Hepatorenal Syndrome: To Treat or NOT to Treat? And How?

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- 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.*

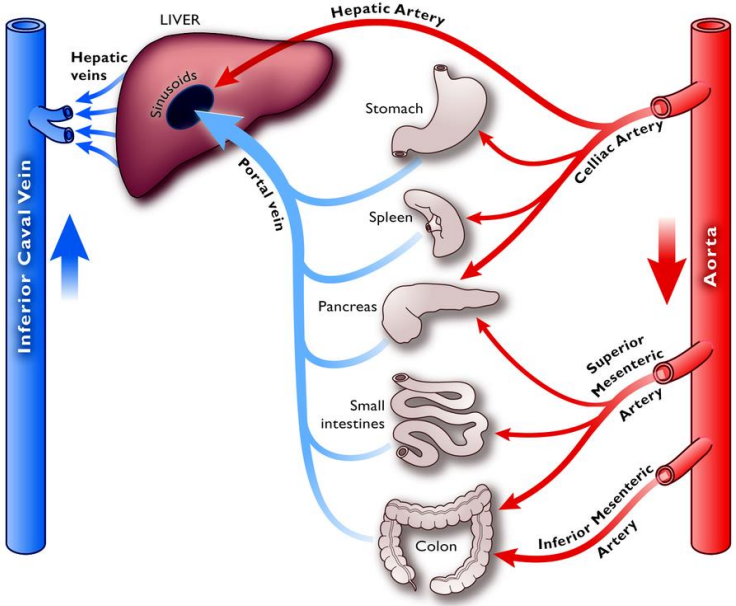
Pathophysiology

