

Liver cirrhosis

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Cirrhosis is an increasing cause of morbidity and mortality in more developed countries, being the 14th most common cause of death worldwide but fourth in central Europe. Increasingly, cirrhosis has been seen to be not a single disease entity, but one that can be subclassified into distinct clinical prognostic stages, with 1-year mortality ranging from 1% to 57% depending on the stage. We review the current understanding of cirrhosis as a dynamic process and outline current therapeutic options for prevention and treatment of complications of cirrhosis, on the basis of the subclassification in clinical stages. The new concept in management of patients with cirrhosis should be prevention and early intervention to stabilise disease progression and to avoid or delay clinical decompensation and the need for liver transplantation. The challenge in the 21st century is to prevent the need for liver transplantation in as many patients with cirrhosis as possible.

Introduction

Cirrhosis results from different mechanisms of liver injury that lead to necroinflammation and fibrogenesis; histologically it is characterised by diffuse nodular regeneration surrounded by dense fibrotic septa with subsequent parenchymal extinction and collapse of liver structures, together causing pronounced distortion of hepatic vascular architecture.^{1,2} This distortion results in increased resistance to portal blood flow and hence in portal hypertension and in hepatic synthetic dysfunction. Clinically, cirrhosis has been regarded as an end-stage disease that invariably leads to death, unless liver transplantation is done, and the only preventive strategies have been screening for oesophageal varices and hepatocellular carcinoma.

Lately, this perception has been challenged, because 1-year mortality in cirrhosis varies widely, from 1% to 57%, depending on the occurrence of clinical decompensating events.³ Histopathologists have proposed that the histological term cirrhosis should be substituted by advanced liver disease, to underline the dynamic processes and variable prognosis of the disorder.⁴ Moreover, fibrosis, even in the cirrhotic range, regresses with specific therapy if available, such as antiviral treatment for chronic hepatitis B⁵ or C.⁶

Here, we review the current understanding of cirrhosis as a dynamic process and outline current therapeutic options for prevention and treatment of complications of cirrhosis, on the basis of the subclassification in clinical prognostic stages.^{3,7} The new concept in management of patients with cirrhosis is the use of non-specific therapies for prevention and early intervention to stabilise disease progression and to avoid or delay decompensation and the need for liver transplantation.

Epidemiology

Cirrhosis is an increasing cause of morbidity and mortality in more developed countries. It is the 14th most common cause of death in adults worldwide but the fourth in central Europe; it results in 1·03 million deaths per year worldwide,⁸ 170 000 per year in Europe,⁹ and 33 539 per year in the USA.¹⁰ Cirrhosis is the main

indication for 5500 liver transplants each year in Europe.⁹ The main causes in more developed countries are infection with hepatitis C virus, alcohol misuse, and, increasingly, non-alcoholic liver disease; infection with hepatitis B virus is the most common cause in sub-Saharan Africa and most parts of Asia. The prevalence of cirrhosis is difficult to assess and probably higher than reported, because the initial stages are asymptomatic so the disorder is undiagnosed. Prevalence was estimated at 0·3% in a French screening programme, and the annual incidence was 15·3–132·6 per 100 000 people in studies in the UK and Sweden.⁹

Pathophysiology

The transition from chronic liver disease to cirrhosis involves inflammation, activation of hepatic stellate cells with ensuing fibrogenesis, angiogenesis, and parenchymal extinction lesions caused by vascular occlusion.¹¹ This process leads to pronounced hepatic microvascular changes, characterised by sinusoidal remodelling (extracellular matrix deposition from proliferating activated stellate cells resulting in capillarisation of hepatic sinusoids), formation of intrahepatic shunts (due to angiogenesis and loss of parenchymal cells), and hepatic endothelial dysfunction.¹² The endothelial dysfunction is characterised by insufficient release of vasodilators, of which the most important is nitric oxide. Release of nitric oxide is inhibited by low activity of endothelial nitric oxide synthetase (as a result of insufficient protein-kinase-B-dependent phosphorylation, lack of cofactors, increased scavenging resulting from oxidative stress, and high concentrations of

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Search strategy and selection criteria

We searched Medline (2000–13) using the search term “liver cirrhosis”. We largely selected publications from the past 5 years, but we did not exclude highly relevant older publications. We selected further relevant publications from the reference lists of articles identified by this search strategy. Review articles and book chapters are cited to provide more details and references than can be cited here.

endogenous inhibitors of nitric oxide), with concomitant increased production of vasoconstrictors (mainly adrenergic stimulation and thromboxane A₂, but also activation of the renin-angiotensin system, antidiuretic hormone, and endothelins).¹³

Increased hepatic resistance to portal blood flow is the primary factor increasing portal pressure in cirrhosis (figure 1). It results from the combination of structural disturbances associated with advanced liver disease (accounting for about 70% of total hepatic vascular resistance) and of functional abnormalities leading to endothelial dysfunction and increased hepatic vascular tone; portal pressure could perhaps therefore be decreased by 30% if this functional abnormality were antagonised. The molecular mechanisms of these abnormalities are being delineated and represent new targets for therapy. Splanchnic vasodilation with an ensuing increase in the inflow of blood into the portal venous system contributes to aggravate the increase in portal pressure. Splanchnic vasodilation is an adaptive response to the changes in intrahepatic haemodynamics in cirrhosis; its mechanisms are directly opposite to those of the increased hepatic vascular tone. Because of this opposition, attempts to correct portal hypertension by acting on hepatic resistance or portal blood inflow should be ideally based on strategies acting as selectively as possible on the intrahepatic or the splanchnic circulation. In advanced cirrhosis, splanchnic vasodilation is so intense as to determine a hyperdynamic splanchnic and systemic circulation, which together with portal hypertension has a major role in the pathogenesis of ascites and hepatorenal syndrome. Systemic vasodilation further

causes pulmonary ventilation/perfusion mismatch that in severe cases leads to hepatopulmonary syndrome and arterial hypoxaemia. Portopulmonary hypertension is characterised by pulmonary vasoconstriction, which is thought to be due to endothelial dysfunction in the pulmonary circulation. Formation and increase in size of varices is driven by anatomical factors, increased portal pressure and collateral blood flow, and by angiogenesis dependent on vascular endothelial growth factor, all of which contribute to variceal bleeding. Dilation of gastric mucosal vessels leads to portal-hypertensive gastropathy. In addition, the shunting of portal blood to the systemic circulation through the portosystemic collaterals is a major determinant of hepatic encephalopathy, of decreased first-pass effect of orally administered drugs, and of decreased reticulo-endothelial system function. However, capillarisation of sinusoids and intrahepatic shunts are also important because these changes interfere with effective hepatocyte perfusion, which is a major determinant of liver failure.

