Cirrhosis derives from the Greek word „kirros” meaning tawny (yellowish-brown, yellowish-red). This term was suggested by Laennec in 1826 referring to the colour of the diseased liver.

**DEFINITION:** Diffuse disorganization of the normal liver structure by regenerative nodules that are surrounded by fibrotic tissue and represent the consequence of fibrosis.

This definition differentiates cirrhosis from focal disorders such as focal nodular hyperplasia, diffuse nodularity of the liver not associated with fibrosis such as nodular regenerative hyperplasia and from liver fibrosis not associated with regenerative nodules called hepatoportal sclerosis (e. g. in schistosomiasis, congenital liver fibrosis).

Cirrhosis represents the consequences of a sustained wound-healing response to chronic liver injury from a variety of causes and should be viewed as a final common pathway of many types of chronic liver injury.
FIGURE 156-1. Gross and microscopic images of a normal and cirrhotic liver. A, Gross image of a normal liver with a smooth surface and homogeneous texture. B, Microscopically, the sinusoids are organized, and vascular structures are normally distributed. C, Gross image of a cirrhotic liver. The liver has an orange-tawny color with an irregular surface and nodular texture. D, Microscopically, the architecture is disorganized, and there are regenerative nodules surrounded by fibrous tissue.
Only chronic, sustained liver injury results in cirrhosis usually, cirrhosis is not occurring in the survivors of acute, fulminant hepatitis or liver cell necrosis induced by halothane.

GENERAL FEATURES:
Loss of functioning hepatocellular mass may lead to jaundice, oedema, coagulopathy and a variety of metabolic abnormalities; fibrosis and distorted vasculature lead to portal hypertension and its sequelae, including gastrooesophageal varices and splenomegaly. Ascites and hepatic encephalopathy result from both hepatocellular insufficiency and portal hypertension.

PATHOGENESIS:
Efforts to identify the cellular source of scar constituents in cirrhosis have established that the stellate cell (perisinusoidal cell, lipocyte) is the main producer of matrix. In both human disease and animal models, these mesenchymal cells undergo characteristic activation from a resting perisinusoidal cell rich in vitamin A to a proliferating, fibrogenic cell type (myofibroblast) with ↓ vit. A content. This early deposition of matrix molecules in the subendothelial space of Disse - so called capillarization of the sinusoid - that directly correlates with
diminished liver function. Increased matrix produced by stellate cells in liver injury results from increased cell numbers as well as enhanced matrix production per cell.
Fig. 22–1. Organization of the liver. The liver is organized into lobules around terminal branches of the hepatic vein. Between the lobules are portal triads. Each triad consists of branches of a bile duct, portal vein, and hepatic artery.
THE STRUCTURE OF HEPATIC LOBULE

CENTRAL VEIN

ZONE I
ZONE II
ZONE III

LIVER CELL PLATES

TERMINAL VENA PORTAE BRANCH

ARTERIA HEPATICA BRANCH

BILE DUCT

VENA PORTAE BRANCH
Normally the bile flow is from the central part of the lobule to the peripheral part and the blood flow is from the peripheral to the central part. The zone I cells have better oxygen and substrate supply, but they are more susceptible to the damaging effect of drugs and toxins, since the concentration of these compounds is the greatest in zone I. The zone III cells have worse oxygen supply, therefore are more susceptible to hypoxia, they are more readily damaged in hepatic congestion and the toxic metabolites of drugs, compounds formed in the liver are accumulating in zone III, therefore they damage mainly this zone.

The necrotic bridges formed in chronic hepatitis between the central vein and portal vein („bridging necrosis”) are the possible anatomical basis of intrahepatic portosystemic shunts.

CLASSIFICATION AND AETIOLOGY:
Cirrhosis has traditionally been classified as either macronodular (>3 mm nodules) or micronodular (<3 mm) or mixed morphologically. However, no appropriate classification of cirrhosis is currently available neither the morphological nor the aetiological (see below) classification in itself is satisfactory, because different
aetiological factors may cause identical morphological appearance and one aetiological factor may cause different morphological appearance. Micronodular cirrhosis develops usually when the damaging agent is continuously present and prevents regeneration at the same time (e.g. alcohol, malnutrition). Macronodular cirrhosis frequently develops in a later stage of disease from micronodular cirrhosis and more likely associated with hepatocellular carcinoma. In micronodular cirrhosis the liver is of normal size or enlarged in macronodular cirrhosis normal size or often shrunken. In the past it has been thought that cirrhosis was never reversible, however, when the underlying insult that has caused cirrhosis has been removed, there can be a reversal of fibrosis (successful treatment of hepatitis C, B, hemochromatosis, abstinence in patients with alcoholic liver disease) !!!

The most frequent aetiology of cirrhosis is chronic B- and C-virus hepatitis, nonalcoholic fatty liver disease and alcohol consumption. In the USA the most frequent aetiology is hepatitis C (45%) in itself or together with alcohol consumption (20%). Alcohol consumption in itself is only the 2nd aetiological factor (10%).
NAFLD is increasingly recognized as an underlying cause of cryptogenic cirrhosis!!!

NAFLD (=nonalcoholic fatty liver disease: simple steatosis NASH (=nonalcoholic steatohepatitis): steatosis with ballooning deg. of hepatocytes and sinusoidal fibrosis

Major risk factors for NAFLD

Obesity, T2DM, Metabolic sy., Dyslipidemia; other risk factors: PCOS, hypothyroidism, hypopituitarism, sleep apnea pathogen.: insulin resistance, influx of nonesterified FFA to hepatocytes
dg: no history of alcohol consumption, steatogenic medications and other causes of liver disease
**Table 153-1  CLASSIFICATION OF HEPATIC FIBROSIS AND CIRRHOSIS**

I. **Presinusoidal fibrosis**
   A. Schistosomiasis
   B. Idiopathic portal fibrosis

II. **Parenchymal (sinusoidal) fibrosis (true cirrhosis)**
   A. Drugs and toxins
      1. Alcohol
      2. Methotrexate
      3. Isoniazid
      4. Vitamin A
      5. Amiodarone
      6. Perhexiline maleate
      7. α-Methyldopa
      8. Oxyphenisatin
   B. Infections
      1. Chronic hepatitis B or C
      2. Brucellosis
      3. Echinococcosis
      4. Congenital or tertiary syphilis
   C. Autoimmune
      1. Autoimmune chronic hepatitis—types 1, 2, and 3
   D. Vascular abnormalities
      1. Chronic, passive congestion due to right-sided heart failure, pericarditis
      2. Hereditary hemorrhagic telangiectasias (Osler-Weber-Rendu)
   E. Metabolic/genetic diseases
      1. Wilson’s disease
      2. Homochromatosis
      3. α1-Antitrypsin deficiency
      4. Carbohydrate disorders (e.g., fructose intolerance, galactosemia, glycogen storage diseases)
      5. Lipid disorders (e.g., Wolman’s disease, abetalipoproteinemia)
      6. Urea cycle defects (e.g., ornithine transcarbamylase)
      7. Porphyria
      8. Amino acid disorders (e.g., tyrosinosis)
      9. Bile acid disorders (e.g., Byler’s disease)
   F. Biliary obstruction
      1. Primary biliary cirrhosis
      2. Secondary (“mechanical”) biliary obstruction
         a. Primary sclerosing cholangitis
         b. Neoplasm of bile ducts or pancreas
         c. Iatrogenic or inflammatory biliary stricture
      3. Cystic fibrosis
      4. Biliary atresia/neonatal hepatitis
      5. Congenital biliary cysts
   G. Idiopathic/miscellaneous
      1. Non-alcoholic steatonecrosis (including jejunoo-ileal bypass, obesity)
      2. Indian childhood cirrhosis
      3. Granulomatous liver disease
      4. Polycystic liver disease

III. **Post-sinusoidal fibrosis**
   A. Veno-occlusive disease
**Epidemiology:**
Up to 40% of patients with cirrhosis are asymptomatic. Mortality in patients with alcoholic disease is considerably higher than in patients with other forms of cirrhosis. Since 1980 overall cirrhosis mortality decreased by 25% in the US possibly reflecting decreasing alcohol consumption and to a lesser extent advent of hepatitis B vaccination and availability of liver transplantation.

