Persons With Decompensated Cirrhosis

Recommended for All Persons With HCV Infection Who Have Decompensated Cirrhosis	
RECOMMENDED	RATING
Persons with HCV infection who have decompensated cirrhosis—moderate or severe hepatic impairment, ie, Child-Turcotte-Pugh 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 individuals receiving direct-acting antiviral (DAA) therapy experience improvement in clinical and biochemical indicators of liver disease between baseline and posttreatment week 12, including those with Child-Turcotte-Pugh (CTP) class C cirrhosis (Manns, 2016); (Welzel, 2016); (Charlton, 2015b); (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 people with a Model for End-Stage Liver Disease (MELD) score >20 or severe portal hypertension complications may be less likely to improve (compared with those with a lower MELD score) 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 persons with cirrhosis and hepatocellular carcinoma (HCC) have lower SVR rates than persons with cirrhosis 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 people 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 (adjusted odds ratio [AOR] 0.38). Whether this lower SVR rate 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 among people with Child-Pugh A cirrhosis but not in those with Child-Pugh B/C cirrhosis. A ≥2 point decrease in MELD score among persons with Child-Pugh B/C cirrhosis was not associated with improved clinical outcome (Krassenburg, 2021). In a large, multicenter, real-world cohort of 642 persons 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, HCC, proton-pump inhibitor use, MELD score <16, and CTP class B/C were significantly associated with decreased odds of attaining 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 subset of people with advanced cirrhosis who receive DAA therapy may not achieve significant long-term improvement in liver function (Verna, 2020). A retrospective study conducted among persons with HCV infection and decompensated cirrhosis found that DAA therapy was associated with reduced all-cause mortality and nonliver related deaths. Among the 88% of persons with HCV infection and decompensated cirrhosis who achieved SVR, the risk of mortality, HCC, 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 people with HCV infection have decreased in the DAA era. However, delisting due to clinical improvement remains low, although such delisting has increased in frequency in the DAA era (6.1% for 2013–2017; 5.2% for 2009–2012; 4% for 2005–2008). Ascites persisted in 48.6% and encephalopathy in 30.5% of persons at delisting, indicating that significant morbidity may persist in some persons over the long term, despite DAA-induced SVR (Bittermann, 2020).

Decompensated Cirrhosis Genotype 1–6

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

Persons 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 dosage of ribavirin (600 mg/d, increase as tolerated to weight-based dosage)	12 weeks	I, A[d]

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

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

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

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

Persons With Decompensated Cirrhosis[a] and Genotype 1–6 Infection in Whom Prior Sofosbuvir-Based 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 dosage of ribavirin (600 mg/d; increase as tolerated to weight-based dosage)	24 weeks	II, C[d]

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

Protease inhibitor-containing regimens (eg, glecaprevir, grazoprevir, paritaprevir, simeprevir, and voxilaprevir) are not recommended for people 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 adults with genotype 1, 2, 3, 4, or 6 infection and decompensated cirrhosis (CTP class B at the time of screening) who were treatment naive (45%) or experienced (55%). Notably, 10% of participants were CTP class A or class C at treatment baseline. Participants 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 estimated glomerular filtration rate (eGFR) ≥50 mL/min/1.73 m^2 (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 participants 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 persons with genotype 1 infection, the SVR rates were 88% in the 12-week sofosbuvir/velpatasvir, 96% in the 12-week sofosbuvir/velpatasvir plus ribavirin arm, and 92% in the 24-week sofosbuvir/velpatasvir arm. Twenty-two participants had virologic failure, including 20 people with relapse and 2 people with on-treatment virologic breakthrough (both genotype 3). The presence of baseline NS5A resistant-associated substitutions (RASs) was not associated with virologic relapse. SVR rates among the 12 participants with CTP class B cirrhosis and genotype 2 infection 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 the 39 participants with CTP class B cirrhosis and genotype 3 infection, 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, persons with genotype 3 infection in particular appear to benefit from the addition of ribavirin to sofosbuvir/velpatasvir. At posttreatment week 12, 47% of participants had an improved CTP score, 42% had no change, and 11% had an increased CTP score. Nine people (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 participants across the 3 study arms. 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 (Curry, 2015b).

