LIVER CIRRHOSIS: NEW CONCEPTS

Irina Ivanova

ESS Gastroenterology, Hepatology and Nutrition, Department of Internal Diseases, Faculty of Medicine, Medical University of Varna

ABSTRACT

The term "cirrhosis" has been used for two centuries to define the end-stage of chronic liver diseases with different etiologies. The clinical manifestations of cirrhosis are related to portal hypertension, hepatic dysfunction progressing to liver failure and development of hepatocellular carcinoma, conditions with unfavorable prognosis. However, recent advances in the diagnosis and treatment of chronic liver diseases have changed the natural history of cirrhosis significantly. According to current concepts, liver cirrhosis is heterogeneous, multi-stage condition with variable prognosis. Cirrhosis is considered a dynamic, biphasic process, based on numerous clinical reports indicating the reversal of advanced fibrosis and cirrhosis after cessation of perpetual injury. This review was focused on current pathology and clinical staging of cirrhosis. The potential mechanism and proofs of concept for reversibility of cirrhosis were also discussed.

Keywords: *liver cirrhosis, fibrosis, portal hypertension, antiviral treatment*

INTRODUCTION AND DEFINITIONS

"Cirrhosis" (by Greek "κίρρος" – tawny), was initially used to describe nodular and firm-appearing liver in patients with chronic "burned out" liver disease, with an emphasis on the end-stage nature of this process and the poor survival. Sheila Sherlock's definition of liver cirrhosis was based on morphology: a *diffuse process of fibrosis and nodule formation*. Extensive fibrosis and disturbed normal lobular and vascular architecture result in progressive portal hypertension and liver dysfunction.

Address for correspondence:
Irina Ivanova
Clinic of Gastroenterology,
UMHAT "St.Marina,
1 Hristo Smirnenski Blv,
Varna 9010, Bulgaria
e-mail: irinaiivanova@abv.bg

Received: January 31, 2016
Accepted: April 11, 2016

The pathological mechanisms in the development of cirrhosis are persisting inflammation and necrosis, deposition and accumulation of aberrant extracellular matrix (fibrosis), "capillarization" of sinusoids, vascular reorganization, with thrombosis, obliteration, recanalization of veins and arteriovenous shunts, neo-angiogenesis with formation of new vessels and collaterals, and regeneration (1). Fibrosis is not strictly "scarring" but rather dynamic balance of fibrogenesis and fibrinolysis and restoration. In general, the cirrhotic liver shows elements of both progression and regression, the balance determined by the severity and persistence of the underlying disease. On a cellular level, common pathogenic mechanisms exist: stellate cells and fibroblasts are the effectors of fibrogenesis, while parenchymal regeneration relies on hepatocytes and hepatic stem/progenitor cells.

Distortion of lobular and vascular architecture results in increased intrahepatic resistance, which in turn leads to portal hypertension. Portal hypertension is defined as a portal pressure greater than

5 mmHg, assessed by the hepatic venous pressure gradient (HVPG). Complications of cirrhosis develop once the portal pressure reaches a threshold level of 10 mmHg. This threshold level (10 mmHg) has been found to be of great prognostic value and has been termed "clinically significant portal hypertension" (CSPH) (2).

Intrahepatic structural abnormalities play a major role in the pathogenesis of portal hypertension. Other factors exist, such as active constriction of intrahepatic vessels (dynamic component) and increase in portal venous inflow, secondary to splanchnic vasodilation and hyperdynamic splanchnic circulation (a dominant factor in the maintenance of portal hypertension in severe cirrhosis).

Natural History of Cirrhosis

The natural history of cirrhosis is characterized by an asymptomatic stage – compensated cirrhosis, followed by a progressive phase marked by the development of complications of portal hypertension and/or liver dysfunction – decompensated cirrhosis. Decompensation is defined by clinical evidence of major complications of cirrhosis: ascites; hepatic encephalopathy; portal hypertensive gastrointestinal bleeding and jaundice. Further progression of a decompensated disease may be accelerated by other important complications, such as spontaneous bacterial peritonitis, refractory ascites, acute kidney injury (hepato-renal syndrome), re-bleeding, hepato-pulmonary syndrome and systemic infections, including sepsis. Development of hepatocellular carcinoma (HCC) can occur at every stage of the disease. Acute-on-chronic liver failure is an acute deterioration of patients with chronic liver disease, after a precipitating factor, characterized by (multi)-organ failure and a high risk of short-term death.