**Clinical Signs:**
**Compensated cirrhosis**
Asymptomatic in 30-40%. No complication (jaundice, encephalopathy, ascites, gastrointestinal haemorrhage) is present, but cirrhosis can be verified. Hepatomegaly, hepatosplenomegaly can be observed during physical examination and liver function tests can be positive or the diagnosis is set up at abdominal surgery performed for other reason or at autopsy. Subfebrility, weight loss, asthenia, loss of appetite, anorexia, meteorism, nausea, vomiting, loss of libido, right upper quadrant abdominal dyscomfort, anaemia, thrombocytopenia, leukopenia may
suggest the diagnosis. The skin and muscoskeletal signs of cirrhosis may also be present:

spider naevi: (most frequently at the territory supplied by SVC: face upper extremities, chest; rarely in the upper part of the abdomen) central arteriole and spider leg-like branches it can be found temporarily in acute viral hepatitis, and may occur in healthy subjects (<5%), sometimes in RA, during pregnancy and oestrogen treatment erythema palmare, - plantare: cause: ↓↓↓↓ oestrogen metabolism may occur in RA, pregnancy, chronic febrile state, leukemia, thyrotoxicosis white nails clubbing: $O_2$ sat ↓, in hepatopulmonary syndrome Dupuytren contracture: in alcoholic cirrhosis, a direct consequence of etanol consumption.
9.7 A typical spider naevus consists of a central spiral arteriole, which supplies a radiating group of small vessels. This spider naevus is of typical size, though larger and smaller examples may occur.

9.8 The spider naevus blanches if the central spiral arteriole is occluded by pressure, demonstrating that this is the single source of its blood supply.
Miscellaneous clinical manifestations of cirrhosis

**General symptoms**

*General deterioration, wasting* is the most frequent clinical sign of cirrhosis. The main complaints are loss of appetite, weight loss, weakness, fatigue. Ascites might increase the anorexia and even if the weight is normal or increased because of the presence of gross ascites, the muscle wasting, asthenia, thin upper body suggest the diagnosis of cirrhosis.

*Fever* is frequent in cirrhosis can be caused by alcoholic hepatitis or intermittent infection.
Haematological alterations

Anaemia: frequent, may be macro-, normo-, microcytic

- macrocytic alcohol inhibits folate absorption
direct bone marrow toxicity of alcohol

- microcytic bleeding

- normocytic splenomegaly, hypersplenism

  - AIHA

  - spur cell haemolytic anaemia

- pancytopenia hypersplenism

  - folate deficiency

  - bone marrow toxic effect of etanol

Coagulopathy: clotting factors (except VIII) ↓, vitamin K synthesis ↓, malabsorption, thrombocytopenia

Endocrine alterations

Endocrine alterations are due to abnormal hepatic metabolisation of hormones or to the direct effect of alcohol.

Feminisation: gynaecomastia, spider naevi, erythema palmare et
plantare, hair loss

_Hypogonadism:_ in males: atrophy of the testes, loss of libido, impotence

in females: oligo-, amenorrhoea, sterility

_Diabetes:_ usually type 2 with hyperinsulinaemia, insulin resistance and hyperglucagonaemia

_Hypoglycaemia:_ in advanced liver disease, hepatocellular cc., or due to alcohol abuse or bacterial infection.

_Cholelithiasis:_ occurs more frequently in cirrhotic patients (bilirubin stones due to haemolysis or increased bilirubin excretion)

_Ventricular ulcer:_ its incidence is increased in cirrhosis, the reason is unclear.

_Abdominal hernia:_ umbilical, inguinal, and scar hernias occur frequently (20%) in patients with ascites. Further complications: incarceration (14%), skin ulceration (35%), rupture (7%).
Decompensated cirrhosis

If any complication due to hepatocellular failure or portal hypertension is present. The most frequent manifestations are: ascites, jaundice, hepatic encephalopathy and gastrointestinal bleeding. Other less frequent complications: portal thrombosis, hepatic hydrothorax, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatopulmonary syndrome, primary pulmonary hypertension, hyperdinamic circulation, coagulopathy, umbilical and inguinal hernias and hepatocellular carcinoma.
<table>
<thead>
<tr>
<th></th>
<th>SEQUELAE OF CIRRHOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Portal hypertension: bleeding from varices in esophagus/stomach (most common), duodenum, rectum, or surgical stomas; bleeding from congestive gastropathy; splenomegaly with hypersplenism</td>
</tr>
<tr>
<td>2</td>
<td>Ascites; spontaneous bacterial peritonitis; hepatic hydrothorax, abdominal hernia</td>
</tr>
<tr>
<td>3</td>
<td>Hepatorenal syndrome</td>
</tr>
<tr>
<td>4</td>
<td>Hepatic encephalopathy</td>
</tr>
<tr>
<td>5</td>
<td>Synthetic dysfunction/coagulopathy</td>
</tr>
<tr>
<td>6</td>
<td>Hepatopulmonary syndrome</td>
</tr>
<tr>
<td>7</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>8</td>
<td>Feminization</td>
</tr>
<tr>
<td>9</td>
<td>Altered drug metabolism</td>
</tr>
<tr>
<td>10</td>
<td>Hepatic osteodystrophy</td>
</tr>
</tbody>
</table>
Specific forms of cirrhosis

1. Alcoholic cirrhosis

Specific features: alcoholic polyneuropathy, Dupuytren contracture, gastroduodenitis, DCM may be present. In severe hepatocellular disease most commonly in alcoholic cirrhosis spur cell haemolytic anaemia (acanthocytosis) may be present due to an abnormal LDL in the pts. blood in which the ratio of unesterified cholesterol to phospholipids is ↑↑ ↑↑ resulting in the same abnormality in the erythrocyte membrane leading to acanthocyte formation.

2. Cardiac cirrhosis

Caused by prolonged right-sided CHF → necrosis of centrilobular hepatocytes, collagen extending outward in a characteristic pattern from the central vein. „Nutmeg liver”: alternating red (congested) and pale (fibrotic) areas in the liver. Constr. pericarditis, TI, TS, severe right sided CHF → dilated neck veins!!

3. Biliary cirrhosis

Results from injury to or prolonged obstruction of either the intrahep. or extrahep. biliary system. It is associated with impaired biliary excretion, destruction of hepatic parench. and progr. fibrosis.
9.44 Acute alcoholic hepatitis. The patient presented with sudden onset jaundice. At first sight, the condition might be confused with acute viral hepatitis, but the patient had a history of several previous admissions after alcoholic excess.

