Patients With Decompensated Cirrhosis

Recommended for All Patients With HCV Infection Who Have Decompensated Cirrhosis

RECOMMENDED	RATING
Patients with HCV infection who have decompensated cirrhosis—moderate or severe hepatic impairment, ie, Child-Turcotte-Pugh (CTP) class B or class C—should be referred to a medical practitioner with expertise in that condition, ideally in a liver transplant center.	I, C

Clinical trial data demonstrate that in the population of persons with decompensated cirrhosis, most patients receiving direct-acting antiviral (DAA) therapy experience improvement in clinical and biochemical indicators of liver disease between baseline and posttreatment week 12, including patients with CTP class C cirrhosis (Manns, 2016); (Welzel, 2016); (Charlton, 2015); (Curry, 2015). Improvements, however, may be insufficient to avoid liver-related death or the need for liver transplantation (Belli, 2016), highlighting that not everyone benefits from DAA therapy (Fernandez-Carrillo, 2016). Most deaths among those receiving DAA therapy relate to the severity of the underlying liver disease. Predictors of improvement or decline have not been clearly identified, although patients with a Model for End-Stage Liver Disease (MELD) score >20 or severe portal hypertension complications may be less likely to improve and might be better served by transplantation than antiviral treatment (El-Sherif, 2018); (Terrault, 2017); (Belli, 2016).

Real-world data comparing DAA response rates demonstrate that patients with cirrhosis and hepatocellular carcinoma (HCC) have lower SVR rates than cirrhotic patients without HCC (Beste, 2017); (Prenner, 2017). In a large VA study including sofosbuvir, ledipasvir/sofosbuvir, and paritaprevir/ritonavir/ombitasvir plus dasabuvir regimens (± ribavirin), overall SVR rates were 91% in patients without HCC versus 74% in those with HCC (Beste, 2017). After adjusting for confounders, the presence of HCC was associated with a lower likelihood of SVR (AOR=0.38). Whether this lower SVR can be overcome with an extended duration of therapy is unknown.

In a real-world study, DAA-induced SVR was associated with reduced risk of clinical disease progression in patients with Child-Pugh A cirrhosis but not in those with Child-Pugh B/C cirrhosis. A ≥2 point decrease in MELD score among patients with Child-Pugh B/C cirrhosis was not associated with improved clinical outcome (Krassenburg, 2021). In a large, multicenter, real-world cohort of 642 patients with advanced cirrhosis (defined as cirrhosis and MELD score ≥10) treated with a variety of DAA regimens, the overall SVR12 rate was 90.5%. Age <60, male sex, ascites, serum albumin <3.5 mg/dL, hepatocellular carcinoma, proton-pump inhibitor use, MELD score <16, and CTP class B/C were significantly associated with decreased odds of SVR12. In long-term follow-up at a median of 4 years after the end of treatment, a clinically meaningful decrease in MELD score of ≥3 occurred in 29% and a final MELD score of <10 was achieved in 25%. These data highlight that a proportion of patients with advanced cirrhosis who receive DAA therapy may not achieve significant long-term improvement in liver function (Verna, 2020). A recent retrospective study conducted in HCV-infected patients with decompensated cirrhosis found that DAA therapy was associated with reduced all-cause mortality and non-liver related deaths. In the 88% of patients who achieved SVR, the risk of mortality, hepatocellular carcinoma and liver transplantation was also reduced (Pageaux, 2022).

With the increased efficacy of DAAs in those with decompensated liver disease, a retrospective cohort study evaluated temporal trends, patient characteristics, and outcomes among adults with decompensated cirrhosis who were waitlisted

for liver transplantation between January 1, 2005 and December 31, 2018. Overall, listing rates for HCV patients have decreased in the DAA era. However, delisting due to clinical improvement remains low, although such delisting has increased in more recent times (6.1% for 2013–2017; 5.2% for 2009–2012; 4% for 2005–2008; p <0.001). Ascites persisted in 48.6% and encephalopathy in 30.5% of patients at delisting, indicating that significant morbidity may persist in some patients over the long term, despite SVR (Bittermann, 2020).

Decompensated Cirrhosis Genotype 1-6

Recommended regimens listed by pangenotypic, evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] Who Have Genotype 1-6 and Are Ribavirin Eligible

RECOMMENDED	DURATION	RATING
Genotype 1-6: Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin[b]	12 weeks	I, A[c]
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg, increase as tolerated to weight-based dose)	12 weeks	I, A[d]

[a] Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.
[b] Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis; increase as tolerated.
[c] Only available data for genotype 6 are in patients with compensated cirrhosis.
[d] Only available data for genotypes 5 and 6 are in a small number of patients with compensated cirrhosis.