Mortality in patients with compensated cirrhosis is low, ranging from 1 to 3% per year, and significantly higher in patients with esophageal varices, compared to patients without esophageal varices. The development of esophageal varices is a major event in compensated cirrhosis, occurring with an incidence of 5 to 8% per year. Overall, decompensation happens at a constant rate of 5% per year and is again more frequent in patients with compensated cirrhosis with esophageal varices. Ascites is the most frequent complication, followed by bleeding, jaundice and encephalopathy. The decompensation event is associated with a one-year survival rate of ~80% (3,4).

The importance of bacterial translocation for the development of the clinical complications of cirrhosis is being recognized recently (5). Although the migration of bacteria or bacterial products from the intestinal lumen to the mesenteric lymph nodes exists in healthy individuals, this process is well controlled. In the presence of portal hypertension this is progressively deregulated to pathological bacterial translocation, leading to inflammation, immune activation and clinical consequences such as spontaneous bacteremia and spontaneous bacterial peritonitis. Furthermore, a pathological inflammatory response to bacterial products has been implicated in the development of encephalopathy, acute kidney injury and the additional increase of portal hypertension (6).

Stages of Cirrhosis

The natural history of cirrhosis has changed significantly in the recent years, as therapeutic advances in the field of chronic liver diseases allow patients with cirrhosis to survive in the long term, often with clinical and histological improvement after a successful etiological treatment. Cirrhosis is an extremely heterogeneous condition, extending from an early asymptomatic stage to an advanced disease with various complications, rather than a terminal stage of different chronic liver injuries (7). The evolution of cirrhosis is a multi-step series of events. To distinguish the heterogeneous phases of cirrhosis a five-stage system is proposed (Fig.1) (8). Although not validated by prospective large studies, this classification is of clinical importance:

- **Stage 1:** fully compensated cirrhosis, absence of varices; 1-year mortality rate ~1.5%; 1-year progression rate to stage 2 ~6.2% or to stage 3 or 4 ~4.2%;
- **Stage 2:** compensated cirrhosis, presence of esophageal varices; 1-year mortality rate is 2%; transition to decompensation (stage 3 or 4) happens in 12.2% patients per year;
- **Stage 3:** bleeding of the GI tract, related to portal hypertension (esophageal varices), without another decompensating event; 1-year mortal-