9.45 Parotid enlargement in association with cirrhosis is most common when alcohol is the cause of the cirrhosis. In addition to painful parotid enlargement, this patient had multiple vascular spiders and early acne rosacea.

9.46 Dupuytren's contracture may be seen in association with alcoholic cirrhosis, though it may also occur as a completely independent abnormality. Contracture of the palmar fascial bands produces flexion contracture of the metacarpophalangeal and proximal interphalangeal joints, the flexor tendon apparatus and the skin itself. Surgical correction is usually possible. Note the tar staining of the fingers of this heavy smoker.

9.47 A red, sore, smooth tongue may be seen in patients with alcoholic cirrhosis as a result of associated vitamin deficiency. A similar appearance may occur in patients with nutritional deficiencies of other origins.
Primary biliary cirrhosis (PBC): chronic inflammation and fibrous obliteration of intrahepatic bile ductules.

Secondary biliary cirrhosis: results from a long-standing obstruction of larger extrahepatic bile ducts.

Primary biliary cirrhosis

* Immune mediated, unknown cause
* Strong female preponderance (10:1)
* Frequently associated with a variety of autoimmune disorders: CREST sy. (calcinosis, Raynaud phen., esophageal dysmotility, sclerodactyly, teleangiectasia), the sicca syndrome, autoimmune thyroiditis and renal tubular acidosis, RA, pernicious anaemia
* In >90% of pts a circulating IgG antimitochondrial antibody (AMA) is present. AMA is directed against the ag. components of E2 subunits of the 2-oxo-dehydrogenase enzyme family (pyruvate dehydrogenase, branched chain α-ketoacid dehydrogenase, α-ketoglutarate dehydrogenase) → M2 antigen (located in the inner mitochondrial membrane).
AMAs are not pathogenic, but rather are useful markers of PBC.

**Pathology**

**Stage I:** chronic nonsuppurative destructive cholangitis, necrotizing inflammatory process of the portal triads, destructing medium, small bile tracts.

**Stage II:** periductal granulomas, proliferation of small bile ducts with periportal inflammation.

**Stage III:** Fibrosis → waning inflammation, ↑-ing septal fibrosis

**Stage IV:** Cirrhosis

**Clinical features and diagnosis**

**Insidious onset.** The earliest symptom is pruritus, fatigue. Then jaundice and gradual darkening of the exposed areas of the skin (melanosis). Steatorrhoea, malabsorption of lipid soluble vitamins. Later xanthelasmas, tendinous and palmar xanthomas, hepatosplenomegaly, signs of associated autoimmune disorders.

**Laboratory findings**

2-5 fold ↑-d SAP, AMA (+), ↑-d IgM, cryoproteins, ↑-d cholesterol
Other autoantibodies: RF (+) in 70%, SMA (+) in 65%, ANA may be positive and anti-TPO, anti-TG
Impaired sulfoxidation of sulfur containing compounds (84%) (!!) not found in other forms of cirrhosis.
late stages: prothrombin time ↑, se albumin ↓
The presence of AMA and a compatible biopsy establishes the dg. of PBC. Extrahepatic obstruction should be excluded by abdominal US !!
dg: middle aged woman with unexplained pruritus, ↑-ed SAP, (+) AMA, and compatible liver biopsy
Treatment:
* Ursodeoxycholic acid (UDCA) 8-10 mg/kg/day slows progression, improves survival free of liver transplantation in moderate or severe disease.
* A, D, E, K vit. replacement, osteoporosis, osteomalacia: +Ca suppl., 1,25 (OH₂)D₃ vit.
* Antipruritic agents: cholestyramin, opioid antagonists, plasmapheresis, rifampin, UV light
* Liver transplantation is usually curative (only rare recurrence)
9.49 & 9.50 Primary biliary cirrhosis.
This 55-year-old woman presented originally with severe pruritus, and jaundice developed slowly over the next 3 years. When these photographs were taken, she had deep jaundice, typical brown pigmentation, spider naevi, xanthelasmata around both eyes, enlargement of the liver and spleen, and ascites. The deepening jaundice and ascites are poor prognostic signs, and are usually followed by encephalopathy and death within weeks or months.
Secondary biliary cirrhosis

At least 6 months of obstruction is usually required for cirrhosis to develop.

* Primary sclerosing cholangitis (associated with IBD)
* Mechanical obstruction: choledocholithiasis, pancreatic cancer, postop. stricture, chronic pancreatitis, biliary cancer
* Childhood: congenital biliary atresia, cystic fibrosis

Treatment

* Surgical decompression
* Stent
* antipruritic treatment
* vitamin replacement

Primary sclerosing cholangitis: UDCA or UDCA + methotrexate → improves biochemical parameters, but does not retard disease progression. Liver transplantation is highly successful.
4. Cirrhosis from autoimmune hepatitis (AIH) or nonalcoholic fatty liver disease (NAFLD)

Positive antinuclear antibody (ANA) and anti-smooth-muscle antibody (ASMA) can be present in both (in NAFLD low grade positivity), in autoimmune hepatitis anti-actin, anti-sialoglycoprotein, anti liver-kidney microsomal 1 and anti-liver cytosol 1 antibodies can also be present.

dg: NAFLD: US, MRI, liver biopsy; AIH: liver biopsy

specific treatment:
NAFLD: dietary restriction, regular exercise
    statins with or without vitamins C and E
    pioglitazone

AIH: prednisone, azathioprine
**DIAGNOSIS OF CIRRHOSIS:**

**Definitive dg:** liver biopsy—seldom used.

Transjugular liver biopsy: **safe and adds additional prognostic information through measurement of hepatic vein pressure gradient (HPVG)**

Without biopsy the dg. can be set up in the presence of clinical signs of hepatocellular failure *(jaundice, coagulopathy)*, portal hypertension *(signs of porto-systemic collateral circulation, ascites, splenomegaly)*, characteristic skin signs *(spider naevi, erythema palmar, plantare, white nails, clubbing)*, laboratory alterations *[↓↓↓]*—d synthesis enzymes, proteins: cholinesterase, albumin, clotting factor conc., thrombocytopenia is the most sensitive and specific sign of cirrhosis *(portal hypertension)* in the setting of chr. liver disease.

Non-invasive fibrosis markers: **direct:** serum procollagen type III N-terminal peptide *(PIIINP)*, hyaluronic acid, **indirect:** AAR *(AST/ALT ratio)*, APRI *(AST to platelet count ratio index)* because more advanced hepatocyte injury is associated with mitochondrial damage as well.
To investigate the aetiology: HBV, HCV, HDV serology, AMA, ANF, SMA, LKM 1,2, serum iron, copper, coeruloplasmin, urine copper, α₁-antitrypsin, AFP

Imaging: Abd. US: the liver parenchyma is echodense and slightly inhomogenous („diffuse hepatic lesion”) due to steatosis and/or fibrosis. Suggests diffuse liver disease, not specific to cirrhosis

Signs of portal hypertension: 1) v. portae diameter >15 mm (100% spec., 50% sens.), 2) visualization of collateral veins (v. coronaria, v. paraumb., collaterals around the spleen), 3) splenomegaly, 4) ascites

Abd. CT: usually not necessary, steatosis → hypodense area, HCC → hypodense area, it can more accurately visualize the extension of cc. than US, arteriography, upper GI endoscopy

Non-invasive fibrosis imaging:

Transient elastography (Fibroscan): Measures liver stiffness. Performed with an ultrasound transducer probe mounted on the axis of a vibrator that produces vibrations. This induces an elastic shear wave, that propagates through the underlying liver tissue. The harder the tissue the faster the shear wave propagates.
Explores a liver mass 100 times bigger than the biopsy sample (more representative). MR elastography ARFI (acoustic radiation force impulse) technique uses the traditional ultrasound to measure liver stiffness real time.