Diagnosis

Most chronic liver disease is notoriously asymptomatic until cirrhosis with clinical decompensation occurs. Decompensating events include ascites, sepsis, variceal bleeding, encephalopathy, and non-obstructive jaundice. Imaging by ultrasonography, CT, or MRI of an irregular and nodular liver together with impaired liver synthetic function is sufficient for the diagnosis of cirrhosis. Other findings include small and shrunken liver, splenomegaly, and evidence of portosystemic collaterals. Differential diagnosis includes congenital hepatic

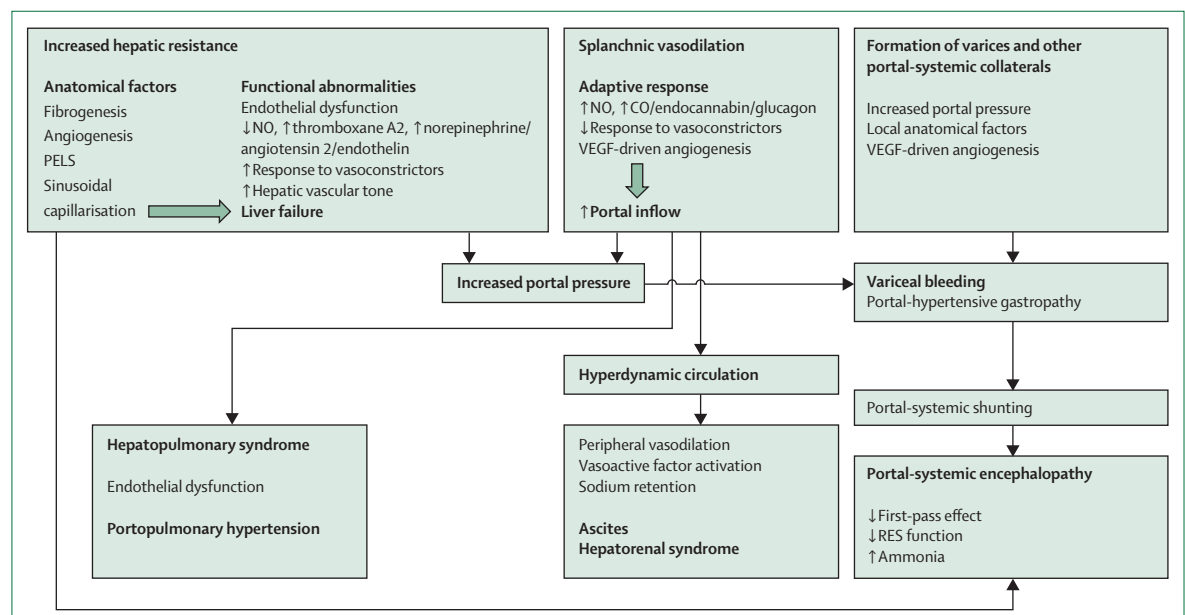


Figure 1: Pathophysiology of portal hypertension in cirrhosis

PELS=parenchymal extinction lesions. NO=nitric oxide. CO=carbon monoxide. VEGF=vascular endothelial growth factor. RES=reticuloendothelial system.

fibrosis (fibrosis without regenerative nodules), nodular regenerative hyperplasia (nodules but no fibrosis), and non-cirrhotic portal hypertension. A liver biopsy is seldom needed but study of a sample can provide a definitive diagnosis and confirm the aetiology in cases of uncertainty. The transjugular approach yields samples of equal quality to the percutaneous one, is safe, and adds additional prognostic information through measurement of hepatic-vein pressure gradient (HVPG).¹⁴

In early cirrhosis, however, conventional imaging can lead to false-negative diagnosis so other strategies are needed. Non-invasive markers of fibrosis are increasingly used; they are more informative at the extremes of the liver fibrosis range—ie, little or no fibrosis, and cirrhosis.¹⁵ They include indirect serum markers (simple, widely available indices), direct serum markers that measure biomarkers of fibrosis, and imaging modalities, such as transient elastography (table). These tests should be used and interpreted only once the aetiology is known.

Natural course

Cirrhosis should no longer be regarded as a terminal disease and the concept of a dynamic process is increasingly accepted. A prognostic clinical subclassification with four distinct stages has been proposed with substantially differing likelihoods of mortality: stage 1 (compensated with no oesophageal varices) has an estimated mortality of 1% per year, and stages 2 (compensated with varices), 3 (decompensated with ascites), and 4 (decompensated with gastrointestinal bleeding) have annual mortality rates of 3·4%, 20%, and 57%, respectively.³ Infections and renal failure have been considered as stage 5, with 67% 1-year mortality.^{16,17} Acute decompensating events that lead to organ failure have mortality of 30%;¹⁸ notably, mortality is higher in previously compensated patients than in those with previous decompensation, which suggests greater tolerance of the latter through the effects of the inflammatory response.¹⁸ Decompensating events are generally triggered by precipitating factors that include infection, portal-vein thrombosis, surgery, and hepatocellular carcinoma.

Components		Aetiology of liver disease	Comments
Imaging modalities			
Ultrasonography	Liver nodularity/signs of portal hypertension	All	Low sensitivity in initial stages of cirrhosis
CT/MRI	Liver nodularity/signs of portal hypertension	All	Low sensitivity in initial stages of cirrhosis
Fibroscan	Measurement of liver stiffness	All	Exact cutoffs for specific fibrosis stages and causes not established
Acoustic radiation force impulse imaging	Measurement of liver stiffness	All	Validation is still underway
MR elastography	Measurement of liver stiffness	All	Not widely available; further validation needed
Indirect serum non-invasive fibrosis tests			
APRI	AST, platelets	HBV, HCV	
FIB4	Age, ALT, AST, platelets	HBV, HCV, NAFLD	
AST/ALT	ALT, AST	All	
Forns index	Age, γ GT, cholesterol, platelets	HBV, HCV	
Proprietary serum non-invasive fibrosis tests			
Fibrotest	γ GT, haptoglobin, bilirubin, A1 apolipoprotein, α 2-macroglobulin	HBV, HCV, NAFLD, ALD	Biopredictive, France
ELF	PIIINP, hyaluronate, TIMP-1	HBV, HCV, NAFLD	Siemens, UK
Hepascore	Age, sex, α 2-macroglobulin, hyaluronate, bilirubin, γ GT	HCV, NAFLD	Pathwest, Australia
Fibrospect II	Hyaluronate, TIMP-1, α 2-macroglobulin	HCV	Prometheus, USA
Fibrometer	Platelets, prothrombin time, macroglobulin, AST, hyaluronate, age, urea	HBV, HCV, NAFLD, ALD	BioLiveScale, France
Combination strategies			
Ultrasonography and Fibroscan	As above	All	Done simultaneously
Fibrotest and Fibroscan	As above	HCV	Done simultaneously; liver biopsy if tests discordant on fibrosis classification
Fibrometer and Fibroscan	As above	HCV	Done simultaneously; results are introduced in a computer algorithm to assess severe fibrosis
APRI and Fibrotest	As above	HCV	Done sequentially; Fibrotest if indeterminate values of APRI