Recommended regimens listed by pangenotypic, evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] Who Have Genotype 1-6 and Are Ribavirin Ineligible

RECOMMENDED	DURATION	RATING
Genotype 1-6: Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	24 weeks	I, A[b]
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	24 weeks	I, A[c]

[a] Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.
[b] Only available data for genotype 6 are in patients with compensated cirrhosis.
[c] Only available data for genotypes 5 and 6 are in a small number of patients with compensated cirrhosis.

Recommended regimens listed by pangenotypic, evidence level and alphabetically for:

Patients With Decompensated Cirrhosis[a] and Genotype 1-6 Infection in Whom Prior Sofosbuvir- or NS5A Inhibitor-Based Treatment Failed

RECOMMENDED	DURATION	RATING
Genotype 1-6: Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) with weight-based ribavirin[b]	24 weeks	II, C[c]
Prior sofosbuvir-based treatment failure, genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) with low initial dose of ribavirin (600 mg; increase as tolerated)	24 weeks	II, C[d]

[a] Includes CTP class B and class C patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.
[b] Low initial dose of ribavirin (600 mg) is recommended for patients with CTP class C cirrhosis.
[c] Only available data for genotypes 5 and 6 are in a small number of patients with compensated cirrhosis.
[d] Only available data for genotype 6 are in patients with compensated cirrhosis.

Protease inhibitor-containing regimens (eg, glecaprevir, grazoprevir, paritaprevir, simeprevir, and voxilaprevir) are not recommended in patients with decompensated liver disease (see “Protease-Inhibitor Containing Regimens” discussion below for details).

Sofosbuvir/Velpatasvir

The phase 3, open-label, multicenter, randomized ASTRAL-4 study enrolled 267 patients with genotype 1, 2, 3, 4, or 6 and decompensated cirrhosis (CTP class B at the time of screening) who were treatment naive (45%) or experienced (55%). Notably, 10% of patients were CTP class A or class C at treatment baseline. Patients were randomly assigned (1:1:1 ratio) to 12 weeks of a daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg); 12 weeks of sofosbuvir/velpatasvir plus weight-based ribavirin (1000 mg/d, weight <75 kg; 1200 mg/d, weight ≥75 kg); or 24 weeks of sofosbuvir/velpatasvir. Randomization was stratified by HCV genotype. All participants had a hemoglobin level >10 g/dL and an eGFR ≥50 mL/min (Curry, 2015b). The genotype/subtype distribution of the participants was 60% (159/267) genotype 1a; 18% (48/267) genotype 1b; 4% (12/267) genotype 2; 15% (39/267) genotype 3; 3% (8/267) genotype 4; and <1% (1/267) genotype 6. Ninety-five percent of patients had a baseline MELD score ≤15. SVR rates were 83% among those in the 12-week sofosbuvir/velpatasvir study arm, 94% in the 12-week sofosbuvir/velpatasvir plus ribavirin arm, and 86% in the 24-week sofosbuvir/velpatasvir arm. Among patients with genotype 1, the SVR rates were 88%, 96%, and 92%, respectively. Twenty-two participants had virologic failure, including 20 patients with relapse and 2 patients (genotype 3) with on-treatment virologic breakthrough. The presence of baseline NS5A resistant substitutions was not associated with virologic relapse. SVR rates among the 12 patients with CTP class B cirrhosis and genotype 2 were 100% (8/8) with sofosbuvir/velpatasvir for 12 weeks (with or without ribavirin), and 75% (3/4) with sofosbuvir/velpatasvir for 24 weeks. Among 39 patients with CTP class B cirrhosis with genotype 3, SVR rates were 50% (7/14) for 12 weeks of sofosbuvir/velpatasvir without ribavirin, 85% (11/13) for 12 weeks of sofosbuvir/velpatasvir plus ribavirin, and 50% (6/12) for 24 weeks of sofosbuvir/velpatasvir. Therefore, genotype 3 patients in particular appear to benefit from the addition of ribavirin to the regimen (Curry, 2015b). A recent real-world study investigated the safety and efficacy of sofosbuvir/velpatasvir with ribavirin in chronic genotype 1-6 HCV-related cirrhosis. All patients included were Childs-Pugh class B or C. After 12 weeks of treatment, of the 96% of patients who achieved SVR, 84.4% had improved Childs-Pugh scores and 64.6% had improved MELD scores. As such, the benefit of ribavirin therapy in addition to sofosbuvir/velpatasvir continues to be seen across all HCV genotypes (Liu, 2021). For patients with decompensated cirrhosis who are ribavirin ineligible, sofosbuvir/velpatasvir for 24 weeks is currently recommended, but additional studies