DIFFERENTIAL DIAGNOSIS OF CIRRHOSIS:
* Any disease associated with positive LFT, hepatomegaly when no complication of cirrhosis is present
* Diseases associated with portal hypertension without hepatocellular damage (congenital hepatic fibrosis, portal thrombosis, schistosomiasis, idiopathic portal fibrosis)

abdominal US: portal vein patent → intrahepatic disease
normal flow in the hepatic veins → liver biopsy
dilated neck veins, pericardial calcification → cardiac cirrhosis → echocardiography
* diseases mimicking decomp. cirrhosis (Budd-Chiari syndrome, veno-occlusive disease, constrictive pericarditis, cardiac cirrhosis)
PROGNOSIS OF CIRRHOSIS:
The 5-year survival in compensated and decompensated cirrhosis is 60% and 20% respectively. The median survival in patients with compensated cirrhosis is 10 years, whereas in decompensated cirrhosis about 2 years. In alcoholic cirrhosis the 5-year survival in pts. who stop drinking is 60%, in pts. who continue to drink is 40%.

<table>
<thead>
<tr>
<th>CLINICAL AND LABORATORY MEASUREMENTS</th>
<th>POINTS SCORED FOR INCREASING ABNORMALITY*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy (grade†)</td>
<td>None</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
</tr>
<tr>
<td>PT (seconds prolonged)</td>
<td>&lt; 4</td>
</tr>
<tr>
<td>[or INR]</td>
<td>&lt; 1.7</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>&gt; 3.5</td>
</tr>
<tr>
<td>Biliubin (mg/dL)</td>
<td>&lt; 2</td>
</tr>
</tbody>
</table>

*Scoring system: 5–6 points, grade A (lowest risk); 7–9 points, grade B; 10–15 points, grade C (highest risk)
†Grade 1: Sleep disturbances; impaired concentration; depression, anxiety, or irritability.
Grade 2: Drowsiness; disorientation; poor short-term memory; disinhibited behavior.
Grade 3: Somnolence; confusion; amnesia; anger, paranoia, or other bizarre behavior.
Grade 4: Coma.
Common complications of cirrhosis

Complications of cirrhosis result from portal hypertension or liver insufficiency. Varices and variceal hemorrhage are a direct consequence of portal hypertension and can be complicated by infectious bacterial peritonitis (SBP) or renal dysfunction (hepatorenal syndrome). Hepatic encephalopathy results from portosystemic shunting (i.e., portal hypertension) and liver insufficiency. Jaundice results solely from liver insufficiency.
Common complications of cirrhosis

1. Ascites

Accumulation of excess fluid within the peritoneal cavity. ≥1500 ml can be diagnosed in the supine patient and ≥500 ml can be detected in a patient in a knee-hand position by physical examination, abdominal US can detect a very small amount of ascites. A greater amount of ascites results in increasing abdominal girth and frequently results in umbilical hernia. Cirrhosis can be recognized at first glance in the presence of gross ascites causing a bulging giant abdomen from a thin or cachectic chest and extremities. Ascites is frequently associated with lower leg oedema (hypalbuminaemia, compression of intrahepatic part of IVC due to cirrhosis and compression of IVC by high intraabdominal pressure resulting from ascites). Peripheral oedema may precede the appearance of ascites by weeks, months.

**PATHOGENESIS:**

Ascites represents a state of total-body sodium and water excess, but the event that initiates this imbalance is unclear.
Fig. 7.32 The characteristic appearance of gross ascites.
1. Sinusoidal hypertension
Initially albumin traverses the porous sinusoid endothelium along with fluid; but as fibrosis progresses, only protein-free fluid can escape from the sinusoid, from where it enters hepatic lymphatics, there it overcomes the capacity for lymphatic drainage and the excess fluid “weeps” out from the liver into the peritoneal cavity.

2. Hypoalbuminaemia
Decreases oncotic pressure.

3. Increased sodium reabsorption by the kidney
Primary or secondary because of sensing the decreased intravascular volume

4. Splanchnic arteriolar vasodilation
Possibly mediated by NO. Leads to underfilling of the arterial vascular space and baroreceptor mediated stimulation of RAAS, sympathetic output and ↓-d sensitivity to ANP

The classic transudate-exsudate concept applied in the classification of pleural fluid is misleading in the case of ascitic fluid. The normal
peritoneal fluid obtained by laparoscopy in women and ascites due to heart failure, which should be a transudate according to the classic transudate-exsudate concept was found to have a high protein content (>2.5 g/dl) (exsudate). Therefore the serum-ascites albumin gradient (SAAG) (serum albumin conc. - ascites fluid albumin conc.) is more informative about the aetiology of ascites.

In the case of portal hypertension the SAAG is greater than or equal to 1.1 g/dl (>95% likelihood of portal hypertension), because albumin cannot cross the sinusoid due to the sinusoid capillarization. If SAAG < 1.1 g/dl the likelihood that the patient has no portal hypertension is >95%.

When ascites is diagnosed first time a diagnostic puncture should be performed.

**TABLE 156-3**

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>SERUM-ASCITES ALBUMIN GRADIENT</th>
<th>ASCITES TOTAL PROTEIN LEVEL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Malignant ascites</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Cardiac ascites</td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

*High is greater than 1.1 g/dL; low is less than 1.1 g/dL.

†High is greater than 2.5 g/dL; low is less than 2.5 g/dL.
Other signs of portal hypertension than ascites are also usually present in decompensated cirrhosis:

1. porto-caval anastomoses:
   a) dilated veins of the abdominal wall (Caput Medusae)
   b) gastrooesophageal varices → bleeding
   c) portal hypertensive gastropathy: congestive gastropathy due to venous hypertension. The mucosa is engorged and friable. „Watermelon” stomach (intermingled erythematous and pale areas) Indolent mucosal bleeding rather than brisk haemorrhage.
   d) ectasia of venae haemorrhoidales
   e) ectasia of the umbilical vein residuum (enormously dilated veins at the site of the umbilical vein below the abdominal skin → loud venous hum → Cruvelhier-Baumgartner syndrome)

2. splenomegaly with hypersplenism

3. hepatic encephalopathy
**9.24** Cirrhosis of the liver. When portal pressure rises, collateral veins open and blood bypasses the liver through dilated fundal and oesophageal varices that eventually drain into the azygos vein and superior vena cava.

**9.27 Oesophageal varices.** A barium swallow, showing the typical appearance of multiple lower oesophageal varices, evident as barium-coated filling defects. In addition, gastric varices can be seen, along the lesser curvature of the stomach. These thin-walled varices are easily damaged, and bleeding is a frequent complication.

