Navigating Liver-Kidney Dynamics: Updates in the Management of Hepatorenal Syndrome

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Objectives

1

Recognize the clinical features and diagnostic challenges of hepatorenal syndrome (HRS)

2

Identify current evidence-based pharmacologic management strategies for HRS, including vasoconstrictors, albumin and emerging therapies

3

Recall evidence-based principles utilized during clinical decision making to optimize treatment, improve safety and enhance outcomes for patients with HRS

Abbreviations

Abbreviation	Definition
ACLF	Acute-on-Chronic Liver Failure
ADH	Antidiuretic Hormone
AKD	Acute Kidney Disease
AKI	Acute Kidney Injury
AEs	Adverse Events
CKD	Chronic Kidney Disease
CRRT	Continuous Renal Replacement Therapy
DAMPs	Damage-Associated Molecular Patterns
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
HRS	Hepatorenal Syndrome
HRS-AKI	Hepatorenal Syndrome-Acute Kidney Injury
HRS-AKD	Hepatorenal Syndrome-Acute Kidney Disease
HRS-CKD	Hepatorenal Syndrome-Chronic Kidney Disease

Abbreviation	Definition
HRS-NAKI	Hepatorenal Syndrome-Non-AKI
ICU	Intensive Care Unit
IV	Intravenous
LOS	Length of Stay
MAP	Mean Arterial Pressure
MELD	Model for End-Stage Liver Disease
MO	Midodrine + Octreotide
NSAIDs	Nonsteroidal Anti-Inflammatory Drugs
PAMPs	Pathogen-Associated Molecular Patterns
RRT	Renal Replacement Therapy
SBP	Spontaneous Bacterial Peritonitis
SC	Subcutaneous
SCr	Serum Creatinine
SNS	Sympathetic Nervous System
TIPS	Transjugular Intrahepatic Portosystemic Shunt
V1	Vasopressin 1 Receptor

Hepatorenal Syndrome (HRS)

Functional renal failure in cirrhosis with ascites characterized by:

Reduced renal perfusion	Reduced GFR	Absence of intrinsic renal disease

Potentially reversible if effective arterial volume restored

Source: Ginès P, Gastroenterology. 2024; Simonetto DA, BMJ. 2020

Why HRS Matters

HRS-AKI is one of the most severe forms of AKI in cirrhosis

~30% in-hospital mortality despite therapy

Median survival is weeks to months without treatment

Poor short-term prognosis and rapid deterioration

Requires prompt diagnosis, vasoconstrictor therapy, and urgent transplant evaluation

Source: Nadim MK, N Engl J Med. 2023

Classification of HRS

Old Term	New Term	Key Features	Diagnostic Criteria
HRS-1	**HRS-AKI**	Acute onset, reversible with volume expansion	• Increase in SCr ≥0.3 mg/dL in 48h or ≥50% in 3 months • No response after albumin 1g/kg/day x48h • Cirrhosis with ascites • No shock • No nephrotoxic drug use • No evidence of intrinsic renal disease

Source: Angeli P, J Hepatol. 2015; Ginès P, Gastroenterology. 2024;

Classification of HRS, *continued*

Old Term	New Term	Subtype	Key Features	Diagnostic Criteria
HRS-2	**HRS-NAKI**	HRS-AKD	Subacute decline, not meeting AKI threshold	• Increase in SCr <50% in 3 months • eGFR <60 ml/min/1.73 m^2 • Cirrhosis with ascites • No other cause of kidney disease
HRS-2		HRS-CKD	Chronic renal impairment	• eGFR <60 ml/min/1.73 m^2 • Cirrhosis with ascites • No other cause of kidney disease

Source: Angeli P, J Hepatol. 2015; Ginès P, Gastroenterology. 2024;

Classification of HRS, *continued*

Features	HRS-AKI	HRS-AKD	HRS-CKD
Onset and Duration	Acute; < 7 days	Subacute; 7-90 days	Chronic; >90 days
Creatinine increase	Rapid	Persistent	Sustained
Reversibility	Potentially reversible with treatment	Variable	Typically, irreversible
Triggering factors	Infection, GI bleeding, hypotension	Same as HRS-AKI; persistent kidney dysfunction after AKI	Advanced liver disease, refractory ascites, repeated episodes of HRS-AKI or HRS-AKD
Treatment	Vasoconstrictors, albumin, liver transplant	Similar to HRS-AKI; prevents progression to HRS-CKD	Long-term renal and liver support, transplantation

Source: Angeli P, J Hepatol. 2015; Ginès P, Gastroenterology. 2024;

Knowledge Check #1

Which clinical feature most supports a diagnosis of hepatorenal syndrome-acute kidney injury (HRS-AKI) in a patient with cirrhosis and ascites?