- 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.*

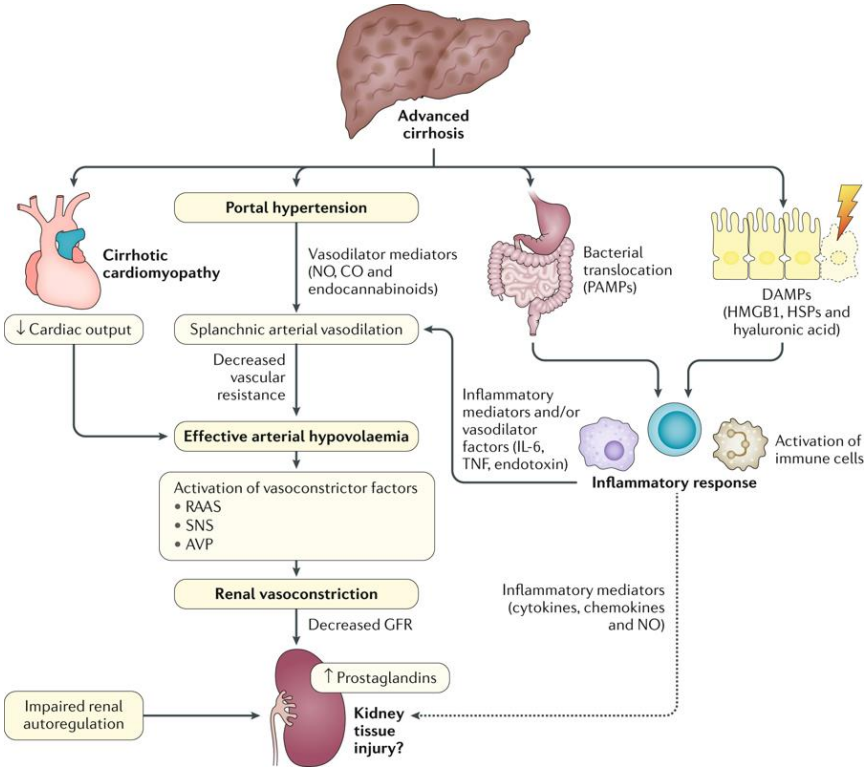
Pathophysiology

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

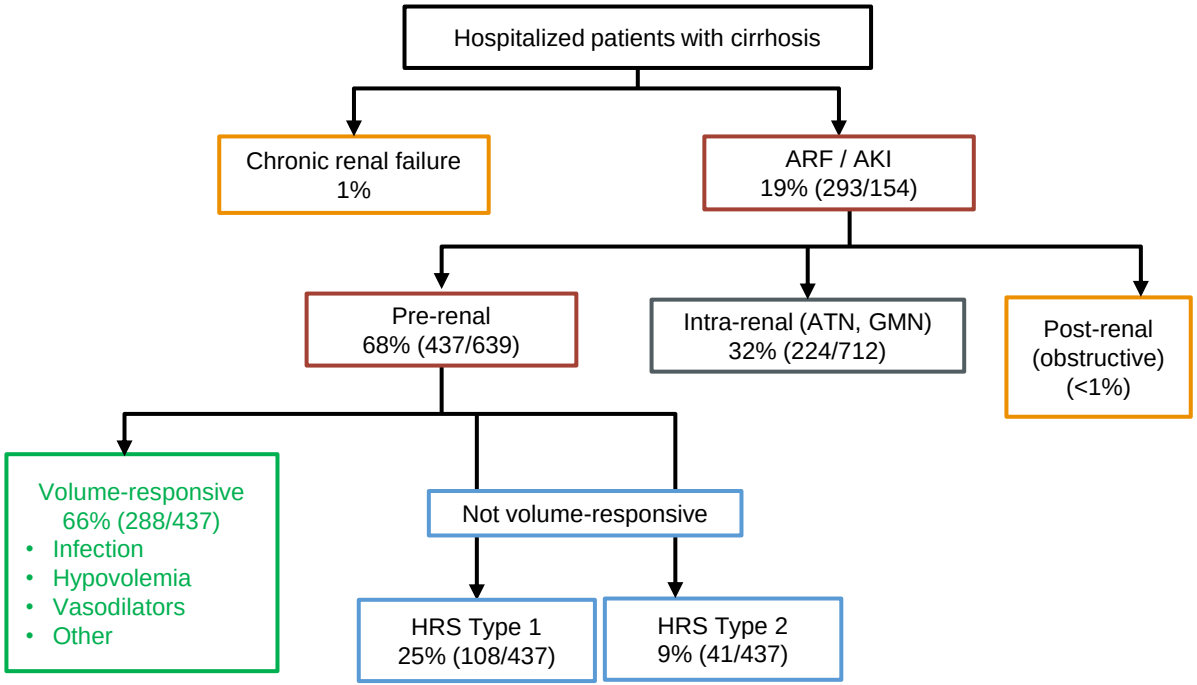
Graupera I et al. *Clin Liver Dis*. 2013;2:128-131.