MR=magnetic resonance. APRI=AST-to-platelet ratio index. AST=aspartate aminotransferase. HBV=hepatitis B virus. HCV=hepatitis C virus. FIB4=fibrosis 4 index. ALT=alanine aminotransferase. NAFLD=non-alcoholic fatty liver disease. γ GT= γ glutamyltranspeptidase. ALD=alcoholic liver disease. PIIINP=N-terminal peptide of type III procollagen. TIMP-1=metalloproteinase inhibitor 1.

Table: Most commonly used non-invasive tests for diagnosis of cirrhosis¹⁵

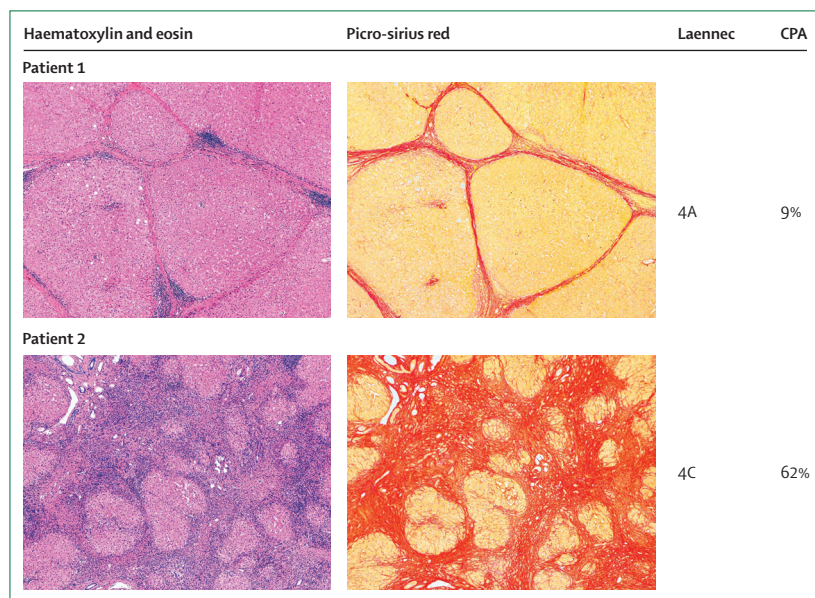


Figure 2: Histological methods of subclassifying cirrhosis

Laennec system (haematoxylin and eosin stain) and quantitative assessment of liver collagen with collagen proportionate area (CPA, picro-sirius red stain, collagen tissue stained red). Patient 1 is a 53-year-old man with chronic hepatitis C; the sample shows early cirrhosis. With haematoxylin and eosin stain, the cirrhotic nodules are large with thin internodular septum; the CPA is 9%. Patient 2 is a 53-year-old man with alcoholic liver disease; the sample shows advanced cirrhosis. Small cirrhotic nodules, thick internodular septum, and large quantity of fibrotic tissue with a CPA of 62% are seen. CPA=collagen proportionate area.

Further prognostication is important, especially for patients in the early asymptomatic phase. The traditional qualitative histological subclassification does not have a stage beyond cirrhosis so cannot be used to refine prognosis further. Semiquantitative histological subclassification based on nodule size and septal width is associated with both HVG and clinical outcomes.¹⁹ Subclassification based on quantitative fibrosis assessment with collagen proportionate area in liver tissue is also associated with HVG and clinical outcomes and is a promising approach (figure 2).²⁰ Non-invasive fibrosis markers, such as Fibroscan, Fibrotest, and ELF, are increasingly being used as prognostic markers.^{21,22} The predictive abilities of these methods should ideally be compared with those of semiquantitative or quantitative histological methods to subclassify cirrhosis.

For patients with more advanced disease, prognostic scores are widely used to predict survival and the need for transplantation. The MELD score is based on creatinine and bilirubin concentrations and international normalised ratio (INR); it predicts 3-month mortality. UKELD adds serum sodium concentration to the MELD components and predicts 1-year mortality. The Child-Pugh score is based on bilirubin and albumin concentrations, INR, and the presence and severity of ascites and encephalopathy.

Prevention and treatment of complications

The focus of this Seminar is on prevention and therapy in the initial stages of cirrhosis, including the first decompensating event.

Population screening

The increasing burden of liver disease and the problem of late presentation with decompensation emphasise the need for population screening to identify patients with chronic liver disease, similar to screening for cardiovascular risk factors. In the USA, screening for chronic hepatitis C is cost effective for people born between 1945 and 1965.²³ Non-invasive fibrosis markers could be screening tools in primary care, especially for non-alcoholic fatty liver disease and for alcohol misusers. The NAFLD fibrosis scores for non-alcoholic fatty liver disease is based on simple indices (age, platelet count, serum albumin, aminotransferases, and diabetes) and has a negative predictive value of 96% for advanced fibrosis.²⁴ Similarly, more complex blood tests have been used to class patients in the community into three prognostic groups to rationalise secondary referrals.²⁵ Transient elastography, now licensed in the USA, has also been used to classify patients,²⁶ although specific test cutoffs need to be established.²⁷

Lifestyle changes and general measures

Lifestyle changes tend to be overlooked in the management of cirrhosis, because life expectancy is judged to be short and the benefit is difficult to measure. Although evidence comes from cohort or case-control studies, lifestyle advice should still be offered to all patients, because it is easily implemented with little risk of side-effects or cost.