A. Structural kidney damage identified on biopsy

B. Lack of improvement in renal function after albumin administration

C. Evidence of nephrotoxic drug–induced tubular injury

D. Chronic hypertension with proteinuria

Knowledge Check #1

Which clinical feature most supports a diagnosis of hepatorenal syndrome-acute kidney injury (HRS-AKI) in a patient with cirrhosis and ascites?

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B. Lack of improvement in renal function after albumin administration

C. Evidence of nephrotoxic drug-induced tubular injury

D. Chronic hypertension with proteinuria

Epidemiology

Unique to patients with advanced cirrhosis with ascites

AKI occurs in up to ~50% of hospitalized patients with cirrhosis

May increase to ~80% among ICU admissions

Source: Nadim MK, N Engl J Med. 2023

Prognosis of HRS

~80% mortality within 2 weeks without treatment

~59% mortality within 1 week-6 months despite vasoconstrictor therapy

~35% of patients achieve HRS reversal with medical treatment

Early liver transplantation evaluation is critical

Source: Angeli P et al. J Hepatol. 2015; Piano S et al. BMJ. 2023; Wong F et al. N Engl J Med. 2021; Wong F et al. Gastroenterology. 2022

Risk/ Precipitating Factors

- Bacterial infections
- Large volume paracentesis without adequate albumin replacement
- Fluid loss
- Use of nephrotoxic drugs
- Over diuresis
- Gastrointestinal bleeding

Source: Biggins SW, Hepatology. 2021

Pathophysiology of HRS

Liver Cirrhosis

- Increased portal pressure
- Splanchnic vasodilation
- Increased cardiac output
- Cirrhotic cardiomyopathy

Leads to: Reduced effective arterial blood volume

Bacterial Translocation & Inflammatory Signals

- Bacterial translocation and PAMPs release
- Cell death and DAMPs release
- Systemic inflammation
- Cytokine and inflammatory mediator release

Source: Ginès P, Gastroenterology. 2024; Khemichian S, Annu Rev Med. 2024; Simonetto DA, BMJ. 2020

Pathophysiology of HRS, *continued*

Low Effective Arterial Volume

- Triggered by splanchnic vasodilation

- Activates:

- RAAS (kidney)
- SNS (spinal cord)
- ADH release (brain)

