

A Review on Medication and Management of Liver Cirrhosis

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Abstract

Cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, which leads to portal hypertension and end stage liver diseases. Recent advances in the understanding of the natural history and pathophysiology of cirrhosis, and in treatment of its complications, have resulted in improved management, quality of life and life expectancy of patients. Liver transplantation remains the only curative options for selected group of patients, but pharmacological treatments that can halt progression to decomposed cirrhosis or even reverse cirrhosis are currently being developed. This review focuses on the history, causes, sign & symptoms, diagnosis, complications, and management of cirrhosis and new clinical and scientific developments.

Keywords: - *Liver Cirrhosis, Pathogenesis, Cytokine, Fibrosis, Etiology, HVPG, Endoscopy.*

INTRODUCTION

Liver cirrhosis is an important and growing global health problem. Which is the 14th most common cause of death all over the world? Liver fibrosis results from chronic damage to the liver in conjunction with the accumulation of extracellular cell matrix (ECM) proteins, which is a characteristic of most types of chronic

liver diseases. Alcohol abuse, hepatitis viral infections, genetic abnormalities, steatohepatitis, autoimmunity and other noninfectious diseases like fatty liver contribute to liver fibrosis. The major causes of chronic liver diseases are given in Figure 1.

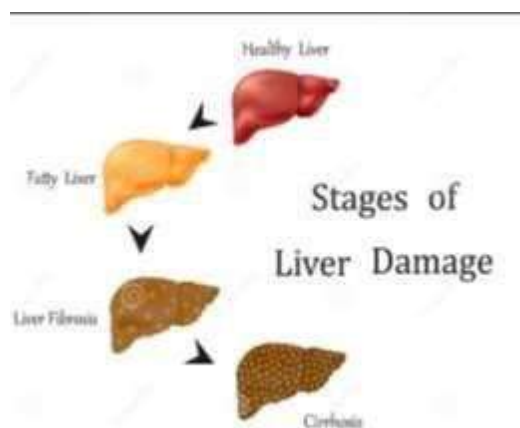


Figure: 1

The accumulation of ECM proteins distorts the hepatic architecture by forming a fibrous scar, and the subsequent development of nodules of regenerating hepatocytes defines cirrhosis, i.e., the so-called advanced liver fibrosis. Cirrhosis produces hepatocellular dysfunction, hepatocellular carcinoma (HCC) and hepatic failure. Fibrosis is a result of excessive accumulation of scar tissue resulting from the inflammation of liver cells. Abnormal spherical areas of cells called nodules form dying liver cells, which will be replaced by regenerating cells. As a result of a series of events resulting in hepatocyte damage, the retainment of inflammatory cells in the injured liver and the activation of collagen producing cells contribute to the liver in becoming hard, finally leading to liver fibrosis. It is characterized by the excessive deposition of ECM proteins, especially collagen type 1, and it is mainly

contributed by hepatic stellate cells (HSCs).^{1–3} Conventional therapy is not effective for the treatment.

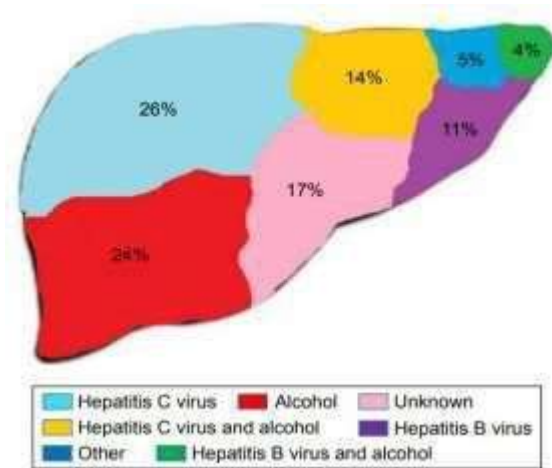


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HISTORY

1. Background

Liver transplantation significantly improves the survival and quality of life of patients with end-stage cirrhosis. However, a large proportion of cirrhotic patients still die while on the transplant list because of an insufficient number of donors and because of the lack of an accurate prediction of life expectancy. Although many prognostic models have been proposed in the last two decades to predict mortality in cirrhosis, the Child–Pugh score is by far the most largely used both in clinical practice and in clinical research. Recently, the model for end stage liver disease (MELD) has replaced the Child–Pugh score in the United States for prioritizing liver donor allocation.

MELD is considered more reproducible than the Child–Pugh score because it does not include subjective variables such as ascites and encephalopathy. However, obtaining the score requires computing and it is, therefore, much less practical than the Child–Pugh score for individual estimates at the bedside. Moreover, the MELD score has not been proven to be superior to the Child–Pugh score in terms of predictive accuracy, and both may be unsatisfactory when applied separately to compensated and decompensated patients. It is in fact well known that life expectancies in compensated and decompensated cirrhosis are strikingly different and it is, therefore, conceivable that prognostic indicators may be different or may have a different weight according to the disease stage.

2. Natural history of cirrhosis

Cirrhosis is the end-stage of every chronic liver disease. Its natural history is characterized by an asymptomatic phase, termed ‘compensated’ cirrhosis followed by a rapidly progressive phase marked by the development of complications of portal hypertension and/or liver dysfunction, termed ‘decompensated cirrhosis’ (Fig. 5). In the compensated phase, portal pressure may be normal or below the threshold level identified for the development of varices or ascites (clinically significant portal

hypertension’). As the disease progresses, portal pressure increases and liver function decreases, resulting in the development of ascites, portal hypertensive gastrointestinal (GI) bleeding, encephalopathy and jaundice. The development of any of these complications marks the transition from a compensated to a decompensated phase. Progression may be accelerated by the development of other complications such as (re)bleeding, renal impairment (refractory ascites, hepatorenal syndrome), hepatopulmonary syndrome and sepsis (spontaneous bacterial peritonitis). The development of hepatocellular carcinoma (HCC) may accelerate the course of the disease at any stage. Classification of cirrhosis into a compensated and a decompensated stage is simple and reproducible and identifies patients at a similar rate of disease progression and survival. Decompensated cirrhosis is defined by the presence of ascites, variceal bleeding, encephalopathy and/or jaundice. Moreover, since ascites is most frequently the first of these signs to appear, it is usually considered a landmark sign of decompensated cirrhosis. Transition from a compensated to a decompensated stage occurs at a rate of 5–7% per year (Fig. 6). Survival of patients with compensated cirrhosis is significantly longer than that of decompensated patients with median

survival times of 0.12 years and 0.2 years, respectively (Fig. 5A).

Patients with compensated cirrhosis die mostly after transition to a decompensated stage. Survival while the patient remains in the compensated stage is calculated by censoring data at the first manifestation of decompensation and, as shown in Fig. 3B, is markedly higher than the probability of survival of a given clinical stage at a given point along the course of the disease, e.g. at diagnosis (Fig. 3A). By combining data from two large natural history studies including 1649 patients [8,10], four clinical stages or status of cirrhosis can be identified, each with distinct clinical features and a markedly different prognosis (Fig. 4). Each stage is defined by the presence or absence of complications of cirrhosis and was agreed upon in the recent Baveno IV consensus conference.

Stage 1 is characterized by the absence of esophageal varices and of ascites. While patients remain in this status, the mortality rate is as low as 1% per year. Patients exit this status at a cumulative rate of 11.4% per year: 7% because of the development of varices and 4.4% because of the development of ascites (with or without varices). Stage 2 is characterized by the presence of esophageal varices without ascites and without bleeding. While patients remain in this status, the mortality rate is 3.4% per year. Patients leave this status by developing ascites (6.6% per year) or by developing variceal bleeding before or at the time of development of ascites (rate 4% per year). Stage 3 is characterized by ascites with or without esophageal varices in a patient that has never bled. While patients remain in this status, the mortality rate is 20% per year, significantly higher than in the two former states. Patients exit this stage by bleeding (7.6% per year).

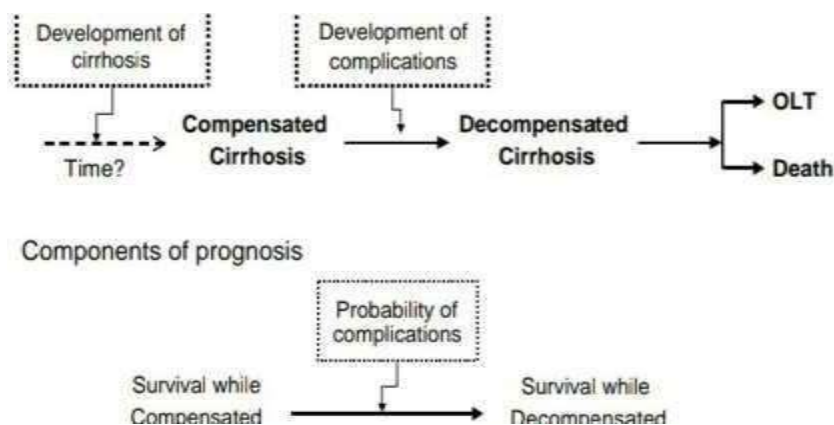


Fig. 3. The natural history of cirrhosis and components of prognosis. A simplified view.

Stage 4 is characterized by GI bleeding with or without ascites. In this stage the one-year mortality rate is 57% (nearly half of these deaths occur within 6 weeks from the initial episode of bleeding). Stages 1 and 2 correspond to patients with compensated cirrhosis while stages 3 and 4 refer to decompensated cirrhosis. HCC develops at a fairly constant rate of 3% per year and is associated with a worse outcome at whatever status it develops. In the aforementioned consensus conference on portal hypertension it was suggested that this status classification should be adopted in future prognostic studies of cirrhosis and in randomized controlled trials.

Predictors of mortality: a systematic review

(A) Methods- All prognostic studies of cirrhosis were considered eligible for this

review if they fulfill the following Criteria: (a) publication in the English language; (b) inclusion of adult patients with cirrhosis; (c) survival analysis was reported; d) follow-up ≥ 6 months, and (e) multivariable analysis of prognostic indicators of death risk was performed.

Exclusion criteria were: (a) studies that included both cirrhotic and non-cirrhotic patients; (b) studies assessing only short term mortality (≤ 6 months); (c) studies evaluating specific therapies (randomized controlled trials, prospective studies of post-therapeutic course, etc.) or prognosis after procedures (e.g. surgical shunts, transjugular intrahepatic portosystemic shunt), (d) studies including only patients with primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), metabolic or genetic liver diseases.

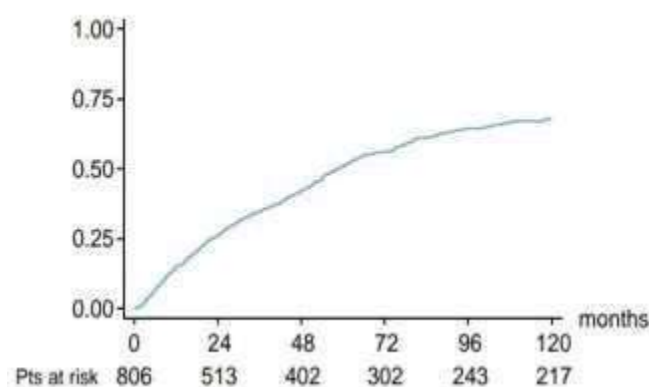


Fig. 4: Cumulative proportion of patients transitioning from a compensated to decompensated stage. Individual patient data from two prospective of the natural history of cirrhosis.

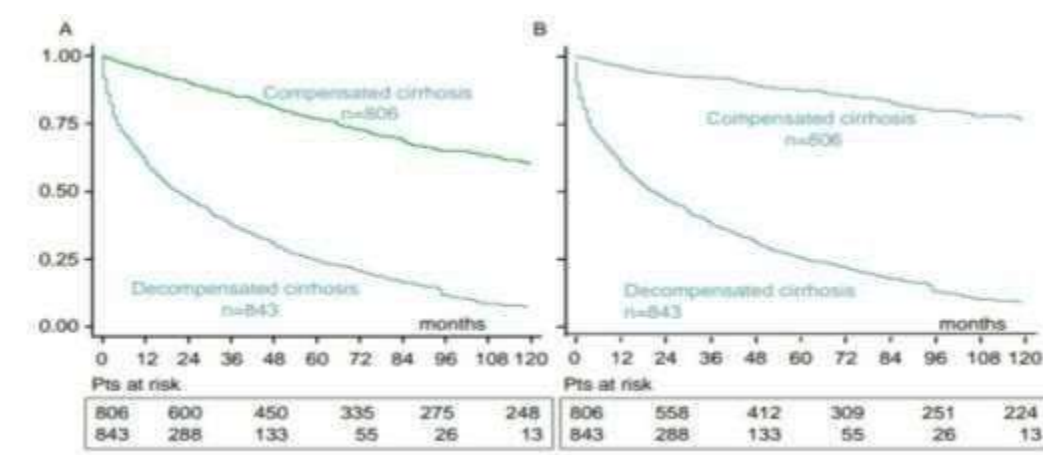


Fig. 5. Survival according to decomposition at diagnosis (A) and while remaining in the compensated or decompensated stages (B). Individual Patient data from two prospective studies of the natural history of cirrhosis.

The following data were extracted by two independent observers, based on pre-defined criteria: (a) aim of the study, explanatory (i.e. assessing the prognostic value of a specific variable according to a biologically plausible hypothesis) or predictive (assessing many variables without a primary concern for understanding the primary mechanism involved in their prognostic value); (b) design (prospective or retrospective); (c) inception cohort, i.e. whether patients entered the study at a well-defined stage; (d) characteristics of included patients; (e) sample size and follow-up; (f) survival analysis and causes of death; (g) analysis of prognostic factors; (h) study validation. The quality of the included studies was assessed according to widely accepted quality criteria for prognostic studies (marked with an asterisk in Table 1). The

following five major quality criteria were used to select 'good' quality studies: (a) inclusion of consecutive patients; (b) relevant baseline patient characteristics were reported (age, gender, etiology of cirrhosis and Child class or components or MELD score); (c) length of follow-up was reported; (d) important variables with a previously established prognostic influence on survival were included in the analysis; (e) number of deaths were reported. Inclusion of patients as an inception cohort was dismissed as a quality criterion because it was reported in only 17 studies. In order to achieve a more homogeneous and clinically sound assessment, the studies were grouped according to whether they included patients with compensated or decompensated cirrhosis. Compensated cirrhosis was variable, we calculated the

ratio between the number of studies in which each variable was significant and the number of studies in which it was assessed. To explore the reliability of the prognostic indicators identified in all studies, a sensitivity analysis was performed by analyzing only the good quality studies.

