



# Recommendations on the Diagnosis and Initial Management of Acute Variceal Bleeding and Hepatorenal Syndrome in Patients with Cirrhosis

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## Abstract

Cirrhosis is a serious and life-threatening condition which imposes a significant socioeconomic burden on affected individuals and healthcare systems. Cirrhosis can result in portal hypertension, which may lead to major complications, including acute variceal bleeding and hepatorenal syndrome. Without prompt treatment, these complications may be life-threatening. Over the past 2 decades, new treatment modalities and treatment strategies have been introduced, which have improved patients' prognosis, but the initial management of these severe complications continues to present a challenge. The present recommendations aim to increase clinicians' knowledge on the importance of early diagnosis and treatment, and to provide evidence-based management strategies to potentially, further improve patient outcomes. Special attention was given to the role of terlipressin. A comprehensive non-systematic literature search was undertaken to evaluate the evidence for the diagnosis and initial management of acute variceal bleeding and hepatorenal syndrome in patients with cirrhosis. Recommendations on the diagnosis and initial management of acute variceal bleeding and hepatorenal syndrome in patients with cirrhosis have been developed based on the best available evidence and the expert opinion of the consensus panel following a comprehensive review of the available clinical data. Prompt identification and timely treatment of acute variceal bleeding and hepatorenal syndrome are essential to reduce the burden.

**Keywords** Acute variceal bleeding · Acute kidney injury · Hepatorenal syndrome · Cirrhosis · Terlipressin · Vasoactive drugs

## Introduction

Cirrhosis is a serious and life-threatening condition which imposes a significant socioeconomic burden on affected individuals and healthcare systems worldwide [1, 2]. According to a population-based study undertaken in the USA, cirrhosis affects over 633,000 adults each year [3] and represents the sixth most common cause of death due to non-communicable diseases worldwide [4]. In Europe, cirrhosis is responsible for 170,000 deaths each year, with wide variations between countries [5]. Many cases may be undiagnosed, and more than half are potentially preventable [3].

Cirrhosis can result in portal hypertension, which may lead to major complications including bleeding gastroesophageal varices and hepatorenal syndrome (HRS), a severe form of acute kidney injury (AKI) that usually presents in patients with decompensated liver cirrhosis. Esophageal varices are present in 30–70% of patients with cirrhosis at the time of diagnosis and tend to increase in size in a linear fashion [6, 7]. Approximately 4–30% of patients with small varices will develop large varices each year and are at risk of bleeding [6]. Gastric varices are less common than esophageal varices, occurring in 5–33% of patients with portal hypertension [6], but bleeding tends to be more severe, with a reported mortality of approximately 45% [8]. In addition, a high proportion of patients with gastric varices rebleed after spontaneous hemostasis [9].

Acute variceal bleeding can be fatal and remains a major public health problem. In the early 1980s, in-house mortality

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after variceal hemorrhage was around 40% [10]; however, in recent years, in-hospital mortality has fallen steadily to 10–20%, due to new knowledge on the pathophysiology of acute variceal bleeding and advances in therapy [11–13]. Although mortality has decreased, bleeding esophageal varices (BEV) still remain of significant clinical importance. The risk of rebleeding, which is most likely to occur within 6 weeks of the original episode, remains appreciably high [14]. In a nationwide audit undertaken in the UK, mortality in those patients who suffered from rebleeding was more than fivefold (39 vs. 7%) greater than those patients who did not rebleed [14].

HRS is a potentially reversible form of AKI that usually presents in patients with decompensated liver cirrhosis. Between 20 and 50% of hospitalized patients with cirrhosis have AKI [15]. HRS is classified into two types based on the clinical course, with type 1 HRS being the predominant type [16]. Type 1 HRS is defined by a rapidly progressive reduction of renal function in less than 2 weeks, while type 2 HRS is a less progressive, moderate course of renal failure characterized by a serum creatinine (sCr) level of > 1.5 mg/dL (> 133  $\mu\text{mol/L}$ ) and is usually accompanied by refractory ascites [17, 18]. In type 1 HRS, a precipitating factor frequently is identified, whereas type 2 HRS arises spontaneously [18]. The prognosis of patients with HRS is poor, with a reported median survival after diagnosis of only 1.7 weeks [19]. Evidence suggests, however, that HRS is potentially reversible if hemodynamic derangements are corrected in a timely fashion [20].

There have been significant advances in the understanding and treatment of acute variceal bleeding and HRS in patients with cirrhosis, and improved survival, but the initial management of these serious complications continues to present a challenge and requires a multidisciplinary approach. The purpose of these recommendations is to provide clinicians with evidence-based management strategies that will potentially, further improve patient outcomes.

