*Perspective*

# Cirrhosis in Hepatitis C Virus–Infected Patients: A Review for Practitioners New to Hepatitis C Care

*Treatment of hepatitis C virus (HCV)-infected patients with cirrhosis remains challenging. Biopsy to stage liver fibrosis remains the standard for identifying cirrhosis, although the noninvasive technique of transient elastography is promising in this regard. Cirrhosis is categorized as compensated or decompensated, with the latter characterized by ascites, hepatic hydrothorax, bleeding varices, hepatic encephalopathy, and hepatorenal syndrome. In the interferon alfa treatment era, patients with compensated cirrhosis have been candidates for interferon alfa–based treatment, whereas those with decompensated cirrhosis have been treated with caution and only at a tertiary care or transplant center. New interferon alfa–free regimens offer safer treatment alternatives to patients with cirrhosis. Response to interferon alfa–based therapy alone and in combination with the first-generation HCV protease inhibitors boceprevir or telaprevir for the treatment of HCV genotype 1 infection has been poorer in patients with cirrhosis than in those without. With regimens that include newer direct-acting antivirals, response rates are tremendously improved for patients with cirrhosis but still slightly lower than those for patients without cirrhosis. As new regimens enter use outside of clinical trials, optimizing efficacy for patients with cirrhosis will be an important goal. Patients with cirrhosis must be taught to practice liver wellness following HCV cure, to lower the risk of progression of their liver disease. Risk of hepatocellular carcinoma also persists in patients with cirrhosis even if cure of HCV infection is achieved. The risk of these complications is dramatically reduced with cure of HCV infection through antiviral treatment. This article summarizes a presentation by Andrew J. Muir, MD, MHS, at the IAS–USA continuing education program held in Atlanta, Georgia, in September 2013.*

**Keywords:** cirrhosis, compensated, DAAs, decompensated, direct-acting antivirals, fibrosis, HIV, HCV, hepatitis C, interferon alfa, protease inhibitors

According to a generally accepted model of the natural history of hepatitis C virus (HCV) infection, chronic HCV infection develops in approximately 75% to 85% of persons with acute HCV infection and cirrhosis develops in approximately 20% of those with chronic HCV infection, with progression to cirrhosis occurring over a period of 20 years to 50 years. More-rapid progression is associated with older age at infection, alcohol use, coinfection with HIV, and periods of immunosuppression following transplantation.

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## Disease Staging

Disease staging has relied on the use of liver biopsy to evaluate level of fibrosis, with Metavir scoring as the most common method of quantification. In this scoring system, F1 indicates portal fibrosis, F2 portal fibrosis with few septa, F3 septal fibrosis (or bridging), and F4 cirrhosis. In practice, limitations in assessment warrant grouping of F3 and F4 as advanced fibrosis, and overall clinical assessment must be taken into account in staging. For example, a patient in whom staging in the past year indicated F3 fibrosis but who currently has a low platelet count (eg, 70,000/µL) should be considered to have cirrhosis. Although liver biopsy is the current gold standard for staging, it is invasive, associated with morbidity in 3 of 1000 cases and mortality in 1 of 10,000 cases, subject to observer variability and sampling error, and costly.

Alternatives to biopsy include serologic panels and radiographic assessments. However, these noninvasive measurements also have limitations, including the inability to reliably differentiate fibrosis stages (ie, they are best used to distinguish between early and advanced fibrosis only) and risk of indeterminate outcomes. Serologic markers such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) can be affected by inflammation and thus are not always reliable.

One useful and inexpensive noninvasive technique for the assessment of liver fibrosis in HCV infection is the AST-to-platelet ratio index (APRI), calculated as (AST/upper limit of normal of AST) x 100 divided by (platelet count/1000). Thus, a patient with an AST level of 82 U/L, with an upper limit of normal of 45 U/L, and a platelet count of 70,000/µL has an APRI of 2.6, strongly suggestive of cirrhosis. A recent meta-analysis comprising 40 studies found that an APRI threshold of 0.7 was predictive of significant fibrosis with 77% sensitivity and 72% specificity and that a threshold of 1.0 was predictive of cirrhosis with 76% sensitivity and 72% specificity.[1] Some recent clinical trials have used an APRI threshold of 2.0 for cirrhosis. Sensitivity and specificity are somewhat poorer in HCV/HIV-coinfected patients because of the lower platelet counts associated with coinfection.

