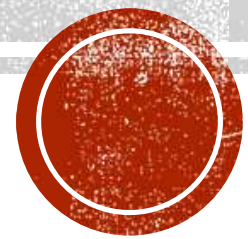
CHRONIC LIVER DISEASE

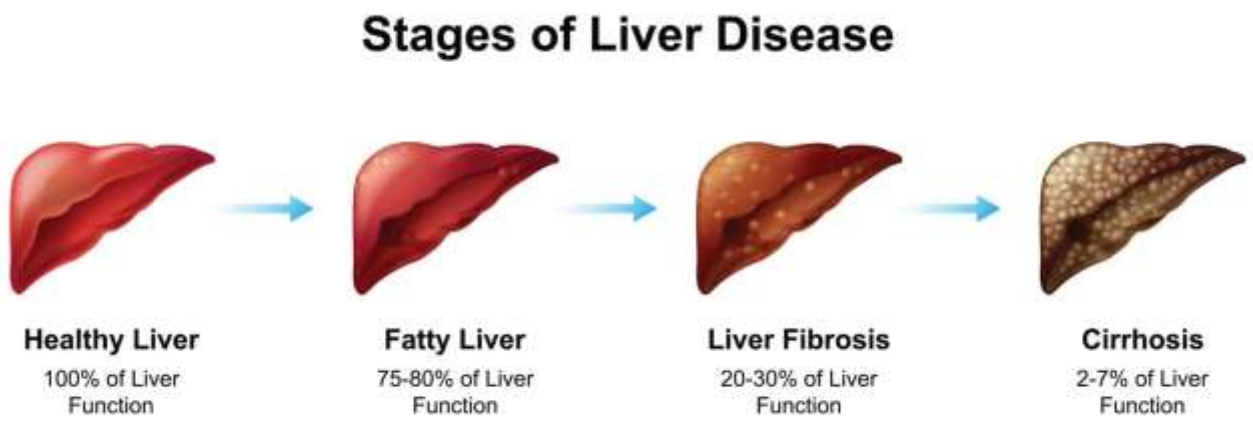
AFRAH ALI

ROLL NO. 9



INTRODUCTION

- *Hepatic injury, inflammation and/or fibrosis occurring in the liver for more than 6 months*
- Leads to deterioration of liver functions including synthesis of clotting factors, protein, detoxification and bile synthesis
- Cirrhosis involves disruption of liver architecture, vascular reorganization, neo-angiogenesis, deposition of extracellular matrix



AETIOLOGY

- Alcoholic Liver Disease
- Chronic Hepatitis (B + C)
- Non Alcoholic Fatty Liver Disease
- Genetic causes (Haemochromatosis, Wilson's Disease, α1-Antitrypsin Deficiency)
- Autoimmune causes (Primary Biliary Cirrhosis, Primary Sclerosing Cholangitis, Autoimmune Hepatitis)
- Other causes such as drugs (amiodarone, isoniazid, methotrexate, phenytoin, nitrofurantoin), Budd Chiari syndrome, Idiopathic

PATHOPHYSIOLOGY

CHRONIC INJURY TO HEPATOCYTES → RELEASE OF CYTOKINES → STELLATE CELL ACTIVATION → UPREGULATION OF RECEPTORS

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MYOFIBROBLASTS ACTIVATED

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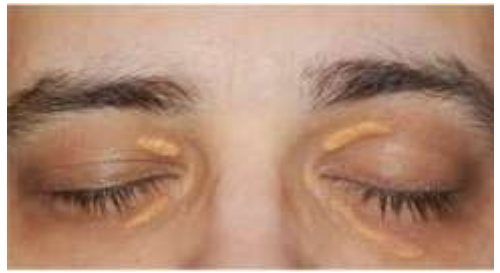
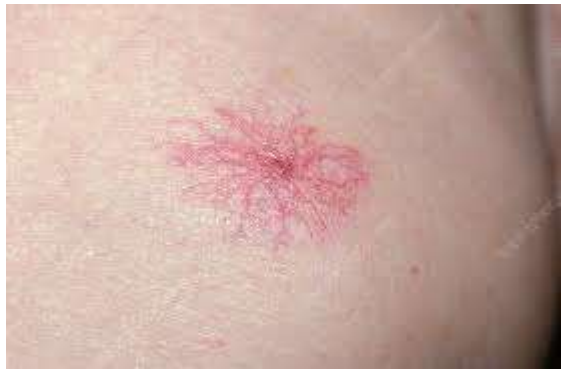
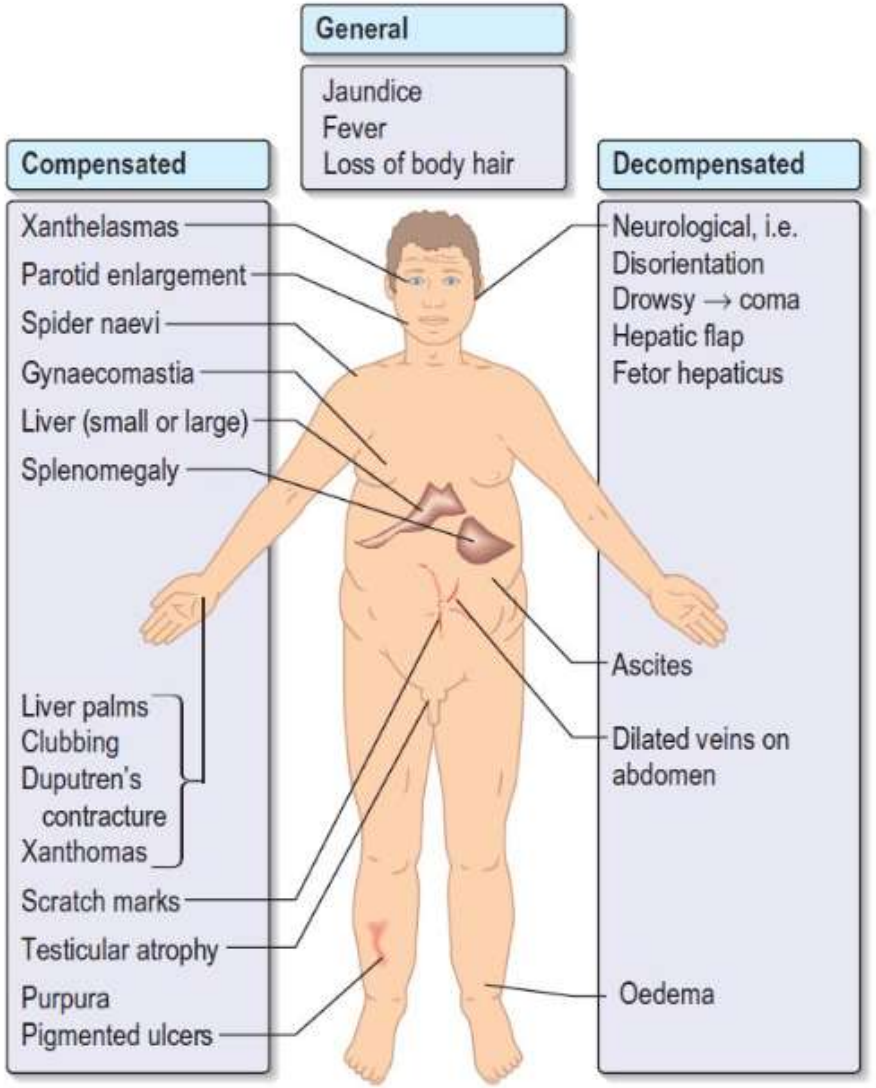
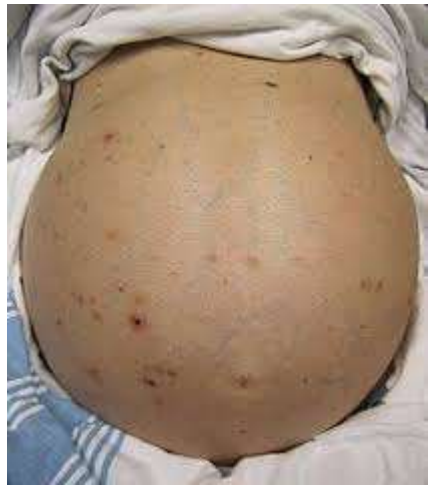
COLLAGEN REPLACES MATRIX → FIBROSIS → LOSS OF FUNCTION DISRUPTED ARCHITECTURE ABERRANT HEPATOCYTE REGENERATION

