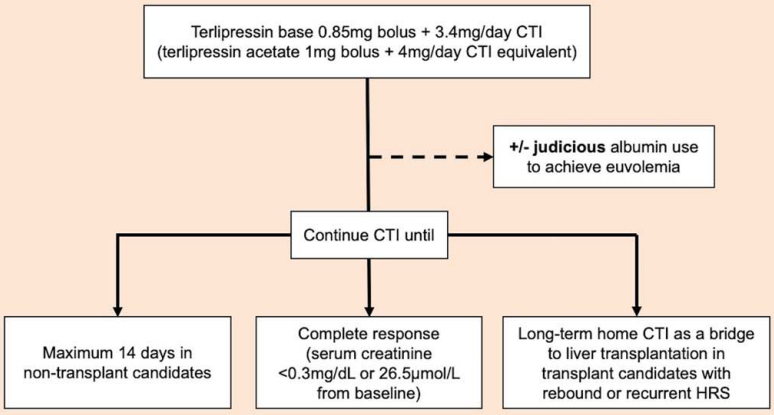
The current applications and future directions of terlipressin

VISUAL ABSTRACT

The current applications and future directions of terlipressin

Local practice for the management of hepatorenal syndrome



Key messages

- Continuous terlipressin infusion (CTI) has greater tolerability and efficacy compared to intermittent bolus dosing for the management of hepatorenal syndrome (HRS)
- Patients with HRS on terlipressin should only be administered albumin if under-volumed, to avoid circulatory overload and pulmonary oedema
- Emerging applications of terlipressin:
  - Long-term home CTI
  - Diuretic-refractory ascites
  - Cardiac dysfunction in decompensated cirrhosis

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REVIEW

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The current applications and future directions of terlipressin

Dorothy Liu[1,2,3] | **Adam Testro**[1,2,3] | **Avik Majumdar**[1,2,3] | **Marie Sinclair**[1,2,3]

[1]Victorian Liver Transplant Unit, Austin Health, Melbourne, Victoria, Australia

[2]Department of Gastroenterology, Austin Health, Melbourne, Victoria, Australia

[3]Department of Medicine, The University of Melbourne, Melbourne, Victoria, Australia

Correspondence
Marie Sinclair, Liver Transplant Unit, Austin Health, 145 Studley Road, Heidelberg, Victoria 3084, Australia.
Email: marie.sinclair@austin.org.au

Abstract

Terlipressin is a vasopressin analog with potent splanchnic vasoconstrictor properties. It has an established role in managing portal hypertensive bleeding and hepatorenal syndrome-acute kidney injury, with a growing body of evidence demonstrating improved safety and efficacy with continuous infusion-based administration compared to bolus dosing. We discuss previously reported adverse effects of terlipressin and evidence-based strategies to maximize the safety of administration. We also review the literature surrounding emerging indications for terlipressin in decompensated cirrhosis, particularly in the management of refractory ascites. Furthermore, we present data on novel ambulatory programs utilizing long-term continuous terlipressin infusion as bridging therapy for liver transplant candidates with recurrent hepatorenal syndrome-acute kidney injury, diuretic-refractory ascites, or hydrothorax.

Keywords: acute variceal bleeding, decompensated cirrhosis, hepatorenal syndrome, portal hypertension, terlipressin

INTRODUCTION

Portal hypertension is a key driver of most clinical complications of cirrhosis, including ascites, variceal bleeding, and hepatic encephalopathy.[1] As portal hypertension progresses, it can lead to hepatorenal syndrome-acute kidney injury (HRS-AKI), cirrhotic cardiomyopathy, and associated multi-organ dysfunction. In addition to addressing the underlying liver disease etiology and managing symptoms, there is increasing interest in therapies that directly target portal hypertension itself.

Terlipressin is a synthetic vasopressin analog that preferentially targets V1a receptors on vascular smooth muscle in the splanchnic vascular bed, inducing vasoconstriction and reducing portal pressure.[2,3] The unique hemodynamic effects of terlipressin have established it as a first-line therapy for acute variceal bleeding (AVB) and HRS-AKI. Safety concerns have limited its broader use, but increasing experience has provided data to optimize administration strategies and minimize adverse events (AEs). For example, continuous terlipressin infusion (CTI) improves tolerability and efficacy compared to bolus dosing, and early initiation of

Abbreviations: ACLF, acute on chronic liver failure; AE, adverse event; AVB, acute variceal bleeding; CTI, continuous terlipressin infusion; EBL, endoscopic band ligation; FDA, U.S. Food and Drug Administration; HRS, hepatorenal syndrome; HRS-AKI, hepatorenal syndrome-acute kidney injury; LT, liver transplantation; RCT, randomized controlled trial; RRT, renal replacement therapy; sCr, serum creatinine.

terlipressin for HRS-AKI with judicious albumin administration reduces the risk of pulmonary edema.[4–8]

Recent studies have explored the role of long-term home CTI for other complications of portal hypertension, including cardiac dysfunction, diuretic-refractory ascites, and hydrothorax.[9–12] Long-term home CTI also has additional benefits on nutritional and functional muscle parameters.[9,13] This review discusses the established roles, safety considerations, and emerging indications for terlipressin in the management of portal hypertension due to decompensated cirrhosis.

TERLIPRESSIN

Terlipressin is an intravenous long-acting synthetic vasopressin analog cleaved by endopeptidases into the active metabolite lysine-vasopressin.[3,14] It is a selective V1a receptor agonist with a pressor effect that is 2-fold greater than its antidiuretic effect via renal V2 receptors.[14,15] Due to its rapid elimination half-life of 50 minutes, terlipressin is typically administered every 4–6 hours.[14,15] Terlipressin causes direct splanchnic vasoconstriction due to V1a receptor activity, which is expressed in vascular smooth muscle cells in the splanchnic circulation, amongst other tissues.[3,14] Terlipressin indirectly induces splanchnic vasoconstriction by inhibiting nitric oxide production.[3] In patients with cirrhosis and portal hypertension, this splanchnic vasoconstriction reduces portal venous blood flow and the HVPG.[2,16,17] Consequently, effective arterial blood volume is redistributed back into the systemic circulation, resulting in increased systemic vascular resistance, increased mean arterial pressure, attenuation of the hyperdynamic cardiac circulation, and reversal of activated neurohormonal pathways (Figure 1).[2,16,17]

CONTINUOUS TERLIPRESSIN INFUSION VERSUS BOLUS TERLIPRESSIN

Current guidelines recommend bolus terlipressin every 4–6 hours for managing AVB or HRS-AKI.[1] These recommendations are based on pharmacokinetic studies in a limited number of healthy individuals.[18–20] Recent clinical data have compared CTI to bolus terlipressin in patients with cirrhosis and portal hypertension and suggest superior efficacy and safety for all indications.