involving larger numbers of patients are needed to define the optimal duration of therapy. At posttreatment week 12, 47% of patients had an improvement in CTP score, 42% had no change, and 11% had an increased CTP score. Nine patients (3%) died due to various causes during the study; no deaths were judged to be related to antiviral therapy. Serious adverse events were reported in 16% to 19% of the treated patients. Anemia (ie, hemoglobin <10 g/dL) was reported in 23% of the group receiving ribavirin, and 8% and 9% in those who received 12 weeks and 24 weeks of sofosbuvir/velpatasvir without ribavirin, respectively. Recently, the efficacy of sofosbuvir/velpatasvir therapy was studied in genotype 1 and 2 HCV-infected patients with decompensated cirrhosis. A small number of patients was treated for 12 weeks with this dual therapy. Therefore, a shorter therapy duration of 12 weeks may be sufficient for patients with decompensated cirrhosis who are ribavirin ineligible (Tada, 2021).

A real-world study that evaluated the safety and efficacy of sofosbuvir/velpatasvir (with or without ribavirin) demonstrated an SVR12 of 88% (intention-to-treat analysis) among patients with genotype 3 and decompensated cirrhosis; the treatment was noted to be safe (Wong, 2021). Sofosbuvir/velpatasvir has also been studied in a small number of patients with CTP class C cirrhosis. In a Japanese phase 3, open-label study of patients with CTP class B (77%) and CTP class C (20%) cirrhosis, 102 patients with genotype 1, 2, or 3 were randomized to 12 weeks of sofosbuvir/velpatasvir, with or without ribavirin (Takehara, 2019). Ribavirin dosing was weight based in CTP class B patients (600 mg/d ≤60 kg; 800 mg/d >60 to 80 kg; 1000 mg/d >80 kg) and 600 mg daily for all CTP class C patients. Overall SVR12 rates were 92% in each arm, but only 75% among patients with CTP class C cirrhosis.

There are no data on the outcomes of patients with decompensated cirrhosis and a history of prior sofosbuvir plus an NS5A inhibitor failure. However, in a phase 2, open-label, single-arm study using 24 weeks of sofosbuvir/velpatasvir plus weight-based ribavirin among patients with a history of treatment failure with an NS5A inhibitor-containing regimen, among 69 patients (28% with compensated cirrhosis) treated with sofosbuvir/velpatasvir plus ribavirin for 24 weeks, SVR rates were 97% for genotype 1 (83% with compensated cirrhosis), 93% for genotype 2 (no patients with cirrhosis), and 78% for genotype 3 (75% with compensated cirrhosis) (Gane, 2017). To date, there are no data for this regimen given for 24 weeks in patients with decompensated cirrhosis.

The phase 3, multicenter ASTRAL-1 trial evaluated the efficacy and safety of a 12-week course of daily fixed-dose sofosbuvir/velpatasvir among treatment-naive and -experienced patients with genotype 1, 2, 4, 5, or 6. The study included 35 patients with genotype 5 and 41 patients with genotype 6 (Feld, 2015). Overall SVR12 rates were 97% (34/35) in genotype 5 patients and 100% (41/41) in those with genotype 6. Of note, 100% SVR12 was achieved in the small number of genotype 5 patients (n=5) and genotype 6 patients (n=6) with compensated cirrhosis enrolled in ASTRAL-1.