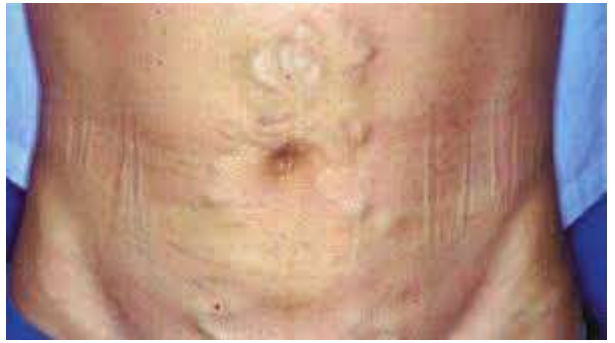
CLINICAL FEATURES











PROGNOSIS

- Cirrhosis can be categorised into two prognostic groups: compensated and decompensated
- Compensated cirrhosis: earlier phase, largely asymptomatic, relatively good prognosis with median survival >12 years.
- Decompensated cirrhosis: later phase, presence of complications, including ascites, variceal bleeding, jaundice and encephalopathy, median survival rate is around 2 years with high variability

24.31 Child–Pugh classification of prognosis in cirrhosis

Score	1	2	3
Encephalopathy	None	Mild	Marked
Bilirubin (μmol/L (*mg/dL*))*			
Primary biliary cholangitis/sclerosing cholangitis	< 68 (*4*)	68–170 (*4–10*)	> 170 (*10*)
Other causes of cirrhosis	< 34 (*2*)	34–50 (*2–3*)	> 50 (*3*)
Albumin (g/L (*g/dL*))	> 35 (*3.5*)	28–35 (*2.8–3.5*)	< 28 (*2.8*)
Prothrombin time (secs prolonged)	< 4	4–6	> 6
Ascites	None	Mild	Marked
Add the individual scores: < 7 = Child's A, 7–9 = Child's B, > 9 = Child's C			

*To convert bilirubin in μmol/L to mg/dL, divide by 17.

24.32 One-year survival rate depending on MELD score

	1-year survival (%)	
MELD score	**No complications**	**Complications***
< 9	97	90
10–19	90	85
20–29	70	65
30–39	70	50
MELD from SI units 10 × (0.378 [ln serum bilirubin (μmol/L)] + 1.12 [ln INR] + 0.957 [ln serum creatinine (μmol/L)] + 0.643)		

COMPLICATIONS

- PORTAL HYPERTENSION
- GASTROESOPHAGEAL VARICES
- ASCITES
- SPONTANEOUS BACTERIAL PERITONITIS
- HEPATORENAL SYNDROME
- HEPATIC ENCEPHALOPATHY
- HEPATOPULMONARY SYNDROME
- HEPATOCELLLAR CARCINOMA

PORTAL HYPERTENSION

- *Increased portal venous tension due to resistance to portal blood flow*
- Hepatic sinusoidal pressure more than or equal to 6 mm Hg
- Increased portal vascular resistance

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reduction in the flow of portal blood to the liver

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development of collateral vessels

