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CLINICAL PRACTICE UPDATES

AGA Clinical Practice Update on the Use of Vasoactive Drugs and Intravenous Albumin in Cirrhosis: Expert Review

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DESCRIPTION: Cirrhosis is a major cause of morbidity and mortality in the United States and worldwide. It consists of compensated, decompensated, and further decompensated stages; median survival is more than 15 years, 2 years, and 9 months for each stage, respectively. With each stage, there is progressive worsening of portal hypertension and the vasodilatory–hyperdynamic circulatory state, resulting in a progressive decrease in effective arterial blood volume and renal perfusion. Vasoconstrictors reduce portal pressure via splanchnic vasoconstriction and are used in the management of variceal hemorrhage. Intravenous (IV) albumin increases effective arterial blood volume and is used in the prevention of acute kidney injury (AKI) and death after large-volume paracentesis and in patients with spontaneous bacterial peritonitis (SBP). The combination of vasoconstrictors and albumin is used in the reversal of hepatorenal syndrome (HRS-AKI), the most lethal complication of cirrhosis. Because a potent vasoconstrictor, terlipressin, was recently approved by the US Food and Drug Administration, and because recent trials have explored use of IV albumin in other settings, it was considered that a best practice update would be relevant regarding the use of vasoactive drugs and IV albumin in the following 3 specific scenarios: variceal hemorrhage, ascites and SBP, and HRS. **METHODS:** This expert review was commissioned and approved by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership. It underwent internal peer review through standard procedures of *Gastroenterology*. These Best Practice Advice statements were drawn from a review of the published literature and from expert opinion. Some of the statements are unchanged from published guidelines because of lack of new evidence in the literature. Because systematic reviews were not performed, these Best Practice Advice statements do not carry formal ratings regarding the quality and evidence or strength of the presented considerations.

BEST PRACTICE ADVICE STATEMENTS

BEST PRACTICE ADVICE 1: Vasoactive drugs should be initiated as soon as the diagnosis of variceal hemorrhage is suspected or confirmed, preferably before diagnostic and/or therapeutic endoscopy. **BEST PRACTICE ADVICE 2:** After initial endoscopic hemostasis, vasoactive drugs should be continued for 2–5 days to prevent early rebleeding. **BEST PRACTICE ADVICE 3:** Octreotide is the vasoactive drug of choice in the management of variceal hemorrhage based on its safety profile. **BEST PRACTICE ADVICE 4:** IV albumin should be administered at the time of large-volume (>5 L) paracentesis. **BEST PRACTICE ADVICE 5:** IV albumin may be considered in patients with SBP. **BEST PRACTICE ADVICE 6:** Albumin should not be used in patients (hospitalized or not) with cirrhosis and uncomplicated ascites. **BEST PRACTICE ADVICE 7:** Vasoconstrictors should not be used in the management of uncomplicated ascites, after large-volume paracentesis or in patients with SBP. **BEST PRACTICE ADVICE 8:** IV albumin is the volume expander of choice in hospitalized patients with cirrhosis and ascites presenting with AKI. **BEST PRACTICE ADVICE 9:** Vasoactive drugs (eg, terlipressin, norepinephrine, and combination of octreotide and midodrine) should be used in the treatment of HRS-AKI, but not in other forms of AKI in cirrhosis. **BEST PRACTICE ADVICE 10:** Terlipressin is the vasoactive drug of choice in the treatment of HRS-AKI and use of concurrent albumin can be considered when accounting for patient's volume status. **BEST PRACTICE ADVICE 11:** Terlipressin treatment does not require intensive care unit monitoring and can be administered intravenously through a peripheral line. **BEST PRACTICE ADVICE 12:** Terlipressin use is contraindicated in patients with hypoxemia and in patients with ongoing coronary, peripheral, or mesenteric ischemia, and should be used with caution in patients with acute-on-chronic liver failure grade 3. The benefits may not outweigh the risks in patients with serum creatinine >5 mg/dL and in patients listed for transplantation with a Model for End-stage Liver Disease ≥35.

