Management of Hepatorenal Syndrome: A Review of Current Therapeutic Options

A PRESENTATION FOR HEALTHTRUST MEMBERS
MAY 31, 2023

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Disclosures

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Objectives for Pharmacists and Nurses

- Recall the pathophysiology and treatment options for hepatorenal syndrome-acute kidney injury (HRS-AKI)
- Recognize the mechanism of action and safety considerations for vasoconstrictors in HRS-AKI
- Identify the role of vasoconstrictors in HRS-AKI based on current literature

Objectives for Pharmacy Technicians

- Recall dosing and how pharmacologic therapies for HRS-AKI are supplied
- Recognize commonly observed adverse reactions associated with vasoconstrictors in HRS-AKI
- Identify challenges in patient management associated with treatment options for HRS-AKI

Presentation Outline

Hepatorenal Syndrome (HRS)

- Background
- Pathophysiology
- Therapeutic options

Review of Therapeutic Options

- Mechanism of action
- Literature
- Role in HRS

HRS Overview

Occurs in patients with decompensated cirrhosis and ascites, in the absence of hypovolemia or significant abnormalities in kidney histology

Epidemiology

- Prevalence ranges from 27% to 53% in hospitalized patients with decompensated cirrhosis and ascites
- 30-day mortality ranges from 29% to 44%
- 30-day readmission rate is 33%
- Median survival without treatment: 2 weeks

Etiology

- Common precipitating factors of AKI include infection, volume loss from excessive diuretic use, gastrointestinal blood loss, or acute hepatitis

Sources: Biggins SW, et al. *Hepatology.* 2021;74(2):1014-1048.
Jamil K, et al. *J Med Econ.* 2019;22:421-429.
Bera C, et al. *Therap Adv Gastroenterol*. 2022 Jun 14.

HRS Overview

Old classification	New classification	Criteria
HRS-1*	HRS-AKI	• Increase in sCr ≥0.3 mg/dL within 48 hours *or* • Urine output ≤0.5 mL/kg ≥ 6 hours** *or* • Increase in sCr by ≥50% using sCr obtained within 3 months as the baseline value
HRS-2	HRS-AKD	• eGFR <60 ml/min per 1.73 m² for **<3 months** in the absence of other (structural) causes • Increase in sCr <50% using sCr obtained within 3 months as the baseline value
	HRS-CKD	• eGFR <60 ml/min per 1.73 m² for **≥3 months** in the absence of other (structural) causes

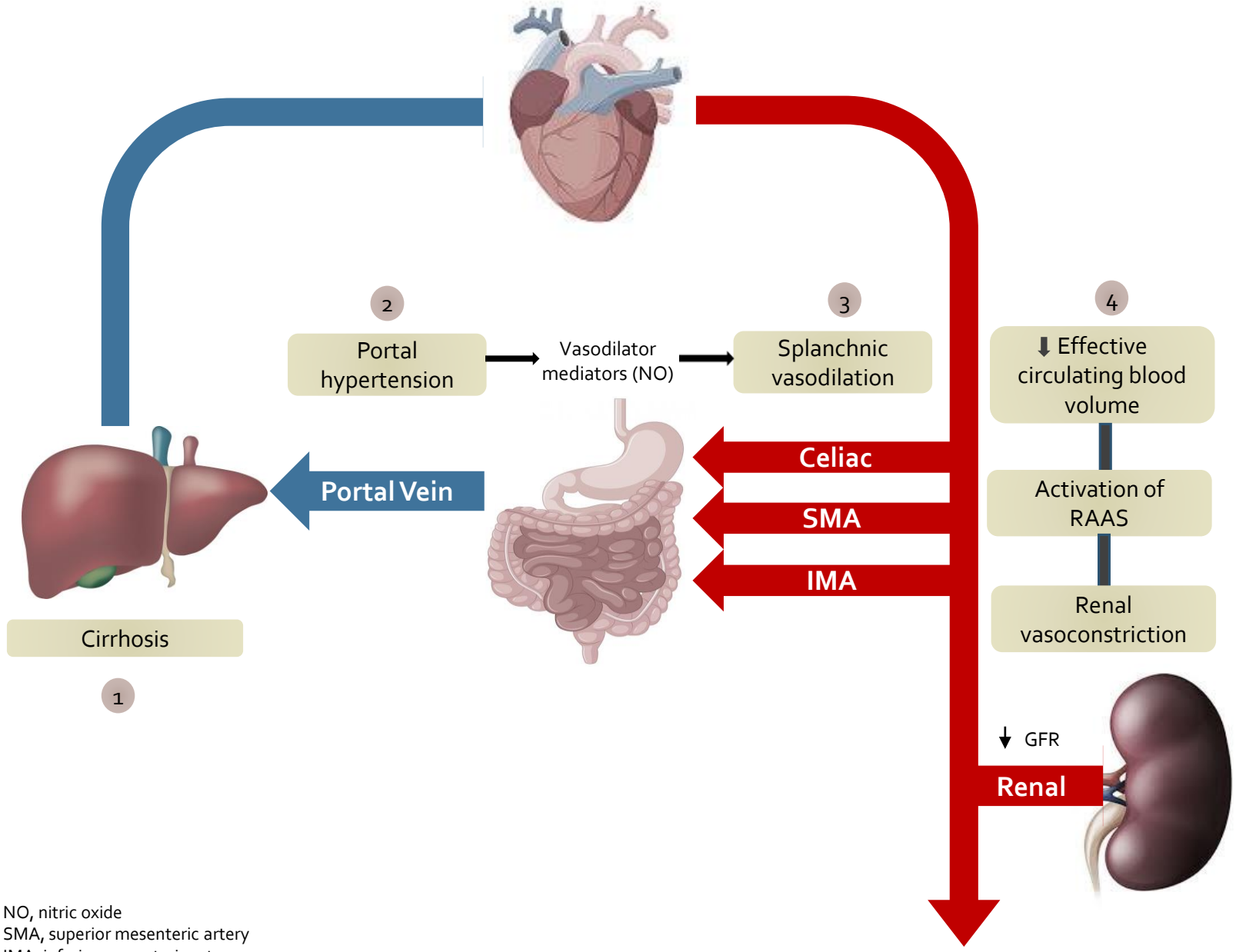
*sCr >1.5 mg/dL or doubling of sCr to ≥2.5 mg/dL in <2 weeks
**evaluation requires placement of a urinary catheter

New definition of AKI in cirrhosis allows for earlier diagnosis and treatment of HRS-AKI

AKD, acute kidney disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; sCr, serum creatinine

Source: Angeli P, et al. *J Hepatol*. 2019 Oct;71(4):811-822.