In patients with cirrhosis and portal hypertension, CTI maintains a stable steady-state drug concentration, unlike the variable peak and trough concentrations seen with bolus terlipressin (Figure 2).[11] The physical and chemical stability of terlipressin at room temperature in 24-hour continuous infusion devices

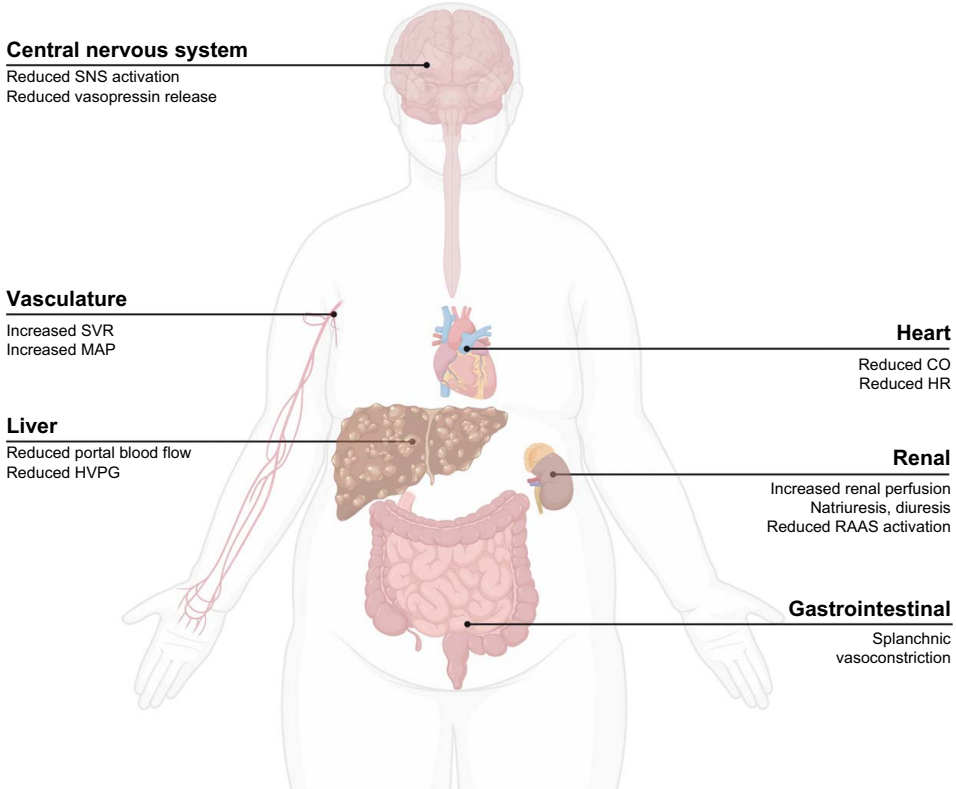

FIGURE 1 Hemodynamic and neurohormonal effects of terlipressin. Abbreviations: CO, cardiac output; HR, heart rate; MAP, mean arterial pressure; RAAS, renin–angiotensin–aldosterone system; SNS, sympathetic nervous system; SVR, systemic vascular resistance.

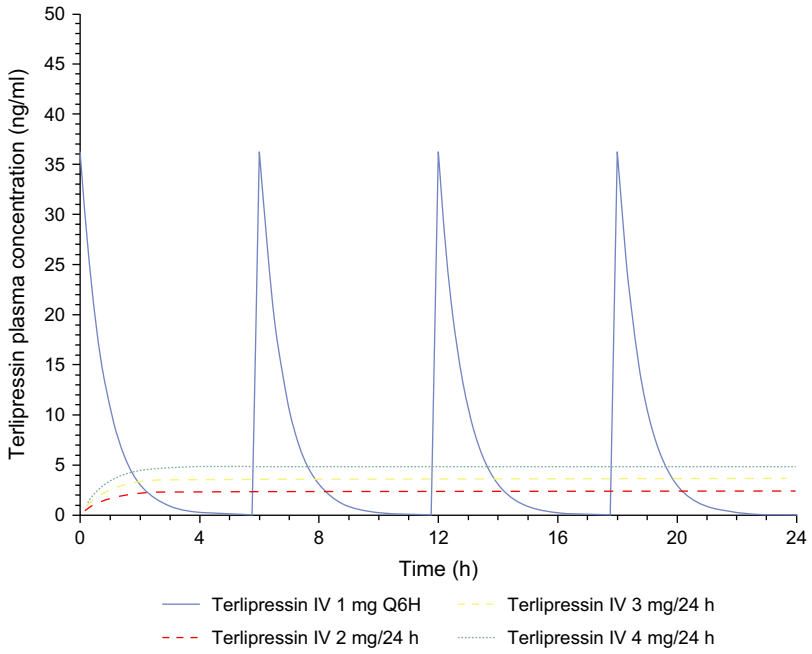

FIGURE 2 Comparison of simulated plasma concentrations of terlipressin administered by continuous infusion versus intermittent bolus. Reproduced from "Safety, tolerability, pharmacokinetics, and efficacy of terlipressin delivered by continuous intravenous infusion in patients with cirrhosis and refractory ascites" by Jasmohan S. Bajaj et al[11], GastroHep, volume 2022, page 5. Licensed under Creative Commons Attribution 4.0 (https://creativecommons.org/licenses/by/4.0/legalcode.en).

has also been demonstrated.[21] The fluctuations in plasma concentrations associated with bolus dosing result in a less effective hemodynamic response compared to CTI.[22] A single 2 mg bolus of terlipressin reduces HVPG and azygous blood flow for only 4 hours, whereas the effects of a 1 mg bolus last no longer than 3 hours.[23] For both doses, peak reduction in HVPG occurs rapidly after 30 minutes, followed by a gradual return to baseline.[23]

The superior hemodynamic effects of CTI over bolus terlipressin are of clinical significance. In patients with AVB, CTI induces a greater reduction in HPVG at 24 hours compared to bolus terlipressin (58.2% vs. 29.1%, $p = 0.003$), despite a lower mean terlipressin dosage (4.25 mg/dL ± 1.26 mg/dL vs. 7.42 mg/dL ± 1.42 mg/dL, $p < 0.001$).[24] A recent meta-analysis found significantly lower rebleeding (RR: 0.43, 95% CI: 0.27–0.69, $p = 0.0004$) and treatment failure (RR: 0.22, 95% CI: 0.06–0.82, $p = 0.02$) in patients with AVB treated with CTI compared to bolus terlipressin.[4] Although comparable treatment response rates between CTI and bolus terlipressin were observed in a cohort of patients with type 1 hepatorenal syndrome (HRS), a lower mean daily terlipressin dose was required to achieve treatment response with CTI (2.23 mg/dL ± 0.65 mg/dL vs. 3.51 mg/dL ± 1.77 mg/dL, $p = 0.0001$).[6]

The favorable safety profile of CTI relative to bolus terlipressin is well-documented.[4,6,11,24,25] A meta-analysis of 5 randomized controlled trials (RCTs) involving 395 patients with cirrhosis and either AVB or type 1 HRS, found a significantly lower risk of AEs with CTI compared to bolus terlipressin (RR: 0.52, 95% CI: 0.43–0.7, $p < 0.00001$).[4] Patients experiencing AEs with bolus terlipressin can also transition to CTI with improved tolerability.[6] The lower effective doses required with CTI, combined with the avoidance of potentially harmful peak concentrations associated with bolus dosing, enhance its overall tolerability.