Ledipasvir/Sofosbuvir

The US-based, multicenter, randomized, open-label, phase 2 SOLAR-1 trial included 108 patients with genotype 1 or 4 and decompensated cirrhosis; 59 were categorized as CTP class B (score 7–9) and 49 were CTP class C (score 10–12). Participants were randomly assigned to 12 weeks or 24 weeks of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin (initial dose of 600 mg, increased as tolerated) (Charlton, 2015b). After excluding the 7 patients who underwent liver transplantation during the study, SVR rates were 87% in CTP class B patients who received 12 weeks of treatment and 89% in those who received 24 weeks of treatment. Similarly, the SVR rates were 86% and 87%, respectively, with 12 weeks and 24 weeks of antiviral therapy in the CTP class C patients. Post-therapy virologic relapse occurred in 8% and 5% of the 12- and 24-week groups, respectively. In the majority of participants with CTP class B or C disease, the MELD and CTP scores decreased between baseline and posttreatment week 4. As expected, the frequency of serious adverse events increased with treatment duration in both the CTP class B group (10%, 12 weeks; 34%, 24 weeks) and the CTP class C group (26%, 12 weeks; 42%, 24 weeks). Most of the serious adverse events were related to ribavirin. The mean daily dose of ribavirin in the patients with decompensated cirrhosis was 600 mg. Therapy was discontinued in 7% of the CTP class B patients and 8% of the CTP class C patients in the 24-week treatment arm.

The multicenter (Europe, Canada, Australia, and New Zealand), randomized, open-label, phase 2 SOLAR-2 study included 160 patients with genotype 1 or 4 and decompensated cirrhosis (CTP class B or C). Study participants, who were treatment-naive or -experienced, were randomly assigned to 12 weeks or 24 weeks of daily fixed-dose ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin (initial dose of 600 mg, increased as tolerated). All participants had a hemoglobin

level >10 g/dL and an estimated glomerular filtration rate (eGFR) >40 mL/min (Manns, 2016). Among the 150 patients with decompensated cirrhosis who completed therapy and had evaluable efficacy results, SVR12 was achieved in 85% (61/72) of those in the 12-week arm (90% [43/48] CTP class B; 75% [18/24] CTP class C). SVR 12 was achieved by 90% (70/78) of patients with decompensated cirrhosis in the 24-week study arm (98% [47/48] CTP class B; 77% [23/30] CTP class C). Post-therapy virologic relapse occurred in 6% (9/150) of the patients with decompensated cirrhosis who completed therapy (7 in 12-week arm; 2 in 24-week arm). Baseline CTP and MELD scores improved in the majority of the treated patients, but some participants experienced worsening hepatic function. Among nontransplanted patients whose MELD score was ≥15 at baseline, 80% (20/25) had a MELD score <15 at SVR12. Among those with a MELD score <15 at baseline, 4% (2/56) had a MELD score ≥15 at SVR12. During the study, 8% (13/160) of the enrolled patients with decompensated cirrhosis (2 CTP class B, 11 CTP class C) died from various causes but none of the deaths were attributed to antiviral therapy. Serious adverse events occurred in approximately 28% of patients with decompensated cirrhosis with no significant difference between the 12- and 24-week treatment arms.

A multicenter, double-blind study from France reported on the use of daily ledipasvir/sofosbuvir for 24 weeks compared to daily ledipasvir/sofosbuvir plus ribavirin for 12 weeks (with a 12-week placebo phase). Study participants included 154 patients with compensated cirrhosis and genotype 1 in whom prior peginterferon/ribavirin treatment failed (for most patients, treatment with peginterferon/ribavirin plus a protease inhibitor also failed) (Bourliere, 2015). The mean MELD score was 7 (range 6–16), 26% of patients had varices, and 13% had a low serum albumin level. The SVR12 rates were 96% with the 12-week regimen and 97% with the 24-week regimen. The most common adverse events were asthenia, headache, and pruritus. The frequency of severe adverse events and the need for early drug discontinuation were low in both treatment groups. In light of these results, it is reasonable to consider daily ledipasvir/sofosbuvir plus ribavirin for 12 weeks in patients with decompensated cirrhosis.

Collectively, the results from these trials indicate that a 12-week course of ledipasvir/sofosbuvir and ribavirin (initial dose of 600 mg, increased as tolerated) is an appropriate regimen for patients with decompensated cirrhosis and genotype 1 or 4. Such therapy may lead to objective improvements in hepatic function and reduce the likelihood of recurrent HCV infection after subsequent transplantation. Most patients received a ribavirin dose of 600 mg/d. Of 17 patients (16 genotype 1; 1 genotype 4) in the SOLAR-1 and SOLAR-2 trials (6 CPT class B; 11 CPT class C) who received ledipasvir/sofosbuvir plus ribavirin for 12 weeks or 24 weeks prior to or up to the time of liver transplantation, all had HCV RNA <15 IU/mL at the time of transplantation. Sixteen of the 17 patients achieved posttransplant SVR12; 1 patient died at postoperative day 15, but the HCV RNA was <15 IU/mL on day 14 (Yoshida, 2017).