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

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

Midodrine and Octreotide

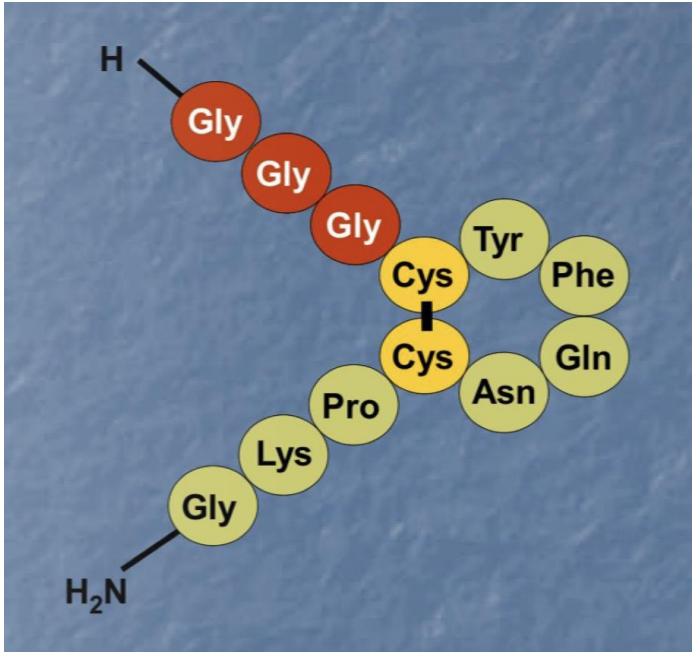
Midodrine

- 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

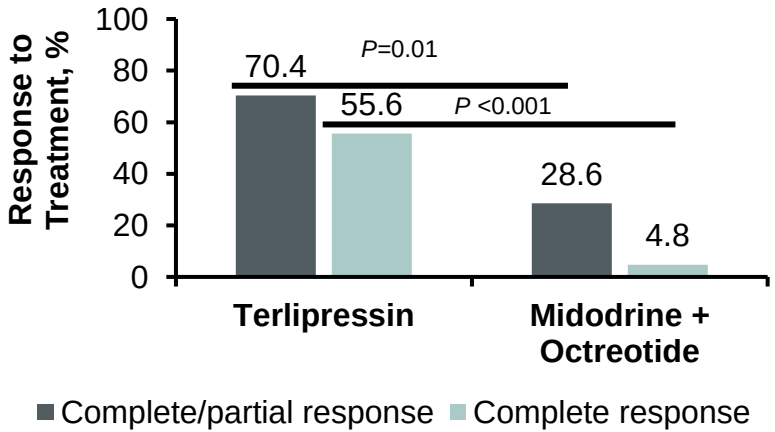
Terlipressin: Not Yet Available in US



- 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

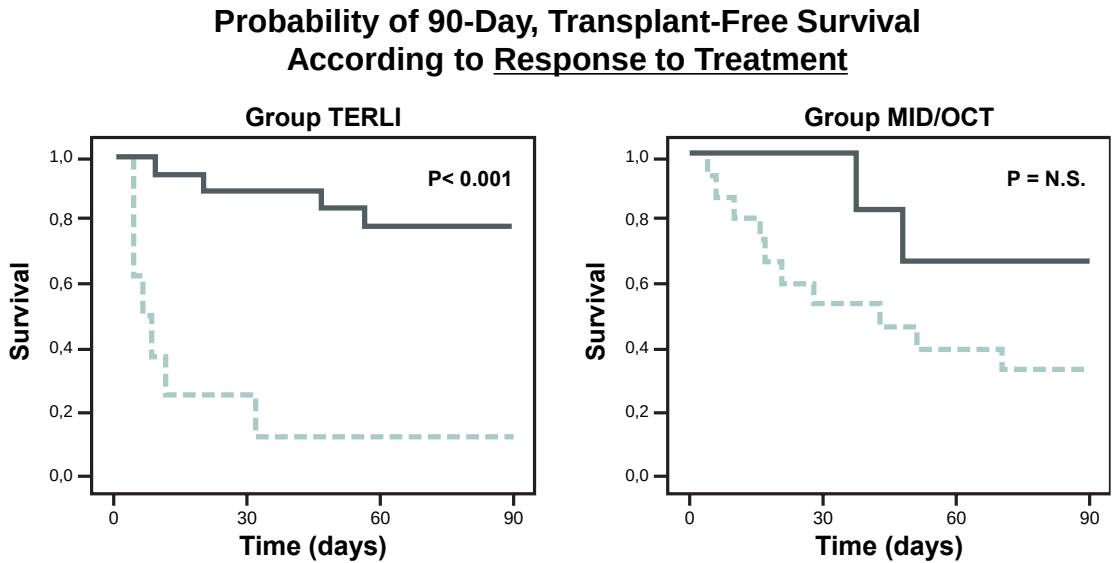
Terlipressin + Albumin vs Midodrine/Octreotide + Albumin: Improvement in Renal Function

