Ministry of Defence

Synopsis of Causation

Cirrhosis of the Liver

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Disclaimer

This synopsis has been completed by medical practitioners. It is based on a literature search at the standard of a textbook of medicine and generalist review articles. It is not intended to be a meta-analysis of the literature on the condition specified.

Every effort has been taken to ensure that the information contained in the synopsis is accurate and consistent with current knowledge and practice and to do this the synopsis has been subject to an external validation process by consultants in a relevant specialty nominated by the Royal Society of Medicine.

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1. Definition

1.1. Cirrhosis of the liver is an irreversible disorder characterised by diffuse hepatic fibrosis and the conversion of normal liver architecture into abnormal nodules. It represents a sustained healing response to chronic injury from a wide variety of causes.[1]

1.2. The condition often develops insidiously without giving rise to symptoms and it is thought that about 30-40% of cases are clinically latent. It may therefore be categorised on clinical grounds as:

- **Compensated cirrhosis**, in which the patient is asymptomatic and the condition is discovered during biochemical screening, routine clinical examination, or abdominal surgery for another condition

- **Decompensated cirrhosis**, in which the most frequent manifestations are jaundice, ascites, encephalopathy and gastric or oesophageal haemorrhage

2. Clinical features

2.1 The commonest clinical presentation is general malaise, with anorexia, weight loss, muscle weakness and fatigue. Other cases may only be recognised when abnormal blood tests indicate liver disease, with no obvious liver-related symptoms. Examination may reveal hepatic and splenic enlargement, though in advanced cirrhosis the liver may shrink. Palmar erythema, and spider naevi may be present.

2.2 **Portal hypertension** Obstruction of the portal venous system causes portal hypertension, with gastric and oesophageal varices and the development of periumbilical collateral vessels. The distended gastric and oesophageal vessels may produce life-threatening haemorrhage. The combination of portal hypertension with low plasma albumin levels due to diminished hepatic protein synthesis, and abnormalities of salt and water handling, leads to ascites.

2.3 **Haematological and endocrine effects** Anaemia is common, and impaired coagulation due to decreased production of coagulation factors by the liver. Endocrine effects such as feminisation and hypogonadism may occur in the male.

2.4 **Cardiorespiratory effects** In advanced cirrhosis there may be a circulatory hyperdynamic state with increased cardiac output and reduced exercise capacity. In a minority of patients disturbances in the pulmonary circulation lead to dyspnoea.

2.5 **Neoplasm** Hepatocellular cancer may complicate cirrhosis – in 2-25% of cases depending on the cause of cirrhosis. Viral and alcohol-related cases are particularly susceptible, and the incidence is much higher in men than women. A hepatocellular cancer may be the presenting feature of cirrhosis.[2]

3. Aetiology

3.1. A wide variety of agents and diseases produce the common end result of cirrhosis of the liver. These may be categorised as:

- alcohol
- chronic viral hepatitis
- drugs and toxins
- autoimmune disease
- non-alcoholic fatty liver disease
- genetic disorders
- diseases predominantly affecting the bile ducts
- venous outflow obstruction

3.2. In addition, a significant proportion of cases have no identifiable cause; so-called 'cryptogenic' cirrhosis, but may represent 'burnt-out' forms many of the above disorders. The aetiology of cirrhosis varies both geographically and socially but in the western world the approximate frequencies of the major categories are: [3]

Alcoholic liver disease:	60-70%
Viral hepatitis:	~10%
Bile duct diseases:	~7%
Auto-immune and genetic causes	~7%
Non-alcoholic fatty liver disease	~5%
Cryptogenic	~10%

3.3. **Alcohol** The exact mechanism whereby alcohol results in parenchymal liver damage is unclear. The process may be attributable to free radical generation, to hypoxia due to the increased oxygen requirement in ethanol acetaldehyde metabolism, or to neo-antigen production in the form of acetaldehyde-protein adducts. Alcohol is a major aetiological factor in hepatic cancer, although the mechanism is as yet imperfectly understood.[4]

3.3.1. Progression to cirrhosis generally pursues a course from fatty liver, which resolves completely in 4 to 6 weeks if alcohol ingestion is discontinued, to alcoholic hepatitis, which may resolve if underlying fibrosis is minimal and the patient stops drinking; otherwise the process continues to cirrhosis. In patients with established cirrhosis abstinence is a crucial determinant of prolonged survival.

3.3.2. Not all alcohol abusers develop cirrhosis, and the predisposition of some individuals to develop it is as yet unexplained. Susceptibility to liver damage is probably caused not by a single gene defect but through a cumulative interaction of a number of genes.[5] As a round estimate, 10% of heavy drinkers (>80 gm alcohol per day = 10 'units') will develop cirrhosis after 10 years, 20% after 20 years. Women are more susceptible to severe alcoholic liver disease than men.