## Methods

A multidisciplinary, consensus panel, comprising gastroenterologists, hepatologists and critical care physicians from Asia, Europe and South America, convened at a meeting in London, UK, in November 2016 to review the available evidence for the diagnosis and initial management of acute variceal bleeding and HRS in patients with cirrhosis and to develop a set of recommendations. A comprehensive, non-systematic search of the relevant literature electronically indexed in PubMed, EMBASE, the Cochrane Library and clinicaltrials.gov was undertaken using the following key words: hepatorenal syndrome, cirrhosis, acute kidney injury, varices, vasoactive, terlipressin, vasopressin,

octreotide, midodrine, noradrenaline. No language limits were set on the database searches. Randomized and non-randomized controlled trials, crossover trials, single-arm studies, cohort studies, case–control studies and case series were included, as well as published data from registries and medical databases. The search results were supplemented by manual searching of relevant journals, reference lists in key journals and other appropriate documents, as well as expert opinion. All recommendations were based on the best available evidence combined with the authors' experiences in managing acute variceal bleeding and HRS in patients with cirrhosis. For each section, recommendations were made and evidence levels graded according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence [21, 22]: Grade A (consistent level 1 studies [systematic review of randomized controlled trials (RCT) and RCT]); Grade B (consistent level 2 or 3 studies or extrapolations from level 1 studies [systematic review of cohort studies, cohort studies, and low quality RCT]); Grade C (level 4 studies [systematic review of case–control studies, case–control studies and case series] or extrapolations from level 2 or 3 studies; Grade D (level 5 studies [expert opinion] or troublingly inconsistent or inconclusive studies at any level).

## Management of Bleeding Gastroesophageal Varices

### Diagnosis of Varices

Current guidelines recommend that all patients with cirrhosis should be screened for the presence of varices at the time of diagnosis, with follow-up every 2–3 years for compensated patients without varices (depending upon liver disease severity) and 1–2 yearly for compensated patients with small varices, to evaluate progression of varices and the need for prophylactic treatment [12, 23]. During follow-up of patients with chronic liver disease, noninvasive methods include transient elastography and use of laboratory and radiological findings, which are useful for the selection of patients for endoscopy [23]. Variceal hemorrhage should be suspected when a patient with known cirrhosis or evidence of portal hypertension presents with upper gastrointestinal hemorrhage [8].

### Recommendation

- All patients with suspicion of cirrhosis should be screened for the presence of gastroesophageal varices (Grade A).
- Noninvasive methods such as elastography are useful to select patients with chronic liver disease for endoscopy to rule out gastroesophageal varices (Grade C).

### Initial Treatment

Prophylactic measures such as non-selective beta blocker (NSBB) use and endoscopic variceal ligation are available to prevent initial bleeding [12, 23]. Acute variceal hemorrhage is a medical emergency that requires prompt treatment and should ideally be managed in an intensive care unit. The key goals of treatment are to control the acute hemorrhage, prevent early (within 5 days) rebleeding and reduce mortality. The optimal management of acute bleeding requires a multifactorial approach. Volume replacement should be initiated as soon as possible to restore and maintain hemodynamic stability [24]. The treatment of acute variceal bleeding includes antibiotic prophylaxis, the use of vasoactive drugs and endoscopic treatment.

### Antibiotic Prophylaxis

Bacterial infections are common due to gut translocation and motility disturbances [6]. Standard practice is to give short-term (maximum 7 days) antibiotic prophylaxis in any patient with cirrhosis and bleeding esophageal varices (BEV) [6, 23, 24]. In a meta-analysis of 5 trials (534 patients), short-term (5–10 days) antibiotic prophylaxis was shown to significantly increase the mean percentage of patients free of infection (32% mean improvement rate, 95% confidence interval [CI] 22–42;  $P < 0.001$ ) and significantly increase short-term survival rate (9.1% mean improvement rate, 95% CI 2.9–15.3;  $P = 0.004$ ) [25].

### Vasoactive Drugs

After resuscitation, volume replacement and prophylactic antibiotics, there are a number of specific treatment options available to treat BEV. To date, the best evidence for efficacy is vasoactive drugs combined with endoscopic treatment as

it achieves better control of acute bleeding than endoscopic treatment alone [26]. In a meta-analysis of 8 trials involving 939 patients, combined use of endoscopic and drug therapy improved initial control of bleeding (relative risk [RR] 1.12, 95% CI 1.02–1.23) and 5-day hemostasis (RR 1.28, 95% CI 1.18–1.39) [26].

A number of vasoactive drugs, including vasopressin, terlipressin, somatostatin and octreotide, are available. In a meta-analysis of 30 RCTs, the use of intravenously administered vasoactive drugs was shown to significantly lower the risk of all-cause mortality within 7 days (RR 0.74, 95% CI 0.57–0.95;  $P = 0.02$ ) and significantly improve hemostasis (RR 1.21, 95% CI 1.13–1.30;  $P < 0.001$ ) compared with control. Studies comparing different vasoactive drugs did not show a difference in efficacy, although the quality of evidence was low [27].

