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<td>Corresponding Author:</td>
<td>Ashwani Singal</td>
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<td>University of South Dakota</td>
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<td>Ashwani Singal</td>
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<td>Rajiv Jalan</td>
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<td>Abstract:</td>
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Terlipressin for Hepatorenal Syndrome: Opportunities, Challenges and Pitfalls

1,2 Ashwani K. Singal, MD MS and 3,4 Rajiv Jalan, MD PhD

1 Department of Medicine, University of South Dakota Sanford School of Medicine; 2 Division of Transplant Hepatology, Avera Transplant Institute; 3 Clinical Research, VA Medical Center, Sioux Falls, South Dakota; 4 Liver Failure Group, Institute for Liver and Digestive Health, UCL Medical School, London, UK. 4 European Foundation for the Study of Chronic Liver Failure, Barcelona, Spain.

Conflict of Interest

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The recent approval of terlipressin by the US Food and Drug Administration (FDA) for the treatment of patients with hepatorenal syndrome (HRS) is a huge advance in the management of patients with this dreaded complication of cirrhosis that accounts for significant morbidity and mortality. It is important to note that outside of the US, terlipressin has been used for the treatment of HRS for many decades with a wealth of experience with its use. This article highlights clinical perspectives on the enormous opportunities this provides and indicates potential challenges and pitfalls in the widespread use of terlipressin for these patients.

HRS, a form of acute kidney injury (AKI), is reported in 15-43% of hospitalized patients with cirrhosis and AKI.\(^1\)\(^-\)\(^3\) Based on a national inpatient database in the US, the population estimate of HRS in the year 2019 was 8.3 / 100,000 population, with an in-hospital mortality of about 26%, and economic burden of 4.2 billion USD for patient care during hospitalization.\(^2\)

HRS-AKI is thought to be the consequence of decreased effective arterial blood volume and cardiac output that results in reduced renal perfusion.\(^1\) Due to their ability to constrict the splanchnic vasculature with a consequent increase in renal blood flow, vasoconstrictors are used as the first line treatment for HRS-AKI in stage 1b or higher (Supplementary Box). Intravenous albumin infusion, 40-50 gm/d is given as an adjuvant to vasoconstrictor treatment, as albumin helps expand the plasma volume, and provides additional beneficial effects on stabilizing the endothelium and reducing capillary permeability.\(^1\) Of three available vasoconstrictors (Table 1), terlipressin is most effective.
as it also reduces portal pressure. Complete HRS reversal with terlipressin (decrease in serum creatinine to <1.5 mg/dL on two readings taken 12 hours apart) is observed in 33-81% patients.\(^4\) Patients with partial response (decrease in serum creatinine by >30% from baseline but still ≥ 0.3 from baseline) should continue receiving terlipressin until complete response or maximum duration of 14-days. Treatment efficacy depends upon the baseline serum creatinine, as can be witnessed with HRS reversal rate of only 29% in the CONFIRM trial, where the mean serum creatinine was 3.5 mg/dL.\(^5\) Recurrence of HRS once treatment is discontinued can occur in up to 20% cases.\(^1,4\) Retreatment is usually effective and there is a potential for outpatient terlipressin infusion in improving transplant free survival of HRS patients.

Liver transplantation (LT) should be considered as a definitive treatment option for HRS, with renal replacement therapy used to optimize renal function while awaiting LT (Supplementary Figure).\(^6\) Patients not responding to vasoconstrictors and ineligible for LT should be considered for discussion of goals of care to improve their quality of life, especially if the renal function does not improve.