Keywords: Portal Hypertension; Octreotide; Terlipressin; Ascites; Hepatorenal Syndrome.

Cirrhosis and liver cancer account for 3.5% of all deaths worldwide; in 2017 there were more than 112 million and 10.6 million cases of compensated and decompensated cirrhosis, respectively.[1] In the United States,

Abbreviations used in this paper: **ACLF, acute-on-chronic liver failure; AGA, American Gastroenterological Association; AKI, acute kidney injury; AVH, acute variceal hemorrhage; FDA, US Food and Drug Administration; HRS, hepatorenal syndrome; ICU, intensive care unit; IV, intravenous; LVP, large-volume paracentesis; NE, norepinephrine; PCD, post-paracentesis circulatory dysfunction; RCT, randomized controlled trial; SBP, spontaneous bacterial peritonitis.**

Most current article

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chronic liver disease is the fourth leading cause of death among adults aged 45–64 years and accounts for more than 44,000 deaths annually.[2,3] Cirrhosis and its complications result in a considerable burden of disability, hospitalizations, and health care resource utilization; inpatient costs alone exceeded $18.8 billion in 2016.[4] Alarmingly, the clinical and economic burden of cirrhosis is increasing due in large part to the increasing prevalence of steatotic liver disease.[5]

Cirrhosis consists of 3 distinct prognostic stages. The compensated stage is defined by the absence of clinically overt complications and is associated with a median survival that exceeds 12 years; the stage of decompensation is marked by the development of ascites, hepatic encephalopathy, and/or gastroesophageal variceal hemorrhage and is associated with a median survival of approximately 2 years.[6] A third stage of "further" decompensation has been defined recently and is characterized by the development of a second (additional) decompensating event, recurrent ascites (requiring large-volume [>5 L] paracentesis [LVP]), recurrent variceal hemorrhage, recurrent hepatic encephalopathy, spontaneous bacterial peritonitis [SBP], acute kidney injury [AKI]/hepatorenal syndrome [HRS], and/or jaundice.[7] Acute-on-chronic liver failure (ACLF) is a severe form of decompensation characterized by 1 or more organ failures.[8] Except for jaundice, these complications are manifestations of portal hypertension with a vasodilatory–hyperdynamic circulatory state, resulting in progressive decreases in effective arterial blood volume and renal perfusion. Vasoactive drugs, including vasopressin (and analogue terlipressin), somatostatin (and analogue octreotide), and α-adrenergic agonists (ie, norepinephrine [NE] and midodrine) are widely used in the management of cirrhosis to reduce portal pressure via splanchnic vasoconstriction and, in conjunction with intravenous (IV) albumin, to increase effective arterial blood volume and improve renal perfusion. Terlipressin, used commonly outside the United States for these indications (ie, acute variceal hemorrhage [AVH] and HRS), has only recently received US Food and Drug Administration (FDA) approval.[9]

The goal of this review was to provide guidance and best practice advice on the use of vasoactive drugs and IV albumin in the following 3 common scenarios: variceal hemorrhage, ascites and SBP, and AKI and HRS. We have developed 12 Best Practice Advice statements to address key, timely, clinical issues faced in patients with decompensated cirrhosis and the above complications. This expert review was commissioned by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee and approved by the AGA Governing Board.

Variceal Hemorrhage

Best Practice Advice 1: Vasoactive drugs should be initiated as soon as the diagnosis of variceal hemorrhage is suspected or confirmed, preferably before diagnostic and/or therapeutic endoscopy.

AVH is a major complication of cirrhosis with an in-hospital mortality rate of 4%–13% and a 6-week mortality rate of 7%–43%.[10] It accounts for approximately 70% of all upper gastrointestinal hemorrhage in patients with cirrhosis. The goals of management of AVH include initial hemostasis, preventing early rebleeding, and reducing in-hospital and 6-week mortality.[11]

Vasoactive drugs for AVH can be divided into somatostatin and its analogues (octreotide in most countries) and vasopressin and its analogues (terlipressin). These vasoactive drugs work via vasoconstriction in the splanchnic circulation and thereby reduce portal pressure.[12] They can halt acute hemorrhage in up to 80% of cases, making subsequent endoscopic hemostasis easier. Therefore, although the diagnosis of AVH can only be confirmed during endoscopy, and patients with cirrhosis are also at a higher risk of other causes of upper gastrointestinal hemorrhage, such as peptic ulcer disease, vasoactive drugs should be initiated as soon as a patient with cirrhosis presents with symptoms and signs of upper gastrointestinal hemorrhage, preferably before diagnostic and/or therapeutic endoscopy.

