Cirrhosis

See also separate Primary Biliary Cirrhosis article.

Cirrhosis is a diffuse hepatic process characterised by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules. Cirrhosis represents the final histological pathway for a wide variety of liver diseases. The progression to cirrhosis is very variable and may occur over weeks or many years. Around 80-90% of the liver parenchyma needs to be destroyed before there are clinical signs of liver failure. However, there is often a poor correlation between the histological findings and the clinical picture.

The fibrosis causes distortion of the hepatic vasculature and can lead to an increased intrahepatic resistance and portal hypertension. Portal hypertension can lead to oesophageal varices as well as hypoperfusion of the kidneys, water and salt retention and increased cardiac output. Damage to liver cells (hepatocytes) causes impaired liver function and the liver becomes less able to synthesise important substances such as clotting factors and is also less able to detoxify other substances (see also separate article Liver Failure).

Causes of cirrhosis

A number of chronic liver diseases can lead to cirrhosis. The cirrhotic process can take from weeks to many years to develop, depending on the underlying cause and other factors, including patient response to the disease process. For example, chronic hepatitis C infection can take up to 40 years to progress to cirrhosis in some people.

- Common causes of cirrhosis include:
  - Alcohol abuse.
  - Hepatitis B infection.
  - Hepatitis C infection (up to 20% can develop cirrhosis).
  - Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) - up to 10% of patients with NASH can develop cirrhosis.

- Less common causes include:
  - Haemochromatosis.
  - Primary biliary cirrhosis.
  - Biliary obstruction (may be due to biliary atresia/neonatal hepatitis, congenital biliary cysts or cystic fibrosis).
  - Autoimmune hepatitis.
  - Inherited metabolic disorders - eg, tyrosinaemia, Wilson's disease, porphyria, alpha-1-antitrypsin deficiency, glycogen storage diseases.
  - Sarcoidosis or other granulomatous disease.
  - Primary sclerosing cholangitis.
  - Venous outflow obstruction in Budd-Chiari syndrome or veno-occlusive disease.
  - Drugs and toxins including methotrexate, amiodarone and isoniazid.
  - Congestive heart failure or tricuspid regurgitation (although this is rarely seen now due to improved management).
  - Infections including congenital and tertiary syphilis and schistosomiasis.

Epidemiology

- It is difficult to estimate the exact prevalence of cirrhosis, as previously undiagnosed cirrhosis is often found at post-mortem.
- There are an estimated 30,000 people living with cirrhosis in the UK and at least 7,000 new cases being diagnosed each year. The number of people living with both alcoholic cirrhosis and non-alcohol-related cirrhosis seems to be rising.
There is concern that there are growing levels of dangerous alcohol consumption in the UK which may lead to increased numbers of people with cirrhosis.

An analysis in the Lancet showed that between 1960 and 2002, total recorded alcohol consumption in Britain doubled. The same report showed that between 1987-1991, and 1997-2001, cirrhosis mortality in men in Scotland more than doubled (104% increase) and in England and Wales rose by over two thirds (69%). Mortality in women increased by almost half (46% in Scotland and 44% in England and Wales).

Risk factors for cirrhosis
- Alcoholic liver disease and hepatitis C are the most common causes in developed countries.
- Hepatitis B is the most common cause in parts of Asia and in sub-Saharan Africa.
- There may also be a genetic predisposition to cirrhosis which may explain the variable rates of its development in people with similar risk factors (such as alcohol abuse or hepatitis C infection).
- Continued alcohol consumption increases the rate of progression of cirrhosis from any cause.
- Risk factors for the development of cirrhosis in those with chronic hepatitis C infection:
  - Regular (moderate) alcohol consumption.
  - Age >50 years.
  - Being male.

- Risk factors for the development of cirrhosis in those with NASH:
  - Older age.
  - Obesity.
  - Insulin resistance or type 2 diabetes.
  - Hypertension.
  - Hyperlipidaemia.

Presentation
Cirrhosis is often asymptomatic until there are obvious complications of liver disease. Up to 40% of people with cirrhosis may be asymptomatic. Blood testing for other reasons may reveal abnormal liver function and prompt further investigation which shows cirrhosis.

The history should include a thorough enquiry for possible underlying causes of cirrhosis, including a full drug and alcohol history (including over-the-counter drugs, complementary medicines and recreational drugs), risk factors for hepatitis infection, and family history of autoimmune or liver diseases.