3.4. **Chronic viral hepatitis** Chronic hepatitis B virus (HBV) and chronic hepatitis C virus (HCV) infections are an important cause of cirrhosis in the western world.

3.4.1. **HBV** is acquired in various ways – at birth or in early childhood from the mother, or in adulthood by transmission through blood or other body fluids (transfusion of blood/blood products, contaminated needles or razors, sexual intercourse). Most people who have an acute attack of HBV clear the virus and have no subsequent chronic liver disease. Only ~5-10% of adults, but ~60% of infants become chronic HBV carriers. In chronic HBV infection the rate of progression to cirrhosis depends upon the replicative activity of the virus and the highly variable immune response of the individual.

3.4.2. **HDV** The hepatitis delta virus (HDV) is unable to replicate on its own and is dependent upon the presence of HBV to render it capable of infecting the human host; the interaction between the two viruses is very complex. Infection with HDV is uncommon in Western countries and is largely confined to intravenous drug users. Fresh and florid cases of the disease are now rare, but in most chronic carriers subversion of the liver architecture is seen early and cirrhosis may develop more rapidly if HBV infection is complicated by the addition of HDV.

3.4.3. **HCV** is mainly transmitted through blood or blood products, and contaminated many blood donations in the West until the early 1990's. Intravenous drug abuse remains a major reservoir of disease. Over 85% of infected individuals become chronic carriers. In chronic HCV infection, progression to cirrhosis is also dependent on the age at exposure and the duration of infection. After middle age the rate of progression appears to accelerate. Even moderate alcohol ingestion increases the degree of inflammation and the rate of progression to cirrhosis.

3.4.4. **HAV and HEV** Type A hepatocellular viral infection (HAV) and Type E (HEV), a common cause of acute hepatitis in the Middle and Far East, do not cause cirrhosis.

3.5. **Other infections** A number of infective agents affect the liver but do not cause cirrhosis; these include schistosomiasis, amoebiasis, malaria, yellow fever and infectious mononucleosis. Schistosomiasis can however cause liver fibrosis with the complications of portal hypertension and gastrointestinal bleeding.

3.6. **Drugs and toxins** A wide variety of drugs and toxins may be implicated in the development of cirrhosis. However their contribution is small compared with that of alcohol and viral hepatitis. They include:

3.6.1. **Methotrexate** Signs of hepatotoxicity may appear following long-term therapy for rheumatoid arthritis, psoriasis or leukaemia.

3.6.2. **Amiodarone** This drug, used in certain cardiac arrhythmias, is known to possess hepatotoxic effects and may result in cirrhosis after prolonged use.

3.6.3. **Vitamin A** Increasingly encountered in dermatology, vitamin A is only slowly metabolised in the liver and toxicity may develop with the ingestion of as little as 50,000 IU over two years.

3.6.4. **Other Drugs and toxins** Long term treatment with other drugs or exposure to toxins should always be considered as potential causes as many cause a chronic inflammation in the liver in a small proportion of individuals, which might cause or contribute to fibrosis of the liver and even cirrhosis. Examples include alpha-methyl dopa, arsenicals, vinyl chloride.

3.7. **Autoimmune hepatitis** This condition, previously known as 'lupoid' hepatitis, is more common in females (female:male = 4:1). It is the result of immune mediated damage to liver cells and can generally be identified by the presence of antibodies in the blood to a variety of liver-associated proteins. Florid cases may present dramatically, and those are characterised by a low rate of spontaneous remission and a high mortality. The disease usually responds well to modest immunosuppression, but without treatment it often progresses to cirrhosis.[6,7]

3.7.1. The triggers for this self-perpetuating autoimmune process, are unknown, but the disease occurs in those whose genetic make-up renders them susceptible to this and other auto-immune diseases. Other immune conditions such as thyroid disease, auto-immune haemolytic anaemia and rheumatoid arthritis are often found in patients or their relatives.

3.8. **Genetic and Metabolic diseases** A number of metabolic disorders may lead to cirrhosis. They include conditions in which there is defective metabolism and storage of specific substances, such as haemochromatosis (iron) and Wilson's disease (copper).[8,9] Some are predominantly childhood diseases (glycogenoses, galactosaemia, tyrosinaemia, hereditary fructose intolerance, progressive familial cholestasis, abetalipoproteinaemia). Those relevant to adulthood are:

3.8.1. **Haemochromatosis.** A genetic predisposition to accumulate iron in the body leads over many years to liver fibrosis and cirrhosis presenting generally in the fourth or fifth decade or above, also with damage to other organs leading to diabetes, arthritis and cardiomyopathy. Not all patients with the genetic predisposition develop the disease, and women (who lose iron menstrually) are relatively protected. Recent genetic advances mean that susceptible patients can be identified as carriers of the predisposing genes, inherited from both parents, and the development of cirrhosis can be prevented by repeated blood-letting to remove iron (e.g. 1 unit a week for a year).