ESTABLISHED INDICATIONS FOR TERLIPRESSIN USE

Acute variceal bleeding

Terlipressin is a recommended first-line treatment for AVB as an adjunct to endoscopic band ligation (EBL). A 2003 meta-analysis compared the efficacy and safety of terlipressin to placebo, other vasoactive drugs (vasopressin, somatostatin, octreotide), and endoscopic therapies (balloon tamponade, endoscopic treatment).[26] Compared to placebo, bolus terlipressin significantly reduced all-cause mortality (RR: 0.66, 95% CI: 0.49–0.88) and the number of procedures needed to stop uncontrolled bleeding or rebleeding (RR: 0.72, 95% CI 0.55–0.93).[26] No difference was found between bolus terlipressin and other vasoactive and endoscopic therapies in all-cause mortality, failure of initial hemostasis and rebleeding, except for a greater risk of failure of initial hemostasis when compared to octreotide (RR: 1.62, 95% CI: 1.05–2.50).[26] There was no difference in AEs leading to

drug discontinuation or death.[26] These findings firmly established terlipressin as a primary treatment for AVB.

Terlipressin versus octreotide in acute variceal bleeding

Octreotide, a somatostatin analog, is an alternative vasoactive therapy used in AVB. Octreotide causes selective vasoconstriction of the splanchnic circulation by inhibiting vasodilator release and reducing splanchnic hyperemia.[27]

The hemodynamic effects of terlipressin are superior to those of octreotide. Terlipressin causes a significantly greater reduction in HVPG and heart rate and an increase in mean arterial pressure, compared to octreotide.[28,29] Unlike the sustained hemodynamic effects of terlipressin, the initial reduction in HVPG induced by octreotide can rebound within 5 minutes.[28,29] Furthermore, in patients with a suboptimal HVPG response to a 250 μg/h somatostatin infusion, a 2 mg bolus of terlipressin achieves a greater reduction in HVPG compared to increasing the somatostatin dose to 500 μg/h.[30] The variable HVPG responses observed with octreotide suggest a potential rapid desensitization of somatostatin receptors to octreotide.[31]

Few prospective studies directly compare terlipressin and octreotide as adjunct therapies to EBL for AVB. A randomized trial involving 324 patients demonstrated that patients treated with bolus terlipressin (2 mg bolus then 1 mg/6 h for 3 d) had less active bleeding at gastroscopy than patients receiving octreotide (100 μg bolus then 50 μg/h for 3 d).[32] When combined with EBL, there were no significant differences in mortality, bleeding control, or transfusion requirements between the 2 therapies.[32] A large multicenter, randomized non-inferiority trial compared outcomes between bolus terlipressin (2 mg bolus then 1 mg/6 h for 5 d), octreotide (50 μg bolus then 25 μg/h for 5 d), and somatostatin (250 μg bolus then 250 μg/h for 5 d) in 780 patients with AVB.[33] Endoscopic therapy included EBL and/or cyanoacrylate injection depending on the varix type. Non-inferiority was demonstrated among the 3 groups regarding bleeding control, rebleeding, mortality, and a composite of these outcomes.[33] Meta-analyses comparing different vasoactive therapies have similarly found no significant differences between bolus terlipressin and octreotide in AVB outcomes.[34–37]

Importantly, no study has compared CTI to octreotide for AVB. Given its ability to maintain portal pressure reduction, CTI would be expected to have a superior impact on AVB outcomes compared to bolus dosing. However, there is currently no clinical data comparing CTI to other therapies for AVB.

Administration of terlipressin in acute variceal bleeding—our approach

Current guidelines recommend intermittent bolus terlipressin for the management of AVB (Table 1). Few studies have demonstrated improved efficacy and tolerability of CTI compared to bolus terlipressin in AVB.[4,24,39,40] A proposed CTI protocol based on our local practice is outlined in Table 1; however, we acknowledge that further RCT evidence in this area is required. Higher daily doses of terlipressin (8 mg/24 h vs. 4 mg/24 h) have not been shown to improve bleeding control or mortality.[41]

Hepatorenal syndrome

Terlipressin has long been the preferred treatment for HRS-AKI in Europe and the Asia-Pacific but was only recently approved by the U.S. Food and Drug Administration (FDA) for this indication. The key RCTs comparing terlipressin to placebo and/or albumin in HRS-AKI are summarized in Table 2.

The first large multicenter RCT included 112 patients with type 1 HRS randomized to receive either bolus terlipressin or placebo.[44] The primary outcome, defined as 2 consecutive serum creatinine (sCr) measurements of ≤ 1.5 mg/dL ≥ 48 hours apart, without intervening renal replacement therapy (RRT), liver transplantation (LT), or death, was not statistically different between groups (25% vs. 12.5%, $p = 0.09$).[44] The low success rates were contributed to by the strict clinical endpoint, high baseline mean sCr (terlipressin: 3.96 mg/dL, placebo: 3.85 mg/dL), a greater proportion of patients with baseline sCr > 7.0 mg/dL randomized to terlipressin (6 vs. 0), and one-third of patients receiving < 3 days of treatment.[44]

TABLE 1 Recommended terlipressin dosing in acute variceal bleeding

Source	Initial dosing	Maintenance dosing	Duration
AASLD[38]	2 mg bolus every 4–6 hours for the first 24–48 hours	1 mg bolus every 4–6 hours	2–5 d
EASL[1]	2 mg bolus every 4 hours for the first 48 hours	1 mg bolus every 4 hours	2–5 d
Local practice[a]	0.85 mg single bolus (equivalent to 1 mg terlipressin acetate)	3.4 mg/24 h infusion (equivalent to 4 mg/24 h terlipressin acetate)	2–5 d

[a]Terlipressin base 0.17 mL/mL (anhydrous, acetate-free) is equivalent to 0.2 mg/mL terlipressin acetate.

TABLE 2 Summary of randomized controlled clinical trials comparing terlipressin to placebo in patients with hepatorenal syndrome

Authors	n	Blinding	HRS type	Treatment arm	CTI vs. bolus terlipressin	Comparator arm	Concurrent albumin dose	Maximum treatment duration	HRS reversal[a] (treatment vs control)	Survival (treatment vs. control)
Solanki et al (2003)[42]	24	Single	HRS-1	Terlipressin 1 mg every 12 h (n = 12)[b]	Bolus	Placebo (n = 12)	20 g/d	15 d	42% vs. 0%[c]	42% vs. 0% at day 15[c]
Neri et al (2008)[43]	52	Unblinded	HRS-1	Terlipressin 0.5–1 mg every 8 h (n = 26)	Bolus	Albumin (n = 26)	1 g/kg BW day 1 then 20–40 g/d	14 d	80% vs. 19%[c]	42% vs. 16% at day 180[c]
Sanyal et al (2008)[44]	112	Double	HRS-1	Terlipressin 1–2 mg every 6 h (n = 56)	Bolus	Placebo (n = 56)	100 g on day 1 then 25 g/d	14 d	34% vs. 13%[c]	43% vs. 38% at day 180
Martin-Llahi et al (2008)[45]	46	Unblinded	HRS-1 HRS-2	Terlipressin 1–2 mg every 4 h (n = 23)	Bolus	Albumin (n = 23)	1 g/kg BW on day 1 then 20–40 g/d	15 d	39% vs. 4%[c]	27% vs. 19% at day 90
Boyer et al (2016)[46]	196	Double	HRS-1	Terlipressin 1–2 mg every 6 h (n = 97)	Bolus	Placebo and albumin (n = 99)	20–40 g/d	14 d	24% vs. 15%	58% vs. 55% at day 90
Wong et al (2021)[47]	300	Double	HRS-1	Terlipressin 1–2 mg every 5.5–6.5 h (n = 199)	Bolus	Placebo and albumin (n = 101)	1 g/kg BW on day 1 then 20–40 g/d	14 d	32% vs. 17%[c]	49% vs. 54% at day 90

[a]Serum creatinine ≤ 1.5 mg/dL.
[b]Concurrent renal vasodilatory doses of dopamine are given for the first 24–48 hours.
[c]$p < 0.05$.
Abbreviations: BW, body weight; CTI, continuous terlipressin infusion; CVP, central venous pressure; HRS, hepatorenal syndrome.

