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Terlipressin for Hepatorenal Syndrome: Opportunities, Challenges and Pitfalls

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Terlipressin for Hepatorenal Syndrome: Opportunities, Challenges and Pitfalls

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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 ofcases.[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

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.[1] 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.

Table 1 Pharmacologic treatment options for HRS-AKI

	Mechanism	Regimen	Maximum dose	Response rate*	SAE and C/I	Advantages	Disadvantages
Terlipressin	V1 receptors in vascular smooth muscle cells	Bolus: 0.85 mg every 6 h. Infusion: 2 mg/d Increase the dose on 4th day if SC <30% increase	Bolus: 1.7 mg every 6 h. Infusion: 8 mg/d	20-81% across 14 randomized controlled trials	SAE: Ischemia (peripheral, cardiac, cerebral) CI: Baseline SpO2<90%, active ischemia, and poor cardiopulmonary status	Most effective in HRS reversal Improvement in transplant free survival Can be used on medical floor	Not effective for MELD>35, high grade ACLF, and serum creatinine >5 mg/dL
Nor-adrenaline	α-adrenergic receptors in vascular smooth muscle cells	0.5 mg/h infusion Increase the dose every 4h if MAP increase <10 mm Hg	3 mg/h infusion	19-83% across 8 randomized controlled trials	SAE: Ischemia (peripheral, cardiac, cerebral) CI: Active ischemia	Simultaneous treatment of shock.	Needs ICU care

Midodrine	α-1 adrenergic receptors	5 mg 3 times/d orally	15 mg 3 times/d orally	5% in one and 20% in another randomized controlled trial with midodrine and octreotide combination	Hypertension	Safety profile Oral use Can be used on medical floor	Cannot be used alone Low efficacy
Octreotide	Binds somatostatin receptors to inhibit release of splanchnic vasodilator peptides	100 mcg s/c injection 3 times/d	200 mcg s/c injection 3 times/d	5% in one and 20% in another randomized controlled trial with midodrine and octreotide combination	Safe and no major SAE	Safety profile Simultaneous treatment of variceal bleed Can be used on medical floor	Cannot be used alone Low efficacy Subcutaneous or IV route

*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.*

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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.*

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)

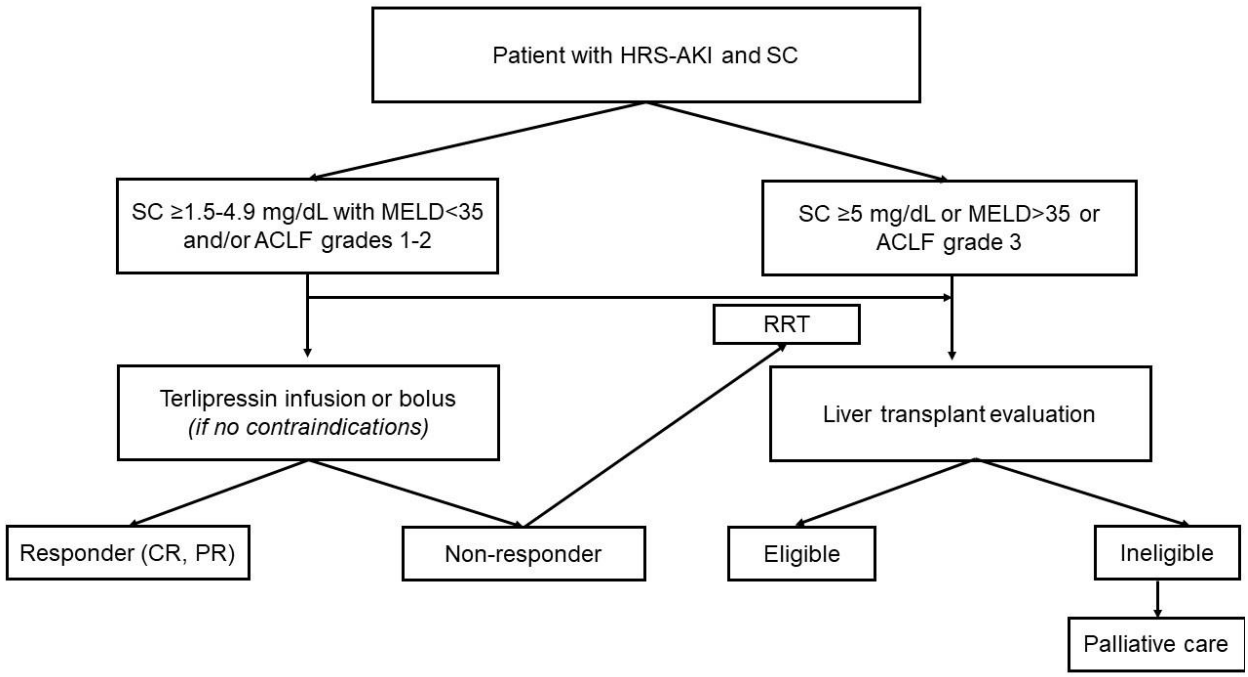
Cirrhosis with portal hypertension and AKI

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. 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: ICJME 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.