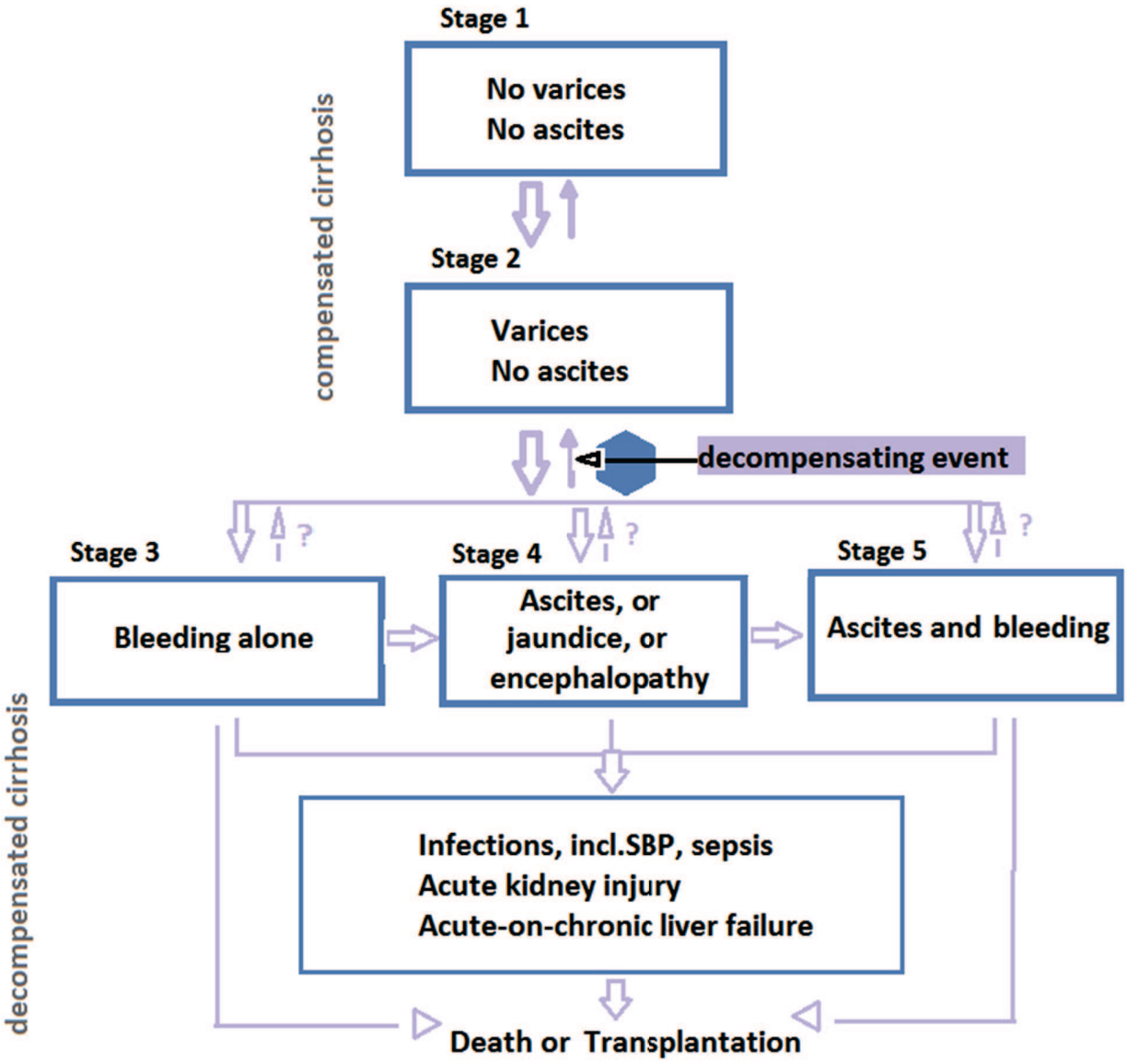

Fig. 1. Classification of severity of liver cirrhosis (five-stage concept model)

ity rate is 10%; 21% of patients develop other decompensating events (mostly ascites) per year;

- **Stage 4:** ascites, jaundice or encephalopathy; 1-year mortality rate increases to 21%; rate of transition to stage 5 is 10% per year;
- **Stage 5:** more than one complication, usually refractory ascites, intermittent encephalopathy, acute kidney injury, advanced liver dysfunction; 1-year mortality in this stage is at least 27%, increasing with the severity of decompensation to 57%.

HCC develops at every stage with a constant rate of 3% per year (Fig. 2). Individual risk factors for HCC have been determined as: age (above 40 years); gender (male); viral infections (HBV>HCV); alcohol consumption; diabetes; positive family history for cirrhosis and HCC; iron overload.

Stage 4 probably marks a critical threshold beyond which the chronic liver disease becomes a definite systemic disorder. The development of infections (spontaneous bacterial peritonitis, spontaneous bacteremia and sepsis) is a very important point in

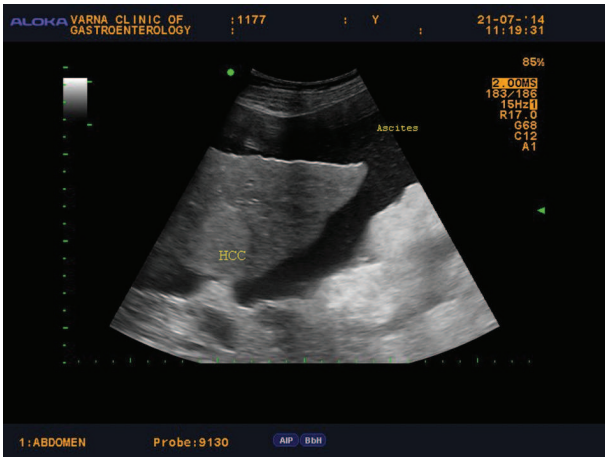

Fig. 2 .Abdominal ultrasound findings in patient with decompensated viral cirrhosis

stage 4 and stage 5 of cirrhosis. Once the infections develop the mortality rate rises four-fold (9).

