ADVANCING GI PATIENT CARE 2022

Powered by: GI Alliance

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SOUTHLAKE, TEXAS

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GI Alliance

IRMCHCS
Rehoboth McKinley Christian Health Care Services

Hepatorenal Syndrome

Steven L. Flamm MD
Chief, Hepatology
Professor of Medicine
Northwestern Feinberg School of Medicine

Disclosures

- Consultant: AbbVie, Gilead, Intercept, Mallinckrodt, Salix
- Research: Direct Pharmaceuticals

HRS-AKI Case

- 59 yo male with NASH and decompensated cirrhosis
- Listed for liver transplant
- History of ascites, HE, esophageal varices with prior bleeding
- Labs 12 weeks ago in clinic: Na 136, Cr 1.3, bilirubin 2.0, INR 1.30, $MELD_{NA}$ 15
- Admitted to the hospital with worsening confusion

HRS-AKI Case (Cont)

- Worsening ascites over the past 3 months despite sodium restriction
- Diuretics recently increased to furosemide 80 mg daily, spironolactone 100 mg daily
- Now requiring therapeutic paracentesis every week (last 5 days ago)
- Takes lactulose and rifaximin for HE
- Takes propranolol for variceal bleeding prophylaxis

HRS- AKI Case (Cont)

- On admission he is awake but disoriented with + asterixis
- Initial BP 102/54 (MAP 70), HR 78, T 37.7C, RR 18, SpO2 95% on ambient air
- Exam shows a distended abdomen, mild tenderness to palpation
- Labs now: Na 130, Cr 1.7, Bili 4.5, INR 2
- Ascites WBC 500 (76% PMNs), Blood cx pending; MELD-Na 29
- Oliguric and urine studies show Na <10 and UA with no protein or cells

Acute Kidney Injury (AKI) in Cirrhosis

- Traditional criteria (International Club of Ascites criteria)[1]
  - 50% increase in SCr over baseline
  - Cut-off value of SCr: 1.5 mg/dL
- New definition of AKI[2]
  - ↑ in SCr ≥0.3 mg/dL within 48 hours

  or

  - ↑ SCr ≥50% from baseline that is known or presumed to have occurred within the prior 7 days

Stage AKI[1]	Criteria
Stage 1	Increase in SCr ≥0.3 mg/dL or an increase in SCr ≥1.5-fold to 2-fold from baseline
Stage 2	Increase in SCr >2- to 3-fold from baseline
Stage 3	Increase of SCr >3-fold from baseline or SCr ≥4.0 mg/dL with an acute increase ≥0.3 mg/dL or initiation of renal replacement therapy

1. Arroyo V. et al. *Hepatology*. 1996; 23: 164-176; 2. Angeli P et al. *J Hepatol*. 2015;62:968-974; *J Hepatol*. 2018;69:406-460.

AKI in Cirrhosis: Differential Diagnosis

- Prerenal
  - Hypovolemia: diuretics, GI bleeding, diarrhea
  - *Hepatorenal syndrome*
- Intrinsic renal disease
  - Acute tubular necrosis
  - Glomerulonephritis
  - Interstitial nephritis
- Obstructive

Graupera I et al. *Clin Liver Dis*. 2013;2:128-131.

AKI in Cirrhosis: When Is It HRS?

- Diagnosis of exclusion in patients with cirrhosis AND ascites
- Diagnosis of AKI according to **International Club of Ascites –** AKI criteria
- No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin (1 g per kg of body weight, 100g max)
- Absence of shock
- No current or recent use of nephrotoxic drugs
- No macroscopic signs of structural kidney injury defined as:
  - Absence of proteinuria (>500 mg/day)
  - Absence of hematuria (>50 RBCs/hpf)
  - Normal findings on renal ultrasonography