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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 wa~~i~~s 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 results~~culminates~~ in reduced renal perfusion.[1] Traditionally, the syndrome was thought to be purely functional in nature with no renal pathology~~ical 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, 40-50gm/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.[1] Of the three available ~~options~~ vasoconstrictors (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.[4] 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.[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 (Figure 1).[6] ~~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~~ing~~ to vasoconsctrictors~~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,~~ T~~t~~he importance of systemic inflammation ~~has been~~ is 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~~s~~ 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 m~~n~~cg/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~~ improve~~d 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 involve~~sing~~ 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 terpliressin~~ in this

context may be that a reduction in the serum creatinine with terlipressin would impact ~~on their~~ the 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 ~~it~~ 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 avoidedand those in patients with ongoing peripheral, coronary, or mesenteric ischemia, due to risk of ischemic events. ThirdFurther, 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[12] 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. Although, there will be a learning curve, hHopefully the learning curveis 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

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**Baseline value is from the closest previous value within the previous 3 months.*

Table 1 Pharmacologic treatment options for HRS-AKI

	Mechanism	Regimen	Maximum dose	Response rate*	SAE and C/I	Advantages	Disadvantages
Terlipressin	V1 receptors in vascular smooth muscle cells	Bolus: 0.85 mg every 6 h. Infusion: 2 mg/d Increase the dose on 4th day if SC <30% increase	Bolus: 1.7 mg every 6 h. Infusion: 8 mg/d	20-81% across 14 randomized controlled trials	SAE: Ischemia (peripheral, cardiac, cerebral) CI: Baseline SpO2<90%, active ischemia, and poor cardiopulmonary status	Most effective in HRS reversal Improvement in transplant free survival Can be used on medical floor	Not effective for MELD>35, high grade ACLF, and serum creatinine >5 mg/dL
Nor-adrenaline	α-adrenergic receptors in vascular smooth muscle cells	0.5 mg/h infusion Increase the dose every 4h if MAP increase <10 mm Hg	3 mg/h infusion	19-83% across 8 randomized controlled trials	SAE: Ischemia (peripheral, cardiac, cerebral) CI: Active ischemia	Simultaneous treatment of shock.	Needs ICU care

Midodrine	α-1 adrenergic receptors	5 mg 3 times/d orally	15 mg 3 times/d orally	5% in one and 20% in another randomized controlled trial with midodrine and octreotide combination	Hypertension	Safety profile Oral use Can be used on medical floor	Cannot be used alone Low efficacy
Octreotide	Binds somatostatin receptors to inhibit release of splanchnic vasodilator peptides	100 mcg s/c injection 3 times/d	200 mcg s/c injection 3 times/d	5% in one and 20% in another randomized controlled trial with midodrine and octreotide combination	Safe and no major SAE	Safety profile Simultaneous treatment of variceal bleed Can be used on medical floor	Cannot be used alone Low efficacy Subcutaneous or IV route

*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.*

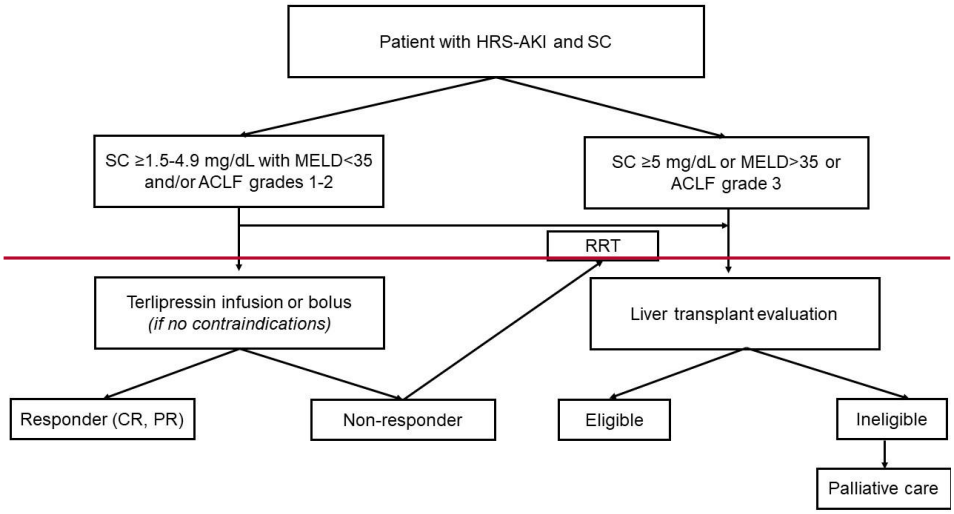

Figure 1 Proposed algorithm in the management of hepatorenal syndrome – acute kidney injury (HRS-AKI). *SC: Serum creatinine; CR: Complete response; PR: Partial response; ACLF: Acute on chronic liver failure; MELD: Model for end-stage liver disease.*

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