Leads to: Intense renal vasoconstriction

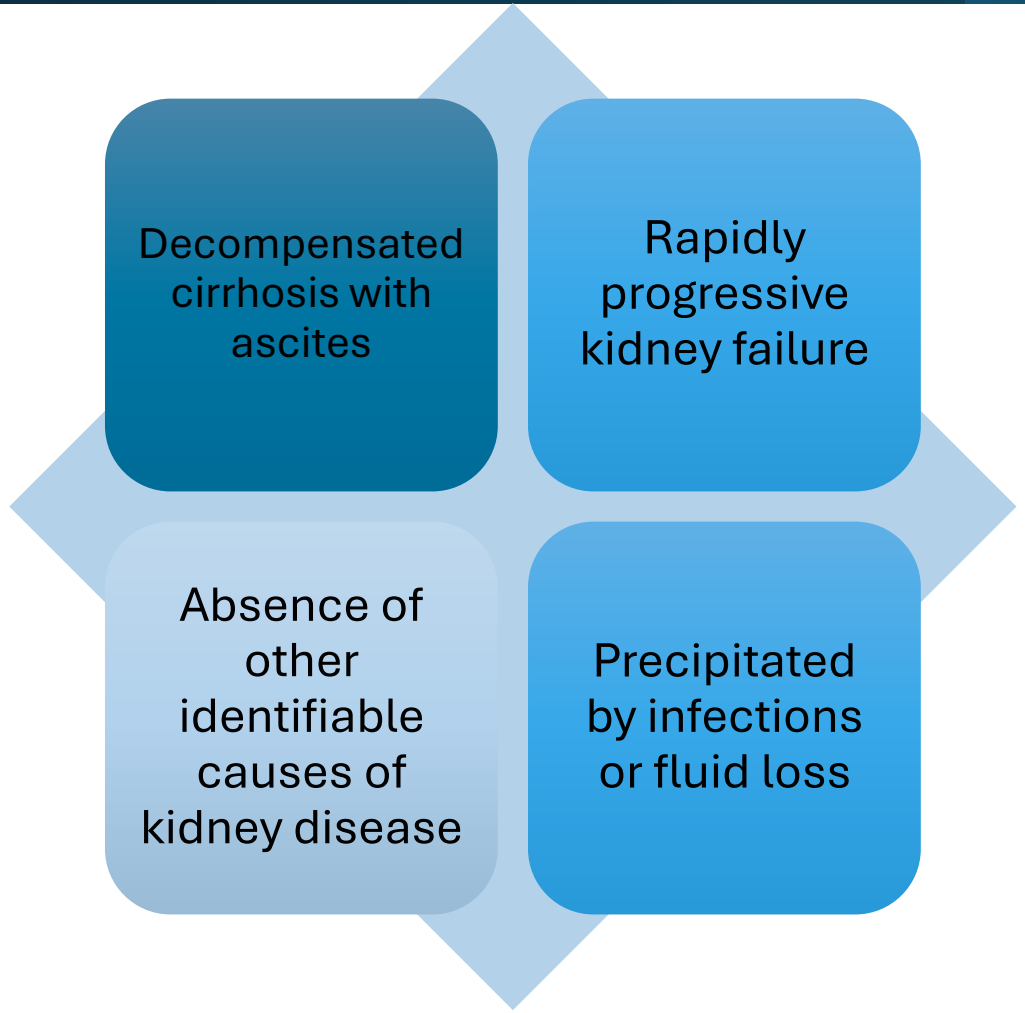
Hepatorenal Syndrome

- Decreased sodium excretion
- Increased water reabsorption
- Increased renal vasoconstriction
- Decreased glomerular filtration rate

Outcome: Functional renal failure in advanced cirrhosis

Source: Ginès P, Gastroenterology. 2024; Khemichian S, Annu Rev Med. 2024; Simonetto DA, BMJ. 2020

Clinical Presentation



Source: Ginès P, Gastroenterology. 2024

Diagnosing HRS, *continued*

Cirrhosis with ascites

Acute kidney injury (AKI) defined as:

- Increase in SCr ≥0.3 mg/dL within 48 hours, or
- ≥50% increase in SCr from known or presumed baseline within 7 days

No improvement after 48 hours of:

- Diuretic discontinuation
- Volume expansion with IV albumin (1 g/kg/day; max 100 g/day)

Source: Angeli P, J Hepatol. 2015; Flamm SL, Clin Gastroenterol Hepatol. 2022

Diagnosing HRS, continued

No evidence of shock

No recent exposure to nephrotoxins

No signs of intrinsic renal disease:

- Proteinuria >500 mg/day
- Microhematuria >50 RBCs/HPF
- Normal renal ultrasound

Source: Angeli P, J Hepatol. 2015; Flamm SL, Clin Gastroenterol Hepatol. 2022

Challenges in Diagnosing HRS

- No gold standard diagnostic test
- Can occur in preexisting chronic kidney disease or other AKI etiologies
- SCr/ GFR underestimates renal dysfunction in cirrhosis
- Difficult to differentiate from other forms of renal damage

Source: Flamm SL, Clin Gastroenterol Hepatol. 2022; Nadim MK, N Engl J Med. 2023

Complications of HRS

- Rapidly progressive renal failure
- Volume overload and pulmonary edema
- Electrolyte/metabolic abnormalities
- Hepatic encephalopathy and infection risk
- Hemodynamic instability and multiorgan dysfunction
- Transplant implications

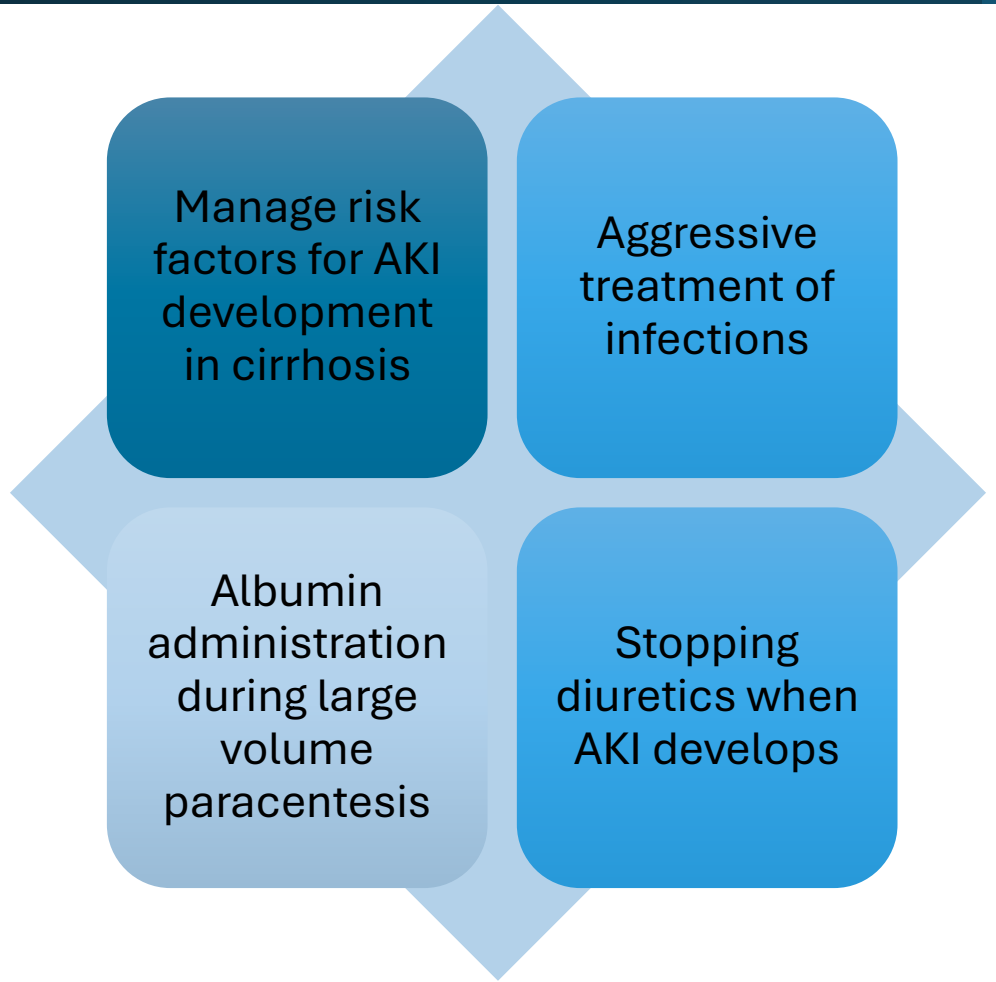
Source: Nadim MK, N Engl J Med. 2023; Karvellas CJ, Hepatology. 2024