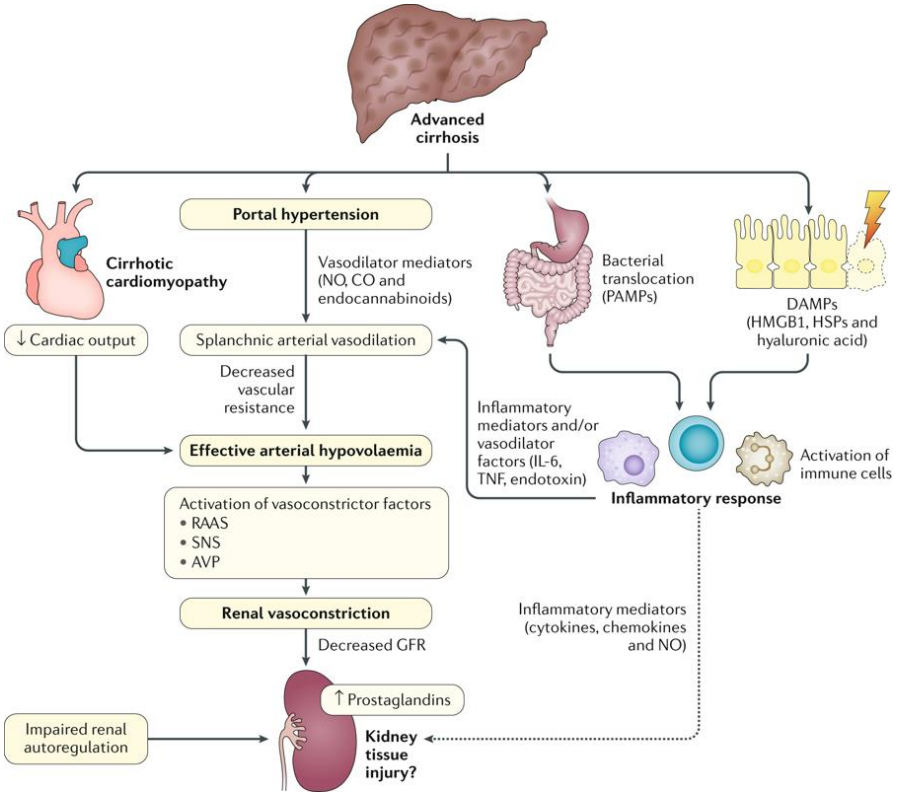
Angeli et al. *Journal of Hepatology*. 2015 vol. 62 968–974.

Revised HRS Definitions and Criteria: No More Type 1 and Type 2

Old classification	New classification	Criteria
HRS-1*	HRS-AKI	a) Absolute increase in sCr ≥0.3 mg/dl within 48h and/*or* b) Urinary output ≤0.5 ml/kg B.W. ≥6h* *or* c) Percent increase in sCr ≥50% using the last available value of outpatient sCr within 3 months as the baseline value
HRS-2*	HRS-NAKI: HRS-AKD	a) eGFR <60 ml/min per 1.73 m^2 for <3 months in the absence of other (structural) causes b) Percent increase in sCr <50% using the last available value of outpatient sCr within 3 months as the baseline value c) eGFR <60 ml/min per 1.73 m^2 for ≥3 months in the absence of other(structural) causes
	HRS-NAKI: HRS-CKD	

Angeli P et al. *J Hepatol*. 2019; 71:811.

Pathogenesis of AKI-HRS



Ginès P et al. *Nat Rev Dis Primers*. 2018;4:23.

