New Concepts in Acute Kidney Injury for the Practicing Gastroenterologist

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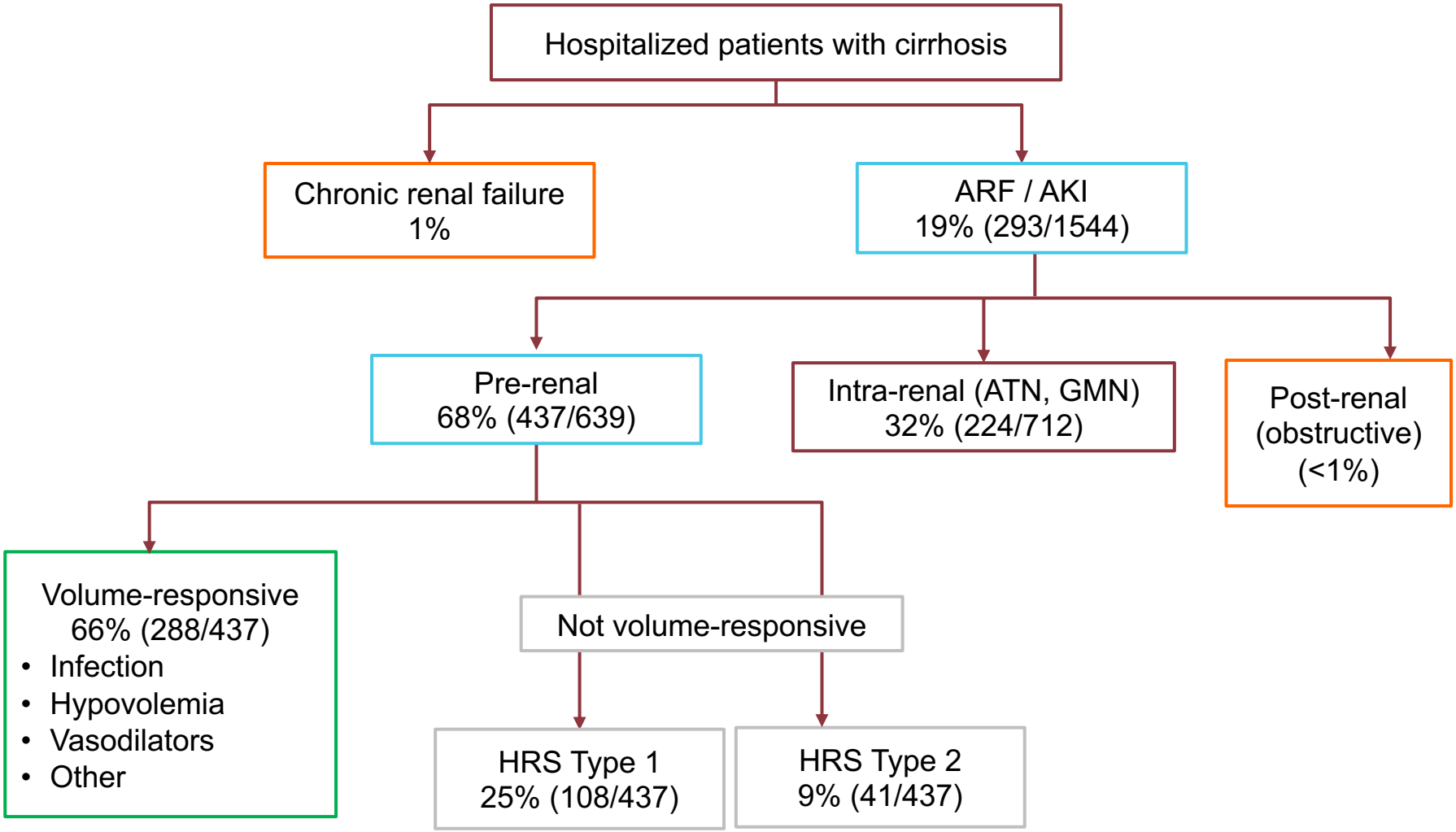
Relevant Disclosure

Consultant and Speaker Bureau: Mallinckrodt

Learning Objectives

- Discuss the diagnosis and management of acute kidney injury (AKI) in cirrhosis and apply these criteria in clinical practice
- Define the classification, prevalence, manifestations, and pathophysiology, of hepatorenal syndrome (HRS)
- Review updated HRS guidelines and recommendations, including treatment goals in HRS

Prevalence and Etiology of HRS-AKI in Cirrhosis



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

Stages of Acute Kidney Injury

AKI Stage	Descriptions	Examples
1	Increase of creatinine ≥0.3 mg/dL up to 2-fold of baseline	0.6 ►1.0
2	Increase in creatinine between 2-fold and 3-fold of baseline	0.6 ►1.8
3	Increase in creatinine >3-fold of baseline or creatinine >4 mg/dL with an acute increase ≥0.3 mg/dL or initiation of RRT	0.6 ►2.4

Biggins SW et al. *Hepatology*. 2021.

