Hepatorenal Syndrome Treatment in the US Today

Nikolaos T. Pyrsopoulos MD, PhD, MBA
Professor and Chief
Department of Medicine
Division of Gastroenterology and Hepatology
Rutgers NJMS
Medical Director Liver Transplantation
University Hospital

Disclosures

- Financial: Grifols, Durect, Salix, AbbVie, Gilead, Prometheus, Mallinckrodt, Novartis

Introduction

- Kidney dysfunction is a common complication in cirrhosis
  - Occurs in between 20-40% of patients with cirrhosis and ascites admitted with decompensation
- Oftentimes, kidney failure is functional
  - No structural abnormalities of the kidney identified
  - Changes primarily due to hemodynamic effects associated with cirrhosis
- Traditionally, Hepatorenal Syndrome (HRS) described as the most severe form of functional kidney disease
  - Not responsive to fluid challenge

Wong F et al. Recent advances in our understanding of hepatorenal syndrome. *Nat Rev of Gastroenterol Hepatol.* 2012. 9:382-391; Adebayo D et al. Ascites and Hepatorenal syndrome. *Clin Liv Dis.* 2019. 23:659-682.

Definition

- The occurrence of renal failure in a patient with advanced liver disease in the absence of an identifiable cause of renal failure
- Definition may be changing

Gines P et al. EASL clinical practice guidelines in the management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome in cirrhosis*. Journal of Hepatology.* 2010. *53:397-417.*

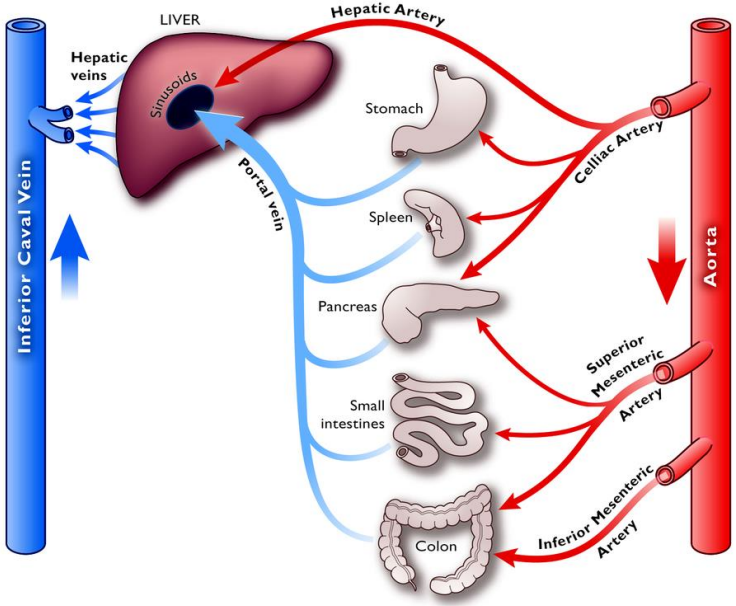
Pathophysiology

- Pathophysiology of HRS is currently described via 2 main hypotheses:
  - Peripheral arterial vasodilation
  - Systemic inflammation/SIRS
    - Splanchnic vasodilatation
    - Activation of vasoconstrictor mechanisms (SNS, RAAS, ADH)
      - Ascites/edema/hyponatremia
    - Cirrhotic cardiomyopathy

Gines P et al. EASL clinical practice guidelines in the management of ascites, spontaneous bacterial peritonitis and hepatorenal syndrome in cirrhosis*. Journal of Hepatology.* (2010) *53:397-417;* Adebayo D et al. Ascites and Hepatorenal syndrome. *Clin Liv Dis.* 2019. 23*:659-682.*

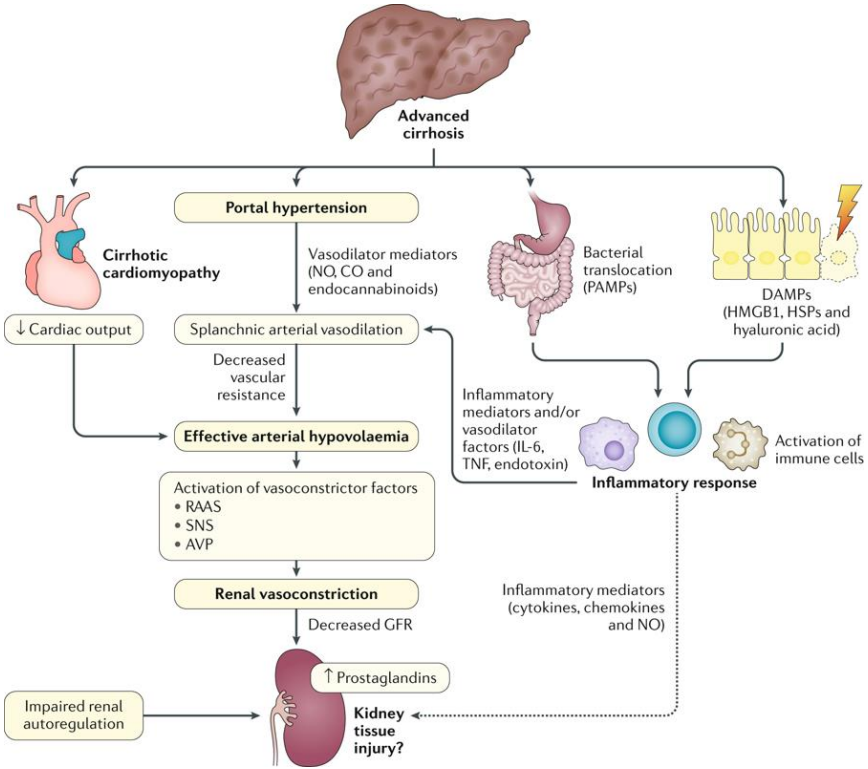
Pathophysiology

Splanchnic Circulation



anesthesiology.pubs.asahq.org.

Pathogenesis of AKI-HRS



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

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. Angeli P et al. *J Hepatol.* 2015;62:968-974; 2. *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

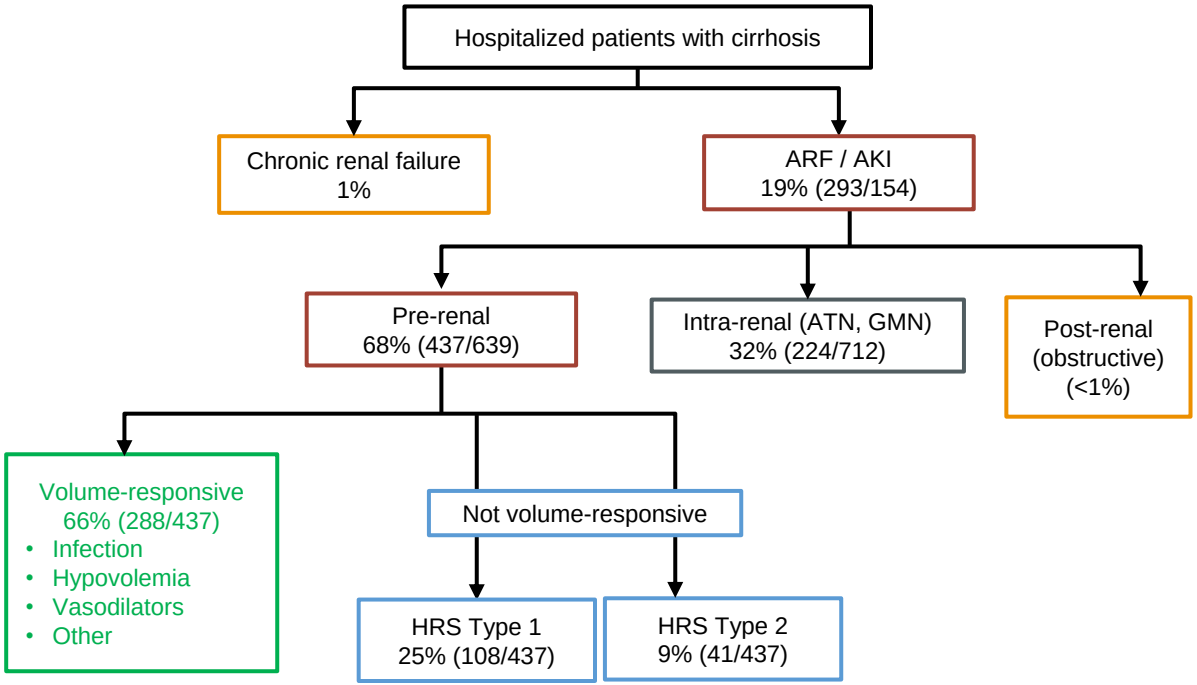
Graupera I et al. *Clin Liver Dis*. 2013;2:128-131.