The subsequent REVERSE trial enrolled 196 patients with type 1 HRS.[46] The study endpoint of "confirmed HRS reversal", defined as 2 consecutive sCr measurements ≤ 1.5 mg/dL ≥ 40 hours apart without intervening RRT or LT, occurred in 19.6% of bolus terlipressin-treated patients and 13.1% of placebo patients ($p = 0.22$).[46] Treatment failure occurred in one-third of the bolus terlipressin group, likely due to the severe renal dysfunction present at baseline (mean sCr: 3.6 ± 1.1 mg/dL).[46] However, bolus terlipressin was associated with a greater reduction in mean sCr (−1.1 mg/dL vs. −0.6 mg/dL, $p < 0.001$), and a strong correlation was observed between changes in sCr and survival ($r = 0.88$, $p < 0.01$).[46]

The 2021 CONFIRM trial, which included 300 patients with type 1 HRS, ultimately led to the FDA approval of terlipressin for the management of HRS-AKI.[47] The primary outcome was defined as 2 consecutive sCr ≤ 1.5 mg/dL ≥ 2 hours apart within the first 14 days, and survival for an additional 10 days without intervening RRT.[47] Contrary to previous trials, a significantly higher proportion of patients in the bolus terlipressin group achieved the primary outcome compared to placebo (32% vs. 17%, $p = 0.006$).[47] Bolus terlipressin was notably associated with a higher risk of respiratory failure (13.5% vs. 5%) and death within 90 days from respiratory failure (11% vs. 2%), compared to placebo.[47] The high rates of respiratory failure observed in the CONFIRM trial were anticipated, given the combined effects of terlipressin-induced increased portal blood return to the systemic circulation and excessive albumin replacement. Furthermore, because terlipressin was initiated later in the course of HRS-AKI (baseline mean sCr 3.5 mg/dL $\pm$ 1.0 mg/dL), many patients may have already progressed to acute tubular necrosis, oliguria, or anuria, impairing their ability to excrete excess fluid (see 'Safety profile of terlipressin'). Current knowledge also suggests that the delayed initiation of terlipressin may have limited the ability of terlipressin to reverse HRS-AKI. Other characteristics of the CONFIRM trial population may also affect generalizability. Alcohol was the predominant cause of cirrhosis (67%), with coexistent alcoholic hepatitis in 41% of patients, which is known to markedly worsen prognosis. There was a small representation of patients with metabolic-associated steatotic liver disease (formerly NAFLD; 21%), which is an important consideration, as older age and metabolic comorbidities (eg, hypertension, diabetes) may contribute to underlying intrinsic renal disease and impair treatment response. Thus, while the CONFIRM trial is the largest RCT on terlipressin to date, its results should be interpreted in the context of the aforementioned limiting factors.

There are several explanations for the variable efficacy of terlipressin in the literature. Firstly, there is considerable heterogeneity in study design and outcome definitions. Secondly, only bolus terlipressin has been investigated in RCTs, despite higher response rates for CTI previously demonstrated in both type 1 HRS and HRS-AKI.[48,49] Thirdly, prior studies used the 2007 International Club of Ascites classification of HRS, which required specific sCr thresholds to be met. This tends to lead to a delayed diagnosis and more severe renal dysfunction, particularly in sarcopenic patients with lower baseline sCr levels. Furthermore, a higher baseline sCr is a predictor of reduced response to terlipressin, suggesting that earlier treatment in the course of HRS-AKI leads to better treatment responses.[50–52] This may be because although HRS-AKI is a functional impairment related to changes in renal perfusion, if untreated or advanced, it may lead to irreversible parenchymal damage.[8,53] In 2015, a revised definition of HRS-AKI was introduced, incorporating changes in sCr rather than specific cutoffs.[53] This new classification allows for earlier diagnosis and treatment, with greater treatment response rates anticipated in clinical practice and future studies.

The recent INFUSE study utilized the revised HRS-AKI classification, comparing 50 CTI patients (0.5 mg bolus then 2–8 mg/24 h) to 50 historical controls treated with noradrenaline or octreotide and midodrine.[5] The CTI group had a lower baseline median sCr than the control group (1.4 mg/dL vs. 2.1 mg/dL, $p < 0.001$), reflecting earlier treatment initiation per the revised HRS-AKI criteria. A markedly higher proportion of CTI-treated patients achieved complete response (decrease $\geq 30\%$ sCr with final sCr ≤ 1.5 mg/dL) compared to historical controls (64% vs. 16%, $p < 0.001$).[5] The CTI group had a favorable safety profile, with no cardiac or ischemic AEs reported, consistent with previous CTI studies.[5,10,13,49,54] The use of CTI, early initiation of therapy, avoidance of protocolized albumin administration, and exclusion of patients with grade 3 acute on chronic liver failure (ACLF), sCr > 5.0 mg/dL and MELD ≥ 35, likely mitigated AEs in this trial.

Current RCTs have not been sufficiently powered to detect a survival difference between terlipressin and placebo for patients with HRS-AKI. While meta-analyses have reported on the efficacy of terlipressin in improving renal function, its impact on mortality remains unclear.[55–59] Nevertheless, terlipressin offers additional benefits for LT candidates, including reduced pretransplant RRT requirements, lower rates of posttransplant chronic kidney disease, and reduced requirement for simultaneous liver–kidney transplantation.[5,10,60,61]

Terlipressin versus octreotide and midodrine in hepatorenal syndrome

In countries with limited access to terlipressin, octreotide, and midodrine are used to treat HRS-AKI. Combination therapy potentiates the vasodilation-inhibitory effects of octreotide with the alpha-adrenergic effects of midodrine, as octreotide alone is ineffective.[62]

Only one head-to-head prospective study has compared terlipressin to octreotide and midodrine in the treatment of HRS-AKI. An RCT randomized 49 patients with type 1 or 2 HRS to either CTI (3 mg/24 h up to 12 mg/24 h) or octreotide and midodrine (100 µg/7.5 mg TDS up to 200 µg/12.5 mg TDS), alongside albumin replacement.[48] A higher proportion of patients in the CTI group achieved HRS reversal compared to the octreotide and midodrine group (55.5% vs. 4.8%, $p < 0.001$).[48] The reduction in sCr in the CTI group (from 326.8 µmol/L ± 88.4 µmol/L to 221.1 µmol/L ± 162.8 µmol/L) was also significantly greater than the octreotide and midodrine group (from 343.9 µmol/L ± 187.5 µmol/L to 326.4 µmol/L ± 273. 2µmol/L, $p = 0.035$).[48] Six nonresponders in the octreotide and midodrine group received rescue therapy with CTI, resulting in improved renal function in 5 patients (83.3%).[48] AEs and survival were comparable between groups.[48] The study was notably not powered for survival analysis and terminated prematurely due to the superior results observed in the CTI arm. The superiority of terlipressin over octreotide and midodrine has similarly been demonstrated in retrospective cohort studies.[63,64]

While large, prospective comparative studies are lacking, the existing literature strongly supports terlipressin as the preferred treatment for HRS-AKI, with further studies in this area being unlikely.

