HRS: Positioning Treatments

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Disclosures

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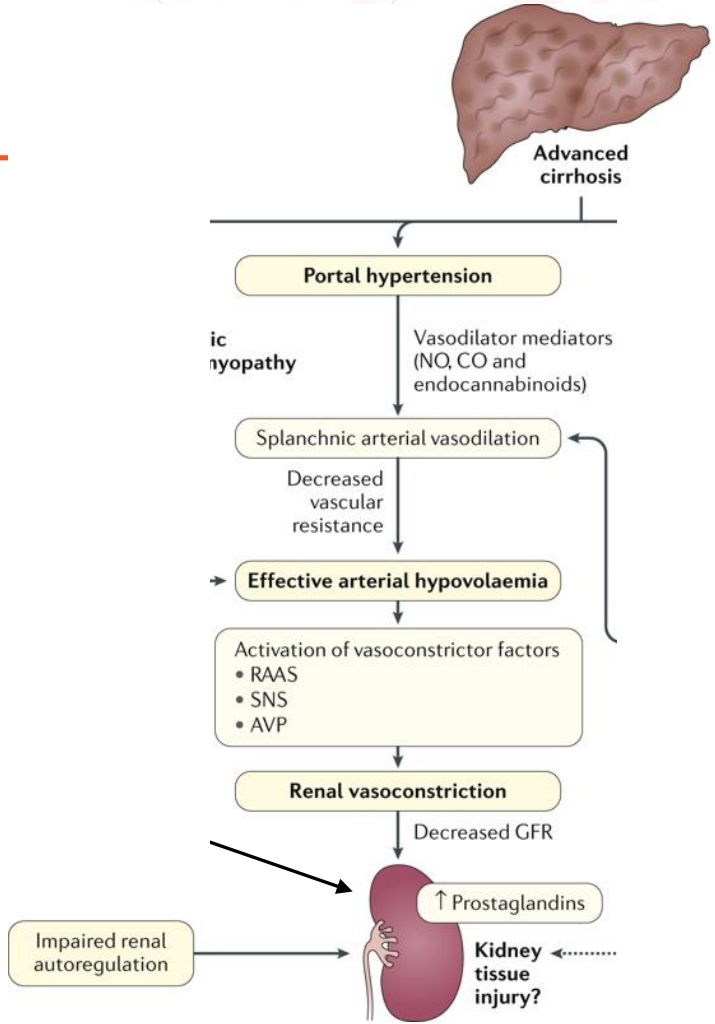
- Consultant/Advisor: Mallinckrodt

Outline

- Overview of pathophysiology of HRS
  - Rationale for treatment strategies
- Octreotide, midodrine
- Norepinephrine
- Terlipressin
- Albumin
- TIPS
- Liver Transplantation

Pathophysiology of AKI-HRS

NO, nitric oxide
CO, carbon monoxide
RAAS, renin angiotensin aldosterone
SNS, sympathetic nervous system
AVP, arginine vasopressin
PAMPs, pathogen-associated molecular patterns
DAMPs, damage-associated molecular patterns
TNF, tumor necrosis factor



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

Treatment of AKI-HRS

Albumin	• Volume expansion • Anti-inflammatory
Vasoconstrictors	• Reduce splanchnic and/or peripheral vasodilation • Increase MAP; downregulate RAAS, SNS • Improve renal perfusion • Examples: Norepinephrine, Terlipressin, Midodrine/Octreotide
Liver Transplantation	• Definitive treatment for the complications of ESLD • Scarce resource • Renal dysfunction may not recover if prolonged/delayed
Renal Replacement Therapy (RRT)	• Does not restore renal function • Does not improve prognosis • Challenging in decompensated cirrhotic patients

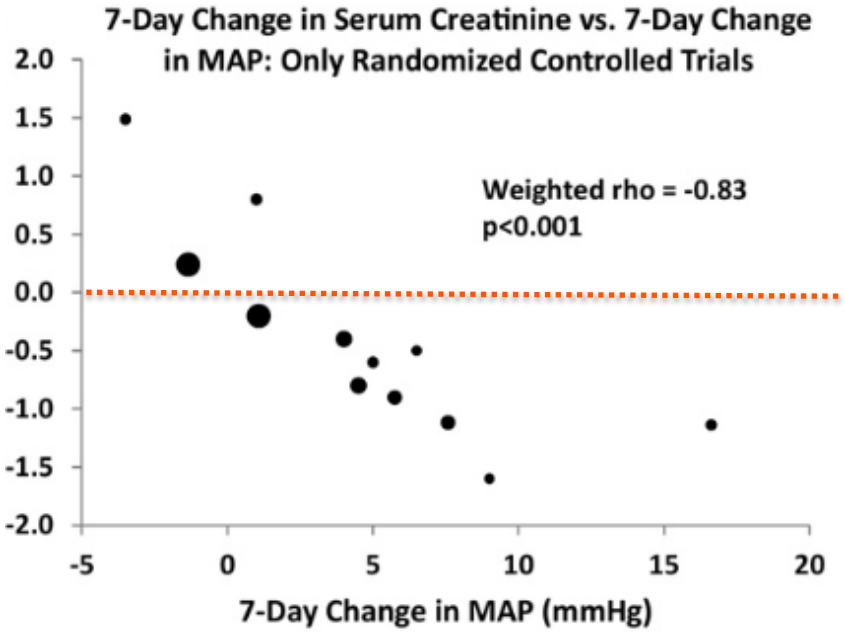
Bernardi M et al. *Critical Care*. 2012;16:211; Garcia-Martinez R et al. *Hepatology*. 2013 Nov;58(5):1836-46. European Association for the Study of the Liver (EASL). *J Hepatol.* 2018;69(2):406-60; Runyon BA. AASLD. *Hepatology*. 2013;57(4):1651-3.