**9.29 Varices may also occur in the gastric fundus in portal hypertension.** In this patient the gastric varices (to the right of the picture) are above the diaphragm in a hiatus hernia. Portal hypertension may also lead to other changes in the stomach, including congestive gastropathy and ‘watermelon’ stomach, in which areas of erythematous and pale mucosa are intermingled.
9.28 Oesophageal varices seen through the endoscope. 'White' varices like these have been shown to have a relatively low risk of immediate bleeding, because they are covered with a thick layer of mucosa. The presence of red lines (red wale markings) or spots (cherry-red spots) is associated with a strong likelihood of bleeding.

9.26 A peritoneovenous shunt in a patient with cirrhosis and severe ascites. The subcutaneous course of the valved shunt is clearly seen. Despite the presence of the shunt, which has helped to maintain his serum albumin level, this patient still has severe ascites.

9.31 Oesophageal varices after treatment by sclerotherapy. The injection of a sclerosant via the endoscope results in local variceal sclerosis, followed by fibrosis and, later, mucosal ulceration. Definitive treatment (transjugular intrahepatic portosystemic stent shunt or portosystemic anastomosis) may subsequently be necessary.

9.32 Insertion of a transjugular intrahepatic portosystemic stent shunt (TIPSS). The hepatic vein is cannulated via the jugular vein and the superior and inferior vena cava. A track is then created between the hepatic vein and the right main portal vein branch using a special needle. The track is dilated using a balloon, and an expandable metal stent is inserted to create the shunt. This view shows the inflated balloon and the expanded stent.

9.33 Umbilical anastomoses in portal hypertension, demonstrated by infrared photography. The patient had ascites but the veins were not obvious clinically. An extensive network of veins radiating from the umbilicus is seen. Note the coexistence of gynaecostasia.

9.22 Splenic venography can be used to delineate the portal venous system in patients with portal hypertension. Contrast is injected via a needle inserted into the enlarged spleen (on the right of the picture). In this patient with advanced cirrhosis, the technique demonstrates the extent of the collateral circulation. Note the dilated splenic and hepatic veins, which contrast with normal intrahepatic vessels (top left), affected by the cirrhotic process. A tortuous, greatly dilated vein leads towards the umbilicus. The patient had a typical dilatation of the subcostal abdominal veins (B31).
2. Hepatic encephalopathy (HE)

**DEFINITION:** A neuropsychiatric syndrome that develops when certain products that are usually metabolized (detoxified) by the liver escape into systemic circulation due to hepatocellular failure and/or porto-systemic shunting.

**PATHOGENESIS:**

* syst. circ. NH$_3$ ↑: (colonic bact. produce NH$_3$ → absorbed to portal circulation)

* amino acid imbalance: pl. aromatic AA ↑ in chr. liver disease
  pl. branched chain AA ↓
  precursors of false neurotransmitters (octopamine, phenylethanolamine)
  ↓
  depletion of true excitatory neurotransmitters

* synergism hypothesis: ↑-d neurotoxic metabolites of
  a) sulfur containing AA (mercaptans)
  b) aromatic AA (phenols)
  c) fatty acids (octanoic acids)
  and these might potentiate the neurotoxicity of NH$_3$. 
* γ-aminobutiric acid (GABA): GABA → main neuroinhibitory neurotransmitter, substance or substances with GABA like actions rather than GABA itself may be involved

* benzodiazepine hypothesis: the postsynaptic GABA receptor is closely linked to the barbiturate and the benzodiazepine receptors. Together this complex of receptors controls the Cl⁻ influx in the postsynaptic neuron and hence responsible for the generation of inhibitory postsynaptic potentials. Stimulation of benzodiazepine and barbiturate receptors potentiates GABA mediated neural inhibition. Flumazenil a benzodiazepine receptor antagonist sometimes reverses HE.

CLASSIFICATION: (On the basis of underlying liver disease)
* Acute liver disease → acute HE
* Chronic liver disease → chronic HE
* Acute precipitating factor in chr. liver disease → ac. and chr. HE
* Portocaval shunt (spont. or surgical) → portosystemic HE with relatively good hepatocellular function
In acute liver failure HE is strongly associated with the development of cerebral oedema and it may present clinically as high fever, tachycardia, tachypnea, hyperventilation, intermittent hypertension, decerebrate posture, profuse sweating or cardiac arrhythmias. Of note is that papilloedema is often absent in cerebral oedema owing to acute liver failure even when cerebral oedema is severe!

HE associated with chronic liver failure can present as subclinical HE, a single episode of HE, or recurrent episodes of HE, chronic HE, hepatocerebral degeneration or spastic paralysis. (subclinical HE= 0-1 stage of HE).

Acute HE → most episodes are precipitated by identifiable factors. Chr. recurrent or protein intolerant HE → occurs despite maintenance ther. and in the absence of excessive protein intake, extremely difficult to manage.

Hepatocerebral degeneration is a chronic unremitting motor disorder of variable severity (tremor, rigidity, hyperreflexia or signs of advanced pyramidal, extrapyramidal and cerebral dysfunction). Extremely rare, occurs in patients with massive porto-systemic shunts.
Table 299-1

Common Precipitants of Hepatic Encephalopathy

<table>
<thead>
<tr>
<th>Increased Nitrogen Load</th>
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<tbody>
<tr>
<td>Gastrointestinal bleeding</td>
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<tr>
<td>Excess dietary protein</td>
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<tr>
<td>Azotemia</td>
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<td>Constipation</td>
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<table>
<thead>
<tr>
<th>Electrolyte and Metabolic Imbalance</th>
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<tbody>
<tr>
<td>Hypokalemia</td>
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<tr>
<td>Alkalosis</td>
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<tr>
<td>Hypoxia</td>
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<td>Hyponatremia</td>
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<table>
<thead>
<tr>
<th>Drugs</th>
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<tbody>
<tr>
<td>Narcotics, tranquilizers, sedatives</td>
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<tr>
<td>Diuretics (see “Electrolyte imbalance”)</td>
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<table>
<thead>
<tr>
<th>Miscellaneous</th>
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<tbody>
<tr>
<td>Infection</td>
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<tr>
<td>Surgery</td>
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<tr>
<td>Superimposed acute liver disease</td>
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<td>Progressive liver disease</td>
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<td>STAGE</td>
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<td>3</td>
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<td>4</td>
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CLINICAL FEATURES AND DIAGNOSIS OF HE:
HE is a diagnosis of exclusion!
The diagnosis of HE should be considered when 4 major factors are present: 1) acute or chronic hepatocellular disease, 2) disturbance of awareness and mentation, 3) shifting combination of neurologic signs: asterixis, rigidity, hyperreflexia, extensor plantar signs, seizures, 4) characteristic (but non-specific) symmetric, high-voltage, slow-wave (2-5/sec) pattern on EEG.

Asterixis="flapping tremor": depends on sustained voluntary muscle contraction, it is not present in the comatose patient. Asterixis is non-specific and also occurs in patients with other forms of metabolic brain disease.

Foetor hepaticus: a unique sweet-smelling, musty odor of the breath and urine believed to be due to mercaptans.
3. Jaundice

In cirrhosis jaundice is mainly due to ↓↓↓-d bilirubin excretion of liver cells (liver insufficiency). In cholestatic disease leading to cirrhosis (PBC, PSC etc.) jaundice is rather due to biliary damage than liver insufficiency. The hyperbilirubinaemia is mixed but predominantly direct. The urine is dark due to bilirubinuria. Other factors than hepatocellular failure may cause jaundice in cirrhotic pts:

1) Haemolysis:
* AIHA associated with liver disease, * spur cell haemolysis (acanthocytes) rarely (5%) associated with alc. liver disease (Zieve sy.)