Terlipressin versus noradrenaline in hepatorenal syndrome

Noradrenaline is a catecholamine with predominant alpha-adrenergic activity and is an alternative to terlipressin in patients with HRS-AKI requiring pressor support in the intensive care setting due to concurrent circulatory failure.

Multiple small, randomized trials have reported comparable HRS reversal rates between bolus terlipressin and noradrenaline.[65–70] Both therapies significantly improved renal function, sodium balance, and circulatory function.[65–70] Rates of AEs were similar between groups.[65,67–69] Two recent meta-analyses further support noradrenaline as a suitable treatment for HRS-AKI. One meta-analysis found no statistical difference in HRS reversal (OR: 1.33, 95% CI: 0.8–2.22, $p = 0.22$) or mortality (OR: 1.5, 95% CI: 0.64–3.53, $p = 0.26$) between noradrenaline and bolus terlipressin.[71] Similarly, the second meta-analysis reported comparable outcomes for both therapies in terms of HRS reversal (RR: 1.15, 95% CI: 0.96–1.37, $p = 0.12$) and mortality (RR: 0.87, 95% CI: 0.74–1.01, $p = 0.08$).[72]

One RCT compared terlipressin to noradrenaline in 120 patients with APASL-defined ACLF and HRS-AKI.[49] Patients received either CTI (2–12 mg/24 h) or noradrenaline (0.5–3 mg/24 h) with concomitant albumin for 14 days.[49] The mean daily dose of terlipressin was low at 2.02 mg ± 0.70 mg. Nevertheless compared to noradrenaline, CTI was associated with higher rates of HRS reversal (40% vs. 16.7%, $p = 0.004$), reduced RRT requirement (56.6% vs. 80%, $p = 0.006$) and greater 28-day survival (48.3% vs. 20%, $p = 0.001$).[49] Although AEs occurred more frequently in the terlipressin group (23.3% vs. 8.3%, $p = 0.02$), they were mild and reversible with drug cessation.[49] The increased efficacy of terlipressin compared to prior studies may result from using CTI instead of bolus terlipressin and early treatment initiation based on HRS-AKI criteria; however, validation with further studies is required.

Administration of terlipressin in hepatorenal syndrome-acute kidney injury —our approach

Our institution has used terlipressin for the treatment of HRS-AKI for over 20 years and routinely transitioned to CTI over bolus dosing over 10 years ago. Following a 0.85 mg i.v. bolus, CTI is commenced at the target dose of 3.4 mg/d (Figure 3). In our experience, most patients respond to a CTI dose of 3.4 mg/d if treatment is initiated early before severe renal dysfunction develops, which is increasingly supported by global data.[5,61,73] Dose escalation due to treatment nonresponse is uncommon in our experience. Albumin administration is minimized to avoid circulatory overload and is used only if patients are under-volumed, typically requiring a short course (eg, 1–2 d) to restore circulating blood volume and renal blood flow. Ongoing coadministration of terlipressin and albumin beyond this point is not recommended. Terlipressin is continued until renal function is restored or up to 14 days in non-transplant candidates. For rebound or recurrent HRS-AKI in transplant candidates, long-term home CTI is instituted as a bridge to LT (see 'Emerging Indications for Terlipressin Use').

CTI is initially administered via a peripheral intravenous catheter that may be transitioned to a peripherally inserted central catheter if a longer duration of therapy is anticipated. Terlipressin is routinely administered in the medical ward at our institution without additional intensive monitoring beyond general nursing care. Following the results of the CONFIRM trial, the American Gastroenterological Association recently published a clinical practice update stating that terlipressin can be administered through a peripheral line and does not require intensive care monitoring.[74] Our real-world and RCT data on long-term CTI have also not demonstrated any serious treatment-related AEs,[9,75] further reinforcing the safety of terlipressin administration in the general ward setting.

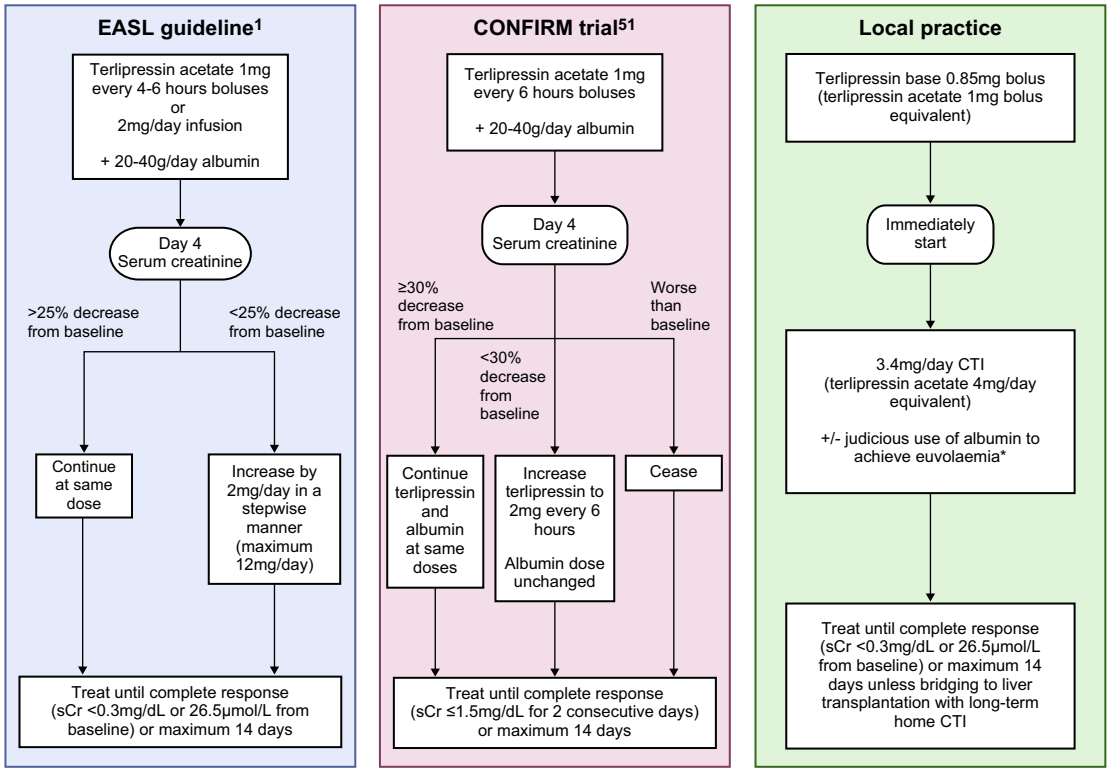

FIGURE 3 Terlipressin dosing algorithms for the management of hepatorenal syndrome-acute kidney injury. *We recommend regular fluid balance assessments and careful, individualized titration of albumin replacement in under-volumed patients to restore circulating blood volume. Albumin administration should be minimized to avoid circulatory overload and pulmonary edema. Abbreviations: CTI, continuous terlipressin infusion; sCr, serum creatinine.