AKI in Cirrhosis and 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.

Etiology of AKI in Cirrhosis



Garcia-Tsao et al. *Hepatology*. 2008.

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)

Albumin

- 50% of plasma proteins
  - Liver produces it, 10-15 g/day
  - 30%-40% remains in the intravascular space
- Structurally:
  - 67 kDa in size, 609 amino acids
  - Charge is net negative (pH 7)
  - Circulates in net reduced form
  - Albumin has heart-shaped tertiary structure with high α-helical content

Garcia-Martinez R et al. *Hepatology*. 2013;58:1836-1846.

Pharmacologic Therapy for AKI-HRS

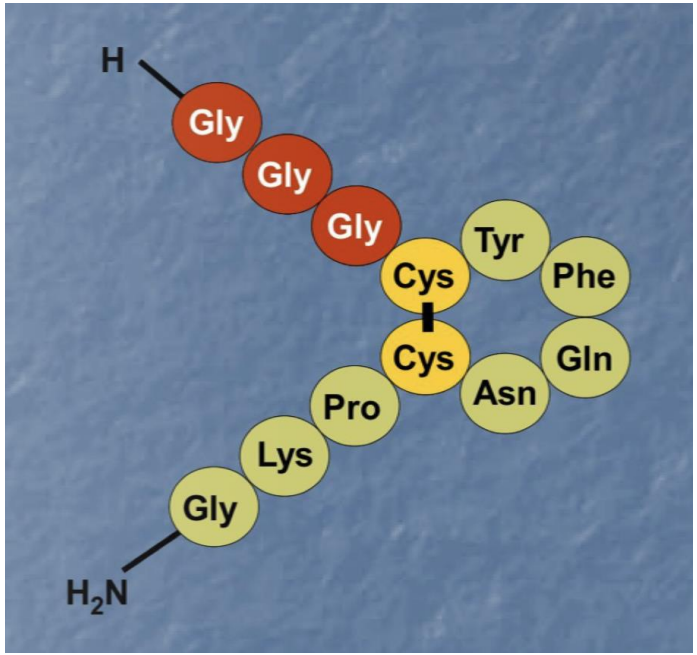
- IV Albumin
  - 0.5-1gm/kg (max 100 gm/d) for resuscitation; then
  - 25 to 50 g/day

Plus

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

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

Terlipressin: Recently Approved in the US



- Widely studied (more than 70 published manuscripts and presented abstracts on clinical data)
- Approved outside the U.S. for more than 30 years and available on five continents
- 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

AASLD and ACG Guidelines: Vasoconstrictor Dosing and Administration for HRS-AKI

Drug	AASLD Dosing and Administration Recommendations[1]
Terlipressin	**Vasoconstrictor of choice for treating HRS-AKI (unapproved in the US at the time this guidance was written*)**
Norepinephrine	**Recommended when terlipressin is not available/cannot be administered** **Continuous IV infusion starting at 0.5 mg/h to achieve an increase in mean arterial pressure of at least 10 mmHg or an increase in urine output of > 200 mL/4 h** **If at least one of these goals is not achieved, increase every 4 h in increments of 0.5 mg/h up to a maximum of 3 mg/h**
Oral midodrine in combination with octreotide	**Recommended when terlipressin and norepinephrine are not available/cannot be administered** **Midodrine 5–15 mg po every 8 h plus octreotide 100–200 µg every 8 h or 50 µg/h via IV**

The **ACG** also suggests that terlipressin or norepinephrine be administered to hospitalized patients with cirrhosis and HRS-AKI without high grade of ACLF or disease.[2]

*Terlipressin was approved in the US on September 14, 2022.

1. Biggins SW et al. Hepatology. 2021;74:1014-1048; 2. Bajaj JS et al. Am J Gastroenterol. 2022;117:225-252.

Terlipressin: Indications, Usage and Black-Boxed Warning

- Indicated to improve kidney function in adults with HRS with rapid reduction in kidney function
- Patients with a serum creatinine >5 mg/dL are unlikely to experience benefit

WARNING: SERIOUS OR FATAL RESPIRATORY FAILURE

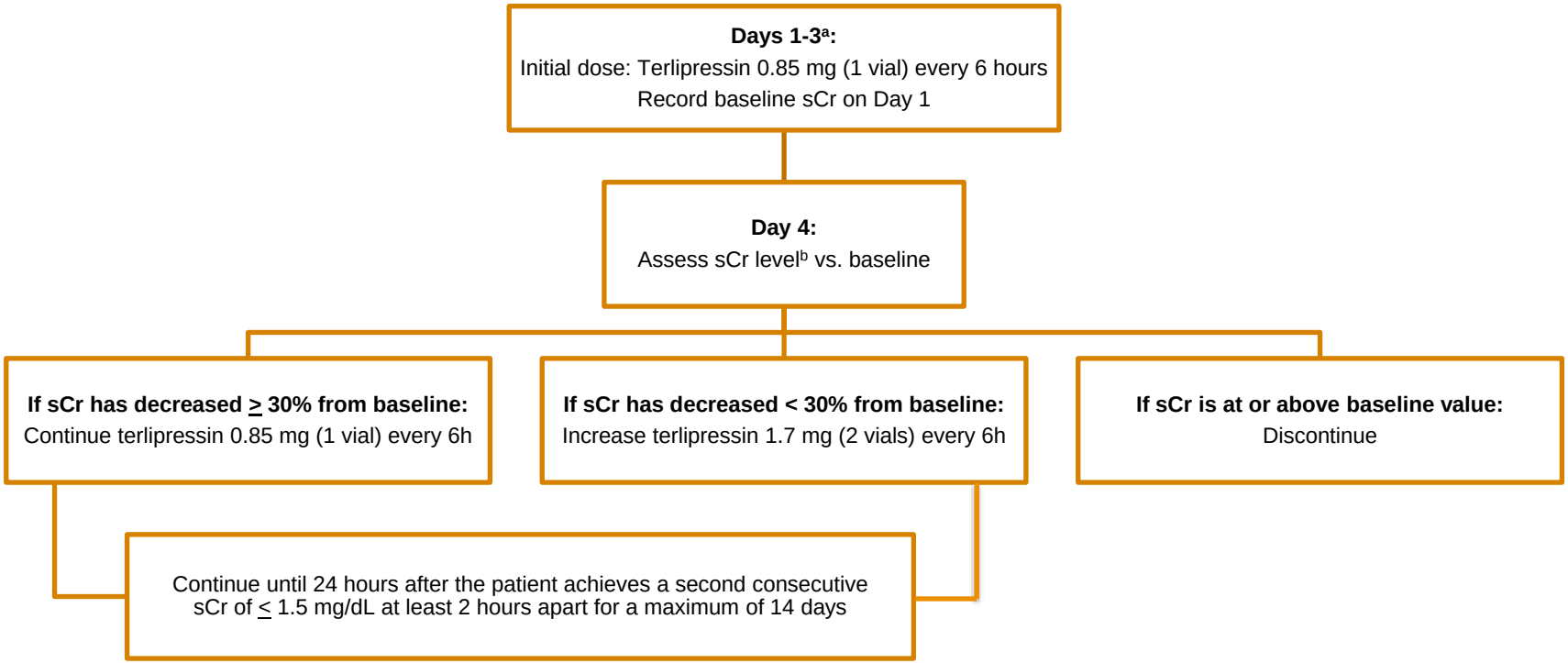
Terlipressin may cause serious or fatal respiratory failure. Patients with volume overload or with ACLF Grade 3 are at increased risk. Assess oxygenation saturation (e.g., SpO2) before initiating terlipressin.