One commercially distributed index incorporates 6 serum biochemical markers—alpha 2 macroglobulin, haptoglobin, gamma globulin, apolipoprotein A1, gamma glutamyltransferase, and total bilirubin—to generate a measurement

of liver fibrosis and has been found to have 75% sensitivity and 85% specificity for Metavir fibrosis stages F2 to F4.[2,3] In practice, high and low scores are generally accurate, but midrange scores are not clinically useful. Other serum marker assays for fibrosis include the European liver fibrosis panel, FIB-4, the Forns index, and the SHASTA index, along with a number of commercially distributed panels.

Among radiographic assessments, conventional ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) studies are not used to stage fibrosis; they are useful to detect complications of advanced disease, such as ascites, obvious varices, or hepatocellular carcinoma (HCC). Transient elastography, a technique using an ultrasonic transducer in which generated shear wave velocity correlates with tissue stiffness, has been available in Europe for years and is now available in the United States. A meta-analysis comprising 50 studies assessed the effectiveness of transient elastography as a diagnostic tool for liver fibrosis and found the mean area under the receiver operating characteristic (AUROC) curve for the diagnosis of significant fibrosis, severe fibrosis, and cirrhosis to be 0.84, 0.89, and 0.94, respectively.[4] Thus far, in clinical practice in the United States, transient elastography appears to be reliable in detecting cirrhosis.

Acoustic radiation force imaging (ARFI) is a similar technology that is becoming more widely available, although transient elastography has been more extensively evaluated than ARFI at this point. Magnetic resonance elastography is also available in the United States and has been found to have 94% sensitivity and 95% specificity for Metavir fibrosis stages F2 to F4 and 92% sensitivity and 96% specificity for stages F3 to F4.[5,6]

## Cirrhosis Characteristics

Cirrhosis is categorized as compensated cirrhosis—that is, cirrhosis diagnosed through biopsy but without complications—or as decompensated cirrhosis, which is characterized by ascites, hepatic hydrothorax, bleeding varices, hepatic encephalopathy, and hepatorenal syndrome. Patients with compensated cirrhosis are candidates for interferon alfa–based treatment. Those with decompensated cirrhosis should receive treatment only at a tertiary care or transplant center.

Insight into the natural history of cirrhosis is provided by an Italian study in which 214 patients with Child-Pugh class A cirrhosis who received no antiviral therapy were followed for 114 months. HCC occurred in 32%, ascites in 23%, upper gastrointestinal bleeding in 6%, hepatic encephalopathy in 1%, and death in 35%, with annual incidences of 3.9%, 2.9%, 0.7%, 0.1%, and 4.0%, respectively.[7] During the study period, 154 patients (72%) remained in Child-Pugh class A. Predictors of poor outcome were alcohol use, hepatitis B virus (HBV) coinfection, and iron overload.

There are a number of scoring systems for categorizing severity of cirrhosis in individual patients. The Child-Pugh score incorporates bilirubin, albumin, prothrombin time, and presence or absence and severity of ascites and hepatic encephalopathy. Although no longer used for liver transplant allocation, the Child-Pugh system does provide guidance on surgical mortality risk and overall prognosis, with class B (1- and 2-year survival of 81% and 57%) and class C (1- and 2-year survival of 45% and 35%) being associated with much poorer survival than class A (1- and 2-year survival of 100% and 85%).[8,9]

The Model for End-Stage Liver Disease (MELD) scoring system has largely replaced the Child-Pugh system in clinical use and incorporates total bilirubin, serum creatinine, and prothrombin time. The American Association for the Study of Liver Diseases (AASLD) criteria for referral for liver transplantation specify evidence of hepatic dysfunction with a Child-Pugh score greater than 7, a MELD score greater than 10 or the onset of ascites, variceal bleeding, or encephalopathy as a first major complication.[10] Patients with HCC with 1 lesion less than 5 cm or 3 lesions each less than 3 cm in diameter are also candidates for liver transplantation.