The importance of systemic inflammation is recently highlighted as a key underlying mechanism, which somewhat complicates the view that HRS is purely functional, and may explain abnormal renal histology in a significant proportion of cases.\(^7\) The best outcome of the patients with terlipressin would be achieved in those that have a pure form of HRS-AKI (Supplementary Box). Recently, urinary level of neutrophil derived gelatinase

\[ \text{neutrophil derived gelatinase} \]
associated lipocalin (NGAL) >220 mcg/g of creatinine on day 3 of AKI has been shown to be 87% (78-95%) accurate in diagnosis of acute tubular necrosis.⁸

Despite improved renal function with terlipressin, short-term mortality rates are not affected as HRS-AKI is often associated with acute on chronic liver failure (ACLF), which involves other organ failures, with 28-day mortality rates of 20-80% depending on the number of organ failures.⁹ Response to terlipressin diminishes with increasing severity of ACLF.¹⁰ Therefore, HRS-AKI should serve as an alarm to consider LT where appropriate. However, one challenge in this context may be that a reduction in the serum creatinine with terlipressin would impact the MELD score, and priority on the LT list. Hence, there is a need for awareness and development of strategies for improving liver allocation to patients treated with terlipressin by considering either MELD exception points or awarding maximum points for renal function, perhaps equating them as if they are receiving dialysis.

Terlipressin is a vasoconstrictor that achieves its effect through stimulating the vasopressin receptors on blood vessels, and therefore one needs to consider potential pitfalls with its use. The most worrying adverse effects include ischemic events resulting in digital infarction, gut ischemia, cerebral ischemia, and cardiac hypo perfusion with failure that can result in pulmonary edema. The risk of these adverse effects is higher in the elderly and those patients with a history of peripheral, cardiac, and cerebral vascular disease.¹¹ Therefore, a careful clinical examination, an ECG and echocardiography are crucial before starting terlipressin. Use of terlipressin as an infusion instead of bolus
reduces adverse events. However, whether terlipressin infusion is allowed without continuous monitoring of fluid and electrolyte balance, oxygen saturation, and cardiac status is not clear.

Given this background, it is not surprising that the terlipressin approval comes with important safety information and guidance on its use in clinical practice (https://www.mallinckrodt.com/about/news-and-media/news-detail/?id=29396). First, terlipressin should be avoided in patients with ACLF grade 3, baseline oxygen saturation below 90%, and those with ongoing peripheral, coronary, or mesenteric ischemia. Further, as the development of ischemic events or respiratory failure may make potential or listed patients ineligible for LT, the benefits of terlipressin may not outweigh its risks in those with high priority for LT such as those with MELD score ≥35.

Until the recent FDA approval of terlipressin, midodrine / octreotide combination was the most frequent drug used for treatment of patients on the medical floors for HRS-AKI, as noradrenaline in most centers requires placement of central line and intensive care.¹ Availability of terlipressin in the US was long awaited and its approval and availability is an exciting news for clinicians and also for researchers as we join the bigger community in Europe and Asia in gathering more real world data on its use. Hopefully the learning curve will be quick and the availability of terlipressin will complete the practice armamentarium of hepatologists in the US, to better manage patients with HRS.
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REFERENCES

Supplementary Box Definition and severity classification of acute kidney injury (AKI) and diagnostic criteria of Hepatorenal Syndrome

**AKI**: Increase in serum creatinine by ≥0.3 mg/dL within 48h from the baseline or increase in serum creatinine by ≥50% within seven days or from the baseline value.*

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Cirrhosis with portal hypertension and AKI

No improvement in serum creatinine after 2 consecutive days of volume expansion

Exclusions:
- *Shock and current or recent use of nephrotoxic drugs*
- *Structural kidney injury (proteinuria >500 mg/d, hematuria >50 red blood cells/high power field)*
- *Urinary tract obstruction on renal ultrasound examination*

*Baseline value is from the closest previous value within the previous 3 months. Stage 1 is stratified to 1a (serum creatinine <1.5 mg/dL) or 1b (serum creatinine ≥1.5 mg/dL).*
Supplementary Figure  Proposed algorithm in the management of hepatorenal syndrome – acute kidney injury (HRS-AKI). SC: Serum creatinine; CR: Complete response; PR: Partial response; ACLF: Acute on chronic liver failure; MELD: Model for end-stage liver disease.
• Comments should be not more than 1000 words with a maximum of 10 references.