Do not initiate terlipressin in patients experiencing hypoxia (e.g., SpO2 <90%) until oxygenation levels improve. Monitor patients for hypoxia using continuous pulse oximetry during treatment and discontinue terlipressin if SpO2 decreases below 90%

ACLF, acute-on-chronic liver failure

Terlivaz (terlipressin) [package insert]. Bedminster, NJ: Mallinckrodt Pharmaceuticals Inc.; 2022

Terlipressin: Dosing and Administration



h, hours; sCr, serum creatinine

[a]Prior to initial dosing, assess patients for ACLF Grade 3 and obtain patient baseline oxygenation level. Monitor patient oxygen saturation with pulse oximetry.

[b]Baseline sCr is the last available sCr before initiating treatment

Terlivaz (terlipressin) [package insert]. Bedminster, NJ: Mallinckrodt Pharmaceuticals Inc.; 2022

Midodrine and Octreotide

Midodrine

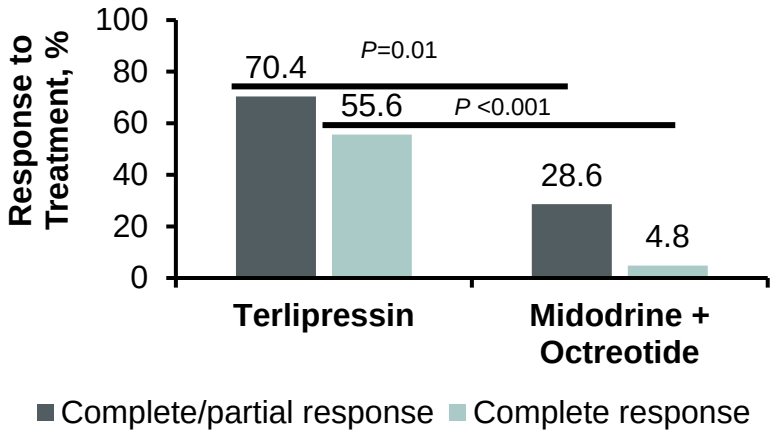
- Midodrine binds to 1-adrenergic receptors
  - Improves systemic blood pressure and hence improves renal perfusion pressure
- Start at 7.5 mg TID
- Titrate midodrine up to 15 mg TID on consecutive doses

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

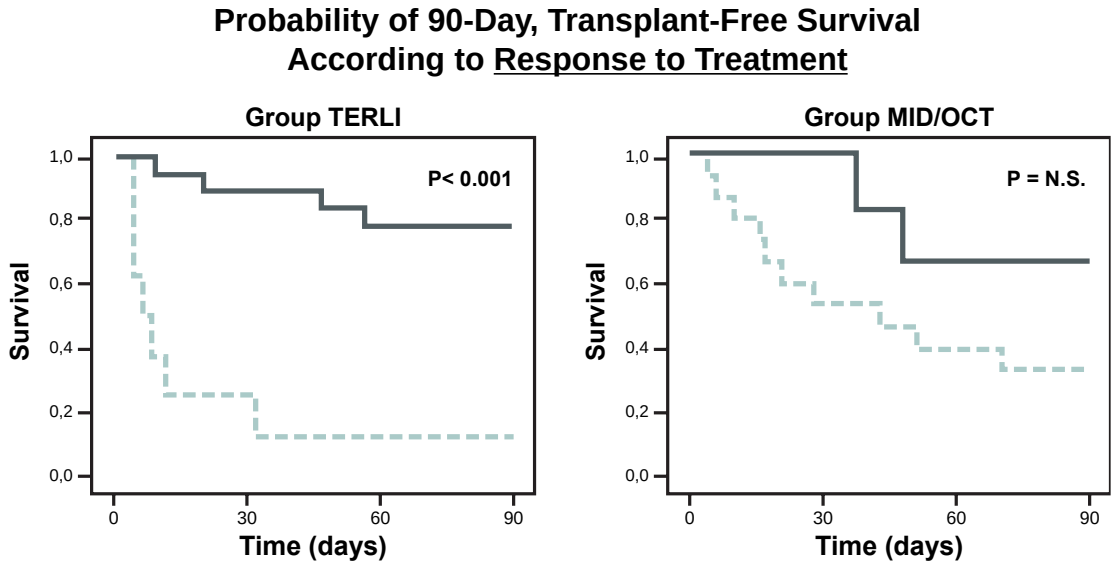
Terlipressin + Albumin vs Midodrine/Octreotide + Albumin: Improvement in Renal Function

- Randomized control study
- 27 patients received terlipressin (IV 3 mg/24 hrs, progressively increased to 12 mg/24 hrs if no response)
- 22 patients received midodrine (orally at 7.5 mg TID with dose increased to max of 12.5 mg TID) and octreotide SC 100 mcg TID up to 200 mcg TID).
- Both groups received albumin IV 1 g/kg of body weight on day 1 and 20-40 g/day thereafter.



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

Terlipressin vs Midodrine/Octreotide: 90-Day Survival



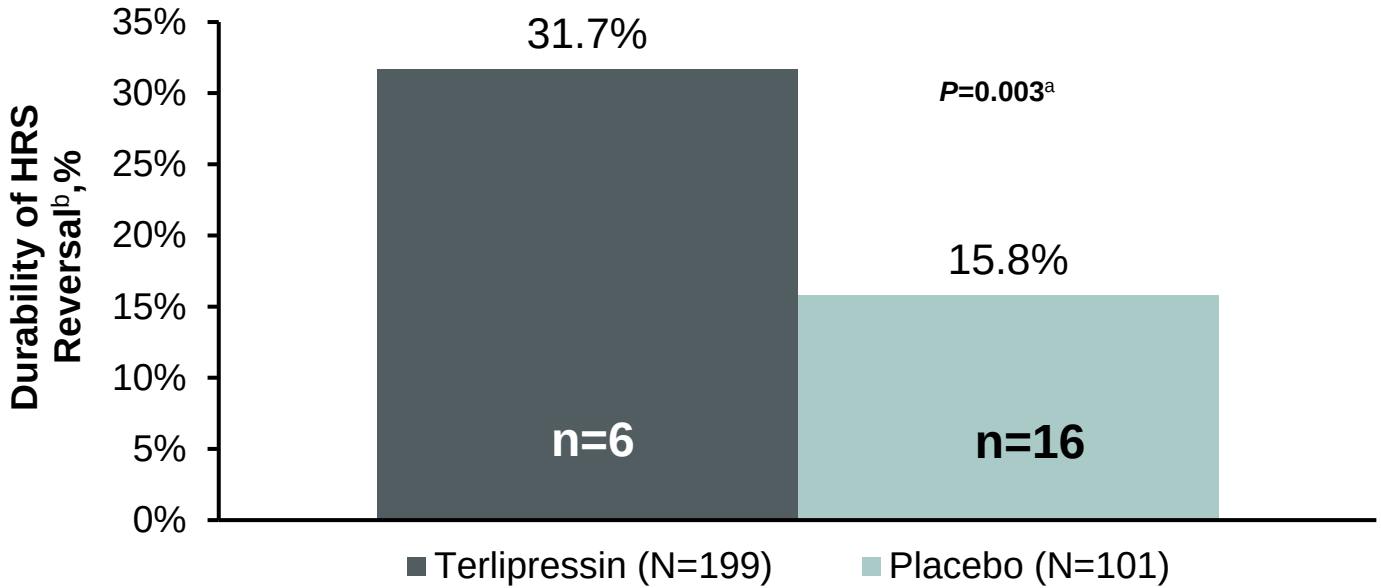
Cumulative 3-month survival in patients who were randomized to terlipressin plus albumin (TERLI group) or to midodrine and octreotide plus albumin (MID/OCT group) according to the response: solid line represents responders; dotted line represents nonresponders.
Abbreviation: N.S., nonsignificant.
Cavallin M et al. *Hepatology*. 2015;62:567-574.

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 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. *N Engl J Med.* 2021;384:818-828.

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. *N Engl J Med.* 2021;384:818-828.

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. *N Engl J Med.* 2021;384:818-828.