Insulin resistance, obesity, and the metabolic syndrome are pathophysiologically linked with non-alcoholic fatty liver disease, but they have deleterious effects irrespective of liver disease aetiology. Obesity is an independent predictor of cirrhosis in alcoholic liver disease,²⁸ and the presence of metabolic syndrome is associated with more severe fibrosis and cirrhosis in chronic liver disease.²⁹ In 161 patients with compensated cirrhosis who were followed up prospectively, obesity was independently associated with clinical decompensation, together with HVG and serum albumin.³⁰ Moreover, insulin resistance and metabolic syndrome were independently associated with liver-related mortality in a NHANES-III cohort of more than 2500 patients with chronic liver disease.³¹ Insulin resistance predicts the occurrence of hepatocellular carcinoma in cirrhosis,³² and in large cohorts, both diabetes³³ and metabolic syndrome³⁴ increased the risk of hepatocellular carcinoma. Overweight patients with compensated cirrhosis (clinical stages I and II) should therefore be advised to lose weight to lower their long-term risk of liver complications. In patients with decompensated cirrhosis, maintenance of adequate nutrition is important to avoid loss of muscle mass. Such patients have low tolerance to long-term fasting, with early onset of gluconeogenesis and subsequent muscle depletion, which can also contribute to development of hepatic encephalopathy. In a randomised controlled trial (RCT),³⁵ a nutritional supplement given

in the late evening over 12 months resulted in body protein accretion equivalent to 2 kg lean tissue; this approach should therefore be advised in such patients.

Alcohol intake is deleterious in patients with alcoholic cirrhosis but also in those with liver disease of other causes. In alcoholic cirrhosis, alcohol ingestion increases HVPG and portocollateral blood flow;³⁶ these effects are likely also in cirrhosis of other causes thereby increasing the risk of variceal bleeding. Only abstinence from alcohol improves survival in alcoholic cirrhosis.³⁷ In patients with chronic hepatitis C, alcohol intake increases the risk of cirrhosis and decompensated liver disease two to three times, even with moderate intake.³⁸ Moreover, alcohol intake is an independent risk factor for hepatocellular carcinoma in chronic hepatitis C³⁹ and non-alcoholic steatohepatitis.⁴⁰ Therefore, all patients with cirrhosis irrespective of clinical stage should be advised to abstain from alcohol with relevant counselling if appropriate. Multidisciplinary alcohol care teams can lower the risk of acute hospital admission and improve the quality of care.⁴¹ In many centres, abstinence irrespective of liver disease aetiology is mandatory for the patient to be considered for liver transplantation.

Vaccination against hepatitis A and B viruses, influenza virus, and pneumococcus should be offered as early as possible, because the antigenic response becomes weaker as cirrhosis progresses.⁴²

Cigarette smoking is associated with more severe fibrosis in chronic hepatitis C, non-alcoholic steatohepatitis, and primary biliary cirrhosis and possibly increases the risk of hepatocellular carcinoma in chronic hepatitis B.⁴³ Cannabis use worsens fibrosis in chronic hepatitis C.⁴⁴ Smoking cessation therefore should be advocated to prevent progression of liver disease and to facilitate eligibility for liver transplantation. Smoking also increases post-transplant morbidity and mortality.⁴⁵

Antioxidant-rich foods and drinks have a potential preventive role in cirrhosis. Coffee consumption improves all-cause mortality⁴⁶ but is also associated with a significant reduction in fibrosis in liver disease of various causes⁴⁷ and with reduced risk of hepatocellular carcinoma as shown in a meta-analysis including 2260 patients with hepatocellular carcinoma.⁴⁸ For most of the benefits described, at least two cups of coffee daily are needed. In a phase 2 RCT, ingestion of dark chocolate blunted the post-prandial HVPG increase in cirrhosis by improving flow-mediated hepatic vasorelaxation and ameliorated systemic hypotension.⁴⁹ The same effect on HVPG was noted with short-term administration of ascorbic acid.⁵⁰

Physicians should always bear in mind drug interactions and the possible need for dose reductions when prescribing for patients with cirrhosis.⁵¹

Cause-specific treatments

Patients with cirrhosis should be treated when possible for the underlying liver disease to stop disease progression; such treatment includes immunosuppression for auto-

immune hepatitis, venesection for haemochromatosis, and copper chelators or zinc for Wilson's disease.

Patients with viral hepatitis should be assessed for antiviral treatment. All patients with cirrhosis who are positive for HBsAg should receive oral antiviral therapy with a potent antiviral (entecavir or tenofovir) irrespective of viral load.⁵² Oral antiviral therapy reduces HVPG⁵³ and delays clinical progression to decompensation in responders.⁵⁴ Treatment with tenofovir for 5 years resulted in regression of cirrhosis associated with hepatitis B virus in 71 (74%) of 96 treated patients.⁵ In patients with hepatitis-C-related cirrhosis without ascites, achievement of sustained virological response significantly reduced liver-related morbidity and mortality.⁶ In a subgroup of patients, there was also regression of cirrhosis.⁶ This strategy is also valid for patients with hepatitis C listed for liver transplantation because of hepatocellular carcinoma rather than complications of portal hypertension, because achievement of sustained virological response reduces post-transplant recurrence of hepatitis C, which is otherwise universal.⁵⁵ The newly licensed direct-acting antiviral drugs boceprevir and telaprevir increase rates of sustained virological response in patients with genotype 1.^{56,57} Supplementary strategies that can increase sustained response rates in this difficult-to-treat group of patients, as shown in cohort studies, include weight loss in obese patients,⁵⁸ vitamin D supplementation when concentrations are low,⁵⁹ statins in patients with diabetes,⁶⁰ and coffee drinking.⁶¹ Patients with cirrhosis who respond to antiviral treatment still need regular surveillance for hepatocellular carcinoma, because the risk, although reduced, is not eliminated.^{6,62}

Portal hypertension, varices, and variceal bleeding

Portal hypertension, rather than hepatocyte failure per se, is the underlying cause of most of the complications of cirrhosis and subsequent mortality. HVPG is a good surrogate marker of portal hypertension and has robust prognostic power.⁶³ Portal hypertension is present when the HVPG is more than 5 mm Hg. However, clinically significant portal hypertension and the threshold for development of oesophageal varices is above 10 mm Hg.⁶⁴ Patients with HVPG of less than 10 mm Hg had a 90% probability of not progressing to decompensation during median follow-up of 4 years,⁶⁵ whereas for those with HVPG of more than 10 mm Hg the incidence of hepatocellular carcinoma was six times higher than in patients with lower HVPG.⁶⁶

Formation of oesophageal varices is the first clinically relevant consequence of portal hypertension and represents clinical stage 2 of cirrhosis. Current recommendations are that all patients with cirrhosis should be screened for varices.⁶⁷ The risk of development and growth of varices is 7% per year,⁶⁸ and that of first variceal bleeding is 12% per year.⁶⁹ Pre-primary, primary, and secondary prophylaxis strategies to prevent variceal