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

Updated Classification

Old	New	
HRS-1	HRS-AKI	
HRS-2	HRS-NAKI	HRS-AKD HRS-CKD

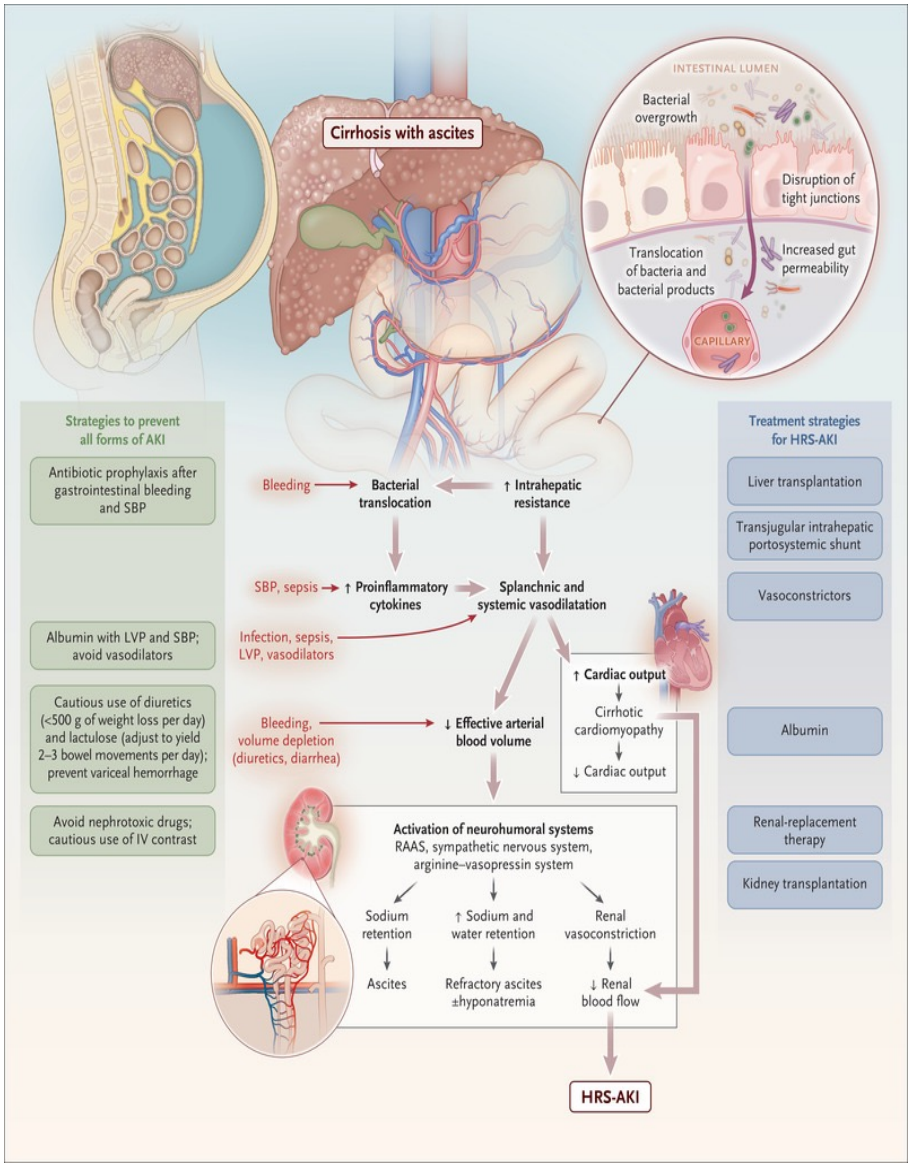
Criteria to Diagnose HRS-AKI

Cirrhosis with ascites
Diagnosis of AKI according to International Club of Ascites-Acute Kidney Injury† criteria
No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin infusion (1 g/kg body weight per day)
Absence of shock
No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, or iodinated contrast media)
No signs of structural kidney injury, as indicated by proteinuria (>500 mg per day), microhematuria (>50 red blood cells per high-power field), and/or abnormal renal ultrasonography

Angeli P et al. *J Hepatol.* 2019.

Pathophysiology of Hepatorenal Syndrome and Acute Kidney Injury in Patients with Cirrhosis

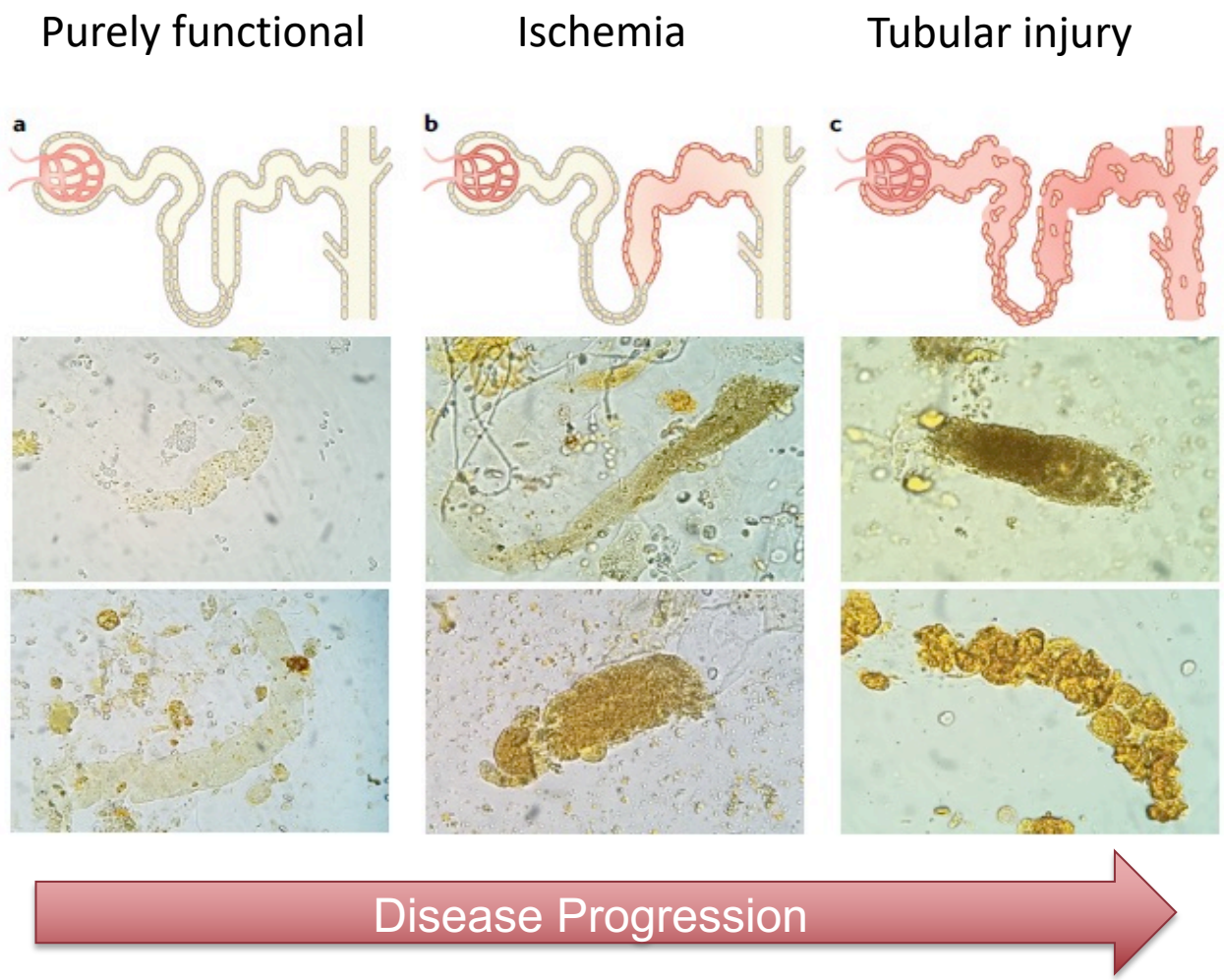
- A sine qua non for the development of HRS-AKI is the presence of ascites and is often associated with hyponatremia, a low mean arterial pressure, and oliguria.
- Factors that can precipitate AKI in a patient with cirrhosis (even without ascites) or HRS-AKI are indicated by red arrows.
- Strategies to prevent all forms of AKI (including HRS-AKI) in patients with cirrhosis are shown.