A real-world study investigated the safety and efficacy of sofosbuvir/velpatasvir with ribavirin in persons with chronic genotype 1-6 HCV-related cirrhosis. All participants had Childs-Pugh class B or C cirrhosis. After 12 weeks of treatment, of the 96% of persons who attained 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 people with decompensated cirrhosis who are ribavirin ineligible, sofosbuvir/velpatasvir for 24 weeks is currently recommended. However, additional studies involving larger numbers of participants are needed to define the optimal duration of therapy. A real-world study evaluated the safety and efficacy of 12 weeks of sofosbuvir/velpatasvir therapy (without ribavirin) among 65 persons with genotype 1 or 2 infection and decompensated cirrhosis. SVR12 rate was 92.3% (60/65). Therefore, a shorter therapy duration of 12 weeks may be sufficient for persons 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 intention-to-treat SVR12 rate of 88% (466/530) among persons with genotype 3 infection and decompensated cirrhosis (Wong, 2021). Sofosbuvir/velpatasvir has also been studied in a small number of persons with CTP class C cirrhosis. In a Japanese phase 3, open-label study of people with CTP class B (77%) and CTP class C (20%) cirrhosis, 102 adults with genotype 1, 2, or 3 infection were randomized to 12 weeks of sofosbuvir/velpatasvir, with or without ribavirin. Ribavirin dosing was weight based for participants with CTP class B cirrhosis (600 mg/d ≤60 kg; 800 mg/d >60 to 80 kg; 1000 mg/d >80 kg). Ribavirin dosage for those CTP class C cirrhosis was 600 mg/d. SVR12 rates were 92% (47/51) in each study arm but only 75% among participants with CTP class C cirrhosis (Takehara, 2019).

There are no data on the outcomes of persons with decompensated cirrhosis and a history of prior sofosbuvir plus an NS5A inhibitor treatment failure. However, a phase 2, open-label, single-arm study evaluated the efficacy of 24 weeks of sofosbuvir/velpatasvir plus weight-based ribavirin among persons with a history of treatment failure with an NS5A inhibitor-containing regimen. Among 69 participants (28% with compensated cirrhosis), SVR12 rates were 97% (36/37) for genotype 1 infection (83% with compensated cirrhosis), 93% (13/14) for genotype 2 infection (no participants with cirrhosis), and 78% (14/18) for genotype 3 (75% with compensated cirrhosis) (Gane, 2017). To date, there are no data for this regimen given for 24 weeks in persons with HCV-related 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 treatment-experienced persons with genotype 1, 2, 4, 5, or 6 infection. The study included 35 participants with genotype 5 infection and 41 with genotype 6 infection. Overall SVR12 rates were 97% (34/35) in those with genotype 5 infection and 100% (41/41) in those with genotype 6 infection. Of note, a 100% SVR12 rate was achieved in the small number of study participants with compensated cirrhosis with genotype 5 infection (n=5) and genotype 6 infection (n=6) (Feld, 2015).

Ledipasvir/Sofosbuvir

The US-based, multicenter, randomized, open-label, phase 2 SOLAR-1 trial included 108 adults with genotype 1 or 4 infection and decompensated cirrhosis; 59 were categorized with CTP class B cirrhosis (score 7–9) and 49 with 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 dosage of 600 mg/d, increased as tolerated) (Charlton, 2015b). After excluding the 7 people who underwent liver transplantation during the study, SVR12 rates were 87% (26/30) in CTP class B participants who received 12 weeks of treatment and 89% (24/27) in those who received 24 weeks of treatment. Similarly, the SVR rates were 86% (19/22) and 87% (20/23), respectively, with 12 weeks and 24 weeks of antiviral therapy among CTP class C participants. Posttherapy virologic relapse occurred in 8% and 5% of the 12-week 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 ribavirin related. The mean ribavirin dosage in the participants with decompensated cirrhosis was 600 mg/d. Therapy was discontinued in 7% and 8% of the CTP class B and C participants, respectively, in the 24-week treatment arm.