Terlipressin is superior to placebo in the control of variceal hemorrhage [28–30] (Table 1). In addition, terlipressin has shown to have mortality benefit in placebo-controlled trials [28, 31] and meta-analysis [32]. Seven studies comparing terlipressin to placebo (443 patients) were included in the meta-analysis by Ioannou et al. [32]. Terlipressin was associated with a statistically significant reduction in all-cause mortality compared with placebo (RR 0.66, 95% CI 0.49–0.88). Conversely, in comparative studies of different vasoactive drugs (terlipressin, somatostatin and octreotide) no significant differences were found among them regarding control of hemorrhage or mortality (Table 2) [33–38]. Many of these original studies, however, were conducted more than 20 years ago and are limited by small sample sizes and study designs.

### Safety of Terlipressin

Most studies have shown that vasoactive drugs have a good safety profile, although vasopressin can cause an increase in

**Table 1** Terlipressin versus placebo in cirrhotic patients with BEV

Author	Study design	Drug	n	Control of bleeding % (P value)	Mortality % (P value)
Söderlund et al. [28]	Randomized, double-blind, placebo-controlled	Terlipressin	31	90.3 (<0.01)	9.7 <sup>a</sup> (0.014)
		Placebo	29	58.6	37.9 <sup>a</sup>
Freeman et al. [29]	Randomized, double-blind, placebo-controlled	Terlipressin	15	60.0 (NS)	20.0 <sup>a</sup> –
		Placebo	16	37.0	25.0 <sup>a</sup>
Walker et al. [30]	Single center, prospective, randomized, double-blind, placebo-controlled	Terlipressin	25 <sup>d</sup>	100 <sup>b</sup> (<0.05)	12.0 <sup>c</sup> (NS)
		Placebo	25 <sup>d</sup>	80.0 <sup>b</sup>	32.0 <sup>c</sup>

NS not significant

<sup>a</sup>At discharge

<sup>b</sup>Within 36 h

<sup>c</sup>Hospital mortality

<sup>d</sup>Bleeding episodes (34 patients in total)

**Table 2** Terlipressin versus somatostatin or octreotide in cirrhotic patients with BEV

Author	Study design	Drug	<i>n</i>	Control of bleeding % ( <i>P</i> value)	Mortality % ( <i>P</i> value)
Feu et al. [35]	Multicenter, double-blind, randomized	Terlipressin	80	80.0 (NS)	16.3 <sup>a</sup> –
		Somatostatin	81	84.0	16.0 <sup>a</sup>
Walker et al. [36]	Double-blind, randomized, placebo controlled	Terlipressin	53 <sup>g</sup>	90.6 –	20.8 <sup>b</sup> (NS)
		Somatostatin	53 <sup>g</sup>	81.1	20.8 <sup>b</sup>
Seo et al. [33]	Non-blinded, non-inferiority	Terlipressin	261	86.2 <sup>c</sup> (NS)	8.0 <sup>c</sup> (NS)
		Somatostatin	259	83.4 <sup>c</sup>	8.9 <sup>c</sup>
		Octreotide	260	83.8 <sup>c</sup>	8.8 <sup>c</sup>
Abid et al. [34]	Single center, randomized, double-blind, placebo-controlled, non-inferiority design	Terlipressin	163	96.9 (NS)	5.5 <sup>d</sup> (NS)
		Octreotide	161	99.4	4.3 <sup>d</sup>
Pedretti et al. [37]	Single center, single-blind, randomized	Terlipressin <sup>e</sup>	30	53.3 (NS)	13.3 (NS)
		Octreotide	30	76.6	10.0
Silvain et al. [38]	Multicenter, randomized	Terlipressin	41	59.0 <sup>f</sup> (NS)	0.0 <sup>f</sup> 28.0 <sup>b</sup> (NS)
		Octreotide	46	78.0 <sup>f</sup>	6.0 <sup>f</sup> 22.0 <sup>b</sup>

NS not significant

<sup>a</sup>6 weeks

<sup>b</sup>30 days

<sup>c</sup>5 days

<sup>d</sup>During the trial

<sup>e</sup>Combined with transdermal nitroglycerine

<sup>f</sup>At 12 h

<sup>g</sup>Bleeding episodes (72 patients in total)

peripheral resistance and reduction in cardiac output, heart rate and coronary blood flow [23]. Terlipressin has a favorable adverse effect profile and is related to fewer cardiovascular side effects when compared to vasopressin due to its preferential binding to V1 receptors [39]. Adverse events (AEs) are mostly cardiovascular and related to vasoconstriction [40]. Side effects include angina pectoris, acute myocardial infarction, bradyarrhythmia, peripheral vascular ischemia, mesenteric ischemia and systemic arterial hypertension [39]. In a meta-analysis by Ioannou et al. [32], there was no significant difference between the terlipressin group and any of the comparison groups in the number of AEs that caused death or withdrawal of medication. Terlipressin should be avoided or used with caution in patients with preexisting cardiovascular disease and in patients over 70 years of age as experience is limited in this patient population.