**Response:** Revised manuscript has 997 words and 10 references.

• Please note we cannot include subheadings

**Response:** We have removed subheadings.

• Only one figure, table or panel may be included in the main text. All other items must go in the appendix

**Response:** We have moved the Box and Figure to supplement section. The main text has only one table in the revised manuscript.

• If you decide to use the Figure in the main text, please supply this as the original "editable" file (eg the original powerpoint or word file, rather than the .jpg)

**Response:** The figure is moved to the supplement section.

• All authors are required to provide a signed author contribution statement form, available to be download [here](#) (completed forms should be uploaded with your revised manuscript if not already submitted). If you are the sole author, this is NOT required.

**Response:** Completed signed author contributions forms from both the authors are uploaded with the revised manuscript.

• All authors should complete and return an ICMJE conflict of interest form, available to download [here](#). The disclosures made should match your statements in the comment.

**Response:** ICMJE COI forms from both the authors are completed.

• We can only have one corresponding author - please provide a point of contact

**Response:** Ashwani K. Singal is the point of contact for correspondence.
Terlipressin for Hepatorenal Syndrome: Opportunities, Challenges and Pitfalls

Ashwani K. Singal, MD MS and Rajiv Jalan, MD PhD

1Department of Medicine, University of South Dakota Sanford School of Medicine; 2Division of Transplant Hepatology, Avera Transplant Institute; 3Clinical Research, VA Medical Center, Sioux Falls, South Dakota; 4Liver Failure Group, Institute for Liver and Digestive Health, UCL Medical School, London, UK. 4European Foundation for the Study of Chronic Liver Failure, Barcelona, Spain.

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The recent approval of terlipressin by the US Food and Drug Administration (FDA) for the treatment of patients with hepatorenal syndrome (HRS) is a huge advance in the management of patients with this dreaded complication of cirrhosis that accounts for significant morbidity and mortality. It is important to note that outside of the US, terlipressin has been used for the treatment of HRS for many decades with and there is a wealth of experience with its use. This article highlights clinical perspectives on into the enormous opportunities this provides and indicates potential challenges and pitfalls in the widespread use of terlipressin for these patients.

**The opportunity**

HRS is a type form of acute kidney injury (AKI) that is reported common in hospitalized patients with a prevalence of in 15-43% of hospitalized patients with cirrhosis and AKI.1-3 Based on a national inpatient database in the US, the population estimate of HRS in the year 2019 was 8.3 / 100,000 population, with an in-hospital mortality of about 26%, and economic burden of 4.2 billion USD for patient care of these patients during their hospitalization stay.2

Pathophysiologically, HRS-AKI is thought to be the consequence of decreased effective arterial blood volume and relatively decreased cardiac output that result in reduced renal perfusion.1 Traditionally, the syndrome was thought to be purely functional in nature with no renal pathological changes in the kidneys. Therefore, pharmacologic treatment with Due to their ability to constrict the splanchnic vasculature with a consequent increase in renal blood flow, vasoconstrictors are used has been considered...
as the first line treatment for HRS-AKI who are in AKI ≥ stage 1b or higher, with a serum creatinine is ≥1.5 mg/dL (Box 1). The rationale of using vasoconstrictors is their ability to constrict the splanchnic vasculature, with a consequent increase in renal blood flow. Intravenous albumin infusion, 40-50 gm/d grams per day is given as an adjuvant to vasoconstrictor treatment, as albumin helps expand the plasma volume due to its oncotic properties, and provides additional beneficial effects on stabilizing the endothelium and reducing capillary permeability. Of the three available options vasconstrictors (Table 1), terlipressin is most effective as it also reduces portal pressure. Complete HRS reversal response following with terlipressin administration (decrease in serum creatinine to <1.5 mg/dL on two readings taken 12 hours apart) on HRS reversal is observed in 33-81% patients. Patients with partial response (decrease in serum creatinine by >30% from baseline but still ≥ 0.3 from baseline) should continue receiving terlipressin to be treated until complete response is achieved or for a maximum duration of 14-days. Treatment should be initiated sooner than later, as the treatment efficacy and success depends upon the baseline serum creatinine, as can be witnessed with HRS reversal rate of only 29% in the CONFIRM trial, where the mean serum creatinine was 3.5 mg/dL. Recurrence of HRS once treatment is discontinued can occur in up to 20% cases. Retreatment is usually effective and there is a potential for outpatient terlipressin infusion in improving transplant free survival of HRS patients.