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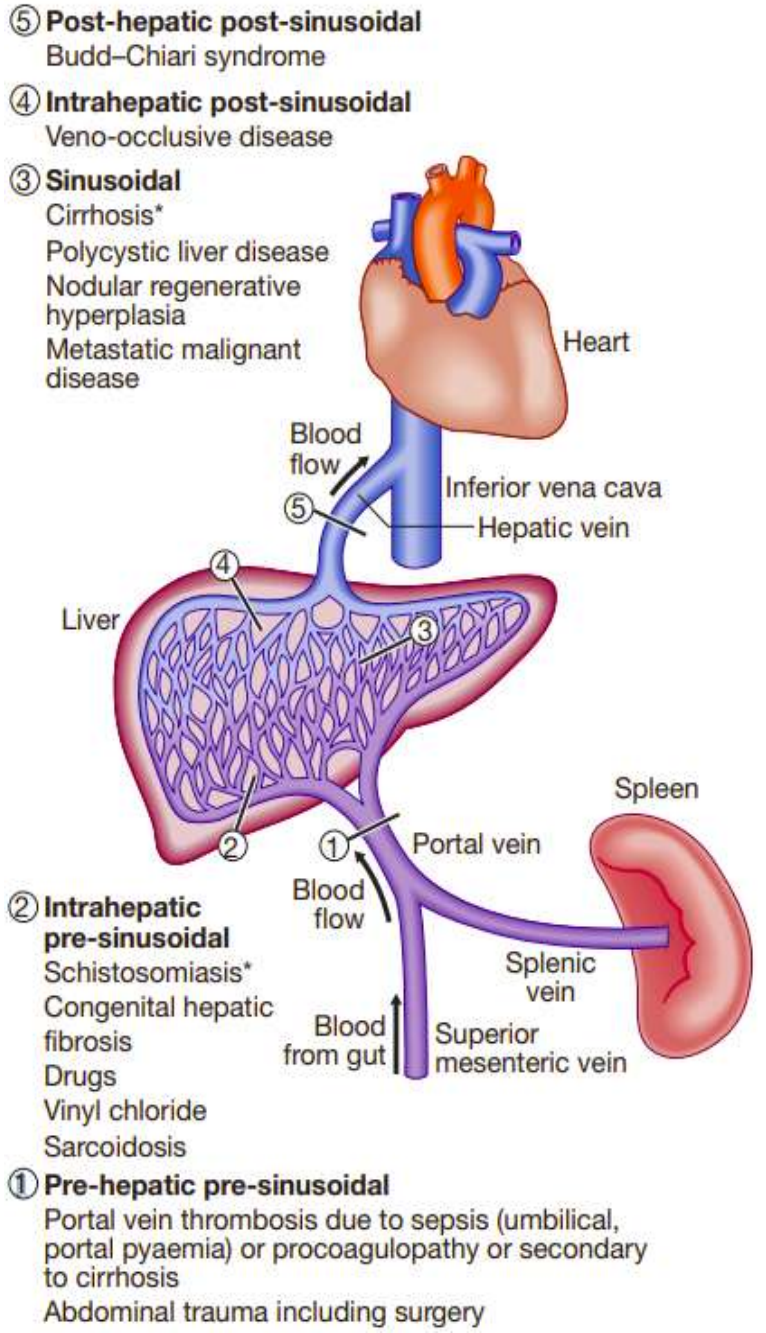
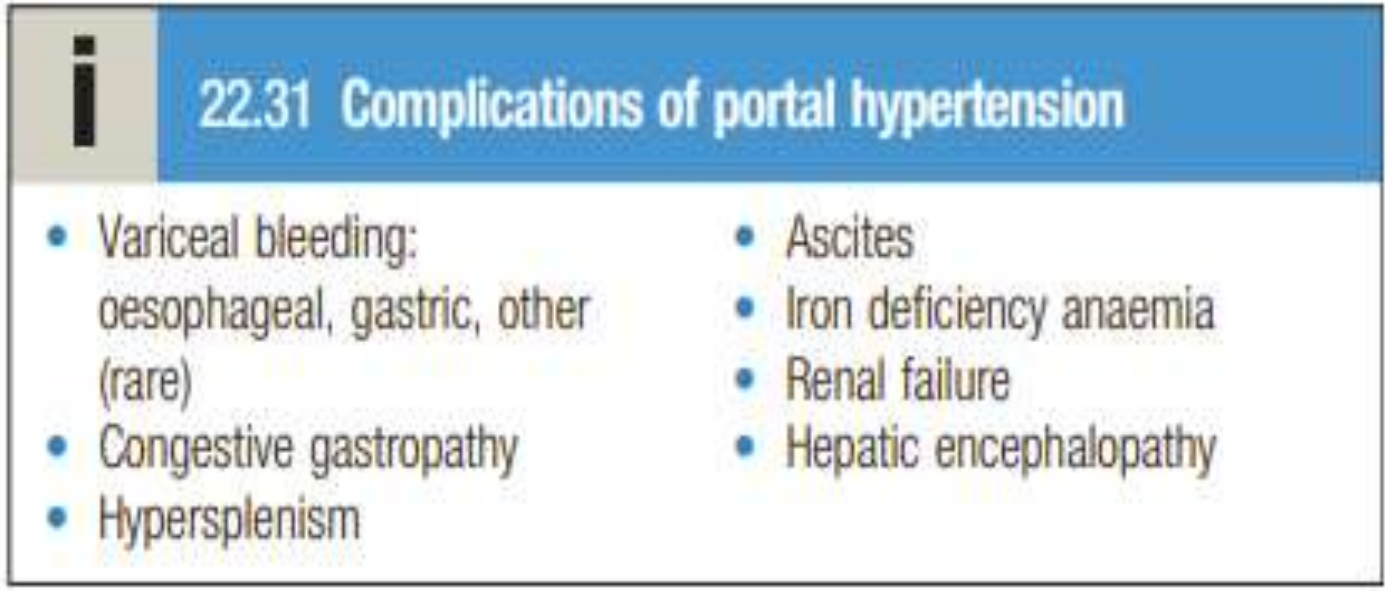
portal blood to bypasses the liver and enters the systemic circulation directly

- Common sites of collateral vessels are eosophagus, stomach, rectum, ant. abdominal wall, renal, ovarian and testicular vasculature
- Consequently varices develop



CLINICAL FEATURES & COMPLICATIONS

- Splenomegaly: cardinal finding, spleen is rarely enlarged more than 5 cm below the left costal margin in adults
- Collateral vessels may be visible on the anterior abdominal wall (as caput medusae).
- The most important collateral vessel formation occurs in the esophagus(located within 3–5 cm of the gastro oesophageal junction) which can lead to severe bleeding.



22.31 Complications of portal hypertension

- Variceal bleeding: oesophageal, gastric, other (rare)
- Congestive gastropathy
- Hypersplenism
- Ascites
- Iron deficiency anaemia
- Renal failure
- Hepatic encephalopathy

INVESTIGATIONS & MANAGEMENT

- *Diagnosis is often made clinically*
- Pressure measurements made using a balloon catheter inserted using the transjugular route (via the inferior vena cava into a hepatic vein and then hepatic venule) to measure the WHVP and calculate HVPG. >5 mm hg indicates portal hypertension and >12 mm Hg indicates high risk for variceal bleeding
- Thrombocytopenia is common due to hypersplenism, and platelet counts are usually in the region of 100 ×109 /L
- The management of portal hypertension is largely focused on the prevention and/or control of variceal hemorrhage.

VARICEAL BLEEDING

- Acute upper gastrointestinal haemorrhage from gastro-oesophageal varices is common in chronic liver disease
- Variceal bleeding can be severe and mortality rate is high

CLINICAL FEATURES

- Haematemesis (coffee grounds appearance), malena, haematochezia
- Significant variceal bleed: pallor, tachypnea, tachycardia, and hypotension
- Syncope caused by hypotension from intravascular volume depletion