Patients receiving terlipressin for the treatment of BEV may develop hyponatremia, which is usually reversible after terlipressin withdrawal [41, 42]. The most likely explanation of terlipressin-induced hyponatremia is the agonistic activity on renal V2 vasopressin receptors causing free water retention. The administration of hypotonic fluid strongly favors the development of

acute hyponatremia in this situation. In two of the studies [41, 42], patients who developed hyponatremia had less advanced liver disease and higher baseline serum sodium concentration, suggesting that in these patients the V2 vasopressin receptors were not yet occupied by endogenous vasopressin. This may explain why hyponatremia is uncommon during the administration of terlipressin for HRS, a situation which occurs in more advanced liver disease. These findings highlight the need for daily monitoring of serum sodium levels in patients receiving terlipressin for acute gastrointestinal bleeding due to portal hypertension, as is routinely performed in all patients with cirrhosis and that in patients with low MELD (Model For End-Stage Liver Disease), and normal to near-normal baseline serum sodium concentrations, hypotonic fluids should be avoided. Whether the administration of albumin might counteract this side effect needs to be explored.

NSBBs should be avoided when treating patients with active BEV with terlipressin since they can potentially induce systemic hypotension [43]. After review of the literature, it is recommended that NSBBs are suspended in patients with BEV during terlipressin infusion and restarted when the terlipressin course is finished.

## Co-administration of Terlipressin and Somatostatin or Octreotide

Kalambokis et al. [44] evaluated the effects of somatostatin, terlipressin and combined treatment with somatostatin and terlipressin on portal hemodynamics in a randomized, placebo-controlled study of 24 patients with cirrhosis and esophageal varices. Combined treatment did not exert an additive portal hypotensive effect as compared to terlipressin alone. A previous study by Lin et al. [45] also showed a lack of an additive portal hypotensive effect of octreotide and terlipressin in patients with cirrhosis.

### Rationale for the Early Use of Vasoactive Drugs

A prospective cohort study of 314 patients with cirrhosis and esophageal varices (173 [55%] with no previous history of variceal bleeding) found that about a quarter of deaths occurred very early after bleeding onset, confirming the need for rapid specific management [46]. Available evidence suggests that early use of vasoactive drugs improves hemostasis before endoscopy [31, 47, 48]. In a prospective, randomized study comprising 76 patients with cirrhosis and active upper gastrointestinal bleeding, terlipressin combined with glyceryl trinitrate administered early (before hospital admission) significantly improved the control of bleeding ( $P=0.034$ ) and reduced mortality at day 15 ( $P=0.035$ ) and day 42 ( $P=0.06$ ) compared with placebo [31]. In a double-blind, prospective study involving 205 patients, at endoscopy, active bleeding from esophageal varices was less frequent ( $P=0.012$ ) and the sclerotherapy procedure was easier ( $P=0.0027$ ) in the somatostatin than in the placebo group [47].

### Optimal Dosage Regimen of Terlipressin

The current standard practice is to give terlipressin as an intravenous injection, initially a 2 mg bolus injection, then 1–2 mg every 4 or 6 h depending on the bodyweight of the patient and their co-morbidities. Escorsell et al. [49] showed that the hemodynamic effect of terlipressin on portal pressure lasts no more than 3–4 h, which raises the question as to whether continuous infusion may have better efficacy than bolus injections. While a continuous infusion is possible, it remains unclear whether or not it should be considered in clinical practice. A clinical trial comparing the safety and efficacy of the two infusion types in patients with BEV is currently underway [50]. In another study, Chang et al. [51] investigated whether a high-dose terlipressin could control acute variceal hemorrhage more effectively than a low-dose terlipressin. Complete control of bleeding during 24 h of drug infusion was achieved in 53% of patients receiving high-dose terlipressin (2 mg) and in 48% of those treated

with low-dose terlipressin (1 mg). Further randomized studies are needed to evaluate the effects of low-dose terlipressin.

Current guidelines recommend that vasoactive drug treatment should be maintained for up to 5 days since this is the time period in which rebleeding is more frequent [12, 23]. Azam et al. [52] investigated whether terlipressin can be administered for a shorter period of time to patients with BEV. Terlipressin given for 24 h was shown to be as effective as a 72-h course when used as an adjunctive therapy to successful endoscopic variceal band ligation.

### Recommendations

- If variceal bleeding is suspected, vasoactive drugs should be given before endoscopy (Grade B). Terlipressin is a drug of choice and should be started as soon as possible when available, and there is no contraindication (Grade A).
- The use of continuous infusion of terlipressin in BEV has not been established (Grade D).
- Close monitoring is required in patients with cardiovascular comorbidity taking terlipressin, and a lower dose should be considered. Serum sodium levels should be monitored and the use of hypotonic fluid avoided (Grade D).
- There is insufficient evidence of the additional effect of co-administration of terlipressin with other vasoactive drugs (Grade D).

### Endoscopic Therapy

Endoscopy should be scheduled in all patients with upper gastrointestinal bleeding. However, the timing is still controversial. There are not enough data to support that endoscopy has to be performed within < 12 h. The endoscopic treatment of choice is band ligation (EBL) [13, 53]. Erythromycin (250 mg IV 30–120 min) before endoscopy in patients with variceal bleeding significantly improves endoscopic visibility and shortens the duration of the index endoscopy [54]. Recommended treatment with combined vasoactive drugs and endoscopic therapy results in successful 5-day control of bleeding in 85–90% of cases [55].