Goals of Therapy for HRS

- Reverse renal vasoconstriction
- Restore renal perfusion and improve GFR
- Delay progression to dialysis or multiorgan failure
- Stabilize hemodynamics
- Treat precipitating factors
- Bridge to liver transplantation
- Improve short-term survival

Source: Garcia-Tsao G, Gastroenterology. 2023

Prevention of HRS



Source: Biggins SW, Hepatology. 2021; Garcia-Tsao G, Gastroenterology. 2023

Overview of HRS Management, *continued*

Initial management

- Withdraw diuretics
- Treat precipitating factors

Vasoconstrictor therapy with albumin (20–40 g/day)

- Terlipressin
- Norepinephrine
- Midodrine plus octreotide

Source: Garcia-Tsao G, Gastroenterology. 2023; Duong N, Clin Gastroenterol Hepatol. 2023

Overview of HRS Management, *continued*

Renal replacement therapy

- Individualized
- Bridge to liver transplantation

Liver transplantation

- Definitive treatment

Source: Garcia-Tsao G, Gastroenterology. 2023; Duong N, Clin Gastroenterol Hepatol. 2023

Pharmacologic Therapy

Agent	Mechanism	FDA Approved	Place in Therapy	Treatment Setting	Route of Administration	Dosing Considerations
Terlipressin	Vasopressin analog	Yes	Preferred 1st line	Medical floor (telemetry monitoring) or ICU	Slow IV bolus over 2 minutes	• Adjust dose on day 4 based on SCr
Norepinephrine	α_1 & β adrenergic receptor agonist	No	2nd line	ICU	IV continuous infusion	• Adjust dose based on MAP or urine output • Requires central IV access
Midodrine	α_1 adrenergic receptor agonist	No	Last line	Medical floor	Oral	—
Octreotide	Somatostatin analog	No	Last line	Medical floor	SC injection or IV continuous infusion	• Rotate injection sites if given SC

Source: Duong N, Clin Gastroenterol Hepatol. 2023

Knowledge Check #2

A pharmacist is reviewing a treatment plan for a patient diagnosed with HRS-AKI.

Which vasoconstrictor would be the preferred first-line therapy based on current evidence and FDA approval?

A. Midodrine

B. Octreotide

C. Norepinephrine

D. Terlipressin

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D. Terlipressin

Albumin - Place in Therapy

Mechanism of Action	- Expands central and effective arterial blood volume - Enhances vasoconstrictor efficacy by counteracting splanchnic vasodilation - Improves renal perfusion
Dose	- 1 g/kg/day (max 100 g/day) for 2 consecutive days - Differentiate HRS-AKI from other causes of AKI in cirrhosis

Source: Garcia-Tsao G, Gastroenterology. 2023; Wong F, N Engl J Med. 2021

Albumin - Place in Therapy, *continued*

Therapeutic Use with Vasoconstrictors

- Dose: 20–40 g/day during vasoconstrictor therapy

Duration

- Not standardized
- Individualized based on hemodynamic response and volume status

