Hepatorenal Syndrome: A Student Handout on HRS-AKI and Kidney Dysfunction in Liver Disease

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Hepatorenal Syndrome: A Student Handout for PA/Medical Students

Learning Objectives

By the end of this session, you should be able to: 1. **Define** hepatorenal syndrome and its updated classification (HRS-AKI vs. HRS-non-AKI) 2. **Explain** the hemodynamic and inflammatory mechanisms linking portal hypertension to kidney dysfunction 3. **Recognize** HRS-AKI using current diagnostic criteria (without arbitrary creatinine thresholds) 4. **Differentiate** HRS from acute tubular necrosis (ATN) and other causes of AKI in cirrhotic patients 5. **Discuss** the role of vasoconstrictors (terlipressin + albumin) as first-line therapy 6. **Interpret** when dialysis is indicated and understand its limitations in HRS 7. **Manage** complications of dialysis in portal hypertensive patients (intradialytic hypotension, bleeding risk)

What Is Hepatorenal Syndrome?

Hepatorenal syndrome represents a **functional form of acute kidney injury** that develops in patients with advanced cirrhosis or acute-on-chronic liver failure. It is not due to primary kidney pathology (no structural injury) but rather results from intense renal vasoconstriction driven by hemodynamic derangements in liver disease.

Key Point

HRS is a **diagnosis of exclusion**—other causes of AKI must be ruled out: prerenal azotemia, acute tubular necrosis (ATN), drug-induced kidney injury, and intrinsic kidney disease.

Why This Matters for You

- Cirrhosis affects ~2% of the U.S. population; HRS develops in ~20-40% of hospitalized cirrhotic patients
- **Untreated HRS has median survival of 8-12 weeks**
- Early recognition and pharmacological intervention can save lives

- You will encounter HRS in ICU, hospital medicine, and nephrology rotation settings
- Understanding HRS is essential for managing complex patients with simultaneous liver and kidney failure

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The Pathophysiology: How Portal Hypertension Breaks the Kidneys

Step 1: Portal Hypertension Creates Splanchnic Vasodilation

- Increased pressure in the portal system triggers vasodilation in the splanchnic vascular bed
- This occurs via endothelial nitric oxide (NO) activation and other vasodilatory factors
- Result: Blood pools in the splanchnic circulation ☐ **"effective hypovolemia"** despite total body fluid overload

Step 2: The Body Tries to Compensate (But It Backfires)

To maintain blood pressure, your body activates: - **RAAS** (renin-angiotensin-aldosterone system) - **Sympathetic nervous system** - **Vasopressin** (antidiuretic hormone)

These normally help restore blood pressure by causing vasoconstriction. **But in HRS, this compensation goes too far.**

Step 3: Intense Renal Vasoconstriction Develops

- The renal arteries constrict severely
- Glomerular filtration rate (GFR) plummets
- **Kidney function fails** — even though the kidneys themselves are structurally normal
- This is why we call it "functional" kidney failure

Step 4: Inflammation Worsens It

Recent research shows that **systemic inflammation** in acute-on-chronic liver failure also contributes: - Dysregulated immune response ☐ inflammatory cytokine release - Bacterial translocation from the gut - Epithelial dysfunction and vascular injury

Pathophysiology Summary

Stage	What Happens	Result
Portal HTN	Splanchnic vasodilation	"Effective hypovolemia"
Compensation	RAAS + SNS activation	Renal vasoconstriction
Renal Failure	Intense vasoconstriction	GFR drops, serum creatinine rises
Inflammation	Cytokine cascade	Endothelial injury, worsens outcome

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Updated Classification: HRS-AKI and HRS-non-AKI

The International Club of Ascites (ICA) revised HRS nomenclature in 2021-2023. **The old "Type 1" and "Type 2" terminology is outdated.** Here's the new framework:

HRS-AKI (Hepatorenal Syndrome-Acute Kidney Injury)

- **Rapidly progressive** kidney dysfunction
- Serum creatinine increase ≥50% from baseline **OR** absolute increase ≥0.3 mg/dL within 48 hours
- Median survival without treatment: **8-12 weeks**
- **Clinical urgency:** Very high — treat immediately with vasoconstrictors

HRS-non-AKI (HRS-NAKI)

- **Slower, progressive** kidney dysfunction
- Includes both HRS-acute kidney disease (AKD) and HRS-chronic kidney disease (CKD)
- Develops over weeks to months
- Lower immediate mortality but requires management to prevent progression

Why the Change Matters

The new criteria **eliminate the need for absolute creatinine thresholds**, which is crucial because: - Many cirrhotic patients are malnourished (sarcopenia) ☐ baseline creatinine is artificially low - A patient with baseline Cr 0.6 who rises to 1.0 has **real kidney dysfunction** but the old criteria might miss this - Dynamic creatinine changes catch more patients earlier