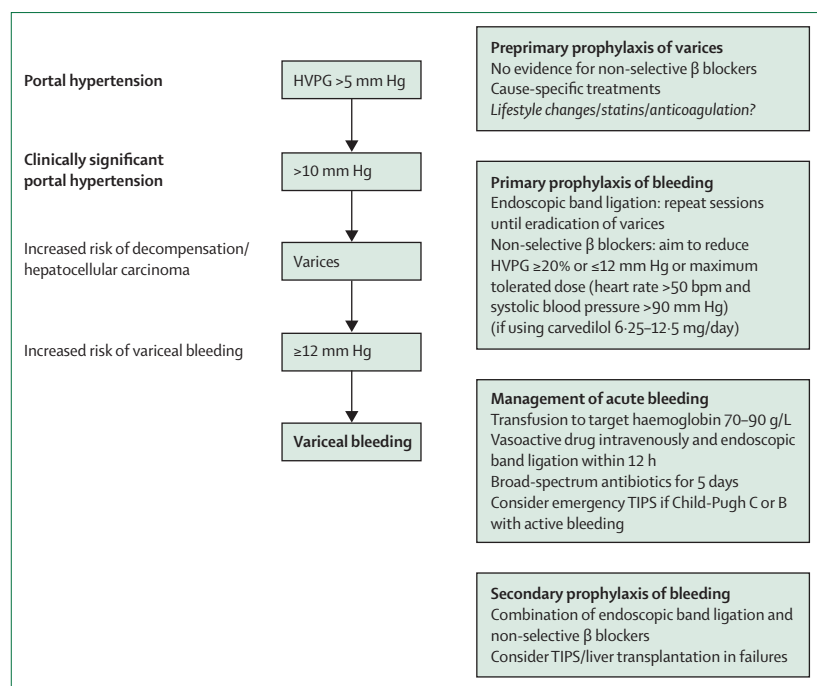


Figure 3: Prevention and treatment of portal hypertension and varices at various degrees of severity
HVPG=hepatic-vein pressure gradient. BPM=beats per minute. TIPS=transjugular intrahepatic portosystemic shunts.

bleeding are available. Treatment options include non-selective β blockers for varices, irrespective of size, or endoscopic band ligation for medium or large varices. A placebo-controlled RCT of timolol for preprimary prevention of varices formation did not show significant benefit.⁶⁴ The study was powered to detect a 20% reduction in varices formation after median follow-up of 4 years, so smaller benefits cannot be excluded, especially since the formation of varices was significantly lower in patients achieving a reduction in HVPG than in those who did not.

Primary prophylaxis of variceal bleeding should be offered to all patients with varices, especially those that are large or have red signs.⁶⁷ Non-selective β blockers and endoscopic band ligation are equally effective in prevention of bleeding and reduction of mortality, as shown in a meta-analysis that included only high-quality trials.⁷⁰ Results from a large meta-analysis of non-selective β blockers versus placebo showed that the number of patients needed to treat with non-selective β blockers to prevent one death is 16.⁷¹ Non-selective β blockers decrease cardiac output and cause splanchnic vasoconstriction thereby reducing portal inflow, as well as decreasing azygous vein blood flow and variceal pressure, which is more pronounced than the reduced portal inflow.⁷² They can also reduce total effective vascular compliance.⁷³ Carvedilol is a β blocker with vasodilating properties resulting from α_1 -blockade; it decreases intrahepatic vascular resistance, which leads to a greater fall in HVPG than with conventional non-selective

β blockers.⁷⁴ In one RCT, carvedilol was more effective than endoscopic band ligation for primary prophylaxis of bleeding.⁷⁵ A decrease in HVPG of at least 20% or to less than 12 mm Hg is associated with a significant reduction in variceal rebleeding compared with patients in whom these changes are not achieved, and defines patients receiving non-selective β blockers as responders.⁷⁶ Measurement of acute haemodynamic response to propranolol could be a substitute for repeated HVPG measurements, because it predicts the risk of first bleeding,⁷⁷ with HVPG reduction cutoffs of 10%⁷⁷ and 12%⁷⁸ in prospective and retrospective studies, respectively. HVPG is not measured routinely, so non-selective β blockers are generally titrated to the maximum tolerated dose, aiming at a heart rate of below 60 bpm.⁶⁹ Side-effects of fatigue, hypotension, and shortness of breath preclude their use in 15–20% of patients; however, specialised nurse-led clinics help to minimise withdrawal and enable successful dose titration.⁷⁹ Carvedilol is titrated against blood pressure and heart rate up to doses of 25 mg/day, because no greater reduction in HVPG is achieved with higher doses.⁷⁴

Endoscopic band ligation consists of placing rubber elastic bands on medium or large varices; it is repeated until the lesions are eradicated. We advocate use of non-selective β blockers as primary prophylaxis, because they are cheap and effective and obviate the need for the expertise that endoscopic band ligation requires.⁸⁰ Moreover, non-selective β blockers also prevent bleeding from portal-hypertensive gastropathy and have other beneficial effects. Endoscopic band ligation has a small iatrogenic risk of death, owing to bleeding from post-banding ulcers.⁸⁰

In one RCT,⁸¹ simvastatin lowered HVPG and improved liver haemodynamics in patients with cirrhosis and varices, and this effect was additive to that of non-selective β blockers. Since statins also significantly reduce the incidence of hepatocellular carcinoma among patients with diabetes⁸² and are not associated with an increased risk of hepatotoxicity in cirrhosis,⁸³ these drugs could be given to patients with cirrhosis and hyperlipidaemia. Trials in non-hyperlipidaemic patients are in progress.

Patients with acute variceal bleeding need a combination of intravenous vasoactive drugs to reduce portal pressure (terlipressin, somatostatin, or octreotide for 2–5 days) and endoscopic therapy, preferably endoscopic band ligation, within 12 h of bleeding.⁸⁴ They should also receive a 5-day course of antibiotics, because infection is pathophysiologically linked with variceal bleeding⁸⁵ and antibiotics reduce early re-bleeding and mortality.⁸⁶ In one RCT,⁸⁷ a transfusion strategy aiming at haemoglobin concentrations of 70–90 g/L was associated with better survival in cirrhosis of Child class A or B than was a more liberal strategy. Transjugular intrahepatic portosystemic shunts are indicated for refractory bleeding despite endoscopic treatment. However, one RCT⁸⁸ showed that in advanced cirrhosis with variceal bleeding (Child-Pugh C,

or B patients with active bleeding at diagnostic endoscopy), early insertion of shunts within the first 72 h resulted in significantly lower risks of rebleeding and mortality. If those results are confirmed, access to emergency transjugular intrahepatic portosystemic shunting will need to be reorganised, because it is available only in specialised centres.