Patients with cirrhosis who are not receiving antiviral treatment should generally be seen by their practitioner every 6 months if they have compensated disease and every 3 months if they have decompensated disease. Assessments should include MELD laboratory evaluations, HCC surveillance, and regular endoscopies to screen for gastroesophageal varices. The risk of developing HCC appears to be 3% to 5% per year in patients with cirrhosis, and the risk persists even if HCV infection is subsequently cured, with cases seen in cirrhosis patients up to 8 years after sustained virologic response (SVR) has been achieved.

AASLD recommendations for HCC surveillance include ultrasound every 6 months.[11] Ultrasound in obese individuals remains challenging. Data on CT and MRI surveillance for HCC are limited but should be considered for obese patients or any patient with an inadequate ultrasound. Alpha-fetoprotein measurement is not sufficiently sensitive or specific to recommend it as a screening tool for HCC in patients with cirrhosis, but it remains part of the diagnostic approach for patients with a liver mass. AASLD guidelines for screening for gastroesophageal varices include an upper endoscopy at diagnosis of cirrhosis and a repeat screening every 3 years in patients with compensated cirrhosis and no varices and annually in those with decompensated disease and no varices.[12] Variceal bleeding carries a mortality risk of 30%. In those with varices, beta blockers and banding ligation are potential treatment options.

## Selection of Patients for Treatment

Until 2013, standard treatment for all patients with HCV infection involved a backbone of peginterferon alfa. Because of the risks associated with peginterferon alfa use and the lower response rates of patients with cirrhosis, few patients with decompensated cirrhosis received treatment with this drug.

The first-generation HCV protease inhibitors (PIs) boceprevir and telaprevir

offered great promise for patients with cirrhosis and did lead to improved response rates, but these drugs also increased the risks associated with treatment. Although data from phase III trials of these drugs suggest that they are well tolerated in patients with cirrhosis,[13-16] outcomes have proved different in clinical practice.

In the French cohort study CUPIC (Compassionate Use of Protease Inhibitors in Cirrhotics), patients with HCV genotype 1 infection and cirrhosis were given early access to triple therapy including boceprevir or telaprevir. Outcomes included serious adverse events in more than half of patients, severe anemia, numerous deaths, grade 3 or 4 infections, and a 5% risk of hepatic decompensation.[17]

Patients with cirrhosis and HCV genotype 2 or 3 infection may be treated with a currently available, effective, interferon alfa–free regimen of sofosbuvir and ribavirin. However, most HCV-infected Americans have genotype 1, and interferon alfa–free regimens for the treatment of HCV genotype 1 infection are expected to be available by the end of 2014. Although treatment is quickly moving to an interferon alfa–free approach, selected patients may still need to consider interferon alfa–based regimens.

If treatment with an interferon alfa–based regimen is being considered in patients with cirrhosis, there should be a discussion about the risks and benefits, documentation of the discussion, and consideration of transplant referral or treatment at a tertiary care center for patients with a MELD score greater than 10, portal hypertension, or thrombocytopenia. Management strategies should be discussed with patients, including the use of dose reduction versus erythropoiesis-stimulating agents in case of anemia. Leukopenia usually poses less of a problem in this setting. The potential use of thrombopoietin agonists should also be addressed. Although effective in increasing platelet count to permit initiation and tolerance of therapy, thrombopoietin agonists pose the risk of portal vein thrombosis that can further compromise liver function and affect candidacy for transplantation.

## Treatment of Patients with Cirrhosis

### HCV Genotype 1

At the time of this update, patients with HCV genotype 1 cirrhosis have the option of treatment with peginterferon alfa, ribavirin, and the polymerase inhibitor sofosbuvir for 12 weeks; sofosbuvir and ribavirin for 24 weeks; or simeprevir plus sofosbuvir, with or without ribavirin, for 12 weeks. In the single-arm, open-label NEUTRINO study of sofosbuvir plus peginterferon alfa and ribavirin in treatment-naive patients with HCV genotype 1, 4, 5, or 6 infection, SVR was achieved in 92% (252 of 273) of patients without cirrhosis and 80% (43 of 54) of patients with cirrhosis.[18] With the caveat that this was a clinical trial, and thus did not include the sicker patients who are and will continue to be encountered in the clinic, treatment was well tolerated. Treatment was discontinued in 2% of patients and serious adverse events were reported in 1%.