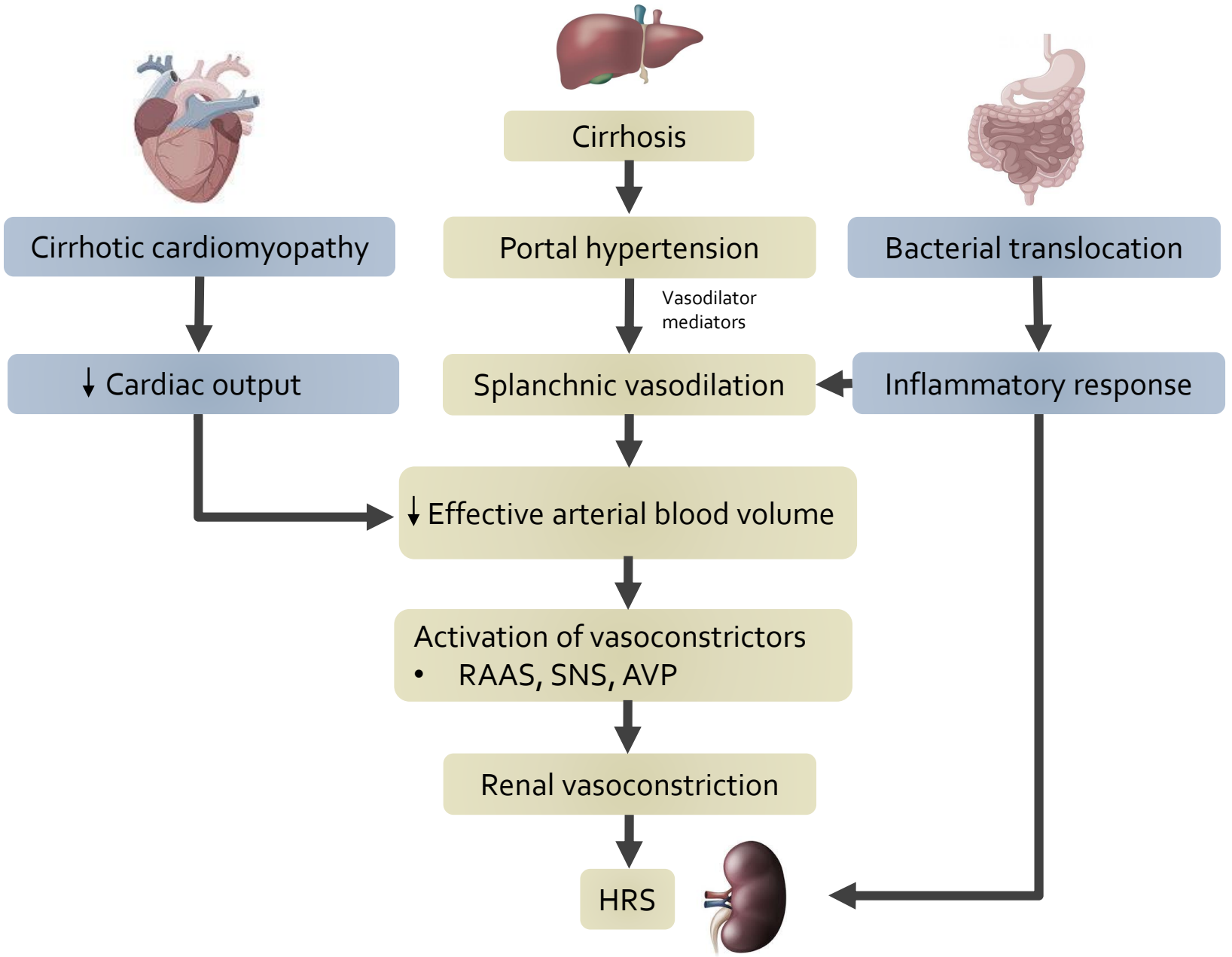
Pathophysiology



NO, nitric oxide
SMA, superior mesenteric artery
IMA, inferior mesenteric artery
RAAS, renin angiotensin aldosterone system
GFR, glomerular filtration rate

Sources: Biggins SW, et al. *Hepatology*. 2021;74(2):1014-1048.
Ginès, P, et al. *Nat Rev Dis Primers*. 2018;4:23.

Pathophysiology



RAAS, renin angiotensin aldosterone system
SNS, sympathetic nervous system
AVP, arginine vasopressin

Sources: Biggins SW, et al. *Hepatology*. 2021;74(2):1014-1048.
Ginès, P, et al. *Nat Rev Dis Primers*. 2018;4:23.

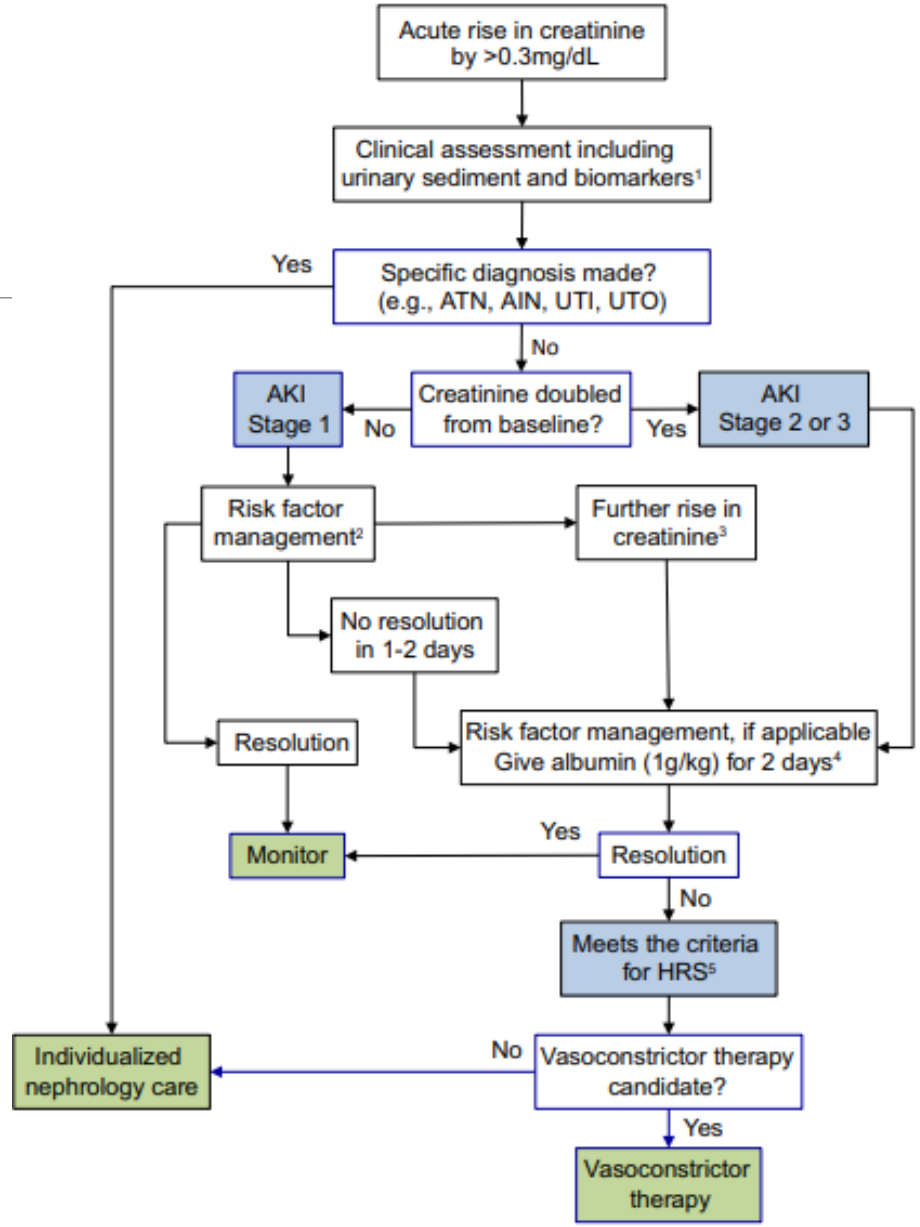
Diagnosis

Diagnosis of exclusion

Etiologies of AKI in cirrhosis

- Pre-renal
  - Hypovolemia
  - **HRS-AKI**
- Intrarenal/Intrinsic
  - Acute tubular necrosis (shock, nephrotoxic agents)
  - Interstitial nephritis or glomerulonephritis
- Post-renal (obstructive uropathy)

Stage of AKI	Criteria
Stage 1	Increase in sCr ≥0.3 mg/dL **up to 2-fold** from baseline
Stage 2	Increase in **sCr >2 to 3-fold** from baseline
Stage 3	Increase in **sCr >3-fold** from baseline or **sCr ≥4 mg/dL** with an acute increase ≥0.3 mg/dL or **initiation of RRT**



RRT, renal replacement therapy

Source: Biggins SW, et al. *Hepatology*. 2021;74(2):1014-1048.