Norepinephrine Was Equivalent to Terlipressin in a Randomized Small Trial

- Alpha adrenergic agonist
- Randomized trial
  - Noradrenalin (0.1–0.7 μg/ kg/min) (10) + albumin vs terlipressin (1–2 mg/4 h) + albumin (12) for increase in baseline mean arterial pressure (MAP) of at least 10 mmHg

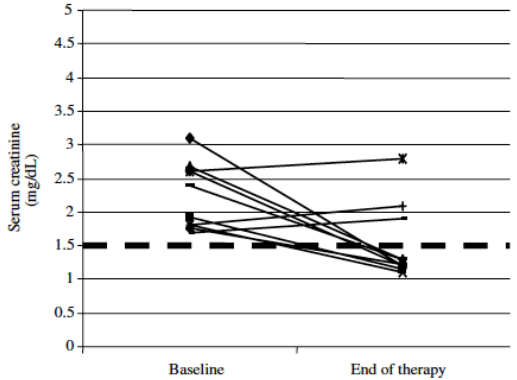


Fig. 1. Individual values of serum creatinine before the initiation and at the end of therapy in patients treated with noradrenalin and albumin.

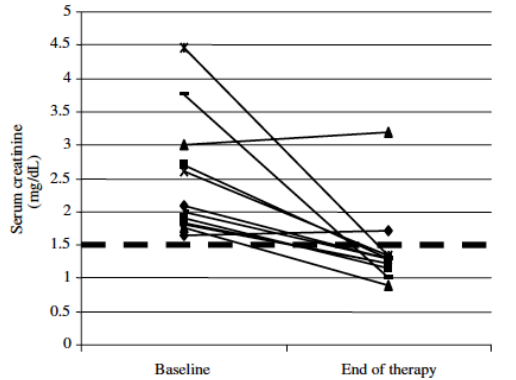


Fig. 2. Individual values of serum creatinine before the initiation and at the end of therapy in patients treated with terlipressin and albumin.

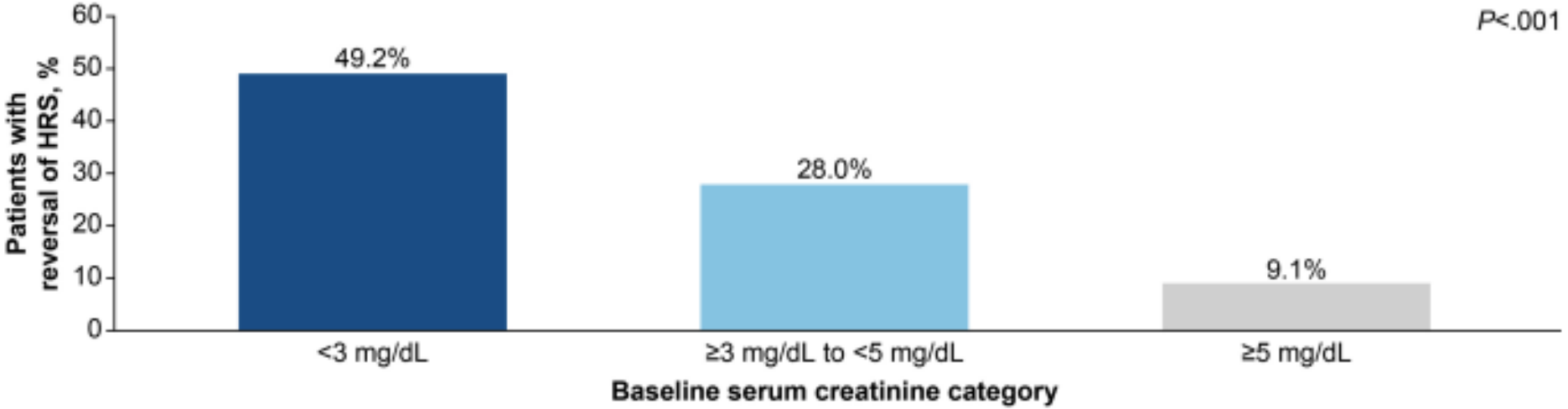
Alessandria C et al. *Journal of Hepatology.* 2007;47:499-505.

Early Treatment with Terlipressin in Patients with Hepatorenal Syndrome Yields Improved Clinical Outcomes in 3 Phase III North American Studies

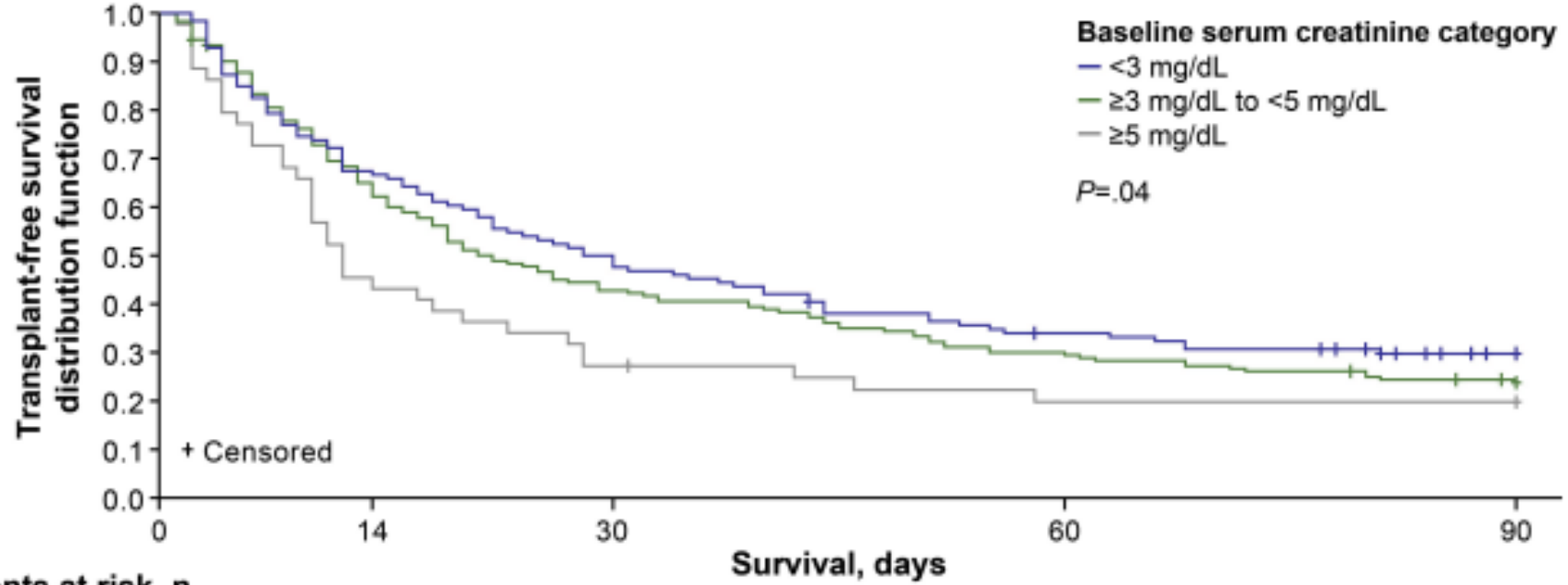
- STUDY AIM
  - retrospective analysis aimed to further delineate the influence of baseline serum creatinine levels on patient clinical outcomes, including treatment response and study drug tolerability. To this end, we examined the largest randomized, prospective database of placebo-controlled studies in patients with HRS who were treated with terlipressin
- METHODS •
  - Data from 3 large-scale, Phase III clinical studies (OT-04015 , REVERSE2, and CONFIRM6)—in which patients with HRS (formerly type 1, now HRS-AKI) were treated with terlipressin 1 mg or placebo were pooled to perform this subgroup analysis
  - Subgroup analyses examined pooled data from terlipress intreated patients with HRS (n=352)—across 3 serum creatinine subgroups

M Curry, HE Vargas, A Befeler, NT Pyrsopoulos, V Patwardhan, K Jamil
Journal of Hepatology 77, S634-S635, 6/2022

Figure 2. Percent of patients in the terlipressin treatment group who had HRS reversal by baseline serum creatinine subgroup (pooled ITT population[a]).



[a] Pooled data were collated from the following Phase III studies: OT-0401[5], REVERSE[2], and CONFIRM[6].
The *P* value was calculated using a chi-square test.
HRS, hepatorenal syndrome; ITT, intent-to-treat.