Vasoactive drugs are given intravenously. Table 1 summarizes the typical regimens for the management of AVH and prevention of early rebleeding. In the United States, terlipressin is registered as a treatment to improve kidney function in adults with HRS-AKI with rapid reduction in kidney function. Although terlipressin has been evaluated for AVH and is one of the standard regimens outside of the United States, the FDA label does not include this indication. In contrast, the European Society of Gastrointestinal Endoscopy supports the use of terlipressin, octreotide, and somatostatin as initial treatments for AVH.[13]

Best Practice Advice 2: After initial endoscopic hemostasis, vasoactive drugs should be continued for 2–5 days to prevent early rebleeding.

Several meta-analyses consistently found that vasoactive drugs improve clinical outcomes in patients with AVH.[14,15] In a systematic review and meta-analysis of 3111 patients from 30 randomized controlled trials (RCTs), vasoactive drugs reduced 7-day mortality (relative risk, 0.74; 95% CI, 0.57–0.95), improved hemostasis (relative risk, 1.21; 95% CI, 1.13–1.30), lowered transfusion requirement (–0.7 units of blood), and shortened hospitalization (–0.7 days) in patients with AVH.[14] The improved outcomes were driven largely by reducing the rate of early variceal rebleeding after initial endoscopic hemostasis. As vasoactive drugs are not expected to work in other causes of acute upper gastrointestinal bleeding (eg, peptic ulcer bleeding), the drugs should be stopped when endoscopy reveals non-variceal upper gastrointestinal bleeding.

Current guidelines recommend the use of vasoactive drugs for 2–5 days to prevent early rebleeding.[8,11] However, current data are insufficient to support a concrete recommendation on the optimal duration of vasoactive drug treatment. Several RCTs suggest that treatment duration (down to 2 days) may not affect the rebleeding rate, but studies are limited by small sample size.[16–18] In contrast, observational studies on treatment duration are inherently confounded by the severity of bleeding (ie, patients with massive bleeding and unstable hemodynamics tend to receive a longer duration of vasoactive drug treatment).

Known risk factors of early rebleeding and in-hospital mortality after AVH can be divided into endoscopic factors

Table 1. Standard Regimens for the Use of Vasoactive Drugs in the Management of Acute Variceal Hemorrhage and Prevention of Early Rebleeding

Drug	Standard regimen	Duration, *d*
Octreotide (somatostatin analogue)	50 μg IV bolus, followed by continuous IV infusion at 50 μg/h; additional IV boluses can be given in case of ongoing bleeding	2–5
Somatostatin	250 μg IV bolus, followed by continuous IV infusion at 250–500 μg/h; additional IV boluses can be given in case of ongoing bleeding	2–5
Terlipressin (vasopressin analogue)[a]	Initial 48 h: 2 mg IV every 4 h until bleeding is controlled Maintenance: 1 mg IV every 4 h	2–5

[a]Although terlipressin has been evaluated for AVH and is one of the standard regimens outside of the United States, the FDA label does not include this indication.

(eg, active bleeding identified during endoscopy, presence of a clot on a varix, extent of varices, and number of bands placed in case of endoscopic variceal ligation) and the severity of cirrhosis (as reflected by the Model for End-stage Liver Disease score, prothrombin time, or presence of ascites), but studies on the use of these predictors to guide vasoactive drug treatment duration are lacking. Before a definitive trial becomes available, it is reasonable to shorten vasoactive drug treatment to 2 days only in selected patients with Child-Pugh class A and B cirrhosis with no active bleeding identified during endoscopy.