The multicenter (Europe, Canada, Australia, and New Zealand), randomized, open-label, phase 2 SOLAR-2 study included 160 adults with genotype 1 or 4 infection and decompensated cirrhosis (CTP class B or C). Study participants, who were treatment-naive or -treatment experienced, were randomly assigned to 12 weeks or 24 weeks of daily fixed-dose ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin (initial dosage of 600 mg/d, increased as tolerated). All participants had a hemoglobin level >10 g/dL and an (eGFR) >40 mL/min/1.73 m^2 (Manns, 2016). Among the 150 enrollees with decompensated cirrhosis who completed

therapy and had evaluable efficacy results, SVR12 was attained 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 participants with decompensated cirrhosis in the 24-week study arm (98% [47/48] CTP class B; 77% [23/30] CTP class C). Posttherapy virologic relapse occurred in 6% (9/150) of the persons 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 persons, although some participants experienced worsening hepatic function. Among nontransplanted participants 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 participants with decompensated cirrhosis (2 CTP class B; 11 CTP class C) died from various causes; none of the deaths were attributed to antiviral therapy. Serious adverse events occurred in approximately 28% of participants with decompensated cirrhosis with no significant difference between the 12-week and 24-week treatment arms (Manns, 2016).

A multicenter, double-blind study from France reported on the use of ledipasvir/sofosbuvir for 24 weeks compared with ledipasvir/sofosbuvir plus ribavirin for 12 weeks (with a 12-week placebo phase). Study participants included 154 persons with compensated cirrhosis and genotype 1 infection in whom prior peginterferon/ribavirin treatment failed. The mean MELD score was 7 (range 6–16); 26% of participants had varices and 13% had a low serum albumin level. The SVR12 rates were 96% (74/77) with the 12-week regimen and 97% (75/77) 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 people with decompensated cirrhosis (Bourlière, 2015).

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

Real-world cohort studies have reported SVR rates among persons 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 people with genotype 1 infection and decompensated cirrhosis. 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 persons received ribavirin. Only 6% discontinued ribavirin while 20% required a ribavirin dosage reduction. MELD scores improved in 42% of treated persons and worsened in 11%. There were 14 deaths; 26% of the persons in the cohort experienced a serious adverse event, none of which were treatment related (Foster, 2016).

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

A phase 2a, open-label study of 14 persons with compensated cirrhosis and genotype 1 infection 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 people with genotype

1 infection (27% with compensated cirrhosis) 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 rate of 98% (50/51), including an SVR12 rate of 100% (14/14) among those 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 optimal drug regimen or treatment duration is unclear, expert consultation should be sought.

Regimens not recommended for:

Persons With Decompensated Cirrhosis[a]

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

[a] Includes persons with moderate or severe hepatic impairment, ie, Child-Turcotte-Pugh class B or class C.

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 people with decompensated cirrhosis and, pending additional safety data, is not recommended for this patient population. In a retrospective analysis among a limited number of persons with portal hypertension, glecaprevir/pibrentasvir therapy for 8 weeks or 12 weeks was equally efficacious in people with and without features of portal hypertension (ie, FibroScan ≥20 kPa, platelets $<100 \times 10^9$/L, or a medical history consistent with portal hypertension). Among those with evidence of portal hypertension, the SVR12 rates were 98% (203/208) and 99% (221/224) in the 8-week and 12-week treatment groups, respectively. The therapy showed similar safety and tolerability features in both treatment groups (Brown, 2022).

To date, the fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) has not been rigorously studied in people with decompensated cirrhosis. A phase 2, nonrandomized, open-label study of elbasvir/grazoprevir (50 mg/50 mg) for 12 weeks was completed in 30 persons with genotype 1 infection and CTP class B cirrhosis (Jacobson, 2019). SVR12 rate was 90% (27/30). One participant died of liver failure at posttreatment week 4; 2 participants relapsed. At follow-up week 12, MELD scores improved in 41% (12/29) of treated participants, 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 dosages of elbasvir/grazoprevir (50 mg/100

mg) in persons with decompensated cirrhosis. Therefore, until further data are available, elbasvir/grazoprevir is not recommended for the treatment of persons with decompensated cirrhosis (CTP class B or class C).

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

Interferon-Based Regimens

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

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