Source: Garcia-Tsao G, Gastroenterology. 2023; Wong F, N Engl J Med. 2021

Albumin - Place in Therapy, *continued*

Goal

- Sustain renal perfusion while avoiding volume overload

Risks of Excess Albumin

- Pulmonary edema, respiratory compromise, and worsening ascites or pleural effusions
- Higher cumulative doses correlate with improved survival and fluid-related complications

Source: Garcia-Tsao G, Gastroenterology. 2023; Wong F, N Engl J Med. 2021

Albumin Use in Cirrhosis – ATTIRE Trial

Study	Population	Outcomes	Findings	Clinical Implications
ATTIRE Trial - Albumin To prevenT Infection in chronic liveR failurE	777 hospitalized adults with decompensated cirrhosis and serum albumin <3.0 g/dL	**Primary:** Composite of new infection, renal dysfunction, or death by day 14 **Secondary:** Individual components of the composite, length of stay, ICU admission, adverse events	No difference in primary outcome between albumin and standard care (29.7% vs 30.2%) Higher rate of pulmonary edema in albumin group (4% vs 1%)	• Albumin infusions targeting serum levels ≥3.0 g/dL did not improve clinical outcomes and increased risk of fluid overload • Routine high-dose albumin without vasoconstrictors is not supported

Source: Wong F, N Engl J Med. 2021

Terlipressin - Place in Therapy

Mechanism of Action

- Synthetic vasopressin analog with selective V1 receptor agonism
- Induces splanchnic vasoconstriction, which increases effective arterial blood volume
- Enhances renal perfusion when co-administered with albumin

Indications

- First-line vasoconstrictor for HRS-AKI
- Requires exclusion of structural kidney disease, shock, and nephrotoxins

Always co-administer with albumin

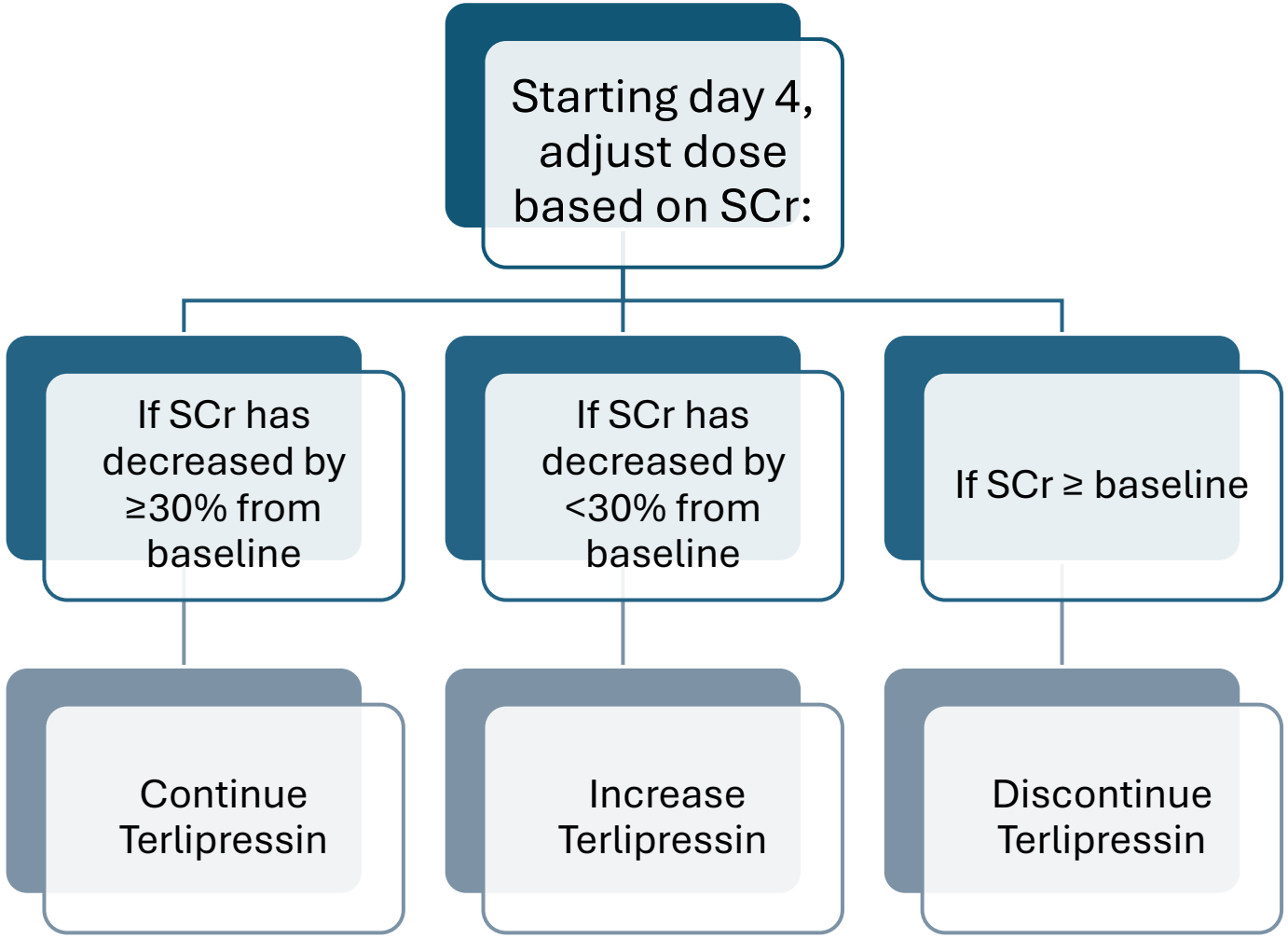
Source: Wong F, N Engl J Med. 2021; Allegretti AS, Hepatology. 2025