Patients who have already experienced a variceal bleed need a combination of endoscopic band ligation and non-selective β blockers, because this strategy significantly reduces the risk of rebleeding, although it does not affect the risk of mortality compared with either treatment alone.⁸⁹ Figure 3 summarises this information.

Portopulmonary hypertension and hepatopulmonary syndrome are rare syndromes that are pathogenetically linked to the presence of portal hypertension: the former is characterised by abnormal pulmonary vasoconstriction and obliterative vascular remodelling and the latter by abnormal pulmonary vascular dilation.^{1,2}

Ascites

In cirrhosis, portal hypertension and splanchnic vasodilation, resulting mainly from increased production of nitric oxide,⁹⁰ is the main pathophysiological mechanism of ascites (figure 4). The effective blood volume is initially maintained as a result of a compensatory increase in cardiac output. However, as cirrhosis progresses, this mechanism is not sufficient and homeostatic activation of vasoconstrictor and antinatriuretic factors develops, with subsequent water and salt retention.⁹¹ Finally, the retained fluid accumulates in the peritoneal cavity as a result of increased portal pressure. The development of renal vasoconstriction leads to the hepatorenal syndrome. Type 1 hepatorenal syndrome is characterised by a doubling of serum creatinine concentrations within 2 weeks, whereas type 2 has a stable, less progressive course. The development of ascites is associated with a 1-year mortality rate of 20%.³ Renal failure is an index of end-stage liver disease and increases the risk of mortality by seven times, with 50% of patients dying within a month.⁷

Reduction of the HVPg should prevent formation of ascites. In 83 patients with large varices followed up for a mean of 53 months, propranolol prevented ascites if it lowered the HVPg by 10% or more.⁹²

In patients with a new presentation of ascites, a diagnostic tap should be used to screen for underlying infection.⁹³ When no underlying cirrhosis is evident, a gradient between serum and ascites fluid in albumin concentration of 11 g/L or more is very accurate for diagnosis of portal hypertension.⁹¹ Initial management consists of education of the patient about limiting dietary sodium to 80–120 mmoles daily (4.0–6.9 g/day) and oral diuretic treatment. Diuretic therapy should start with a morning dose of spironolactone 100 mg with or without furosemide 40 mg. An RCT showed that combined therapy is associated with better responses than sequential

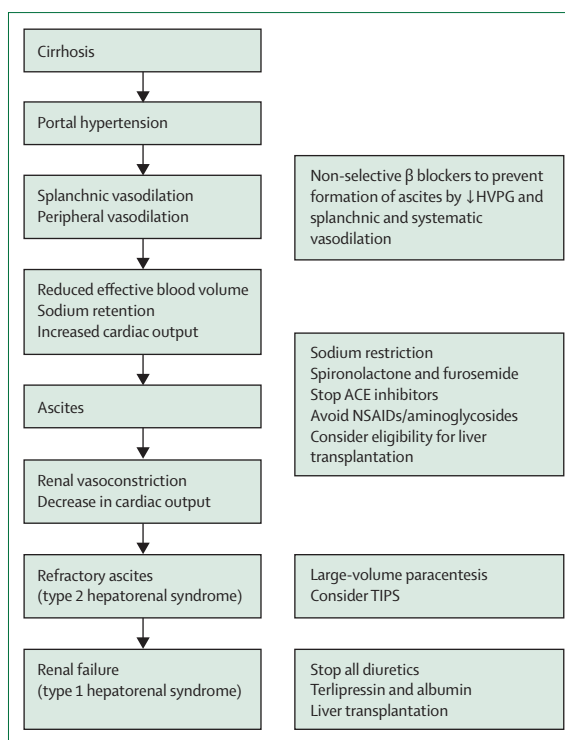


Figure 4: Prevention and treatment of ascites at various degrees of severity. HVPg=hepatic-vein pressure gradient. ACE=angiotensin-converting enzyme. NSAIDs=non-steroidal anti-inflammatory drugs. TIPS=transjugular intrahepatic portosystemic shunt.

therapy.⁹⁴ Current European guidelines advocate sequential treatment for first presentation of ascites and combination therapy from presentation for recurrent ascites.⁹⁵ Renal function and serum electrolyte concentrations should be monitored during diuretic treatment, particularly when doses are being gradually increased to achieve adequate weight loss, which should not exceed 1 kg per day in patients with peripheral oedema or 0.5 kg per day in those without. Maximum doses of 400 mg spironolactone and 160 mg furosemide are suggested, but few patients tolerate these doses without developing renal dysfunction. Random measurement of urinary sodium concentration is useful to monitor adherence to low-salt diet and response to diuretics.⁹¹ Ascites that does not respond to maximum tolerated diuretic doses is termed refractory.⁹¹ Midodrine together with standard medical treatment was superior to standard treatment alone in an RCT investigating recurrent or refractory ascites; it also improved systemic haemodynamics.⁹⁶ Refractory or difficult-to-control ascites necessitates an assessment for liver transplantation. Such patients should be treated by large-volume paracentesis with intravenous albumin administration (8 g/L) when the volume drained exceeds 5 L, to reduce the risk of post-paracentesis circulatory syndrome.⁹⁷

An alternative approach that significantly improves transplant-free survival is a transjugular intrahepatic

portosystemic shunt for patients with refractory ascites and preserved synthetic function.⁹⁸ A combination of serum bilirubin concentration below 50 $\mu\text{mol/L}$ and a platelet count above $75 \times 10^9/\text{L}$ was predictive of survival in 105 patients with refractory ascites treated in this way.⁹⁹

Non-steroidal anti-inflammatory drugs should not be given to patients with ascites, because their renal function is highly dependent on renal prostaglandin synthesis and renal failure can be induced.⁹⁵ Similarly, although inhibitors of angiotensin-converting enzyme reduce portal pressure and can potentiate or substitute for non-selective β blockers in patients with varices and no ascites,¹⁰⁰ they should be stopped if ascites develops.¹⁰¹ Aminoglycosides are associated with a high incidence of nephrotoxicity so other antibiotics should be used if possible.⁹⁵ A single retrospective study reported reduced survival in patients with refractory ascites who received propranolol, attributed to paracentesis-induced circulatory dysfunction.¹⁰² However, the doses used were large and rarely administered in routine clinical practice, so decisions should be made on an individual basis with close monitoring.¹⁰³