Diagnosis

HRS-AKI
Cirrhosis with ascites
Increase in sCr ≥0.3 mg/dL within 48 hours OR Increase in sCr by ≥50% occurring within 7 days
Absence of shock
No improvement after 48 hours of diuretic withdrawal and volume expansion with albumin
No current or recent treatment with nephrotoxic drugs
Absence of structural kidney disease • No proteinuria (<500 mg/d) • No microhematuria (<50 RBCs per high-power field) • Normal renal ultrasonography

Sources: Biggins SW, et al. *Hepatology*. 2021;74(2):1014-1048.
Angeli P, et al. *J Hepatol*. 2015 Apr;62(4):968-974.

Assessment Question #1

Pharmacists and Nurses

Which of the following statements accurately describes the pathogenesis for HRS-AKI? Select all that apply:

A. Portal hypertension leads to an increase in vasodilator mediators and subsequent splanchnic vasodilation

B. Portal hypertension leads to an increase in vasodilator mediators and subsequent splanchnic vasoconstriction

C. Increase in effective arterial blood volume leads to activation of vasoconstrictors leading to renal vasoconstriction

D. Decrease in effective arterial blood volume leads to activation of vasoconstrictors leading to renal vasoconstriction

Assessment Question #1: Correct Response

Pharmacists and Nurses

Which of the following statements accurately describes the pathogenesis for HRS-AKI? Select all that apply:

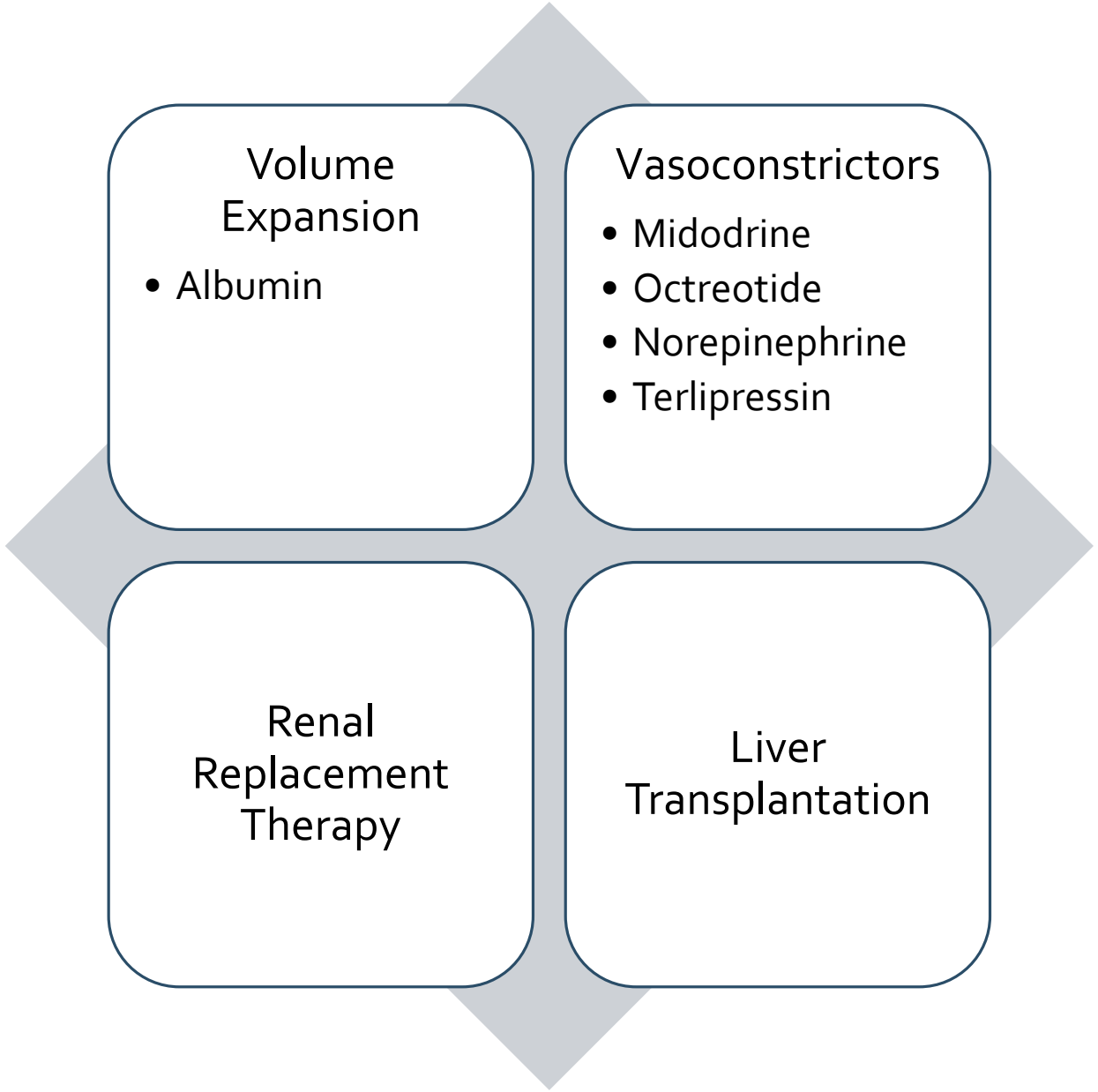
A. **Portal hypertension leads to an increase in vasodilator mediators and subsequent splanchnic vasodilation**

B. Portal hypertension leads to an increase in vasodilator mediators and subsequent splanchnic vasoconstriction

C. Increase in effective arterial blood volume leads to activation of vasoconstrictors leading to renal vasoconstriction

D. **Decrease in effective arterial blood volume leads to activation of vasoconstrictors leading to renal vasoconstriction**

Treatment Overview



Treatment Options

Guideline Recommendations

AASLD 2021

- Treatment of choice for HRS-AKI is vasoconstrictor drugs in combination with albumin. Preferred drug is terlipressin.
- If terlipressin is not available, norepinephrine should be given
- If neither can be administered, a trial of midodrine in combination with octreotide may be considered

ACG 2022

- In hospitalized patients with cirrhosis and HRS-AKI without high grade ACLF or disease, terlipressin or norepinephrine is suggested to improve renal function

AASLD, American Association for the Study of Liver Diseases; ACG, American College of Gastroenterology; ACLF, acute on chronic liver failure

Sources: Biggins SW, et al. *Hepatology*. 2021;74(2):1014-1048.
Bajaj KS, et al. *Am J Gastroenterol*. 2022;117:225-252.