INVESTIGATION

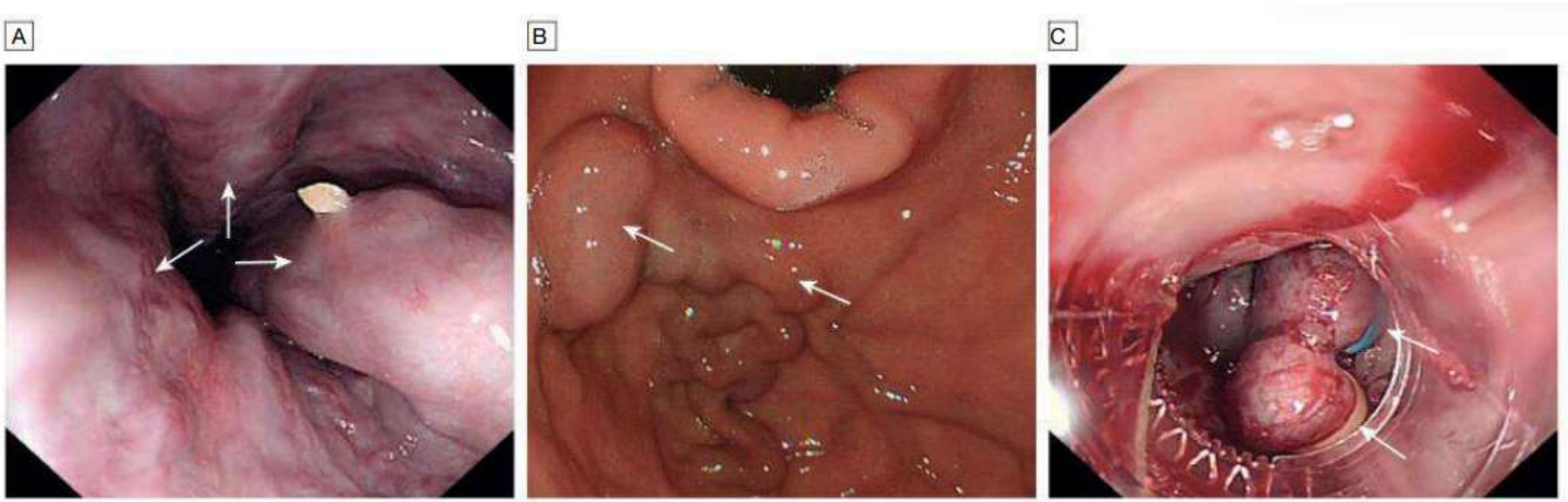


Fig. 24.17 Varices: endoscopic views. A Oesophageal varices (arrows) at the lower end of the oesophagus with a prominent white fibrin plug at the site of recent haemorrhage. B Gastric varices (arrows). C Appearance of oesophageal varices following application of strangulating bands (band ligation, arrows).

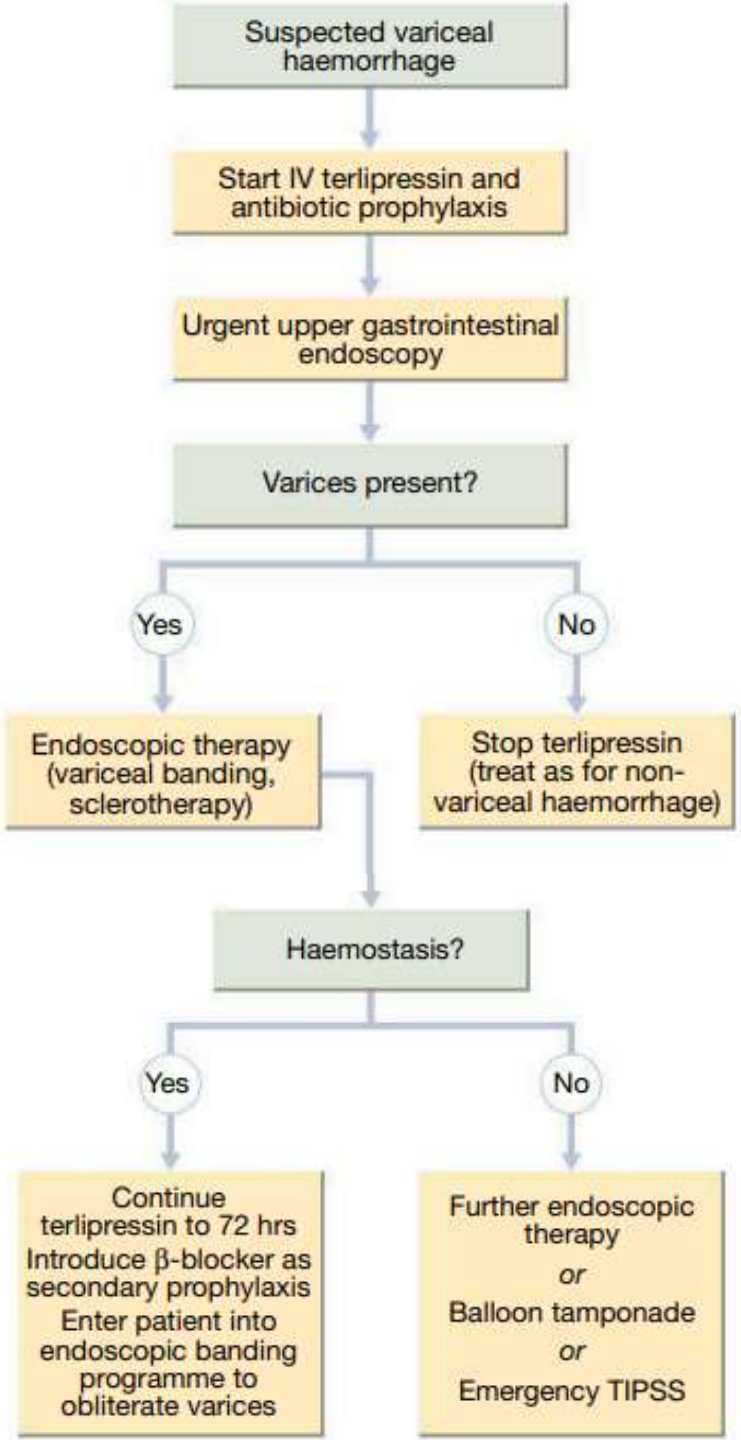
MANAGEMENT

1. **Primary prevention of variceal bleeding**

- If non-bleeding varices are identified at endoscopy, β-blocker therapy with propranolol (80–160 mg/ day) or nadolol (40–240 mg/day) is effective.
- In patients with cirrhosis, treatment with propranolol reduces variceal bleeding by 47% and mortality by 22%
- Carvedilol, a non-cardioselective β-blocker, is also effective

2. **Management of acute variceal bleeding**

- The priority in acute bleeding is to restore the circulation with blood and plasma
- The source of bleeding should always be confirmed by endoscopy because about 20% of patients are bleeding from non-variceal lesions



24.34 Emergency management of bleeding

Management	Reason
Intravenous fluids	To replace extracellular volume
Vasopressor (terlipressin)*	To reduce portal pressure, acute bleeding and risk of early rebleeding
Prophylactic antibiotics (cephalosporin IV)	To reduce incidence of spontaneous bacterial peritonitis
Emergency endoscopy	To confirm variceal rather than ulcer bleed
Variceal band ligation	To stop bleeding
Proton pump inhibitor	To prevent peptic ulcers
Phosphate enema and/or lactulose	To prevent hepatic encephalopathy

*Caution in patients with significant coronary artery, peripheral or other vascular disease.