Symptoms
Cirrhosis may present with vague symptoms such as fatigue, malaise, anorexia, nausea and weight loss. In advanced, decompensated liver disease, presentation may include:

- Oedema.
- Ascites.
- Easy bruising.
- Poor concentration and memory.
- Bleeding oesophageal varices.
- Spontaneous bacterial peritonitis.

Signs
Physical signs are variable and depend upon the extent of disease.

- Cutaneous features of cirrhosis include:
  - Jaundice.
  - Scratch marks secondary to pruritus.
  - Spider angioma/naevi (mainly found on the trunk and face).
  - Skin telangiectasias (called 'paper money skin').
  - Palmar erythema.
• Bruising.
• Petechiae or purpura.
• Hair loss.
• White nails (horizontal white bands or a proximal white nail plate; sign of hypoalbuminaemia).
• Finger clubbing.
• Dupuytren’s contracture.

• Other signs include:
  • Hepatomegaly and a nodular liver.
  • Oedema.
  • Gynaecomastia and male hair loss pattern.
  • Hypogonadism/testicular atrophy/amenorrhoea (due to the direct toxic effect of alcohol in alcoholic cirrhosis or iron in haemochromatosis).
  • Kayser-Fleischer ring (a brown-green ring of copper deposit around the cornea, pathognomonic for Wilson's disease).

• Signs of portal hypertension include:
  • Ascites (can be detected clinically when ≥1.5 litres of fluid is present).
  • Caput medusae (veins seen radiating from the umbilicus).
  • Enlarged spleen.

• Signs of hepatic encephalopathy:
  • Asterixis (‘flapping tremor’); suggests hepatic encephalopathy. To detect asterixis, take the patient’s hand and gently hyperextend the wrist and joints of the hand, pushing gently on the tips of the four fingers. Ignore the thumb. Hold that position for several seconds and you will feel a slow, clonic flexion-relaxation movement against your hand if asterixis is present.

Investigations

These will depend to a considerable extent upon clinical suspicion of the aetiology.

Blood tests

• LFTs: should include aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), bilirubin, gamma-glutamyltransferase (gamma-GT); AST and ALT are raised due to hepatocyte damage; gamma-GT is high in active alcoholics.
• Albumin: there is hypoalbuminaemia in advanced cirrhosis.
• FBC: occult bleeding may produce anaemia; hypersplenism may cause thrombocytopenia; macrocytosis can suggest alcohol abuse.
• Renal function tests and electrolytes: hyponatraemia may be present (due to increased activity of antidiuretic hormone). Poor renal function may represent hepatorenal syndrome.
• Red cell folate: alcohol abuse is often associated with a diet inadequate in folate.
• Coagulation screen: abnormalities of coagulation are a sensitive test of liver function; prothrombin time is reduced in advanced cirrhosis.
• Ferritin: low ferritin may indicate iron deficiency from diet or blood loss; ferritin is raised in haemochromatosis.
• Viral antibody screen: to look for evidence of hepatitis B or C infection.
• Fasting glucose/insulin/triglycerides and uric acid levels: these should be measured if NASH is suspected.
• Autoantibody screen: anti-mitochondrial antibodies are a very strong indicator of primary biliary cirrhosis.
• Alpha-1-antitrypsin level: to assess for alpha-1-antitrypsin deficiency.
• Ceruloplasmin and urinary copper: to look for Wilson’s disease.
• Fasting transferrin saturation and HFE (haemochromatosis C282Y) mutation: along with a raised ferritin, these tests can screen for haemochromatosis.

Imaging

• Ultrasound scan of liver and possibly CT or MRI scan: their main use is to detect complications of cirrhosis, such as splenomegaly, ascites or hepatocellular carcinoma.
CXR: this may show an elevated diaphragm and even pleural effusion (due to the passage of ascitic fluid across the diaphragm).\[13\]

**Liver biopsy**
See separate Liver Biopsy article.

- Histology is usually needed for the definitive diagnosis of cirrhosis and liver biopsy is the gold standard.\[3\]
- It may also give a clue to the underlying cause.
- Any coagulation defect must be corrected first and blood must be available for transfusion.
- If there are clear signs of cirrhosis, such as ascites, coagulopathy and a shrunken nodular-appearing liver, confirmation of diagnosis by biopsy may not be necessary.\[3\]

**Classification systems for cirrhosis**
The Child-Pugh-Turcotte (CPT) classification system is a widely used and validated way to estimate prognosis in those with cirrhosis.\[3\]