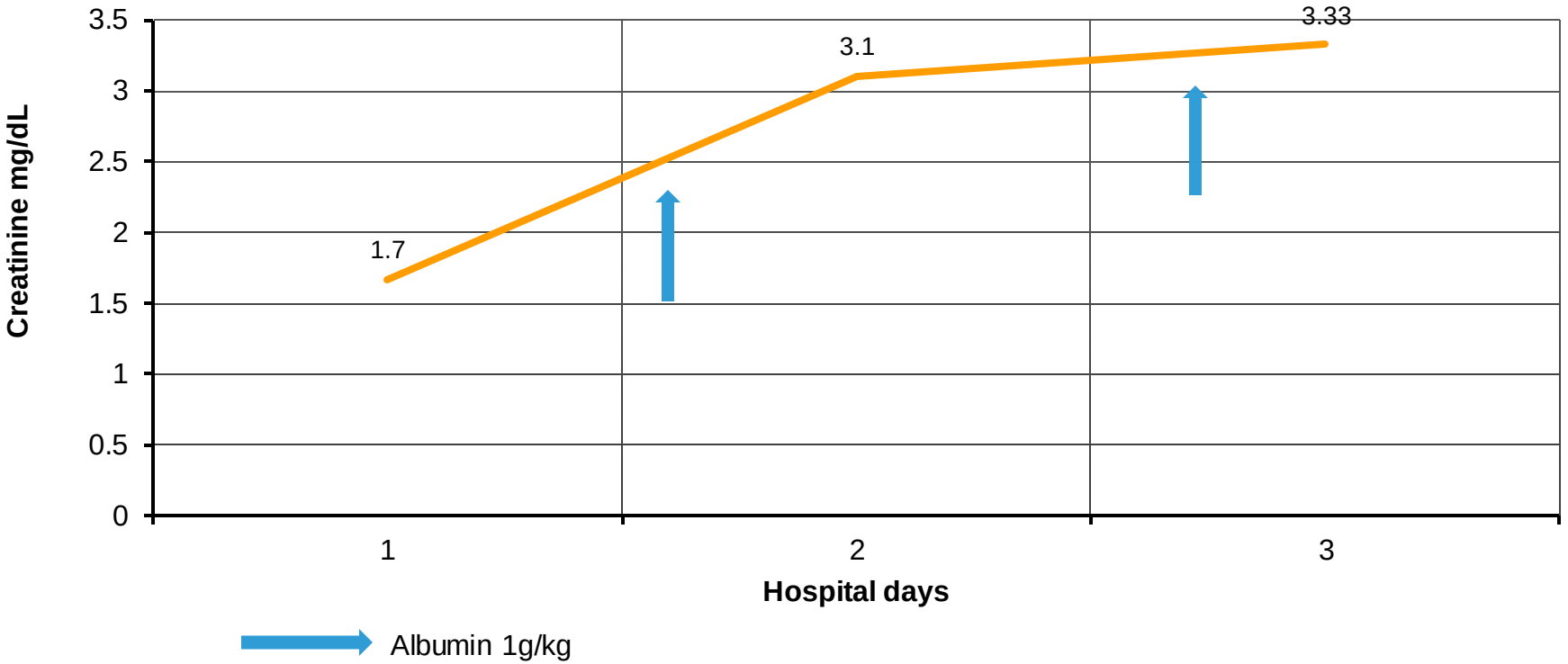
HRS-AKI Case

- Diagnosis
  - AKI (Stage 1)
  - Hepatic Encephalopathy (Stage 2)
  - Spontaneous Bacterial Peritonitis
  - Acute on Chronic Liver Failure (renal, CNS and coagulation)

HRS-AKI Case

- Doppler US of abdomen shows moderate ascites, no liver masses, no hydronephrosis, no thrombosis, and normal appearing kidneys
- Repeat BP is 88/52 (MAP 64), HR 108
- Started on IV ceftriaxone
- IV albumin infused (1 gm/kg) X 2 days
- Furosemide, spironolactone, and propranolol are discontinued
- Lactulose and rifaximin are continued

HRS-AKI Case – Renal Function

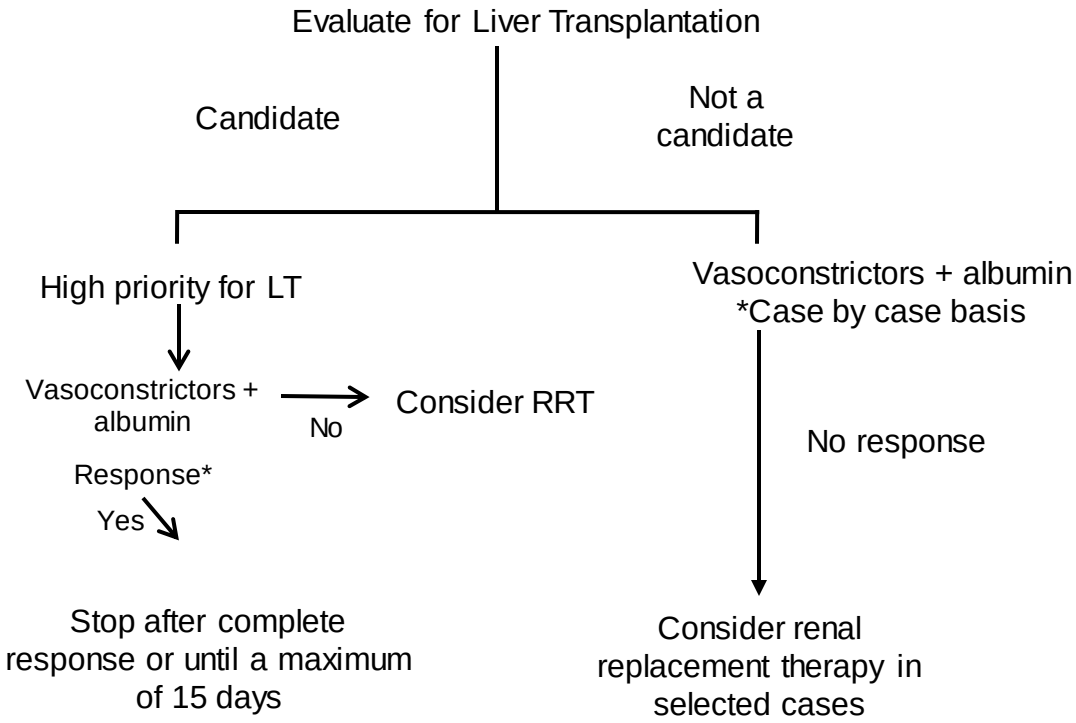


Nonpharmacologic Therapy

- Liver transplantation
  - Definitive treatment
  - Timely transplantation optimal for renal recovery
  - Consider simultaneous liver-kidney transplantation if HRS is persistent

European Association for the Study of the Liver. *J Hepatol.* 2018;69:406-460.

Hepatorenal Syndrome



Options Assuming Medications Are Available

A. Transfer to ICU, begin dopamine

B. Begin midodrine 7.5 mg TID, octreotide 100 mcg SC TID

C. Continue IV albumin 1 gm/kg/24h

D. Continue IV albumin 1 gm/kg/24h, introduce terlipressin

AKI-HRS Treatment Desired Outcomes

- **Less RRT**
  - Improve RRT-free survival
- **Facilitate medical management**
- **Potential to return to compensated state**
- **Shorter ICU stays**
- **Liver transplant patients**
  - Less RRT
  - Improved survival

Pharmacologic Therapy for AKI-HRS

IV Albumin

- 0.5-1gm/kg (max 100 gm/d) for resuscitation; then
- 25 to 50 g/day

Plus

Vasoconstrictors

- Midodrine (+/- octreotide)
- Norepinephrine
- Terlipressin

Ginès P et al. *Nat Rev Dis Primers*. 2018;4:23.