Terlipressin – Place in Therapy, *continued*

Bolus regimen	• Start at 0.5-1 mg IV every 4-6 hours; titrate up to 12 mg/day based on response
Continuous infusion	• 2-4 mg/day IV preferred in some centers for improved tolerability
Duration	• Up to 14 days or until HRS reversal (defined by SCr <1.5 mg/dL)

Source: Wong F, N Engl J Med. 2021; Allegretti AS, Hepatology. 2025

Terlipressin – Place in Therapy, continued



Source: Wong F, N Engl J Med. 2021; Allegretti AS, Hepatology. 2025

Terlipressin - Place in Therapy, *continued*

Advantages

- Strongest evidence for HRS-AKI reversal
- Improves renal function
- Decreases need for renal replacement therapy

Limitations

- Does not improve overall mortality
- Requires careful monitoring for adverse events
- Continuous infusion preferred to reduce cumulative dose and side effects

Source: Olson JC, PLoS One. 2023; Pitre T, Crit Care Med. 2022

Terlipressin - Place in Therapy, *continued*

Adverse effects

- Respiratory failure (boxed warning)
- Ischemia
- Hemodynamic instability
- Electrolytes imbalance
- Gastrointestinal

Monitoring

- Respiratory
- Cardiovascular
- Renal function
- Electrolytes
- Volume status
- Infection

Source: Olson JC, PLoS One. 2023; Pitre T, Crit Care Med. 2022

Knowledge Check #3

A 68-year-old patient with cirrhosis is diagnosed with HRS-AKI and started on albumin and terlipressin therapy. The patient's baseline serum creatinine (SCr) is 2.4 mg/dL.

After 4 days of treatment, the patient's SCr is 1.6 mg/dL.

What is the most appropriate next step in this patient's terlipressin therapy?

A. Continue the current terlipressin regimen
B. Increase the terlipressin dose
C. Discontinue terlipressin
D. Hold terlipressin until creatinine decreases to ≤1.5 mg/dL

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Terlipressin in HRS-AKI

Study	Population	Outcomes	Findings	Clinical Implications
Terlipressin plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome	300 adults with HRS-AKI (CONFIRM trial, North America)	**Primary:** Verified HRS reversal **Secondary:** HRS reversal without RRT, mortality, adverse events	HRS reversal: 32% (terlipressin) vs 17% (placebo) HRS reversal without RRT: 34% vs 17% Increase Respiratory failure: 11% vs 2%	• Terlipressin improves HRS reversal but increases risk of respiratory failure • Supports albumin co-administration and early risk stratification

Source: Wong F, N Engl J Med. 2021

Norepinephrine - Place in Therapy

Mechanism of Action

- Potent α1-adrenergic agonist which causes systemic vasoconstriction
- Increases mean arterial pressure (MAP) and renal perfusion
- Less splanchnic selectivity than terlipressin
- Restores effective arterial volume

Indications

- Alternative vasoconstrictor for HRS-AKI in ICU settings

Source: Olson JC, PLoS One. 2023; Pitre T, Crit Care Med. 2022

Norepinephrine - Place in Therapy, *continued*

Dosing

- **Standard ICU regimen:**
- **Typical range:**
- **Low-dose protocol (non-ICU):**

Always co-administer with albumin

Source: Olson JC, PLoS One. 2023; Pitre T, Crit Care Med. 2022

Norepinephrine - Place in Therapy, *continued*

Advantages

- Preferred when terlipressin is unavailable or contraindicated
- Comparable to terlipressin
- Widely available and inexpensive
- Lower serious adverse events

Limitations

- Requires ICU-level monitoring
- Requires central line
- Greater nursing and pharmacy workload