- 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



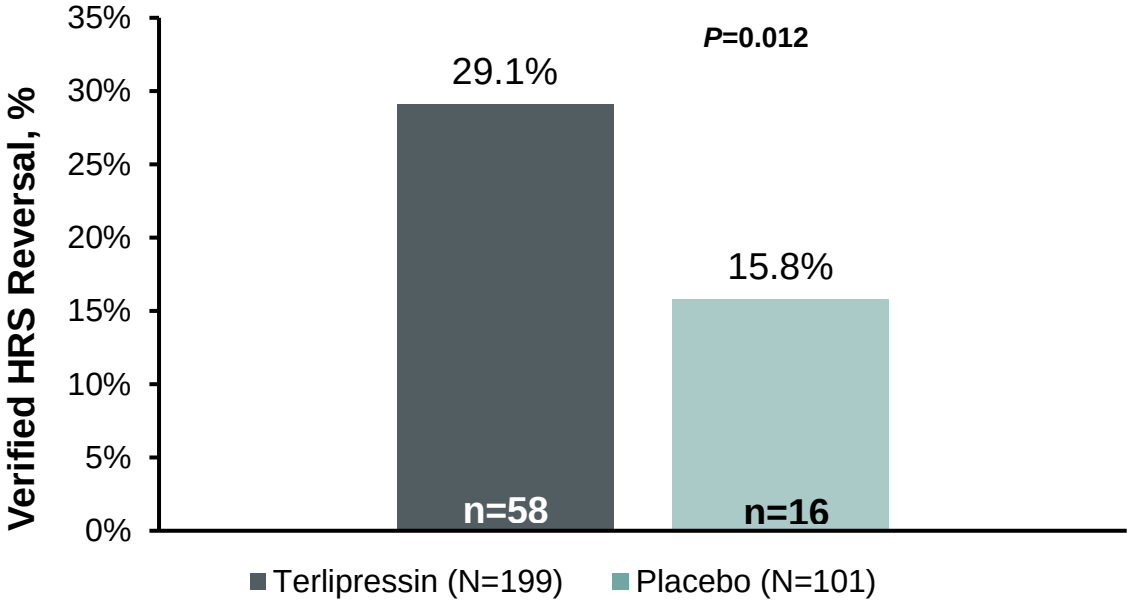
Cumulative 3-month survival in patients who were randomized to terlipressin plus albumin (TERLI group) or to midodrine and octreotide plus albumin (MID/OCT group) according to the response: solid line represents responders; dotted line represents nonresponders.
Abbreviation: N.S., nonsignificant.
Cavallin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

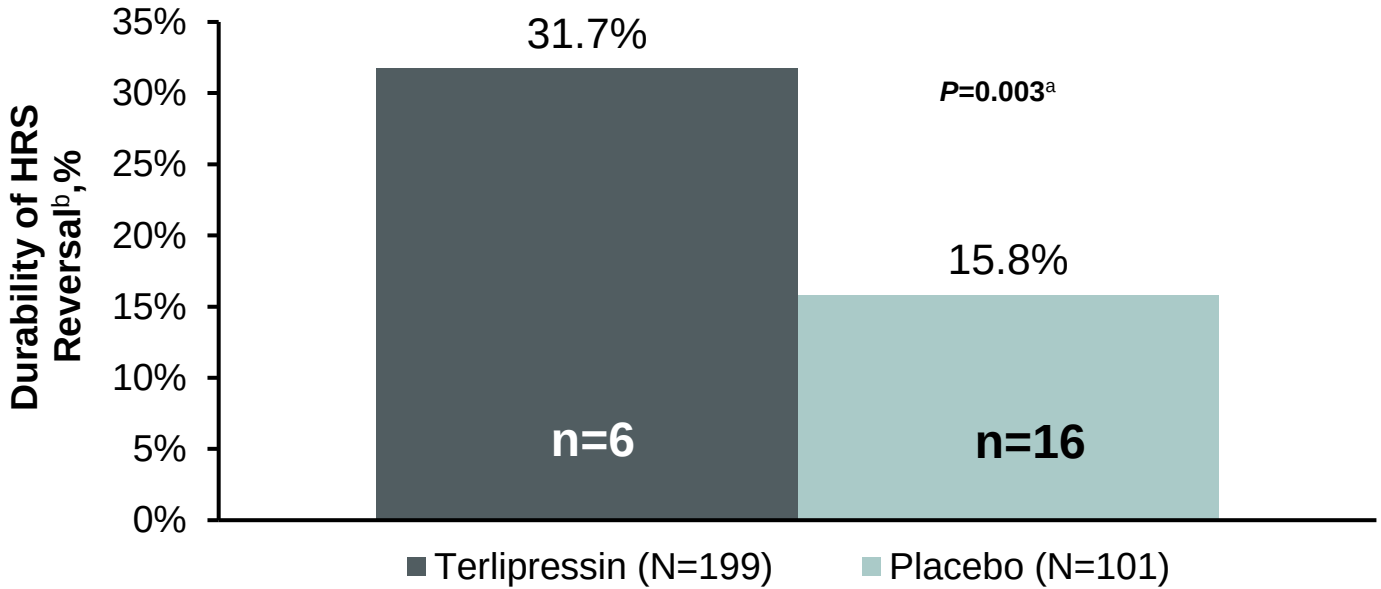
Wong F et al. *The Liver Meeting.* Boston, MA 2019, Abstract LO5.