AASLD Recommendations Regarding Vasoconstrictor Treatment in HRS

Therapeutic Strategy	AASLD Recommendation
Midodrine/octreotide plus albumin	Is of much lower efficacy than terlipressin
Norepinephrine plus albumin	Given as continuous IV infusion, typically in an ICU setting Appears to be equally effective to terlipressin, although there are fewer data
Terlipressin plus albumin	Currently under review by the US FDA The CONFIRM study demonstrates that terlipressin, in combination with albumin, is associated with higher likelihood of reversal of HRS and 10-day survival without RRT compared with placebo (29.1% vs. 15.8%, P = 0.012).

AASLD, American Association for the Study of Liver Diseases
Biggins SW et al. *Hepatology*. 2021;74:1014-1048.

HRS 2018 EASL Guidelines

EASL 2018 guidelines

First line therapy: Terlipressin + albumin

- Not available in the United States and Canada

Noradrenaline can be an alternative to terlipressin

- Requires central venous line and generally ICU

Midodrine + octreotide if terlipressin or noradrenaline unavailable

- Efficacy lower

Albumin 20 to 40 g/day

- Dose not well established
- Ideally, monitor CVP and titrate dose

EASL. *J Hepatol*. 2018;69:406-460.

How Do We Define Response to Treatment?

Complete response

Final SCr **within 0.3 mg/dL** of the baseline value

Partial response

Regression of AKI stage to a final SCr **≥0.3 mg/dL** above baseline value

- In cases of recurrence of HRS-AKI upon treatment cessation, repeat course of therapy

EASL. *J Hepatol*. 2018.

Midodrine and Octreotide

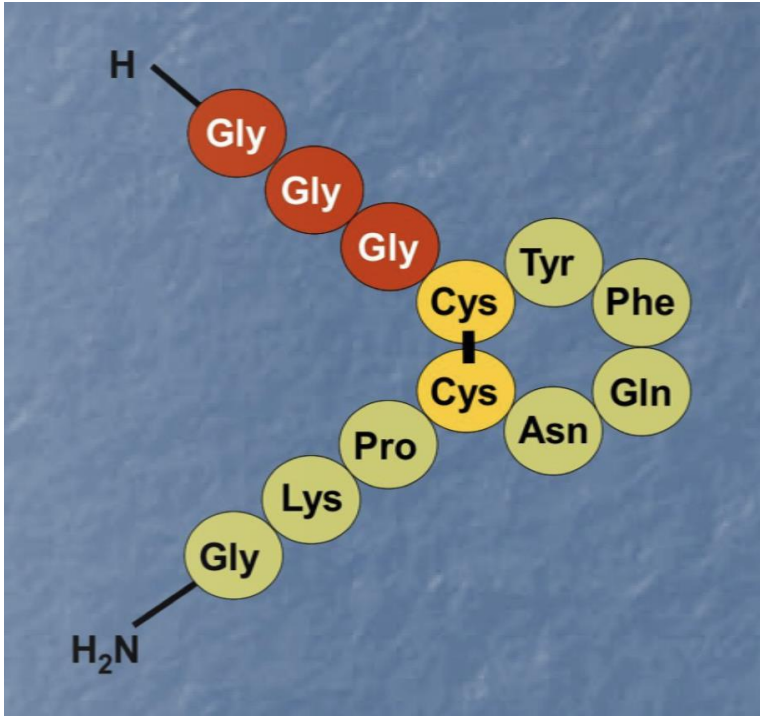
Midodrine

- Midodrine binds to alpha-1-adrenergic receptors
  - Improves systemic blood pressure and hence improves renal perfusion pressure
- Start at 7.5 mg TID
- Titrate midodrine up to 15 mg TID on consecutive doses to a mean arterial pressure of >80 mmHg

Octreotide

- Octreotide is a splanchnic vasoconstrictor that antagonizes the action of various splanchnic vasodilators
  - Not effective alone
- Start octreotide 100-200 mcg TID or IV infusion 50 mcg/hr to raise MAP by 15 mm Hg
- Maximum dose 200 mcg SC TID

Terlipressin (Not Available in US)



- Approved in many ex-US countries for years
- Synthetic 12 amino acid peptide
- Pro-drug
- Constrictive activity via V-1 receptors
  - Vascular and extra vascular smooth muscle cells
- Splanchnic vasoconstriction reduces portal blood flow and portal pressure
- Systemic vasoconstriction
  - Increases effective blood volume
  - Reduces renin and angiotensin
    - Can lead to renal vasodilation
    - Can lead to improvement in serum creatinine
- V-2 agonist activity
  - Could possibly cause hyponatremia