Albumin

- Mechanism
  - Increases intravascular oncotic pressure to maintain intravascular volume
  - Anti-inflammatory and anti-oxidant properties
- Dosing
  - **To differentiate prerenal causes of AKI from HRS-AKI**: 1 g/kg IV (maximum: 100 g/day) x 2 d
  - **To use with vasoconstrictors**: 1 g/kg IV on day 1 → 20-50 g/d for remainder of therapy
  - Goal: central venous pressure between 4-10 mmHg
- Safety Considerations
  - Intravascular volume overload
  - Cardiopulmonary compromise

Sources: Biggins SW, et al. *Hepatology*. 2021;74(2):1014-1048.
Bera C, et al. *Therap Adv Gastroenterol*. 2022 Jun 14.

Albumin

- Use in HRS-AKI
  - Adjunctive therapy to vasoconstrictors
  - Used for its volume expanding and anti-inflammatory properties
  - Suggested to use IV albumin + vasoconstrictors over albumin alone to improve sCr
  - Albumin alone has not been shown to be effective for HRS-AKI

Sources: Biggins SW, et al. *Hepatology*. 2021;74(2):1014-1048.
Bajaj KS, et al. *Am J Gastroenterol*. 2022;117:225-252.

Albumin

Albumin Use in HRS

	Guevara et al (1998)	Ortega et al (2002)
Study Design	Prospective	Prospective, non-randomized

Intervention	n=16
	• Ornipressin + albumin
	  • Albumin 1 g/kg x 1 d → 20-40 g/d
	  • 3 days (n=8) vs 15 days (n=8)
		n=21
		• Terlipressin + albumin (n=13)
		  • Albumin: 1 g/kg x 2 d → 20-40 g/d
		• Terlipressin alone (n=7)

Efficacy Outcomes	**3-day treatment with albumin** • Normalization of RAAS, slight improvement in renal function **15-day treatment with albumin** • Remarkable improvement in renal function (normalization of sCr, increase in GFR, suppression of RAAS)	**Complete response (CR)** (sCr ≤1.5 mg/dL) • 12/21 (57%) **Predictive factor of CR: albumin** • Terlipressin + albumin **(77%)** vs terlipressin alone **(25%), p=0.03**

Albumin appears to improve the circulatory and renal benefits of vasoconstrictor therapy

Sources: Guevara M, et al. *Hepatology*. 1998 Jan;27(1):35-41.
Ortega R, et al. *Hepatology*. 2002;36(4):941-948.

Vasoconstrictors

Reduce portal pressure
Decrease splanchnic vasodilation
Increase effective arterial blood volume
Improve MAP and renal perfusion pressure

Vasoconstrictor (combined with albumin)	Mechanism
Midodrine	α_1-adrenergic receptor agonist
Octreotide	Somatostatin analog → inhibits release of vasodilators
Norepinephrine	α_1 , β_1 adrenergic receptor agonist
Terlipressin	Synthetic vasopressin analog with greater selectivity for V_1 receptors than V_2 receptors

Midodrine

- Mechanism
  - Peripheral α_1-adrenergic receptor agonist → vasoconstriction
- Dosing
  - 5 to 15 mg orally every 8 hours
- Safety Considerations
  - Supine and sitting hypertension, paresthesias, pruritus, chills, bradycardia
  - Urinary urgency, retention, and frequency
- Use in HRS-AKI
  - Given in combination with octreotide when a first line vasoconstrictor is not available or cannot be administered

Sources: Biggins SW, et al. *Hepatology*. 2021;74(2):1014-1048.
Midodrine hydrochloride [prescribing information]. Morgantown, WV: Mylan Pharmaceuticals, Inc.; 2020.
Flamm SL, et al. *Liver Transpl*. 2021 Aug;27(8):1191-1202.

Octreotide

- Mechanism
  - Somatostatin analog which inhibits release of glucagon and other vasodilator peptides, leading to vasoconstriction in splanchnic, portal, and systemic circulation
- Dosing
  - Subcutaneous (SQ): 100 to 200 mcg every 8 hours
  - Intravenous (IV): 50 mcg/hour continuous infusion
- Safety Considerations
  - Nausea, diarrhea, headache, arthralgia, peripheral swelling, increased serum glucose, emesis, abdominal discomfort, dyspepsia, sinusitis, osteoarthritis
- Use in HRS-AKI
  - Given with midodrine
  - Can be administered outside of the ICU

Sources: Biggins SW, et al. *Hepatology*. 2021;74(2):1014-1048.
Sandostatin (octreotide acetate) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2021.
Flamm SL, et al. *Liver Transpl*. 2021 Aug;27(8):1191-1202.

Midodrine/Octreotide (M/O)

	Pomier-Layrargues et al (2003)	Esrailian et al (2007)	Skagen et al (2009)
Design	Randomized, cross-over	Retrospective, single-center	Retrospective, cohort
Population	HRS-1 and 2	HRS-1	HRS-1 and 2
Intervention	n=14 • Octreotide + albumin first (n=6) • Albumin alone first (n=8) • 4 days each	n=81 • M/O + albumin (n=60) • Albumin only (n=21)	n=162 • M/O + albumin (n=75) • Historical control (n=87)
Results	Improvement in renal function at 4 d • Response identical in both groups	Mortality • M/O (43%) vs albumin (71%), p<0.05 Sustained reduction in sCr • M/O (40%) vs albumin (10%), p<0.05	Median transplant-free survival • M/O (101 d) vs control (18 d), p<0.0001 Renal function at 1 month • Improved with M/O vs control, p=0.03
Conclusion	Octreotide infusion + albumin not effective at improving renal function	M/O appears to improve 30-day survival vs albumin only	M/O + albumin appears to improve short-term survival and renal function in HRS

Sources: Pomier-Layrargues G, et al. *Hepatology.* 2003 Jul;38(1):238-43.
Esrailian E, et al. *Dig Dis Sci.* 2007 Mar;52(3):742-8.
Skagen , et al. *J Clin Gastroenterol.* 2009 Aug;43(7):680-5.

Norepinephrine

- Mechanism
  - α_1 , β_1 adrenergic receptor agonist → vasoconstriction
- Dosing (IV)
  - Start: 0.5 mg/h
  - Titrate: Increase Q4H in increments of 0.5 mg/h
  - Maximum: 3 mg/h
  - Goal
    - Increase in MAP of ≥ 10 mmHg OR increase in urine output of >200 mL/4 hours
- Safety Considerations
  - Cardiac and digital ischemia, tachyarrhythmias, extravasation and tissue necrosis

MAP, mean arterial pressure

Sources: Biggins SW, et al. *Hepatology*. 2021;74(2):1014-1048.
Levophed (norepinephrine bitartrate) [prescribing information]. Lake Forest, IL: Hospira, Inc.; 2020.
Flamm SL, et al. *Liver Transpl*. 2021 Aug;27(8):1191-1202.

Norepinephrine

- <u>Use in HRS-AKI</u>
  - May require higher level of care
  - Similar efficacy to terlipressin
  - Considered first line by many institutions in the US
  - In hospitalized patients with cirrhosis and HRS without high grade ACLF or disease, ACG guidelines suggest terlipressin (*moderate quality, conditional recommendation*) or norepinephrine (*low quality, conditional recommendation*) to improve renal function

Sources: Biggins SW, et al. *Hepatology*. 2021;74(2):1014-1048.
Levophed (norepinephrine bitartrate) [prescribing information]. Lake Forest, IL: Hospira, Inc.; 2020.
Flamm SL, et al. *Liver Transpl*. 2021 Aug;27(8):1191-1202.