Patients at risk, n

Baseline serum creatinine					
<3 mg/dL	126	85	63	41	25
≥3 to <5 mg/dL	182	117	77	54	40
≥5 mg/dL	44	20	12	8	8

[a] Transplant-free survival includes events for death and transplantation

CONCLUSIONS

- This subgroup analysis demonstrated that serum creatinine levels were significantly associated with HRS reversal by both univariate and multivariate logistic regression analyses
- Patients with HRS who were treated with terlipressin at a lower baseline serum creatinine level experienced a higher rate of HRS reversal than those patients with a higher baseline serum creatinine
- Moreover, survival outcomes (ie, overall survival, transplant-free survival, RRT-free survival) for patients with HRS who were treated with terlipressin were also inversely correlated with baseline serum creatinine level
- Among terlipressin-treated patients, the incidence of any AE was similar across serum creatinine subgroup levels, whereas the incidence of SAEs increased as the baseline serum creatinine subgroup level increased
- Thus, this analysis supports the need to identify and treat patients with HRS early—when they have lower serum creatinine levels, and a greater probability of clinical response to terlipressin

Early Treatment with Terlipressin in Patients with Hepatorenal Syndrome Yields Improved Clinical Outcomes in 3 Phase III North American Studies

Michael P. Curry[1], Hugo E. Vargas[2], Alex S. Befeler[3], Nikolaos T. Pyrsopoulos[4], Vilas R. Patwardhan[1], and Khurram Jamil[5]

[1]Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA; [2]Mayo Clinic, Phoenix, AZ, USA; [3]Department of Internal Medicine, Division of Gastroenterology, Saint Louis University, St. Louis, MO, USA; [4]Division of Gastroenterology and Hepatology, Liver Transplantation, Rutgers-New Jersey Medical School University Hospital, Newark, NJ, USA; [5]Mallinckrodt Pharmaceuticals, Clinton, NJ, USA

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INTRODUCTION

- Hepatorenal syndrome (HRS) is a serious complication of advanced cirrhosis and a potentially reversible form of acute kidney injury[1,2]
- HRS type 1 (also known as HRS-acute kidney injury [HRS-AKI]) is characterized by splanchnic dilatation, reduced renal perfusion, reduced renal blood flow, and rapidly deteriorating kidney function[2]
- Terlipressin, a synthetic vasopressin analogue, binds to vasopressin receptors and acts as a systemic vasoconstrictor, thereby counteracting the splanchnic arterial vasodilation associated with HRS and restoring blood flow to the kidneys[1]
- While liver transplantation remains the only curative treatment for decompensated cirrhosis[3], terlipressin treatment can successfully reverse HRS[1] and may, therefore, improve patient survival while awaiting liver transplantation
- However, patients with higher baseline serum creatinine levels have a reduced response to terlipressin[4]

STUDY AIM

- This retrospective analysis aimed to further delineate the influence of baseline serum creatinine levels on patient clinical outcomes, including treatment response and study drug tolerability. To this end, we examined the largest randomized, prospective database of placebo-controlled studies in patients with HRS who were treated with terlipressin

METHODS

- Data from 3 large-scale, Phase III clinical studies (OT-0401[5], REVERSE[2], and CONFIRM[6])—in which patients with HRS (formerly type 1, now HRS-AKI) were treated with terlipressin 1 mg or placebo (**Figure 1**)[4-6]—were pooled to perform this subgroup analysis
- Subgroup analyses examined pooled data from terlipressin-treated patients with HRS (n=352)—across 3 serum creatinine subgroups (<3 mg/dL, ≥3 mg/dL to <5 mg/dL, and ≥5 mg/dL)—to delineate their correlation with HRS reversal, renal replacement therapy (RRT)-free survival, transplant-free survival, and overall survival. Safety was also assessed.

Figure 1. Study Design

RESULTS

- Baseline demographics were similar across the serum creatinine subgroups in terlipressin-treated patients in the pooled intent-to-treat (ITT) population (**Table 1**)
- As expected, the baseline model for end-stage liver disease (MELD) score was significantly higher among patients in the 2 higher serum creatinine subgroups compared with those in the lowest serum creatinine subgroup (median MELD: ≥5 mg/dL, 38.0; ≥3 mg/dL to <5 mg/dL, 35.5; <3 mg/dL, 31.0; *P*<.0001)

Table 1. Baseline demographics and clinical characteristics in the terlipressin group of the ITT Population[a]

Parameter	Terlipressin			*P* Value[b]
	Baseline Serum Creatinine Subgroup (N=352)			
	<3 mg/dL (n=126)	≥3 to <5 mg/dL (n=182)	≥5 mg/dL (n=44)	
Age, y, median (range)	56.8 (26.8–73.7)	54.2 (23.2–78.0)	56.2 (26.7–77.0)	.2670
Sex, Male	74 (58.7)	111 (61.0)	28 (63.6)	.8518
Baseline MELD Score Median (range)	(n=113) 31.0 (16.0–40.0)	(n=158) 35.5 (20.0–40.0)	(n=41) 38.0 (21.0–40.0)	<.0001
Child-Pugh Class C	84 (66.7)	121 (66.5)	27 (61.4)	.7931
MAP, mm Hg, median (range)	77.8 (52.3–106.7)	75.2 (47.0–117.7)	75.7 (53.3–100.7)	.1959
Ascites[c] Grade 3	50 (39.7)	66 (36.3)	20 (45.5)	.5084
Alcoholic Hepatitis	42 (33.3)	60 (33.0)	19 (43.2)	.4325
Alcoholic Hepatitis, Baseline MAP <70 mm Hg, or SIRS	82 (65.1)	121 (66.5)	30 (68.2)	.9257
Precipitating factors for HRS	50 (39.7)	80 (44.0)	19 (43.2)	.7662
Prior midodrine and octreotide	56 (44.4)	69 (37.9)	22 (50.0)	.2555
SIRS subgroup[d]	41 (38.0)	55 (35.9)	16 (45.7)	.7176
Baseline ACLF Grade 0 / 1 2 / 3	2 (1.6) / 64 (50.8) 38 (30.2) / 22 (17.5)	0 / 82 (45.1) 61 (33.5) / 39 (21.4)	0 / 16 (36.4) 17 (38.6) / 11 (25.0)	.3567

Data are presented as *n* (%) unless otherwise stated.
[a] Pooled data were collated from the following Phase III studies: OT-0401[5], REVERSE[2], and CONFIRM[6].
[b] The *P* values for continuous variables are based on a comparison of baseline serum creatinine categories using the Kruskal-Wallis test; for categorical variables, a Fisher's Exact test was used.
[c] Per protocol, every patient had to have a documented history of cirrhosis and ascites to participate in the clinical studies in the pooled ITT population.
[d] Criteria to define the SIRS subgroup were not collected for OT-0401[5]; percentages are based on the number of patients in the terlipressin treatment group for REVERSE[2] and CONFIRM[6] only (<3 mg/dL, n=108, ≥3 mg/dL to <5 mg/dL, n=153; ≥5 mg/dL, n=35).
ACLF, acute on chronic liver failure; HRS, hepatorenal syndrome; ITT, intent-to-treat; MAP, mean arterial pressure; MELD, model for end-stage liver disease; SIRS, systemic inflammatory response syndrome.

- Among patients with HRS, the incidence of HRS reversal inversely correlated with serum creatinine subgroup (**Figure 2**) (*P*<.001)

Figure 2. Percent of patients in the terlipressin treatment group who had HRS reversal by baseline serum creatinine subgroup (pooled ITT population[a]).

