

Treatment of Hepatitis C in Patients with Compensated and Decompensated Cirrhosis



Elie Ghoulam



Nancy Reau

The course of chronic hepatitis C virus (HCV) progression can take decades and differs among individuals. Many patients are unaware of their HCV infection and some will develop only mild inflammation and fibrosis of the liver. Yet, a significant number of these patients will develop cirrhosis, decompensated cirrhosis and hepatocellular carcinoma (HCC). Many studies have shown that attaining sustained viral response (SVR) in both groups decreases all cause mortality and reduces the risk of HCC development. HCV treatment of compensated and decompensated cirrhosis differs because of the marginal hepatic function, increased mortality and high risk of complications in decompensated cirrhosis. Before the development of oral direct acting antivirals (DAAs), treating patients with decompensated cirrhosis was not an option. This article will address the management, the most recent recommended treatment and post cure monitoring of patients with compensated and decompensated HCV cirrhosis.

INTRODUCTION

Hepatitis C virus (HCV) was previously identified as non-A non-B hepatitis until its existence was proven in 1989.¹ Hepatitis C is a contagious, blood borne, ssRNA virus and exists in multiple genotypes.² Risk factors for acquiring include injection drug use, inadequate sterilization of medical equipment and

transfusion of unscreened blood and blood products.³ HCV can also be transmitted sexually and vertically, but these modes of transmission are less efficient. Globally, 130–150 million people have HCV.³ According to the Centers for Disease Control and Prevention (CDC), an estimated 3.2 million people in the United States

Elie Ghoulam MD, MS Post-Doctoral Research Fellow, Section of Hepatology, Rush University Medical Center, Chicago, IL Nancy Reau, MD Professor of Medicine Chief, Section of Hepatology, Associate Director, Solid Organ Transplantation, Rush University Medical Center, Chicago, IL

Table 1. Recommended Treatment of Compensated Cirrhosis ¹⁴

Regimen	1a	1b	2	3	4	5	6
Ledipasvir/Sofosbuvir	✓	✓	✗	✗	✓	✓	✓
Glecaprevir/pibrentasvir	✓	✓	✓	✓	✓ (+RBV)	✓	✓
Elbasvir/Grazoprevir	✓ (NS5A RAS)	✓	✗	✗	✓	✗	✗
Sofosbuvir/Velpatasvir	✓	✓	✓	✓	✓	✓	✓
PrOD(Paritaprevir/ritonavir/ ombitasvir + dasabuvir)	✗	✓	✗	✗	✗	✓	✗
Daclatasvir+Sofosbuvir +/- RBV	✗	✗	✗	✓ (24 Weeks)	✗	✗	✗

✓ Recommended; ✗ Not recommended; Ribavirin(RBV)

(USA) are living with chronic hepatitis C infection, many of whom are unaware of their infection.⁴ There is a high seroprevalence of HCV infection in persons born from 1945-1965, one-half of whom already had severe fibrosis or cirrhosis based on a study by Klevens et al. This data prompted the CDC to recommend one-time hepatitis C virus antibody testing in this group of people.^{5,6}

The course of chronic HCV disease progression occurs over decades and is varied among individuals.⁷ Factors that impact disease progression are older age, male gender, diabetes, obesity, steatosis, iron overload, genotype 3, alcohol intake and human immunodeficiency virus (HIV) or hepatitis B (HBV) coinfection.^{8,9,10} Over the first 20 years of infection, most patients do not develop liver disease beyond inflammation and moderate fibrosis.¹⁰ A percentage of these patients will then progress to cirrhosis, possibly decompensated or symptomatic, and HCC.⁸ The chances of developing decompensated cirrhosis in the cirrhotic populations are 11.7% with a four-year survival of 50%. The risk of developing HCC is 1%-5% annually.^{8,11}

Hepatitis C therapy has evolved significantly since first using interferon and ribavirin. This evolution has allowed the expansion of therapy to groups of individuals previously without treatment options. Although, even in the interferon era, individuals with well compensated cirrhosis could contemplate therapy, there were occasions of decompensation and significant

toxicity. All-oral options have now made therapy commonplace for those with asymptomatic cirrhosis and an option to consider in those with decompensation.