Liver transplantation (LT) should be considered as a definitive treatment option for HRS with renal replacement therapy used to optimize renal function while awaiting LT (Figure 1). Patients are often maintained on bridging therapy especially renal replacement
therapy to stabilize and optimize their renal function while they are awaiting LT (Figure 1). Patients who do not respond to vasoconstrictor pharmacological therapy and are also ineligible for LT should be considered for palliative care and discussion of goals of care to improve their quality of life, especially if the renal function does not improve.7

The Challenges

First, the importance of systemic inflammation has been recently highlighted as being a key underlying mechanism, which somewhat complicates the view that HRS is purely functional and in nature. This possibly may explain abnormal renal histology why the kidneys in patients with HRS are not histologically normal in a significant proportion of cases.8 The best outcome of the patients with terlipressin would be achieved in those that have a pure form of HRS-AKI (Box 1). Recently, urinary level of neutrophil derived gelatinase associated lipocalin (NGAL) on day 3 of AKI >220 mcg/g of creatinine on day 3 of AKI has been shown to be 87% (78-95%) accurate in diagnosis of acute tubular necrosis ATN.9

Second, it is important to note that in spite although terlipressin has the potential to improved the renal function with terlipressin, short-term mortality rates are not affected as... This is possibly because HRS-AKI is often associated occurs in concert with acute on chronic liver failure (ACLF), which involving other organ failures including HRS-AKI, and is associated with 28-day mortality rates of 20-80% depending on the number of organ failures.10 Response to administration of terlipressin diminishes with increasing severity of ACLF.11 Therefore, HRS-AKI should serve as an alarm to consider referral for LT where appropriate. However, one major challenge with the use of terlipressin in this
context may be that a reduction in the serum creatinine with terlipressin would impact on their MELD score, and therefore priority on the LT list. Hence, there is a need for awareness and development of strategies for improving liver allocation to patients treated with terlipressin by considering either MELD exception points or awarding maximum points for renal function, perhaps equating them as if they are receiving dialysis.

**The pitfalls**

Terlipressin is a vasoconstrictor that achieves its effect through stimulating the vasopressin receptors on blood vessels, and therefore one needs to consider potential pitfalls with its use. The most worrying adverse effects include ischemic events resulting in digital infarction, gut ischemia, cerebral ischemia, and cardiac hypoperfusion with failure that can result in pulmonary edema. The risk of these adverse effects is higher in the elderly and those patients with a history of peripheral, cardiac, and cerebral vascular disease.¹ Therefore, a thorough work up including a careful clinical examination, an ECG and echocardiography are crucial before starting terlipressin. Due to effect of terlipressin on V2 receptors, there is a risk of hyponatremia, making monitoring of sodium levels mandatory during treatment. Terlipressin infusion instead of bolus use reduced these serious adverse events. One strategy to reduce these complications is administer terlipressin as a continuous infusion instead of as bolus. However, whether terlipressin infusion is allowed to be administered as an infusion without continuous monitoring of fluid and electrolyte balance, oxygen saturation, and cardiac status is not clear. Given the potential cardiotoxicity, the risk of pulmonary edema is an ever-present danger. It is, therefore, important to carefully monitor fluid balance, albumin levels and oxygen saturations regularly.
Given this background, it is not surprising that the terlipressin approval comes with important safety information and guidance on its use in clinical practice (https://www.mallinckrodt.com/about/news-and-media/news-detail/?id=29396). First, terlipressin should be avoided in patients with ACLF grade 3, and those with baseline hypoxemia with oxygen saturation below 90%, as it can cause serious or fatal respiratory failure in these patients. Second, it should be avoided in patients with ongoing peripheral, coronary, or mesenteric ischemia, due to risk of ischemic events. Third, further, as the development of ischemic events or respiratory failure may make potential or listed patients ineligible for LT, the benefits of terlipressin may not outweigh its risks in those with high priority for LT such as those with MELD score ≥35.