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Score 1 point</th>
<th>Score 2 points</th>
<th>Score 3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum albumin (g/L)</td>
<td>&gt;35</td>
<td>28-35</td>
<td>&lt;28</td>
</tr>
<tr>
<td>Serum bilirubin (total)</td>
<td>&lt;34 μmol/L (&lt;2 mg/dL)</td>
<td>34-50 μmol/L (2-3 mg/dL)</td>
<td>&gt;50 μmol/L (&gt;3 mg/dL)</td>
</tr>
<tr>
<td>International Normalized Ratio (INR)</td>
<td>&lt;1.7</td>
<td>1.7-2.2</td>
<td>&gt;2.2</td>
</tr>
<tr>
<td>Ascites</td>
<td>Absent</td>
<td>Controlled medically</td>
<td>Poorly controlled</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Absent</td>
<td>Controlled medically</td>
<td>Poorly controlled</td>
</tr>
</tbody>
</table>

A score of 5-6 is class A (life expectancy 15-20 years); a score of 7-9 is class B (life expectancy 4-14 years); a score of 10-15 is class C (life expectancy 1-3 years). This aligns with a perioperative mortality (for abdominal surgery) of 10%, 30%, and 80% respectively.

A statistical model for end-stage liver disease (MELD) has also been developed to help to predict survival in cirrhosis and to help with timing and allocation of liver transplantation.\[14, 15\]

**Management**\[1\]
The aim of treatment is to delay progression of cirrhosis and to prevent and/or treat any complications of cirrhosis.

- Specific treatment for the underlying cause.
- Ensure adequate nutrition, including calorie and protein intake.
- Alcohol: the most important measure for someone with alcoholic cirrhosis is for them to stop drinking. Continued alcohol intake can also increase the rate of progression of cirrhosis from any cause.
- Zinc deficiency is often seen in patients with cirrhosis and treatment with zinc supplements may be helpful.
- Pruritus is a common complaint in cholestatic and non-cholestatic liver diseases. Mild itching complaints may respond to treatment with antihistamines and topical ammonium lactate. Colestyramine is the mainstay of therapy for the pruritus of liver disease. Rifampicin has helped some patients unresponsive to colestyramine. Severe pruritus may require treatment with ultraviolet light or plasmapheresis.
- Patients with cirrhosis may develop osteoporosis and those at risk of osteoporosis should be given preventative treatment. See also separate Osteoporosis Risk Assessment and Primary Prevention article.
- Regular exercise should be encouraged and is important to prevent muscle wasting.
- Prophylactic antibiotic use in patients with cirrhosis and upper gastrointestinal bleeding significantly reduces bacterial infections and seems to reduce all-cause mortality, bacterial infection mortality, rebleeding events and length of hospitalisation.\[16\]
Patients with chronic liver disease should receive vaccination to protect them against hepatitis A, influenza and pneumococci.

Drug prescribing: care is essential to avoid any drug that may not be properly metabolised in the presence of liver failure, have an adverse effect on the degree of liver failure or be a cause of drug-induced liver disease. See prescribing in Drug-induced Hepatitis article.

Liver transplantation is the ultimate treatment for cirrhosis and end-stage liver disease. See the separate Liver Transplantation article. For the future: various antifibrotic drugs have been postulated that may slow down, or even reverse, the fibrotic process in cirrhosis and clinical trials have been carried out/are underway. Stem cell or hepatocyte transplantation aimed at restoring liver function is also being investigated.

Monitoring
- Surveillance of oesophageal varices.
- Surveillance for hepatocellular carcinoma.

Clinical Editor's notes (July 2017)
Dr Hayley Willacy would like to remind you of the three quality statements relating to cirrhosis in NICE's recent quality statement release:
1. Young people and adults with risk factors for cirrhosis are offered non-invasive testing for cirrhosis. Non-invasive testing for cirrhosis includes transient elastography (for all people with risk factors for cirrhosis) or acoustic radiation force impulse imaging (for young people and adults with non-alcoholic fatty liver disease and advanced liver fibrosis).
2. Adults with cirrhosis are offered six-monthly surveillance for hepatocellular carcinoma.
3. Young people and adults with cirrhosis and upper gastrointestinal bleeding are given prophylactic intravenous antibiotics at presentation.

Complications
If complications develop, the patient should be transferred to a specialised liver unit where there is the expertise to manage the complications and where the patient can also be assessed as to their suitability for liver transplantation.