IV-intravenous, LVP large-volume paracentesis, RAAS renin–angiotensin–aldosterone system, and SBP spontaneous bacterial peritonitis.

Nadmi MK. Garcia-Tsao G. *NEJM*. 2023

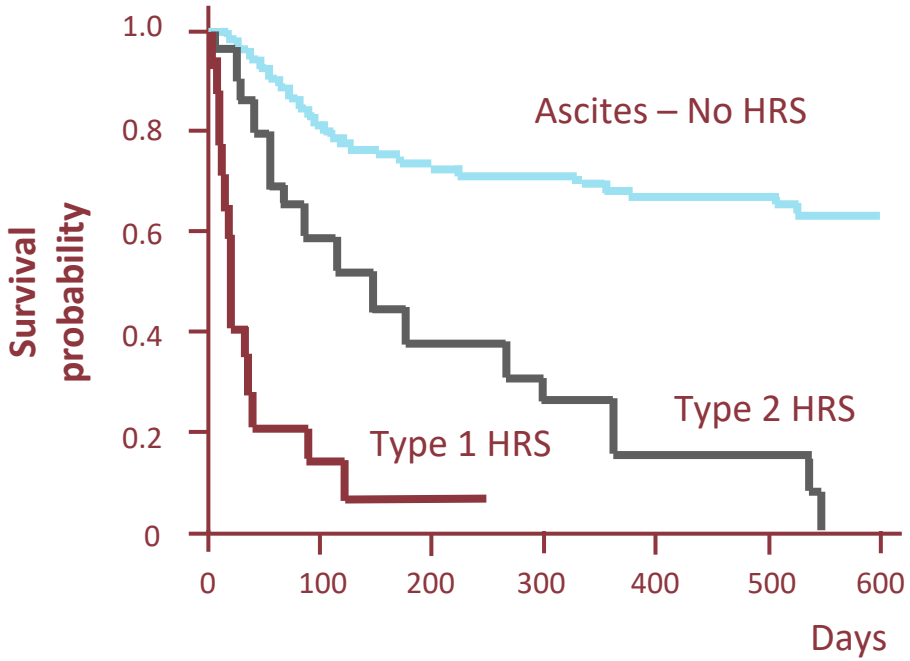
Model Showing the Evolution of HRS-1



Velez J, et al. *Nephrology*. 2020

Outcome of Hepatorenal Syndrome

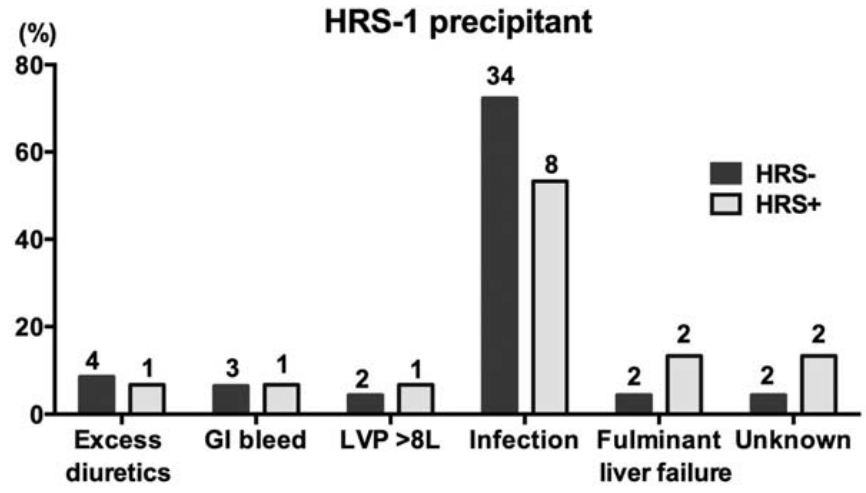
- Increased mortality
- Dependency on hemodialysis
- Increased health care utilization
- Decrease quality of life
- Decrease post-transplant renal function



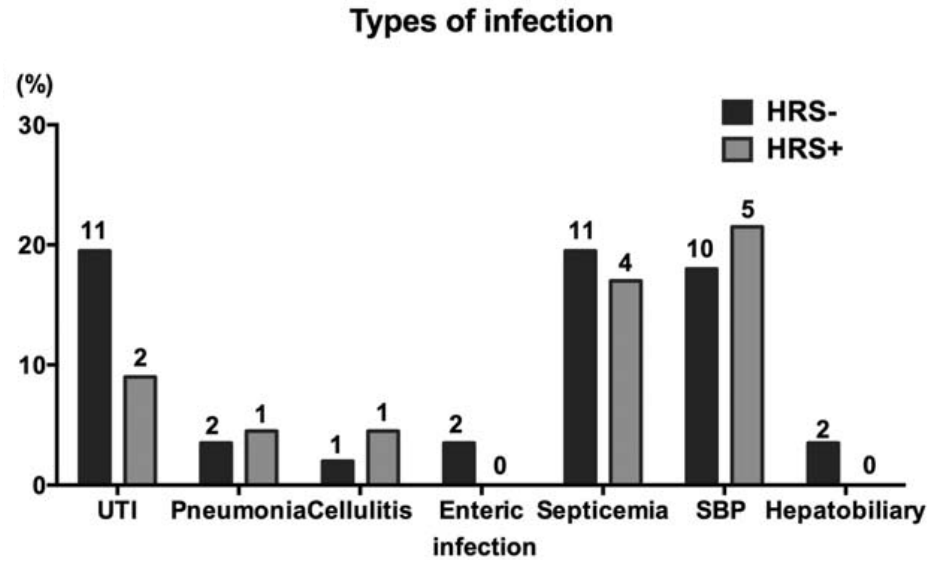
Arroyo et al. *J Hepatol.* 2007.