2) Bacterial infection resulting in cholestasis

3) alcoholic hepatitis: if jaundice is significant in a cirrhotic patient the possibility of alcoholic hepatitis should be first considered.

4) Other associated disease: acute viral hepatitis, choledocholithiasis, tumor, chronic pancreatitis should also be considered.

Jaundice is usually not severe in cirrhosis, frequently intermittent. If irreversible and the underlying cause cannot be corrected the prognosis is poor.
4. Gastrointestinal bleeding

Usually rupture of gastrooesophageal varices results in GI bleeding, the diff. dg. includes bleeding from acute gastroduodenal erosion, ulcer, Mallory-Weiss syndrome, portal hypertensive gastropathy.

Further less common complications of cirrhosis

1. Spontaneous bacterial peritonitis (SBP)

Advanced liver disease \(\rightarrow\) ↓-d ascitic fluid albumin conc
\(\rightarrow\) ↓-d opsonic proteins in ascitic fluid

susceptibility to bacterial infection

Bacteria contributing to SBP are probably derived from the bowel and eventually are spread to ascitic fluid by the haematogenous route, after transmigration through the bowel wall and transversing the lymphatics. Although the colon has polymicrobial flora, the SBP is usually monomicrobial [the Gram (-) bacteria can more easily
transmigrate through the bowel wall than Gram(+) ones

Features: abrupt onset of fever, chills, generalized abdominal pain, rebound abdominal tenderness accompanied by cloudy ascitic fluid with a high white cell content and positive bacterial cultures. However, the symptoms can be minimal and some patients manifest only worsening jaundice or encephalopathy in the absence of localizing abdominal pain.

diagnosis: ascitic fluid WBC >500 cells/µl
PMNL >250 cells/µl
protein content usually <1 g/dl

The presence of WBC >10000 cells/µl, multiple organisms (polymicrobial), protein conc. >1 g/dl, glucose <50 mg/dl, LDH >225 mU/ml or greater than upper normal limit of serum LDH, amylase conc. >5 times higher than serum amylase in the ascitic fluid suggest secondary (or surgical) bacterial peritonitis due to perforation, and WBC >10000 cells/µl, polymicrobial culture can be due also to infection elsewhere in the body (secondary nonperforation bacterial peritonitis → e. g. due to abdominal abscess)
2. Portal vein thrombosis

In advancing cirrhosis the flow in the portal vein ↓, the direction becomes intermittently hepatopetal and hepatofugal. Ultimately the direction of blood flow is reversed (hepatofugal). It might be the result of cirrhosis with significantly shrunken liver, hepatocellular cc., sclerotherapy of GI varices, splenectomy, portosystemic shunt operation, intraabdominal inflammation (appendicitis, cholangitis, IBD, pancreatitis, peritonitis), connective tissue diseases, myeloproliferative diseases, anticoncipients.

The clinical signs depend on the rapidity of thrombus formation its location and extension. Usually there is no ascites (no hypalbuminaemia, and no ↑-ed sinusoidal pressure). If the portal vein thrombosis develops slowly, there is time for collateral formation, in this case only the signs of portal hypertension are increasing. It can also increase the signs of hepatocellular failure in cirrhosis. The hepatotroph factors (the best known is insulin) are
not delivered to the liver cells in portal vein thrombosis, this results in segmental hepatic atrophy or hepatic infarction. If the thrombosis involves the mesenteric vein, fatal bowel necrosis is the consequence (abdominal cramps, bloody ascites, oedema of the bowel wall can be detected by plain abd. X ray, US, CT). The development of portal vein thrombosis indicates severe liver disease, liver transplantation should be considered. Suspicion of portal vein thrombosis: GE varices, upper GI bleeding without the signs and symptoms of liver disease!

3. Hepatic hydrothorax
Incidence: 5-6%. Its cause is a defect(s) on the right side of the diaphragm, which develops in patients with large quantity of ascites. The ascitic fluid goes to the pleural cavity due to the intraabdominal-intrathoracal pressure gradient. It is practically almost always right sided (66% right sided, 17% bilateral, 17% left sided). Always occurs in the presence of ascites. If the defect on the diaphragm is larger, it may happen, that if the ascites production is not very rapid, the ascitic fluid can immediately go to the pleural
cavity at the time of its production → only pleural fluid is detectable without ascites.

4. Bloody ascites
The RBC in ascitic fluid without complication <1000/µl.
In the case of bloody ascites RBC >50000/µl.
Occurs in 2-5% of cirrhotic patients.
Only 1/4-1/3 of cases are due to hepatocellular cc., the cause is not identifiable in 50-70%. Other causes of bloody ascites: 1) traumatic liver, spleen injury, 2) spleen infarction, 3) carcinosis peritonei, 4) rupture of a dilated collateral vein or hepatic duct. When no identifiable explanation is found, the latter possibility may be the cause.

5. Hepatorenal syndrome (HRS)
Characterized by worsening azotaemia with avid Na⁺ retention and oliguria in the absence of identifiable specific causes of renal dysfunction in a patient with cirrhosis and ascites. The kidneys are
structurally intact; urinalysis, US are normal. Kidneys from such patients have been used successfully for renal transplantation.

**PATHOGENESIS:** similar to that of ascites → except more intensive vasodilation → more significant underfilling → ↑-ed CO cannot compensate → more intensive vasoconstriction in nonsplanchnic vascular beds including renal vasoconstriction → locally formed renal vasodilators (PG, NO) try to compensate for renal vasoconstriction.

Do not administer NSAID, aminoglycoside!

**CLINICAL FEATURES, DIAGNOSIS:** worsening azotaemia, hypotension, hyponatraemia, progressive oliguria, ↓-d Na⁺ excretion in the urine (<10 mE/l), urine/serum osmolality >1, normal urinalysis, morphologically normal kidneys in a cirrhotic patient with ascites.

Type 1 HRS: rapidly progressive ARF within 2 weeks, Type 2 HRS: more slowly progressive, better prognosis.

**DIFF. DG.:** praerenal azotaemia, acute tubular necrosis (ATN) due to hypovolaemia (GI bleeeing, diuretic overdose), ↑-d N-load (bleeding), drug nephrotoxicity. In ATN urinary Na⁺ excretion >10 mE/l, the
urinary sediment shows granular cylinders, cell debris, in praerrenal azotaemia CVP, PCWP↓, in HRS CVP, PCWP normal.

6. Hepatopulmonary syndrome (HPS)

**DEFINITION:** Hypoxaemia caused by vasodilation in patients with portal hypertension; dyspnea and hypoxaemia are worse in upright position. In 30-50% of cirrhotic patients.

Arterial hypoxaemia (pO₂ <80 mmHg; O₂ sat: 92-94%) without associated primary pulmonary or cardiac disease, not due to mechanical cause: tense ascites, pleural fluid.

**CLINICAL SIGNS:** cyanosis, clubbing, dyspnoe

**PATHOGENESIS:** ↑-ed hepatic production or ↓-ed clearance of vasodilators, possibly involving NO → microscopic pulmonary AV dilatations → cause overperfusion relative to ventilation → hypoxaemia
[atelectasy in lower lung lobes due to ascites; normal pulmonary capillaries are 8 \( \mu \text{m} \) in diameter and RBCs (slightly < 8\( \mu \text{m} \)) pass through them one cell at a time, thereby facilitating oxygenation. In HPS the pulmonary capillaries are dilated up to 500 \( \mu \text{m} \), so passage of RBCs may be many cells thick. As a result a large number of RBCs are not oxygenated, which is equivalent to a \( \text{R} \rightarrow \text{L} \) shunt].