Primary Endpoint: Verified HRS Reversal (CONFIRM Study)



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

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

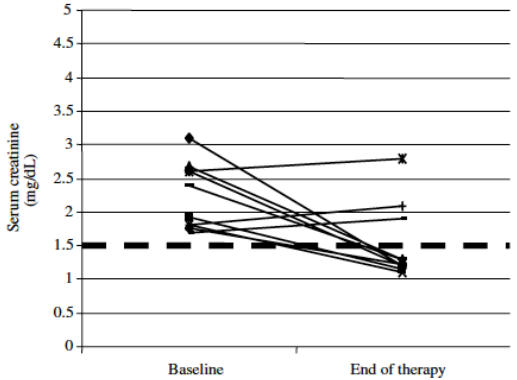


Fig. 1. Individual values of serum creatinine before the initiation and at the end of therapy in patients treated with noradrenalin and albumin.

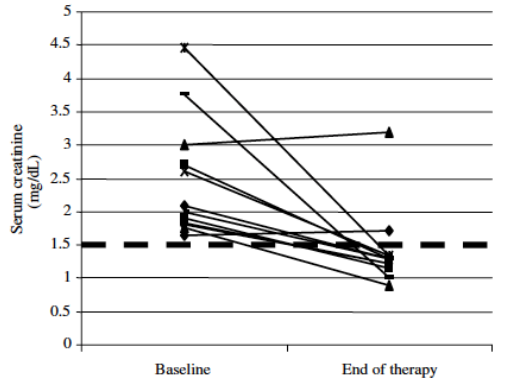


Fig. 2. Individual values of serum creatinine before the initiation and at the end of therapy in patients treated with terlipressin and albumin.

Journal of Hepatology. 2007;47:499-505.

AKI and Cirrhosis

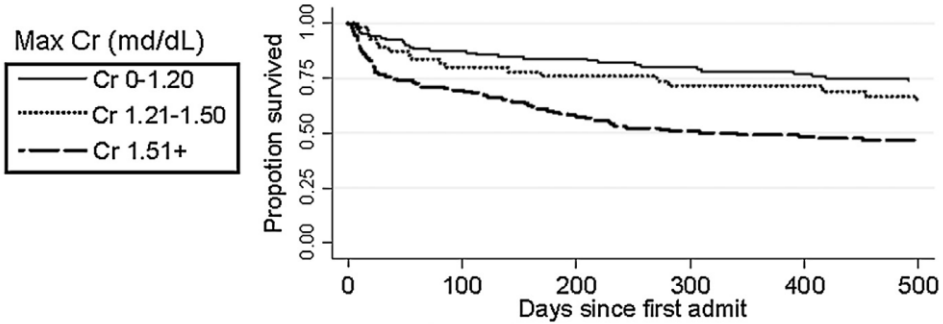
- AKI diagnosed with AKIN criteria associated with increased mortality in patients with cirrhosis[1]
- Progression through stages strongly correlates with increased mortality[2]
- However, serum creatinine cutoff of 1.5 mg/dL is still prognostic[3]
- New AKI-HRS criteria enable earlier treatment at lower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

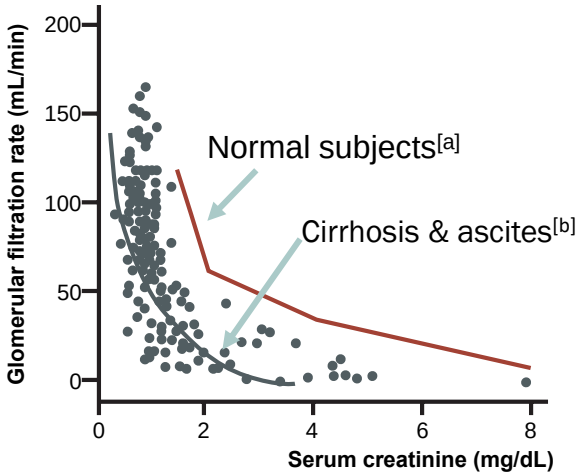
Data from 636 admissions were used. Deaths were recorded for 169 out of 339 patients in this sample.