SAFETY PROFILE OF TERLIPRESSIN

When evaluating the safety profile of terlipressin, it is important to consider the clinical context: patients with AVB have a 6-week mortality risk of 15%, and those with HRS-AKI have a 3-month mortality risk of 90% if untreated.[38,76] A recent meta-analysis of 78 prospective and retrospective studies reported a pooled incidence of treatment-related AEs of 22% and serious AEs of 5%.[77] Unsurprisingly, patients with advanced cirrhosis were at greatest risk of serious AEs. Patients with bilirubin >4.3 mg/dL had a higher rate of treatment-related serious AEs than those with bilirubin ≤ 4.3 mg/dL (8% vs. 1%, $p=0.04$).[77] Additionally, patients with HRS-AKI had more treatment-related serious AEs than those with AVB or ascites (8% vs. 1% vs. 7%, $p=0.02$).[77] However, previous meta-analyses of RCTs have reassuringly found terlipressin-related AEs to be mild to moderate in severity, with rates comparable to other vasoconstrictive therapies, despite the high acuity of the patient population.[35,56,58,59,78]

Increasing real-world experience with terlipressin has provided valuable data to inform best-practice administration strategies that minimize AEs, as summarized below and in Table 3.

Gastrointestinal symptoms

Diarrhea and abdominal pain are the most common terlipressin AEs, with incidences of 10% and 9%, respectively.[56,77] Gastrointestinal AEs are often mild, self-limited, or reversible with dose reduction. Gastrointestinal AEs may be minimized with CTI compared to bolus dosing.[77]

Pulmonary edema and respiratory failure

The incidence of terlipressin-induced dyspnea, pulmonary edema, and respiratory failure, was reported in the aforementioned recent meta-analysis as 9%, 7%, and 4%, respectively.[77] Despite these low rates, the FDA has a black box warning for terlipressin regarding the potential for respiratory failure, particularly in patients with circulatory overload or grade 3 ACLF. This warning stems from the high proportion of respiratory failure-related deaths that occurred with bolus terlipressin compared to placebo in the CONFIRM trial (11% vs. 2%).[47] Respiratory failure was more likely in patients with grade 3 ACLF than in those with lower grades (30% vs. 9.4%, $p=0.002$).[79] Understanding the pathophysiology leading to respiratory failure can help clinicians

TABLE 3 Key adverse effects associated with terlipressin use and methods to mitigate risk

Adverse effect	Risk factors	Protective factors
Gastrointestinal		• Dose reduction or temporary pause in treatment • CTI over bolus dosing
Respiratory failure	• Advanced HRS-AKI • Oliguric renal failure • Excess albumin replacement • Cardiac failure	• Early initiation of treatment • Regular fluid balance assessment • Judicious and personalized administration of albumin based on volume status • Avoid in NYHA class 3–4 cardiac failure
Hyponatremia	• High serum sodium • Low serum creatinine • Low Child–Pugh or MELD score • Rapid changes in fluid status	• Monitor serum sodium regularly • Active titration of diuretics with treatment response • CTI over bolus dosing
Organ ischemia	• Hypovolaemia • Atherosclerotic risk factors (eg, smoking, T2DM) • Underlying severe coronary artery disease • Underlying severe peripheral vascular disease or venous insufficiency • Concomitant use of vasopressors	• Ensure volume is replete prior to commencing terlipressin, including correction of anemia if required • Avoid severe coronary artery disease (eg, class 3–4 angina, untreated significant ischemia on coronary stress testing, untreated extensive, or severe stenosis on angiography) • Avoid in severe peripheral vascular disease (eg, critical limb ischemia, untreated extensive, or severe stenosis on angiography) • CTI over bolus dosing

Abbreviations: ACLF, acute on chronic liver failure; CTI, continuous terlipressin infusion; HRS-AKI, hepatorenal syndrome-acute kidney injury; NYHA, New York Heart Association; sCr, serum creatinine; T2DM, type 2 diabetes mellitus.

understand why this cohort was particularly vulnerable to respiratory failure.

Splanchnic vasoconstriction induced by terlipressin contracts the total circulating blood volume and returns portal blood to the systemic circulation, thereby increasing hydrostatic pressure, cardiac preload, and afterload (via increasing systemic vascular resistance). Regular albumin administration increases oncotic pressure, preventing fluid from escaping extravascular, and further increasing hydrostatic pressure. If oliguria has developed in the context of advanced HRS-AKI, the kidneys cannot effectively excrete excess volume, and respiratory failure may ensue. In contrast, patients with early HRS-AKI or AVB are able to increase urine output to compensate for the change in volume status.[80]

Several factors contributed to the high rates of respiratory failure observed in the CONFIRM trial. Participants had advanced type 1 HRS with baseline severe renal dysfunction (mean sCr: bolus terlipressin 3.5 mg/dL ± 1.0 mg/dL, placebo 3.5 mg/dL ± 1.1 mg/dL). Albumin administration was strongly recommended at a dose of 1 g/kg/body weight up to 100 g on day 1 and 20–40 g/day thereafter. High doses of albumin were administered both prior to randomization and during treatment (mean total albumin dose: terlipressin 534.4 g, placebo 610.2 g), likely causing circulatory overload in the context of oliguric renal failure.[80] While the amount of albumin administered before treatment was not a predictor of respiratory failure,[79] the total amount of albumin given prior to randomization and during treatment is important to consider, as the cumulative dose likely contributed to the development of respiratory failure. It is unsurprising that respiratory failure occurred more frequently in patients with grade 3 ACLF, who have a high baseline risk for systemic inflammatory response syndrome and non-hydrostatic pulmonary edema, which can be further exacerbated by circulatory overload from excess albumin.[79]

The risk of respiratory failure is mitigated by initiating terlipressin early in HRS-AKI before oliguria develops. The requirement for 48 hours of albumin prior to treatment is no longer recommended, particularly in patients who are euvolemic or have signs of circulatory overload.[8] This approach can delay diagnosis and treatment initiation, and may also increase the risk of respiratory failure.[8] Although current guidelines recommend the coadministration of terlipressin and 20–40 g of albumin per day, this has not been demonstrated to improve HRS reversal rates compared to terlipressin alone.[7] Thus, regular fluid balance assessments should accompany careful, individualized titration of albumin and diuretics, rather than a protocolized approach. Diuretic administration and a temporary pause in albumin in patients with circulatory overload may avoid the complete discontinuation of terlipressin therapy.[8]

Hyponatremia

The overall incidence of terlipressin-induced hyponatremia is ~9%.[77] Despite its selectivity for V1a receptors, terlipressin also activates renal V2 receptors that mobilize aquaporin-2 channels into the collecting ducts, resulting in water retention and dilutional hyponatremia.[14]