1. **VARICEAL BANDING**:

- Most widely used initial treatment
- It stops variceal bleeding in over 90% of patients and can be repeated if bleeding recurs
- Band ligation involves the varices being sucked into a cap placed on the end of the endoscope, allowing them to be occluded with a tight rubber band

2. **BALLOON TAMPONADE**

- Minnesota tube, which consists of two balloons that can be positioned in the fundus of the stomach and in the lower oesophagus
- The tube should be passed through the mouth into the stomach. The gastric balloon should be inflated with 200–250mL of air, and gentle traction applied to compress the gastro-oesophageal junction

3. **TIPSS**

- stent placed between the portal vein and the hepatic vein within the liver to provide a portosystemic shunt and reduce portal pressure

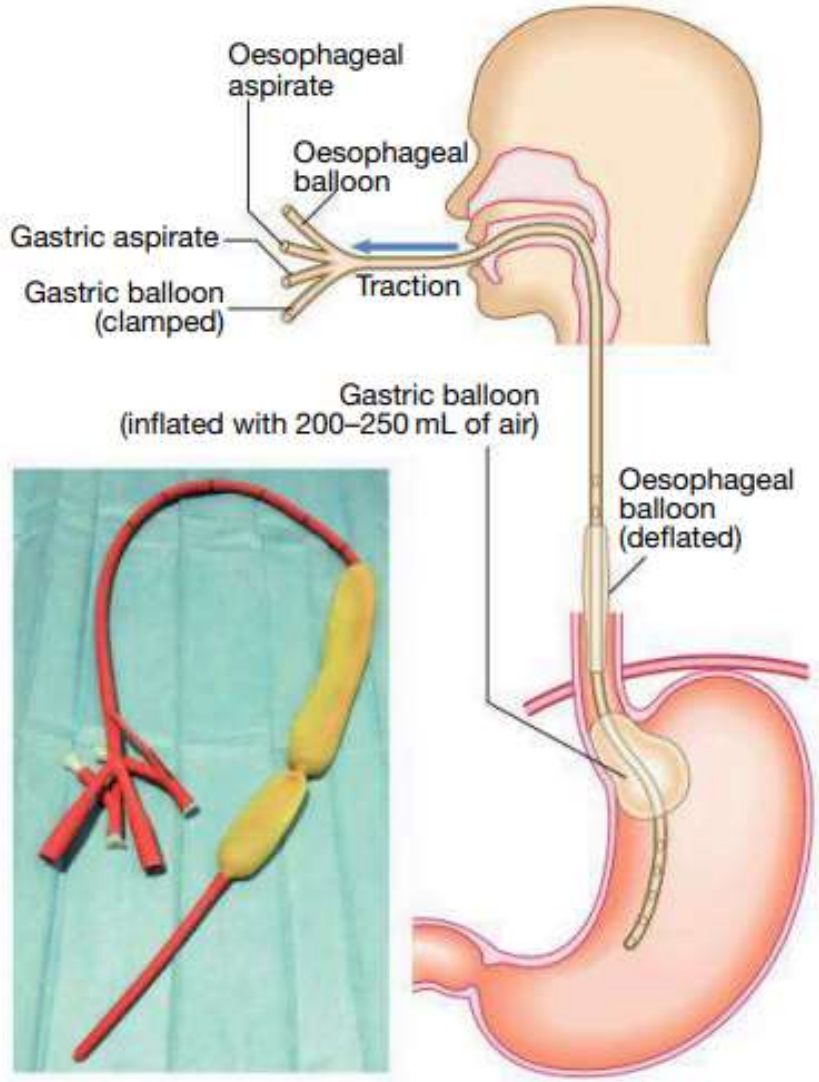


Fig. 24.23 Minnesota tube.

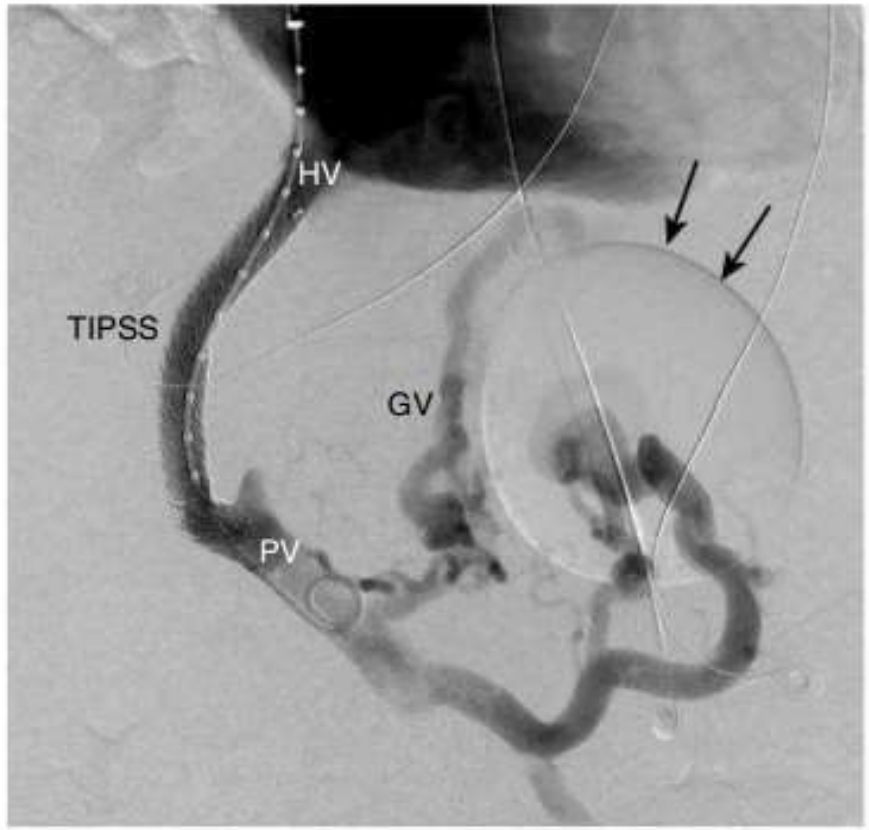
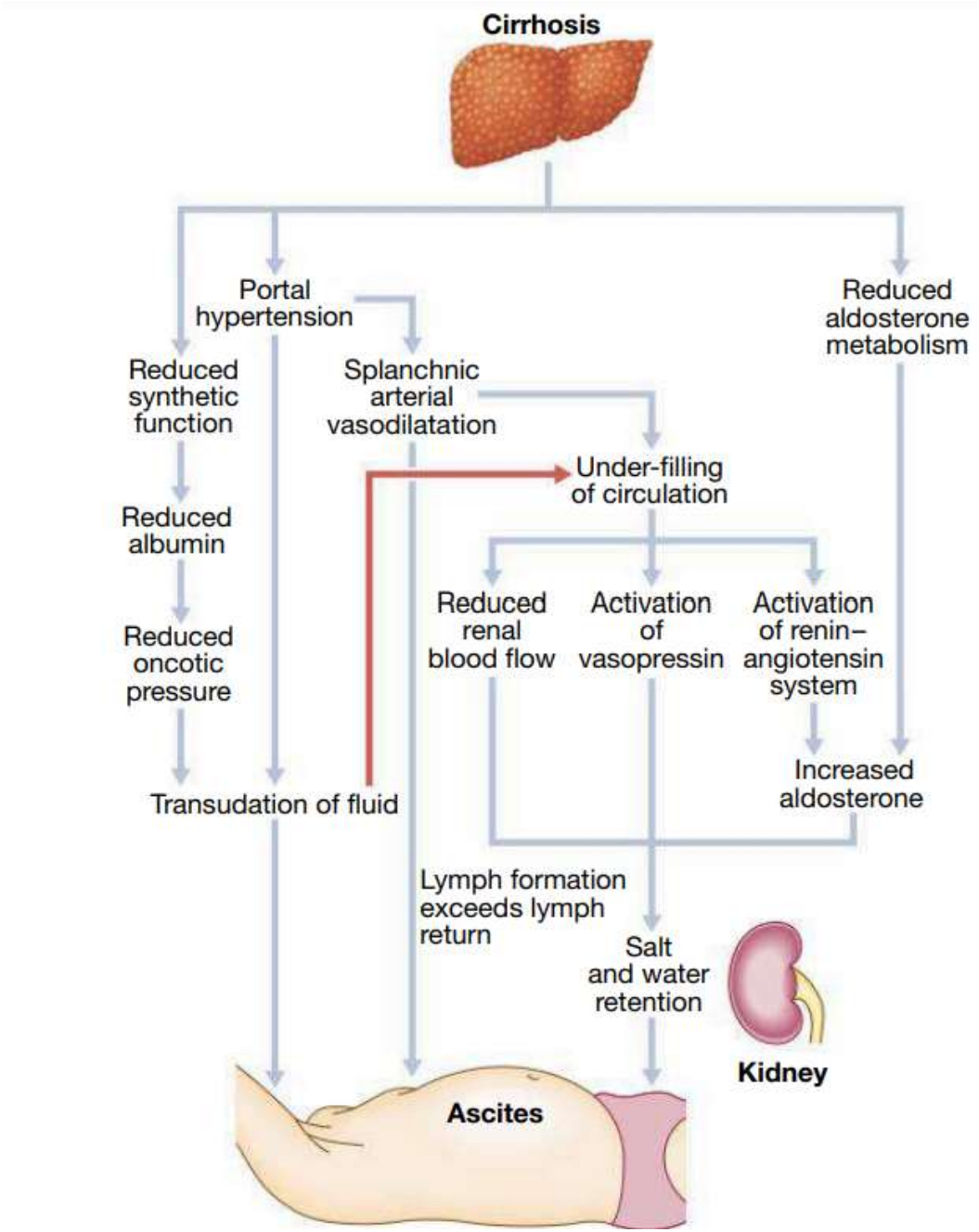