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.

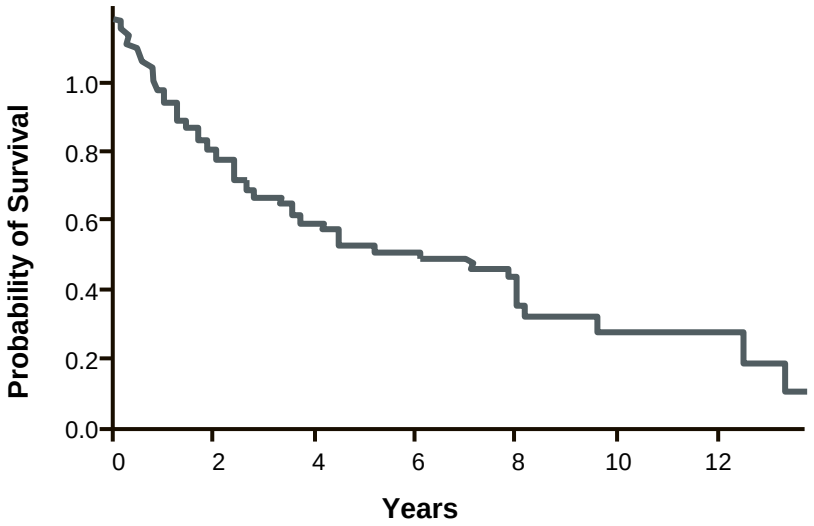
Relationship Between SCr and GFR in Patients With Cirrhosis

- 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



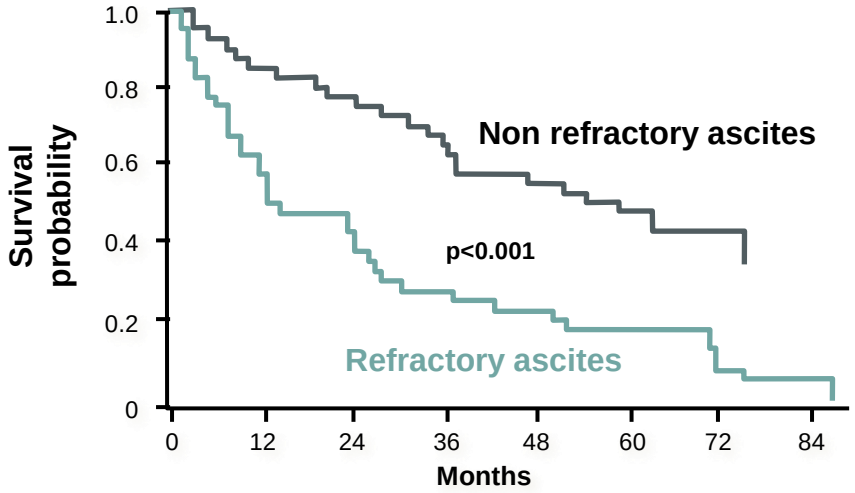
a. Inker LA, Perrone R et al. UpToDate.
b. Arroyo V et al. *Zakim and Boyer's Hepatology*: A Textbook of Liver Disease. 2006.