Vasoconstrictors for HRS

Agent	MOA	Dosing
Midodrine plus octreotide	α-adrenergic agonist and somatostatin analog	Begin midodrine at 7.5mg to 12.5mg oral Q8h and octretide at dose 100µg to 200µg SC Q8h or 50 μg/h IV infusion Goal: increase MAP by 10 mmHg
Norepinephrine	α and Beta-adrenergic agonist	Dose 0.5mg/hr to 3.0mg/hr continuous IV Goal: increase MAP by 10 mmHg
Terlipressin	Vasopressin analog (V1a, V1b > V2)	Bolus: Begin 1 mg IVP Q6h; Increase to 2mg IVP Q6h if SCr does not decrease by ≥ 25% from baseline by d3-4 Continuous: Bolus 0.5mg IVP, then continuous IV 2mg/24h; titrate to maximum 12mg/24h

Vasoconstrictors in HRS: Pooled Analysis – Importance of MAP

- 501 patients with AKI-HRS (mostly type-1) across 21 studies
- Increase in MAP associated with improvement in kidney function regardless of drug(s) studied
- The higher the baseline SCr, the greater the increase in MAP needed



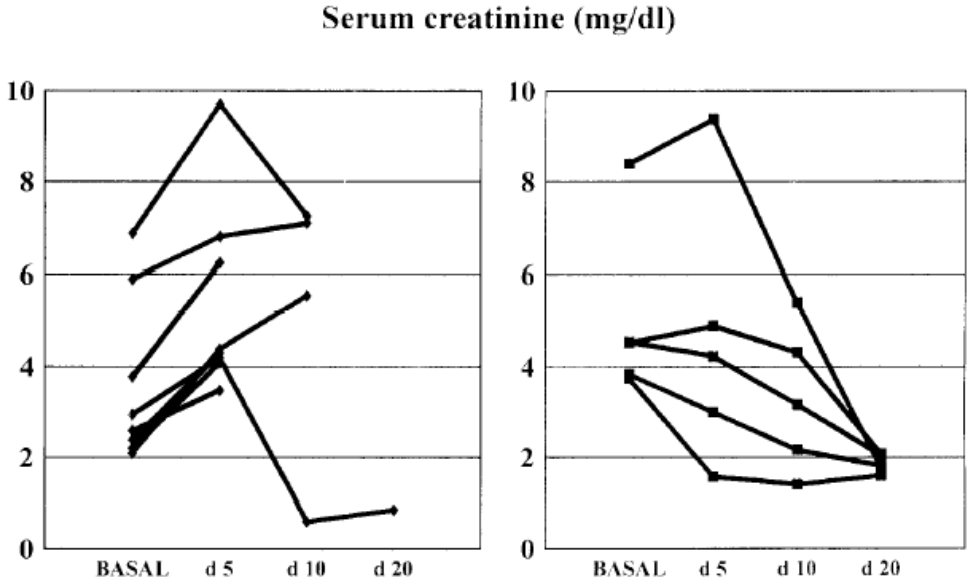
Velez JCQ, Nitert, PJ. *Am J Kidney Dis*. 2011;58:928-938.

Octreotide and Midodrine for HRS

- Angeli – Midodrine alone – no benefit in HRS-2 (n=8) (Hep 1998)
  - Despite reducing plasma renin; despite improved GFR in non-HRS w/ ascites
- Pomier-Layrargues – Octreotide+Alb – no benefit (n=14) (Hep 2003)
- Angeli – Octreotide and Midodrine – pilot (n=5) (Hep 1999)
- Esrailian et al – Octreotide and Midodrine – retrospective
  - 60 pts vs 21 controls; sustained improvement in renal function in 40% vs 10% (p = 0.01); 30-day mortality 43% vs 71% (p = 0.03)
- Skagen et al – Octreotide and Midodrine – retrospective
- No RCT of combined M+O against placebo

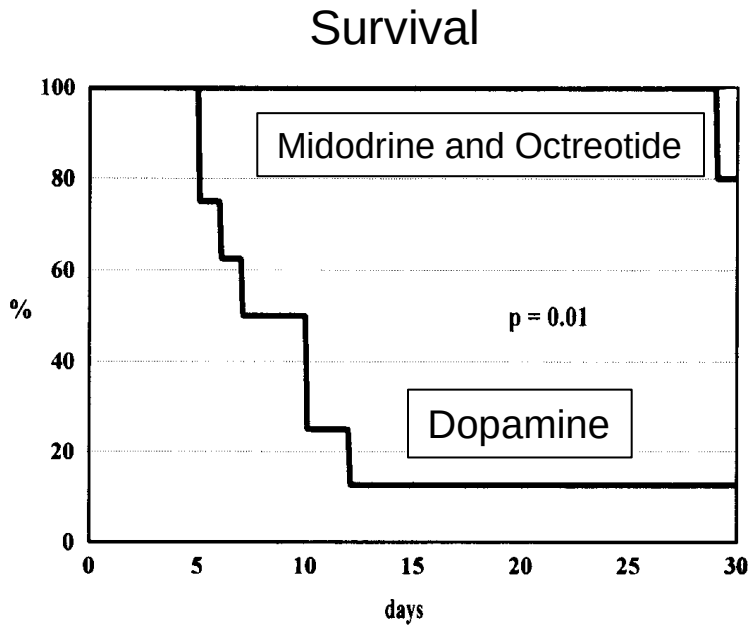
Angeli et al. *Hep*. 1998; Pomier-Layrargues et al. *Hep*. 2003; Angeli et al. *Hep*. 1999; Esrailian et al. *DDS*. 2007; Skagen et al. *J Clin Gastro.* 2009.