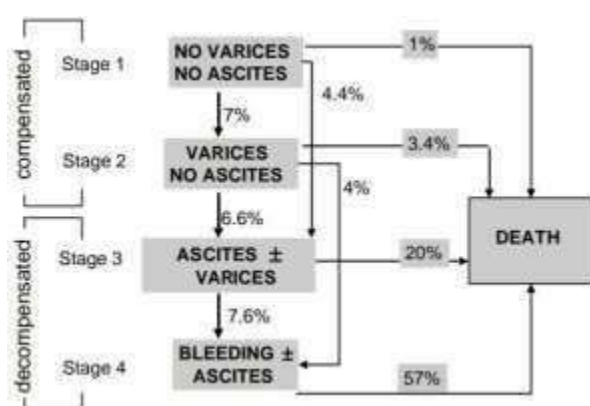


Fig. 6. Clinical course of cirrhosis: 1-year outcome probabilities according to clinical stages.

CAUSES

Liver problems are among the most causes of death due to alcohol abuse in many countries. On the other hand, nonalcoholic fatty liver disease (NAFLD) is a common hepatic abnormality in the Western world, and progresses to cirrhosis and hepatocellular carcinoma in a significant portion of cases . It has been estimated that in about 20-30% of patients suffering from chronic hepatitis C cirrhosis develops in almost 20 years. The virus causing the disease (HCV) possesses some certain

proteins, including core and NS5A that induce derangement of lipid metabolism or alter signal transduction of infected hepatocytes which leads to the production of reactive oxygen radicals and profibrogenic mediators, in particular TGF-beta1 . The effect of telaprevir-based antiviral regimens on improving liver health in patients infected HCV has been studied . In that retrospective study, 1208 patients treated with a telaprevir-based regimen were included. The base of grouping patients was their baseline Metavir score (F0-F1, F2 and F3-F4). The results obtained from non-invasive biomarker tests, Fibro Test, APRI, FIB-4 and Forms' Score, were then monitored before and after HCV treatment. It was concluded that attaining treatment with telaprevir-based regimen led to significant improvements in liver health as determined by four biomarker examinations . Liver fibrosis also occurs in other liver diseases including autoimmune and cholestasis liver diseases . It is known that the mechanism of pathogenesis primary biliary cirrhosis, a cholestatic liver disease, is different from other chronic liver diseases. Portal fibroblasts located in the connective tissue surrounding bile ducts are some-how different from hepatic stellate cells regarding an appropriate response to the profibrogenic and

mitogenic stimuli and expression of marker proteins. On the other hand, many liver diseases originated from various causes in children and younger patients could become complicated by development of liver fibrosis and progression to cirrhosis. In the case of paediatric liver disease, too, liver fibrosis has different histopatho-logical patterns and their management depends on the stage of liver fibrosis. In addition to modification of many liver functions, among the most important consequences of fibrosis in liver is portal hypertension. This abnormal condition results from an increased intrahepatic resistance and increased hepatic and portal arterial blood flow. The various changes in fibrotic and angio-architecture of liver tissue cause increased intrahepatic resistance. On the other hand, the progressive failure of one of the detoxification mechanisms of liver together with toxic substances from the splanchnic circulation and end-products of bacterial functions lead to a systemic pro-inflammatory state with further accelerating disease progression.

SIGN AND SYMPTOMS

Symptoms of Cirrhosis Initially, a person may have no symptoms at all. This is called compensated cirrhosis. In fact, a person may live many years with cirrhosis

without being aware that his or her liver is scarred. This is because the pressure in the portal vein is not yet too high and there are still enough healthy liver cells to keep up with the body's needs. However, if nothing is done about the cause of cirrhosis, (continuing to drink heavily, for example) or if the underlying disease such as hepatitis goes untreated, the pressure in the portal vein may increase to the point where the few remaining worker cells are overwhelmed. As cirrhosis progresses, the most common symptoms are:

- Weakness
- Fatigue
- Loss of appetite
- Nausea
- Vomiting
- Weight loss
- Abdominal pain and bloating when fluid accumulates in the abdomen
- Itching
- Spiderlike blood vessels on the skin

PATHOGENESIS OF LIVER CIRRHOSIS

Liver cirrhosis is a serious health problem. If not treated, it may lead to advanced liver cirrhosis and hepatocellular carcinoma (HCC). Fibro genesis is initiated by myofibril-blast activation and proliferation because activated myofibroblasts are the major source of ECM in

the injured liver. Although activated hepatic stellate cells (aHSCs) are the major source of myofibroblasts in the fibrotic liver, they are not the only precursors. Endogenous portal fibroblasts, fibrocytes, bone marrow-derived cells, and liver parenchymal cell-derived myofibroblasts that undergo epithelial-mesenchymal transition (EMT) give rise to a significant percent of myofibroblasts in the fibrotic liver. Different cell types activate myofibroblasts depending on the etiology of liver fibrosis. A previous study demonstrated that aHSCs are the source of myofibroblasts in a carbon tetrachloride (CCl₄)-induced liver fibrosis model, whereas portal fibroblasts give rise to myofibroblasts in the cholestatic liver. Bone marrow-derived cells represent a substantial fraction of the total fibrogenic population in a more chronic injury. In the quiescent state, HSCs are known as quiescent HSCs (qHSCs), and they are responsible for the storage of vitamin A in the liver. As a result of liver injury, qHSCs are activated by inflammatory mediators, which in turn differentiate into myofibroblasts. In this way, tissue remodeling is initiated in the liver by the secretion of ECM proteins and matrix metalloproteinases (MMPs) by aHSCs.

MULTIPLE CELL TYPES CONTRIBUTE TO PATHOGENESIS OF LIVER CIRRHOSIS

The liver is formed by parenchymal cells (i.e., hepatocytes) and other cells commonly known as nonparenchymal cells. The walls of hepatic sinusoids are lined by three different nonparenchymal cells: liver sinusoidal endothelial cells (LSECs), Kupffer cells (KCs), and hepatic stellate cells (HSCs). Both hepatic parenchymal and nonparenchymal cells are involved in the initiation and progression of liver fibrosis and cirrhosis.

HSCs

HSCs, formerly known as fat-storing cells, Ito cells, lipocytes, perisinusoidal cells, or vitamin A-rich cells, reside in the space of Disse in the normal liver and their main function is storage of vitamin A and other retinoids. Following multiple injurious insults and/or exposure to inflammatory cytokines such as platelet-derived growth factor (PDGF), transforming growth factor (TGF)- β , tumor necrosis factor (TNF)- α , and interleukin (IL)-1, HSCs undergo the transition from a quiescent to activated state. HSC activation is a pivotal event in initiation and progression of hepatic fibrosis and a major contributor to collagen deposition. Activation of HSCs is characterized by cell proliferation and

migration, contraction after transforming into myofibroblasts, generation of a large amount of collagen and other extracellular matrix (ECM), ultimately leading to liver fibrosis.

LSECs

LSECs constitute the sinusoidal wall, also called the endothelium, or endothelial lining. The structural characteristic of LSECs is the fenestrae on the surface of the endothelium. The endothelial fenestrae measure 150-175 nm in diameter, and act as a dynamic filter facilitating the exchange of fluids, solutes and particles between sinusoidal blood and the parenchymal cells. LSECs have high endocytotic capacity. Chronic alcohol abuse could result in defenestration, and a decrease in the number of fenestrae. In cirrhotic liver, defenestration of sinusoidal endothelium and the presence of a subendothelial basement membrane are frequently present. It is known that retinol deficiency can activate and transform HSCs into myofibroblasts with enhanced ECM production, resulting in perisinusoidal fibrosis and ultimately in cirrhosis[1]. Defenestration and capillarization of the hepatic endothelium are believed to be important in the initiation of perisinusoidal fibrosis by altering retinol metabolism. Studies in animals and

humans have revealed that LSECs can secrete the cytokine IL-33 to activate HSCs and promote fibrosis. Defenestration and capillarization of LSECs lead to impaired substrate exchange and are considered major contributing factors for hepatic dysfunction in liver cirrhosis. On the contrary, differentiated LSECs can promote reversion of activated HSCs to quiescence and thereby accelerate regression and prevent progression of fibrosis through vascular endothelial growth factor (VEGF)-stimulated NO production. HSCs are capable of expressing different chemokine receptors; such as CXC chemokine receptor (CXCR) 3; C-C chemokine receptor (CCR) 5; CCR7; and ligands, including chemokine ligand (CCL) 2, CCL3, CCL5, CXC chemokine ligand (CXCL) 1, CXCL8, CXCL9, and CXCL10. Chemokines are a class of small chemotactic molecules that regulate inflammation. Even though the role of each specific chemokine in liver fibrogenesis is still being studied, the migration ability of fibrogenic cells to the injury site is known to be promoted by chemokines, thus increasing the number of cells and inflammation at the site of injury. Both profibrogenic and antifibrogenic effects occur on interaction between chemokine receptors and ligands. CCR5, CCR1, and CXCL4 cause fibrosis,

whereas the in-teraction of CXCL9 and CXCR3 protects against fibrosis.

KCs

KCs, also known as Browicz-Kupffer cells and stellate macrophages, are specialized macrophages located in the lining walls of the sinusoids of the liver that form part of the reticuloendothelial system (RES). Studies in animal models have shown that KCs are implicated in the pathogenesis of various liver diseases. KCs can be activated by many injurious factors such as viral infection, alcohol, high-fat diet, and iron deposition. Activated KCs destroy hepatocytes by producing harmful soluble mediators and serving as antigen-presenting cells during viral infection. KC-mediated hepatic inflammation is considered to aggravate liver injury and fibrosis [49,50]. KCs are involved in the activation of HSCs and formation of fibrosis. In vitro studies have shown that KC-conditioned medium can promote activation of cultured rat HSCs with enhanced matrix synthesis and cell proliferation by eliciting expression of PDGF receptor in HSCs. KC-derived TGF- β 1 stimulates proliferation and collagen formation of HSCs derived from rats fed with high-fat diet and ethanol [52,53]. Alcohol can induce the circulating level of Gram-negative

bacterial lipopolysaccharide (LPS), which is a strong activator of KCs. In genetic hemochromatosis, iron overload in KCs could induce the expression of intercellular adhesion molecule (ICAM)-1 on hepatocytes, therefore facilitating activation of HSCs and collagen deposition in the hepatic tissues. Gelatinase secreted by activated KCs triggers the phenotypic change in HSCs by degrading collagen type IV. KCs engulf apoptotic bodies and produce death ligands, including Fas ligand and TNF- α , thereby promotes inflammation and fibrogenesis. In addition, KCs activated by β -glucans increase portal pressure through the release of thromboxane A2 in normal and fibrotic livers.

Hepatocytes

Hepatocytes are the primary liver parenchymal cells, and play complicated roles in fibrosis and cirrhosis. Hepatocytes are targets for most hepatotoxic agents, including hepatitis viruses, alcohol metabolites, and bile acids. Chronic liver diseases either promotes apoptosis or trigger compensatory regeneration of hepatocytes. Damaged hepatocytes release reactive oxygen species (ROS) and fibrogenic mediators, induce activation of HSCs, and stimulate the fibrogenic actions of myofibroblasts. Apoptosis of

hepatocytes is a common event in liver injury and contributes to tissue inflammation, fibrogenesis, and development of cirrhosis. Steatohepatitis enhances Fas-mediated hepatocyte apoptosis, which correlates with active nuclear factor (NF)- κ B and disease severity. Both HCV infection and ethanol consumption induce hepatocyte apoptosis in animal models and humans, and induction may be related to down regulation of Bcl-2 signaling. Chronic HCV infection can induce hepatocyte G1 arrest and impair hepatocellular function

and limit hepatic regeneration. In CCl₄-induced liver injury, hepatocyte apoptosis is induced at the early phase, which is followed by constant proliferation and if it persists, liver cirrhosis ensues at a later stage. Hepatocytes are the major sources of matrix metalloproteinases (MMP-2, MMP-3 and MMP-13) and tissue inhibitors of matrix metalloproteinases (TIMP-1 and TIMP-2); all of which are involved in the pathogenesis of liver cirrhosis in CCl₄-induced liver cirrhosis in rats[66].

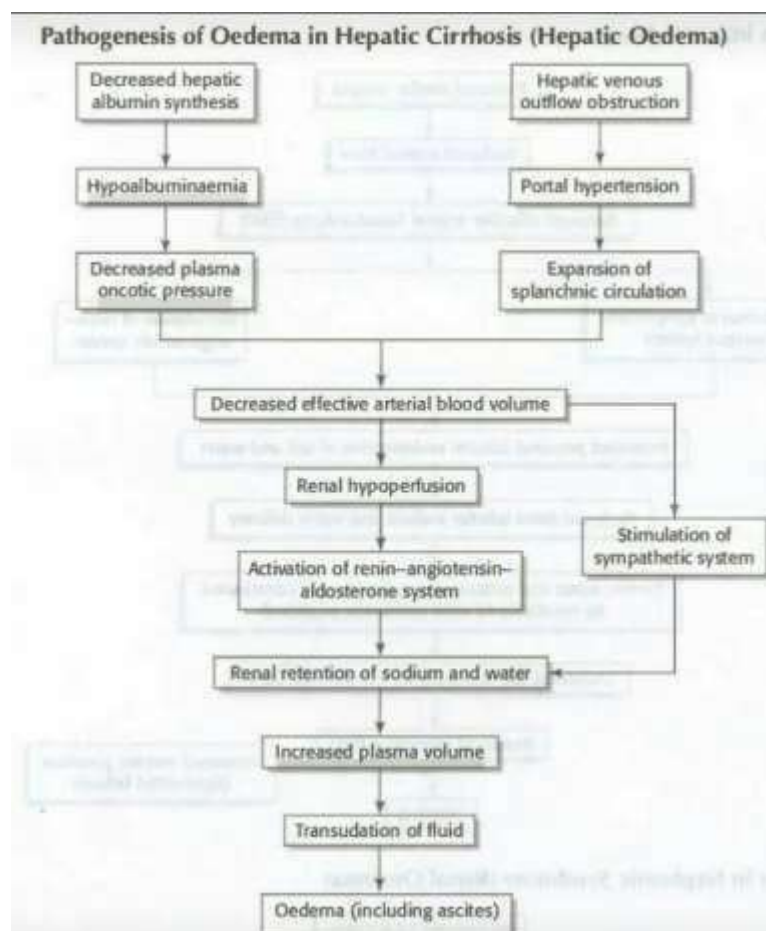


Fig.7 Show a Pathogenesis

In the last fibrotic stage or cirrhosis, hypoxic hepatocytes become a predominant source of TGF- β 1, further exacerbating hepatic fibrogenesis. Recently, it has been shown that hepatocyte telomere shortening and senescence can result in fibrotic scarring at the cirrhosis stage, presenting a novel explanation for the pathophysiology of cirrhosis.

ROLE OF CYTOKINES IN LIVER FIBROSIS AND CIRRHOSIS

Liver cirrhosis is orchestrated by a complex network of cytokine-mediated signaling pathways regulating the activation of HSCs and fibrogenesis.