The prognostic indicators in cirrhosis are: a model for end-stage liver disease (MELD), HVPG, Child-Turcotte-Pugh (CTP) score (and every component of the CTP score), obesity as well as presence of malnutrition. The age of the patient was also found to be predictive of survival. The MELD serves better than the CTP score for estimating 3-month and 6-month mortality. MELD includes objectively defined variables and has a dynamic nature, expressed within a continuous scale of 34 points. However, the CTP score determines better the long-term mortality and is well validated in the different etiologies of advanced chronic liver diseases.

Histological Classification of Cirrhosis ("Going Beyond Cirrhosis")

The approved systems for histological classification (Knodell, METAVIR, Scheuer-Batts, Kleiner scoring designed for non-alcoholic fatty liver disease) describe cirrhosis as a final single stage "4". Recently, a Modified Laennec Scoring System has been proposed by the International Liver Pathology Study Group, assessing three histological stages of cirrhosis, based on the thickness of fibrosis septa and the nodule size (10,11). Stage 4a corresponds to large, visible nodules with rounded contours and marked septation, but most septa are thin (only 1 broad septum is allowed). Stage 4b, or moderate cirrhosis, describes at least 2 broad septa (but not very broad); less than half of the biopsy length is composed by minute nodules. Stage 4c, or severe cirrhosis, is related to at least 1 very broad septum or more than a half of the biopsy length is composed of micronodules. Small nodule size is indicative of greater architectural distortion, massive tissue extinction, extensive scars and respectively low functional reserve of the liver and high intrahepatic resistance. The greater fibrosis area (liver collagen proportionate area calculated by quantitative image analysis and measurement of fibrosis septa), the greater the obstruction to the portal flow. The histological stages are significantly related to the severity of portal hypertension, proved by clinical studies with combining modalities of patient assessment (biopsy and HVPG measurement) (11-15).

Clinical Modalities for Diagnosis and Staging of Cirrhosis

Diagnosis of the etiology of cirrhosis is of key importance for the proper treatment (Table 1). The main causes of cirrhosis include chronic viral hepatitis (B, C, B+D), alcoholic liver disease and non-alcoholic fatty liver disease, autoimmune liver diseases, several inherited metabolic disorders and biliary diseases. Different etiologies cause variable patterns of fibrosis distribution, of regeneration and different rates of progression.

Liver biopsy (percutaneous or transjugular) remains the "gold" standard for diagnosis and staging of a diffuse liver disease, including cirrhosis. An important starting point is the adequate biopsy, containing at least 5 portal areas (11 are optimal), with a biopsy length of above 15 (20) mm, obtained with a needle of at least 17 gauge. A liver biopsy is an invasive procedure, associated with a small risk of severe complications like intraabdominal bleeding and biliary peritonitis. The limitations are related to a possibility of a "sample error", as the area of the obtained material is less than 1:10 000 of the whole liver size. Essentially, the disease stage is more than histologic fibrosis. Anamnesis for the duration of the liver disease and confounding factors, as well as physical exam showing skin changes of liver cirrhosis, palpation of firm liver, collaterals of anterior abdominal wall, splenomegaly and ascites **should not be forgotten as initial investigations.** Several clinical modalities are well validated for the assessment of severity and the staging of the chronic liver disease, measuring liver function and pathophysiology and estimating signs of portal hypertension:

Table 1. Main causes of cirrhosis and corresponding treatment

Etiology	Therapy
Viral hepatitis	
◆ Hepatitis B	Continuous viral suppression with nucleoside and nucleotide analogues
◆ Hepatitis C	Direct acting antivirals achieving HCV eradication
◆ Hepatitis B/D	Interferon-alpha
Alcoholic liver disease	Alcohol abstinence
Non-alcoholic fatty liver disease	Treatment of metabolic syndrome components
Autoimmune hepatitis	Corticosteroids and other immunosuppressive drugs
Metabolic	
◆ Hereditary hemochromatosis	Phlebotomy, iron-chelators
◆ Copper overload (Wilson's disease)	Copper chelators
◆ Alpha-1-antitrypsin deficiency	Transplant
◆ Type IV glycogenesis	Transplant
◆ Galactosaemia	Withdrawing of milk and dairy products
◆ Tyrosinaemia	Withdrawing of dietary tyrosine. Transplant
Drugs and toxins	Identify and stop the factor
Cholestatic (biliary) cirrhosis	
◆ Primary biliary cirrhosis	Urso-deoxy-cholic acid (UDCA)
◆ Primary sclerosing cholangitis	Transplant
◆ Overlap syndrome	UDCA, immuneosuppressive drugs, transplantation
◆ Secondary biliary cirrhosis	Relieve biliary obstruction
Hepatic venous outflow block	
◆ Budd-Chiari syndrome	Relieve main vein block. Transplant
◆ Cardiac cirrhosis	Treatment of cardiac cause
Cryptogenic	-