Precipitants and Types of Infection Associated with Hepatorenal Syndrome

Frequencies of precipitants for HRS1 in the HRS– (reversed) and HRS+ groups

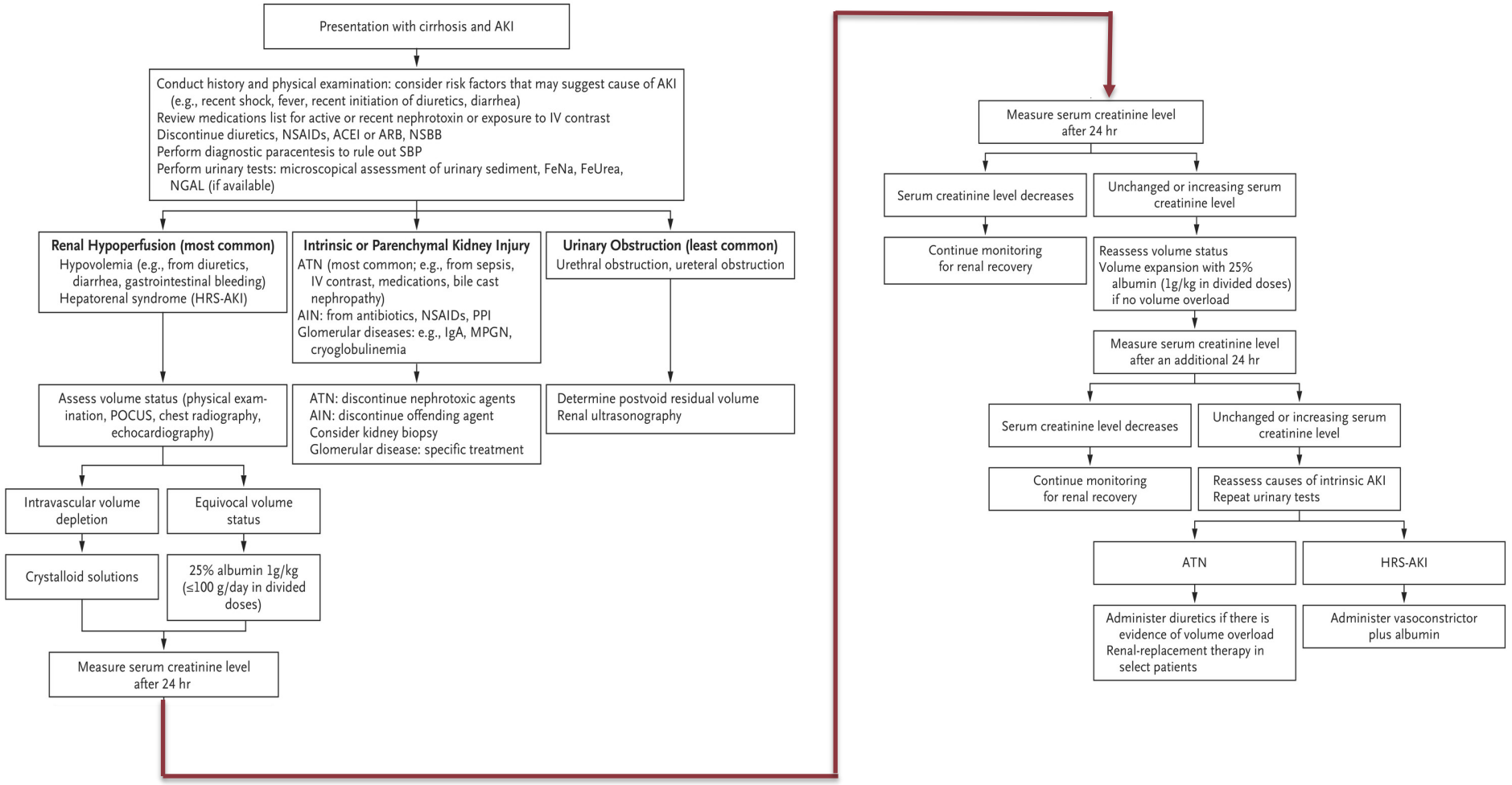


Frequencies of types of infections as precipitants for HRS1 in HRS– (reversed) and HRS+ groups



Wong F, et al. *Liv Transplant* 2015

Workup and Management of Acute Kidney Injury in a Patient with Cirrhosis



Nadmi MK. Garcia-Tsao G. *NEJM*. 2023

Vasoconstrictor Dosing and Administration for HRS-AKI

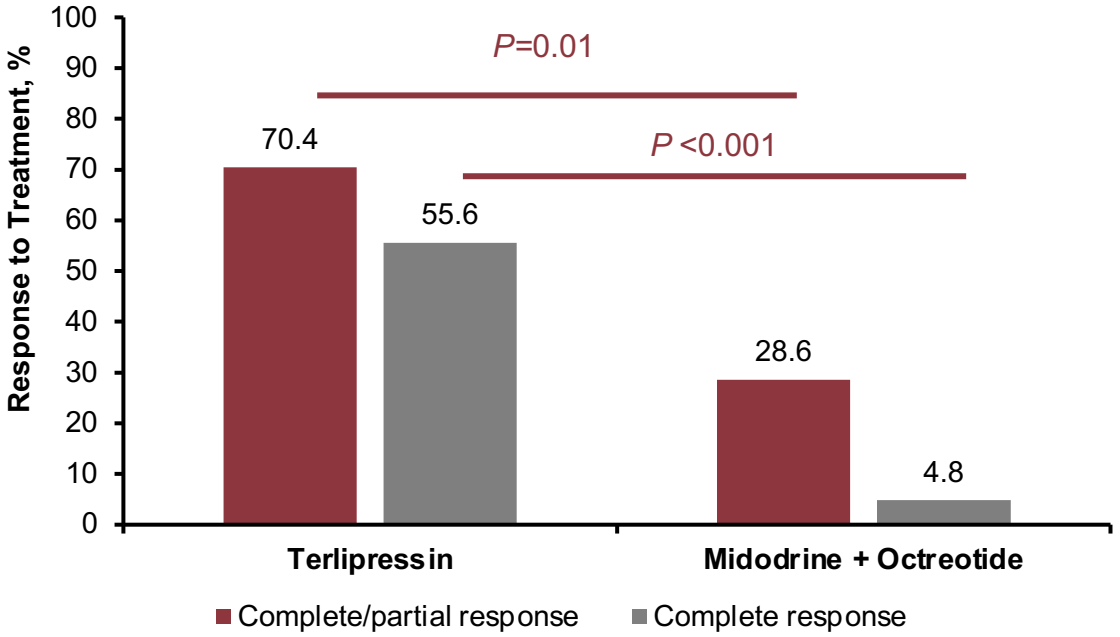
- Several randomized controlled trials and meta-analyses have shown that vasoconstrictors, either terlipressin or norepinephrine, in combination with albumin are effective in improving kidney function in patients with HRS-AKI, with the response rate of 20%-80%