- Moreover, serum creatinine levels were significantly associated with HRS reversal by both univariate and multivariate logistic regression analyses (**Tables 2** and **3**) (univariate, odds ratio, 0.483 [95% CI: 0.361–0.645] *P*<.001; multivariate, odds ratio, 0.518 [95% CI: 0.381–0.704] *P*<.001)

Table 2. Univariate logistic regression of baseline characteristics on HRS reversal (terlipressin group; pooled ITT population[a])

Baseline Parameter	Terlipressin			
	n[b]	Odds Ratio	95% Confidence Interval	*P* Value
Baseline serum creatinine	352	0.483	0.361–0.645	<.001
Alcoholic hepatitis	352	1.382	0.871–2.192	.17
Age <65 years	352	1.099	0.590–2.049	.77
Male sex	352	1.126	0.714–1.776	.61
Race group (White vs non-White)	348	1.778	0.781–4.048	.17
Baseline MELD score	312	0.925	0.891–0.961	<.001
Baseline Child-Turcotte-Pugh score	337	0.908	0.806–1.021	.11
Baseline MAP, mm Hg	352	0.995	0.977–1.014	.62
Baseline MAP <65, mm Hg	352	0.538	0.264–1.096	.09
Baseline serum sodium	349	0.985	0.950–1.021	.42
Baseline total bilirubin	338	0.973	0.954–0.992	<.01
No precipitating factors for HRS	352	1.028	0.656–1.611	.90
Prior midodrine or octreotide	352	1.699	1.085–2.661	.02

[a] Pooled data were collated from the following Phase III studies: OT-0401[5], REVERSE[2], and CONFIRM[6].
[b] This represents the evaluable number of patients for each baseline parameter.
HRS, hepatorenal syndrome; ITT, intent-to-treat; MAP, mean arterial pressure; MELD, model for end-stage liver disease.

Table 3. Multivariate logistic regression of baseline characteristics on HRS reversal (terlipressin group; pooled ITT population[a])

Baseline Parameter	Terlipressin			
	n[b]	Odds Ratio	95% Confidence Interval	*P* Value
Serum creatinine	312	0.518	0.381–0.704	<.001
MELD score	312	0.939	0.902–0.977	<.01
Prior midodrine and octreotide	312	1.849	1.106–3.091	.02

[a] Pooled data were collated from the following Phase III studies: OT-0401[5], REVERSE[2], and CONFIRM[6].
[b] This represents the evaluable number of patients for each baseline parameter.
HRS, hepatorenal syndrome; ITT, intent-to-treat; MELD, model for end-stage liver disease.

- Among patients in the terlipressin group, 57.9% in the lowest baseline serum creatinine subgroup (<3 mg/dL) were alive at Day 90 compared with 52.7% in the ≥3 mg/dL to <5 mg/dL subgroup, and 29.5% in the highest subgroup (>5 mg/dL; *P*=.0003)
- Terlipressin-treated patients with HRS who had lower baseline serum creatine levels, also had significantly higher transplant-free survival at Day 90 (*P*=.04) (**Figure 3**)

Figure 3. Transplant-free survival[a] up to 90 days by baseline serum creatinine subgroup (terlipressin group, pooled ITT population[b]).

Safety

- Across all 3 serum creatinine subgroups, most terlipressin-treated patients experienced an adverse event (AE; 3 mg/dL, 87.8%; ≥3 mg/dL to <5 mg/dL, 92.3%; ≥5 mg/dL; 95.5%) (**Table 4**)
- The serious AEs (SAEs) by System Organ Class that were reported most frequently (in ≥5% of patients) are presented in **Table 4**

Table 4. Summary of adverse events in patients with HRS (pooled safety population[a])

Parameter, n (%)	Terlipressin		
	Baseline Serum Creatinine Subgroup (N=349)		
	<3 mg/dL (n=123)	≥3 to <5 mg/dL (n=182)	≥5 mg/dL (n=44)
Any AE[b]	108 (87.8)	168 (92.3)	42 (95.5)
Permanent Withdrawals Due to AEs[c]	15 (12.2)	27 (14.8)	5 (11.4)
Any SAE	72 (58.5)	118 (64.8)	37 (84.1)
SAEs Reported by ≥5% of Patients within a Treatment Group[d] by System Organ Class / Preferred Term			
Cardiac disorders	8 (6.5)	7 (3.8)	5 (11.4)
Gastrointestinal disorders	15 (12.2)	25 (13.7)	8 (18.2)
Abdominal pain	5 (4.1)	7 (3.8)	3 (6.8)
General disorders and administration-site conditions	7 (5.7)	16 (8.8)	7 (15.9)

[a] Pooled data were collated from the following Phase III studies: OT-0401[5], REVERSE[2], and CONFIRM[6].
[b] Patients experiencing multiple AEs are counted once; up to 7 days posttreatment.
[c] For CONFIRM and REVERSE, permanent withdrawals due to an AE occurred when action taken was reported as treatment permanently stopped. For OT-0401, permanent withdrawals due to an AE occurred when action taken with study drug was reported as discontinued permanently.
[d] Up to 30 days posttreatment.
AE, adverse event; HRS, hepatorenal syndrome; SAE, serious adverse event.

CONCLUSIONS

- This subgroup analysis demonstrated that serum creatinine levels were significantly associated with HRS reversal by both univariate and multivariate logistic regression analyses
- Patients with HRS who were treated with terlipressin at a lower baseline serum creatinine level experienced a higher rate of HRS reversal than those patients with a higher baseline serum creatinine
- Moreover, survival outcomes (ie, overall survival, transplant-free survival, RRT-free survival) for patients with HRS who were treated with terlipressin were also inversely correlated with baseline serum creatinine level
- Among terlipressin-treated patients, the incidence of any AE was similar across serum creatinine subgroup levels, whereas the incidence of SAEs increased as the baseline serum creatinine subgroup level increased
- Thus, this analysis supports the need to identify and treat patients with HRS early—when they have lower serum creatinine levels, and a greater probability of clinical response to terlipressin

AKI and Cirrhosis

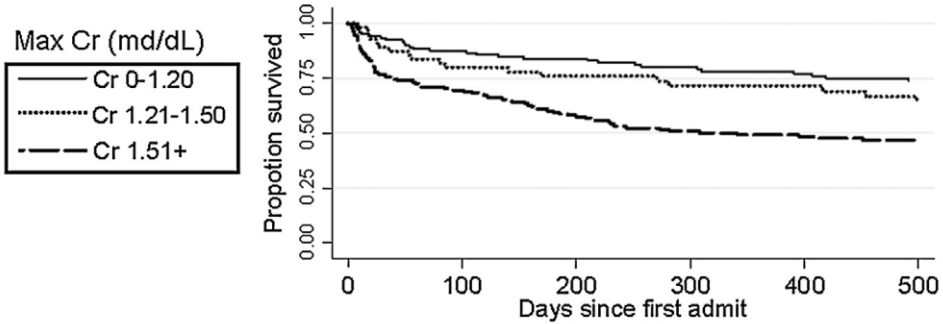
- AKI diagnosed with AKIN criteria associated with increased mortality in patients with cirrhosis[1]
- Progression through stages strongly correlates with increased mortality[2]
- However, serum creatinine cutoff of 1.5 mg/dL is still prognostic[3]
- New AKI-HRS criteria enable earlier treatment at lower creatinine (1 mg/dL lower)[4]
  - Baseline serum creatinine is a predictor of response to therapy

1. Piano S et al. *Hepatology*. 2013;57:753-762; 2. Belcher JM et al. *Hepatology*. 2013;57:753-762;
3. Fagundes C et al. *J Hepatol*. 2013;59:474-481; 4. Wong F et al. *Journal Hepatology*. 2019;70(1)Supp.

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

HRS-CKD

SCr Is an Independent Predictor of Mortality in Patients with Cirrhosis



Number at risk at time

Cr 0-1.20	119	101	91	81	75	61
Cr 1.21-1.50	56	42	37	32	30	24
Cr 1.51+	164	112	88	73	64	56

Time scale: Days since patient's first admission

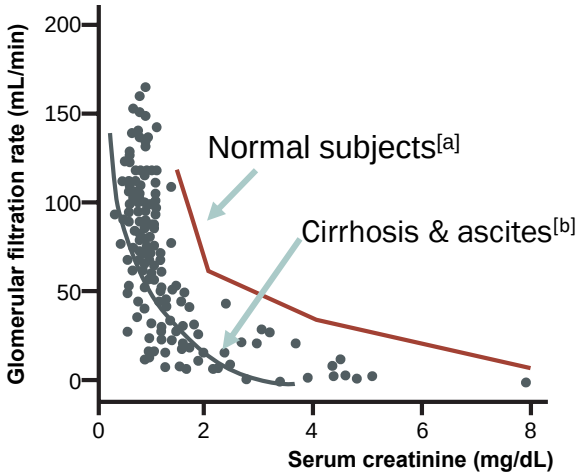
Data from 636 admissions were used. Deaths were recorded for 169 out of 339 patients in this sample.