Fig. 24.24 **Transjugular intrahepatic portosystemic stent shunt (TIPSS).** X-ray showing placement of a TIPSS, allowing blood to flow from the portal vein (PV) into the hepatic vein (HV). Contrast can be also be seen in gastric varices (GV). Arrows show the outline of the gastric balloon of a Sengstaken tube.

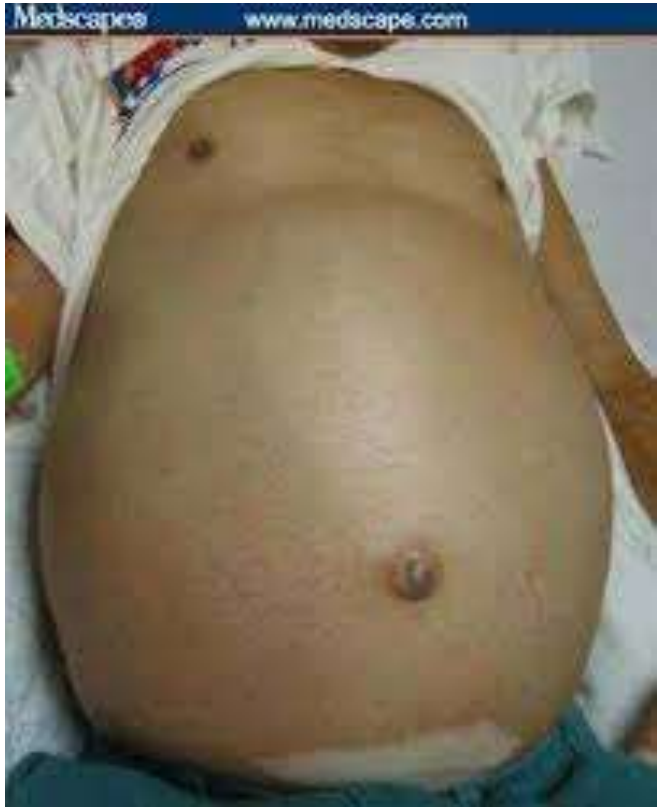
ASCITES

- *Accumulation of excessive volume of free fluid in the peritoneal cavity*
- Fluid appears clear, straw coloured or light green



CLINICAL FEATURES

- Abdominal distension (stomach appears larger, clothes do not fit the same)
- Abdominal pain, loss of appetite
- shortness of breath
- nausea, vomiting
- pedal edema
- Bulging flanks, everted umbilicus, prominent venous collaterals (caput medusa),puddle sign (120 mL), shifting dullness (>500 mL), fluid thrill (1-1.5L)



INVESTIGATIONS

- Ultrasonography is the best means of detecting ascites, particularly in the obese and those with small volumes of fluid.
- Paracentesis can be used to obtain ascitic fluid for analysis
- Chest x-ray can be done. (right sided pleural effusion in ≈10% of patients).
- Cirrhotic patients typically develop ascites with a low protein concentration i.e transudative, SAAG >1.1 G/dL, protein <2.5 g/dL and relatively few cells
- High protein ascites ('exudate'; protein concentration > 25 g/L (2.5 g/dL) or a SAAG of < 11 g/L (1.1 g/dL) maybe due to infection (especially tuberculosis), malignancy, pancreatic ascites rarely, hypothyroidism

MANAGEMENT

- Successful treatment relieves discomfort but does not prolong life.

1. SODIUM AND WATER RESTRICTION

- Restriction of sodium intake to 100 mmol/24 hrs ('no added salt diet') is usually adequate.
- Drugs containing relatively large amounts of sodium(phenytoin, sodium valproate, antacids, alginates etc) and those promoting sodium retention(NSAID'S, metoclopramide, glucocorticoids) must be avoided.

2. DIURETICS

- Spironolactone is the drug of choice(100-400mg/day). Amiloride can be used as substitute.

3. TIPSS

- Can be used as alternative to large volume paracentesis in cases of resistant ascites.