### Transjugular Intrahepatic Portosystemic Shunt Placement

Studies have shown that transjugular intrahepatic portosystemic shunt (TIPS) is an extremely useful technique for the treatment of BEV in rescue situations and in high-risk patients. In a RCT of 63 high-risk patients with cirrhosis and BEV who had been treated with vasoactive drugs plus endoscopic therapy, the early use of TIPS was associated with significant reductions in treatment failure and mortality.

Rebleeding or failure to control bleeding occurred in 14 patients in the pharmacotherapy-endoscopic band ligation (EBL) group compared with 1 patient in the early TIPS group ( $P = 0.001$ ). The 1-year actuarial survival was 61% in the pharmacotherapy-EBL group compared with 86% in the early TIPS group ( $P < 0.001$ ) [13]. High-risk patients were defined as Child–Pugh Class B patients with persistent bleeding at endoscopy and Child–Pugh Class C (score  $< 14$ ). A post-RCT surveillance study confirms these findings in clinical practice [53]. Patients treated with early TIPS had a much lower incidence of failure to control bleeding or rebleeding than patients receiving drugs and endoscopic therapy (3 vs. 15;  $P < 0.001$ ). The same was observed for mortality [53]. The value of early TIPS outside high-risk patients is currently being investigated.

### Recommendations

- Band ligation is the endotherapy of choice (Grade A).
- Pre-endoscopy infusion of erythromycin should be considered to avoid aspiration pneumonia (Grade B).
- Early TIPS is the treatment of choice in Child–Pugh Class B patients with persistent bleeding during endoscopy and in Child–Pugh Class C (score  $< 14$ ) patients (Grade A).

### Cyanoacrylate Injection Therapy

There are still limited data on the use of tissue glue cyanoacrylate (*N*-butyl-2-cyanoacrylate) in the treatment of BEV in patients with cirrhosis, although in one prospective cohort study of 133 consecutive patients, initial hemostasis was achieved in 94.2% of patients with active bleeding (95% CI 85.1–98.5). Overall, early recurrent bleeding occurred in 5.2% of patients (95% CI 2.3–10.1) [56]. These findings are supported by the results of another prospective study of 63 patients with cirrhosis admitted with an acute episode of BEV. Bleeding was controlled in almost 75% of patients during the first 5 days after treatment, and 54% of patients were free of bleeding at 6 weeks after treatment [57].

### Recommendation

- There are limited data on the use of cyanoacrylate injection therapy in the treatment of BEV in patients with cirrhosis (Grade D).

### Management of Acute Gastric Variceal Bleeding

The optimal treatment for bleeding gastric varices remains unclear as there are few RCTs. General consensus is that the initial management is similar to that of BEV, including the use of prophylactic antibiotics, careful fluid

resuscitation with a restrictive transfusion policy and the early administration of vasoactive drugs (terlipressin, somatostatin or a somatostatin analogue [12, 58]. There are limited data on the efficacy of vasoactive drugs in controlling acute gastric variceal bleeding [36], but general consensus is that terlipressin can be considered for patients with acute gastric variceal bleeding when used alongside glue injection of the varices.

Cyanoacrylate has been successfully used in many countries and is effective in the management of bleeding gastric varices [59–62]. Al-Ali et al. [63] retrospectively reviewed 37 patients with portal hypertension secondary to liver disease and active bleeding treated with cyanoacrylate. Hemostasis was achieved in 95% of patients. Early rebleeding occurred in only 3 patients (8%) during the same hospital admission. However, a Cochrane review undertaken in 2015 concluded that the comparison of cyanoacrylate versus alcohol compounds to treat gastric variceal bleeding remains uncertain due to the very low quality of the evidence [64].

In treatment failures, TIPS is considered the treatment of choice [65, 66]. In a study by Chau et al. [65], 112 consecutive patients with uncontrolled bleeding required emergency TIPS (84 with esophageal varices unresponsive to endoscopic therapy and vasoactive drugs and 28 with gastric varices unresponsive to vasoactive drugs). Variceal bleeding was controlled in all patients after TIPS except for one in each group. During a median follow-up period of 7 months, 20 in the BEV group (24%) and 8 in the gastric varices group (29%) developed clinical rebleeding. Most early rebleeding (within 7 days after TIPS) was related to esophageal ulceration secondary to previous sclerotherapy. In another study comprising 58 patients refractory to sclerotherapy and pharmacological treatment, hemorrhage was controlled following salvage TIPS in 90% of patients. Bleeding persisted in 10% of patients and recurred in 7% [66]. There is a place for TIPS in the prevention of gastric variceal rebleeding; a RCT of TIPS versus cyanoacrylate injection concluded that TIPS proved more effective than cyanoacrylate in preventing rebleeding from gastric varices [67].