Because the lesions frequently are more numerous at the lung bases, **HPS causes platypnea and orthodeoxia (hypoxaemia) in the seated or upright position that subside with recumbency.**

**Norm. L → R shunt (v. pulm. → v. azygos), portal hypertension → collat.-s to SVC and v. azygos, → v. azygos pr. ↑ → R → L shunt**

**DG:** contrast echocardiography: IV microbubbles from agitated saline that are normally obstructed by pulmonary capillaries rapidly transit the lung and appear in the left atrium within 7 beats. Similarly IV \(^{99}\text{Tc}\) albumin-macroaggregate used during perfusion pulmonary scintigraphy may transit the lungs and appear in extrathoracal organs: the kidney, liver and brain in HPS.
7. Primary pulmonary hypertension (PPH)

3,5-12% in cirrhosis, chronic liver disease, 0.1% in general population.

**PATHOGENESIS:**
Thrombi in portal and mesenteric veins → embolism through porto-caval (spont. or surgical) shunts
Hyperdinamic circulation → CO ↑
Vasculitis ↓-ed elimination or ↑-ed production of vasoconstrictors (e.g. endothelin)

**PATHOLOGY:**
1) thromboembolic type, 2) plexogen pulmonary arteriopathy, 3) pulmonary venoocclusive disease

The thromboembolic type and plexogen pulmonary arteriopathy involve the small muscular pulmonary arteries, the veno-occlusive pulmonary disease doesn’t involve the small muscular arteries, only the pulmonary veins and particularly the venules.
CLINICAL SIGNS:
Dyspnoe to physical exercise (81%), syncope to exercise (24%), chest pain (24%), haemoptoe (12%), orthopnoe (12%), Raynaud syndrome (7%), fatigue.
Physical signs: PII!, split II heart sound, ejection type syst. murmur pst.
ECG: right axis dev., P-pulm., RVH
chest X-ray: centro-perif. discrep., RA ↑, RV ↑
in the veno-occlusive type apico-basal discrep, Kerley B lines, interstitial, alveolar oedema due to ↑-ed pulmonary venous pressure
echocard: TI, PI, SPAP ↑
PCWP normal in plexogen pulmonary arteriopathy, PCWP ↑ in the veno-occlusive type
PROGNOSIS: poor, average survival: 3 years, in the presence of portal hypertension 15 months.
8. Cardiac complications

*Hyperdinamic circulation*: mild tachycardia, hypotension, CO↑, TPR↓, → erythema palmare, warm extremities, pulsus altus et celer

portal hypertension → endotoxinaemia → NO↑
cirrhosis → hepatocell. dysfunction → ↓-ed elimination of vaso-
circ. vasodilators → dilation
renal vasoconstr. → symp. outflow ↑ → CO ↑
catechol. ↑

art. hypotension, TPR ↓

*Decreased LV function*: in cirrhosis in the absence of any other cause
symp. outflow ↑ → β-receptor downregulation

*Pericardial fluid*: in 60% of cirrhotic patients without any other cause!

9. Hepatocellular carcinoma (HCC)

In 10-25% of cirrhosis, HBV, HCV, haemochromatosis, α₁-antitrypsin def., alcohol predisposing

Dg: liver mass by US+ ↑ -d AFP
TREATMENT OF CIRRHOSIS:

Compensated cirrhosis:
Diet: 1 g/kg protein, alcohol abstinence, avoid hepatotoxic agents
Antioxidant rich foods (coffein, dark chocolate), silymarin?

 Decompensated cirrhosis:
Ascites
Salt restriction: ≤ 2000 mg salt intake only might be sufficient if ascites is of recent onset, underlying liver disease is reversible, a precipitating factor can be corrected.
Albumin infusion (weekly 25 g for 1 year, then infusions every other week) might have a mortality benefit
Fluid restriction is necessary only when serious hyponatraemia (< 120 mEq/l) is present.
Diuretics: spironolactone or other distal tubule acting diuretics are the drugs of choice because of hyperaldosteronism.
triamterene, amiloride
Usually more potent proximally acting diuretics (furosemide, thiazide, ethacrynic acid) are also added → potentiating effect
100-400 mg spironolactone → to achieve a weight loss of 0.5-0.75 kg
+ 40-160 mg furosemide daily in patients without peripheral
oedema. More rapid weight loss is safe
if peripheral oedema is present.

10% fail to respond to standard therapy
addition of a 3rd diuretic (thiazide)
therapeutic paracentesis: removal of 4-6 l is
safe in pts. with periph. oedema.

In non-oedematous patients replacement of 6-8 g albumin/liter of
ascites removed is necessary by albumin infusion, or the less
expensive plasma expanders (e.g. dextran 70) can also be used.
Repeated paracentesis → risk of bacterial peritonitis ↑.

Refractory ascites

*Peritoneovenous shunt (Le Veen shunt):* subcutaneous catheter
between SVC and peritoneum with a pressure sensitive one-way
valve → allowing flow of ascitic fluid from the peritoneum to SVC.
Complications: infection, shunt thrombosis, DIC

*Transjugular intrahepatic portosystemic shunt (TIPS):* percutaneous
catheter via internal jugular vein → SVC → RA → IVC → right
hepatic vein → creating an intrahepatic channel connecting the right hepatic vein with a vena portae branch through US guidance, thereby decompressing the vena portae system (dilation of intrahepatic channel, then stent implantation).

Complications: 1) vena hepatica thrombosis, 2) bleeding from hepatic artery (acute complications), 3) HE (late complication)

Polytetrafluoroethylene-covered TIPS stents are associated with lower occlusion rates and HE than uncovered TIPS stents

*midodrine (3X7.5 mg)* or *midodrine+clonidine*

Hepatic hydrothorax: same treatment as for ascites

Spontaneous bacterial peritonitis (SBP)

2X2 g cefotaxime, 1X1-2 g ceftriaxone or 3X1/0.5 g iv.

The recurrence rate of SBP is >70% in 1 year

Prevention: 400 mg/day norfloxacin → selective GI decontamination → eliminating Gram (-) bact. selectively.

Prophylactic norfloxacin in high risk patients (GI bleeding, low protein ascites <1g/L, jaundice, hyponatraemia, renal dysfunction) before the first SBP episode → especially for candidates of liver transplantation.
Hepatorenal syndrome: The mainstay of ther. is liver transplant. Ther. used as bridge to transplantation: terlipressin (4-6X0.5-2.0 mg IV.) or octreotide 3X100-200 µg sc + α-agonist midodrine 3X7.5-12.5 mg orally + albumin. Avoid NSAID, aminoglycosides.