The combination of sofosbuvir and ribavirin was studied in the SPARE[19] and PHOTON-1[20] trials and produced SVR rates of 68% and 76%, respectively. This regimen has been evaluated in patients with advanced cirrhosis and liver cancer, prior to transplantation, and was found to prevent HCV infection recurrence after transplant.[21]

Although not an approved indication by the US Food and Drug Administration (FDA), the use of a combination of the second-generation PI simeprevir with sofosbuvir has been endorsed by the AASLD/Infectious Diseases Society of America (IDSA)/IAS–USA HCV treatment Guidance[22] and has been well received by patients and clinicians. This regimen was studied for 12 weeks to 24 weeks, with or without ribavirin, in the COSMOS (A Study of TMC435 in Combination with PSI-7977 [GS7977] in Chronic Hepatitis C Genotype 1 -Infected Prior Null Responders to Peginterferon/Ribavirin Therapy or HCV Treatment-Naive Patients) trial.[23] The 87 patients in the second cohort included those who were treatment naive and those with a null response, and 47% had cirrhosis. The regimen was very well tolerated and led to SVR in 94% of patients overall. No clear differences were seen based on treatment duration or ribavirin use. Owing to the increased exposure, simeprevir has not been extensively studied and must be used with caution in patients with Child-Pugh class B or C cirrhosis.

Two other interferon alfa–free regimens are expected to be available in late 2014 for patients with HCV genotype 1 infection. One regimen is the investigational combination of the ritonavir-boosted PI ABT-450, the nonstructural protein 5A (NS5A) inhibitor ombitasvir (formerly ABT-267), the nonnucleoside polymerase inhibitor dasabuvir (formerly ABT-333), and ribavirin. A recently reported phase III trial enrolled treatment-naive and -experienced patients, and all 380 patients had Child-Pugh class A cirrhosis.[24] The SVR rates were 91.8% in the 12-week arm and 95.9% in the 24-week arm. Anemia, defined as a hemoglobin level less than 10 g/dL, occurred in 7.2% of the 12-week arm and 11.0% of the 24-week arm. Overall, treatment was very well tolerated in these patients with compensated cirrhosis.

Another well-tolerated treatment, expected to be available in the fall of 2014, is the combination of sofosbuvir and the investigational NS5A inhibitor ledipasvir. The phase III ION-1 study of treatment-naive patients and the ION-2 study of treatment-experienced patients included patients with cirrhosis (15%-20% of patients in each treatment arm) and examined 12 weeks versus 24 weeks of treatment and the role of ribavirin.[25,26] In the ION-1 study, all study arms achieved SVR rates greater than 95%, with no obvious impact from the presence of cirrhosis. In the ION-2 study, the SVR rates were 94% and 96% in the 12-week arms, respectively, and 99% in each of the 24-week arms. In the 12-week arms, the presence of cirrhosis did appear to impact outcome. The SVR rates in the 12-week arms were 86% with sofosbuvir plus ledipasvir and 82% with sofosbuvir, ledipasvir, and ribavirin, compared with 100% in the 24-week arms. Further recommendations on treatment duration

with these regimens are expected at the time of regulatory approval. In any event, these regimens offer patients with compensated cirrhosis excellent efficacy outcomes with well-tolerated regimens. These regimens will require further study to determine if they are appropriate for patients with decompensated cirrhosis.