PDGF

PDGF is the strongest mitogen to HSCs among all polypeptide growth factors. PDGF family has four members, PDGF-A, -B, -C and -D. PDGF and its receptors are markedly overexpressed in fibrous tissues, and its activity increases with the degree of liver fibrosis. A variety of factors such as viruses, chemicals, or mechanical damage to hepatocytes can induce KCs to synthesize and release PDGF. Upon binding to its specific receptor on the membrane of HSCs, PDGF activates corresponding signal molecules and transcription factors, leading to the

activation of its downstream target genes and activation of HSCs. PDGF has been shown to upregulate the expression of MMP-2, MMP-9 and TIMP-1, and inhibit the activity of collagenase, thereby reducing ECM degradation. PDGF-B and PDGF-D are potent PDGF isoforms in PDGF receptor (PDGFR) β signaling within HSCs, as evidenced by PDGFR β autophosphorylation and activation of extracellular signal-regulated kinase (ERK)1/2, C-Jun N-terminal kinase (JNK), p38 mitogenactivated protein kinase (MAPK), and protein kinase (PK)B/Akt pathways[75-77]. PDGF-D can activate HSCs and exerts mitogenic and fibrogenic effects, and therefore plays an important role in matrix remodeling in liver fibrosis.

TGF- β

TGF- β is the strongest known inducer of fibrogenesis in hepatic fibrosis. TGF- β is mainly synthesized by HSCs/myofibroblasts, KCs, LSECs, and hepatocytes in the liver. The TGF- β 1 family is composed of six members, and among them, TGF- β 1 has been shown to play a key role in the initiation and maintenance of liver fibrosis. The expression level of TGF- β 1 is increased in fibrotic liver and reaches a maximum at cirrhosis. The pro-fibrogenesis effect of TGF- β 1 is complicated, involving multiple

aspects: the primary effect of TGF- β 1 is to stimulate activation of HSCs, and the TGF- β 1 autocrine loop in activated HSCs is an important positive feedback to the progression of liver fibrosis. TGF- β 1 induces expression of the matrix-producing genes and inhibits degradation of ECM by downregulating expression of MMPs and promoting TIMP, leading to excessive deposition of collagenous fibers and promoting the development of liver fibrosis. In addition, TGF- β 1 has been shown to inhibit DNA synthesis and induces apoptosis of hepatocytes. TGF- β 1-induced apoptosis is thought to be responsible for tissue loss and decrease in liver size seen in cirrhosis. Given the critical role of TGF- β 1 in the pathogenesis of liver cirrhosis, specific blockade of TGF- β 1/Smad3 signaling has shown some therapeutic value for liver fibrosis.

TNF- α

TNF- α is mainly produced by monocyte, macrophage, HSCs, and KCs. It has proinflammatory activities and cytotoxic effects in these cells. In the process of liver fibrosis, TNF- α plays an important role in the activation of HSCs and synthesis of ECM. TNF- α can reduce the spontaneous apoptosis of activated rat HSCs by upregulating the antiapoptotic factors NF- κ B, Bcl-XL and p21WAF1, as well as

downregulating the proapoptotic factor p53. However, the effects of TNF- α on HSCs and fibrosis are complicated and even paradoxical, as demonstrated by studies showing that TNF- α could induce apoptosis in HSCs. TNF- α has also been shown to exert antifibrogenic effect in rat HSCs by reducing glutathione and inhibiting pro-collagen α 1 expression. In a rat model of nonalcoholic steatohepatitis (NASH), TNF- α antibody was shown to reduce the inflammation, necrosis and fibrosis in liver. TNF- α signaling through activation of KCs plays an essential role in the pathogenesis of liver fibrosis in animal models of NASH.

ILs

ILs are a group of cytokines initially found to be expressed by leukocytes, but later on were shown to be produced by a wide variety of cells, such as CD4 T lymphocytes, monocytes, macrophages, and endothelial cells. ILs have a complicated role in immune response, inflammation, and liver fibrogenesis.

Pro-fibrogenic ILs

KCs and SECs can rapidly produce ILs in response to liver tissue damage. IL-1 can directly activate HSCs and stimulate them to produce MMP-9, MMP-13 and TIMP-1, resulting in liver fibrogenesis. In contrast,

IL-1-receptor-deficient mice are less likely to sustain liver damage and exhibit reduced susceptibility to develop fibrosis. Deficiency of IL-1 α or IL-1 β also makes the mice less susceptible to develop liver fibrosis in animal models of steatohepatitis[98]. Similarly, IL-1 receptor antagonists were found to protect rats from developing liver fibrosis in response to dimethylnitrosamine, and blocking IL-1 signaling could markedly attenuate alcohol-induced liver inflammation and steatosis. IL-1 β was reported to increase the inflammatory and prosteatotic chemokine monocyte chemoattractant protein-1 in hepatocytes, and augment Toll-like receptor (TLR4)dependent upregulation of inflammatory signaling in macrophages. Another profibrotic cytokine is IL-17, whose expression level increases with degree of liver fibrosis indicating that IL-17 may be involved in disease progression and chronicity. Studies in mice have shown that L-17 induces liver fibrosis through multiple mechanisms, including upregulation of TNF- α , TGF- β 1, and collagen 1 α , which is dependent on signal transducer and activator of transcription (STAT)3 signaling pathway, and promotion of myofibroblast-like change of HSCs.

Antifibrogenic ILs

IL-10 is a cytokine that downregulates the proinflammatory response and has a modulatory effect on hepatic fibrogenesis. IL-10 may have therapeutic potential for patients with HCV-related liver fibrosis who do not respond to IFN-based therapy. IL-10 has been shown to exert antifibrotic effects through inhibiting HSC activity, and this was demonstrated in a rat model in which exogenous IL-10 was shown to reverse CCl₄-induced hepatic fibrosis by inhibiting the expression of TGF- β 1, MMP-2 and TIMP-1. IL-22 is known to play a key role in promoting antimicrobial immunity, inflammation, and tissue repair at barrier surfaces. IL-22 has been shown to induce HSC senescence, restrict liver fibrosis, and accelerate the resolution of liver fibrosis during recovery in a mouse model. IL-6 is a pleiotropic cytokine involved in inflammatory pathways, hematopoiesis and immune regulation. IL-6 can attenuate apoptosis and promote regeneration of hepatocytes through NF- κ B signaling and the Ras-MAPK pathway. IL-6 reduces CCl₄-induced acute and chronic liver injury and fibrosis. Pretreatment of fibrotic liver with IL-6 improves hepatic microenvironment and primes it for mesenchymal stem cell transplantation, leading to improvement in liver injury after fibrosis. Meanwhile,

increased blood level of IL-6 has been found in patients with NAFLD, and IL-6 could induce insulin resistance and

inflammation in the liver, suggesting that IL-6 may play a role in the development of NAFLD.

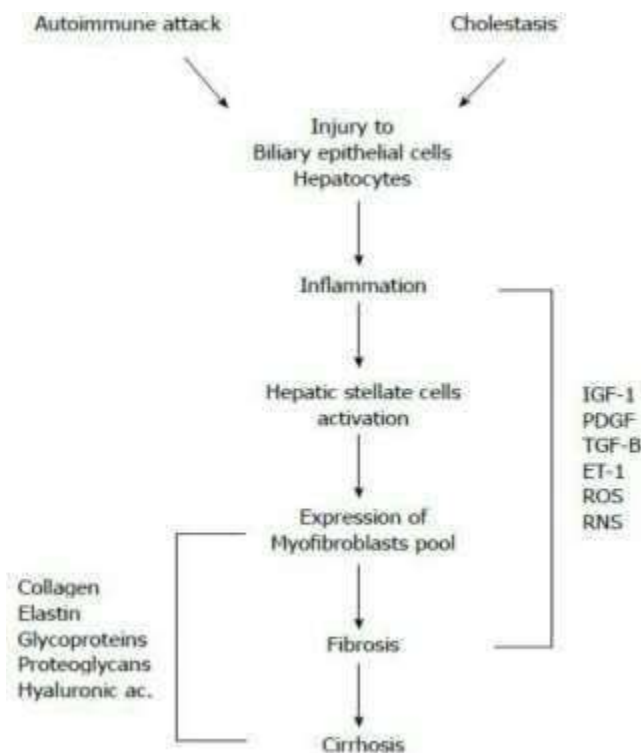


Fig.8: Show mechsinsam of fibrosis or cirrhosis

ETIOLOGY

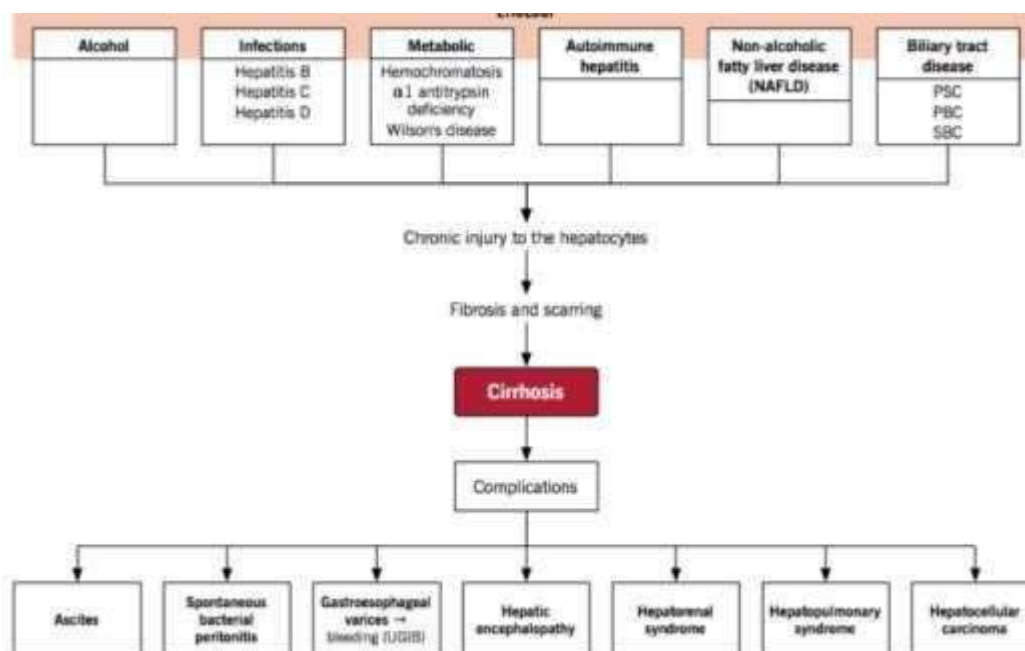


Fig.9: Shows brief over view of etiology of cirrhosis

CLINICAL EVIDENCE OF REVERSIBILITY ACCORDING TO ETIOLOGY

Hepatitis B virus-related liver disease

Chronic hepatitis B (CHB) is a significant worldwide problem as CHB patients develop cirrhosis and hepatocellular carcinoma. Standard treatments include pegylated IFN- α and nucleos(t)ide analogues. Several studies have demonstrated that hepatitis B virus (HBV) DNA suppression is associated with biochemical and histological responses. There is currently evidence that these surrogate markers correlate with improved long-term clinical outcome. IFN has been used in the treatment of CHB since the 1980s. Peginterferon therapy has been shown to reduce fibrosis progression in hepatitis B envelop antigen (HBeAg)-positive patients, with a greater response seen in those who sustain HBeAg seroconversion, as well as in HBeAg negative patients with a sustained virologic/biochemical response. In one experimental study, IFN- α therapy exhibited antifibrotic activity by inhibiting the production of TGF- β , reducing HSC activation, and stimulating HSC apoptosis in vitro. Another study observed the antifibrotic effect that IFN- γ exerted in liver cells through STAT-1 phosphorylation and impaired TGF- β

signaling. Long-term therapy with nucleoside analogues has also been shown to improve liver fibrosis and disease progression. In a 3-year study of lamivudine for hepatitis B treatment, follow-up liver biopsies indicated reversal of cirrhosis in eight of 11 patients (73%). Entecavir, which is a more potent inhibitor of viral replication in CHB, improves liver fibrosis. In a recent study, 96% of patients had histological improvement after long-term treatment with entecavir. Ten of the 57 patients had advanced fibrosis or cirrhosis (Ishak score 4 to 6) at baseline. All 10 patients achieved at least a 1-point reduction in the Ishak fibrosis score after long-term entecavir therapy. In a more recent 5-year study with tenofovir treatment for chronic HBV infection that included patients with liver cirrhosis at the start of the study, 74% demonstrated extensive histological improvement, such that they were no longer considered to be cirrhotic. Recently, instead of liver biopsy, transient elastography (TE) has been applied for the clinical assessment of liver fibrosis. A large prospective cohort study of 426 individuals reported a significant decline in TE values in CHB patients after 3 years of antiviral treatment. However, the significant reduction in TE values at follow-up, compared to those at baseline, was limited in patients who had initially

elevated alanine transaminase (ALT) levels . To exclude the confounding effect of high ALT.

Hepatitis C virus-related liver disease

Patients with compensated cirrhosis and chronic hepatitis C (CHC) benefit from IFN-based antiviral treatment. Viral eradication can be achieved in up to 40% of patients with genotype 1, and in 70% of patients with genotypes 2 or 3, reducing the risk of developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma [100]. In a 5-year follow-up study of CHC patients with stage 2 or greater fibrosis at baseline, 82% of patients who had achieved sustained virologic response (SVR) after IFN treatment had decreased fibrosis scores. Another study demonstrated a reduction in clinical events after SVR . In addition to IFN, excellent efficacy has been reported with several new directly acting antiviral agents (DAA) for HCV. Although little data were reported on follow-up liver biopsy, a recent report showed the possibility of reversal of liver fibrosis and cirrhosis by indirect measurement. TE values as well as FIB-4 and APRI scores were evaluated prior to therapy and within 18 months after DAA therapy; patients who had achieved SVR after DAA therapy showed significant regression of TE values and

improvement of FIB-4 and APRI scores . Liver fibrosis and cirrhosis are expected to improve in these patients with resolution of HCV infection.

Alcoholic liver disease

Clinical evidence for regression of fibrosis in alcoholic liver disease is limited. Results from randomized controlled trials (RCTs) assessing the effects of pharmacological agents on alcoholic fibrosis and cirrhosis have been disappointing. A Cochrane Intervention Review assessing the effect of colchicine for alcoholic and non-alcoholic liver fibrosis and cirrhosis from 15 RCTs reported the absence of statistically significant improvements in any significant clinical outcome.