SPONTANEOUS BACTERIAL PERITONITIS

- Most common bacterial infection in patients with cirrhosis
- Caused by translocation of bacteria from small intestine to ascites
- Causative organisms include gram-negative *Escherichia coli* and *Klebsiella pneumoniae* and gram-positive organisms such as *Streptococcus pneumoniae*, *Staphylococcus aureus,* and *Enterococcus* species
- **CLINICAL FEATURES**: classic triad is fever, abdominal pain, altered mental status
- Associated with high rate of acute kidney injury and high mortality
- **Diagnosis**: Paracentesis may show cloudy fluid, and an ascites neutrophil count of > 250 × 106 /L almost invariably indicates infection
- **Treatment**: Broad spectrum antibiotics like cefotaxime, recurrence can be reduced through prophylactic quinolones such as norfloxacin (400 mg/day), ciprofloxacin (750 mg/week) or cotrimoxazole (960 mg/day)

HEPATORENAL SYNDROME

- Renal dysfunction
- Occurs due to decreased renal perfusion occurring due to haemodynamic alterations in arterial circulation and overactivity of endogenous vasoactive systems.
- Classified into HRS-AKI and HRS-NAKI
- HRS-AKI-progressive oliguria, rapid rise of the serum creatinine, very poor prognosis
- Precipitated by an acute event such as GI hemorrage, bacterial infection, alcoholic hepatitis, etc
- HRS-NAKI-more slowly progressive and chronic

24.25 Diagnostic criteria for HRS-AKI

- Diagnosis of cirrhosis, acute liver failure, acute on chronic liver failure
- Increase in serum creatinine ≥ 26.5 µmol/L (≥ 0.3 mg/dl) within 48 hours or ≥ 50% from baseline according to IAC-AKI criteria
  and/or
- Urinary output ≤ 0.5 ml/kg per hr for ≥ 6 hrs
- No response after 2 consecutive days of diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg body weight to a maximum of 100 g
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease, as defined as
  1 Absence of proteinuria (> 500 mg/day)
  2 Absence of microhaematuria (> 50 RBC per high power field)
  3 Normal findings on renal ultrasound

(AKI = acute kidney injury; HRS = hepatorenal syndrome; IAC = International Aascites Club; RBC = red blood cells)

MANAGEMENT

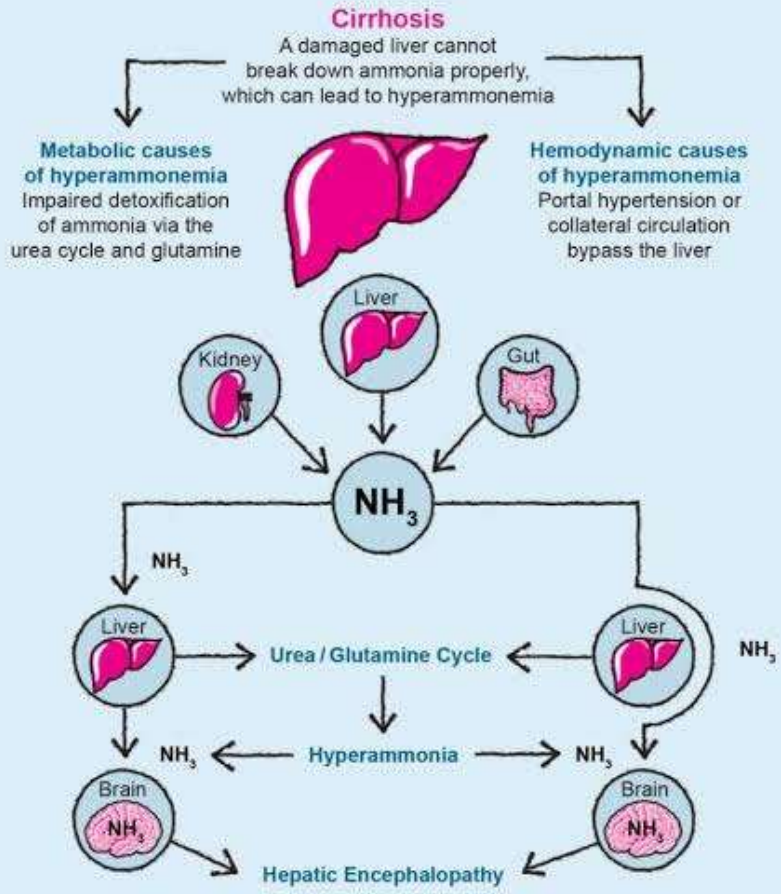
- Identifying and treating precipitating factors
- Diuretics and beta blockers should be blocked
- Nephrotoxic drugs (vasodilators, NSAIDS) should be stopped
- Volume replacement to treat fluid loss/deficits
- IV albumin infusions with in combination with Terlipressin
- TIPSS

HEPATIC ENCEPHALOPATHY

- Alteration in mental status and cognitive function in presence of liver failure

24.16 How to assess clinical grade of hepatic encephalopathy

Clinical grade	Clinical signs
Grade 1	Poor concentration, slurred speech, slow mentation, disordered sleep rhythm
Grade 2	Drowsy but easily rousable, occasional aggressive behaviour, lethargic
Grade 3	Marked delirium, drowsy, sleepy but responds to pain and voice, gross disorientation
Grade 4	Unresponsive to voice, may or may not respond to painful stimuli, unconscious



24.27 Factors precipitating hepatic encephalopathy

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

CLINICAL FEATURES

- Alteration of sleep cycle is an early symptom
- Confusion, restlessness, drowsiness, disorientation, stupor seen in severe cases
- Examination: Flapping tremor, constructional apraxia, hyperreflexia and bilateral extensor plantar responses may be seen.

INVESTIGATIONS

- Serum ammonia level
- Electroencephalogram
- Serum electrolytes, urea, creatinine, glucose, etc
- Brain imaging (CT or MRI) is required if stroke is suspected.

MANAGEMENT

- Lactulose 15-30 mL 3 times daily - osmotic laxative effect, reduces the pH of the colonic content, thereby limiting colonic ammonia absorption, and promotes the incorporation of nitrogen into bacteria
- Rifamixin 550 mg twice daily - effective in reducing episodes of recurrent hepatic encephalopathy
- Flumazenil
- Dietary protein should be restricted
- Opioids and sedatives should be avoided

HEPATOPULMONARY SYNDROME

- *Arterial hypoxaemia* in a patient with cirrhosis without significant lung disease.
- Intrapulmonary vascular dilations resulting in blood shunting past alveoli and significant ventilation-perfusion mismatch.
- **CLINICAL SYMPTOMS**: dypsnea, platypnea
- **DIAGNOSIS:** Demonstrating hypoxemia, no evidence of significant lung disease, and shunt on bubble echocardiography

- **TREATMENT** : Oxygen supplementation, liver transplantation

HEPATOCELLULAR CARCINOMA

- Most common primary liver tumour, and the sixth most frequent cause of cancer worldwide
- Associated with liver cirrhosis in 75-90% of cases
- **CLINICAL FEATURES:**

✓ Worsening ascites

✓ Jaundice

✓ Variceal hemorrhage

✓ Weight loss, anorexia, abdominal pain

✓ Tumor appears as a single nodule or multiple nodules

✓ Spread occurs by invasion into the portal vein and its radicals. Lymph node metastases are common.