Source: Olson JC, PLoS One. 2023; Pitre T, Crit Care Med. 2022

Norepinephrine - Place in Therapy, *continued*

Adverse effects

- Cardiovascular events
- Peripheral ischemia
- Mild gastrointestinal symptoms

Monitoring

- Hemodynamics (MAP, heart rate, perfusion)
- Cardiac rhythm
- Renal function
- Volume status
- Infusion site

Source: Olson JC, PLoS One. 2023; Pitre T, Crit Care Med. 2022

Terlipressin versus Norepinephrine in HRS

Study	Population	Outcomes	Findings	Clinical Implications
Comparative Efficacy of Terlipressin and Norepinephrine for Treatment of HRS-AKI: A Systematic Review and Meta-Analysis	376 patients across 7 RCTs comparing norepinephrine vs terlipressin	Primary: HRS reversal Secondary: Short-term survival, adverse events, treatment discontinuation	• HRS reversal: OR 1.33 (95% CI 0.80–2.22), favoring terlipressin • Short-term survival: OR 1.50 (95% CI 0.64–3.53), favoring terlipressin • Discontinuation due to adverse events: 5.3% (terlipressin) vs 2.7% (norepinephrine) • AE profiles differed: GI symptoms (terlipressin) vs cardiovascular events (norepinephrine)	• Norepinephrine demonstrates comparable efficacy to terlipressin for HRS reversal and survival. • Lower discontinuation rates and distinct AE profile support its use as a viable alternative, particularly in ICU settings or where terlipressin is contraindicated or unavailable

Source: Olson JC, PLoS One. 2023

Midodrine + Octreotide - Place in Therapy

Midodrine

Oral α1-adrenergic agonist: results in systemic vasoconstriction, increases MAP

Octreotide

Somatostatin analog: inhibits vasodilatory peptides, reduces splanchnic vasodilation

Combined effect aims to restore effective arterial blood volume and renal perfusion

Source: Duong N, Clin Gastroenterol Hepatol. 2023

Midodrine + Octreotide - Place in Therapy, *continued*

Indications

- Third-line therapy
- Used only when terlipressin is unavailable or contraindicated
- May be initiated in non-ICU settings with close monitoring

Dosing and Administration

- Midodrine: 7.5–12.5 mg orally three times daily
- Octreotide: 100–200 mcg subcutaneously three times daily

Source: Duong N, Clin Gastroenterol Hepatol. 2023

Midodrine + Octreotide - Place in Therapy, *continued*

Duration

- Typically limited to 24–48 hours pending response or escalation

Adverse Effects

- **Midodrine:** Headache, piloerection, blurred vision, palpitations, rash
- **Octreotide:** Nausea, abdominal pain, emesis, fatigue, back pain

Monitoring

- Blood pressure and MAP
- Renal function
- Volume status
- Heart rate and GI symptoms

Source: Duong N, Clin Gastroenterol Hepatol. 2023

Midodrine + Octreotide - Place in Therapy, *continued*

Advantages

- Can be used when terlipressin or norepinephrine is unavailable
- Less risk of respiratory failure compared to terlipressin

Limitation

- Less effective than terlipressin or norepinephrine
- Unclear superiority over placebo

Source: Duong N, Clin Gastroenterol Hepatol. 2023

Comparative Effectiveness of Vasoactive Agents in HRS-AKI

Study	Population	Interventions	Outcomes	Findings	Clinical Implications
The Comparative Effectiveness of Vasoactive Treatments for Hepatorenal Syndrome: A Systematic Review and Network Meta-Analysis	1,736 patients with HRS (type 1 or 2) across 26 RCTs	Terlipressin + albumin Norepinephrine + albumin Midodrine + octreotide + albumin (Placebo ± albumin)	**Primary:** HRS reversal **Secondary:** Mortality, serious adverse events	• Terlipressin increases HRS reversal vs placebo (142/1,000; high certainty) • Norepinephrine increases HRS reversal vs placebo • Midodrine + octreotide: effect uncertain • Terlipressin may reduce mortality • Terlipressin likely increase serious AEs vs placebo	• Terlipressin and norepinephrine are most effective for HRS reversal • Midodrine + octreotide has limited and uncertain benefit • Terlipressin may improve survival but increases adverse events • Supports individualized vasopressor selection based on efficacy, safety, and monitoring capacity