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

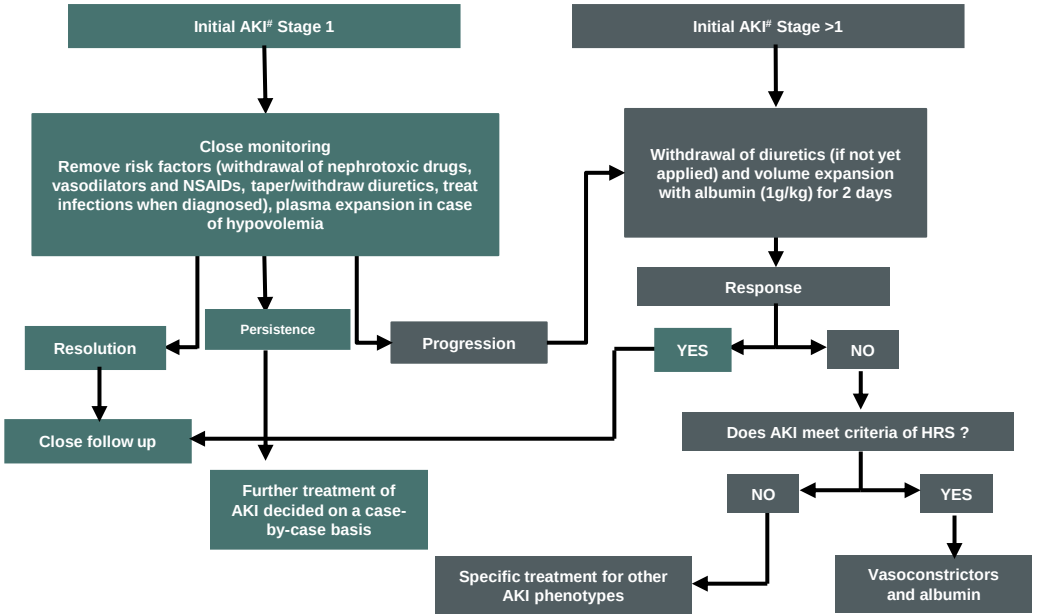


Salerno et al. *Am J Gastroenterol*. 1993; 88:514.

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

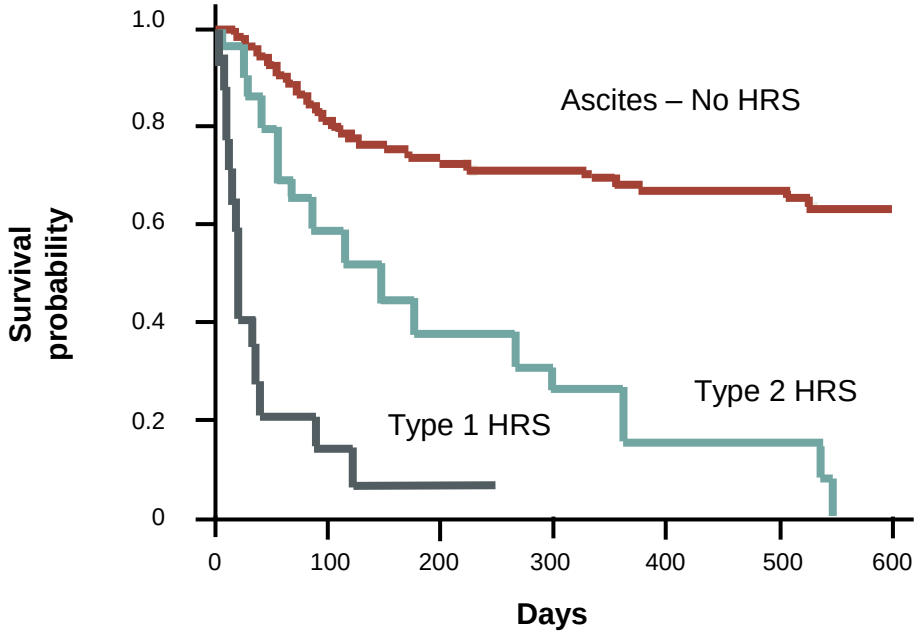
Approach to the Patient With AKI in Cirrhotic Patients Stage 2-3: HRS

- 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

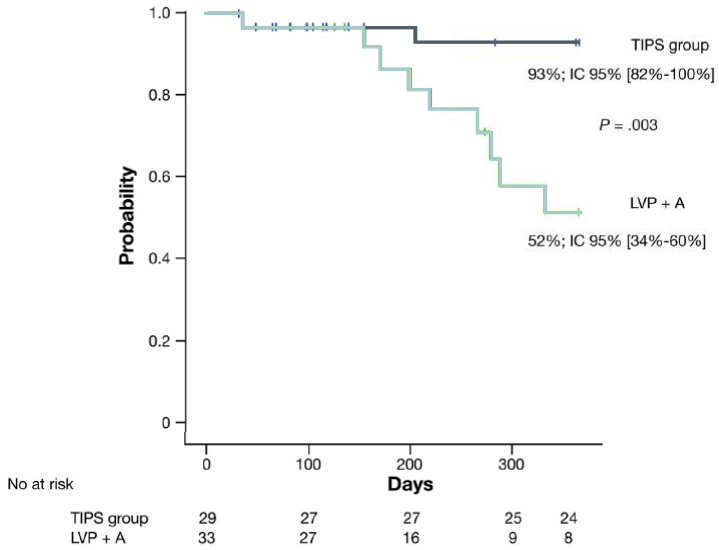
Survival in Patients With Ascites and HRS



Arroyo et al. *J Hepatol*. 2007.