Octreotide and Midodrine vs Dopamine – Pilot



Dopamine

Midodrine and Octreotide



Oct+Mido: 5/5 improved; 2 LTs and 1 other alive 16mos f/u; 2 others died at 29,75d
Controls (Dopa+Alb): 7/8 died within 2 weeks, 1 improved → LT

Angeli et al. *Hepatology.* 1999;29:1690-97

Oct/Mido for HRS-1 – Retrospective Study

- 81 patients (IAC criteria), 2000-2002
  - 60 treated with Octreotide 100-200mcg SQ TID and Midodrine 5-15mg PO TID (for inc MAP 15 mmHG)
    - Mean 16 days of treatment
  - 21 concurrent untreated controls
  - All received albumin prior to confirming diagnosis (average 120g)
- Sustained improvement in renal function in 40 vs. 10% (p = 0.01)
- 30-day mortality 43 vs. 71% (p = 0.03)

Esrailian et al. *Dig Dis Sci*. 2007.

Oct/Mido for HRS – Retrospective Study

- 162 patients with HRS (IAC, HRS-1, n=102; HRS-2, n=60)
- Historical Control group (n=87), 1997- April 2001
- Treatment Group (n=75), May 2001- June 2004
  - Octreotide, 100-200mcg SQ TID, Midodrine 7.5-15mg PO TID
    - Mean duration 8.4 +/- 9.6 days (range 1-50 days)
  - Both groups given Albumin 50-100gm/day
- After mean f/u 115 days:
  - Survival improved with treatment (OR 0.39, 0.25-0.61, p=0.0001)
    - Median transplant-free survival: 101d vs. 18d (p<0.0001)
  - GFR improved over 30 days (p=0.03),
    - But creatinine did not (p=0.11)
  - More transplants in treated group, 45% vs. 26% (p=0.02)

Skagen et al. *J Clin Gastro*. 2009.

Norepinephrine for Treatment of HRS

- Alpha- and beta- adrenergic agonist
- Inotropic effect with increased CO
- Peripheral vasoconstrictor to increase MAP
- Risk of arrhythmias, ischemia
- Typically requires central line placement and ICU monitoring
- Pilot study in HRS-1 (n=12) – reversal in 10/12 patients (1)
- No RCT vs placebo
- Two small RCT showing equivalent (2) and superior (3) to Midodrine and Octreotide
- Additional studies compared to terlipressin

(1) Duvoux C et al. *Hepatology.* 2002; (2) Tavakkoli et al. *IJPM.* 2012; (3) Mahmoud E et al. *Frontiers Pharm.* 2021.

Low-Dose Norepinephrine for AKI-HRS: Outside the ICU

Retrospective case series:

AKI-HRS by updated ICA criteria

n=20 (M+O non-responders)

NE continuous infusion

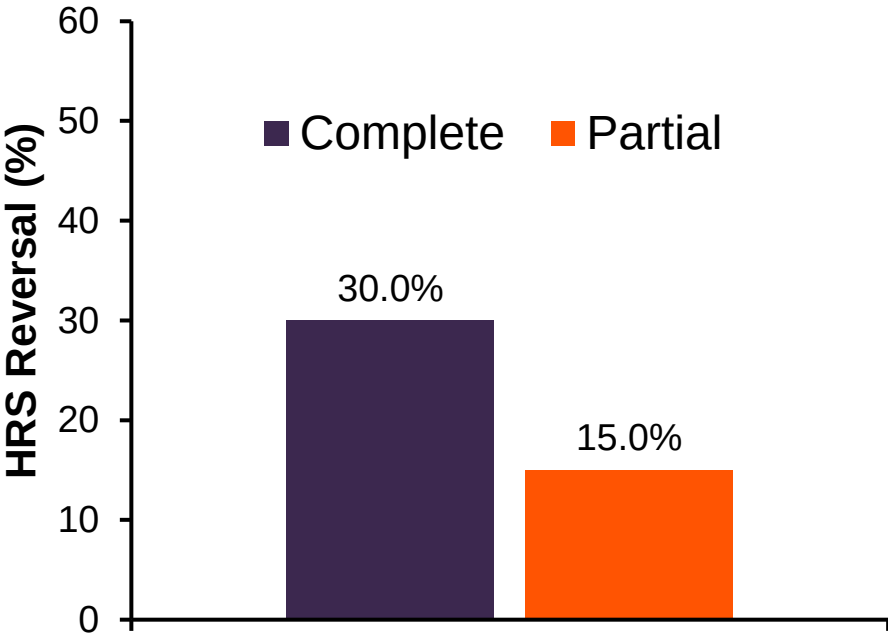
- 5->10 mcg/min (0.3->0.6 mg/h) titrated
- Target increase MAP by 10 mmHg

30% complete and 15% partial response

Achieving MAP goal ≥ 10 mmHg predicted response (89% vs 36%, p=0.05)