Anaemia, thrombocytopenia and coagulopathy
- Anaemia may result from folate deficiency, haemolysis or hypersplenism.
- Thrombocytopenia is usually secondary to hypersplenism and decreased levels of thrombopoietin.
- Coagulopathy results from decreased hepatic production of coagulation factors. If present, cholestasis causes decreased vitamin K absorption, leading to reduced hepatic production of factors II, VII, IX and X.
- Patients with cirrhosis also may develop fibrinolysis and disseminated intravascular coagulation.

Oesophageal varices
- These can occur as a result of portal hypertension.
- See separate Oesophageal Varices article for more details.

Ascites
- This is a common feature of cirrhosis.
- It is an accumulation of excessive fluid within the peritoneal cavity due to the increased plasma volume ’spilling over’ into the abdominal cavity.
- The clinical detection of ascites is described in the separate Abdominal Examination article but much smaller volumes may be detected by ultrasound.
- Its aetiology and management are discussed in the separate Ascites and Ascites Tapping articles.

Spontaneous bacterial peritonitis
- Ascites may be associated with spontaneous bacterial peritonitis.
- It is thought to be caused by the spread of bacteria across the gut wall and/or haematogenous bacterial spread. Escherichia coli is among the most common organisms implicated.
- This may be prevented by adequately treating ascites and treating those with high neutrophil counts in their ascitic fluid (>250 neutrophils/ml) with empirical intravenous antibiotics and albumin.
Patients who survive an episode of spontaneous bacterial peritonitis should receive long-term prophylaxis with oral antibiotics such as norfloxacin, levofloxacin or trimethoprim. \[3, 14\]

**Hepatocellular carcinoma**

- Cirrhosis is a major risk factor for hepatocellular carcinoma. See separate Hepatocellular Carcinoma article. \[3\]
- The risk varies according to the cause of cirrhosis.
- It is most often associated with cirrhosis caused by hepatitis C infection, followed by cirrhosis caused by hereditary haemochromatosis. \[3\]
- Worldwide, hepatocellular carcinoma as a result of cirrhosis secondary to hepatitis B infection causes a large number of deaths.
- The risk of hepatocellular carcinoma is lower in those with alcoholic cirrhosis (8% five-year occurrence) or primary biliary cirrhosis (4% five-year occurrence). \[3\]
- Patients with cirrhosis should be screened for hepatocellular carcinoma.
- The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) guidelines recommend at least one screening per year for hepatocellular carcinoma in patients with cirrhosis, using imaging with ultrasonography, triphasic CT or gadolinium-enhanced MRI. \[20\]

Screening using serum alpha-fetoprotein is no longer recommended because of its poor sensitivity and specificity. \[3\]

**Other complications**

Other less common complications can include:

- Cirrhotic cardiomyopathy - there is cardiac hypertrophy and a blunted stress response of the heart. May cause significant problems perioperatively and mean that liver transplantation may be too dangerous. \[3\]
- Hepatopulmonary syndrome - there is pulmonary arteriolar vasodilation, shunting and hypoxaemia. Transplantation may reverse this. \[3\]
- Portopulmonary hypertension - an irreversible condition that can occur in those with refractory ascites. \[3\]
- Surgery and general anaesthesia have increased risks in the patient with cirrhosis.

**Prognosis**

- This depends on the underlying cause and on the success of the treatment of the underlying cause. Prognosis is discussed in the separate articles for the conditions that can lead to cirrhosis.
- If someone with alcoholic cirrhosis continues to drink alcohol, the rate of decompensation can be rapid. \[3\]
- Patients with fulminant hepatic failure have a 50-80% mortality rate unless they receive a liver transplant. \[1\]

**Prevention**

- Worldwide, the most important factor in prevention of cirrhosis is immunisation against hepatitis B.
- There is no vaccine against hepatitis C but some treatments may delay progression and alcohol must be avoided.
- Sensible drinking is essential for everyone and patients should be advised about the recommended limits.
- There are various separate articles providing further information about the assessment and management of harmful drinking and alcohol dependence: Alcohol Use Disorders Identification Test (AUDIT), CAGE Questionnaire, Alcohol-related Problems, Alcoholism - Recognition and Assessment and Alcoholism and Alcohol Abuse - Management.
- Beware of hepatotoxic medications, including herbal remedies.
- Weight reduction and exercise can improve liver function in patients with NASH. \[21\]

**Further reading & references**

- Cirrhosis in over 16s - assessment and management; NICE Guideline (July 2016)
- British Liver Trust


17. Liver disease; NICE Quality standard (June 2017)


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