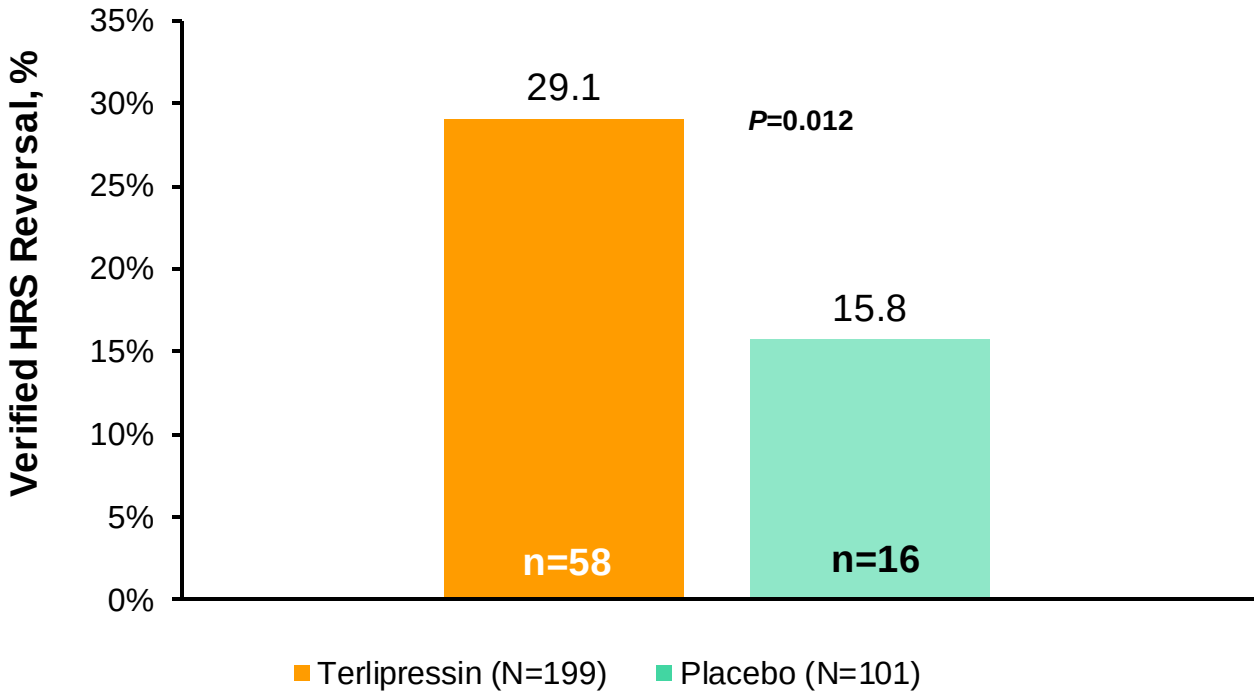
*FDA Complete Response Letter issued September 12, 2020

Terlipressin + Albumin vs Albumin Alone for HRS-1 (CONFIRM Study)

- Randomized, placebo-controlled study in 300 patients
- 2:1 to terlipressin (1 mg IV every 6 hours) or placebo, plus albumin in both groups
- Treatment for up to 14 days unless one of the following occurred:
  - Verified HRS reversal (VHRSR) (decrease in SCr to ≤1.5 mg/dL)
  - Renal replacement therapy (RRT)
  - Liver transplantation (LT) or
  - SCr at or above baseline (BL) at Day 4
- Primary Endpoint
  - VHRSR defined as 2 consecutive SCr values ≤1.5 mg/dL, at least 2 hours apart, with patient alive without RRT for ≥10 days after the second SCr ≤1.5 mg/dL

Wong F et al. *The Liver Meeting*. 2019. Boston, MA. Abstract LO5.

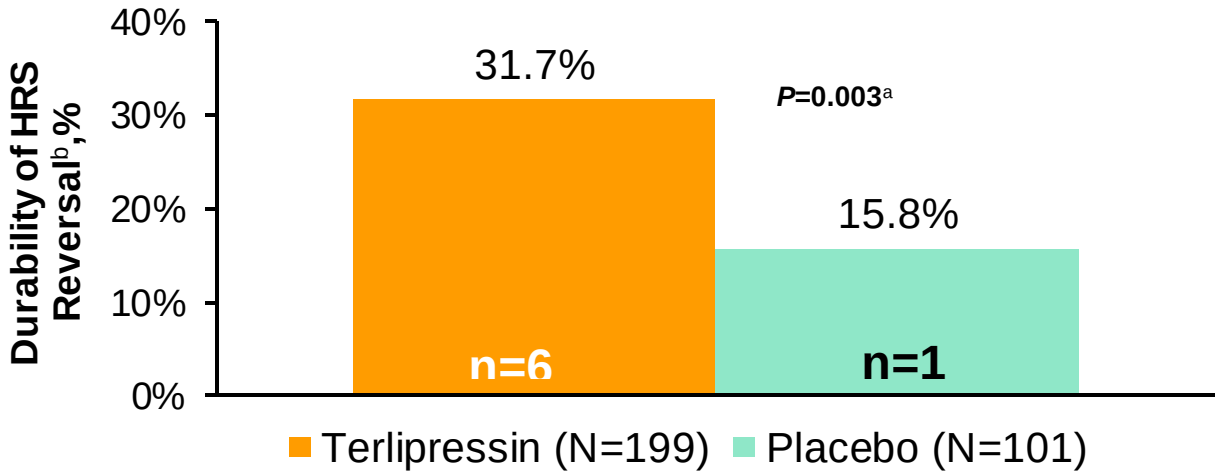
Primary Endpoint: Verified HRS Reversal (CONFIRM Study)



Z score=2.52618. The final analysis is successful if the score is >1.97743.