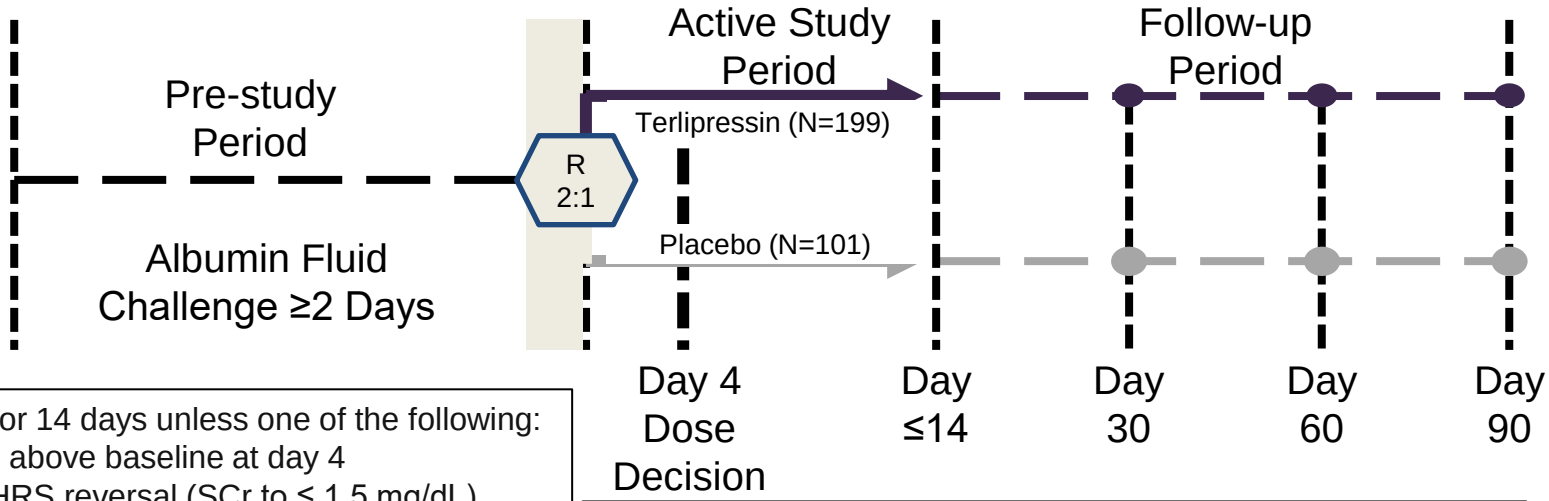
AEs – 25% w/ arrhythmias (ST, SVT, VT)

– 2 discontinued therapy early



Kwong A et al. *Liver Transplantation*. 27;1095–1105 2021.

Terlipressin – CONFIRM Study Design

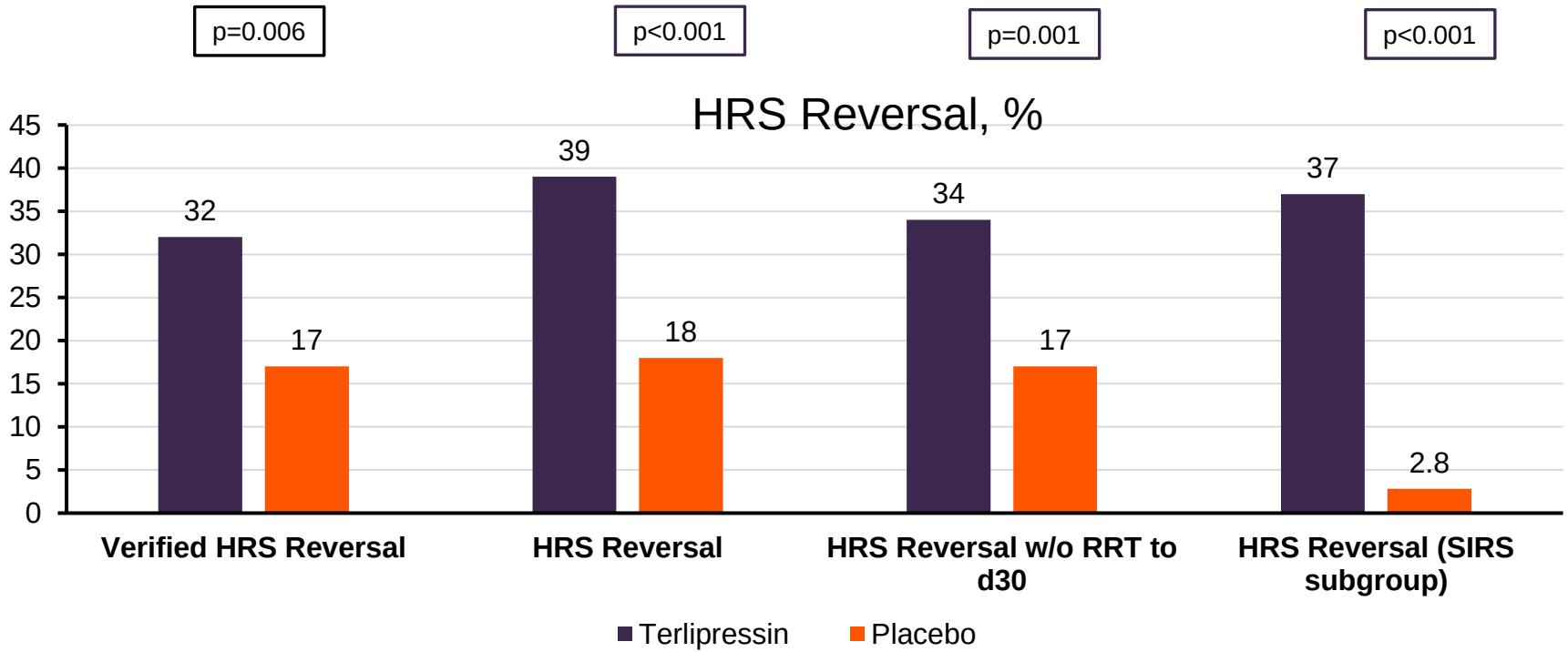


Treatment for 14 days unless one of the following:
- SCr at or above baseline at day 4
- Verified HRS reversal (SCr to ≤ 1.5 mg/dL)
- Renal replacement therapy (RRT)
- Liver transplantation