- **Transient elastography (TE, FibroScan):** quantifying the mechanical characteristics of the liver tissue – liver stiffness, related to loss of elasticity. Liver stiffness >20 kPa has been found to be in an excellent correlation with HVPG ≥10 mmHg (CSPH) in patients with chronic hepatitis C. According to the Baveno VI practice guidelines TE values < 10 kPa in the absence of other known clinical signs rule out cirrhosis; values between 10 and 15 kPa are suggestive of an advanced compensated liver disease but need further tests for confirmation; values >15 kPa are highly suggestive of cirrhosis, particularly with a viral etiology (2).
- **Serum markers and panels such as:** APRI; FibroTest; FibroMeter; Hepascore; ELF score; FibroSpect, combining laboratory findings of extensive fibrosis (decrease of platelet count, AST/ALT ratio above 0.8, lab tests for a decreased liver synthetic function) with serum levels of direct markers of extracellular matrix turn-over (hyaluronate, procollagen III N-terminal peptide, tissue inhibitors of matrix metalloproteinase-I, transforming growth factor-beta etc.) (16);
- **Clinical scores with prognostic value:** Child-Turcotte-Pugh (CTP) and MELD scores;
- **Abdominal ultrasound** assessment of the anterior liver surface, spleen size, Doppler parameters of portal hypertension; ascites; liver hydrothorax; presence and severity of collaterals (abdominal varices);
- **Upper endoscopy** for esophageal and gastric varices and/or portal hypertensive gastropathy; grading of varices and estimating the risk of bleeding;
- **Direct measurement of HVPG** by cannulation of the external jugular vein: a gold-standard procedure for an assessment of portal hyper-

tension and a definition of CSPH (HVPG≥10 mmHg), method with a great importance for the prognosis of cirrhosis and a tool for an estimation of the therapeutic efficacy.

Recently, an integrative clinical, histologic and hemodynamic approach has been proposed for the evaluation of a patient with advanced chronic liver disease (10). An integrated clinicopathologic approach should develop the diagnosis of advanced stage of liver disease with an emphasis on etiology, stage of cirrhosis and grade the severity in respect of prognosis, reveal the presence of other diseases (cofactors and comorbidities) and risk factors for malignancy (Fig. 3).