Wong F et al. *The Liver Meeting*. 2019. Boston, MA. Abstract LO5.

Secondary Endpoint: Durability of HRS Reversal (CONFIRM Study)



[a]From a CMH Test stratified by qualifying serum creatinine (<3.4 vs ≥3.4 mg/dL) and prior LVP within 14 days of randomization (at least one single event of ≥4 vs <4 L).

[b]Percentage of subjects with HRS reversal without RRT to day 30.

Wong F et al. *The Liver Meeting*. 2019. Boston, MA. Abstract LO5.

Incidence of Adverse Events (>10% Terlipressin Patients) (CONFIRM Study)

Preferred Term[a]	Terlipressin (N=200)[b] % (n)	Placebo (N=99)[b] % (n)
Abdominal pain	19.5 (39)	6.1 (6)
Nausea	16.0 (32)	10.1 (10)
Diarrhea	13.0 (26)	7.1 (7)
Dyspnea	12.5 (25)	5.1 (5)
Respiratory failure	10.5 (21)	5.1 (5)
Hepatic encephalopathy	10.0 (20)	13.1 (13)

Respiratory Failure higher in both cohorts in CONFIRM than REVERSE trial;
REVERSE T 5.4% vs P 2.1%; none of the respiratory failure were reported as related to study drug.

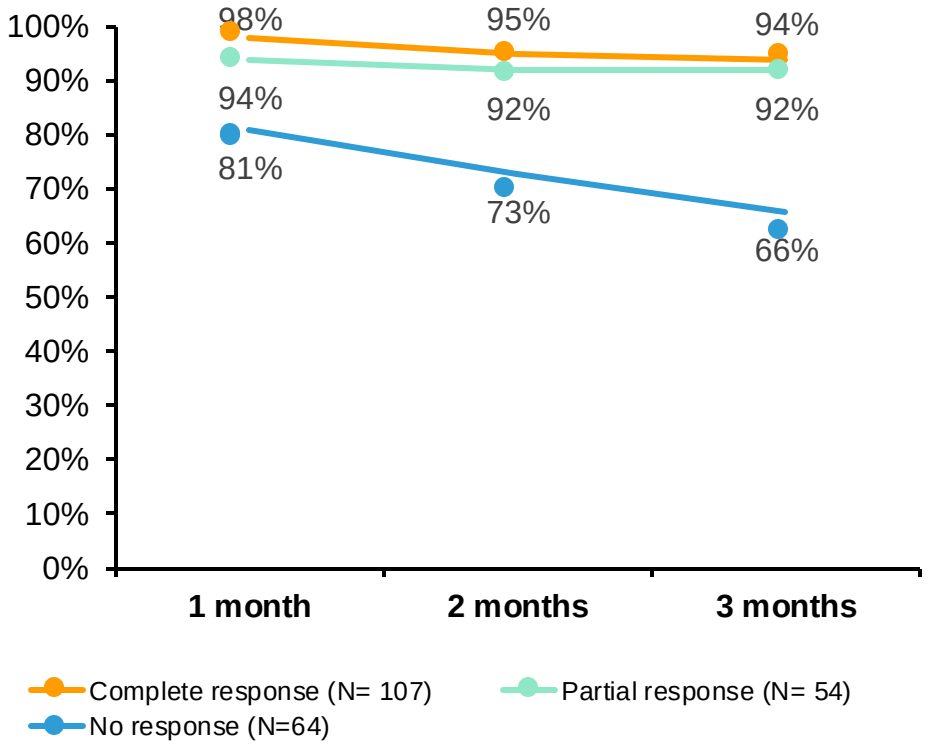
AEs, adverse events; N, number of subjects in the treatment group; n, number of subjects in the category of subjects in the treatment group.
[a]Up to 7 days posttreatment. [b]Subjects experiencing multiple episodes of a given adverse event are counted once within each preferred term.
Wong F et al. *The Liver Meeting*. 2019. Boston, MA. Abstract LO5.