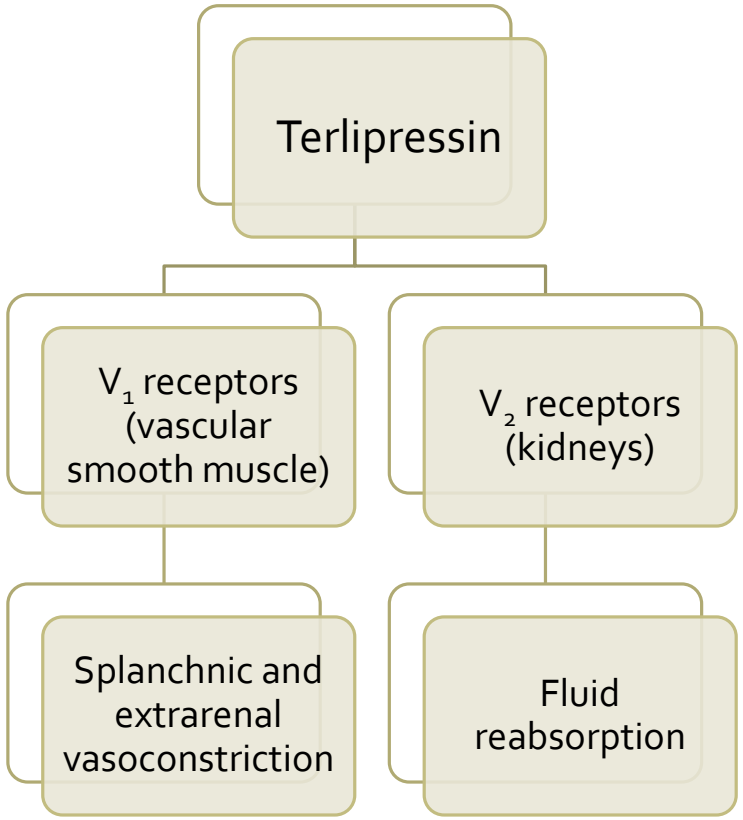
Norepinephrine vs Midodrine/Octreotide

Norepinephrine (NE) vs Midodrine/Octreotide (M/O) in HRS-AKI	
Study Design	Parallel-group, open-label, randomized controlled trial
Population	Inclusion: cirrhosis, ascites, HRS-AKI diagnosis (ICA 2015 criteria) Exclusion: sCr >7 mg/dL, hypotension (MAP <70 mmHg), sepsis
Intervention	n=60 Given with albumin 20-40 g/d • NE: 0.5-3 mg/h • M/O: Midodrine 5-12.5 mg PO TID + octreotide 100-200 mcg SQ Q6H Duration: maximum 10 days
Efficacy Outcomes	Full response (return of sCr within 0.3 mg/dL of baseline at end of treatment) • **NE (57.6%) vs M/O (20%), p=0.006** 30-day survival • NE (42.3%) vs M/O (24%), p=0.166
Safety	No significant difference in serious adverse events (hepatic encephalopathy, infection, bleeding)

ICA, International Club of Ascites

Source: El-Desoki Mahmoud EI, et al. *Front Pharmacol*. 2021 Jul 2;12:675948.

Terlipressin
Mechanism of Action



Synthetic vasopressin analog

Twice the selectivity for V_1 receptors, targeting the splanchnic circulation, versus V_2 receptors

Prodrug for lysine-vasopressin with pharmacologic activity of its own

Increases renal blood flow in HRS by:

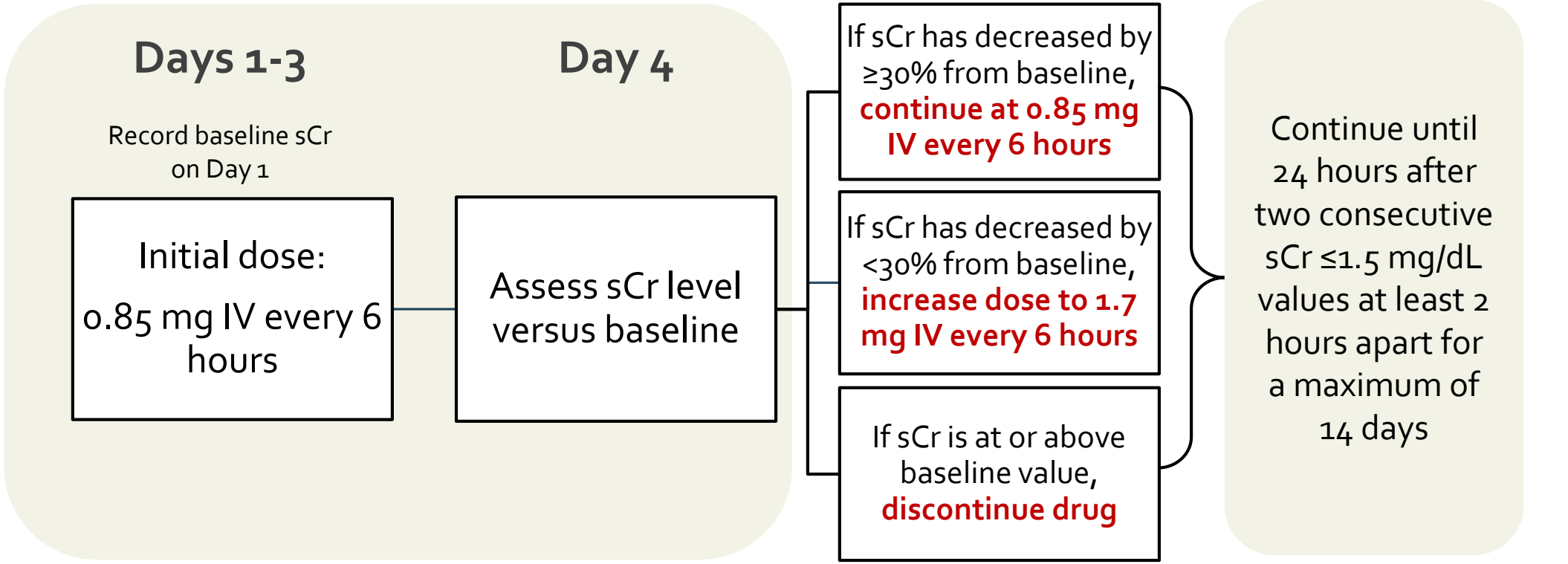
- Reducing portal hypertension and blood circulation in portal vessels
- Increasing effective arterial volume and MAP

Source: Terlivaz (terlipressin) [prescribing information]. Bedminster, NJ: Mallinckrodt Hospital Products Inc.; 2022.