The clinical benefit of viral eradication in those with advanced liver disease has been unarguably established through several long-term observational trials. Development of cirrhosis, decompensation and HCC are all considerably reduced after sustained viral response (SVR) with either interferon based or all oral direct acting antiviral (DAA) therapy. The rate of liver transplant wait-listing for HCV secondary to decompensated cirrhosis has decreased by 32% as a result of DAA therapy.¹² Not only has there been demonstrable benefit to liver-related mortality, but all-cause mortality is also improved with viral eradication.¹³ However, clinicians still need to be aware that not all patients with cirrhosis are the same. Those with symptomatic cirrhosis (decompensated cirrhosis) are at higher risk for adverse events and drug toxicity. Historically, treatment of this group of individuals was contraindicated. As the toxicity and efficacy of therapy improved, we have been able to expand therapy to increasingly sicker patients, although the benefit of doing so remains controversial.

Recognizing Cirrhosis

Our guidance recommends staging each patient with hepatitis C.¹⁴ Cirrhosis can be quite subtle, and can easily be missed.

Table 2. Recommended Treatment of Decompensated Cirrhosis¹⁴

Regimen	1a	1b	2	3	4	5	6
Ledipasvir/Sofosbuvir	✓	✓	×	×	✓	✓	✓
PrOD (Paritaprevir/ritonavir/ombitasvir + dasabuvir)	×	×	×	×	×	×	×
Elbasvir/Grazoprevir	×	×	×	×	×	×	×
Sofosbuvir/Velpatasvir	✓	✓	✓	✓	✓	✓	✓
Simeprevir+Sofosbuvir	×	×	×	×	×	×	×
Daclatasvir+Sofosbuvir +/- RBV	✓	✓	✓	✓	✓	×	×

*Treatment duration: 12 weeks with Ribavirin (RBV) and 24 weeks without RBV

✓ Recommended; × Not recommended

Cirrhosis

Cirrhosis is defined as the late stage of progressive hepatic fibrosis characterized by change of hepatic architecture and the formation of regenerative nodules.¹⁵ In its advanced stages it is considered to be irreversible, but in its earlier stages it may improve or even reverse if specific treatments aimed at the underlying etiology of liver disease are addressed.¹⁶

Signs and symptoms of cirrhosis can be nonspecific such as anorexia, weight loss, weakness, fatigue or signs and symptoms of hepatic decompensation such as jaundice, pruritus, upper gastrointestinal bleeding, abdominal distension from ascites and confusion due to hepatic encephalopathy.¹⁶

Physical findings consist of spider angiomas, palmar erythema, gynecomastia, testicular atrophy, amenorrhea, parotid/lacrimal gland hypertrophy, Dupuytren's contractures, clubbing and jaundice.¹⁶

Laboratory abnormalities may be striking such as elevated serum bilirubin or coagulopathy. However, laboratory findings may be subtler such as a platelet count <150 or AST>ALT. Several clinical calculators can help identify those at higher risk for cirrhosis such as APRI or FIB4.¹⁷

Diagnosis

If cirrhosis is evident clinically (nodularity on imaging, splenomegaly, low platelets, ascites, encephalopathy, jaundice, etc.), no further assessment is required.

However, most patients with advanced disease lack these clinical cues. Several non-invasive means have been validated to assess for fibrosis. All have diagnostic utility, yet a combination of concordant serum markers and elastography is felt to have the most reliability outside of biopsy.¹⁴

Compensated vs Decompensated Cirrhosis

Patients who develop complications of cirrhosis are considered to have decompensated cirrhosis and those who have not developed major complications are classified as having compensated cirrhosis.¹⁸ The median survival of patients with compensated cirrhosis is >12 years.¹⁸ Patients that develop varices but not variceal bleeding are still considered as having compensated cirrhosis but have a 2.1 percent increase in one-year mortality.¹⁸ Several factors can predispose to decompensation in a patient with cirrhosis. Risk factors include bleeding, infection, alcohol intake, medications, dehydration, obesity and constipation.^{19,20}

Predictive Models

Two predictive models, the Child-Pugh classification (CP) and Model for End-Stage Liver Disease (MELD) score, are most commonly used today in attempt to predict the prognosis of cirrhotic patients. Based on clinical and laboratory information, these models have been derived from multiple studies.^{21,22}

Child-Pugh Classification

The variables included in the CP classification are the serum albumin and bilirubin, ascites, encephalopathy and prothrombin time. The score ranges from 5 to 15. Patients with a score of 5 or 6 have Child-Pugh class A cirrhosis (well-compensated cirrhosis), those with a score of 7 to 9 have Child-Pugh class B cirrhosis (significant functional compromise) and those with a score of 10 to 15 have Child-Pugh class C cirrhosis (decompensated cirrhosis).²¹