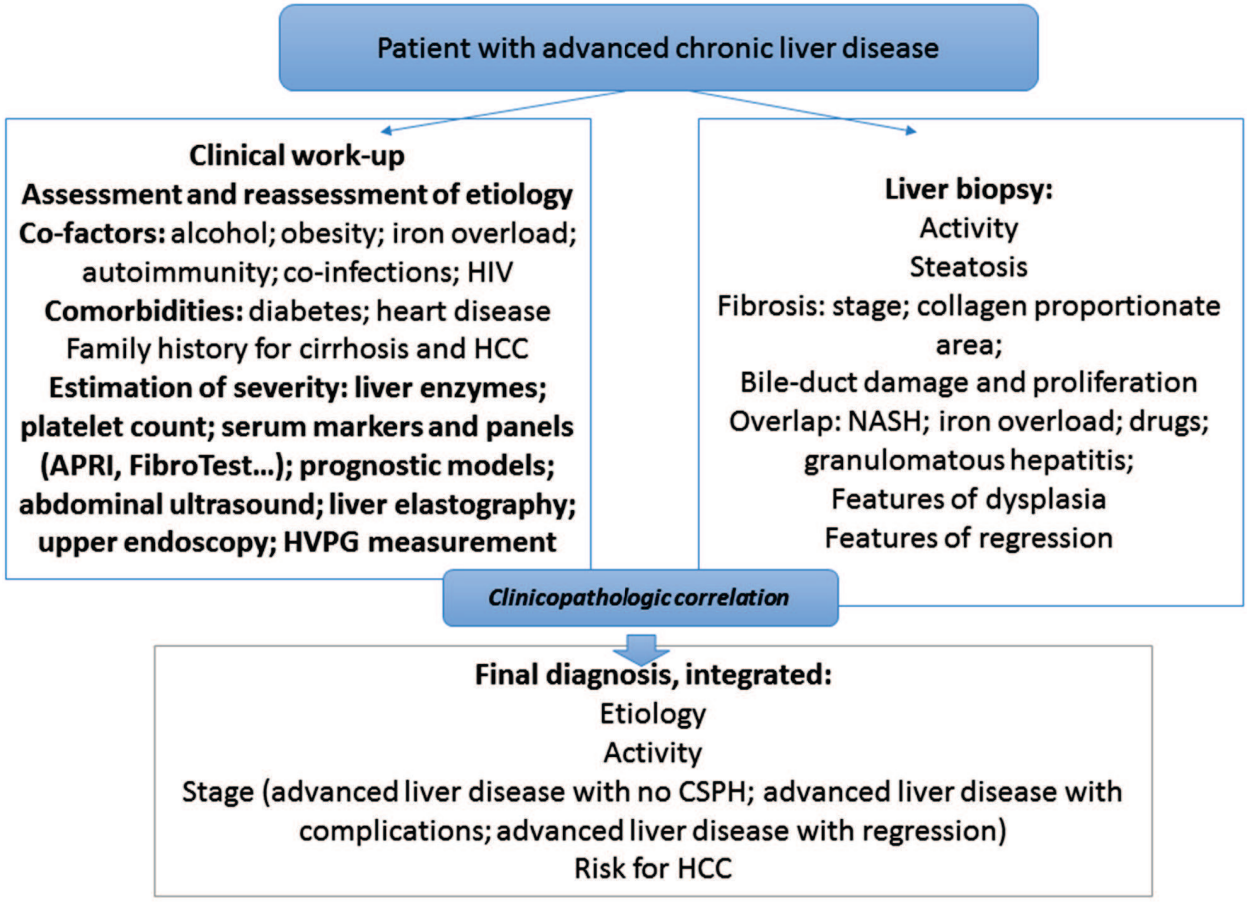

Fig. 3. An integrated approach to a patient with an advanced chronic liver disease

Cirrhosis Is Not "the End" of a Story

Fibrosis may regress after HCV eradication, HBV viral suppression, control of autoimmune inflammation, removal of persistent injury (alcohol, iron overload) (17-19). The theory of the potential to stop progression and even to reverse advanced liver disease has a growing evidence of support. Fibrosis septa can become thinner, more densely compacted and eventually fragmented; adjacent nodules may aggregate into larger islands, so an incomplete septal cirrhosis could appear as a part of the remodeling of the cirrhotic liver. The histologic features of regression are termed "hepatic repair complex": delicate, perforated fibrous septa; isolated, thick collagen fibers; delicate periportal fibrous spikes; portal tract remnants; hepatocytes within portal tracts or splitting septa; minute regenerative nodules; aberrant parenchymal veins (20). Regression is usually associated with an improvement of the clinical status, but with a variable degree depending on the reversibility of vascular alterations. It is proven that some vas-

cular changes may persist (e.g., intrahepatic shunts, small portal vein branch obliteration, venous outflow or arterial inflow alteration with chronic ischemic effect) resulting in persistent portal hypertension and limited improvement of the liver function. Extensive scar with elastosis (consisting of stable, highly complexed collagen) and/or parenchymal extinction is unlikely to regress. Perhaps "the point of no return" is situated near the transition of Laennec stage 4b to 4c. Data from clinical trials and prospective follow-up of patients with compensated or moderate cirrhosis on antiviral therapy showed clinical and laboratory improvement, decrease of the need for liver transplantation and liver-related deaths, persisting, but lower, risk for HCC (21,22). Perhaps, patients with stable condition (showing no regression) could benefit from an anti-fibrotic therapy. Management of patients with liver cirrhosis has to be focused on the prevention of hepatic decompensation and early detection of HCC (2).

CONCLUSIONS AND TAKE-HOME MESSAGES

- Cirrhosis is not an end-stage disease with an imminent death of patients.
- Etiological treatment may reduce portal hypertension and prevent complications in patients with an advanced chronic liver disease.
- The term "cirrhosis" does not incorporate the concept of a multi-stage evolution of an advanced liver disease and a potential for reversibility. In the future, "advanced chronic liver disease" will become a preferred terminology.
- Each patient with an advanced chronic liver disease should be provided with treatment on the base of the clinicopathologic correlation of all available findings.