Hepatopulmonary syndrome: O₂, liver transplantation

Hepatic encephalopathy (HE):
* Identification and correction of precipitants
* P. os lactulose (non-absorbable disacharide)
  3X15-30 ml to produce 2-4 soft bowel movements
Metabolism of lactulose by colonic bacteria results in an acid pH that favors conversion of NH₃ to poorly absorbed NH₄⁺.

\[
\text{NH}_4^+ + \text{OH}^- \rightarrow \text{NH}_3 + \text{HOH}
\]
cathartic → ↓ NH₃ absorption

* neomycin 1-2 g/day or metronidazole 3X250 mg, or rifamixin 2X550 mg (very effective without the side effects of neomycin and metronidazol)
* Dietary protein restriction no longer recommended (its negative impact on overall nutrition outweighs its benefit) !!
* Probiotics: decreasing urease-producing bacteria and promoting growth of no-urease producing bacteria (lactobacillus, bifidobacteria)
* Oral L-ornithine-L-aspartate (LOLA): Lovers blood ammonia levels by increasing metabolism of ammonia to glutamine. Effective in treating mild HE.
* (branched chain aminoacids → normalize aromatic AA/BCAA ratio, clinical trials failed to show beneficial effects, not recommended)
* flumazenil in selected patients
* bromocriptine may be useful in selected patients with hepatocerebral degeneration or spastic paralysis.
GI bleeding (variceal haemorrhage)

Risk factors that correlate with ↑-ed likelihood of variceal bleeding include: 1) variceal size (large varices → ↑-ed wall tension → thinning of vessel wall), 2) endoscopic signs: cherry red spots overlying the varix representing haemorrhage within the vessel wall, red wale signs, hematocystic spots, diffuse erythema, bluish color, white-nipple spots, 3) WHVP >12 mmHg, 4) poor liver function with ascites and/or jaundice

Bleeding is most commonly from gastrooesophageal varices. (A rare cause of gastric variceal haemorrhage is splenic vein thrombosis due to pancreatic or retroperitoneal disease → localized obstruction of short gastric veins leads haemorrhage from gastric varices in the absence of oesophageal varices)

Endoscopic criteria of variceal haemorrhage:
1) Visible venous haemorrhage (not pulsating) from one or more varices; 2) no visible bleeding, but blood clots are seen on the surface of a varix(ces); 3) a white nipple overlying a varix; 4) no bleeding, no clot visible, there are varices, no other bleeding source identified
Portal hypertensive gastropathy (or congestive gastropathy)

Submucosal gastric veins engorged as a result of portal hypertension → bleeding can occur, but usually not serious.

Treatment
* Replacement of fluid and blood → avoid overexpanding volume
* Once the patients condition is stabilized vigorous gastric lavage through a nasogastric tube, in about 30 % the bleeding stops.
* Endoscopy to identify the bleeding source
* Endoscopic evidence of variceal bleeding → endoscopic methods:
  1) band ligation (rubber ligature placed around the varix)
     (lower incidence of oesophageal ulceration and other side effects, more rapid variceal obliteration than with sclerotherapy)
  2) sclerotherapy
* Pharmacological therapy:
The somatostatin analogue octreotide (50 µg bolus, then 50 µg/hour iv.) or terlipressin. Prophylactic antibiotics: 2X400 mg norfloxacin or 1X1 g ceftriaxone iv. for 5-7 days
* In patients who continue to bleed after endoscopic or pharmacologic therapy a Minnesota or Sengstaken-Blakemore tube can be used for ballontamponade of varices at the gastroesophageal junction, Linton-Nachlas tube for gastric varices.

* In whom haemodynamic stabilization is not possible because of persistent haemorrhage → TIPS (for liver transpl. candidates)
  - oesophageal staple-transection
  - emergent porto-caval shunt → end to side or mesocaval

(transection of gastrooesophageal junction then reanastomosis by a stapling machine together with ligation of vessels around the proximal third of the stomach) → poor prognosis

Prevention of recurrent and initial variceal bleeding:

Recurrent

* Combination of nonselective β-blockers (propranolol, nadolol, carvedilol) titrated to the maximum tolerated dose, or carvedilol in a max. dose of 2X25 mg and endoscopic band ligation

* Elective portocaval shunt surgery: distal splenorenal shunt →
portal flow is reserved, it is associated with a lower rate of HE and ascites

* **TIPS** in patients who fail to respond to pharmacological and endoscopic treatment, increases the risk of HE

**Initial:**

* nonselective β-blockers or endoscopic variceal ligation who cannot tolerate or have contraindications to β-blockers

**Portal vein thrombosis**
Anticoagulation, surgical decompression (distal splenorenal shunt if splenic vein patent, if not mesocaval shunt)

**Portal hypertensive gastropathy**
β-blockers

**Orthotopic liver transplantation** is the definitive therapy for cirrhosis is indicated when the risk of dying from liver disease is greater than the risk of dying from transplantation (in patients with a Child-Pugh score ≥7)!!
The portal circulation is a low pressure system (5-10 mmHg portal pressure). Portal pressure normally exceeds IVCP by up to 4 mmHg (portal venous gradient). Portal pressure >10 mmHg is defined as portal hypertension. Portal haemodynamics can be measured more directly by hepatic vein catheterization with a balloon-tipped catheter within the liver. When deflated, the catheter measures systemic venous (i.e. IVC) pressure. When inflated within the liver this "wedged" hepatic vein pressure (WHVP) reflects the pressure distal to the balloon (i.e. within the hepatic parenchyma). The WHVP↑ in sinusoidal and postsinusoidal, and normal in praesinusoidal portal hypertension.
The difference between WHVP and IVCP is the wedged hepatic gradient (WHPG), which is normally $<5$ mmHg. Once WHPG $>12$ mmHg $\rightarrow$ variceal haemorrhage. In cirrhosis, which is the most common cause of portal hypertension, the lesion is intrahepatic and primarily sinusoidal (WHVP ↑). Portal hypertension may also arise from praesinusoidal obstruction either outside (e. g. portal vein thrombosis) or within (schistosomiasis) the liver (WHVP normal). Similarly lesions leading to portal hypertension may be postsinusoidal either within the liver (e. g. veno-occlusive disease) or distal to it (e. g. Budd-Chiari syndrome, right sided heart failure (WHVP ↑)).
<table>
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<tr>
<th>Classification of Portal Hypertension</th>
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<tbody>
<tr>
<td><strong>Prehepatic</strong></td>
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<tr>
<td>Portal vein thrombosis</td>
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<tr>
<td>Splenic vein thrombosis</td>
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<tr>
<td>Massive splenomegaly (Banti’s syndrome)</td>
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<tr>
<td><strong>Hepatic</strong></td>
</tr>
<tr>
<td>Presinusoidal</td>
</tr>
<tr>
<td>Schistosomiasis</td>
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<tr>
<td>Congenital hepatic fibrosis</td>
</tr>
<tr>
<td>Sinusoidal</td>
</tr>
<tr>
<td>Cirrhosis—many causes</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
</tr>
<tr>
<td>Postsinusoidal</td>
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<tr>
<td>Hepatic sinusoidal obstruction (venoocclusive syndrome)</td>
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<tr>
<td><strong>Posthepatic</strong></td>
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<tr>
<td>Budd-Chiari syndrome</td>
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<tr>
<td>Inferior vena caval webs</td>
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<tr>
<td><strong>Cardiac causes</strong></td>
</tr>
<tr>
<td>Restrictive cardiomyopathy</td>
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<tr>
<td>Constrictive pericarditis</td>
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<tr>
<td>Severe congestive heart failure</td>
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</table>
9.24 Cirrhosis. In this typical histopathological section, bands of fibrous tissue run between nodules of regenerated hepatocytes. Only some nodules contain a central vein, and the bile ducts and portal vessels run in the fibrous septa. These changes are associated with portal hypertension.