Primary endpoint:
Verified HRS reversal (SCr ≤1.5, twice), alive w/o RRT for ≥10d

Wong F et al. *NEJM.* 2021

Terlipressin CONFIRM Trial – Primary and Key Secondary Endpoints



Wong F et al. *NEJM.* 2021

Terlipressin Bolus vs Continuous Infusion

- Cavallin et al – RCT HRS-1, n=78
  - Overall response rates similar, 76% v 65%
    - And similar complete response rates, 56 v 46%
  - Overall dose lower w/ continuous, 2.2 vs 3.5mg/d
  - Overall lower rates of AEs w/ continuous, 35 vs 62%
    - And lower rates of severe AEs, 21 v 43%
- InFUSE Study – prospective study of continuous terlipressin in AKI-HRS in the US, n=50
  - Abstract to be presented at EASL 6/2023

Cavallin M et al. *Hepatology*. 2016; Reddy R et al. EASL. 2023.

Vasoconstrictors in HRS: Terlipressin vs Midodrine+Octreotide

RCT (non-blinded):

n=49 (27 Terli; 22 Mid+Oct)

HRS-1 or severe HRS-2 (SCr>2.5mg/dL)

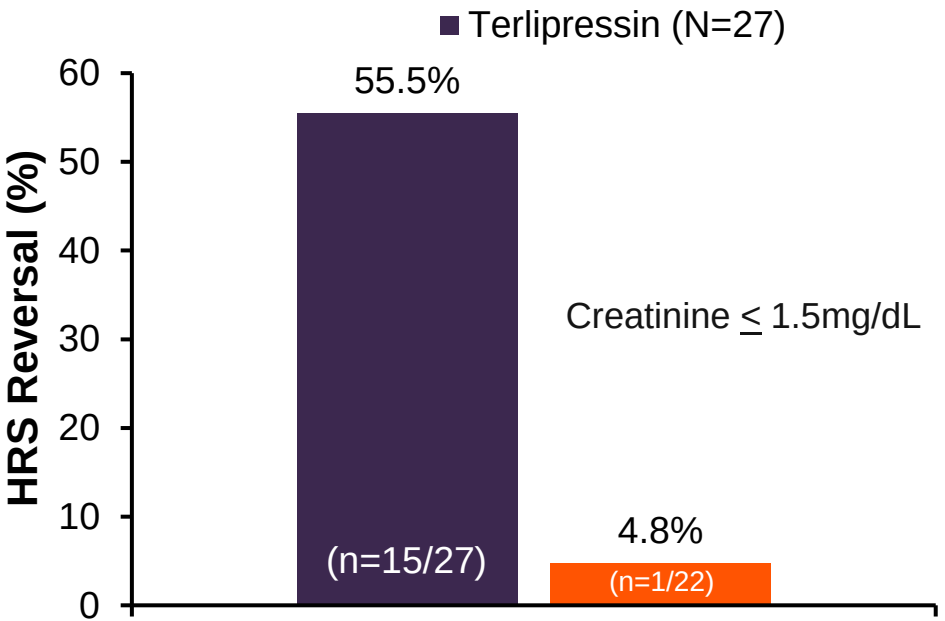
Terlipressin by continuous infusion: 3->12 mg/d

Midodrine (PO) + Octreotide (SQ)

- (M) Titrated 7.5mg TID -> 12.5mg TID
- (O) Titrated 100mcg TID -> 200mcg TID

Albumin 1g/kg D1 and then 20-40g/d

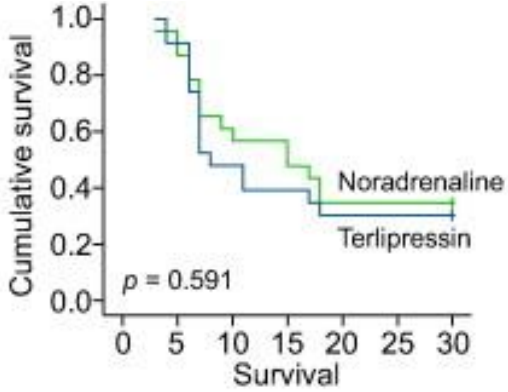
MAP significantly increased w/ Terli but not M+O



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

Vasoconstrictors in HRS: Terlipressin vs Norepinephrine

- n= 46 patients, RCT
- HRS reversal achieved in
  - 9 (39.1%) patients w/ terlipressin
  - 10 (43.4%) patients w/ NE
  - (p = 0.764)



Patients at risk	Day					
	5	10	15	20	25	30
Terlipressin group (n = 23)	20	11	9	7	7	7
Noradrenaline group (n = 23)	21	13	11	8	8	8

Singh V et al. *Journal of Hepatology*. 2012.