Drug	Dosing and Administration
Terlipressin	Vasoconstrictor of choice for treating HRS-AKI
Norepinephrine	Continuous IV infusion starting at 0.5 mg/hour to achieve an increase in mean arterial pressure of at least 10 mm Hg or an increase in urine output of >200 mL/4 hours If at least one of these goals is not achieved, increase every 4 hours in increments of 0.5 mg/hour up to a maximum of 3 mg/hour
Oral midodrine in combination with octreotide	Midodrine 5 to 15 mg per os every 8 hours Octreotide 100 to 200 µg every 8 hours or 50 µg/hour IV

Biggins SW et al. *Hepatology*. 2021.

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

- Randomized controlled study (not blinded)
- 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



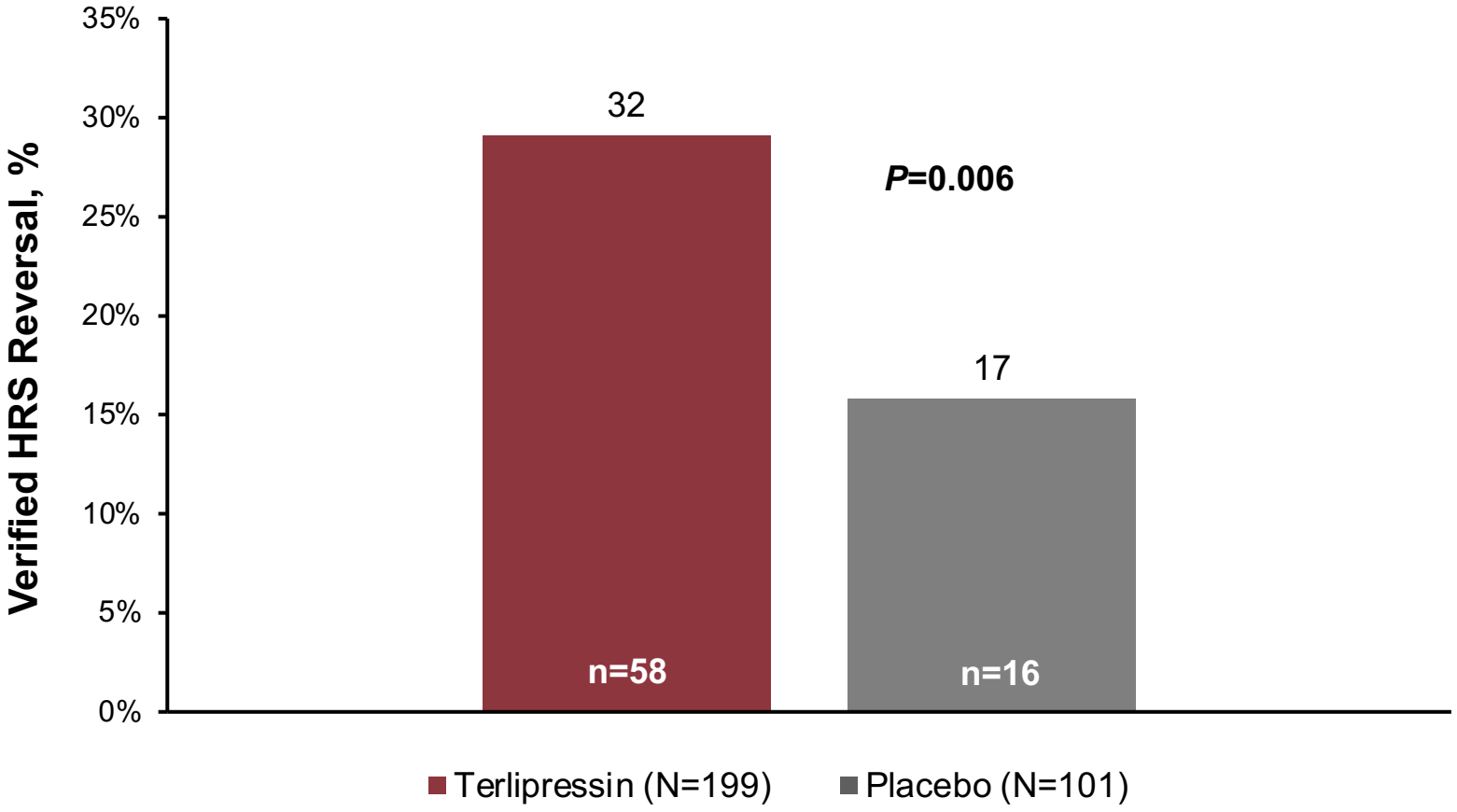
Cavallin M et al. *Hepatology.* 2015

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. *N Engl J Med*. 2021.

Primary Endpoint: Verified HRS Reversal (CONFIRM Study)



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

Primary End Points Included in Multiplicity Adjustment

End Point	Terlipressin (n [%])	Placebo (n [%])	P Value
Verified reversal of HRS† Clinical success	63/199 (32)	17/101 (17)	0.006
Clinical failure*	121/199 (61)	81/101 (80)	
Competing event‡			
Liver transplantation	10/199 (5)	2/101 (2)	
Death	5/199 (3)	0/101	

*All patients who discontinued their assigned regimen before meeting the criteria for clinical success: if the sCr level had not improved by day 4; or if the sCr level had not decreased to 1.5 mg or less by day 14. If they received renal-replacement therapy, underwent TIPS placement, or received open-label vasopressor therapy or underwent liver transplantation before day 14

†Verified reversal of HRS was defined as two consecutive serum creatinine measurements of 1.5 mg per deciliter or less at least 2 hours apart and survival without renal-replacement therapy for at least 10 days.