Source: Pitre T, Crit Care Med. 2022; Best LM, Cochrane Database Syst Rev. 2019

Comparison of Terlipressin vs Midodrine Plus Octreotide

Study	Population	Outcomes	Findings	Clinical Implications
Real-World Indirect Treatment Comparison of Terlipressin vs Midodrine Plus Octreotide in Hepatorenal Syndrome-Acute Kidney Injury	Adults with HRS-AKI and cirrhosis; excluded if MELD ≥35 or listed for transplant. Final matched cohorts: 159 patients per group.	**Primary:** HRS reversal (sCr ≤1.5 mg/dL without dialysis or death) **Secondary:** 30-day mortality, RRT use, ICU admission, hospital length of stay	• HRS reversal: 35.2% (terlipressin) vs 16.4% (MO); aOR 2.79 (95% CI: 1.52–5.13) • 30-day mortality: 20.1% vs 31.4%; aOR 0.53 (95% CI: 0.29–0.98) • RRT: 9.4% vs 18.2%; aOR 0.45 (95% CI: 0.21–0.97) • ICU admission and LOS lower with terlipressin	• Terlipressin showed superior real-world effectiveness over Midodrine + Octreotide in HRS reversal, mortality, and RRT reduction. • Supports formulary preference for terlipressin in eligible HRS-AKI patients not listed for transplant. • May reduce ICU burden and justify acquisition cost.

Source: Gonzalez SA, Clin Transl Gastroenterol. 2026

Liver Transplantation – Definitive Therapy

Only curative treatment for HRS-AKI

Renal dysfunction is generally reversible post-transplant

- ~25% remain dialysis-dependent post-transplant
- Risk factors: pre-existing CKD, pre-transplant RRT, younger age

Non-responders to vasoconstrictor therapy who are not transplant candidates should be referred for palliative care

Consider simultaneous liver-kidney transplant if RRT >6 weeks pre-transplant

Source: Karvellas CJ, Hepatology. 2024

Transjugular Intrahepatic Porto-systemic Shunt (TIPS)

Source: Gonzalez-Garay AG, Cochrane Database Syst Rev. 2024; Ponzo P, Dig Liver Dis. 2022; Li R, Dig Dis Sci. 2025; Ripoll C, Trials. 2023

Renal Replacement Therapy (RRT)

- Bridge to liver transplantation
  - Supportive, not curative
- **Indications:** Life-threatening complications (hyperkalemia, severe acidosis, volume overload, uremia)
- No RCTs guiding timing
  - Similar mortality in HRS-AKI vs ATN on RRT
- CRRT preferred in hemodynamically unstable patients
- **Transplant consideration:**
  - >6 weeks RRT
  - Evaluate for simultaneous liver–kidney transplant

Source: Karvellas CJ, Hepatology. 2024; Ostermann M, Lancet. 2025

Identifying Treatment Success & Failure

Treatment Response

- Serum creatinine decreased to <1.5 mg/dL or within 0.3 mg/dL of baseline within 14 days
- Early discontinuation recommended if <25% SCr reduction after 4 days at max tolerated dose

Indicators of Treatment Success

- HRS reversal without dialysis by day 30
- Increased MAP correlates with renal recovery

Source: Wong F, N Engl J Med. 2021; Allegretti AS, Hepatology. 2025

Identifying Treatment Success & Failure, continued

- **Indicators of Treatment Failure**
  - No SCr reduction by day 4
  - Serious adverse events
  - Worsening volume overload
  - Higher ACLF (acute-on-chronic liver failure) grades = lower response rates

- **Recurrence & Prognosis**
  - Recurrence possible
    - Retreatment may be needed
  - Even responders have high short-term mortality
    - Urgent transplant evaluation essential

Source: Wong F, N Engl J Med. 2021; Allegretti AS, Hepatology. 2025

Emerging Therapies for HRS

- **Ambrisentan**
  - Endothelin receptor antagonist
  - Improve renal hemodynamics and reduce vasoconstriction
- **Ifetroban**
  - Thromboxane receptor antagonist
  - Targets inflammation and renal perfusion
- **Ilofotase alfa**
  - Recombinant alkaline phosphatase
  - Kidney protective and anti-inflammatory effects
  - Studied mainly in AKI with potential HRS application

Source: Chandna S, J Clin Gastroenterol. 2026; Khemichian S, Annu Rev Med. 2024

Future of HRS

HRS has a high mortality without transplantation

Emerging therapies targets vasoconstriction, fluid balance, and inflammation

Rising liver disease prevalence, improved diagnostics and multimodal therapy continues to drive research and development

Barriers: high costs, limited awareness, safety concerns, and organ scarcity

Source: Chandna S, J Clin Gastroenterol. 2026; Khemichian S, Annu Rev Med. 2024

Key Takeaways

HRS-AKI is a rapidly progressive, functional renal failure with high mortality if untreated.

Diagnosis requires exclusion of structural kidney disease and poor response to albumin challenge.

Terlipressin + albumin is first-line therapy; norepinephrine and midodrine/octreotide are alternatives.

Early diagnosis and transplant are critical to improving outcomes.

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THANK YOU

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