Vasoconstrictors in HRS (ACLF/Sepsis): Terlipressin vs Norepinephrine

RCT (open label):

n=120 (60 Terli; 60 Norepi)

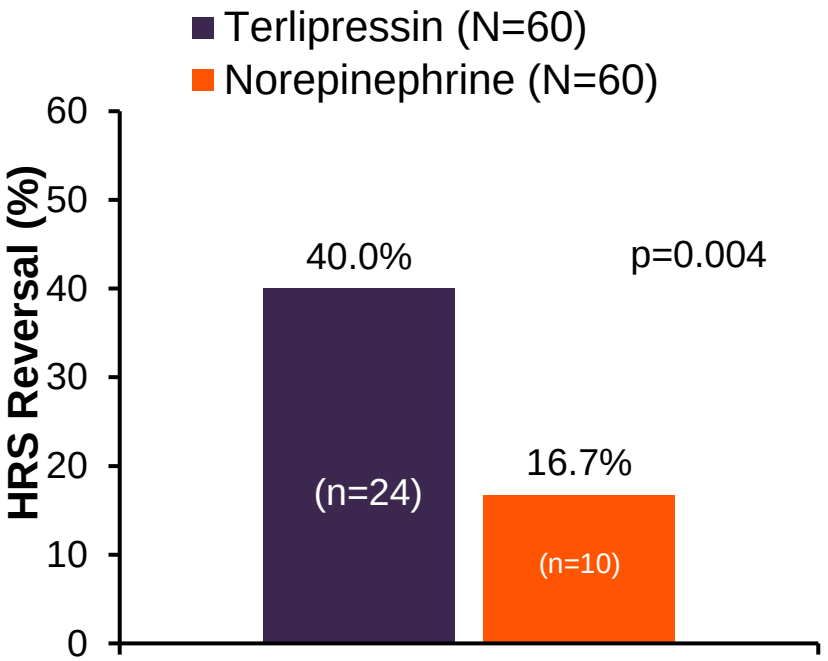
ACLF/sepsis w/ AKI-HRS (Stage 2-3 AKI)

Terlipressin continuous infusion: 2->12 mg/day

Norepinephrine continuous infusion: 0.5->3.0 mg/h

Albumin 1g/kg D1-2 and then 20-40g/d

Significant higher HRS Reversal w/ Terlipressin



Arora V et al. *Hepatology.* 2020;71:600-610.

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RCT (open label):

n=120 (60 Terli; 60 Norepi)

ACLF/sepsis w/ AKI-HRS (Stage 2-3 AKI)

Terlipressin continuous infusion: 2->12 mg/day

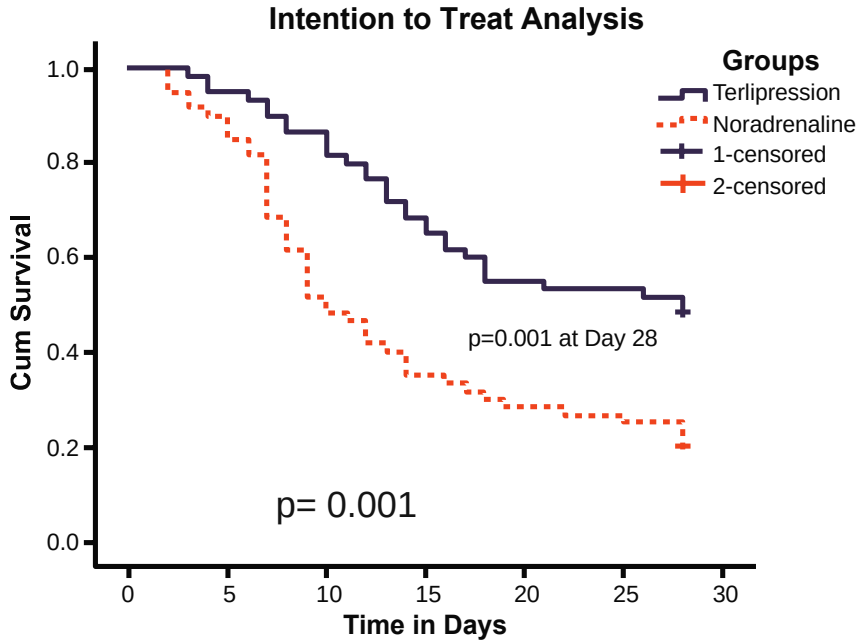
Norepinephrine continuous infusion: 0.5->3.0 mg/h

Albumin 1g/kg D1-2 and then 20-40g/d

Significant reduction in RRT w/ Terli (57% vs. 80%; p= 0.006)

Improved 28-day survival w/ Terli (48% vs. 20%; p= 0.001)

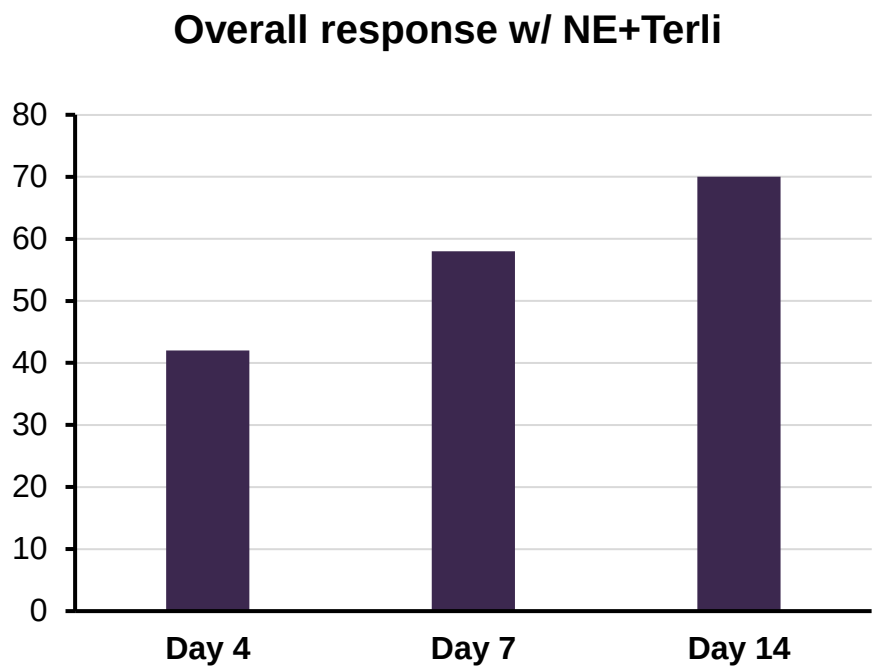
AEs (drug-related): Terli 23% vs Norepi 8% (p= 0.02)