Any increment increase in SCr within 48 hours from hospitalization is associated with a higher mortality, provided the peak SCr within 48 hours is >1.2 mg/dL.

Nuthalapati A et al. *J Clin Exp Hepatol*. 2017;7:290-299.

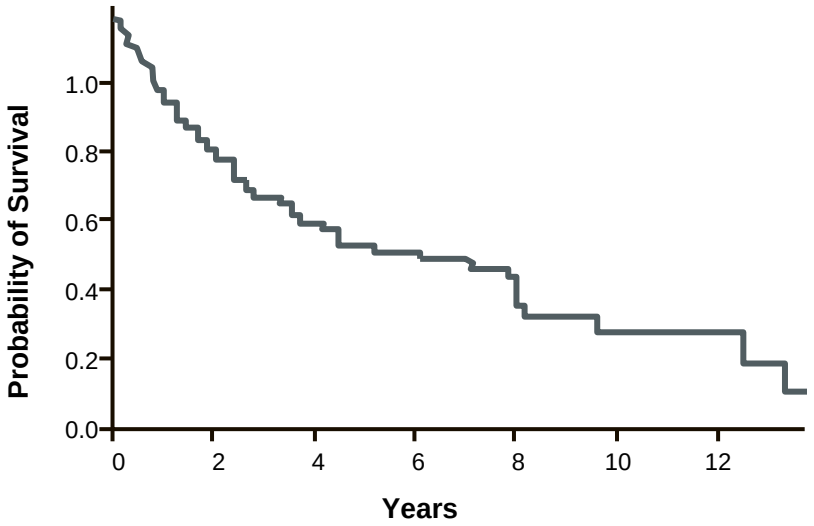
Relationship Between SCr and GFR in Patients With Cirrhosis

- Serum creatinine of 1.5 g/dL corresponds to GFR of ~30 mL/min in cirrhosis
- Due to low muscle mass in cirrhosis, SCr overestimates renal function



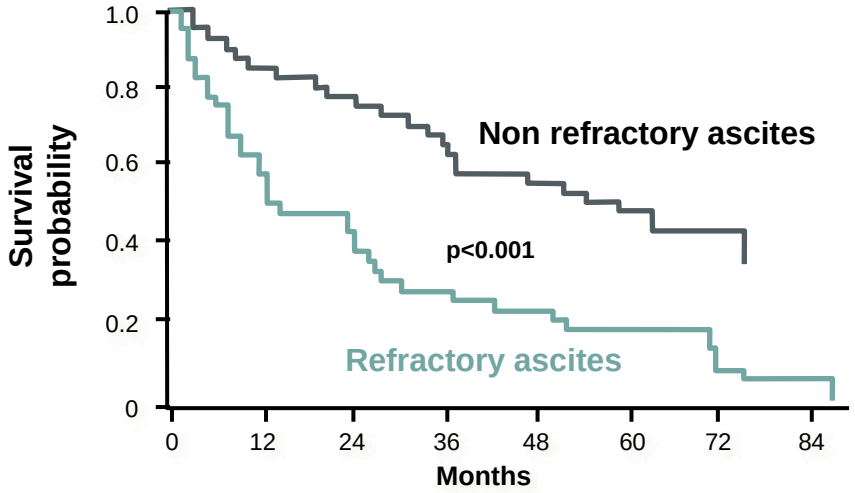
a. Inker LA, Perrone R et al. UpToDate.
b. Arroyo V et al. *Zakim and Boyer's Hepatology*: A Textbook of Liver Disease. 2006.

Prognosis of Patients With Cirrhosis at Onset of Ascites



Arroyo V, Colmenero J, et al. *J Hepatol*. 2003;38:S69-S89.

Patients With Refractory Ascites

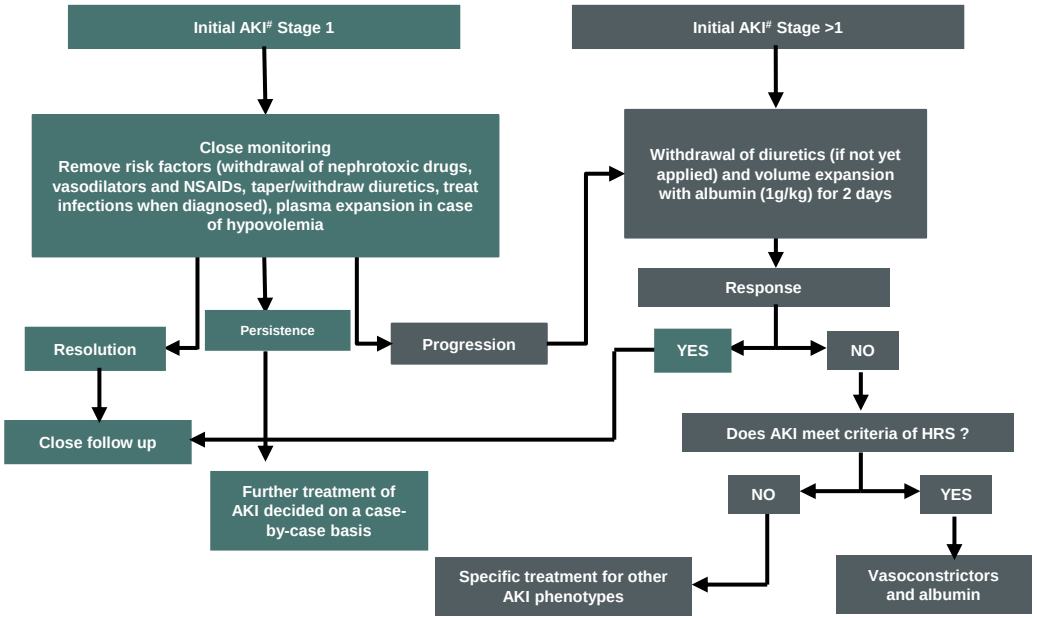


Salerno et al. *Am J Gastroenterol*. 1993; 88:514.

HRS: Type 1 vs Type 2

- Type 1 HRS
  - More serious type
  - Increase in SCr ≥0.3 mg/dL or an increase in SCr ≥1.5-fold to 2-fold from baseline during a period of <2 weeks
  - At the time of diagnosis, some patients have a urine output <400 to 500 mL per day
- Type 2 HRS
  - Renal impairment that is less severe than that observed with Type 1 HRS
  - The major clinical feature is ascites that is resistant to diuretics

Algorithm for AKI Management in Patients With Cirrhosis



= AKI at the first fulfilling of KDIGO criteria.
Angeli P et al. *J Hepatol*. 2015;62:968-974.

Approach to the Patient With AKI in Cirrhotic Patients Stage 1

- Can you improve liver function?
  - Treat alcoholic hepatitis, decompensated HBV, AIH
- Plasma volume expansion in patients with clinically suspected hypovolemia
  - Crystalloids, albumin or blood (in patients who had AKI as a result of gastrointestinal bleeding) according to clinical judgment

Approach to the Patient With AKI in Cirrhotic Patients Stage 1

- If Cr returns to within 0.3 mg/dl of baseline value, follow closely until DC
  - Check as outpatient at least every 2–4 weeks during the first 6 months after the discharge for early identification of new episodes of AKI
- If not improved, treat as Stage 2/3 AKI

Approach to the Patient with AKI in Cirrhotic Patients Stage 2-3

- Withdrawal of diuretics, if not previously implemented
- Expansion of plasma volume with intravenous albumin at the dose of 1 g/kg body weight per day for two consecutive days up to 100 g per day
- If Cr returns to within 0.3 mg/dl of baseline value follow closely until DC
  - Check as outpatient at least every 2-4 weeks during the first 6 months after the discharge for early identification of new episodes of AKI