‡ Competing events included deaths or liver transplantations that occurred before the patient met the criteria for clinical success or failure.

Wong F et al. *N Engl J Med*. 2021

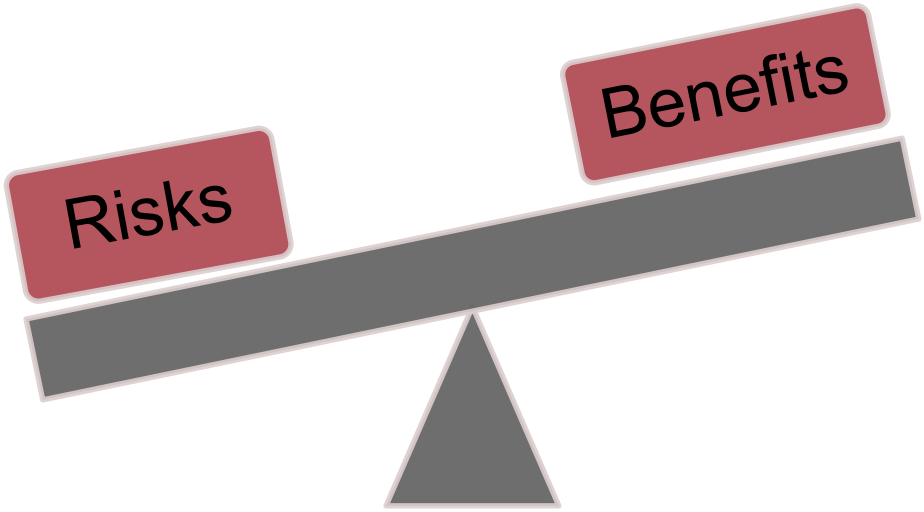
Incidence of Adverse Events (>10% Terlipressin Patients) (CONFIRM Study)

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.

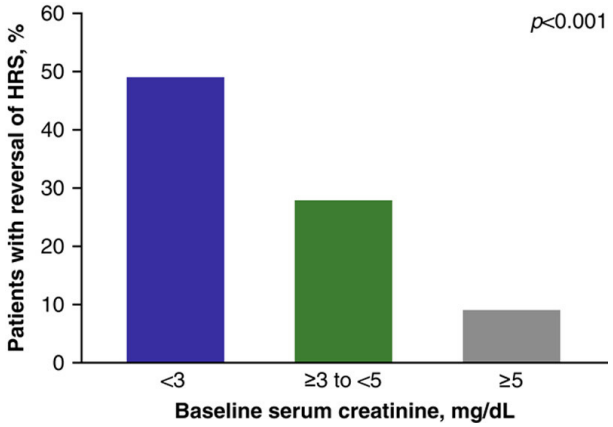
Tipping the Scale of Terlipressin: Benefits and Risks



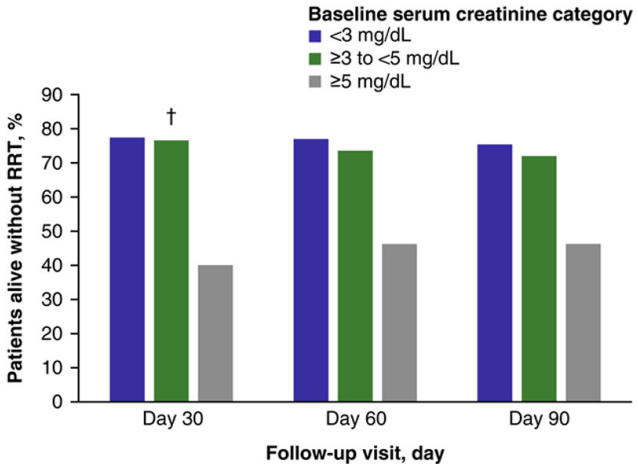
- Serum Creatinine > 5mg/dL
- ACLF 3
- Patients with fluid overload
- SpO_2 <90%

Improved Response to Terlipressin in Patients with Hepatorenal Response when Treated Earlier

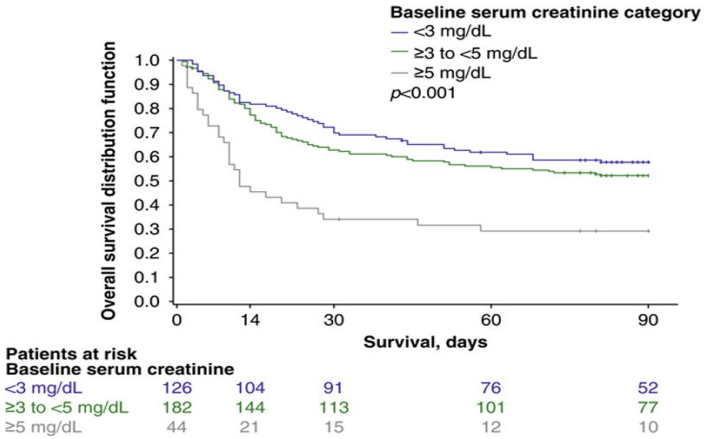
Percent of patients in the terlipressin treatment group who had HRS reversal



Percent of patients who were alive without in terlipressin group



Overall survival in terlipressin group



Curry MP et al, *Hepatology Communications*:e1307, January 2023

Acute on Chronic Liver Failure (ACLF)

ACLF grade 1 includes 3 subgroups:

- patients with single kidney failure

- patients with single liver, coagulation, circulatory or lung failure that is associated with creatinine levels ranging from 1.5 mg/dl to 1.9 mg/dl or hepatic encephalopathy grade 1 or grade 2, or both patients with single brain failure with creatinine levels ranging from 1.5 mg/dl to 1.9 mg/dl