Best Practice Advice 3: Octreotide is the vasoactive drug of choice in the management of variceal hemorrhage based on its safety profile.

Vasopressin is no longer advised in patients with AVH because of a high risk of cardiovascular adverse events. In a 2021 updated systematic review and meta-analysis involving 21 RCTs, the use of terlipressin or vasopressin compared with octreotide or somatostatin resulted in similar rates of mortality, hemostasis, early rebleeding (less than 5 days), late rebleeding (more than 5 days), blood transfusion, and hospital stay.[19] However, adverse events increased by 2.39-fold in patients receiving terlipressin or vasopressin. Adverse events that were increased considerably in the terlipressin/vasopressin group included abdominal pain, chest pain, diarrhea, and hyponatremia. In another systematic review and meta-analysis involving 3344 patients from 30 RCTs, terlipressin was less effective than octreotide in terms of bleeding control within 24 hours. Terlipressin also had a higher risk of complications than somatostatin (Table 2).[15]

In terms of hemodynamic response, a study in 2005 found that a single 2-mg dose of IV terlipressin decreased hepatic venous pressure gradient acutely from 22.2 mm Hg to 19.1 mm Hg in patients with AVH with suboptimal response to standard somatostatin infusion (250 μg bolus followed by 250 μg/h)—a reduction that appears to be greater than what was achieved with increasing somatostatin infusion to 500 μg/h.[20]

Traditionally, terlipressin was given as bolus injections, but emerging data in patients with HRS-AKI support giving it as a continuous infusion (see below). Data on the use of terlipressin infusion for AVH are scarce. In a single-center RCT from India, compared with bolus injection of terlipressin at a dose of 2 mg/4 h, continuous terlipressin infusion at a dose of 4 mg/24 h led to a >10% decline in hepatic venous pressure gradient at both 12 hours (72% vs 49%) and 24 hours (85% vs 58%).[21] This translated into a lower rebleeding rate between 2 and 5 days (15% vs 2%). In addition, similar to what is observed in HRS-AKI, continuous terlipressin infusion allows the administration of the drug at a lower dose, resulting in fewer adverse events. Although the results are encouraging, it should be noted that patients receiving continuous terlipressin infusion had dose adjustment according to hepatic venous pressure gradient measurements at 12 and 24 hours. This may not be feasible in most settings. Similar findings were observed in another single-center RCT from India.[22]

Terlipressin is contraindicated in patients experiencing hypoxia or worsening respiratory symptoms, and those with ongoing coronary, peripheral, or mesenteric ischemia. Common adverse reactions include abdominal pain, nausea, respiratory failure, diarrhea, and dyspnea.[21] In contrast, octreotide treatment may result in both hypoglycemia and hyperglycemia.[23] Adjustment of insulin dosage may be necessary. Bradycardia and pancreatitis have also been reported, although it is unclear whether the adverse events are due to the drug or patient comorbidities.

Ascites and Spontaneous Bacterial Peritonitis

Best Practice Advice 4: IV albumin should be administered at the time of large-volume (>5 L) paracentesis.

Paracentesis is advised in patients with cirrhosis and ascites that is no longer responding to diuretics and/or is tense. Although single 5-L LVPs do not result in deleterious hemodynamic or renal effects,[24] in an RCT including 105 patients with tense ascites, daily 5-L paracenteses unaccompanied by IV albumin were associated with AKI in 21% of patients; AKI did not occur in any patient receiving albumin.[25] In addition, plasma renin activity and plasma aldosterone increased significantly 48 hours after LVP in the control but not albumin group. This increase in plasma

Table 2. Adverse Events Related to Vasoactive Drugs and Albumin

Drug	Reported in ≥10%	Reported in <10%
Octreotide	Bradycardia Cardiac conduction abnormalities Diarrhea Loose stool Nausea Abdominal discomfort Hyperglycemia	Arrhythmia Abdominal distension Severe epigastric pain Hypoglycemia Headache Dizziness Fatigue
Somatostatin	Diarrhea Abdominal pain Nausea	Constipation Flatulence Vomiting Loose stool Arthralgia Headache
Terlipressin	Abdominal pain Nausea Respiratory failure Diarrhea Dyspnea	Fluid overload Pleural effusion Sepsis Bradycardia Skin discoloration Cyanosis Myocardial ischemia Stroke Intestinal ischemia
Albumin	—	Fluid overload Pulmonary edema Rigors Hypotension/tachycardia Pyrexia Nausea/vomiting Rash/pruritus