The Child-Pugh classification system is not only used in staging of cirrhosis but has been found to correlate with survival of patients not undergoing surgery with decrease survival rates as you progress from Child-Pugh A to C.²³ It is also associated with likelihood of developing complications of cirrhosis. Child-Pugh C patients are much more likely to develop variceal bleeding for example than Child-Pugh A.²⁴

MELD Score

Another model to predict prognosis in patients with cirrhosis is the MELD score. Based on bilirubin levels, creatinine, INR and the etiology of cirrhosis, the MELD score has been adopted for use in prioritizing patients awaiting liver transplantation and has an expanding role in predicting outcomes in patients with liver disease in the non-transplantation setting as well. In January 2016, Organ Procurement and Transplantation Network Policy 9.1 (MELD Score) was updated to include serum sodium as a factor in the calculation of the MELD score. The MELDNa score can be calculated online.

Consider Consequences of Cirrhosis

Individuals with advanced liver disease are at risk for complications of portal hypertension and liver cancer. Once cirrhosis is recognized, it is advised to obtain abdominal imaging with ultrasonography to screen for hepatocellular cancer (HCC). If ultrasound is of poor quality, cross sectional imaging should be done.

Ascites may be clinically evident, but is not infrequently identified first on imaging done for liver cancer screening. The development of ascites carries significant impact on prognosis, decreasing expected 5-year survival to <60%. If the ascites is refractory to

diuretics, associated with dilutional hyponatremia or type 2 hepatorenal syndrome (HRS), the anticipated 1-year survival is 30%.²⁶

Several clinical algorithms exist to help identify those cirrhotics that are at higher risk for complications of portal hypertension. Those individuals with liver stiffness scores <20 kPa and serum platelet count >150,000/mm³ are unlikely to have high-risk varices. Recently updated AASLD guidelines²⁷ recommended performing an upper endoscopy to evaluate for gastroesophageal varices for all individuals that do not meet those criteria. If high-risk for bleeding (the presence of medium/large varices), primary prophylaxis with either non-selective beta-blockers or band ligation should be initiated.

Other routine health maintenance includes vaccinating against hepatitis A (HAV), hepatitis B, yearly influenza and avoidance of hepatotoxins. Patients with a CP score of >7 or MELD score >18 are at high risk for complications and should be co-managed by an experienced clinician.²⁸

HCV and Genotypes and Treatment

Although pan genotypic therapy exists, the genotype of HCV remains an important variable as this may determine the efficacy and duration of therapy.¹⁴

Treatment of HCV in Patients with Compensated Cirrhosis

Individuals with HCV cirrhosis that lack symptoms (ascites, variceal bleeding, coagulopathy, jaundice, encephalopathy) are considered compensated. The Child-Pugh Class (CP) can be used to confirm prognosis. CP A is considered well compensated.²⁹

No therapeutic agent is contraindicated in a patient with compensated cirrhosis, however certain regimens are recommended depending on genotype and treatment experience. Recommended regimens are generally prioritized due to shorter duration and the omission of ribavirin (RBV) to achieve higher efficacy. The most up to date therapeutic recommendations can be found in the American Association for the Study of Liver Disease/ Infectious Disease Society of America (AASLD/ IDSA) guidance document.¹⁴ Table 1 summarizes the recommended and alternative, or not recommended, treatment choices for treatment naïve and treatment experienced (exposed to interferon, ribavirin or sofosbuvir) patients with cirrhosis.

(continued on page 44)

(continued from page 42)

Treatment of HCV with Decompensated Cirrhosis

The treatment of patients with CP class B or C cirrhosis is controversial, as most will require liver transplantation for optimal long-term survival. In patients who are not transplant candidates, the goal is to achieve SVR with the hope that there will be an improvement in clinical condition. For patients who are transplant candidates, the goals are not as straightforward. SVR before transplantation prevents re-infection of the new liver which could improve post-transplant outcomes and survival of the graft.^{14,30} However, viral eradication pre-transplant prevents the use of HCV exposed organs and treatment post-transplant is safe and effective.

Marginal hepatic function limits treatment options. In the era of IFN-based therapies, treatment in decompensated cirrhosis was contraindicated.³¹ All-oral therapy has significantly better efficacy and safety, however drug toxicity must still be considered. Although safe and effective in CP class A, protease inhibitors are not advised for those with CP class B/C cirrhosis.