ACLF grade 2 includes patients with 2 organ failures

ACLF grade 3 includes patients with 3 organ failures or more had ACLF grade 3

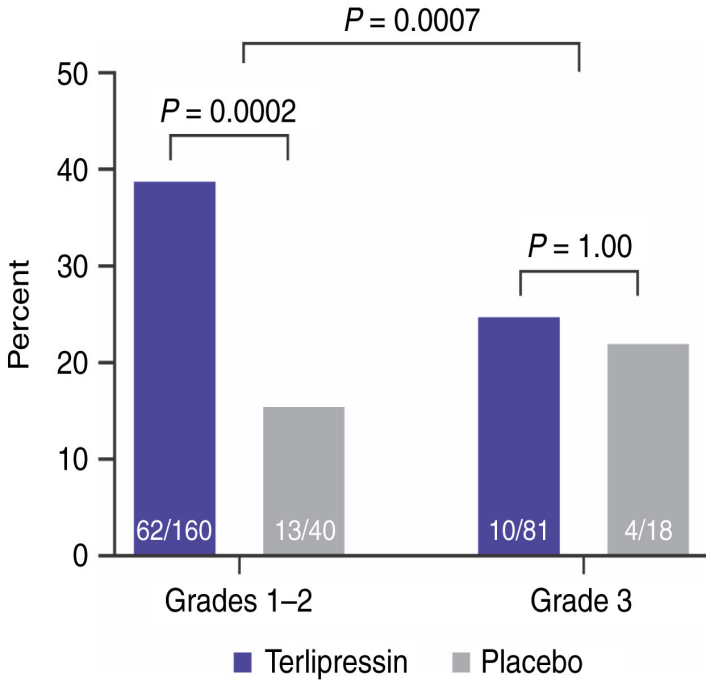
The Chronic Liver Failure-Consortium Organ Failure scale				
Organ system	**Variable**	**Scale**		
		1 point	2 points	3 points
Liver	Bilirubin (mg/dl)	<6.0	≥6.0 to <12.0	≥12
Kidney	Creatinine (mg/dl)	<1.5	≥2.0 to <3.5	≥3.5 or use of RRT
		>1.5 to <2.0		
Cerebral	HE grade (West Haven criteria)	0	I - II	III – IV or endotracheal intubation for HE
Coagulation	INR	<2.0	≥2.0 to <2.5	≥2.5
Circulation	MAP (mm Hg)	≥70	<70	Use of vasopressors
Respiration	PaO_2/FiO_2 SpO_2/FiO_2	>300 >357	>200 to ≤300 >214 to ≤357	≤200 ≤214 Or use of mechanical ventilation

Calculator: https://www.efclif.com/scientific-activity/score-calculators/clif-c-aclf

Zaccherini G, et al. *J Hepatol* 2021

Terlipressin use and respiratory failure in patients with HRS-1 and severe acute-on-chronic liver failure

Renal failure reversal by ACLF* grade with terlipressin versus placebo.



Quartiles of prior albumin (g)	Incidence of respiratory failure n/N (%)	
	Terlipressin	Placebo
≤218.75 g	5/50 (10%)	1/24 (4.2%)
>218.75 g to ≤325 g	9/59 (15.3%)	2/23 (8.7%)
>325 g to ≤450 g	10/53 (18.9%)	1/24 (4.2%)
>450 g	4/36 (11.1%)	1/27 (3.7%)

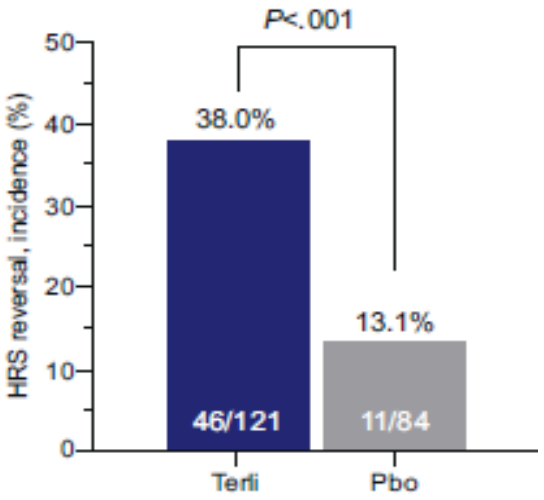
*ACLF ~ acute-on-chronic liver failure

Wong F, et al. *Aliment Pharmacol Ther* 2022

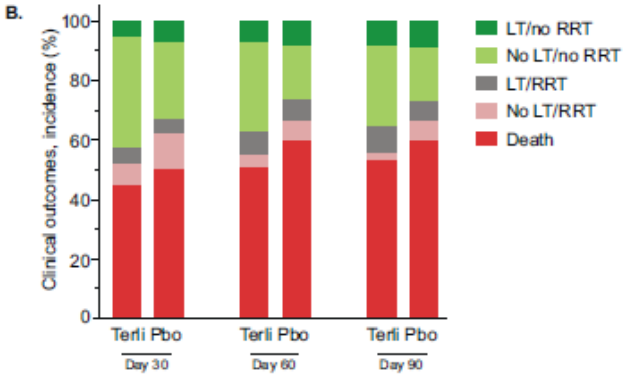
Terlipressin Treatment Is Associated With Reversal of HRS in Patients With Alcoholic Hepatitis

	Terlipressin N=121	Placebo N=84
ACLF grade 3	70.2%	72.6%
Mean MELD score	35.5	35.0
Prior steroid therapy	17.4%	11.9%