NOTE. In general, adverse events are dose-dependent. However, adverse events can still develop in patients receiving these treatments at a lower dose.

renin after LVP, named "post-paracentesis circulatory dysfunction" (PCD), results from vasodilation and a consequent decrease in "effective" arterial blood volume.[26]

Albumin was compared with synthetic volume expanders in a multicenter RCT including 289 patients, showing no differences in PCD when volumes <5 L were removed. However, with removal >5 L (ie, LVP), PCD was significantly lower in patients randomized to albumin (18%) compared with those randomized to dextran-70 or polygeline (34% and 38%, respectively).[27] These results were confirmed in a meta-analysis of 8 trials including 694 patients.[28] Although PCD had been related to decreased survival,[27] a Cochrane meta-analysis comparing no volume expansion with volume expansion after LVP found no differences in renal dysfunction or mortality.[29] Therefore, further data are necessary regarding robust outcomes, other than PCD, in the evaluation of albumin after LVP.

Until more evidence is available, society guidelines state that albumin infusion at the time of LVP of >5 L is recommended to mitigate the risk of PCD.[8,30] The suggested dose of albumin, based on expert opinion, is 6–8 g/L of ascites removed, but lower doses (4 g/L) may be sufficient.[31] In patients with ACLF, albumin should be administered during paracentesis at a dose of 6–8 g/L regardless of amount of ascites removed.[32]

Best Practice Advice 5: IV albumin may be considered in patients with SBP.

AKI is a frequent complication of SBP, may progress to HRS-AKI even after SBP resolution, and is the strongest predictor of death in patients with SBP.[33] Therefore, it is essential to prevent or treat AKI as soon as SBP is diagnosed.

The mechanism of AKI in SBP is systemic inflammation leading to vasodilation and decreased effective arterial blood volume that improves with albumin.[34] In a multicenter RCT including 105 patients with SBP, those who received antibiotics accompanied by IV albumin had a significantly lower rate of AKI (10% vs 33%) and death (10% vs 29%) compared with those who received antibiotics only.[35] In subgroup analysis, patients with serum bilirubin >4 mg/dL and AKI at baseline (creatinine >1.0 mg/dL and blood urea nitrogen >30 mg/dL) were at higher risk of AKI and most likely to benefit from albumin.

Two meta-analyses have confirmed the benefits of albumin in SBP.[36,37] In the most recent,[37] including 5 RCTs, albumin was compared with no therapy in 3 RCTs, with hydroxyethyl starch in one,[38] and with terlipressin in another.[39] In 4 of the 5 studies, the empirical dose of albumin recommended was used (ie, 1.5 mg/kg of body weight on day 1 and 1 g/kg of body weight on day 3).[35] In the remaining study,[40] albeit small, patients randomized to receive albumin received only 10 g/d from days 1–3 after SBP diagnosis, despite which they still had lower renal dysfunction (7% vs 20%) and in-hospital mortality (27% vs 40%) rates than controls, supporting results of a small trial that also found that lower doses of albumin were effective in reducing AKI.[41]

Regarding alternatives to albumin, an RCT comparing hydroxyethyl starch with albumin in 20 patients with SBP found albumin to be superior in improving systemic hemodynamics.[38]

Because society guidelines are tied to evidence obtained from RCTs, recommendations are that patients with SBP should receive IV albumin (1.5 g/kg at day 1 and 1 g/kg at day 3) in addition to antibiotics, specifying that patients with AKI and/or jaundice are more likely to benefit from albumin.[8,30]

Importantly, 3 RCTs[42–44] and a meta-analysis[45] comparing albumin with no albumin in patients with cirrhosis and infections other than SBP found that albumin does not reduce the risk of AKI or mortality and was associated with more pulmonary edema. Therefore, albumin is not advised in infections other than SBP, unless associated with AKI (see Best Practice Advice 8).