Accordingly, the AASLD, IDSA and the European Association for the Study of the Liver (EASL) guidelines recommend only all-oral DAA regimens containing sofosbuvir, ledipasvir, daclatasvir and RBV as show in Table 2.³¹

Individuals with decompensated cirrhosis are at high risk for complications. It is advised that treatment should be performed by a highly experienced medical practitioner, preferably associated with a transplant center.^{14,30}

Post-Cure Monitoring

It is important to recognize that although SVR substantially lowers the risk of progression or liver cancer, it does not eliminate this risk. All patients with cirrhosis, despite demonstration of regression by biopsy or non-invasive measurements, still require longitudinal follow-up. Liver cancer screening remains necessary as risk for malignancy remains. Recent analysis of a large Veterans Administration (VA) database demonstrates that age, gender and diabetes increase this risk.³²

CONCLUSION

Compensated HCV cirrhosis has excellent long-term prognosis and a chance of reversal if SVR is attainable. Decompensated cirrhosis carries high risk of mortality

and should be performed by highly experienced HCV providers. Early referral for transplant for patients with CTP >7 and MELD >18 is key for better patient outcomes as early treatment of HCV can prevent many life threatening complications and reduce HCC risk. ■

References

- Houghton M. The long and winding road leading to the identification of the hepatitis C virus. *Journal of Hepatology*. 2009;51(5):939–948. doi:10.1016/j.jhep.2009.08.004.
- Kim CW, Chang K-M. Hepatitis C virus: Virology and life cycle. *Clinical and Molecular Hepatology*. 2013;19(1):17. doi:10.3350/cmh.2013.19.1.17.
- WHO. Hepatitis C. World Health Organization. <http://www.who.int/mediacentre/factsheets/fs164/en/>. Accessed February 18, 2017.
- CDC. Hepatitis C. <http://www.cdc.gov/hepatitis/hcv/cfaq.htm>. Accessed February 18, 2017.
- Foundation C, Klevens M, Huang X, et al. The Burden of Liver Disease Among Persons With Hepatitis C in the United States. <http://www.croiconference.org/sessions/burden-liver-disease-among-persons-hepatitis-c-united-states>. Accessed February 18, 2017.
- CDC. People born 1945-1965 & hepatitis C. <http://www.cdc.gov/hepatitis/populations/1945-1965.htm>. Accessed February 18, 2017.
- Maasoumy B, Wedemeyer H. Natural history of acute and chronic hepatitis C. *Best Practice & Research Clinical Gastroenterology*. 2012;26(4):401–412. doi:10.1016/j.bpg.2012.09.009.
- Davis GL, Alter MJ, El-SeragHashem, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: A multiple cohort model of HCV prevalence and disease progression. *Gastroenterology*. 2010;138(2):513–521.e6. doi:10.1053/j.gastro.2009.09.067.
- Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. *The Lancet*. 1997;349(9055):825–832. doi:10.1016/s0140-6736(96)07642-8.
- Poynard T, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. *Journal of Hepatology*. 2001;34(5):730–739. doi:10.1016/s0168-8278(00)00097-0.
- Planas R, Ballesté B, Antonio Álvarez M, et al. Natural history of decompensated hepatitis C virus-related cirrhosis. A study of 200 patients. *Journal of Hepatology*. 2004;40(5):823–830. doi:10.1016/j.jhep.2004.01.005.
- Flemming JA, Kim WR, Brosgart CL, Terrault NA. Reduction in liver transplant wait-listing in the era of direct-acting antiviral therapy. *Hepatology*. December 2016. doi:10.1002/hep.28923.
- van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained Virological response and all-cause mortality among patients with chronic hepatitis C and advanced Hepatic fibrosis. *JAMA*. 2012;308(24):2584. doi:10.1001/jama.2012.144878.
- AASLD, IDSA. INITIAL TREATMENT OF HCV INFECTION. <http://www.hcvguidelines.org/full-report/initial-treatment-hcv-infection>. Accessed February 18, 2017.
- Bataller R, Brenner DA. Liver fibrosis. *Journal of*

(continued on page 46)

(continued from page 44)