Arora V et al. *Hepatology.* 2020;71:600-610.

Add-On Terlipressin to NE Failure – AKI-HRS

- Progressive AKI despite NE infusion
- Mean age 40
- ASH, NASH, and Viral
- Baseline SCr 2.7
- Mean MELD 26
- “Low dose” bolus Terlipressin added (0.5mg q12h)
- Well tolerated



N=33 patients

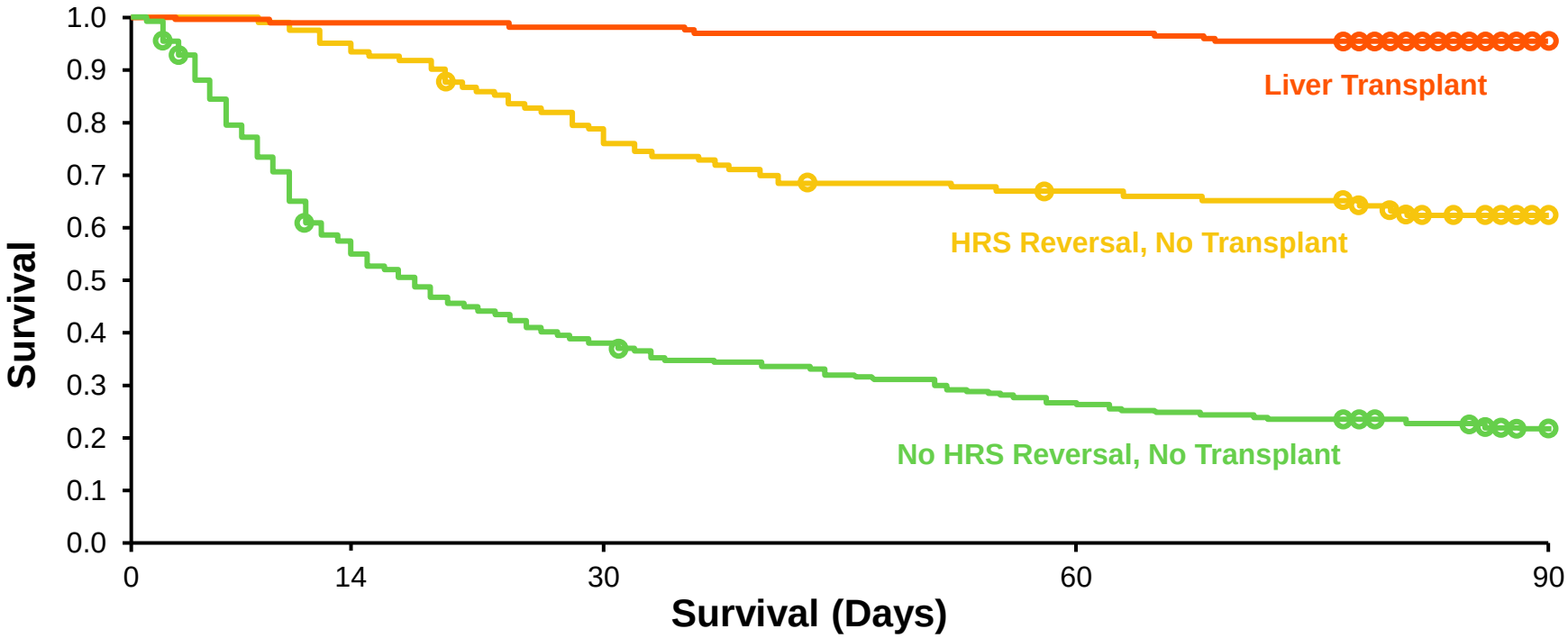
Arora et al. AASLD 2021 Oral Abstract #166.

Meta-analysis of Vasoconstrictors in HRS

	Short term mortality		Reversal of HRS	
	Odds ratio (95% CI)	**Quality of evidence**	**Odds ratio (95% CI)**	**Quality of evidence**
Efficacy vs placebo				
Midodrine + Octreotide Norepinephrine Terlipressin	0.61 (0.19-1.93) 0.75 (0.32-1.76) 0.65 (0.41-1.05)	Low Low Moderate	0.44 (0.06-3.23) **4.17 (1.37-12.50)** **4.48 (1.88-10.67)**	Low Low Low
Efficacy vs Midodrine + Octreotide				
Norepinephrine Terlipressin	1.50 (0.60-3.78) 1.14 (0.39-3.33)	Low Very Low	**10 (1.49-50.00)** **26.25 (3.07-225.21)**	Low Moderate
Efficacy vs Norepinephrine				
Terlipressin	0.93 (0.43-1.98)	Low	**0.99 (0.43-2.23)**	**Very Low**

Facciorusso et al. *Lancet Gastroenterol Hepatol.* 2017; 2: 94–102.