Best Practice Advice 6: Albumin should not be used in patients (hospitalized or not) with cirrhosis and uncomplicated ascites.

Standard therapy for cirrhotic ascites is sodium restriction plus diuretics (spironolactone with or without furosemide).[8,30,46] Whether the co-administration of albumin improves response to diuretics is still unclear. This was first

explored in 1962 in 16 patients, showing no improvement in control of ascites with albumin.[47] Furthermore, in a crossover randomized study, albumin failed to enhance the diuretic effect of furosemide.[48] However, in a unblinded RCT including 126 patients not responsive to salt restriction alone, resolution of ascites was faster and recurrence of ascites was lower with albumin[49]; however, it did not demonstrate a survival benefit and showed that the albumin strategy was not cost-effective.

Beyond the effect of albumin on diuresis (or after LVP or with SBP), 3 RCTs have analyzed the effect on survival of chronic weekly administration of albumin in patients with cirrhosis and ascites.[50–52] The first, performed in 100 patients with new-onset ascites,[50] found an improvement in survival and a lower recurrence of ascites. In the second,[51] a large RCT (ANSWER [Albumin for the Treatment of Ascites in Patients With Hepatic Cirrhosis]) enrolling 431 patients with "persistent" (despite diuretics) ascites, those randomized to weekly albumin infusions had significantly lower 18-month mortality, a lower need for LVP, and less hyponatremia, SBP, and HRS-AKI. However, these 2 trials were unblinded and were not placebo-controlled. A third RCT (MACHT [Effect of Midodrine and Albumine in the Prevention of Complications in Cirrhotic Patients Awaiting Liver Transplantation]),[52] a better designed, placebo-controlled study comparing albumin plus midodrine with a double placebo, found no differences in mortality or other complications of ascites.

In an inpatient setting, another RCT (ATTIRE [Albumin to Prevent Infection in Chronic Liver Failure)[53] including 777 inpatients with cirrhosis and new or worsening ascites, found a lack of effect of albumin in preventing bacterial infection, AKI, or death. Albumin infusions were administered at a dose aimed at maintaining a serum albumin level $\geq$3.0 g/L throughout hospitalization. Notably, the albumin group (which received 10 times the amount of albumin than the control group) had a higher rate of pulmonary edema.

Therefore, the exact outpatient or inpatient population that will benefit from albumin administration beyond its use with LVP, SBP, and AKI remains to be determined.

Best Practice Advice 7: Vasoconstrictors should not be used in the management of uncomplicated ascites, after LVP, or in patients with SBP.

Because vasodilation is the main pathogenic mechanism leading to sodium retention, ascites, and AKI in SBP, it makes pathophysiological sense to use vasoconstrictors instead of or together with diuretics and/or albumin in the management of these complications.

Vasoconstrictors in Uncomplicated Ascites

The use of midodrine has been explored in 2 small RCTs. In 1 RCT, midodrine improved systemic hemodynamics and sodium excretion in 12 patients, which was not observed in 8 patients on placebo.[54] However, patients were not on diuretics. The other RCT, a crossover trial with 15 patients found no differences in natriuretic response or urine volume between furosemide plus midodrine or placebo.[55] Evidence is insufficient to use midodrine as an adjuvant to diuretics, or to use more potent vasoconstrictors in this setting.

Vasoconstrictors After Large-Volume Paracentesis

A meta-analysis including 5 small studies (totaling 80 patients) found no differences in PCD between albumin and different vasoconstrictors (eg, terlipressin, midodrine, and NE).[28] Another small RCT that compared albumin with octreotide plus midodrine in 25 patients found no differences in PCD or recurrence of ascites between groups, but more AKI in the vasoconstrictor group.[56] Although it appears that vasoconstrictors are as effective as albumin in preventing PCD, evidence is insufficient to recommend this strategy unless confirmed by larger trials with relevant outcomes, such as AKI.