Real-world cohort studies have reported SVR rates in patients with decompensated cirrhosis. Investigators from the United Kingdom reported on the use of 12 weeks of ledipasvir (90 mg)/sofosbuvir (400 mg) or daclatasvir (60 mg)/sofosbuvir (400 mg), with or without ribavirin, among 235 genotype 1 patients (Foster, 2016). SVR rates were similar in the participants receiving ledipasvir/sofosbuvir plus ribavirin or ledipasvir/sofosbuvir (86% and 81%, respectively). In this observational cohort study, 91% of the patients received ribavirin; only 6% discontinued ribavirin while 20% required a ribavirin dose reduction. MELD scores improved in 42% of treated patients and worsened in 11%. There were 14 deaths and 26% of the patients had a serious adverse event; none were treatment related.

The multicenter, prospective, observational HCV-TARGET study examined the real-world efficacy of ledipasvir/sofosbuvir (with or without ribavirin) for various treatment durations. SVR12 among genotype 1 patients with a history of clinically decompensated cirrhosis was 90% (263/293) among evaluable patients (Terrault, 2016). In this cohort, 29% of patients with decompensated cirrhosis were treated with ribavirin and 48% received 24 weeks of treatment.

A phase 2a, open-label study of 14 patients with compensated cirrhosis and genotype 1 in whom prior sofosbuvir-based therapy failed demonstrated that ledipasvir/sofosbuvir for 12 weeks was associated with a 100% SVR rate (Osinusi, 2014). In addition, results of an open-label, phase 2 study of 51 genotype 1 patients in whom prior sofosbuvir-based therapy failed demonstrated that a 12-week course of ledipasvir/sofosbuvir plus weight-based ribavirin (1000 mg/d to 1200 mg/d) led to an overall SVR12 of 98%, including 100% (14/14) among those patients with compensated cirrhosis (Wyles, 2015b).

Mixed Genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with DAAs are sparse but utilization of a pangenotypic regimen should be considered. When the correct drug combination or treatment duration is unclear, expert consultation should be sought.

Regimens not recommended for:

Patients With Decompensated Cirrhosis (Moderate or Severe Hepatic Impairment; Child-Turcotte-Pugh Class B or C)

NOT RECOMMENDED	RATING
Any protease inhibitor-containing regimen (eg, glecaprevir, grazoprevir, and voxilaprevir).	III, B
Interferon-based regimens	III, B

Protease-Inhibitor Containing Regimens

The daily fixed dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills has not been studied in patients with decompensated cirrhosis and, pending additional safety data, is not recommended. In a retrospective analysis in a limited number of patients with portal hypertension, glecaprevir/pibrentasvir therapy for 8 or 12 weeks was equally efficacious in patients with and without features of portal hypertension. The therapy showed similar safety and tolerability features in both patient groups (Brown, 2022).

To date, the fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) has not been rigorously studied in patients with decompensated cirrhosis. A phase 2, nonrandomized, open-label study of elbasvir/grazoprevir (50 mg/50 mg) for 12 weeks was completed in 30 genotype 1 patients with CTP class B cirrhosis (Jacobson, 2019). SVR12 was 90% (27/30); 1 patient died of liver failure at posttreatment week 4 and 2 patients relapsed. At follow-up week 12, MELD scores improved in 41% (12/29) of treated patients, were unchanged in 38% (11/29), and worsened in 21% (6/29). However, there are no safety or efficacy data regarding the US Food and Drug Administration (FDA)-approved elbasvir/grazoprevir doses in patients with decompensated cirrhosis. Therefore, until further data are available, treatment of patients with decompensated cirrhosis with elbasvir/grazoprevir is not recommended.

Similarly, the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) has not been extensively studied in patients with hepatic decompensation. Thus, this regimen is not recommended for patients with decompensated cirrhosis (CTP class B or C) until further data are available. A recent real-world study conducted in a small number of patients with genotype 3 HCV infection and liver cirrhosis showed that the sofosbuvir/velpatasvir/voxilaprevir triple therapy was highly efficacious. However, poor tolerability was seen in patients with advanced liver disease (Papaluca, 2021). Similarly, a recent single-center retrospective case review study found this triple therapy to be highly efficacious, in patients with decompensated cirrhosis, when administered under careful observation to patients with a high likelihood of achieving SVR (Patel, 2021).

Interferon-Based Regimens

Interferon should not be given to patients with decompensated cirrhosis (moderate or severe hepatic impairment, CTP class B or C) because of the potential for worsening hepatic decompensation.

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