Non-alcoholic fatty liver disease

There are currently no approved treatments for non-alcoholic fatty liver disease (NAFLD) and therapies are based on targeting risk factors. Although there have been several studies defining the benefits of various pharmacological agents for NAFLD, these studies have been limited by small study populations and short-term follow-up periods . Weight reduction through lifestyle modification is the first treatment strategy in NAFLD patients. Weight reduction is often associated with

beneficial effects on multiple components of metabolic syndrome. Histological improvements have also been observed, particularly with respect to steatosis, but evidence of fibrosis regression is controversial. A RCT assessing the effect of weight reduction through lifestyle modification in 31 NASH patients over a 48-week period demonstrated significant improvements in the NASH histological activity score following an average weight loss of 9.3%, but failed to show a significant change in fibrosis.

Autoimmune hepatitis

Approximately 40% of patients with autoimmune hepatitis develop cirrhosis under current therapies. Although the course is variable depending on the period of observation, the annual occurrence of cirrhosis is estimated at 3% per year. Several studies have not only demonstrated the antifibrotic effects of immuno-suppressive therapy in autoimmune hepatitis but have also strengthened the association between the indices of hepatic inflammation and the progression of liver fibrosis. Fibrosis scores using the Ishak system improved in 46 of 87 treated patients (53%) with autoimmune hepatitis during 63 months, and the histological activity index decreased concurrently. They suggested

that improvement of hepatic fibrosis is possible in the majority of treated patients with autoimmune hepatitis and that failure to suppress liver inflammation worsens fibrosis.

DIAGNOSIS OF CIRRHOSIS

Direct Estimation of Hepatic Fibrosis and PHT

Liver biopsy and histological analysis

Cirrhosis is defined by anatomical changes within the liver parenchyma, including fibrosis and the development of regenerating nodules, and its assessment is based on histologic examination. A liver biopsy is considered the gold standard for the diagnosis of cirrhosis. In general, histologic scoring systems assess the grade and stage of chronic hepatitis. The grade is used as a measure of necro-inflammatory activity, and the stage is used as a measure of fibrosis and architectural changes. These scoring systems use scales of four (1-4), five (0-4), or seven (0-6) stages for chronic hepatitis. For biopsies, an adequate specimen needs to have a length of at least 1.5 cm or the presence of six to eight portal tract. However, the width of the biopsy core is also important because the hepatic architecture is difficult to appreciate in thin biopsies, and biopsy specimens obtained from subcapsular locations generally contain more fibrous

tissue, which should be considered. However, in clinical practice, liver biopsies have important limitations, such as invasiveness, potential for complications, sampling error, and inter- and intraobserver variability. Another important limitation is that a biopsy only represents approximately 1/50000 of the liver parenchyma. Furthermore, the histologic diagnosis of cirrhosis maybe impossible in cases with large parenchymal nodules or so-called incomplete septal cirrhosis. However, despite these limitations, liver biopsy and histologic analysis have revolutionized the assessment of disease severity in chronic liver disease. Hepatic fibrosis is currently viewed as a dynamic process, in some cases, even the excess fibrous tissue of cirrhotic liver may regress over time. Distinguishing between the amount of hepatic fibrosis and the disease stage, which is related to both fibrosis and architectural changes, is important for the assessment of the effects of antifibrotic treatments. Nevertheless, a one-stage description of cirrhosis is inadequate, and subclassification has potential clinical utility. From the aspect of histology, such subclassifications might allow better the prediction of prognosis and be helpful clinically. A few recent studies have

shown the possibility of the clinical application of histological subclassification. In these studies, fibrosis scores, derived from nodule size and septal thickness, showed a significant correlation with the clinical stage and prognosis as well as the HVG (Figure 10). Currently, the proportion of the liver biopsy specimen occupied by collagen (collagen proportion area, CPA) on Picro-Sirius stained histologic sections, as assessed by computer-assisted digital image analysis, has emerged as a useful continuous variable for the quantitative assessment of fibrosis in various clinical situations. The CPA measurement is based on the segmentation of digital images to measure the area occupied by collagen compared with the entire area of liver tissue. The CPA has been reported to correlate with the HVG in liver transplant recipients with hepatitis C virus infections, with or without cirrhosis, and the CPA measured at 1-year post-transplantation was found to be a predictor of clinical decompensation in later years. This parameter has also been found to correlate with the liver stiffness (LS) measurements, as assessed by transient elastography (TE), in patients with chronic viral hepatitis. Therefore, the quantitative assessment of hepatic fibrosis in liver biopsy.

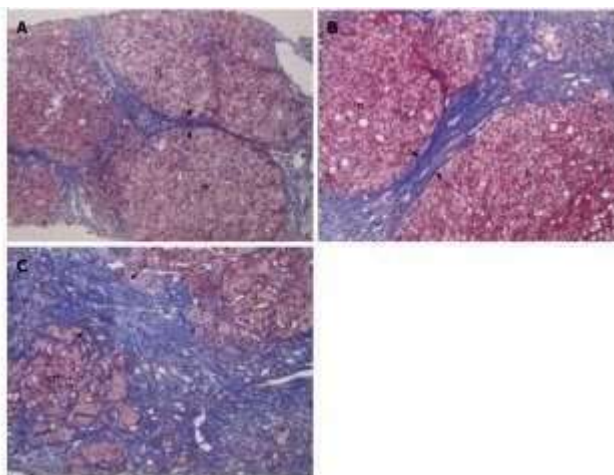


Figure 10: Heterogeneity of cirrhosis in histology. All pictures are histological finding of cirrhosis however, they show different feature in thickness of septa and the size of nodules. A: Shows mild cirrhosis with thin septa (MTC stain, $\times 100$); B: Shows moderate cirrhosis with at least two broad septa; C: Shows severe cirrhosis with at least one very broad septa (MTC stain, respectively, $\times 200$).

A, B, C are correspond to subclass of Laennec fibrosis scoring system F4A, F4B and F4C respectively, The widths between two arrows show the significant difference among subclass of cirrhosis. n: Regenerating nodule; MTC: Masson trichrome stain.

HVPG measurement for PHT

The measurement of the HVPG is the gold standard technique for the evaluation of PHT in liver disease. The HVPG is the difference between the wedged hepatic venous pressure (WHVP) and the free hepatic venous pressure (FHVP). The WHVP is measured by occluding the hepatic vein as stopping the blood flow causes a static column of blood to be formed, which is equal in pressure to the hepatic sinusoids. FHVP is a measure of the pressure of the non-occluded hepatic vein. In cirrhosis, WHVP provides an accurate estimate of portal pressure, as has been demonstrated in both alcoholic and viral cirrhosis patients. In patients with

cirrhosis, HVPG measurements provide independent prognostic information on survival and the risk of decompensation. Clinically significant PHT (CSPH, HVPG ≥ 10 mmHg) is necessary for the formation of esophageal varices, its bleeding, and the development of decompensation. In patients who have already developed decompensation, HVPG provides predictive information about the risk of mortality in the future. HVPG can also reflect liver parenchymal function, and correlates with the degree of histological liver fibrosis. In addition, in some studies on HCV-related fibrosis and cirrhosis, HVPG showed a good correlation with the therapeutic response which suggested that

the repeated HVPG measurements could be helpful in estimating the progression or regression of cirrhosis in patients with advanced hepatitis C virus (HCV)-related chronic liver disease. HVPG also showed usefulness in identifying those patients who were at highest risk of decompensation by the recurrence of severe hepatitis C among those who had undergone post-liver transplantation for HCV-related cirrhosis. CSPH is an independent predictor of the risk of developing hepatocellular carcinoma (HCC), and it also increases the risk of liver failure and death after liver resection in patients with compensated chronic liver disease or hepatocellular carcinoma. However, in case of non-cirrhotic portal fibrosis (NCPF) and extra-hepatic PV obstruction (EHPVO) which present only with features of PHT without any evidence of significant parenchymal dysfunction, HVPG is normal in EHPVO, whereas it is normal or slightly elevated in NCPF (median 7 mmHg). So, HVPG is not useful in the estimation of the severity of PHT and EV bleeding risk in EHPVO or NCPF. The HVPG response to pharmacological therapy enables the identification of those patients with PHT who are most likely to benefit from treatment. The development of esophageal varices is less likely if the HVPG is < 10

mmHg. The development of variceal bleeding and the presence of ascites have been known to occur when the HVPG is ≥ 12 mmHg. If the HVPG falls to ≤ 12 mmHg with drug therapy, such as nonselective β blockers, the development of variceal bleeding can be prevented, and varices that are already present may decrease in size. However, even if this target is not achieved, a decrease in the HVPG of $\geq 20\%$ from baseline levels has shown similar effects to having an HVPG of < 12 mmHg. In addition, this response markedly decreases the rebleeding risk in secondary prevention. In addition, a good hemodynamic response was independently associated with a decreased risk of ascites and spontaneous bacterial peritonitis on follow-up and was an independent predictor of survival. The evaluation of the acute HVPG response to intravenous propranolol therapy has been known to be useful for predicting the efficacy of nonselective β blockers at preventing the first bleed or rebleeding. Furthermore, the acute HVPG response to propranolol is independently associated with survival in patients with cirrhosis and PHT. However, although the HVPG measurement procedure is very well tolerated, its invasiveness and limited availability at hospitals has led to attempts to develop noninvasive alternatives, such as

laboratory tests, imaging techniques, and LS measurements. However, there has been no noninvasive alternative that can replace the HVPG measurement until now.

NON-INVASIVE DIAGNOSIS OF HEPATIC FIBROSIS AND PHT

Laboratory tests

Because of the attractiveness, such as offering a sampling that reflects the whole liver, allowing repeated testing, reducing invasiveness, and increasing simplicity, many hematological and biochemical serum markers of fibrosis have been studied. In general, serum markers of fibrosis can be divided into two groups: —indirect markers, which reflect the degree of fibrosis indirectly, and —direct markers, which directly measure liver matrix components or enzymes that participate in matrix regulation. Indirect markers in blood test include parameters related to cell lysis or inflammation (AST and ALT), cholestasis (γ GT and bilirubin), hepatocyte synthetic function (INR, cholesterol, ApoA1, haptoglobin, and N-glycans), and hypersplenism due to PHT (platelet count). Many scores or indices of indirect parameters have been studied and the Fibrotest [α 2-macroglobulin (α 2M), ApoA1, bilirubin, γ GT, and haptoglobin combination and AST to platelet ratio index (APRI) have been the most widely

validated. In some studies, these indices have been shown to be good predictors of fibrosis and cirrhosis (AUROC = 0.92, 0.80, respectively), but in a meta-analysis of chronic hepatitis C, they lacked reliability in the discrimination of the fibrosis stage. Direct markers allow the quantitative assessment of the total amount of the hepatic extracellular matrix and its deposition or removal. To improve accuracy, the use of a combination of markers is preferable to the use of a single marker, and various panels of direct markers have been described. The original European Liver Fibrosis panel is an example of such a panel of biomarkers shown to be accurate in diagnosing significant fibrosis in a large, mixed liver disease population. This panel incorporates hyaluronic acid, tissue inhibitor of matrix metalloproteinases-1, procollagen type III propeptide and age. The panel has since been simplified by removing age while maintaining diagnostic accuracy, as the enhanced liver fibrosis (ELF) test, which has been shown to be accurate in predicting significant liver fibrosis in independent populations. ELF score predicts liver outcomes, with people having the highest ELF scores being significantly more likely to have clinical outcomes than those in lower-score groups with hazard ratios of 75 (ELF

score 12.52-16.67), (10.426-12.51) and (8.34-10.425) compared with patients with ELF < 8.34. In non-alcoholic fatty liver disease (NAFLD), one study reported favorable results of AUROC = 0.90, sensitivity 80%, and specificity 90% for advanced liver fibrosis, but this test needs to be further investigated. A Cytokeratin-18 fragment in plasma indicates the apoptosis of liver cells and is the marker of NASH. Plasma cytokeratin-18 fragment levels increased significantly in patients with steatohepatitis compare to normal or simple fatty liver patients. CK-18 fragment level showed a possibility as a screening test for NASH by showing favorable results (sensitivity 78%, specificity 87%, AUROC = 0.82) in meta-analysis. However, this marker is currently unavailable in the clinical practice yet and the standard cut-off value for diagnosis also has to be established. NAFLD Fibrosis Score (NFS) is one of the most widely-studied biochemical panels for the diagnosis of fibrosis in NAFLD, and it is composed of 6 markers (age, BMI, diabetes/impaired glucose tolerance, platelet count, albumin level, AST/ALT ratio) which are clinically or biochemically measured and calculated easily in the website (<http://nafldscore.com>). NFS has

two cut-off values, [< -1.455 (low probability) and $> +0.676$ (high probability)] in evaluating liver fibrosis. According to a meta-analysis of 13 studies performed on 3064 patients, NFS showed a high AUROC value of 0.85 in diagnosing liver fibrosis greater than stage F3. By taking < -1.455 as cut-off, sensitivity was 90% and specificity was 60% in excluding advanced liver fibrosis. By taking $> +0.676$ as cut-off, sensitivity was 67% and specificity 97% in diagnosing advanced liver fibrosis. However, about 20%-58% of patients showed middle values between those two cut-off values (indeterminate probability), so in these case, liver biopsy has to be considered. About the noninvasive estimation of PHT using laboratory test, just a few studies have been reported. Direct markers such as serum laminin levels, serum hyaluronic acid and procollagen type III propeptide were evaluated in an old small population studies and laminin and hyaluronic acid showed correlation with HVPG, however these markers has limitations in clinical application because of low predictive values for the presence of severe PHT and EVs[66-68].

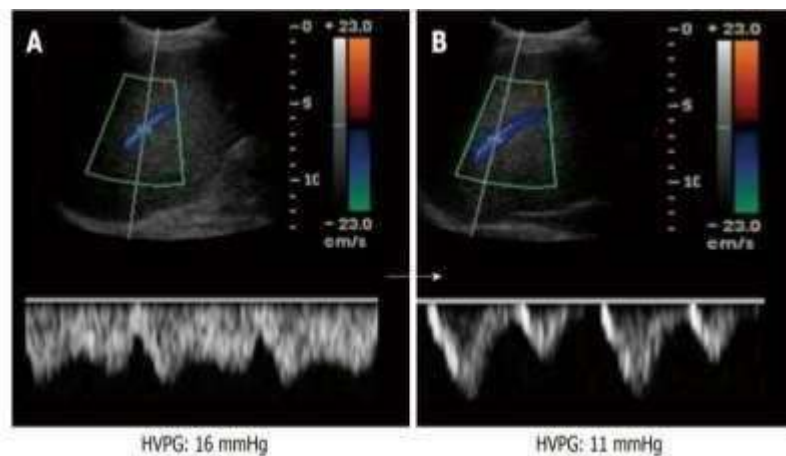


Figure 11 Doppler ultrasonography showing change in the hepatic vein waveform and damping index (A) before and (B) 3 mo after propranolol treatment in a patient with liver cirrhosis. Hepatic vein waveform changed from biphasic to near triphasic, quantitative measurement of damping index (DI) decreased from 0.61 to 0.33 in association with a hepatic venous pressure gradient (HVPG) decrease from 18 to 11 mmHg[92]. HVPG: Hepatic venous pressure gradient.