- Clinical Investigation. 2005;115(2):209–218. doi:10.1172/jci200524282.
16. Schuppan D, Afdhal NH. Liver cirrhosis. *The Lancet*. 2008;371(9615):838–851. doi:10.1016/s0140-6736(08)60383-9.
 17. Fibrosis-4 (FIB-4) calculator. 2017. <http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4>. Accessed February 18, 2017.
 18. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. *Journal of Hepatology*. 2006;44(1):217–31. doi:10.1016/j.jhep.2005.10.013.
 19. Mumtaz K, Syed U, Ahmed, Abid S, Baig N, Hamid S. Precipitating factors and the outcome of Hepatic Encephalopathy in liver cirrhosis. *Journal of the College of Physicians and Surgeons Pakistan*. 2010;(8):20–514. http://ecommons.aku.edu/cgi/viewcontent.cgi?article=1000&context=pakistan_fhs_mc_med_gastroenterol. Accessed February 18, 2017.
 20. Berzigotti A, Garcia-Tsao G, Bosch J, et al. Obesity is an independent risk factor for clinical decompensation in patients with cirrhosis. *Hepatology*. 2011;54(2):555–561. doi:10.1002/hep.24418.
 21. Liou I. Referral for liver transplantation. Core Concepts-Hepatitis C Online. <http://www.hepatitisc.uw.edu/go/management-cirrhosis-related-complications/liver-transplantation-referral/core-concept/all>. Accessed February 18, 2017.
 22. Wiesner R, Edwards E, Freeman R, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology*. 2003;124(1):91–96. doi:10.1053/gast.2003.50016.
 23. Infante-Rivard C, Esnaola S, Villeneuve J-P. Clinical and statistical validity of conventional prognostic factors in predicting short-term survival among cirrhotics. *Hepatology*. 1987;7(4):660–664. doi:10.1002/hep.1840070408.
 24. di Franchis R, Primignani M. Why Do Varices Bleed? *Gastroenterol Clin North America*. 1992;21(1):85–101.
 25. MELD serum sodium policy changes. <http://optn.transplant.hrsa.gov/news/meld-serum-sodium-policy-changes>. Accessed February 18, 2017.
 26. Planas R, Montoliu S, Ballesté B, et al. Natural history of patients hospitalized for management of Cirrhotic Ascites. *Clinical Gastroenterology and Hepatology*. 2006;4(11):1385–1394.e1. doi:10.1016/j.cgh.2006.08.007.
 27. AASLD Practice Guideline Update. <http://www.aasld.org/publications/practice-guidelines-0>. Accessed February 18, 2017.
 28. Lewis JH, Stine JG. Review article: Prescribing medications in patients with cirrhosis - a practical guide. *Alimentary Pharmacology & Therapeutics*. 2013;37(12):1132–1156. doi:10.1111/apt.12324.
 29. Imler T. Resources for Gastroenterology and Hepatology. GI Hep. <http://www.gihep.com>. Accessed February 18, 2017.
 30. David Spach. Treatment of hepatitis C in patients with cirrhosis module 6: Treatment of special populations and special situations lesson 4: Treatment of hepatitis C in patients with cirrhosis contents: Background treatment of HCV in patients with compensated Cirrhosi, (2017). <http://www.hepatitisc.uw.edu/pdf/special-populations-situations/treatment-cirrhosis/core-concept/all>. Accessed February 18, 2017.
 31. Bunchorntavakul C, Reddy KR. Treat chronic hepatitis C virus infection in decompensated cirrhosis - pre- or post-liver transplantation? The ironic conundrum in the era of effective and well-tolerated therapy. *Journal of Viral Hepatitis*. 2016;23(6):408–418. doi:10.1111/jvh.12534.
 32. Kasmari A, Welch A, Liu G, Leslie D, McGarrity T, Riley T. Independent of cirrhosis, Hepatocellular carcinoma risk is increased with diabetes and metabolic syndrome: A retrospective cohort study. *The American Journal of Medicine*. January 2017. doi:10.1016/j.amjmed.2016.12.029.



A Token of Our APPreciation© for Our Loyal Readers

Download PRACTICAL GASTROENTEROLOGY to your Mobile Device Available for Free on iTunes, Google Play and Amazon

Add the App instantly to your iPad or iPhone:

<http://itunes.apple.com/us/app/practical-gastroenterology/id525788285?mt=8&ign-mpt=uo%3D4>

Add the App instantly to your Android:

<https://market.android.com/details?id=com.texterity.android.PracticalGastroApp>

<http://www.amazon.com/gp/product/B00820QCSE>