Terlipressin Response Across AKI Severity

	By treatment group (N=225)			By AKI severity, terlipressin treated patients (N= 203)[d]			
	Terlipressin (N=203)	Other vasopressor[b] (N=22)	*P* value[c]	Mild (N=67)	Moderate (N=73)	Severe (N=63)	*P* value[e]
Pre-treatment SCr (mg/dL), mean (SD)	3.23 (1.70)	3.38 (1.11)	0.071	1.84 (0.27)	2.85 (0.41)	5.17 (1.73)	<0.001
SCr ar end of therapy, mean (SD)[a]	2.34 (1.87)	2.17 (0.72)	0.091	1.39 (0.84)	1.96 (1.37)	3.80 (2.27)	<0.001
Change in SCr, mean (SD)	0.89 (1.77)	1.22 (1.24)	0.569	0.44 (0.89)	0.90 (1.40)	1.37 (2.58)	<0.001
Complete response, N (%)	102 (50.2)	5 (22.7)	0.014	53 (79.1)	40 (54.8)	9 (14.3)	<0.001
Overall response (complete or partial, N (%)	148 (72.9)	13 (59.1)	0.172	53 (79.1)	57 (78.1)	38 (60.3)	0.025
Time to response in days, median (95% CI)	8 (8, 11)	11 (4, 11)	0.230	7 (5, 8)	8 (6,8)	9 (7, 11)	<0.001

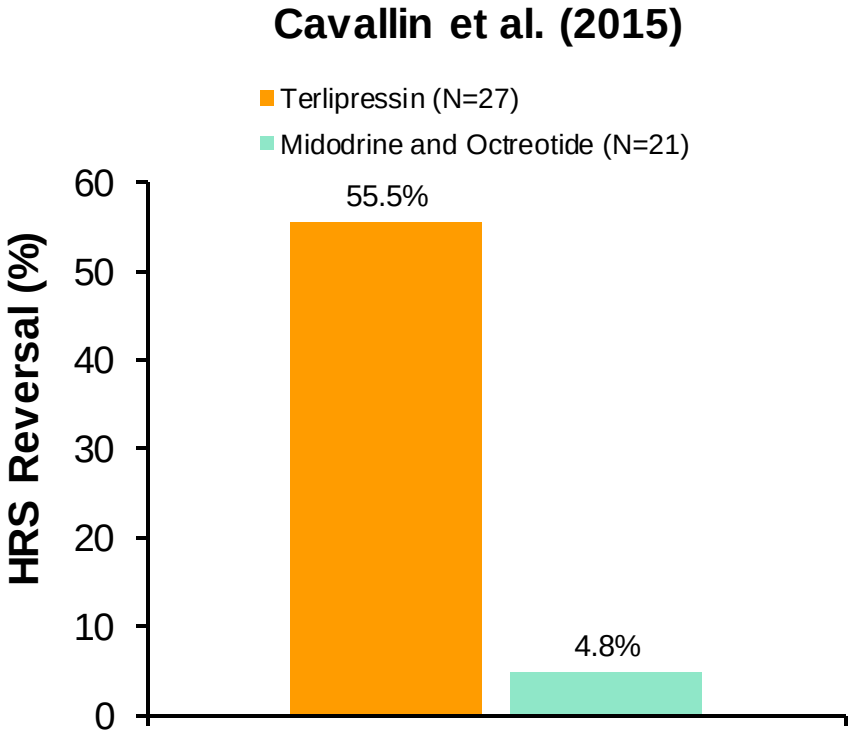
Moore K et al. *Aliment Pharmacol Ther*. 2020 Jun 4. doi: 10.1111/apt.15836.

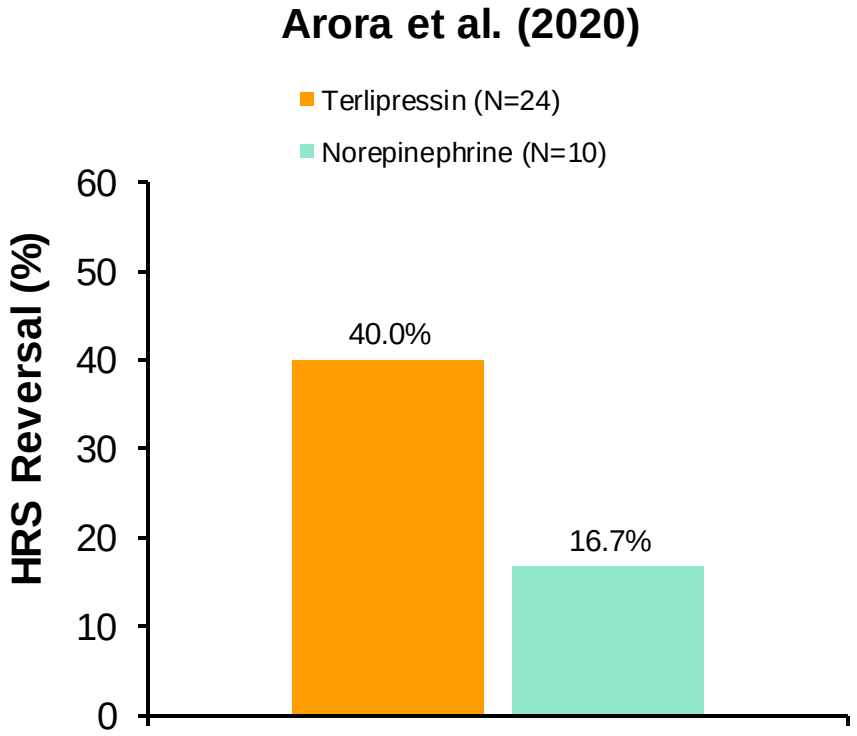
Terlipressin: Renal Response and Survival



Moore K et al. *Aliment Pharmacol Ther*. 2020 Jun 4. doi: 10.1111/apt.15836.