In case of Fibrotest, it has a significant correlation with HVPG (Pearson correlation coefficient = 0.58), however, the correlation was weaker in cirrhosis patients (Pearson correlation coefficient = 0.24) and the AUROC for the diagnosis of severe PHT (HVPG > 12 mmHg) was only 0.79[69]. Additional study is needed to estimate the clinical usefulness of Fibrotest for the diagnosis of PHT. The platelet count, and the ratio of the platelet count to spleen diameter have shown to be able to exclude the existence of EVs, however, in the other studies, the results were not constant[70-72]. In case of APRI score also showed low AUROC in recent study in the prediction of the presence of EVs (EVs 0.62, large EVs 0.71).

DIAGNOSTIC IMAGING MODALITIES

In chronic liver disease, the imaging diagnosis plays several significant roles in patient management, both in terms of diagnosing hepatocellular carcinoma and predicting its progression to cirrhosis. The basic diagnostic imaging modalities consist of ultrasound (US), computed tomography (CT), and magnetic resonance (MR) based methods, and many specific techniques derived from these basic methods are currently being developed to achieve convenient, non-invasive, and accurate diagnoses.

US based LS measurement: TE, acoustic radiation force impulse, supersonic shear-wave elastography, and real-time elastography. The increase in LS associated

with chronic liver disease is primarily due to the presence of fibrosis. Tissue elastography, which was introduced in 1992, is used to visualize differences in the mechanical properties among tissues. The most attractive advantage of tissue

elastography is its ability to quantify the viscoelasticity of the tissue, which means that it can be used to measure hepatic fibrosis in the liver.

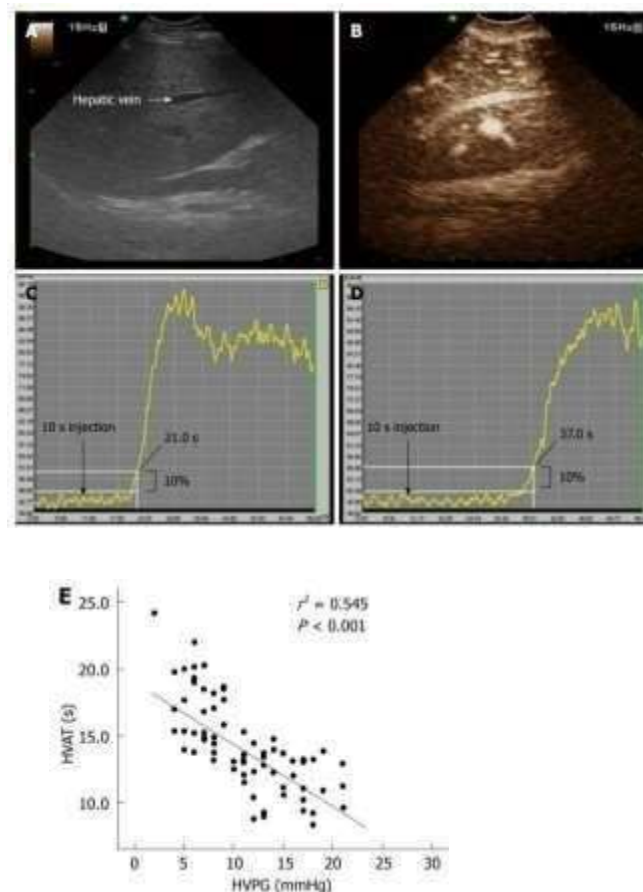


Figure 12 Hepatic vein enhancement with microbubble contrast-enhanced ultrasound and measurement of Hepatic vein arrival time and the correlation between Hepatic Venous Pressure Gradient and Hepatic vein arrival time. A: Ultrasound images showing the HV (white arrows) before the contrast injection; B: Arrival of microbubble contrast agent in the HV after contrast enhancement; HVAT was calculated as the time (in seconds) from injection to a sustained increase in signal in the TIC to more than 10% above baseline; C: Recorded TIC profile shows early HVAT (11.0 s; the 10-s lead time was subtracted from 21.0 s) in a patient with cirrhosis with HVPg of 20 mmHg; D: Recorded TIC profile shows an HVAT of 27.0 s (37.0 min 10 s) in a healthy control; E: HVAT was significantly linearly correlated with HVPg in the patients with compensated cirrhosis ($r^2 = 0.545$; $P < 0.001$). HV: Hepatic vein; CEUS: Contrast-enhanced ultrasonography; HVAT: Hepatic vein arrival time; HVPg: Hepatic venous pressure gradient; TIC: Time intensity curve.

To date, two US elastography techniques have been used to measure LS: shear-wave based elastography and real-time elastography. Shearwave based elastography includes TE (Fibroscan), which is the most widely evaluated and used, acoustic radiation force impulse (ARFI) imaging, and supersonic shear-wave elastography (SSWE). Shear-wave based elastography involves using an ultrasonic beam to measure the propagation velocity of a shear wave through the soft tissue under investigation, and LS is displayed in kilopascals (kPa) or centimeters per second (cm/s).

TE is the first commercialized elastography protocol that was developed to noninvasively assess the stiffness of deep soft tissues such as the liver. A mechanical vibrator generates a low-frequency elastic wave at 50 Hz to produce a shear stress in the target tissue at a distance of 4 cm, after which, as mentioned above, the velocity of the shear wave is measured using an ultrasound signal. TE has been validated extensively by numerous investigations targeted at patients with chronic liver disease and cirrhosis, and TE findings are generally accepted to be strongly correlated with the stage of liver fibrosis. However, it does not provide a B-mode image which is very

helpful for targeting, and it has a high measurement failure rate (15%-20%), mainly due to limiting factors such as obesity and ascites[107]. ARFI imaging and SSWE use focused high-intensity, short-duration acoustic pulses instead of the mechanical vibration used in TE to produce a shear wave in the target tissue[108]. Similar to TE, the shear-wave velocity is observed by aiming repeated ultrasound beam pulses across the region of interest (ROI). SSWE is a new type of the shear-wave based US elastography technique and uses multiple acoustic radiation force impulses[109]. It can assess the viscoelastic properties in all areas within the ROI, and the results are displayed on a color-coded lookup table. ARFI imaging and SSWE are expected to overcome the limitations of TE, such as measurement failures due to severe obesity, thick subcutaneous fat, and ascites. Moreover, they are able to display a gray scale US image on the background of the elastography and are thus more reliable and familiar to physicians who use conventional US. However, a high level of clinical experience and evidence are needed to apply either ARFI imaging or SSWE for the diagnosis of liver fibrosis. Most clinical studies about TE have focused on its ability to identify significant fibrosis and cirrhosis, because of an

indication for antiviral treatment and initiating surveillance program for the early detection of hepatocellular carcinoma (HCC) development. A number of studies have demonstrated that TE values are significantly correlated with histological fibrosis stage and have high diagnostic accuracy. In chronic hepatitis C (CHC), the AUROC of TE ranged from 0.77 to 0.90, with a cutoff value of 6.2-8.7 kPa for assessment of significant fibrosis ($F \geq 2$), and an AUROC of 0.90-0.97 and cutoff value of 9.6-14.8 kPa for assessment of cirrhosis. For chronic hepatitis B (CHB), AUROC and cutoff value of TE for predicting significant fibrosis and cirrhosis are 0.81-0.95, 6.3-7.9 kPa and 0.80-0.98 kPa, 9-13.8 kPa respectively. In a recent meta-analysis, TE also showed high sensitivity and specificity in hepatic fibrosis assessment of NAFLD[119-123]. However, in case of obesity [(body mass index (BMI) ≥ 30 kg/m²] which is commonly associated in patients with NAFLD, the accuracy of TE decreases, and test may not be performable in some cases (5%-13%). Recently introduced CAP is known to relatively accurately evaluate the degree of fatty infiltration, and a large number of clinical studies are anticipated to report meaningful results. TE also reflects a progressive rise in PHT due to increased

hepatic vascular resistance related with hepatic fibrosis. TE has a good performance in discriminating between patients with and without CSPH (AUROC = 0.82-0.94)[127]. In addition, TE value < 13 kPa exclude reliably CSPH, while values > 21 kPa had an accuracy equal to that of HVP ≥ 10 mmHg for the prediction of first clinical decompensation in patients with compensated cirrhosis. As variceal bleeding is the most important complication of PHT, the relationship between TE values and the presence of EVs has been also investigated in several studies, and these studies showed that there is a significant correlations between TE values and the presence of EVs. However, TE still has limitations in clinical application because of the cutoff values (range, 13.9-21.5 kPa) and performance of TE variability among the studies (AUROC: 0.76-0.85).

CT- and MRI-based approaches

Cross-sectional imaging studies such as CT and MRI are useful imaging modalities for the diagnosis of cirrhosis. These modalities are considered to be standard methods for the diagnosis of HCC on the background of chronic liver disease, including cirrhosis. The radiologic features of advanced cirrhosis are normally obvious and include surface nodularity, prominent

fibrous septa, shrinkage of liver volume, and an enlarged portal venous system including varices and splenomegaly due to PHT. However, it is difficult to diagnose the early stage of cirrhosis. As such, various functional techniques using CT and MRI have been developed recently and described in many hepatology and radiology journals.

Hemodynamic changes

Hemodynamically, the cirrhotic liver is highly resistant to portal inflow, and the systemic response that increase the splanchnic circulation aggravates the situation, creating a vicious cycle that may result in the development of PHT, hyperdynamic circulation and its complications. Because conventional CT and MRI are not functional imaging modalities, they are not appropriate for evaluating the hemodynamic changes in the liver. However, they are useful for observing the secondary changes of PHT in a cirrhotic patient, such as portosystemic collateral formation, splenomegaly, portal hypertensive gastropathy, portal hypertensive colopathy, and ascites. Esophageal and paraesophageal varices are common complications of cirrhosis, and arise from the impaired venous drainage of the esophageal vein due to increased portal

venous pressure. A gastric varix is less common than an esophageal varix and occurs in approximately 20% of patients with PHT. In general, the estimation of the risk of variceal bleeding is made by using endoscopic findings such as the size, color, and location of varices.

However, in the era of multidetector CT, which enables CT scanning at a submillimeter thickness, CT can be used to obtain information not only about the cirrhotic liver itself but also about the PHT caused by cirrhosis. Various portosystemic collateral veins can also be depicted in the CT scan, and physicians can plan a strategy for the treatment of varices, including the insertion of a transjugular intrahepatic portosystemic shunt and balloon-occluded retrograde transvenous obliteration. Moreover, as with endoscopy, demonstrating the presence of esophageal and gastric varices is now possible using CT. The sensitivity and specificity of CT were found to be 96% and 55%, respectively, to detect esophageal varices and 93% and 80%, respectively to detect high-risk esophageal varices. Using the 1- to 3-mm multiplanar reformat or surface-shaded display can also increase the specificity of CT for the risk stratification of esophageal varices¹⁰¹. With regard to gastric varices, the sensitivity and

specificity were 83%-89% and 75%-79%, respectively. Although these results are not bad, the accuracy for small varices remains low.

MRE

MRE is an emerging technology that is used to quantitatively assess the elasticity of the liver. This modality can improve the contrast between different tissues in the body compared with other imaging modalities, such as ultrasound, CT, and conventional MRI. MRE has been used in clinical practice for the assessment of hepatic fibrosis since 2006. Several clinical studies have established the feasibility of MRE for the evaluation of hepatic fibrosis, and in a recent meta-analysis, the overall sensitivity, specificity, and AUROC of MRE for histological grade $\geq$ F2 were 0.94, 0.95, and 0.98 and for $\geq$ F4 were 0.99, 0.94, and 0.99 respectively. There are several advantages of MRE over US based elastography, such as not being influenced by body habitus, not being operator dependent, and its potential ability to assess the entire liver. However, this technique is expensive and cannot yet be regularly used in all medical institutions and further research is required to validate liver MRE against long-term clinical outcomes.

TREATMENT

Treatment varies

Treatments focus on the underlying cause. In advanced cases, a liver transplant may be required.

- Self-care
- Medications
- Medical procedure
- Surgery

Self-care

Self-care is most important for the prevent early stage of cirrhosis. For the starting stage patients should avoid alcohol and take low sodium in diet.

- Low sodium in diet
- Avoid Alcohol

Low Sodium in Diet

If you have cirrhosis of the liver that is causing ascites, then your doctor may recommend a low-sodium diet. It is often recommended to limit sodium to 2,000 mg a day. Ascites is an accumulation of fluid in the abdominal area. Lowering the sodium you eat will lessen your body's tendency to retain fluid. Think of sodium as like a sponge, causing your body to hold onto fluid. Read labels for the mg of sodium. Generally, look for entrée-type foods to be less than 500 mg, and side dish items to be less than 140 mg, of sodium per serving.

What to eat when limiting sodium

- Homemade, fresh meals instead of restaurant meals
- Fresh meats without a brine or sodium solution added.
- Fresh, plain, frozen or well-drained canned vegetables.
- Fruit.
- Reduced-sodium processed foods, such as reduced-sodium soup, tuna and tomato sauce.
- Pepper, garlic powder, onion powder or herb mix seasonings with your meals. Ask your doctor before you use a salt substitute.

Below are tips to lowering sodium

1. Avoid processed foods as much as possible. Examples of processed foods are:

- Canned foods, such as canned meats, soups, meals (beef stew) and canned pasta meals. Frozen meals, entrees and pizza.
- Boxed package meals and side dishes, such as boxed pasta, rice and potato mixes and meal helpers.
- Processed and deli meats, such as hot dogs, brats, frozen breaded chicken and fish patties, sausage, bacon and luncheon meat.

- Cheese — especially processed cheese food, cheese slices and cottage cheese.

2. Limit eating out in restaurant

- Fast food meals can easily have 1,000 mg of sodium.
- Limit meals with sauces, gravies, processed meats and cheese.
- Limit casserole/mixture-type items, such as pasta dishes or stir-fry dishes with sauce.
- Choose the plainest food items possible, such as plain hamburger, plain grilled chicken with fresh vegetable toppings, plain meat with baked potato and unsalted vegetables.

MEDICATION

Medication use for the second stage or early stage. The following types of drugs are use in cirrhosis.