Vasoconstrictors With Spontaneous Bacterial Peritonitis

An RCT that randomized 200 patients with SBP at high risk of developing AKI to the following 4 arms: albumin alone, terlipressin alone, low-dose albumin plus terlipressin, or midodrine alone[39] found a significant increase in systemic vascular resistance in the 2 terlipressin arms. However, there was no significant difference in renal impairment or mortality among study groups. Therefore, evidence is currently insufficient to recommend vasoconstrictor use with SBP.

Acute Kidney Injury and Hepatorenal Syndrome

Best Practice Advice 8: IV albumin is the volume expander of choice in hospitalized patients with cirrhosis and ascites presenting with AKI.

In patients with cirrhosis presenting with AKI and evidence of intravascular volume depletion, the current recommendations include a trial of volume expansion specifically with albumin, at a dose of 1 g/kg of body weight daily for 2 consecutive days (with a cap of 100 g/d).[30,57] This is based on the fact that, in cirrhosis with ascites, albumin is more effective in restoring effective arterial blood volume than saline solution.[58] Lack of response to volume expansion with albumin is one of the diagnostic criteria of HRS-AKI.[59]

Routine administration of a fixed albumin dose in any patient with AKI, however, might either be insufficient or lead to volume overload and complications, such as pulmonary edema.[53,60,61] Although ideally volume replacement with albumin should be tailored to the volume status of the patient, the best method to assess volume is still unknown.

Best Practice Advice 9: Vasoactive drugs (terlipressin, NE, or combination of octreotide/midodrine) should be used in the treatment of HRS-AKI but not in other forms of AKI in cirrhosis.

Among patients with cirrhosis hospitalized with AKI, between 15% and 43% have HRS-AKI.[62] The pathophysiology of HRS-AKI is characterized by extreme splanchnic vasodilation resulting in low effective arterial blood volume, with ensuing activation of vasoactive systems leading to renal vasoconstriction and decreases in renal blood flow

and glomerular filtration rate. Treatment with vasoconstrictors counteract splanchnic vasodilation, increasing renal blood flow and glomerular filtration rate,[62] and are only effective when the underlying pathophysiology is that of HRS-AKI.

The diagnosis of HRS-AKI is currently based on the clinical presentation and exclusion of other causes (as detailed in the specific AGA Clinical Practice Update[57]), although more than 1 phenotype of AKI might coexist. Recent data suggest that urine biomarkers, such as neutrophil gelatinase–associated lipocalin, could aid in the differentiation of HRS-AKI from acute tubular necrosis[63–65] and in the selection of patients that might respond to vasoconstrictors,[65] but this requires further validation.[66]

Vasoconstrictors for HRS-AKI have been studied in the context of what was previously known as HRS type I, defined as an abrupt decline in kidney function with a 100% increase in creatinine to a value >2.5 mg/dL.[67] The pivotal CONFIRM (Study to Confirm Efficacy and Safety of Terlipressin in Hepatorenal Syndrome Type 1) trial lowered the threshold for inclusion to 2.25 mg/dL. Higher levels of creatinine are associated with lower chances of improvement with vasoconstrictors,[68] supporting the relevance of starting vasoconstrictor therapy early.[59,69] Patients with creatinine >5 mg/dL have low rates of response and are unlikely to benefit from treatment with vasoconstrictors.

Best Practice Advice 10: Terlipressin is the vasoactive drug of choice in the treatment of HRS-AKI and use of concurrent albumin can be considered when accounting for patient's volume status.

The best level of evidence for the use of vasoconstrictors in HRS-AKI comes from placebo-controlled RCTs using terlipressin,[68,70–72] which found an improvement in renal function and a decrease in the need for renal replacement therapy. There was no decrease in mortality, which could be expected because terlipressin does not have an impact on the underlying liver disease.