3.8.2. **Wilson's disease**. This genetic autosomal recessive condition may present with liver disease (either as acute liver failure or with chronic disease leading to cirrhosis), episodes of haemolysis, or neurological disease (ataxia, unsteadiness). A genetic deficiency of copper transport in the cell is responsible. Treatment with agents to bind copper in the blood can halt the progression of the disease.

3.8.3. **Alpha$_1$-antitrypsin deficiency** is a genetically determined disorder in which this liver-produced protein is abnormal, becomes trapped in the liver cells, and does not enter the blood stream This allows the unopposed action of proteases. The main effects are on the lungs (emphysema due to destruction of tissue by proteases) and liver (where the defective protein is stored).

3.8.4. **Miscellaneous** Some rare metabolic conditions are associated with cirrhosis in adults – e.g. some forms of porphyria. Some congenital diseases which are not true cirrhosis may be associated with portal hypertension and clinically mimic cirrhosis, e.g. congenital hepatic fibrosis, hereditary haemorrhagic telangiectasia

3.9. **Disease of the bile ducts.** There are two main types of bile duct disease that can lead to cirrhosis – primary and secondary. Primary bile duct diseases are endogenous and probably of immune aetiology (primary biliary cirrhosis and primary sclerosing cholangitis). Secondary bile duct diseases are usually due to previous surgery to the bile duct resulting in delayed excretion of bile.

3.9.1. **Primary biliary cirrhosis** This is a disease of uncertain cause in which intrahepatic bile ducts are progressively but very slowly destroyed. It is associated with a characteristic immunological profile – circulating antibodies to mitochondria. 90% of patients are female, usually in the 5th to 7th decade. It is considered likely that environmental factors, including infections acting on a genetically predisposed host may cause the condition.[10] The disease may be slowly progressive over many decades and only identified when blood tests reveal anti-mitochondrial antibodies. Many patients with these antibodies are labelled as having primary biliary cirrhosis when their livers are at a pre-cirrhotic stage and only show mild focal inflammation in the bile ducts; true cirrhosis may not occur for decades, if ever.

3.9.2. **Primary sclerosing cholangitis** Underlying this condition is a chronic fibrosing inflammatory process involving all parts of the biliary tree, which is ultimately destroyed, resulting in biliary cirrhosis. The cause of the condition is not known although in about 70% of cases the patient also suffers from ulcerative colitis. It is thought that the process occurs in immunologically susceptible individuals when an infective agent penetrating the abnormally porous bowel wall reaches the liver by blood-borne spread.

3.9.3. **Veno-occlusive disease and Budd-Chiari syndrome** In this group of conditions there is narrowing or obliteration of the lumen of large or small hepatic veins by thrombosis, congenital abnormalities ('webs' of connective tissue) or inflammation, leading to hepatomegaly, abdominal pain and ascites.. Cirrhosis may ensue if the condition is sufficiently prolonged. A number of agents and conditions may be responsible:

- myeloproliferative diseases and chemotherapeutic drugs

- genetic disorders pre-disposing to thrombosis
- pregnancy
- oral contraceptives
- sickle cell disease
- malignancy
- blunt trauma
- ingestion of plant alkaloids as in some native herbal teas
- radiation damage after therapeutic abdominal irradiation. (Sensitivity to therapeutic radiation varies between individuals, but damage rarely occurs at doses of less than 0.3Gy. For comparison, the dosage from a chest X-ray is about 0.0001Gy and from a CT scan about 0.008Gy)

3.10. **Non Alcoholic Fatty Liver** Fatty liver, common in the general population, is now increasingly recognised as having the potential to lead to cirrhosis.[11,12] In some individuals, simple fatty liver (non-alcoholic fatty liver [NAFL]) becomes complicated by inflammation (steato-hepatitis, non-alcoholic steato-hepatitis [NASH]) which is indistinguishable on microscopic appearance from alcoholic steato-hepatitis. This can lead to fibrosis and cirrhosis. NAFL and NASH are associated with obesity, type 2 diabetes, and abnormal blood lipid profiles. The presence of liver disease may be unsuspected until cirrhosis has developed, and when cirrhosis has occurred the appearances of the liver may no longer show fat deposition, so many of these patients are described as having cryptogenic cirrhosis. In patients who have undergone jejuno-ileal bypass for morbid obesity a similar sequence of events may occur.

3.11. **Cryptogenic cirrhosis** In this heterogeneous group the cause of the cirrhosis is unknown, and many represent 'burnt-out' cases of the causes listed above in which the characteristics of the original cause such as auto-immunity, alcohol or fatty liver are no longer distinguishable. Since the clarification of the role of hepatitis C virus in the early 1990s the number of cases falling into this category has dropped considerably. About 15% of cases are now thought to represent long term consequences of NASH.