### Recommendations

- Limited data are available on the efficacy of vasoactive drugs in controlling acute gastric variceal bleeding. Terlipressin can be considered when used alongside glue injection of the varices (Grade D).
- TIPS should be considered in patients who have uncontrolled gastric variceal bleeding refractory to endoscopic therapy and vasoactive drugs and for the prevention of gastric variceal rebleed (Grade C).

## Management of Hepatorenal Syndrome

### Diagnosis of HRS-AKI

The most widely accepted diagnostic criteria for HRS were published by the International Club of Ascites (ICA) in 1996 [68] and modified in 2007 [17]. In 2015, the ICA proposed a new definition for cirrhosis-related AKI and further modifications of the diagnostic criteria for HRS-related AKI [69]. These revisions were needed because the definition of type 1 HRS did not allow physicians to initiate potentially effective treatment, specifically vasoactive drugs and albumin, until the sCr increased to  $\geq 2.5$  mg/dL [69]. Studies have shown that a higher sCr at the beginning of treatment leads to a lower probability of treatment response with terlipressin and albumin [70, 71].

The ICA define AKI as the increase in sCr of at least 0.3 mg/dL (26  $\mu\text{mol/L}$ ) within 48 h or a percentage increase  $\text{sCr} \geq 50\%$  from baseline, which is known, or presumed, to have occurred within the prior 7 days [69]. Once AKI is diagnosed, the stage of AKI should be identified (Table 3).

For patients to be diagnosed with HRS-AKI using these criteria, they need first to progress from Stage 1 to Stage 2 and 3 AKI, when the withdrawal of diuretics is recommended (if they have not been withdrawn already), and volume expansion with albumin (1 g/kg) should be administered for 2 days. If the patient then fails to respond, the HRS-AKI criteria should be used to determine whether the patient has HRS-AKI or another AKI phenotype [69]. The ICA criteria for the diagnosis of HRS-AKI are summarized in Table 4. At present, these guidelines do not differentiate between type 1 and type 2 HRS, although there are clear differences between the two and the management of patients differs depending on HRS subtype.

### Recommendations

- It is important to make the diagnosis of HRS-AKI or identify other known causes of renal failure in cirrhosis as early as possible. The diagnosis should be based on the revised criteria for HRS-AKI defined by the ICA (Grade A).

## Pharmacological Treatment

### Type 1 HRS

The general management of patients with cirrhosis and type 1 HRS depends on the severity of kidney failure and associated complications. Once diagnosed, it is recommended that

**Table 3** International Club of Ascites definitions for the staging of AKI in patients with cirrhosis [69]

Stage 1	Stage 2	Stage 3
Increase in serum creatinine $\geq 26.5$ $\mu\text{mol/L}$ (0.3 mg/dL) or an increase in serum creatinine $\geq 1.5$ -fold to 2-fold from baseline	Increase in serum creatinine > twofold to threefold from baseline	Increase in serum creatinine > threefold from baseline or serum creatinine $\geq 353.6$ $\mu\text{mol/L}$ (4.0 mg/dL) with an increase $\geq 26.5$ $\mu\text{mol/L}$ (0.3 mg/dL) or initiation of renal replacement therapy

**Table 4** International Club of Ascites diagnostic criteria of HRS type of AKI in patients with cirrhosis (HRS-AKI) [69]

Diagnosis of cirrhosis and ascites
Diagnosis of AKI according to ICA-AKI criteria
No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g per kg of body weight
Absence of shock
No current or recent use of nephrotoxic drugs (non-steroidal anti-inflammatory drugs, aminoglycosides, iodinated contrast media, etc.)
No macroscopic signs of structural kidney injury <sup>a</sup> , defined as:
Absence of proteinuria (> 500 mg/day)
Absence of microhematuria (> 50 red blood cells per high power field)
Normal findings on renal ultrasonography

<sup>a</sup>Patients who fulfill these criteria may still have structural damage such as tubular damage

treatment is started early in order to prevent the progression of renal failure [72]. The goal of treatment is to improve renal function. The administration of vasoactive drugs (terlipressin, noradrenaline and midodrine plus octreotide) in combination with albumin is currently considered the treatment of choice. Albumin has been shown to improve circulatory function in cirrhosis by expanding central blood volume and increasing cardiac output [73]. Among the vasoactive drugs, terlipressin is the most widely studied for the treatment of type 1 HRS.

In clinical trials and published meta-analyses [20, 74, 75], terlipressin treatment was superior to placebo for achieving reversal of HRS. Meta-analysis of 12 RCTs enrolling 700 patients with type 1 HRS supports the beneficial effect of terlipressin on renal function [20]. Treatment with

terlipressin in combination with albumin led to HRS reversal more frequently than albumin alone or placebo (RR 2.54, 95% CI 1.51–4.26), although the mortality benefit was less clear. Noradrenaline was effective in reversing HRS, but trials were small and non-blinded [20].