Terlipressin

Dosing and Administration

0.85 mg terlipressin = 1 mg terlipressin acetate = 1 vial

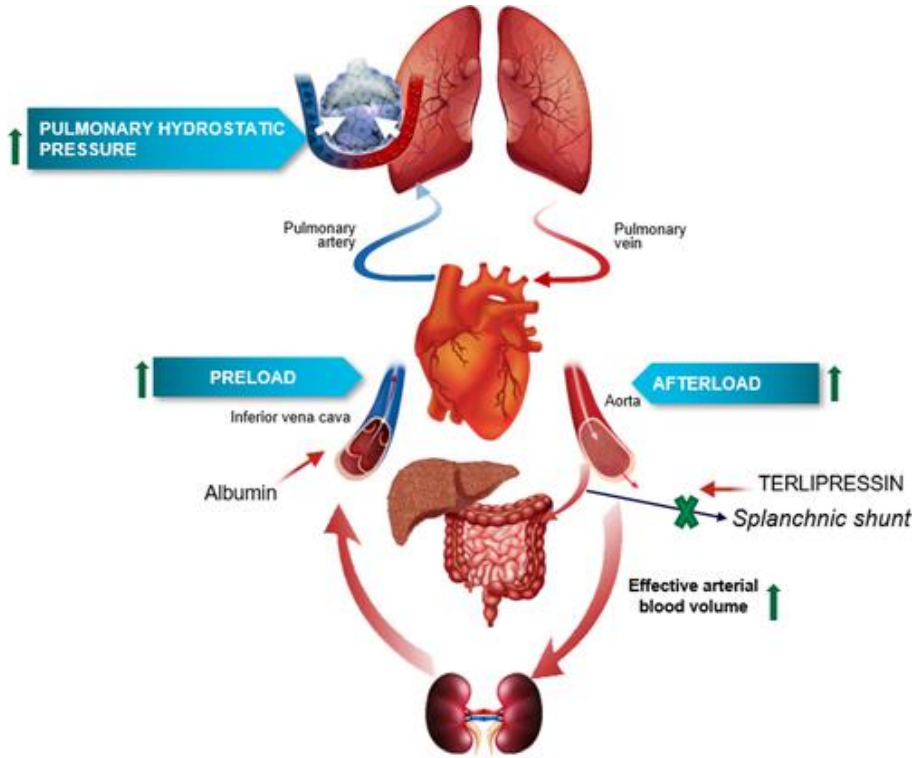


Reconstitute 1 vial (0.85 mg) with 5 mL 0.9% sodium chloride → Administer through a peripheral or central line by slow IV bolus over 2 minutes → Flush line after administration

Source: Terlivaz (terlipressin) [prescribing information]. Bedminster, NJ: Mallinckrodt Hospital Products Inc.; 2022.

Terlipressin
Safety Considerations

- Warnings
  - **Serious or fatal respiratory failure (Boxed Warning)**
    - Increased risk with volume overload or ACLF Grade 3
  - Ineligibility for LT due to adverse reactions (MELD ≥35)
  - Ischemic events
  - Embryo-fetal toxicity
- Contraindications
  - Hypoxia or respiratory insufficiency
  - Coronary, peripheral, or mesenteric ischemia
- Adverse Reactions
  - Abdominal pain, nausea, diarrhea, dyspnea, respiratory failure
- Incidence of adverse events may be reduced when given as a continuous infusion
- Patients with sCr >5 mg/dL are unlikely to experience benefit



LT, liver transplantation; MELD, model for end-stage liver disease

Sources: Terlivaz (terlipressin) [prescribing information]. Bedminster, NJ: Mallinckrodt Hospital Products Inc.; 2022.
Allegretti AS, et al. *Liver Int*. 2022 Oct;42(10):2124-2130.

Assessment Question #2

Pharmacists and Nurses

Which statement matches the drug to its mechanism of action in HRS-AKI?

A. Midodrine: α- and β-adrenergic receptor agonist acting as a peripheral vasoconstrictor

B. Terlipressin: α-receptor agonist only acting as a peripheral vasoconstrictor

C. Norepinephrine: acts as a synthetic vasopressin analogue with greater selectivity for vasopressin V_1 receptors versus V_2 receptors

D. Octreotide: acts as a somatostatin analog reducing splanchnic blood flow

Assessment Question #2: Correct Response

Pharmacists and Nurses

Which statement matches the drug to its mechanism of action in HRS-AKI?

A. Midodrine: α- and β-adrenergic receptor agonist acting as a peripheral vasoconstrictor

B. Terlipressin: α-receptor agonist only acting as a peripheral vasoconstrictor

C. Norepinephrine: acts as a synthetic vasopressin analogue with greater selectivity for vasopressin V_1 receptors versus V_2 receptors

D. **Octreotide: acts as a somatostatin analog reducing splanchnic blood flow**

Assessment Question #3

Pharmacy Technicians

Which of the following medication regimens is appropriate for HRS-AKI?

A. Terlipressin 0.85 mg orally every 6 hours for 3 days

B. Midodrine 5 mg orally every 8 hours

C. Norepinephrine 0.85 mg intravenous every 6 hours for 3 days

D. Octreotide 100 mcg via inhalation every 8 hours

Assessment Question #3: Correct Response

Pharmacy Technicians

Which of the following medication regimens is appropriate for HRS-AKI?

A. Terlipressin 0.85 mg orally every 6 hours for 3 days

B. **Midodrine 5 mg orally every 8 hours**

C. Norepinephrine 0.85 mg intravenous every 6 hours for 3 days

D. Octreotide 100 mcg via inhalation every 8 hours

Assessment Question #4

Pharmacy Technicians

Which of the following statements is TRUE regarding safety considerations for vasoconstrictor therapy in HRS-AKI?

A. Terlipressin is safe to use in pregnant patients

B. A common side effect of octreotide is supine hypertension

C. Norepinephrine can lead to digital ischemia and arrhythmias

D. Terlipressin can be safely used in patients with worsening hypoxia or respiratory symptoms

Assessment Question #4: Correct Response

Pharmacy Technicians

Which of the following statements is TRUE regarding safety considerations for vasoconstrictor therapy in HRS-AKI?

A. Terlipressin is safe to use in pregnant patients

B. A common side effect of octreotide is supine hypertension

C. **Norepinephrine can lead to digital ischemia and arrhythmias**

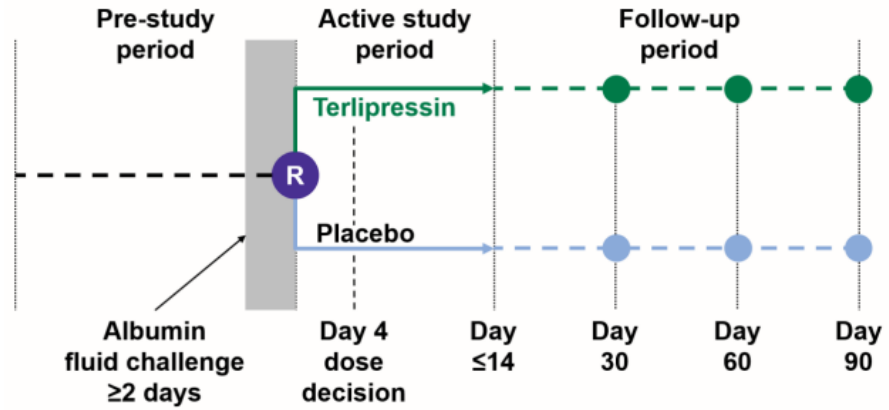
D. Terlipressin can be safely used in patients with worsening hypoxia or respiratory symptoms

CONFIRM Trial

Terlipressin + Albumin for Treatment of HRS-Type 1	
Population	• Cirrhosis, ascites, HRS with rapid reduction in renal function (with trajectory for sCr to double within 2 weeks) to a **sCr ≥2.25 mg/dL** without sustained improvement in renal function 48 hours after diuretic withdrawal and albumin challenge • Mean baseline sCr: 3.5 mg/dL • Mean baseline MELD score: 32-33

Intervention	**n=300**
	• **Terlipressin (n=199)**
	  • 1 mg IV Q4-6H → increased to 2 mg IV Q4-6H → maximum of 12 mg daily if <30% reduction in sCr by day 4 after at least 10 doses
	• **Placebo (n=101)**
	• Albumin given in both groups
	  • 1 g/kg IV on Day 1 (max 100 g) → 20-40 g/d

Figure S1. Study Design



R: Randomization

Source: Wong F, et al. *N Engl J Med* 2021; 384: 818–828.