4. Prognosis

4.1. The life expectancy after the diagnosis of cirrhosis is made is highly variable and a 50% 5-year survival is commonly quoted. If the cause is remediable (e.g. total abstention from alcohol, successful immunosuppression for auto-immune liver disease), survival may be prolonged. Some patients with cirrhosis are completely asymptomatic and have a reasonably normal life expectancy. If however patients present with advanced or decompensated liver disease, over half will die within two years after diagnosis.

4.2. In most patients with cirrhosis death is due to cirrhosis-related causes; most frequently variceal bleeding, closely followed by infections.[13] Prognosis is related to the effect of the cirrhotic process on liver function, commonly evaluated by calculation of the Child-Pugh score, which is defined by a number of biochemical and clinical parameters.[14]

5. Summary

5.1. Cirrhosis is a process of diffuse fibrosis of the liver parenchyma with nodule formation. There are a very large number of causes, the most important of which are alcohol abuse and chronic hepatocellular viral infection, but assessment of cause requires an extensive series of investigations including full clinical history, blood tests, imaging of the liver and frequently liver biopsy.

6. Related Synopses

Hepatitis

7. Glossary

ascites	An effusion and accumulation of serous fluid in the abdominal cavity.
autosomal dominant	Requires that only one parent need have the trait (characteristic) in order to pass it to the offspring.
autosomal recessive	Requires that two affected parents have the trait (characteristic) in order to pass it to the offspring.
calculus, calculi	An abnormal concretion occurring within the body, usually composed of mineral salts.
encephalopathy	Any degenerative condition affecting the brain.
erythema	Redness.
fibrosis	A process whereby normal tissue is replaced by scar tissue.
hepatic	Referring to the liver. Hence hepatogenic, hepatocellular, hepatitis, hepatotoxic, etc.
portal venous system	That part of the circulation which collects blood from the intestine and spleen and delivers it to the liver. Portal hypertension refers to increased pressure within that system.
varix, *pl.* varices	Uneven, permanent dilatation of a vein.
vena cava	The large vein that returns blood to the heart. The inferior vena cava receives blood from the lower extremities, pelvis and abdominal organs.

8. References

[1] Sherlock S, Dooley J. Diseases of the liver and biliary system. Oxford: Blackwell Science Ltd., 2002. p. 365-80.
[2] El-Serag HB. Epidemiology of hepatocellular carcinoma. Clinics in Liver Disease 2001;5(1):87-107,vi.
[3] Crawford JM. Liver cirrhosis. In: MacSween RN, et al, editors. Pathology of the liver. London: Churchill Livingstone; 2002. p. 575-619.
[4] Stickel F, et al. Cocarcinogenic effects of alcohol in hepatocarcinogenesis. Gut. 2002;51.(1):132-9.
[5] Maher JJ. Alcoholic liver disease. In: Goldman L, Bennett JC, editors. Goldman: Cecil textbook of medicine. 21st ed. Philadelphia: W.B.Saunders Company; 2000. p. 1375-87.
[6] Czaja AJ. Autoimmune hepatitis. In: Feldman M, Friedman LS, Sleisenger MH, editors. Feldman: Sleisenger & Fordtran's gastrointestinal and liver disease. 7th ed. Philadelphia: Saunders; 2002. p. 1462-73.
[7] Gish RG. Autoimmune liver disease. Current standards, future directions. Clin Liver Dis 2001;5(2):287-314.
[8] Maher JJ. Inherited, infiltrative, and metabolic disorders involving the liver. In: Goldman L, Bennett JC, editors. Goldman: Cecil textbook of medicine. 21st ed. Philadelphia: W.B.Saunders Company; 2000. p. 801-4.
[9] Leonis MA, Balistreri WF. Inherited metabolic disorders of the liver. In: Feldman M, Friedman LS, Sleisenger MH, editors. Feldman: Sleisenger & Fordtran's gastrointestinal and liver disease. 7th ed. Philadelphia: Saunders; 2002. p. 1240-59.
10 Angulo P, Lindor KD. Primary biliary cirrhosis. In: Feldman M, Friedman LS, Sleisenger MH, editors. Feldman: Sleisenger & Fordtran's gastrointestinal and liver disease. 7th ed. Philadelphia: Saunders; 2002. p. 1474-83.
[11] Matos C et al. Nutrition and chronic liver disease. J Clin Gastroenterol 2002;35(5):391-7.
[12] Festi D, Colecchia A, Sacco T, et al. Hepatic steatosis in obese patients: clinical aspects and prognostic significance. Obes Rev 2004;5(1):27-42.
[13] Vilstrup H. Cirrhosis and bacterial infections. Rom J Gastroenterol 2003;12(4):297-302.
[14] Pugh RN, Murray-Lyon IM, Dawson JL et al. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:649-9.