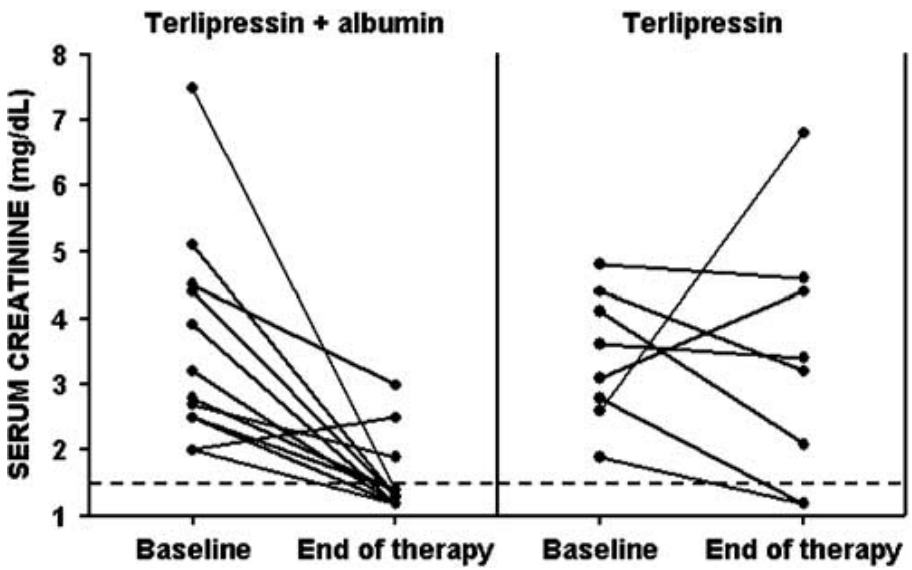
Overall Survival to 90 Days by LT and HRS Reversal Status – *Pooled ITT (3 RCTs, Terlipressin)*



Albumin in HRS

Prospective non-randomized study in HRS-1/2 (n=21)

- Terlipressin w/ or w/o albumin
- HRS reversal in 57%
  - 77% w/ albumin vs 25% without albumin (p=0.03)



Ortega R et al. *Hepatology*. 2002.

Albumin in HRS – Double Edged Sword

- Required for both diagnosis and clinical efficacy
- Benefits beyond oncotic support
- Dosing unclear – range 20-50g/d
- Caution in patients w/ volume overload, hypoxia
- Avoid in patients with CHF, pulmonary edema

TIPS for HRS

- Wong et al – Oct+Mido+Alb for HRS-1 → TIPS (n=14)
  - 10/14 responders to M+O; 5/10 -> TIPS (other 5 contraindicated)
  - All 5 w/ TIPS survived >6M (one transplanted)
    - Normalized renal function,
    - Normalized renin, aldosterone
    - Resolved ascites
- Meta-analysis of TIPS for HRS 1/2 – 9 studies, n=128
  - High rates or improved renal function, 83-93%
  - High rates of hepatic encephalopathy, 49%
  - Suggested mortality benefit, 47-64% at 1-yr

Wong F et al. *Hepatology*. 2004; Song T et al. *Dig Liv Dis*. 2018.

HRS Treatment Guidelines

- AGA – Clinical Practice Update AKI in Cirrhosis (2022)
  - Albumin along with vasoactive agents (terlipressin; if terlipressin is not available, either a combination of octreotide and midodrine; or norepinephrine, depending on institutional preferences).
- ACG – ACLF Clinical Guidelines (2022)
  - In hospitalized patients with HRS-AKI without high grade ACLF or major cardiopulmonary or vascular disease, we suggest terlipressin (moderate quality, conditional recommendation) or norepinephrine (low quality, conditional recommendation) to improve renal function.
- AASLD – Practice Guidance Ascites, SBP, HRS (2021)
  - Vasoconstrictor drugs in combination with albumin. The preferred drug is terlipressin, either as IV bolus or continuous infusion. In settings where terlipressin is not available, norepinephrine should be given. If neither can be administered, a trial of oral midodrine in combination with octreotide may be considered, yet the efficacy is low.
- EASL – Clinical Practice Guidelines Decompensated Cirrhosis (2018)
  - Vasoconstrictors and albumin are recommended in all patients w/ AKI-HRS stage >1A. Terlipressin should be considered first-line. Can be used by IV bolus at 1 mg every 4–6h. However, continuous infusion (initial dose 2mg/day) can reduce the global daily dose and rate of adverse effects. Noradrenaline can be an alternative to terlipressin. However, limited information is available. Midodrine plus octreotide can be an option only when terlipressin or noradrenaline are unavailable, but its efficacy is much lower than that of terlipressin.

Flamm SL et al. *CGH.* 2022; Bajaj JS et al. *AJG.* 2022; Biggins SW et al. *Hepatology.* 2021; Angeli P et al. *J Hepatol.* 2018.

Summary

- AKI-HRS a serious but reversible syndrome
- Early identification and treatment improves outcomes
- Vasoconstrictors+albumin for Stage 2-3, or Stage 1 not responding to supportive care
- Terlipressin first line where available; continuous infusion demonstrates improved benefit:risk profile
- Norepinephrine reasonable option for ICU
- Midodrine and octreotide with minimal benefit
- TIPS can be considered for selected patients
- Liver transplantation is only treatment w/ improved survival