- Diuretics
- Ammonia Reducer
- Beta blocker
- Antibiotics
- Antiviral

DIURETICS

The usually advised first-line therapy includes sodium restriction to 88 mmol/d (2000 mg sodium per day) . Oralduretics and total abstinence from alcohol are both

considered the second line of treatment . Spironolactone is the first-line diuretic recommended for a patient with cirrhosis and edema, initiating with a dose of 50 mg. With its long half-life, doses are altered after 3 to 4 days. Maximum titration sometimes requires higher doses, up to 400 mg per day. However, this may cause gynecomastia Spironolactone when used alone was as effective as its combined therapy with furosemide. Amiloride can be used as an alternative, initiating with 5 mg per day and titrating up to 20 mg per day. However it is not as effective as spironolactone .In case of an inadequate response to spironolactone, thiazide diuretics are added to the regimen. Depending upon the patient's renal status, doses of 40 mg per day to a maximum of 160 mg per day can be used. Thiazides are terminated if the patient does not respond after 3 days and replaced with a loop diuretic. In patients with renal impairment, frequent doses of moderate amounts are preferred instead of a single large dose. If results are not desirable, spironolactone and thiazides may be added to the regimen. Dietary salt restriction should be ordered in all patients. In comparing the efficacy of furosemide and spironolactone in a randomized comparative study, the activity of the renin angiotensin system proved to alter the action of these

diuretics. Patients with high renin and aldosterone levels failed to respond to furosemide but were successfully treated with 300 mg per day of spironolactone. When compared to furosemide, the long acting torsemide produced greater urinary output. Similar results were obtained in an RCT conducted over 70 days with torsemide when compared to furosemide. Administration of octreotide in combination with diuretics not only suppressed both plasma glucagon levels and renin angiotensin system, thereby improving portal and systemic hemodynamics. In a prospective cohort study, human serum albumin was administered to patients who had serum albumin concentration less than 3.5 g/dL and were being treated with furosemide and spironolactone. The body weight loss recorded was dependent upon the amount of human serum albumin administered instead of the dose of diuretics. A reduction in plasma renin concentration was observed in patients treated with human serum albumin combined with diuretic therapy. Combined therapy of 200 mg per day of potassium canrenoate and 50 mg per day of furosemide was more effective when compared with sequential therapy in patients with moderate ascites. Complications such as hyperkalemia were more profound in patients being treated

with sequential therapy. Potassium canrenoate and spironolactone are both in the aldosterone antagonist family, having a common metabolite called canrenone. Spironolactone is more potent and has in addition sulfur-containing metabolites, which have a high renal clearance, thereby

allowing access to their site of activity via the renal tubular fluid. For treatment of ascites in hospitalized patients, therapeutic paracentesis along with plasma expanders has replaced diuretic therapy and results in fewer complications.

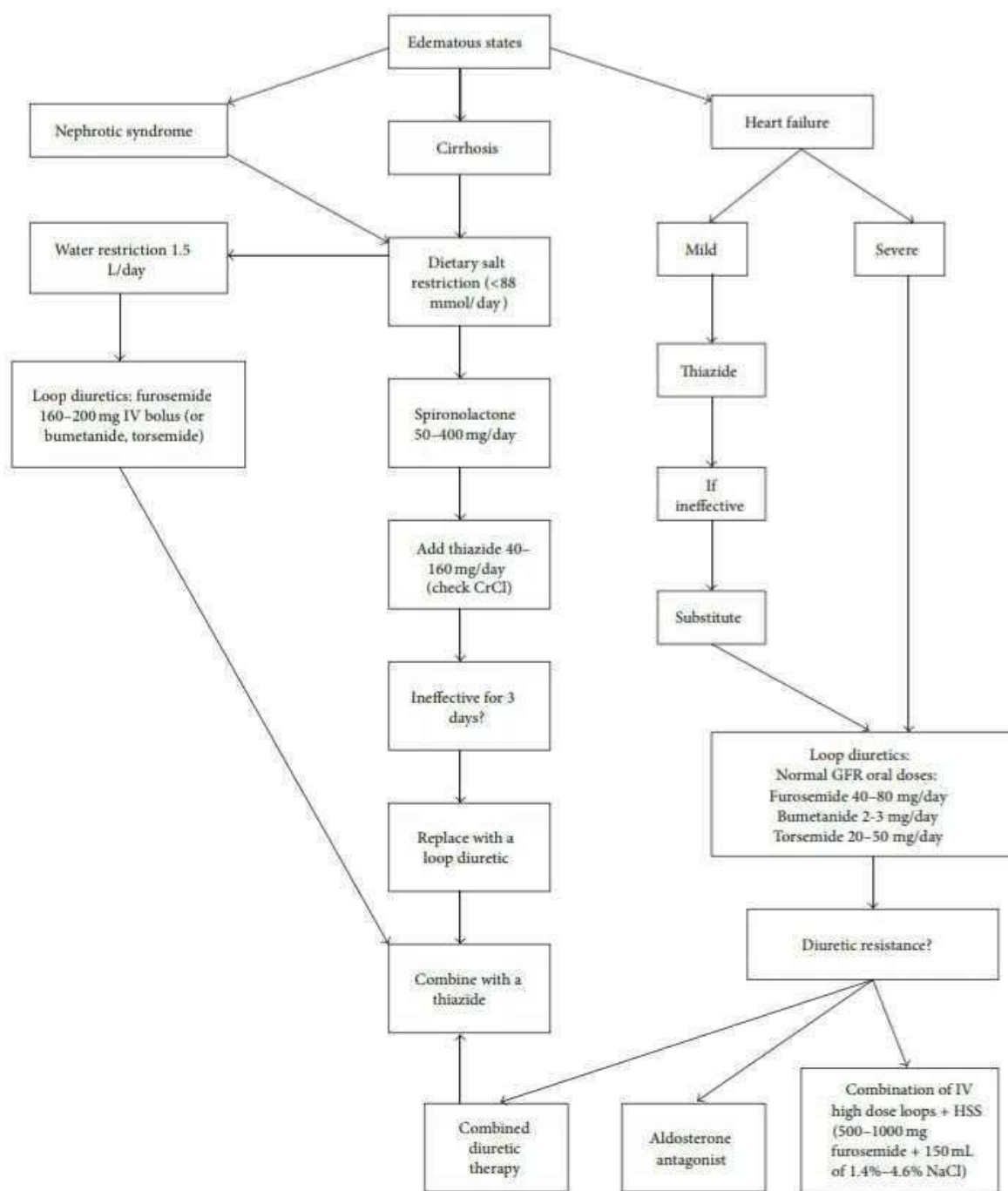


Fig.13: Show a use of diuretic in cirrhosis

BETA-BLOCKER

Brief overview of the pathophysiological

basis for using beta-blockers in cirrhosis

Portal venous pressure increases in the setting of liver cirrhosis, first, due to increased resistance to portal blood inflow at the hepatic circulation. This has a mechanical component related to distortion of liver microvascular architecture and a dynamic component related to endothelial dysfunction, which results in decreased availability of endogenous vasodilators, mainly nitric oxide (NO), and increased release of vasoconstrictors (prostanoids, endothelins and angiotensin), leading to an increased hepatic vascular tone. At a later stage, portosystemic collaterals develop because of dilatation of pre-existing vascular conduits caused by increased portal pressure, as well as vascular endothelial growth factor mediated

angiogenesis.¹⁴ This heralds splanchnic vasodilation with increased blood inflow to splanchnic organs and the portal system. Splanchnic vasodilation leads to systemic vasodilation; the ensuing effective hypovolemia triggers expansion of the plasma volume and increases the cardiac output. This hyperkinetic circulation further increases the blood flow to splanchnic organs, which contributes to an additional increase in portal pressure. The effects of NSBBs are summarised in Fig.14. NSBBs, via β_1 -adrenergic blockade, reduce heart rate and cardiac output with a decrease in flow of about 20%. Whereas via β_2 -adrenergic blockade, NSBBs cause splanchnic vasoconstriction due to un-opposed adrenergic tone, with a subsequent additional decrease in portal-collateral blood flow of about 15%, for a total 35% reduction in portal venous inflow.

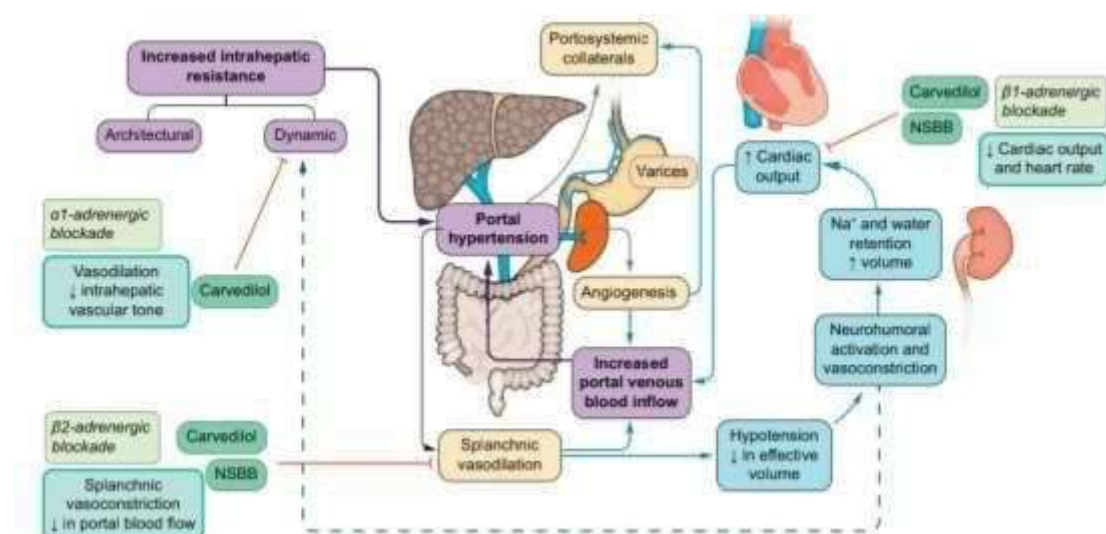


Fig. 14.. Pathophysiology of portal hypertension in cirrhosis and mechanisms and sites of action of non-selective beta-blockers. NSBB, non-selective beta blocker.

This is the mechanism by which NSBBs decrease the portal pressure by approximately 15%. Via an unopposed adrenergic tone, NSBBs cause a mild increase in peripheral and hepatic resistance, which explains why patients under NSBB do not develop arterial hypotension and why the effect on portal pressure is relatively mild. Carvedilol is a NSBB that has an intrinsic anti- α_1 adrenergic effect, which causes intrahepatic vasodilatation and further decreases portal pressure. Although carvedilol is more effective in reducing hepatic venous pressure gradient (HVPG) than propranolol or nadolol, at relatively high doses (over 25 mg/d) it may decrease mean arterial pressure (MAP). At low doses (6.25–12.5 mg/d) carvedilol does not

cause hypotension but decreases portal pressure significantly more than propranolol. Low doses cause only a moderate decrease in cardiac output and heart rate. This could explain why carvedilol has been better tolerated than therapeutic doses of propranolol, established after titration according to heart rate, arterial pressure and clinical tolerance.¹³ Clinical benefit from NSBBs stems from a significant reduction in the portal pressure gradient, determined clinically at hepatic vein catheterisation as the HVPG. The gradient must decrease by at least 10% of baseline (preferably by at least 20%) or below 12 mmHg to prevent first variceal bleeding (or liver decompensation).¹⁶

Pre-primary prophylaxis	Prevention of decompensation	Prevention of first variceal bleeding	Prevention of variceal rebleeding	Gastric varices	Portal hypertensive gastropathy
>1 RCT failed to show prevention of large varices and more adverse events	1 RCT in compensated patients with CSPH	Various RCT meta-analyses: - Decreases bleeding - Improves survival Compensated and high-risk varices: I:1 Decompensated and high-risk varices: I:1 Both GRADE 1 Level 1a	Various RCT meta-analyses: - Decreases rebleeding - Improves survival Patients without and with ascites and previous variceal bleeding: I:1 GRADE 1 Level 1a	Prevention of first bleeding GOV1-2, IGV1: III:2 Indication Prevention of rebleeding: cyanoacrylate superior (RCT) and no additional benefit from NSBB GRADE 2, Level III No strong evidence of indication	1 RCT: - Decreases rebleeding No RCT designed for prevention of first bleeding: I:1 GRADE 1 Level 1b Indication
No indication to prevent varices or progression	Indication	Indication	Indication		

Indications for beta-blockers in cirrhosis: levels of evidence and grade of recommendation

Fig. 15 Levels of evidence for non-selective beta-blockers in cirrhosis according to indication. CSPH, clinically significant portal hypertension; GOV1-2, gastroesophageal varices type 1/2; IGV1, isolated gastric varices type 1; NSBB, non-selective beta blocker; RCT, randomised controlled trial reflecting a favourable impact on the natural history of the disease; this is one of the advantages of NSBBs compared to endoscopic therapy. The level of evidence for NSBB use in the main indications of cirrhosis is summarised in Fig. 15.

To prevent rebleeding, it should drop by at least 20% or below 12 mmHg.^{2,13,17–20} Although this is achieved in about 50% of patients receiving propranolol,²¹ the proportion of responders increases to about 75% when using carvedilol (even in propranolol non-responders). Satisfactory responses to NSBBs are associated with a decreased risk of bleeding, as well as a lower risk of ascites, SBP, hepatorenal syndrome (HRS) and a better survival rate.

INDICATIONS

Prevention of first variceal bleeding (primary prophylaxis)

Patients with high-risk varices and compensated cirrhosis. Currently, NSBBs and endoscopic band ligation (EBL) are considered equally effective in preventing first bleeding in patients with high-risk varices, i.e. medium to large varices or small varices with red wale marks or in patients with decompensated cirrhosis (Child-Pugh B/C). NSBBs are favoured over endoscopic therapy in patients with small, high-risk varices, given the size of the varices. In patients with compensated cirrhosis and high-risk varices, the primary goal of therapy is not limited to bleeding prevention (that is not the most common event), but must also focus on preventing decompensation of cirrhosis (ascites, variceal bleeding or hepatic

encephalopathy). However, the vast majority of studies were only designed to evaluate reductions in the risk of haemorrhage and subsequent bleeding-related death. Moreover, most studies included both compensated and decompensated patients. As stated above, it is now preferred to consider therapy according to the stage of the disease; treating compensated patients to prevent decompensation and decompensated patients to prevent liver transplantation and death. Considering this, pharmacological therapy may be a better approach than endoscopic treatment, given its ability to prevent decompensation. It is well known that ascites may be prevented in haemodynamic responders to NSBBs, while this is not possible with endoscopic treatments. NSBBs are effective in preventing first bleeding event in patients with cirrhosis, independent of disease severity. In 1999, a meta-analysis of RCTs selected 8 studies including patients with medium-large varices. This meta-analysis compared NSBBs (propranolol/nadolol) to placebo or nonactive treatment and demonstrated a clear reduction in absolute risk of bleeding and bleeding-related mortality, but not overall mortality. The absolute risk reduction of first variceal haemorrhage within 2 years of follow-up was –10% in patients with NSBBs vs.

placebo. A small decline in absolute mortality rate, of -4% was found, approaching statistical significance. When the analysis was stratified to patients with high-risk varices, the bleeding rate in treated patients diminished significantly, by -16%.