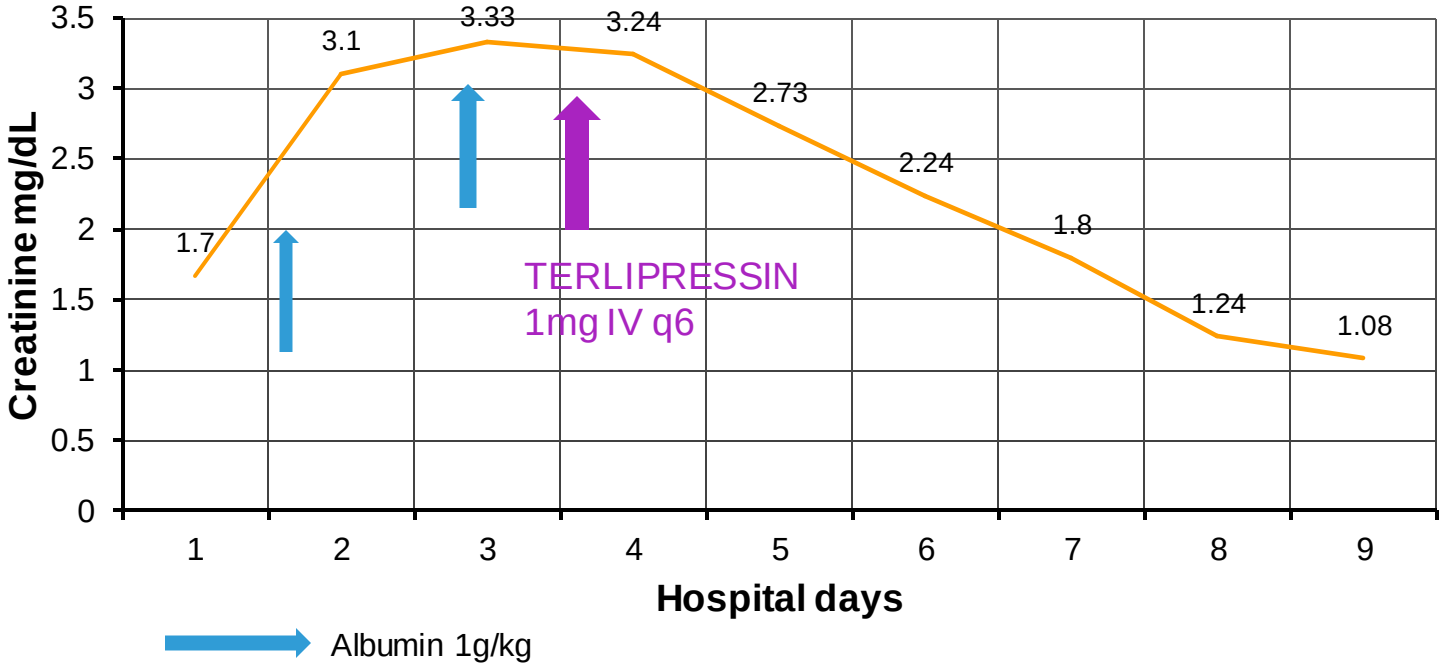
Vasoconstrictors Available in US vs Terlipressin





Cavallin M et al. *Hepatology*. 2015;62:567-574; Arora V et al. *Hepatology*. 2020.

HRS-AKI Case Renal Function



Prevention of AKI-HRS in Patients With Cirrhosis

- Avoid NSAIDs
- Avoid ACE inhibitors
- Decrease/withdraw diuretics when decompensated
- Limiting lactulose dose to accomplish 2-3 BMs per day
- Threshold at which to discontinue beta-blockers?
- Maintain mean arterial pressure (MAP)
- IV Albumin in the setting of SBP

Tapper EB et al. *Am J Med*. 2016; 129: 461-467.

Take Home Points

- HRS is defined as AKI that does not respond to volume resuscitation upon correction of sepsis and in the absence of other nephrotoxic insult
- Current classification expedites the recognition of HRS-AKI and allows for potential earlier intervention
- Vasoactive agents (terlipressin and norepinephrine) can reverse HRS-AKI in a significant percentage of patients and are more effective than midodrine and octreotide
- Terlipressin is superior to other agents in reversing HRS with expected survival benefits
  - Phase 3 CONFIRM US study results now available