INVESTIGATIONS

- AFP is present in 60% of cases. A progressive increase in AFP or AFP of > 400 ng/mL is suggestive of HCC.
- Ultrasound : will detect focal liver lesions as small as 2–3 cm, also show evidence of portal vein involvement and features of coexistent cirrhosis
- Multidetector row CT, following intravenous contrast, identifies HCC by its classical hypervascular appearance
- LIVER BIOPSY : can be done for histological confirmation.
- Angiography
- Blood tests to measure liver function

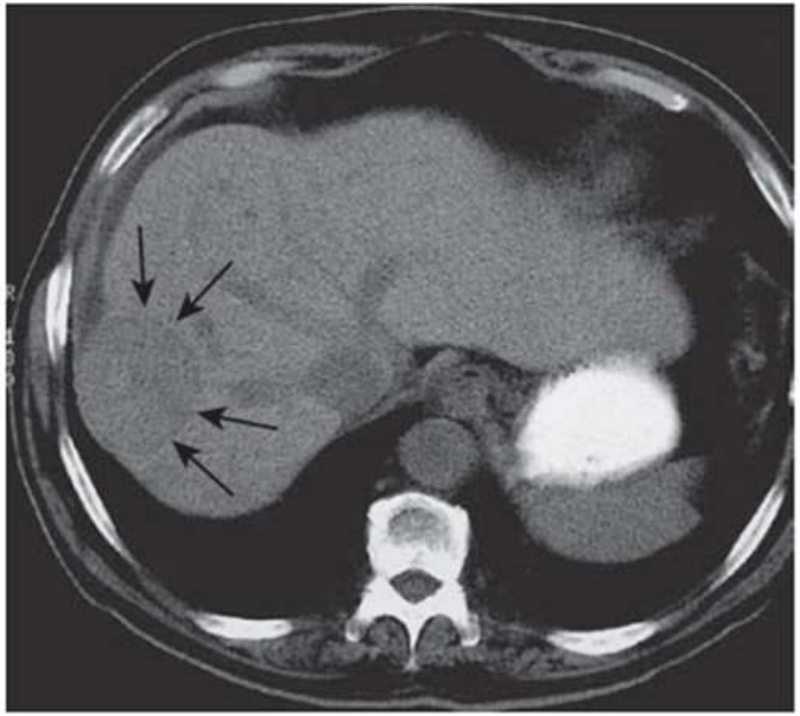


Fig. 22.35 Computed tomogram showing a large hepatocellular carcinoma (arrows). *Courtesy of Dr D. Redhead, Royal Infirmary of*

MANAGEMENT

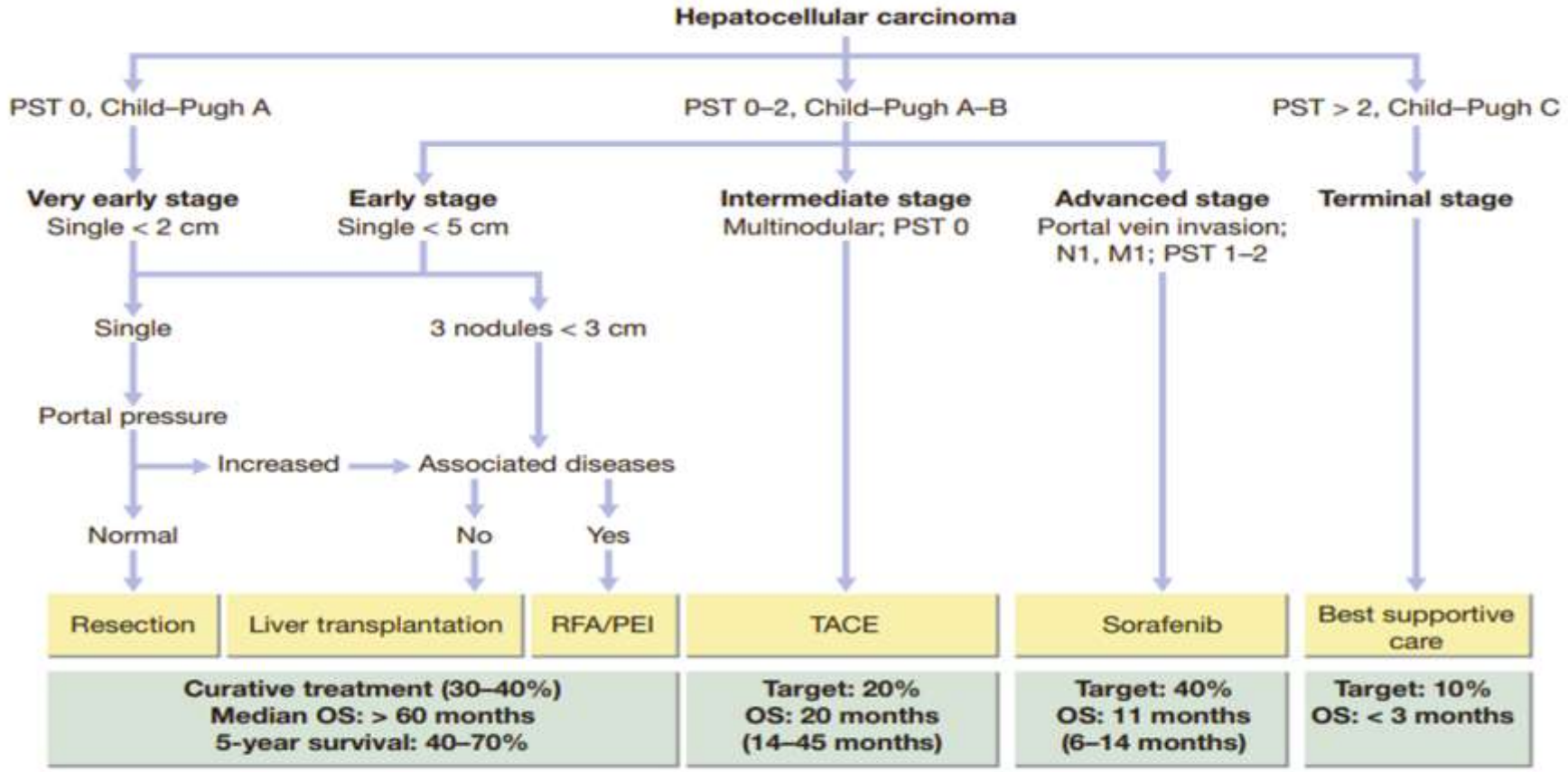


Fig. 22.36 Management of hepatocellular carcinoma complicating cirrhosis. Performance status (PST; see Box 33.3, p. 1322): 0 = fully active, no symptoms; >2 = limited self-care, confined to bed or chair for 50% of waking hours. Child–Pugh score: see Box 22.29, p. 867. N1, M1: lymph node involvement and metastases (for TNM classification, see Box 33.4, p. 1322) (OS = overall survival; PEI = percutaneous ethanol injection; RFA = radiofrequency ablation; TACE = trans-arterial chemo-embolisation). *Based on European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer. EASL–EORTC clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol 2012; 56:908–943.*

THANK YOU