Studies have also shown that the administration of terlipressin, together with albumin, is effective in improving renal function in patients with cirrhosis and HRS compared with albumin administration alone [76–80]. In REVERSE [76], a large, phase 3 multicenter, randomized, placebo-controlled trial, which included 196 patients with cirrhosis and type 1 HRS, terlipressin plus albumin was more effective than placebo plus albumin in improving renal function, based on a significant decrease in SCr value from baseline to end of treatment ( $P < 0.001$ ). However, there was no significant difference in the incidence of confirmed HRS reversal (19.6 vs. 13.1%) or HRS reversal (23.7 vs. 15.2%) between the two groups. Further analysis of pooled data from REVERSE and OT-0401, a similarly designed phase 2 clinical study comprising 308 patients, demonstrated that the addition of terlipressin to albumin provides a significant benefit in terms of HRS reversal in patients with type 1 HRS [77].

Other drugs currently used in the management of type 1 HRS include noradrenaline and midodrine, alpha-adrenergic agonists that lead to constriction of vascular smooth muscle and increase systemic vascular resistance [20]. Their effectiveness has been studied in several studies, and data suggest that noradrenaline is as effective as terlipressin in improving renal function in patients with cirrhosis and HRS (Table 5) [81–84]. Midodrine is often used in combination with octreotide. Cavallin et al. [85] compared the effectiveness of terlipressin plus albumin with oral midodrine and

**Table 5** Terlipressin versus noradrenaline in patients with type 1 HRS

Author	Study design	Drug <sup>d</sup>	<i>n</i>	Reversal of HRS % ( <i>P</i> value)	Survival % ( <i>P</i> value)		
Alessandria et al. [84]	Single center, prospective, randomized, non-blinded, pilot	Terlipressin	5	80.0	–	80.0 <sup>a</sup>	–
		Noradrenaline	4	75.0		50.0 <sup>a</sup>	
Sharma et al. [83]	Single center, open label, pilot, randomized controlled	Terlipressin	20	50.0	(NS)	55.0 <sup>b</sup>	(NS)
		Noradrenaline	20	50.0		55.0 <sup>b</sup>	
Singh et al. [82]	Single center, prospective, randomized, non-blinded	Terlipressin	23	39.1	(NS)	39.1 <sup>b</sup>	(NS)
		Noradrenaline	23	43.4		47.8 <sup>b</sup>	
Goyal et al. [81]	Single center, prospective, open label, randomized	Terlipressin	20	45.0	(NS)	45.0 <sup>c</sup>	–
		Noradrenaline	21	47.6		47.6 <sup>c</sup>	

NS not significant

<sup>a</sup>180-day survival

<sup>b</sup>15-day survival

<sup>c</sup>14-day survival

<sup>d</sup>Albumin was administered in combination with these drugs



octreotide plus albumin in a randomized trial comprising 49 patients with cirrhosis and type 1 or 2 HRS. There was a significantly higher rate of recovery of renal function in patients randomized to the terlipressin plus albumin group than in patients randomized to the oral midodrine and octreotide plus albumin group (70.4 vs. 28.6%;  $P=0.01$ ).

Reporting of AEs in patients with HRS treated with vasoactive drugs varies between studies. In a meta-analysis by Gifford et al. [20], there were fewer ischemic AEs with noradrenaline, although sample sizes were small in published studies. In the REVERSE study, the safety profile of terlipressin generally was consistent with previous clinical studies and included AEs expected with vasoactive drugs. The overall AE rate did not differ between the terlipressin and placebo groups. Gastrointestinal events, most commonly abdominal pain and diarrhea, were the most frequent treatment-related AEs. Ischemic events were more common in patients receiving terlipressin, as was expected [76]. Tailoring treatment, such as modifying the dose and the method of administration, can help reduce these side effects.

### Optimal Dosage Regimen of Terlipressin

Current guidelines recommend that terlipressin 1 mg should be given every 4–6 h by intravenous bolus injection, in combination with albumin [72]. The aim of treatment is to improve renal function by decreasing sCr < 133  $\mu\text{mol/L}$  (< 1.5 mg/dL), which indicates complete response [72]. In some countries, a lower initial dose of terlipressin is given in daily practice (0.5 mg) [16]. This dose has been found to be as effective as 1 mg in clinical practice, but benefits from fewer side effects.

In a RCT, Cavallin et al. [86] demonstrated that terlipressin given by continuous infusion was better tolerated than intravenous boluses in the treatment of type 1 HRS and presented fewer side effects (35.3 vs. 62.2%;  $P<0.025$ ). Terlipressin was also effective at doses lower than those required for intravenous bolus administration. The rate of response to treatment, including both complete and partial response, was not significantly different between the two groups (76.5 vs. 64.9%).

### Recommendations

- Terlipressin can be given as a continuous intravenous infusion (Grade B).
- Bolus administration of terlipressin, which was originally tested and recommended, can also be considered, although with more side effects and similar effectiveness (Grade A).
- Patients who meet diagnostic criteria of HRS-AKI should be given terlipressin 1 mg every 4–6 h by intravenous bolus injection, when available and there is no contrain-

dication, in combination with albumin (Grade A). Terlipressin can be administered at a lower initial dose of 0.5 mg in type 1 HRS (Grade C).