Multiple retrospective analyses have identified risk factors for hyponatremia in patients with AVB treated with terlipressin. Baseline serum sodium consistently emerges as an independent risk factor, with higher levels associated with increased hyponatremia risk.[81–87] Other predictors include a low baseline sCr and low MELD or Child–Pugh scores.[83,85–87] In patients with relatively preserved liver and renal function, serum sodium levels are higher, and there is less occupation of renal V2 receptors by endogenous vasopressin.[82,84,85,87] Conversely, terlipressin-induced hyponatremia is uncommon in HRS-AKI, as renal V2 receptors are saturated by endogenous vasopressin in response to reduced renal perfusion in advanced portal hypertension.[82,84,85,87] Indeed, increased or stable serum sodium has been observed in terlipressin-treated patients with HRS-AKI or diuretic-refractory ascites, reflecting improvements in circulatory function and downregulation of neurohormonal pathways.[9,43,75,88,89]

Hyponatremia typically develops within 2–3 days of terlipressin commencement.[82,87] The risk can be mitigated with early monitoring of serum sodium, particularly in patients with AVB and relatively preserved liver and kidney function. Larger doses of bolus terlipressin may increase the risk of hyponatremia in patients with AVB;[86] therefore, CTI is recommended. CTI achieves greater efficacy and safety in AVB with a lower mean total dose compared to bolus terlipressin.[24,39] Patients with HRS-AKI should also be monitored with active diuretic titration, as urinary sodium excretion and diuretic responsiveness improve with restoration of renal perfusion during terlipressin therapy.[9,89] Terlipressin-induced hyponatremia resolves quickly following treatment interruption, especially if identified early.[82,83,85,87]

Organ ischemia

Organ ischemia secondary to terlipressin is rare and, similar to hyponatremia, typically occurs within 2–3 days of treatment initiation.[39,77] Ischemic AEs are usually mitigated by terlipressin cessation, reducing the dose, or changing from bolus administration to CTI.[8,25,90]

Terlipressin-induced coronary ischemia occurs due to coronary artery vasoconstriction, vasospasm, and increased procoagulant activity through platelet aggregation.[15,91] This may rarely result in chest pain, arrhythmia, and myocardial infarction in up to 2% of patients.[77] Cases of terlipressin-induced coronary ischemia have occurred in both the presence and absence of underlying coronary artery disease.[44,91–93] Nevertheless, terlipressin should be avoided in high-risk patients with severe preexisting coronary artery disease.

Terlipressin-induced peripheral ischemia occurs in 2% of cases.[77] An analysis of published case reports of terlipressin-induced skin ischemia found that most cases occurred within 3 days of treatment commencement.[90] Common sites of involvement were the legs and abdomen.[90] Risk factors for skin ischemia include hypovolaemia, vasopressor use, comorbid peripheral vascular disease, venous insufficiency, and obesity.[90] Risk minimization strategies include ensuring euvolemia prior to terlipressin commencement and monitoring for early signs of skin ischemia (eg, cyanosis, livedo reticularis). Terlipressin should be avoided in patients with severe peripheral vascular disease or venous insufficiency.

Limited literature exists on terlipressin-induced mesenteric ischemia due to its low incidence of 1%.[77,94–96] However, risk mitigation strategies for mesenteric ischemia are perceived to be similar to those for other end-organ ischemia.

EMERGING INDICATIONS FOR TERLIPRESSIN USE

Diuretic-refractory ascites

There is an emerging literature on the role of terlipressin in managing diuretic-refractory ascites. Terlipressin induces diuresis and natriuresis by restoring renal perfusion and decreasing neurohormonal pathway activity.[97,98]

Several proof-of-concept studies have demonstrated improved ascites control with terlipressin. In 26 patients with diuretic-refractory ascites, 3 weeks of bolus terlipressin (1 mg/6 h) and albumin therapy reduced ascites volume in two-thirds of patients.[99] A study of 5 patients receiving CTI (3.4 mg/24 h) for 4 weeks observed significant natriuresis, reduced ascites volume, and paracentesis frequency in all patients.[89] Another CTI study similarly reported a marked reduction in the number and volume of paracenteses after 28 days of CTI (up to 4 mg/24 h), sustained for an additional 28 days of follow-up.[11] No serious AEs were reported in these studies.

Our center recently published a randomized crossover study evaluating home CTI in 30 patients with diuretic-refractory ascites and sarcopenia.[9] Patients were randomized to 12 weeks of home CTI (3.4 mg/24 h) or observation before crossing over to the alternate treatment arm. The co-primary outcomes were changes in paracentesis volume and handgrip strength. Paracentesis volume decreased significantly by a mean adjusted difference of 11.39 L (95% CI: 2.99–19.85 L, $p < 0.001$) with 1.75 (95% CI: 0.925–2.59, $p < 0.001$) fewer paracenteses required on CTI compared to observation.[9] Handgrip strength improved significantly by a mean adjusted difference of 3.09 kg (95% CI: 1.11–5.08 kg, $p = 0.006$), and quality of life improved across all domains of the Chronic Liver Disease

Questionnaire.[9] There were no treatment-related serious AEs or treatment withdrawal due to AEs. There was no significant change in serum sodium levels and, importantly, no ischemic events or pulmonary edema. We have reported similar real-world data from a cohort of over 100 patients, encompassing over 13,000 patient days of CTI over a 10-year period.[75] This larger cohort, with a similar median treatment duration to our crossover study, also demonstrated a significant reduction in paracentesis requirements.[75]

Long-term home continuous terlipressin infusion

The hepatorenal syndrome can recur in 20% of patients despite an initial response to terlipressin, particularly if there is no treatment for the underlying liver disease etiology.[1,55] While re-treatment is often effective, continuous recurrence can lead to a cohort of terlipressin-dependent patients requiring long-term hospitalization. It was for this cohort of patients that our center developed a Hospital-in-the-Home program that provides CTI in the ambulatory setting for terlipressin-dependent LT candidates. Originally established for the treatment of recurrent HRS-AKI, the program has expanded to include select patients with diuretic-refractory ascites or hydrothorax.

Long-term home CTI is initiated in the hospital for all patients. A peripherally inserted central catheter is placed, and as for the inpatient management of HRS-AKI, long-term home CTI is initiated with a 0.85 mg i.v. bolus (terlipressin acetate 1 mg equivalent) immediately followed by a 3.4 mg/day infusion (terlipressin acetate 4 mg/day equivalent). Ambulatory infusion pumps are used to deliver long-term home CTI (Table 4). As most terlipressin-related AEs occur within 48–72 hours of treatment initiation,[39] patients who tolerate CTI during this observation period can be safely discharged home for ongoing long-term CTI. Patients on long-term home CTI are jointly monitored by the treating hepatologist and Hospital-in-the-Home medical and nursing staff. Hospital-in-the-Home nursing staff performs daily 1-hour home visits to facilitate medication change, central venous access device management (eg, dressing change), blood collection, and measurement of vital signs and weight. Patients and nursing staff are educated on reportable terlipressin-related AEs. Face-to-face hepatology clinic reviews occur every 4 weeks; however, laboratory testing is conducted twice a week for the first 4 weeks and then weekly thereafter, provided the patient's electrolytes remain stable.