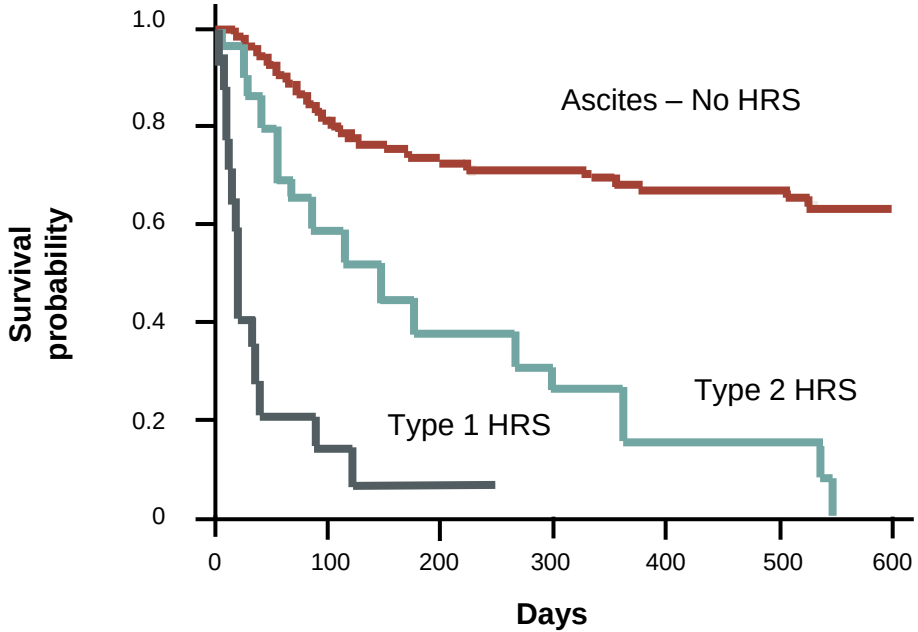
Approach to the Patient With AKI in Cirrhotic Patients Stage 2-3: HRS

- No response
- Criteria for HRS met?
- Consult Nephrology (if not already following)
- Assess transplant status (if not already done)
- Vasoconstrictors and albumin (20-40 g/day)
  - Terlipressin (not approved in US but being studied)
    - 1-2 mg every 4-6 hrs

  OR

  - Midodrine/Octreotide: start at 7.5 mg TID with octreotide 100-200 mcg TID or IV infusion 50 mcg/hr to raise MAP by 15 mm Hg
    - Titrate midodrine up to 15 mg TID on consecutive doses

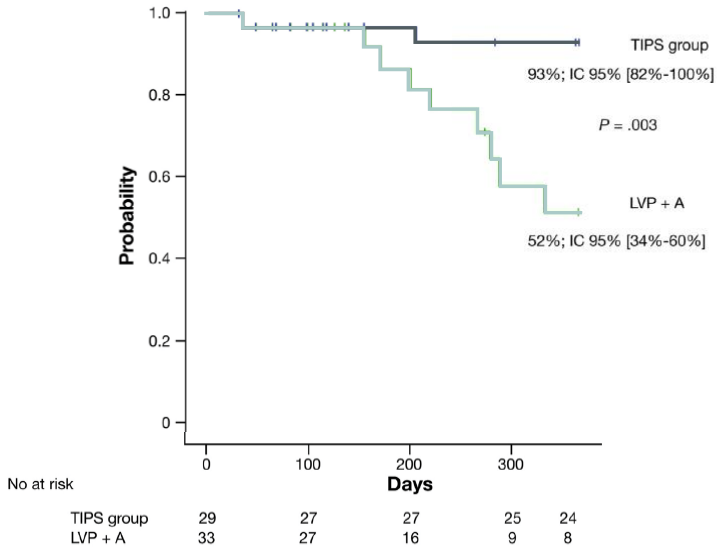
Survival in Patients With Ascites and HRS



Arroyo et al. *J Hepatol*. 2007.

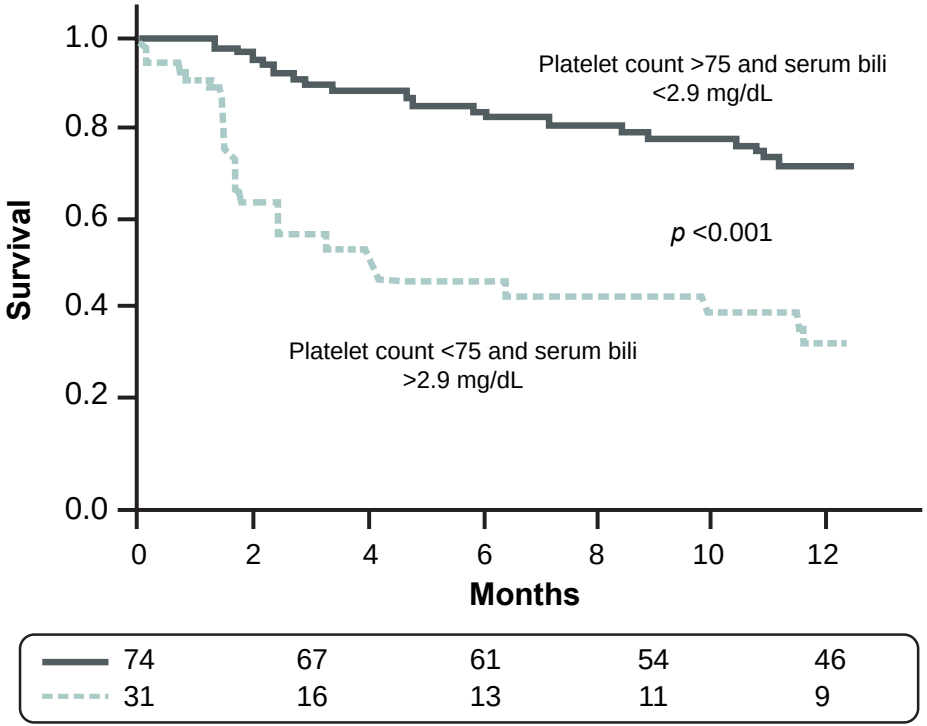
TIPS vs LVP For Refractory Ascites

Probability of survival without liver transplantation in patients allocated to covered TIPS group and in those allocated to LVP+A group.



Bureau et al. *Gastro*. 2017.

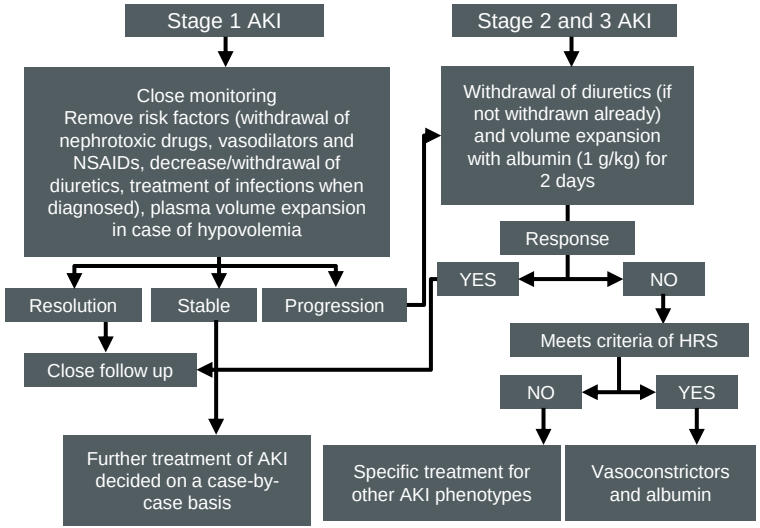
TIPS: Patient Selection



Bureau et al. *J Hepatol*. 2011.

AKI – Initial Management

- Early identification
- Assess and treat bacterial infection
  - Blood, urine, ascitic fluid culture, CXR
- Assess and treat GI bleeding
- Avoid large-volume paracentesis (diagnostic OK)
- Stop β-blockers
- Stop nephrotoxic medications: NSAIDs, diuretics
- Volume expansion
  - Saline for those with definite or suspected volume depletion
  - Albumin for those with AKI Stage 1B or higher



Tapper EB et al. *Am J Med*. 2016;129:461-467; Angeli P et al. *J Hepatology*. 2015.

Summary – AKI in Cirrhosis

- Early recognition and intervention is needed
- Consider the differential diagnosis of AKI
  - More than one cause may be evident
  - Management and prognosis vary depending on etiology
  - AKI-HRS remains a diagnosis of exclusion
- Not all AKI in cirrhosis is HRS

- Significant cause of morbidity/mortality
- Need to differentiate AKI-HRS from other causes of AKI
- AKI-HRS may co-exist with other forms of AKI
- Review of medication list critical to care
- AKI-HRS requires aggressive management strategy