**Conclusions**

Until the recent FDA approval of terlipressin, midodrine / octreotide combination was the most frequent drug used for treatment of patients on the medical floors for HRS-AKI as noradrenaline in most centers requires placement of central line and intensive care. Availability of terlipressin in the US was long awaited and its approval and availability is an exciting news for clinicians and also for researchers as we join the bigger community in Europe and Asia in gathering more real world data on its use. Although, there will be a learning curve, hopefully the learning curve will be quick and the availability of terlipressin will complete the practice armamentarium of hepatologists in the US, to better manage patients with HRS.
**Box 1. Definition and severity classification of acute kidney injury (AKI) and diagnostic criteria of Hepatorenal Syndrome**

**AKI:** Increase in serum creatinine by ≥0.3 mg/dL within 48h from the baseline or increase in serum creatinine by ≥50% within seven days or from the baseline value. *

**Stage 1 AKI:** Increase in serum creatinine by ≥0.3 mg/dL or 1.5-2.0 folds from baseline value.

**Stage 2 AKI:** Increase in serum creatinine by >2.0 to 3.0 folds from baseline value.

**Stage 3 AKI:** Increase in serum creatinine by >3 folds from baseline value, or AKI with absolute value of ≥ 4.0 mg/dL, or AKI requiring renal replacement therapy.

**Criteria for diagnosis of hepatorenal syndrome as a cause of AKI (HRS-AKI)**

- Cirrhosis with portal hypertension and AKI
- No improvement in serum creatinine after 2 consecutive days of volume expansion

**Exclusions:**
- Shock and current or recent use of nephrotoxic drugs
- Structural kidney injury (proteinuria >500 mg/d, hematuria >50 red blood cells/high-power field)
- Urinary tract obstruction on renal ultrasound examination

*Baseline value is from the closest previous value within the previous 3 months.*
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<td>SAE: ischemia (peripheral, cardiac, cerebral)</td>
<td>Most effective in HRS reversal</td>
<td>Not effective for MELD&gt;35, high grade ACLF, and serum creatinine &gt;5 mg/dL</td>
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<td>Infusion: 2 mg/d</td>
<td>Infusion: 8 mg/d</td>
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<td>CI: Baseline</td>
<td>Improvement in transplant free survival</td>
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<td>Increase the dose on 4th day if SC &lt;30% increase</td>
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<td>SpO2&lt;90%, active ischemia, and poor cardiopulmonary status</td>
<td>Can be used on medical floor</td>
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<td>Nor-adrenaline</td>
<td>0.5 mg/h infusion</td>
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<td>SAE: ischemia (peripheral, cardiac, cerebral)</td>
<td>Simultaneous treatment of shock.</td>
<td>Needs ICU care</td>
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<td>Increase the dose every 4h if MAP increase &lt;10 mm Hg</td>
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<td>CI: Active ischemia</td>
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<td>Dose</td>
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</table>

Response is defined as **complete response** (decrease in serum creatinine to <1.5 mg/dL or to within 0.3 mg/dL of the baseline value) or **partial response** (>30% decrease with serum creatinine ≥0.3 mg/dL of the baseline value. **Non-response** is no change or worsening of serum creatinine from the pre-treatment value.
Figure 1. Proposed algorithm in the management of hepatorenal syndrome – acute kidney injury (HRS-AKI). SC: Serum creatinine; CR: Complete response; PR: Partial response; ACLF: Acute on chronic liver failure; MELD: Model for end-stage liver disease.
REFERENCES