### HCV Genotypes 2 and 3

The interferon alfa–free regimen of sofosbuvir and ribavirin is FDA approved and available for patients with HCV genotype 2 or 3 infection. For patients with HCV genotype 2, sofosbuvir and ribavirin for 12 weeks is a highly effective regimen. In the FISSION trial of treatment-naive patients, the overall SVR rate for those with HCV genotype 2 infection was 92% (85 of 92) for patients without cirrhosis and 94% (16 of 17) for patients with cirrhosis.[18]

In the FUSION trial of treatment-experienced patients, the SVR rate was 90% (26 of 29) for patients without cirrhosis and 60% (6 of 10) in patients with cirrhosis.[27] The FUSION study examined 16 weeks of treatment and reported an SVR rate of 78% (7 of 9) in patients with HCV genotype 2 infection and cirrhosis. Although a small number, the lower response rate at 12 weeks led the AASLD/IDSA/IAS–USA HCV Guidance to recommend consideration of a 16-week treatment duration for treatment-experienced, HCV genotype 2–infected patients with cirrhosis. For patients with HCV genotype 3 infection, the FISSION and FUSION trials demonstrated that outcomes with 12 weeks of sofosbuvir and ribavirin were inadequate. Outcomes were especially poor for patients with HCV genotype 3 who had cirrhosis, with SVR rates of 34% for treatment-naive patients and 19% for -experienced patients.

Longer treatment duration was explored in the VALENCE trial of treatment-naive and -experienced patients. The study was amended to extend treatment from 12 weeks to 24 weeks for patients with HCV genotype 3 infection. For treatment-naive HCV geno-type 3–infected patients, SVR rates were 93% (86 of 92) for those without cirrhosis and 92% (12 of 13) for those with cirrhosis. For treatment-experienced HCV genotype 3–infected patients, SVR rates were 87% (87 of 100) for those without cirrhosis and 62% (28 of 45) for those with cirrhosis.

Two recent studies have examined the role of peginterferon alfa in combination with sofosbuvir and ribavirin for 12 weeks. In the LONESTAR-2 trial, 83% (10 of 12) of treatment-experienced HCV genotype 3–infected patients achieved SVR with this regimen.[28] In another study, of HCV genotype 2– and 3–infected patients whose previous treatment with sofosbuvir had failed, subjects were randomized to receive peginterferon alfa in combination with sofosbuvir and ribavirin for 12 weeks or only sofosbuvir and ribavirin for 24 weeks.[29] Among HCV genotype 3–infected patients with cirrhosis, 88% (7 of 8) achieved SVR with a peginterferon alfa–containing regimen compared with 47% (7 of 15) in the group that received sofosbuvir plus ribavirin alone. This collection of results, especially among treatment-experienced patients with cirrhosis, highlights the need for further developments in treatment of HCV genotype 3 infection. Currently, 24 weeks of ribavirin is a very reasonable and safe treatment option for HCV genotype 3–infected patients with cirrhosis, and clinicians may consider the role of peginterferon alfa after examining its risks and benefits. Regularly updated recommendations for testing, managing, and treating HCV infection can be found at http://www.hcvguidelines.org.

## Conclusion

Patients at risk for cirrhosis must be monitored closely, including for complications of portal hypertension, indicators of HCC, and support of overall liver health, alcohol abstinence, maintenance of healthy weight, and getting appropriate vaccinations. Well tolerated and effective interferon alfa–free regimens are available now for patients with HCV genotype 2 or 3 infection and are expected to be available, by the end of 2014, for those with HCV genotype 1 infection. Selected patients may consider the addition of peginterferon alfa to these regimens after potential risks have been evaluated. Patients with cirrhosis should be urged to seek evaluation for antiviral treatment, to prevent progression of their liver disease.

*Presented by Andrew J. Muir, MD, MHS, in September 2013, and updated in July 2014 to reflect developments in treatment. First draft prepared from transcripts by Matthew Stenger. Reviewed and edited by Dr Muir in July 2014.*

*Financial affiliations in the past 12 months: Dr Muir has received grants and research support from AbbVie, Achillion Pharmaceuticals, Inc, Bristol-Myers Squibb, Gilead Sciences, Inc, GlaxoSmithKline, Merck & Co, Inc, Roche, and Vertex Pharmaceuticals, Inc. He has served as a consultant to AbbVie, Achillion Pharmaceuticals, Inc, Bristol-Myers Squibb, Gilead Sciences, Inc, GlaxoSmithKline, Merck & Co, Inc, and Vertex Pharmaceuticals, Inc, and has received funding awarded to his institution for educational activities from Salix Pharmaceuticals.*

## Refersences


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## Additional Suggested Reading


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