Infection

Infection increases mortality in cirrhosis four times and has a poor prognosis, with 30% of patients dying within a month of infection and another 30% within a year.¹⁶ Most frequently diagnosed are spontaneous bacterial peritonitis, urinary-tract infections, pneumonia, and skin infections; the incidence increases with worsening liver function.^{93,104} Decreased bowel motility, bacterial overgrowth, and increased intestinal permeability all increase the risk of the translocation of intestinal microbiota to the mesenteric lymph nodes,¹⁰⁵ which predisposes patients to infection, most commonly spontaneous bacterial peritonitis, but is also the source of endotoxin and other bacterial products that influence systemic haemodynamics.¹⁰⁶ Certain genetic polymorphisms also predispose to spontaneous bacterial peritonitis and indicate patients at increased risk.¹⁰⁷ Bacterial DNA in non-infected patients with cirrhosis is associated with aggravation of peripheral vasodilation and worsening of intrahepatic endothelial dysfunction;¹⁰⁸ it is also associated with poor prognosis.¹⁰⁹ Defects in Kupffer cells and neutrophil function¹¹⁰ and an exaggerated proinflammatory response of mononuclear cells¹¹¹ are commonly present and predispose to a poor outcome.

A meta-analysis showed that non-selective β blockers reduced the incidence of spontaneous bacterial peritonitis in patients with ascites, probably by increasing bowel motility and thus decreasing bacterial translocation.¹¹² Intestinal permeability also improved and this effect is partly independent of the haemodynamic response.¹¹³ Indeed, in a rat model of cirrhosis, splanchnic sympathectomy reduced bacterial translocation.¹¹⁴ An RCT showed that selective intestinal

decontamination with oral norfloxacin for 2 weeks partly reverses the hyperdynamic circulation of cirrhosis, without influencing the hepatic and renal circulation.¹¹⁵ Primary prophylaxis of spontaneous bacterial peritonitis with norfloxacin improves survival in patients with advanced cirrhosis or impaired renal function and low ascites protein concentrations ($<15 \text{ g/L}$).¹¹⁶ Since the risk of infections with quinolone-resistant bacteria is high, we advocate primary prophylaxis only in patients listed for liver transplantation, because the period of administration is short and patients can be maintained in better condition. By contrast, secondary prevention with oral quinolones should be offered to all patients with a previous episode of spontaneous bacterial peritonitis.⁹¹ No best strategy for prevention, if spontaneous bacterial peritonitis with quinolone-resistant organisms develops, has been established; available options include no prophylaxis or a rolling scheme of antibiotics.

Spontaneous bacterial peritonitis is diagnosed if ascitic neutrophil count is more than 250 per μL and can be asymptomatic.⁹⁵ Treatment consists of intravenous antibiotics and human albumin. The choice of antibiotics is influenced by previous quinolone prophylaxis, local prevalence of bacterial strains, and whether the infection was acquired in the community or in hospital. A 5-day course of intravenous cefotaxime is generally sufficient in most community-acquired cases.¹¹⁷ An RCT showed that intravenous albumin (1.5 g/kg on day 1 and 1.0 g/kg on day 3) lowers the risk of renal impairment and death from 30% to 10%.¹¹⁸ This effect is possibly limited if bilirubin concentration is more than $68.4 \mu\text{mol/L}$ or creatinine more than $88.4 \mu\text{mol/L}$.¹¹⁹ In an RCT of 110 patients with infections that excluded spontaneous bacterial peritonitis, albumin also showed beneficial effects on renal and circulatory function, but not on survival.¹²⁰ Proton-pump inhibitors should be used sparingly in cirrhosis with ascites, because the risk of spontaneous bacterial peritonitis is 4.3 times higher than without such treatment,¹²¹ and should be avoided in inpatients (except for those with peptic ulcer bleeding), because the risk of infection with *Clostridium difficile* is increased.¹²²

Encephalopathy

The development of encephalopathy is an ominous sign in cirrhosis, because the associated 1-year mortality rate is up to 64%.¹²³ Patients who develop encephalopathy despite preserved liver function should be screened for the presence of spontaneous portosystemic shunts. Embolisation of large shunts is safe and effective in selected patients.¹²⁴ Overt encephalopathy is generally transient and linked with a precipitating event, such as use of sedatives, constipation, dehydration, infection, or gastrointestinal bleeding. Lactulose is the first-choice drug for prevention of recurrent encephalopathy; in an RCT, the risk of recurrent encephalopathy was 20% compared with 47% in placebo-treated pat-

ients.¹²⁵ L-ornithine-l-aspartate is equivalent to lactulose as a first-line treatment.¹²⁶ Rifaximin, a non-absorbable antibiotic, is effective when added to lactulose if encephalopathy recurs; it reduces the risk of further recurrence from 46% to 21%.¹²⁷

Subclinical encephalopathy or minimal hepatic encephalopathy is more common than overt encephalopathy, and influences complex cognitive or coordination skills such as driving, leading to increased risks of accidents.¹²⁸ A cost-effectiveness analysis concluded that patients with cirrhosis who drive should be screened for minimal hepatic encephalopathy, and treated with lactulose if necessary.¹²⁹ Rifaximin significantly improved driving simulation skills in an RCT of 42 patients with the disorder,¹²⁸ but it is not currently cost effective.¹²⁹ Minimal hepatic encephalopathy is significantly associated with risk of falling.¹³⁰

Hepatocellular carcinoma

Guidelines recommend 6-monthly ultrasonographic screening, because it results in more effective treatment of smaller hepatocellular carcinomas, although this approach has been inadequately assessed by RCT investigations. However, routine surveillance occurred in only 12% of a US cohort of 13 002 patients with cirrhosis.¹³¹ The carcinoma can develop in all stages of cirrhosis, of all causes.³⁹

Liver transplantation

Liver transplantation is a therapeutic option in patients who develop decompensation or hepatocellular carcinoma with cirrhosis. Listing, prioritisation, and organ allocation are decided on the basis of scores for reasons of equity, owing to the shortage of donor organs. The indications and contraindications for transplantation are given in the panel. The most commonly used scores are MELD in the USA and UKELD in the UK.