HRS reversal



Clinical outcomes by treatment in patients with alcoholic hepatitis



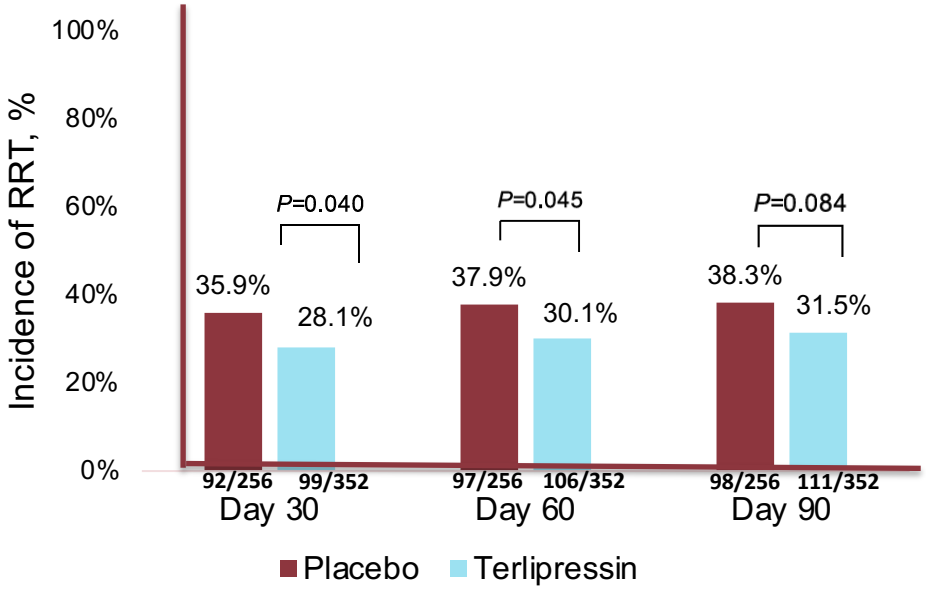
Outcomes, n (%)	Day 30		Day 60		Day 90	
	Terli	Pbo	Terli	Pbo	Terli	Pbo
LT/no RRT	7 (5.8)	6 (7.1)	9 (7.4)	7 (8.3)	10 (8.3)	7 (8.3)
No LT/no RRT	45 (37.2)	22 (26.2)	36 (29.8)	15 (17.9)	33 (27.3)	15 (17.9)
LT/RRT	6 (5.0)	4 (4.8)	10 (8.3)	6 (7.1)	10 (8.3)	6 (7.1)
No LT/RRT	9 (7.4)	10 (11.9)	5 (4.1)	6 (7.1)	4 (3.3)	5 (6.0)
Death	54 (44.6)	42 (50.0)	61 (50.4)	50 (59.5)	64 (52.9)	51 (60.7)

Data were pooled from A Double-Blind, Randomized, Placebo-Controlled, Multicenter Phase III Study of Intravenous Terlipressin in Patients With Hepatorenal Syndrome Type 1 (OT-0401), A Multi-Center, Randomized, Placebo-controlled, Double-Blind Study to Confirm the Reversal of Hepatorenal Syndrome Type 1 With Lucassin® (Terlipressin) (The REVERSE Study), and A Multi-Center, Randomized, Placebo-Controlled, Double-Blind Study to Confirm Efficacy and Safety of Terlipressin in Sub-jects With Hepatorenal Syndrome Type 1 (The CONFIRM Study). ITT, intent-to-treat; LT, liver transplantation; Pbo, pla-cebo; RRT, renal replacement therapy; Terli, terlipressin.

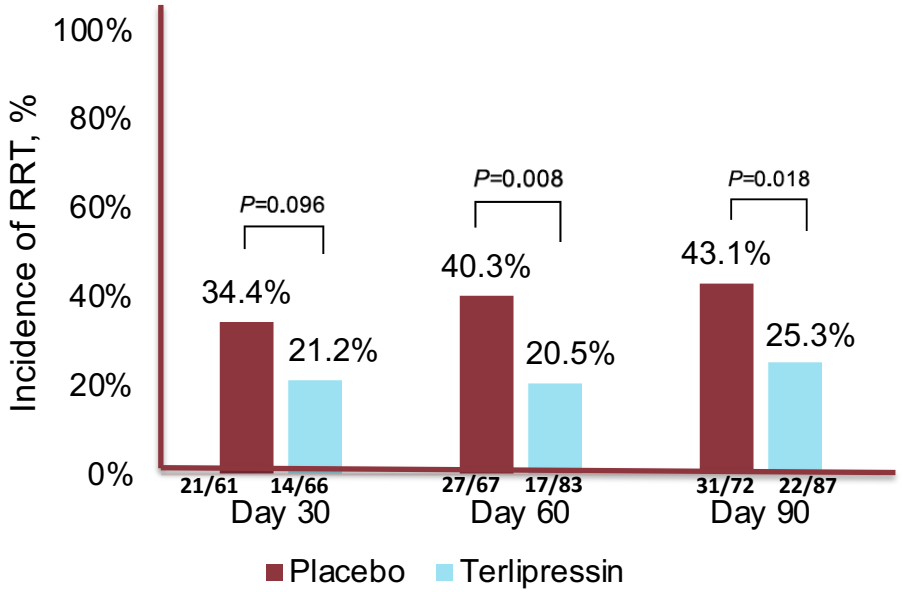
Sigal SH, et al. *Clin Gastroenterol Hepatol*. 2023.

Incidence of Renal Replacement Therapy all Patients and in Liver Transplant Recipients

Renal Replacement Therapy all Patients



Renal Replacement Therapy all Patients and in Liver Transplant Recipients



[a] Patients with an SLKT were excluded.

[b] For percentages, the denominator is number of patients who had a LT, and the numerator is the number of patients who had RRT after the LT, calculated from Day 1 to each time point.

[c] Population pooled from OT-040111, REVERSE12, and CONFIRM 13 studies.

ITT, intent-to-treat, LT, liver transplantation; RRT, renal replacement therapy, SLKT, simultaneous liver-kidney transplant

Velez JC, et al. *Kidney360* 2023

HRS Reversibility: Impact on MELD Score

- Impact on improving renal function and lowering MELD score on transplant prioritization

- How to ascribe the correct priority on the waiting list to responders to pharmacological treatment.
  - Rescue prioritization strategy
  - Weighted pretreatment sCreatinine

- When should a simultaneous liver kidney transplantation (SLK) be considered in non-responders to pharmacological treatment

Angeli P, et al. *J Hepatology*. 2015; Sharma P, et al. *Liv Transpl*. 2020.

Prevention and Risk Factor Management of HRS-AKI in Patients With Cirrhosis

Prevention

- 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

Risk Factor Management

- Withdrawal of nephrotoxic drugs
- Reduction or withdrawal of diuretics
- Detection and treatment of infections
- Volume replacement (if severely volume-depleted) initially using 25% albumin or crystalloids, preferentially balanced

Tapper EB et al. *Am J Med.* 2016.

Future Directions

- Continuous infusion vs bolus
- Outpatient treatment
- Better measures of kidney function for defining AKI and HRS

Conclusions

- HRS is defined as AKI that does not respond to volume resuscitation upon correction of sepsis and in the absence of other renal toxic insult
- Significant cause of morbidity/mortality and early recognition and intervention is needed
- HRS-AKI requires an aggressive management strategy

Thank you!