Prevention of decompensation

Data from trials demonstrating the effect of NSBBs on the prevention of clinical decompensation were non-existent. Previous trials illustrated that decompensation risk was concentrated almost exclusively in patients with a baseline HVPG >10 mmHg, the threshold defining CSPH.⁵² Moreover, patients with CSPH exhibit a greater HVPG response to NSBBs than those without, suggesting that NSBBs may be an effective option to prevent decompensation, and that compensated patients with CSPH, but without high-risk varices, would be the ideal population to test this hypothesis. The PREDESCI trial, a multicenter, double-blind, RCT adopted this set-up and investigated whether long-term treatment of patients with compensated cirrhosis and CSPH with NSBBs might prevent progression to clinical decompensation or death. Patients developing moderate-large varices in both arms received EBL. This is the first RCT

to show that long-term treatment with NSBBs decreases clinical decompensation or liver-related death by half. This was mainly due to decreased rates of ascites, which is the most common decompensating event and for which there was previously no effective preventive drug therapy. There were no differences in the bleeding incidence in the study, probably due to the use of EBL in patients developing high-risk varices. One likely explanation is that the study showed that NSBBs, but not placebo, significantly reduced the HVPG at each yearly control, and that reductions of at least 10% from baseline or to below 10 mmHg conferred marked protection from decompensation and death during follow-up.

Prevention of the formation or growth of varices (preprimary prophylaxis)

Patients with no varices or non-high-risk varices and compensated cirrhosis. Presently, there is not enough evidence to support the use of NSBBs to prevent the development or growth of varices in patients with cirrhosis without varices or with small varices without red wale signs. One French study evaluated the effect of propranolol on preventing the development of large oesophageal varices over 2 years in patients with or without small varices.⁴⁵ More than twice the

patients assigned to propranolol developed varices compared to placebo, but one-third of the patients were lost to follow-up, in addition to those who suspended therapy because of intolerance. Bleeding and mortality rates were similar. A multicentre, single, double-blind RCT of timolol vs. placebo showed that, after 55 months, 39% and 40% of patients in the timolol and placebo groups, respectively, developed varices. Additionally, adverse events were more frequent in the timolol group. However, the study disclosed that the development of large varices, variceal bleeding, ascites, encephalopathy, and death did not occur when HVPG remained below 10 mmHg, and that varices developed much less frequently when HVPG was decreased by over 10% of baseline. A therapeutic benefit of timolol in preprimary prophylaxis could not be established.⁴⁶ Among possible causes are sample size distribution and inclusion of patients without CSPH (HVPG < 10 mmHg). Around 50% of the patients did not have CSPH and, thus, had not fully developed a hyperdynamic circulatory state. At this stage, the effect of propranolol on portal pressure has been shown to be almost negligible. More recently, Sarin et al. showed that in patients with cirrhosis and small oesophageal varices, NSBBs were unable

to prevent the growth of varices, variceal haemorrhage, or mortality. In contrast, 2 studies showed evidence in favour of beta blockers to delay growth of small varices. One RCT comparing nadolol to placebo reported cumulative risks of variceal progression in 20% vs. 51%, for the nadolol and placebo groups, respectively. The cumulative probability of variceal bleeding was also lower in patients randomised to nadolol ($p = 0.02$). Survival was not different and adverse effects resulting in withdrawal were more common in the nadolol group. Carvedilol was tested in another RCT against placebo to assess the delay in small varices progression; this study showed that 79% of patients in carvedilol group vs. 61% of patients in placebo group were free from progression to large varices ($p = 0.04$). No differences were found regarding bleeding events, mortality or adverse side effects. A meta-analysis of 6 RCTs including patients with no or small varices found no significant benefit for NSBBs compared to placebo for the prevention of large varices, first variceal bleeding and death. Overall, the evidence is conflicting regarding an impact of beta-blockers on slowing the progression of small varices to large varices in patients with cirrhosis. At this stage, treatment should be centred on eliminating or controlling the cause of

liver disease to attempt regression of architectural changes and reduction of intrahepatic resistance.

Prevention of rebleeding and death (secondary prophylaxis)

The main goal of treating patients with cirrhosis after an acute variceal haemorrhage, as first decompensating event, has been to prevent recurrent variceal bleeding. However, these patients very frequently show additional manifestations of decompensation, such as ascites or hepatic encephalopathy, and have a poor prognosis. Thus, since Baveno VI, the aim of therapy in these cases should be liver transplantation and death prevention, while decreasing further decompensation rates would represent a secondary endpoint. Nonetheless, to date, trials have aimed primarily at recurrent variceal bleeding prevention, so the available data on outcomes, as per Baveno VI, are limited. Baveno VI recommends a combination of NSBBs (propranolol or nadolol) and EBL for rebleeding prevention. A meta-analysis of 12 RCTs comparing NSBBs vs. placebo showed a mean absolute reduction of rebleeding of 21% in the NSBB group.⁵³ Nine RCTs comparing propranolol and sclerotherapy were analysed. Sclerotherapy was more effective in preventing variceal rebleeding,

but with significantly higher adverse event rates, and no difference in survival rates. In a meta-analysis, the combination of NSBBs and low-dose ISMN was not significantly better than NSBBs alone, but had a higher rate of adverse events. In 2012, a meta-analysis of 9 trials assessed the effects of EBL plus NSBBs±ISMN vs. monotherapy (EBL or NSBBs±ISMN) for secondary prevention of recurrent bleeding. Combination therapy reduced mortality related to rebleeding (RR 0.52; number needed to treat = 33) and the risk of recurrent bleeding from oesophageal varices (RR 0.68; number needed to treat = 8). Four trials comparing drugs alone (NSBB+ISMN) or associated with EBL, including 409 patients, demonstrated that variceal rebleeding decreased with combined therapy ($p < 0.01$), but rebleeding from oesophageal ulcers increased ($p = 0.01$). Overall, there was a trend towards lower rebleeding (RR 0.76; 95% CI 0.58–1.00) without significant effects on mortality (RR 1.24; 95% CI 0.90–1.70). Combination therapy (NSBB+ISMN) was only slightly more effective than drug monotherapy. An individual patient data meta-analysis of 7 trials comparing combined EBL + NSBB vs. monotherapy (either NSBBs or EBL) showed that compared with EBL alone, EBL + NSBB reduced rebleeding in both

Child-Pugh A and B/C patients, with a significant reduction in mortality in Child-Pugh B/C patients (incidence rate ratio[IRR] 0.46; 95% CI 0.25–0.85), whereas NSBBs alone performed as well as combination therapy. This study highlighted the independent role that NSBBs play in modifying survival, particularly in patients with advanced liver failure (Child-Pugh B/C). Thus, it has been suggested that patients with contraindications or who cannot tolerate NSBBs should be considered for transjugular intrahepatic portosystemic shunt (TIPS), particularly in the presence of another indication, i.e., difficult to treat or refractory ascites.

Regarding carvedilol, 1 trial compared the safety and efficacy of carvedilol to nadolol plus ISMN in preventing variceal rebleeding. The treatments were equally effective with similar mortality rates, but the carvedilol group had significantly less adverse events (3% vs. 46%, $p < 0.0001$).⁵⁷ A multicentre RCT with 64 patients compared carvedilol and EBL and reported no difference for rebleeding and a trend towards reduced mortality for carvedilol (27% vs. 52%, $p = 0.110$).

More recently, a meta-analysis compared the efficacy and safety of carvedilol plus

EBL vs. traditional NSBBs plus EBL in preventing variceal rebleeding. Carvedilol decreased rebleeding rates ($p < 0.001$) and drug-related adverse events ($p < 0.001$) more than traditional NSBBs. No difference was noted with respect to mortality. Nevertheless, these findings must be interpreted cautiously given the overall suboptimal quality of the eligible studies and the lack of HVPg.

BETA-BLOCKER

CONTRAINDICATIONS, DOSAGE AND SIDE EFFECTS

Contraindications and dosage

Absolute or relative contraindications for NSBBs are present in around 15% of patients because of coexisting conditions and, in another 15%, dose reduction or withdrawal may be necessary because of adverse effects. These limitations should not discourage patients and clinicians from using NSBBs for the indications previously described, given the firm evidence of their efficacy in cirrhosis and PH. Although limited data shows that there is no correlation between the decrease in HVPg and a decrease in heart rate, current clinical practice recommends an approximate 25% decrease in heart rate as evidence of adequate beta-adrenergic blockade with NSBBs. It is usually advised that NSBBs be titrated until the

maximum tolerated dose, provided the systolic blood pressure remains above 90 mmHg and heart rate above 55 bpm. Specific data on titration, frequency of administration, and maximum doses for each NSBB in tabel . Once started, NSBBs should be maintained for life. According to Baveno I-VI, no endoscopic surveillance is required once patients have achieved a stable maintenance dose. (See Table 1)

Side effect

NSBBs can have a negative impact on a patient's quality of life. This is mainly due

to adverse effects such as worsening fatigue, reduced exercise capacity and sexual dysfunction. These symptoms are unspecific and can be attributed to cirrhosis or depression. Therefore, dose reduction or switch to another NSBB (for instance, carvedilol if the patient was on propranolol or nadolol) is recommended rather than discontinuing therapy. After initiating NSBBs, they should be reevaluated periodically as intolerance or contraindications can develop later on.

Table 1

Beta blocker	Dosing	Target	Follow up
Propranolol	Start 20-40 mg orally twice a day Increase by 20 mg twice a day steps every 2–3 days until target; reduce gradually if intolerant U Maximal dosage:- 320 mg/d (no ascites) 160 mg/d	Resting heart rate of 55-60 bpm Avoid systolic pressure <90 mmHg Final dose tolerate	Assess target heart rate and tolerance at each visit Lifelong, assess compliance No follow-up endoscopy required
Nadolol	Start 20-40 mg orally once a day 20 mg once a day increments every 2–3 days until target; reduce gradually if intolerant Maximal dosage:- 160 mg/d (no visible ascites)- 80 mg/d (visible ascites)		
Carvedilol	Start with 6.25 mg once a day After 3 days increase to 6.25 mg twice a day Maximal dose:- 12.5 mg/d (if arterial hypertension, consider 25 mg/d)	Avoid systolic blood pressure 90 mmHg Final dose tolerated	Lifelong, assess compliance No follow-up endoscopy required

It is currently unknown which threshold of blood pressure and/or heart rate and cardiac output reduction can be considered safe, particularly in patients with decompensated cirrhosis. Specific studies examining this issue are warranted, although it is clear that adverse events are dose related.

ANTI-BIOTICS

Treatment of bacterial infections

The commonest infection in cirrhotic patients is spontaneous bacterial peritonitis (SBP), followed by urinary tract infection, pneumonia, bacteremia following a therapeutic procedure, cellulitis, and spontaneous bacteremia. Culture positive infections are reported in 50-70% of cases. The causative organisms of community acquired infection are Gram-negative bacilli (GNB), especially *Escherichia coli* (*E. coli*), in about 60%, Gram-positive cocci (GPC) in about 30-35% and mixed in 5-10%. The figures are reversed for nosocomial infections; 60% GPC and 30-35% GNB, due to previous antibiotic exposure.

With *E. coli* being the commonest in community, the next most frequently isolated bacteria are *Staphylococcus aureus* (*S. aureus*), *Enterococcus faecalis*, and *Streptococcus pneumoniae* (*S.*

pneumoniae). In the case of SBP, less-virulent strains of *E. coli* may be causative as liver function deteriorates, suggesting that in advanced cirrhosis, bacteria do not need to develop strategies to confound host defences and invade the host. Fungal infections (*Candida* spp.) are responsible for up to 15% of severe sepsis in patients with cirrhosis. Cirrhotic patients with severe sepsis and septic shock require emergency care during the early stage of sepsis (especially the first 6 h). Early and appropriate initiation of antibiotics correlates with higher survival rate.

A retrospective study by Kumar et al suggested that each hour of delay decreased survival by 7.6%. Choosing adequate empiric antimicrobial treatment will therefore improve the prognosis of patients. Microbiological samples should be taken as early as possible when infection is suspected, before starting empiric antibiotic therapy and empiric antimicrobial therapy will need to be adapted to local epidemiology, prevalence of antibiotic resistance and results of bacterial cultures. Empiric antibiotic treatments for classical community-acquired bacterial infections are shown in Table 2.

Table 2: Empirical antibiotic therapy for community-acquired bacterial infections in cirrhosis

Type of infection	Organism	Antibiotics
Spontaneous bacterial peritonitis (SBP)	Escherichia coli Streptococcus viridans Enterobacterspp	Cefotaxime (2g/6 h or 2g/12 h IV) or amoxicillin/clavulanic acid (1-0.2 g/8 h then 0.5-0.125g/8 h PO) or ofloxacin (400 mg/12 h PO) or ciprofloxacin (200 mg/12 h IV then 500 mg/12 h PO)
Urinary tract infections	Escherichia coli Klebsiellapneumoniae Enterococcus spp.	Ciprofloxacin (500 mg/12 h PO) or cotrimoxazole (160-800 mg/12 h PO) or amoxicillin/clavulanic acid(1-0.2 g/8 h IV)
Pneumonia	Streptococcus pneumonia Staphylococcus aureus Escherichia coli	Amoxicillin/clavulanic acid (1-0.2 g/8 h IV) and macrolide or moxifloxacin (400 mg/24 h PO)
Soft tissue infections	Staphylococcus aureus Streptococcus pyogenes Klebsiellapneumoniae Escherichia coli Pseudomonas aeruginosa	Ceftazidime (2 g/8 h IV + oxacillin 2 g/6 h IV)

MEDICAL PROCEDURE

Medical procedure 3 methods are use

- Rubber band ligation
- Therapeutic endoscopy
- Transjugularintraheptic portosystemic shunt



Figure 16: Endoscopic images of fundic gastric varices before (A), during (B, C) and after (D) thrombin injection.

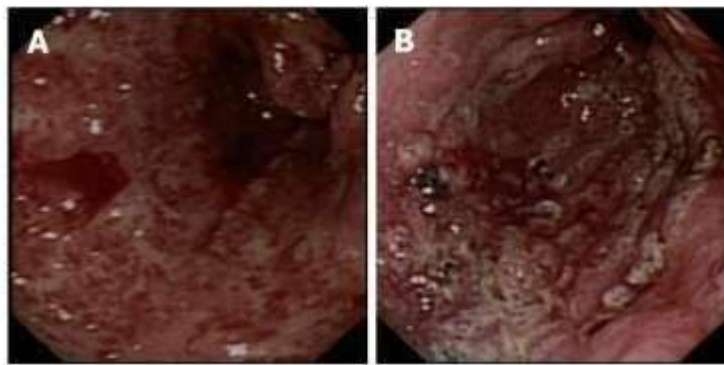


Figure 17: Endoscopic image. A: Gastric antral vascular ectasia (GAVE) (diffusetype) with active bleeding prior to argon plasma coagulation (APC) treatment; B: GAVE (diffuse type) immediately after APC treatment.