Future therapies

Currently licensed drugs, such as non-selective β blockers, statins, oral antibiotics, and anticoagulants are likely to be used in various combinations to prevent and treat complications of cirrhosis in the near future.^{42,132} Statins reduce HVPg and are associated with reduced incidence of hepatocellular carcinoma. Anticoagulation used to be considered a contraindication in cirrhosis; however, stable cirrhosis is characterised by normal thrombin generation and even hypercoagulability.¹³³ Currently, anticoagulation is considered only in patients with portal-vein thrombosis awaiting liver transplantation.¹³⁴ However, an RCT of enoxaparin in 70 patients with advanced cirrhosis showed that the drug was associated not only with lower risk of portal-vein thrombosis, but also with delayed decompensation and improved survival.¹³⁵ Confirmatory trials are needed before these findings can be translated into clinical practice. A surgically implanted pump transferring ascites to the bladder has been tested for

refractory ascites, but RCT evidence and safety data are needed.¹³⁶ Rifaximin is a potential alternative for prevention of spontaneous bacterial peritonitis since no bacterial resistance has been documented, and in observational studies HVPg and plasma endotoxin concentrations were lower with this treatment;¹³⁷ systemic haemodynamics and renal function also improved,¹³⁸ but these findings need confirmation. Metformin was independently associated with reduced incidence of hepatocellular carcinoma in a prospective cohort study of patients with hepatitis-C-related cirrhosis¹³⁹ and in a case-control study of 97 430 hepatocellular carcinoma patients,¹⁴⁰ the latter in a dose-dependent manner; this drug could have preventive properties in stage 1 or 2 cirrhosis.

Panel: Indications and contraindications for liver transplantation in patients with cirrhosis

Indications

Cirrhosis with decompensation

Generally for patients with clinical stage 3 and above—ie, at least with ascites as assessed by disease-severity scores; intractable pruritus, recurrent cholangitis, and hepatopulmonary syndrome are potential exceptions of listing on the basis of such scores.

Hepatocellular carcinoma with background cirrhosis

Most centres use the Milan criteria for listing—one lesion ≤ 5 cm or no more than three lesions ≤ 3 cm each with no macrovascular invasion and no extrahepatic disease.

Contraindications

Active illicit substance misuse

Patients on drug substitution such as methadone are not generally excluded.

AIDS

Controlled HIV infection alone is not a contraindication. HIV and hepatitis C virus co-infection is a contraindication in some centres.

Extrahepatic malignancy

Neuroendocrine tumours and haemangioendotheliomas are a possible exception in selected cases.

Uncontrolled sepsis

Transplantation contraindicated until infection is successfully treated.

Extrahepatic organ failure (lungs, heart)

Echocardiography and if needed catheterisation are essential in liver transplant work-up; pulmonary pressure of >50 mm Hg despite medical treatment is an absolute contraindication.

Extensive splanchnic thrombosis extending to the superior mesenteric vein

Technical contraindication.

Indications are limited to patients with established cirrhosis, therefore this list should not be regarded as exhaustive; see also Schuppan and colleagues (2008)¹ and Dooley and colleagues (2011).²

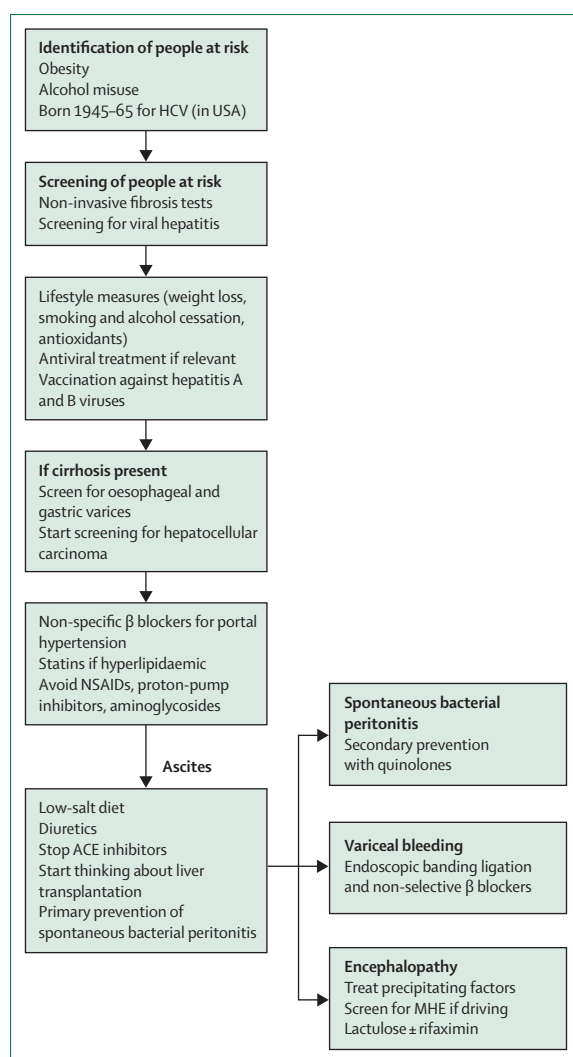


Figure 5: Roadmap for preventing and treating complications in early cirrhosis
HCV=hepatitis C virus. ACE=angiotensin-converting enzyme. NSAIDs=non-steroidal anti-inflammatory drugs. MHE=minimal hepatic encephalopathy.

Conclusions—future directions

Cirrhosis should no longer be considered as a single disease stage, because it has distinct clinical prognostic stages with substantial differences in 1-year survival.⁷ Preventive and therapeutic strategies are summarised in figure 5. Clinicians should try to diagnose advanced liver disease as early as possible and to prevent the progression to further clinical stages and the advent of complications. We have previously reviewed the potential expansion of current indications of widely used drugs for preventing such complications.⁴² A combination of propranolol, simvastatin, norfloxacin, and warfarin for a year would cost £128 per patient (US\$200).¹³² Strategies for population screening need to be tested aiming at early diagnosis of advanced fibrosis or high risk of progression. General lifestyle measures including alcohol and smoking cessation and weight loss should be advised, and every

contact with health providers should be exploited for health education. Diagnosis before decompensation and implementation of these measures, as well as specific treatments when applicable, are important steps towards reducing the mortality of end-stage liver disease. All patients with decompensation should be closely monitored and followed up, because they might become candidates for liver transplantation depending on the course of their liver disease. The challenge in the 21st century is to prevent the need for liver transplantation in as many patients with cirrhosis as possible.

Contributors

All authors conceptualised the Seminar, drafted parts of the paper, revised the paper for important intellectual content, and approved final submission.

Conflicts of interest

We declare that we have no conflicts of interest.

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