- Terlipressin should be used with caution in patients with underlying severe cardiovascular or peripheral arterial disease. Patients should be closely monitored for cardiovascular or ischemic side effects (Grade A).

### Acute on Chronic Liver Failure and Type 1 HRS

Acute on chronic liver failure (ACLF) is a recognized syndrome that develops in patients with cirrhosis and is characterized by acute decompensation of cirrhosis, single or multiple organ failures, severe systemic inflammation and high short-term mortality [87]. AKI is one of the defining features of ACLF and is important for grading the severity of ACLF [88]. ACLF is graded into three stages: ACLF-1 = single renal failure or single non-renal organ failure if associated with renal dysfunction and/or cerebral dysfunction; ACLF-2 = two organ failures; and ACLF-3 = three to six organ failures, with increasing 28-day mortality rate [89]. In order that appropriate and early management can be initiated, it is important to distinguish between non-HRS-AKI and HRS-AKI when reviewing patients with ACLF and AKI [88]. Terlipressin infusion provides earlier response (Day 7: 41.7 vs. 20.0%;  $P=0.01$ ), greater HRS reversal (40.0 vs. 16.7%;  $P=0.004$ ) and improved survival (28-day: 48.3 vs. 20.0%;  $P=0.001$ ) compared to noradrenaline in ACLF patients with HRS-AKI [90].

Terlipressin and albumin are effective treatments for type 1 HRS; however, the effects of ACLF grade on response to treatment are not clear [91]. In a recent retrospective analysis of four different cohorts of consecutive patients with HRS treated with terlipressin and albumin, ACLF grade was the largest determinant of response. Of patients with grade 1 ACLF, 60% responded to treatment; among those with grade 2 ACLF, 48% responded, and among those with grade 3 ACLF, 29% responded ( $P<0.001$  for comparison between grades) [91].

### Recommendations

- Treatment with terlipressin in patients with ACLF and HRS is associated with an improvement in kidney function and should be started as soon as possible after the diagnosis of type 1 HRS. The success depends on the grade of ACLF (Grade B).

### Type 2 HRS

There is limited evidence for the use of vasoactive drugs in patients who have type 2 HRS. Some trials combined patients with type 1 and type 2 HRS, but the sample sizes

were small. Two studies evaluated the use of terlipressin in this patient population [92, 93]. In a randomized study of 46 patients with cirrhosis and HRS, improvement of renal function was more frequent in patients with type 2 HRS compared with that of patients with type 1 HRS (67 vs. 35%, respectively) treated with terlipressin and albumin, although the difference was not statistically significant [92].

### Recommendations

- There is limited evidence for the use of terlipressin in combination with albumin for patients who have cirrhosis and type 2 HRS, although it has been shown to be effective in clinical practice (Grade C).
- Further prospective studies are needed to assess the efficacy of terlipressin in patients with cirrhosis and type 2 HRS (Grade D).

### Conclusions

Variceal bleeding and HRS are severe complications of cirrhosis associated with significant morbidity and mortality. Data have shown that early diagnosis and intervention improve patients' prognosis. The primary goals of treatment for BEV are to control the acute hemorrhage, prevent early rebleeding and reduce mortality. Vasoactive drugs are used as initial treatment of BEV before endoscopy. Evidence from a multitude of clinical trials and meta-analyses comparing different vasoactive drugs suggests near equivalence in efficacy in terms of initial hemostasis. With terlipressin, mortality benefit was observed. In order to further improve the tolerability of terlipressin, the use of continuous intravenous infusion is currently being explored.

The primary goal of pharmacological therapy in HRS is normalization of renal function. The revised ICA HRS-AKI criteria allow physicians to initiate potentially effective treatment, earlier, which might further improve the survival of these patients. The administration of vasoactive drugs (terlipressin, noradrenaline and midodrine plus octreotide) in combination with albumin is currently considered the treatment of choice. In this regard, terlipressin significantly improves reversal of HRS compared to placebo.

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### Compliance with ethical standards

**Conflicts of interest** Frederik Nevens has received a consultancy grant from Ferring. Manuel Mendizabal has received payments for lectures from Bristol-Myers Squibb, AbbVie, Gilead, Ferring and Bayer; honoraria for consulting from Ferring and Gilead. Paolo Angeli declares the following: 2014–2018: Sequana Medical AG Advisory Board; 2016–2018: Biovie Advisory Board and patent application; 2016 Gilead (Italy): Advisory board and grant; 2014 Bhering: travel grant; 2016 Kedrion: speaker invitation. Paulo Lisboa Bittencourt, Minneke J Coenraad, Huiguo Ding, Ming-Chih Hou, Pierre-François Laterre, Nayeli Xochiquetzal Ortiz-Olivera, Julio D. Vorobioff, Wenhong Zhang declare that they have no conflict of interest.

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