CONFIRM Trial

	Terlipressin + albumin (n=199)	Placebo + albumin (n=101)	p-value
Primary Endpoint			
VHRSR	63 (32)	17 (17)	0.006
Other Endpoints			
HRS reversal	78 (39)	18 (18)	<0.001
HRS reversal with no RRT through day 30	68 (34)	17 (17)	0.001
Liver transplant (LT) at day 90	46 (23)	29 (29)	-
Mortality at day 90	101 (51)	45 (45)	-
Adverse events*	28 (14)	5 (5)	-

Data represented as number (%)
*Abdominal pain, nausea, diarrhea, or respiratory failure

Verified HRS reversal (VHRSR):

- Two consecutive sCr ≤1.5 mg/dL 2 h apart by Day 14 or discharge
- Survival without RRT for at least 10 days after completion of treatment

Prespecified Endpoints from Post Hoc Analysis

- Incidence of RRT through day 14 and day 30: lower with terlipressin
- Incidence of RRT pre-LT and post-LT: lower with terlipressin

Sources: Wong F, et al. *N Engl J Med* 2021; 384: 818–828.
Terlivaz (terlipressin) [prescribing information]. Bedminster, NJ: Mallinckrodt Hospital Products Inc.; 2022.

Overview: Phase 3 Studies

	OT-0401	REVERSE	CONFIRM
Sample size	n=112	n=196	n=300
Primary Endpoint†	**Treatment Success** at Day 14* • 25% vs 12.5%, **p=0.093**	**Confirmed HRS Reversal (CHRSR)**** • 19.6% vs 13.1%, **p=0.22**	**VHRSR***** • 32% vs 17%, **p=0.006**
Secondary Endpoints†	**HRS Reversal** • 33.9% vs 12.5%, **p=0.008** **Overall and LT-free survival** • No difference	**HRS Reversal** • 23.7% vs 15.2%, **p=0.13** **Overall and LT-free survival** • No difference	**HRS Reversal** • 39% vs 18%, **p<0.001** **Overall and LT-free survival** • No difference
Safety	Similar rate of adverse events • One nonfatal myocardial infarction with terlipressin	Similar number of adverse events • More ischemic events in terlipressin group	Higher rates of adverse events with terlipressin • More respiratory failure

† Endpoint described as incidence in terlipressin group vs placebo

*Treatment success : sCr ≤1.5 mg/dL, with 2 measurements at least 48 hours apart without dialysis, death or HRS relapse

**CHRSR: sCr ≤1.5 mg/dL, with 2 measurements at least 40 hours apart without intervening RRT or LT

***VHRSR: two consecutive sCr ≤1.5 mg/dL 2 h apart by day 14 or discharge, and survival without RRT for ≥10 days after completion of treatment

Sources: Sanyal AJ, et al. *Gastroenterol.* 2008;134:1360-1368.
Boyer T, et al. *Gastroenterol*. 2016;150:1579-1589.
Wong F, et al. *N Engl J Med* 2021; 384: 818–828.

Midodrine/Octreotide vs Terlipressin

Midodrine/Octreotide vs Terlipressin in HRS-AKI	
Study Design	Multi-center, open-label, randomized controlled trial
Population	Cirrhosis, type 1, or severe type 2 HRS (sCr >2.5 mg/dL)
Intervention	n=49 Concomitant albumin 1 g/kg IV on day 1 → 20-40 g/d • **Terlipressin (n=27): continuous IV infusion** 3 mg/24 h → response evaluated at 48 h (if sCr <25% of pretreatment value, dose increased to 12 mg/24 h) • **M/O (n=22):** Midodrine 7.5-12.5 mg PO TID AND octreotide 100 mcg-200 mg SQ Q6H Duration: maximum 14 days
Efficacy Outcomes	**Partial or complete response (≥50% decrease in sCr from baseline to a final value >1.5mg/dL)** • Terlipressin: (70.4%) vs M/O (28.6%), **p=0.01** **Complete response (sCr ≤1.5 mg/dL)** • Terlipressin: (55.5%) vs M/O (4.8%), **p<0.001**
Safety	• No significant difference in serious adverse events

Source: Cavallin M, et al. *Hepatology*. 2015 Aug;62(2):567-74.

Norepinephrine vs Terlipressin

	Singh et al (2012)	Goyal et al (2016)
Study Design	Randomized, single-center open label	Randomized, single-center open label
Population	HRS-1	HRS-1
Intervention	n=46 • Terlipressin (n=23): 0.5–2 mg/6h • NE (n=23) 0.5–3 mg/h	n=41 • Terlipressin (n=20): 0.5-2 mg/6h • NE (n=21): 0.5–3 mg/h
Efficacy Outcomes	**HRS reversal** • Terlipressin (39.1%) vs NE (43.5%), p=0.764	**HRS Reversal** • Terlipressin (45%) vs NE (47.6%), p=1.00
Safety	No major adverse effects	Higher rates of adverse events with terlipressin

Sources: Singh V, et al. *J Hepatol* 2012; 56: 1293–1298.
Goyal O, et al. *J Assoc Physicians India* 2016;64:30-35.

Norepinephrine vs Terlipressin

	Saif et al (2018)	Arora et al (2020)
Study Design	Randomized, single-center study	Randomized, single-center open label
Population	HRS-1	ACLF patients with HRS-AKI
Intervention	n=60 • Terlipressin (n=30): 0.5–2 mg/6h • NE (n=30) 0.5–3 mg/h	n=120 • Terlipressin (n=60): 2–12 mg/d • NE (n=60): 0.5–3 mg/h
Efficacy Outcomes	**HRS Reversal** • Terlipressin (57%) vs NE (53%), p>0.05	**Reversal of HRS-AKI** • Terlipressin (40%) vs NE (16.7%), **p=0.004** **Lower requirement of RRT (p=0.006) and improved 28-day survival (p=0.001) with terlipressin**
Safety	No major adverse effects	Higher rates of adverse events with terlipressin (23.3% vs 8.3%, p=0.02)

Majority of studies have shown no difference in efficacy outcomes between terlipressin and norepinephrine

Sources: Saif RU, et al. *Indian J Gastroenterol* 2018; 37: 424–429.
Arora V, et al. *Hepatology* 2020;71:600-610.

Summary

Midodrine/Octreotide

Placebo

- M/O has unclear benefit vs placebo

Norepinephrine

Placebo

- NE may ↑ HRS reversal vs placebo

Midodrine/Octreotide

- NE may ↑ HRS reversal vs M/O

Terlipressin

Placebo

- Terli may ↑ HRS reversal vs placebo, but is associated with more adverse events

Midodrine/Octreotide

- Terli may ↑ HRS reversal vs M/O

Norepinephrine

- Similar efficacy outcomes
- Terli may cause more adverse events vs. NE

M/O, midodrine/octreotide; NE, norepinephrine; Terli, terlipressin

Meta-Analyses Findings

Midodrine/ Octreotide	• No significant mortality benefit or improved HRS reversal over placebo
Norepinephrine	• May improve HRS reversal vs midodrine/octreotide • Low-quality evidence suggesting potential mortality benefit
Terlipressin	• Improves HRS reversal vs placebo and midodrine/octreotide • Low-quality evidence suggesting similar efficacy outcomes with norepinephrine • Low-quality evidence suggesting potential short-term mortality benefit

Sources: Facciorusso A, et al. *Lancet Gastroenterol Hepatol*. 2017;2:94-102.
Pitre T, et al. *Crit Care Med.* 2022 Oct 1;50(10):1419-1429.
Flamm SL, et al. *Liver Transpl*. 2021 Aug;27(8):1191-1202.