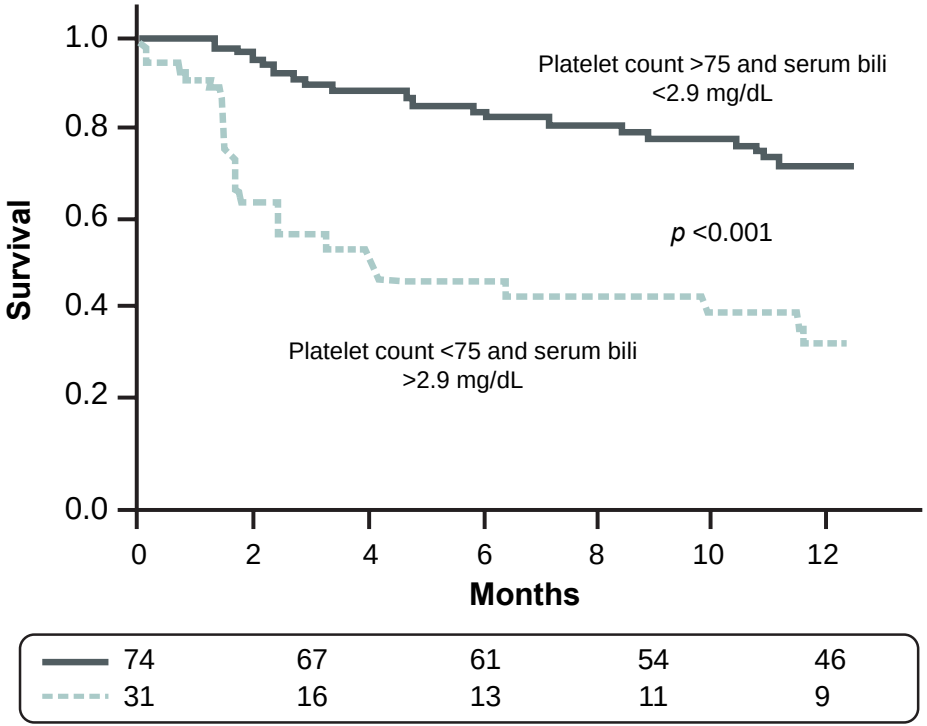
TIPS vs LVP For Refractory Ascites

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.

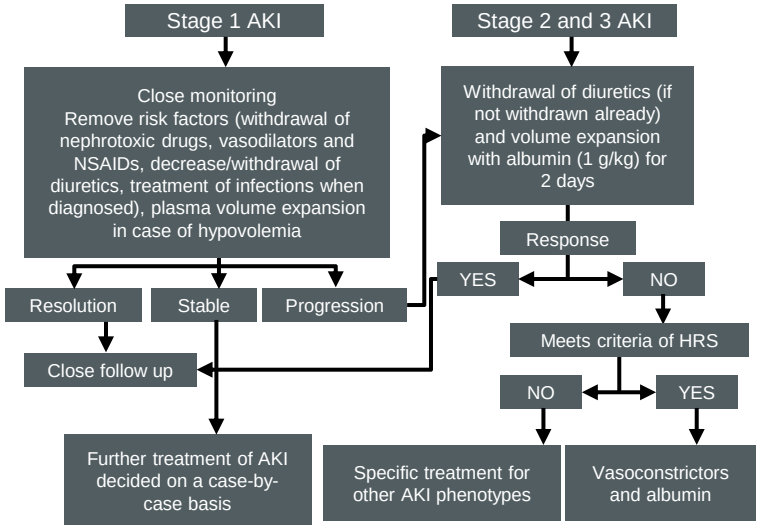
TIPS: Patient Selection



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