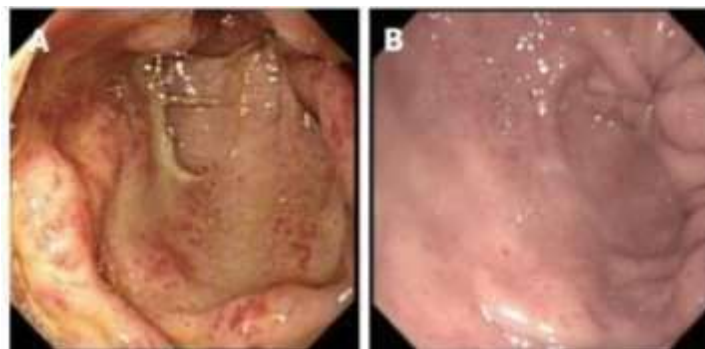


Figure 18: Endoscopic image. A: Gastric antral vascular ectasia-induced symp-tomatic anemia; B: Endoscopic image of the same patient 2 years later, after several argon plasma coagulation sessions. The number of angioectatic lesions in the gastric outlet had dramatically decreased

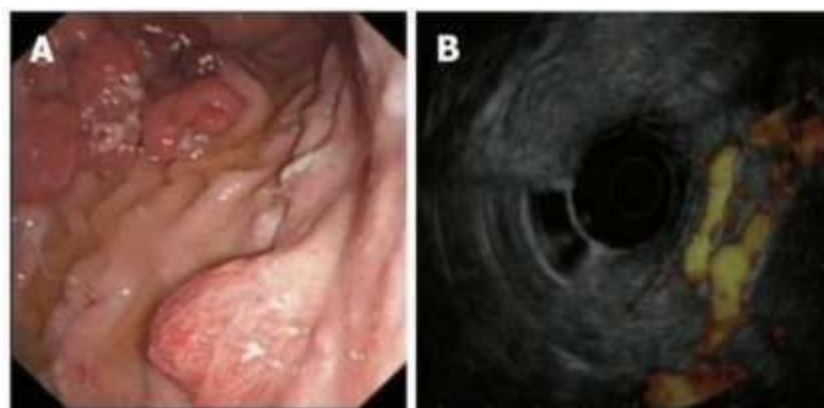


Figure 19: Endoscopic image of gastric irregular submucosal lesion. A: Gastric irregular submucosal lesion in a patient with portal hypertension; B: The same lesion examined under color Doppler endoscopic ultrasound. The submucosal lesion was hypervascular and represented a gastric varix.

Gastric antral vascular ectasia

Gastric antral vascular ectasia (GAVE) is related to portal hypertension in about 30% of patients, and accounts for 4% of nonvariceal upper GI bleeds. Unlike PHG, GAVE does not respond well to reduction in portal pressure. The Nd:YAG laser has been widely used in the treatment of GAVE and is the most commonly reported endoscopic modality in cirrhotic and non-cirrhotic patients, with a reported overall success rate of almost 90%, although the authors did not distinguish the etiology of GAVE when reporting the outcomes. APC has also proved to be effective for the treatment of GAVE-related bleeding, and it is extensively used in our unit, with a success rate of > 85%; success is defined as control of bleeding, stabilization of hemoglobin at >100 g/dL, or hemoglobin increase >10% from pretreatment level, and reduction of transfusion requirements by >50% in transfusion-dependent patients. An average of four sessions of APC is usually required (Figures 17 and 18). In two published studies, with a total of 37 patients with cirrhosis, success rates in controlling bleeding were very high, and the reported rebleeding rates were between 12% and 20% after 2 years follow-up. Although the success rates of the two aforementioned modalities are comparable, APC treatment is probably

the therapy of choice due to the technical ease, safety and low cost. Other endoscopic techniques have been positively reopendoscopic mucosal ablation and cryotherapy.

ADVANCED ENDOSCOPIC PROCEDURES AND THEIR VALUE IN LIVER DISEASE EUS

EUS has been used to assist in the management of portal hypertension. Doppler EUS is of significant value in differentiating ectopic varices from other submucosal lesions (Figure 19), and several EUS-assisted techniques have been used to identify the precise site for the intravariceal injection of sclerosant agents. Linear color EUS-guided sclerotherapy has proved to be effective in the eradication of esophageal varices, in two small studies with recurrence reported at 0% and 8.3%, respectively. EUS catheter probes and high-frequency (20 MHz) miniprobe have both been used successfully before and after esophageal variceal sclerosant injection in two different studies to assess eradication and variceal recurrence. After a mean followup of 24 mo, variceal recurrence was reported at 16.6% and 26.3%, respectively. Although the overall patient numbers are small, linear EUS seems to be the superior

modality in assisting treatment of esophageal varices, because it permits the targeting of the feeding vessels. EUS-assisted injection of cyanoacrylate for the treatment of gastric varices has been described in 54 patients with a mean follow-up of 24 mo. Varices recurred in 35% of patients. Furthermore, a series of 15 patients with gastric or ectopic varices treated with thrombin injection in conjunction with a variety of EUS techniques (Figure 20) has recently been reported in our unit, and this proved to be effective in controlling active bleeding and achieving variceal eradication.



Figure 20: Color doppler endoscopic ultrasound image of duodenal varices after thrombin injection. The absence of blood flow and the speckled appearances were suggestive of thrombus formation.

Capsule endoscopy

Esophageal capsule endoscopy (OCE) is an alternative to conventional upper GI endoscopy for the diagnosis of varices in

complex patients with portal hypertension. In a recent meta-analysis of seven studies involving 446 patients, OCE had a sensitivity of 85.8% and specificity 80.5% in detecting esophageal varices. However, a multicenter trial evaluating the efficacy of OCE in esophageal varices screening was less encouraging, because the standard of < 10% difference between capsule and conventional endoscopy was not met. This is not surprising, because the two techniques differ in that during conventional endoscopy, the esophagus is inevitably insufflated with air and varices can appear more flattened than during OCE examination. Further studies to take this into account are necessary. Nevertheless, OCE remains a useful tool for screening of varices in certain patient groups; patients who poorly tolerate endoscopy or who have significant comorbidity, thus increasing the risks of repeated endoscopy, and patients with high risk of variant Creutzfeldt-Jakob disease. Although this technique is limited by availability and high costs, OCE can be cost-effective for variceal screening of patients with coagulation abnormalities (e.g., hemophilia) with coexisting liver disease, because it does not require prophylactic clotting factor administration, unlike conventional endoscopy. Serial capsule examinations in the same patient

may provide significant diagnostic information regarding progression of varices. Small bowel capsule endoscopy (SBCE) has been used to characterize PHE (Figure 21), and is of value in the diagnosis of this condition in patients with advanced liver disease who continue to bleed despite treatment of esophageal/gastric varices or portal gastropathy (Figure 22). The role of SBCE in portal hypertension has yet to be defined, but it is likely that it will remain a valuable tool in certain groups of patients with liver disease.



Figure 21: Small bowel capsule image of portal hypertensive enteropathy and stigmata of recent bleeding. Engorged small bowel villi and microhemorrhagic spots were visible.



Figure 22: Small bowel capsule image of portal hypertensive enteropathy with snake-skin-like appearance of the mucosa and red spots as stigmata of recent bleeding.

Novel techniques and the biliary tree

Novel endoscopic modalities have been compared with conventional ERCP and brushcytology.

Transpapillarycholangioscopy with tissue sampling has proved to be more sensitive (92% vs 66%) and specific (93% vs 51%) than ERCP to detect cholangiocarcinoma in PSC. In a small study, narrow band imaging has demonstrated superior visualization of biliary lesions compared with conventional white light imaging. In another study, transpapillaryintraductal ultrasound was superior to ERCP for the detection of cholangiocarcinoma in PSC in terms of sensitivity (87.5% vs 62.5%) and specificity (90.6% vs 53.1%).Spyglass™

is a new single-operator system used for the diagnosis of a variety of pancreatobiliary disorders, such as the definition of indeterminate strictures and filling defects prior to stone extraction.

Confocal laser endomicroscopy (—miniprobe) is a new field of endoluminal imaging that offers extremely high magnification and resolution. This technique allows visualization of pancreatic and biliary ducts. In a pilot study of 14 patients with biliary strictures, miniprobe based microscopy after fluorescein administration proved to be more accurate than brushings and biopsy in distinguishing benign from malignant

strictures (Figure 23). A novel alternative is direct cholangioscopy using ultra-slim endoscopes (4.9-5.9 mm). These endoscopes, initially developed for transnasal endoscopy, can be safely inserted into the bile duct following sphincterotomy, and not only permit high-resolution images, but also biopsy and other interventional procedures in the bile ducts, such as hydraulic lithotripsy and division of strictures in benign biliary disease. This technique is currently under development and after a full range of endoscopic accessories are available for endobiliary interventions, it could be an effective and safe approach for patients with difficult to manage biliary disease.

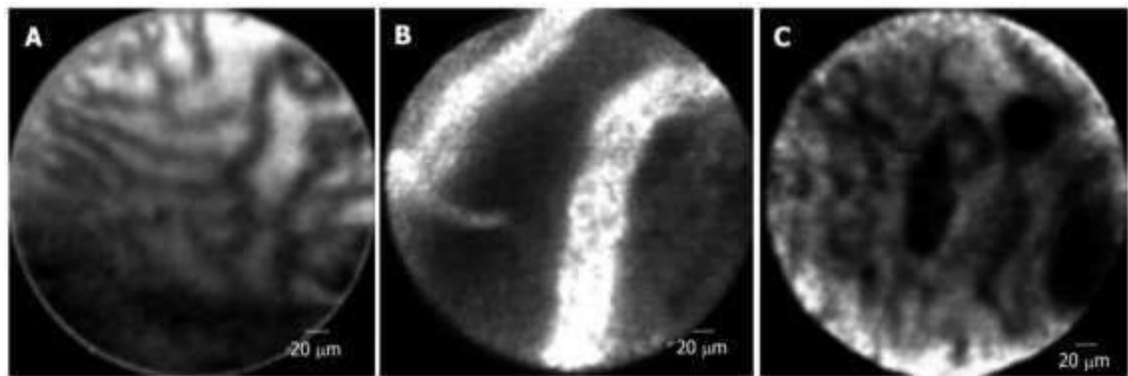


Figure 23: Endomicroscopy image. A: Image from Cellvizio bile duct endomicroscopy. The regular reticular pattern of thin dark structures with low signal (dark) characterized the normal bile duct (Image courtesy of www.cellvizio.net); B: Abnormal bile duct appearances in Cellvizio endomicroscopy; isolated blood vessels with very strong signal (with strands) suggestive of tumor neovascularization of cholangiocarcinoma (Image courtesy of www.cellvizio.net); C: Reticular pattern of dark bands and dark clumps or glands suggestive of cholangiocarcinoma (Image courtesy of www.cellvizio.net).

SURGERY

Most surgical procedures, whether performed under general, spinal or epidural anesthesia, are followed by minor elevations in serum liver biochemical test levels (1, 2). Minor postoperative elevations of serum aminotransferase, alkaline phosphatase or bilirubin levels in patients without underlying liver disease are not clinically significant. However, in patients with underlying liver disease, and especially those with compromised hepatic synthetic function, surgery can precipitate hepatic decompensation. Operative risk correlates with the severity of the underlying liver disease and the nature of the surgical procedure. In patients with cirrhosis, the Child class and Model for End-Stage Liver Disease (MELD) score have been demonstrated to correlate with preoperative risk.

Reduced Hepatic Blood Flow, Hypoxemia, and Altered Drug Metabolism

Cirrhosis causes a hyperdynamic circulation with increased cardiac output and decreased systemic vascular resistance. At baseline, hepatic arterial and venous perfusion of the cirrhotic liver may be decreased: portal blood flow is reduced as a result of portal hypertension, and arterial blood flow can be decreased

because of impaired autoregulation. Moreover, patients with cirrhosis may have alterations in the systemic circulation due to arteriovenous shunting and reduced splanchnic inflow. The decreased hepatic perfusion at baseline makes the cirrhotic liver more susceptible to hypoxemia and hypotension in the operating room. Anesthetic agents may reduce hepatic blood flow by 30–50%, and agents such as isoflurane, desflurane, sevoflurane and propofol, which cause less perturbation in hepatic arterial blood flow than other inhaled anesthetic agents, are preferred for patients with liver disease. Additional factors that may contribute to decreased hepatic blood flow intraoperatively include hypotension, hemorrhage and vasoactive drugs. Intermittent positive-pressure ventilation and pneumoperitoneum during laparoscopic surgery mechanically decrease hepatic blood flow. In addition, traction on abdominal viscera may cause reflex dilatation of splanchnic veins and thereby lower hepatic blood flow. Risk factors for acute intraoperative hypoxemia in patients with cirrhosis include ascites, hepatic hydrothorax, hepatopulmonary syndrome (the triad of liver disease, an increased alveolar-arterial gradient and intrapulmonary shunting), which is found in 5–32% of cirrhotic patients followed at transplant centers, and portopulmonary

hypertension, which is found in up to 6% of patients with advanced liver disease and which increases postoperative mortality after noncardiac surgery. In general, ascites and hepatic hydrothorax should be treated preoperatively, and elective surgery should be avoided in patients with either hepatopulmonary syndrome or portopulmonary hypertension.

Operative Risk in Patients with Liver Disease

In a patient with liver disease, surgical risk depends on the severity of liver disease, nature of the surgical procedure and presence of comorbid conditions. There are a number of liver-related contraindications to elective surgery (Table 1). When these contraindications are absent, patients should undergo a thorough preoperative evaluation, and their conditions should be optimized prior to elective surgery. Patients found to have advanced liver disease may benefit from alternative nonsurgical therapies when available and appropriate. Once liver disease is identified in a patient in need of surgery, an assessment of the severity of liver disease should be undertaken, as should an evaluation for other known risk factors for perioperative mortality (Table 2). Data from studies of patients with cirrhosis suggest that the severity of liver

disease can best be assessed by the Child-Turcotte-Pugh (CTP) score (Child, or Child-Pugh, class) and MELD score (see later). The majority of published studies describing.

Table 3: Contraindications to Elective Surgery in Patients With Liver Disease

Acute liver failure
Acute renal failure
Acute viral hepatitis
Alcoholic hepatitis
Cardiomyopathy
Hypoxemia
Severe coagulopathy (despite treatment)

Table 4: Risk Factors in Patients with Cirrhosis Who Undergo Surgery

Patient Characteristics:
Ascites
Child class
Encephalopathy
Hypoalbuminemia
Hypoxemia
Infection
Malnutrition
MELD score
Portal hypertension
Prolonged prothrombin time (2.5 seconds) that does not Correct with vitamin K

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