Assessment Question #5

Pharmacists and Nurses

Which of the following statements appropriately describes the findings from studies evaluating vasoconstrictor therapy in HRS-AKI?

A. Patients receiving norepinephrine had significantly higher rates of verified reversal of HRS compared to terlipressin

B. Patients receiving terlipressin had significantly higher rates of verified reversal of HRS compared to placebo

C. Patients receiving midodrine/octreotide had significantly lower rates of mortality at 90 days compared to norepinephrine

D. Patients receiving octreotide monotherapy had significantly higher rates of HRS reversal compared to placebo

Assessment Question #5: Correct Response

Pharmacists and Nurses

Which of the following statements appropriately describes the findings from studies evaluating vasoconstrictor therapy in HRS-AKI?

A. Patients receiving norepinephrine had significantly higher rates of verified reversal of HRS compared to terlipressin

B. **Patients receiving terlipressin had significantly higher rates of verified reversal of HRS compared to placebo**

C. Patients receiving midodrine/octreotide had significantly lower rates of mortality at 90 days compared to norepinephrine

D. Patients receiving octreotide monotherapy had significantly higher rates of HRS reversal compared to placebo

Considerations for Vasoconstrictor Use

Norepinephrine

- May require ICU admission
- May require central line for administration
- Inexpensive
- Monitoring:
  - Tachyarrhythmias
  - Digital ischemia
  - Extravasation

Terlipressin

- Does not require ICU admission
- Does not require central line for administration
- Costly
- Monitoring:
  - Respiratory status
  - Renal function
  - Signs of volume overload
  - MELD score for eligibility/ineligibility of LT

Current guidelines from varying organizations have differing recommendations regarding vasoconstrictor of choice

Considerations for Vasoconstrictor Use

- Inconclusive data regarding preference of one agent over another
  - Significant heterogeneity, small sample size, varying definitions of HRS and HRS reversal
  - No proven mortality benefit
  - HRS reversal and lower incidence of RRT may improve survival and post-LT outcomes

- Future Directions
  - Predictors of response to therapy
  - Studies used older classification of HRS-AKI (enrolled at advanced stages)
    - Potentially greater benefit and lower rates of adverse events with earlier vasoconstrictor use based on the current definition of HRS
  - Further trials evaluating terlipressin continuous infusion vs bolus dosing to minimize adverse effects

Renal Replacement Therapy

AASLD 2021

- Use in candidates for LT with worsening renal function or electrolyte disturbances or increasing volume overload unresponsive to vasoconstrictor therapy
- Initiation of RRT in patients who are not candidates for LT must be made with a clear endpoint in mind

ACG 2022

- Recommended for patients with HRS-AKI who are on the LT waiting list and have failed pharmacotherapy
- Often required while patients are waiting for LT

Complications

Intradialytic hypotension, increased risk of cardiac events, complications related to venous access, potential nonrecovery after LT, poor quality of life

Sources: Biggins SW, et al. *Hepatology*. 2021;74(2):1014-1048.
Bajaj KS, et al. *Am J Gastroenterol*. 2022;117:225-252.
Flamm SL, et al. *Liver Transpl*. 2021 Aug;27(8):1191-1202.

Liver Transplant

AASLD 2021

- All patients with cirrhosis and AKI should be considered for urgent LT evaluation given the high short-term mortality even in responders to vasoconstrictors

ACG 2022

- LT is the definitive treatment for HRS-AKI
- Referral should not be delayed as duration of pretransplant RRT (14 days) is the strongest predictor for nonrecovery of renal function post LT

Many patients are not eligible due to having contraindications to LT, limited organ availability, or have factors that adversely impact their prioritization
(e.g., pharmacological treatment lowering MELD scores)

Sources: Biggins SW, et al. *Hepatology*. 2021;74(2):1014-1048.
Bajaj KS, et al. *Am J Gastroenterol*. 2022;117:225-252.
Flamm SL, et al. *Liver Transpl*. 2021 Aug;27(8):1191-1202.

Liver Transplant

	Outcomes of Patients with Cirrhosis and HRS-Type 1 treated with LT
Study Design	Retrospective chart review
Population	HRS-1
Intervention	n=62 • 38 patients received midodrine, octreotide, and albumin without success and received dialysis • 1 patient received dialysis without pharmacotherapy
Results	**HRS-1 resolution: 47/62 (75.8%)** • Mean time: 13 ± 2 days **Patients without HRS-1 reversal** • Higher pretransplant sCr, longer duration of HRS-1 and pretransplant dialysis, increased posttransplant mortality **Predictor of HRS-1 non-reversal**: duration of pretransplant dialysis • 6% increased risk of non-reversal with each day on dialysis
Conclusion	Patients with HRS-1 should receive a timely LT to improve outcomes

Source: Wong F, et al. *Liver Transpl.* 2015 Mar;21(3):300-7.

Liver Transplant

- Recovery of kidney function after LT not always predictable
  - Preexisting comorbidities (CKD or diabetes)
  - Unexpected intraoperative events
  - Posttransplant immunosuppression
  - Unrecognized intrinsic renal disease
- Simultaneous liver and kidney transplantation for patients may be an option for patients who are unlikely to recover kidney function
  - Shortage of donated kidneys
  - Eligibility Criteria by the Organ Procurement Transplant Network
    - Includes duration of AKI, need for dialysis, and evidence of CKD
    - Safety net approach to guarantee prioritization of kidney transplantation for those with persistent kidney dysfunction

Sources: Biggins SW, et al. *Hepatology*. 2021;74(2):1014-1048.
Bajaj KS, et al. *Am J Gastroenterol*. 2022;117:225-252.
Flamm SL, et al. *Liver Transpl*. 2021 Aug;27(8):1191-1202.

Assessment Question #6

Pharmacy Technicians

What are potential challenges associated with management of HRS-AKI?
Select all that apply:

A. Complications associated with RRT and low eligibility of patients for LT

B. Need for ICU admission with midodrine

C. Cost associated with terlipressin

D. A & C

Assessment Question #6: Correct Response

Pharmacy Technicians

What are potential challenges associated with management of HRS-AKI?
Select all that apply:

A. Complications associated with RRT and low eligibility of patients for LT

B. Need for ICU admission with midodrine

C. Cost associated with terlipressin

D. A & C

Summary

Treatment of choice for HRS-AKI is vasoconstrictor drugs with albumin

- Norepinephrine or terlipressin are suggested to improve renal function
- While terlipressin showed a higher rate of verified HRS reversal vs placebo, it may be associated with an increase in serious adverse events and higher drug costs

LT remains the most effective intervention for HRS-AKI, but few are eligible

RRT is a temporary life-saving intervention but may be associated with many complications and worsen outcomes

- Consider in patients who are LT candidates as a bridge to LT

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Thank you!

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