There is limited evidence comparing NE with terlipressin. The largest RCT included 120 patients and found greater chances of reversal of HRS-AKI and better survival with terlipressin (given as a continuous infusion) compared with NE.[73] A recent network meta-analysis suggested a slight advantage of terlipressin (with low certainty).[74] NE is commonly used in places where terlipressin is not approved but requires admission to an intensive care unit (ICU). The combination of midodrine and octreotide is less effective than terlipressin[75] or NE,[62] and it is unclear whether it is better than placebo.[74]

Most of the patients included in the trials comparing terlipressin with placebo received albumin (20–40 g/d) during terlipressin treatment. The rationale to give albumin is to fill the central circulation, enhancing the effects of splanchnic vasoconstriction in improving renal blood flow, but this is likely achieved after a short course (1–2 days) of albumin administration. Therefore, the need for continuation of albumin should be assessed carefully based on volume status. The optimal method is still unknown, but point-of-care ultrasonography has been suggested.[76] A nonrandomized study including only 21 patients suggested that terlipressin without albumin is less effective than the combination of both.[77] It has been suggested that albumin might have additional effects by attenuating systemic inflammatory responses,[78] although it is uncertain whether effects beyond volume expansion mediate its clinical effect.[79]

Best Practice Advice 11: Terlipressin treatment does not require ICU monitoring and can be administered intravenously through a peripheral line.

In the pivotal CONFIRM trial, terlipressin was administered at an initial dose of 1-mg IV boluses of terlipressin (1 vial) every 6 hours, without requirement of central line or ICU monitoring.[68] This dose could be increased to 2 mg every 6 hours on day 4 in case of insufficient response (<30% decrease in creatinine). This is the schedule approved by the FDA for use in the United States. Treatment is maintained for up to 14 days and can be discontinued 24 hours after creatinine decreases to <1.5 mg/dL. A trial comparing IV boluses vs continuous infusion of terlipressin (starting at 2 mg/d) found a lower rate of complications with the continuous infusion, with similar efficacy.[80]

Best Practice Advice 12: Terlipressin use is contraindicated in patients with hypoxemia and in patients with ongoing coronary, peripheral, or mesenteric ischemia, and should be used with caution in patients with ACLF grade 3. The benefits may not outweigh the risks in patients with serum creatinine >5 mg/dL and in patients listed for transplantation with a Model for End-stage Liver Disease ≥35.

Terlipressin is contraindicated in patients with known significant vascular disease. Patients with a serum creatinine >5 mg/dL are unlikely to benefit and terlipressin treatment is not advised. In the CONFIRM trial, there was an increased rate of respiratory failure (14% vs 5% in placebo) and death related to respiratory failure (11% vs 2% on placebo).[68] This could be due to an increase in cardiac afterload, together with volume expansion with albumin. There was a trend for higher amounts of albumin given before terlipressin administration in patients developing respiratory failure.[60] Therefore, as suggested above, judicious use of albumin before and during treatment with terlipressin is necessary. Patients with ACLF grade 3 (at least 3 organ failures), are at increased risk of respiratory failure.[60] These patients are typically managed in an ICU setting and closely monitored.

In patients with HRS, terlipressin should not be given if SpO_2 is <90%. The FDA label suggests continuous monitoring for hypoxia with continuous pulse oximetry during the treatment. This might pose a challenge for the use of terlipressin outside of the ICU. In places where terlipressin has been used for the treatment of HRS for many years, continuous monitoring is not required. This suggests that assessment of vital signs (including pulse oximetry) every 2–4 hours can substitute continuous pulse oximetry in patients at low risk of respiratory failure (ACLF grade <3).

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Conflicts of interest
These authors disclose the following: Juan G. Abraldes has served as a consultant for Advanz, Boehringer Ingelheim, 89bio, and AstraZeneca. He also received grants from Cook and Gilead. Nicole E. Rich has served as a consultant and on advisory boards for AstraZeneca. Vincent Wai-Sun Wong serves as a consultant for AbbVie, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Inventiva, Novo Nordisk, Pfizer, Sagimet Biosciences, TARGET PharmaSolutions, and Visirna. He has lectured for Abbott, AbbVie, Gilead Sciences, Novo Nordisk, and Unilab. He receives research support from Gilead Sciences and is the co-founder of Illuminatio Medical Technology Limited. The remaining author discloses no conflicts.