Our center has provided long-term home CTI for over 10 years, publishing extensively on its efficacy and safety.[10,13,54,89,100,101] Our largest real-world data includes 105 patients and 13,246 patient days of home CTI, with a median treatment duration of 83 days (range: 15–899 d).[75] Recurrent HRS-AKI was the most common indication for CTI (52%), followed by diuretic-refractory ascites (41%) and hydrothorax (7%). Patients with HRS-AKI had significant improvements in sCr, decreasing from 174 μmol/L (1.97 mg/dL) to 106 μmol/L (1.2 mg/dL).[75] The early initiation of CTI optimized treatment response rates, reducing the need for simultaneous liver–kidney transplantation. Of 60 patients bridged to LT, only one required a simultaneous liver–kidney transplant. Patients with diuretic-refractory ascites or hydrothorax had a 58% reduction in paracentesis and thoracocentesis frequency ($p = 0.001$).[75] Similar to our randomized crossover CTI study, serum sodium remained unchanged, with no reported ischemic or pulmonary AEs.

Long-term CTI also confers additional benefits on malnutrition and sarcopenia in patients with decompensated cirrhosis, where progressive functional decline is associated with increased waitlist mortality.[102] Nutritional and functional muscle parameters were first assessed in a prospective study of 19 LT candidates with recurrent HRS or diuretic-refractory ascites receiving CTI (3.4 mg/24 h) for a median of 51 days (IQR 29–222 d).[13]

TABLE 4 Ambulatory infusion pumps used to deliver long-term home continuous terlipressin infusion

	Surefuser+100 mL pump	Continuous Ambulatory Drug Delivery (CADD) pump
Pump logistics	• Elastomeric pump • Single use (changed every 24 h) • Medication made up by nursing staff in the home everyday • Pump carried in a waist bag • Pump and central venous access site covered in plastic when showering	• Rechargeable battery • Medication made up by nursing staff in the home everyday • Pump carried in a waist bag • Pump and central venous access site covered in plastic when showering
Benefits	• Lightweight, durable • No batteries required • Easy for nursing staff to set up	• Provides alert if the infusion is interrupted • Lower cost
Drawbacks	• No alert if the infusion is interrupted (eg, line blocked) • Higher cost	• Heavier, less durable • Potential technical or battery issues • Maintenance of pump required • More training on pump setup and usage for nursing staff

Terlipressin significantly improved protein and energy intake ($p < 0.001$), with most patients approaching recommended nutritional requirements.[13] Handgrip strength increased from 25.36 kg ± 8.13 kg to 28.49 kg ± 7.63 kg ($p = 0.001$).[13] The reduction in ascites volume ($p = 0.001$) may have contributed to these improvements in dietary intake and handgrip strength, as maintaining ascites at body temperature requires considerable energy.[13,103] However, portal hypertension contributes to sarcopenia through multiple mechanisms, including systemic inflammation, anorexia, and portal hypertensive enteropathy.[104] Therefore, terlipressin's ability to reduce portal pressure likely has a multifaceted impact on nutritional status. Importantly, our randomized crossover CTI study confirmed the positive effect on handgrip strength,[9] which again aligns with our real-world data from a larger cohort of long-term CTI patients.[75]

There is a strong rationale for implementing long-term home CTI for select LT candidates with portal hypertensive complications, particularly in centers with prolonged waiting times. We recommend home CTI for all candidates with recurrent or refractory HRS-AKI. The implementation of CTI for patients with diuretic-refractory ascites or hydrothorax requires a nuanced discussion with the patient regarding potential benefits but is particularly considered in those with significant sarcopenia. The impact of CTI on cardiac reserve may also prevent HRS-AKI in patients with refractory ascites and hydrothorax,[12] thus a low cardiac reserve can inform decision-making when echocardiographic data are available. In those without this information, low mean arterial pressure may be a reasonable surrogate to incorporate into decision-making discussions.[105,106]

While terlipressin can lower the MELD score, patients on long-term CTI are not disadvantaged in our center, as we take terlipressin into account in waitlist prioritization.[10] However, in countries like the United States, MELD-exemption points or a MELD score "lock" may be necessary if long-term CTI is adopted to ensure patients can access treatment without compromising their waitlist status.[107]

Despite promising results for long-term home CTI at our institution, adequately powered multicenter studies are required to validate these findings elsewhere and determine whether these benefits translate to important clinical outcomes, including peri-LT hospitalization, morbidity, and mortality. What also remains lacking is cost–benefit analyses in various jurisdictions that will dictate access to this therapy and identify appropriate indications for widespread implementation.

Cardiac dysfunction in decompensated cirrhosis

The understanding of cardiac dysfunction in the pathogenesis of HRS-AKI has evolved in recent years. Most patients with decompensated cirrhosis have an elevated resting cardiac output, reflecting cardiac compensation in the context of expanded total blood volume due to splanchnic vasodilation. However, some of these patients are unable to augment their cardiac compensation in response to stress, leading to reduced renal perfusion and a cascade of hemodynamic events that leads to HRS-AKI.[108–110] In fact, patients with decompensated cirrhosis and impaired cardiac reserve have a 4-fold risk of developing HRS-AKI.[108]

We recently demonstrated that CTI may be the first therapy to improve subclinical cardiac dysfunction in decompensated cirrhosis. Twenty-two patients from our randomized crossover CTI study underwent dobutamine stress echocardiography to assess cardiac function before and 12 weeks after CTI.[9,12] A significant increase in cardiac output in response to low-dose dobutamine was observed post-CTI compared to baseline ($p = 0.0001$), driven by improved contractility.[12] The proportion of patients with impaired cardiac reserve (< 25% increase in cardiac output after low-dose dobutamine) decreased from 81.8% to 40.9% after CTI ($p = 0.02$).[12] By targeting both cardiac dysfunction and the hyperdynamic circulatory state, it is plausible that early intervention with terlipressin may reduce the risk of HRS-AKI in patients with diuretic-refractory ascites.

The beneficial effects of terlipressin on cardiac function may be limited in patients with cirrhotic cardiomyopathy and systolic dysfunction. An Indian study of 140 patients with HRS-AKI treated with 72 hours of CTI found a reduction in heart rate, mean arterial pressure, and cardiac index in patients with systolic dysfunction compared to those without ($p < 0.05$), along with an increased risk of nonresponse to CTI (47% vs. 21%, $p < 0.001$).[111] This may be because an impaired left ventricle is unable to adapt to the increased venous return induced by splanchnic vasoconstriction. Indeed, patients with systolic dysfunction were excluded from our CTI trial for this reason.

CONCLUSIONS

Terlipressin is a cornerstone in the management of portal hypertensive complications of decompensated cirrhosis. Key strategies for optimizing the safety and efficacy of terlipressin include using CTI over bolus terlipressin and initiating therapy early with judicious albumin use in HRS-AKI. Long-term home CTI may expand therapeutic indications to include recurrent HRS-AKI, diuretic-refractory ascites, and hydrothorax. The increasing positive data for long-term home CTI require further validation in adequately powered multicenter cohorts to determine if a longer duration of therapy can reduce clinical decompensation events, reduce waitlist mortality, and optimize peri-transplant outcomes.

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CONFLICTS OF INTEREST

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ORCID

Dorothy Liu https://orcid.org/0000–0002–7802–2803
Adam Testro https://orcid.org/0000–0001–6776–3115
Avik Majumdar https://orcid.org/0000–0003–2975–4327
Marie Sinclair https://orcid.org/0000–0003–0657–3048

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