REFERENCES

1. Schuppan D, Afdhal NH, Israel B. Liver cirrhosis. Lancet. 2008;371:838–51.
2. De Franchis R. Expanding consensus in portal hypertension. J Hepatol. 2016; 30;63(3):743–52.
3. Bruno S, Zuin M, Crosignani A, Rossi S, Zadra F, Roffi L, et al. Predicting mortality risk in patients with compensated HCV-induced cirrhosis: a long-term prospective study. Am J Gastroenterol.2009; 104(5):1147–58.
4. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. J Hepatol. 2006; 44:217–31.
5. Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. J Hepatol. 2014; 60(1):197–209.
6. Schnabl B, Brenner DA. Interactions between the intestinal microbiome and liver diseases. Gastroenterology. 2014; 146(6):1513–24.
7. Friedman SL. Replacing a crystal ball with a calculator in predicting liver disease outcomes. J Hepatol. 2014;60(5):905–6.
8. Garcia-Tsao G, Friedman S, Iredale J, Pinzani M. Now there are many (stages) where before there was one: In search of a pathophysiological classification of cirrhosis. Hepatology. 2010; 51: 445–9.
9. Arvaniti V, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, et al. Infections in Patients With Cirrhosis Increase Mortality Four-Fold and Should Be Used in Determining Prognosis. Gastroenterology. 2010;139(4):1246–56.
10. Hytiroglou P, Snover DC, Alves V, Balabaud C, Bhathal PS, Bioulac-Sage P, et al. Beyond "cirrhosis." American Journal of Clinical Pathology. 2012; 137 (1): 5–9.
11. Kim MY, Cho MY, Baik SK, Park HJ, Jeon HK, Im CK, et al. Histological subclassification of cirrhosis using the Laennec fibrosis scoring system correlates with clinical stage and grade of portal hypertension. J Hepatol. 2011;55(5):1004–9.
12. Nagula S, Jain D, Groszmann RJ, Garcia-Tsao G. Histological-hemodynamic correlation in cirrhosis - A histological classification of the severity of cirrhosis. J Hepatol. 2006;44:111–7.
13. Tsochatzis E, Bruno S, Isgro G, Hall A, Theocharidou E, Manousou P, et al. Collagen proportionate area is superior to other histological methods for sub-classifying cirrhosis and determining prognosis. J Hepatol. 2014;60(5):948–54.
14. Kumar M, Sakhuja P, Kumar a., Manglik N, Choudhury a., Hissar S, et al. Histological subclassification of cirrhosis based on histological- haemodynamic correlation. Aliment Pharmacol Ther. 2008;27(9):771–9.
15. Sethasine S, Jain D, Groszmann RJ, Garcia-Tsao G. Quantitative histological-hemodynamic correlations in cirrhosis. Hepatology. 2012;55(4):1146–53.

16. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol. 2015;63(1):237–64.

17. Pellicoro A, Ramachandran P, Iredale JP, Fallowfield J. Liver fibrosis and repair: immune regulation of wound healing in a solid organ. Nat Rev Immunol. 2014;14(3):181–94.

18. Akhtar E, Manne V, Saab S. Cirrhosis regression in hepatitis C patients with sustained virological response after antiviral therapy: a meta-analysis. Liver Int. 2015; 35(1):30–6.

19. Calvaruso V, Craxì A. Regression of fibrosis after HBV antiviral therapy: Is cirrhosis reversible? Liver International. 2014; 34 (Suppl.1). 85–90.

20. Wanless IR, Nakashima E, Sherman M. Regression of human cirrhosis. Morphologic features and the genesis of incomplete septal cirrhosis. Arch Pathol Lab Med. 2000; 124(11):1599–607.

21. D'Ambrosio R, Aghemo A. Treatment of patients with HCV related cirrhosis: Many rewards with very few risks. Hepat Mon. 2012;12:102–9.

22. Aghemo A, Lampertico P, Colombo M. Assessing long-term treatment efficacy in chronic hepatitis B and C: between evidence and common sense. J Hepatol. 2012;57(6):1326–35.