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Diagnostic Approach

Clinical Suspicion

You should suspect HRS when you see: 1. A patient with **known cirrhosis or advanced liver disease** 2. **Acute rise in serum creatinine** (≥50% from baseline OR ≥0.3 mg/dL in 48 hours) 3. **Oliguria** (urine output <500 mL/day) 4. **Absence of shock** (unlike prerenal AKI, blood pressure may be normal or low-normal) 5. **No response to albumin + fluid challenge** (500 mL normal saline over 2 hours)

Essential Workup to Rule Out Other Causes

Before diagnosing HRS, **exclude**:

Alternative Diagnosis	How to Distinguish
Prerenal AKI	BUN:Cr ratio >20:1; improves with volume; urine Na+ <20 mEq/L
ATN	Granular casts, muddy casts on UA; urine Na+ >40 mEq/L; FENa >2%

Alternative Diagnosis	How to Distinguish
Drug-induced (aminoglycosides, NSAIDs, ACE-I)	Timeline of drug exposure; eosinophiluria if rhabdomyolysis
Glomerulonephritis	Hematuria, RBC casts, proteinuria; elevated creatinine in context
Hepatic cirrhosis with structural kidney disease	Biopsy shows intrinsic GN; different clinical context

Key Diagnostic Clue: The Urine Sodium

In HRS, the kidneys are **avidly reabsorbing sodium** due to RAAS activation: - **Urine sodium typically <10 mEq/L** (very low) - **Fractional excretion of sodium (FENa) <0.1%** (very low)

This contrasts with ATN where FENa is >2%, showing the tubules are damaged and can't reabsorb sodium.

Clinical Features at Presentation

Symptoms

- Fatigue, weakness (from uremia)
- Nausea, anorexia
- Encephalopathy (confusion, asterixis) — from ammonia + uremia
- Abdominal distention (ascites)
- Dyspnea (from fluid overload, hepatopulmonary syndrome)

Physical Examination

- **Stigmata of cirrhosis:** Spider telangiectasias, palmar erythema, jaundice, caput medusae
- **Signs of portal hypertension:** Ascites, splenomegaly, dilated veins
- **Volume status:** Often paradoxical — ascitic but dehydrated systemically
- **Encephalopathy:** Altered mental status, tremor, asterixis

Laboratory Findings

Test	Typical Finding	Interpretation
Serum Creatinine	Rising (50%+ increase)	Evidence of AKI
BUN	Elevated	AKI confirmed
Urinalysis	Minimal proteinuria; no casts	No intrinsic kidney disease
Urine Na+	<10 mEq/L (very low)	Intact tubular reabsorption
FENa	<0.1%	Functional (not structural) injury
Albumin	Low (<2.5 g/dL)	Hepatic synthetic dysfunction
INR/PT	Prolonged	Liver failure
Bilirubin	Elevated	Liver failure

Test	Typical Finding	Interpretation
Platelets	Low (<100)	Bone marrow suppression, splenic sequestration

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Management: The Stepwise Approach

Step 1: Rule Out Other Causes (First 24-48 Hours)

- Correct hypovolemia if present (IV albumin + NS challenge)
- Stop nephrotoxic drugs (NSAIDs, ACE inhibitors, aminoglycosides)
- Assess for active infection (SBP, UTI, pneumonia) and treat
- Correct electrolyte abnormalities

Step 2: First-Line Pharmacological Therapy

Terlipressin + Albumin is the gold standard for HRS-AKI.

Terlipressin

- **Mechanism:** Selective vasopressin V1 receptor agonist ☐ renal and splanchnic vasoconstriction
- **Dose:** 1-2 mg IV every 4-6 hours (max 12 mg/day)
- **Recent milestone:** FDA approved in 2023 for HRS-AKI — first agent approved specifically for this indication
- **Duration:** Continue for 5-7 days or until renal function improves
- **Side effects:** Hypertension, ischemic complications (rare at doses used)

Albumin

- **Dose:** 1 g/kg on day 1 (max 100 g), then 20-40 g daily during terlipressin course
- **Mechanism:** Expands effective intravascular volume, improves renal perfusion pressure
- **Rationale:** Albumin + vasoconstrictor is superior to either agent alone

Combination Therapy Outcomes Studies show ~40-50% of patients have **reversible HRS** with terlipressin + albumin: - Serum creatinine returns to near-baseline - Can avoid or delay dialysis - Improves survival

Step 3: When to Add Dialysis

Dialysis is **not primary treatment** but rather a **bridging intervention** when: 1. **Failure to respond to medical therapy** (no improvement after 5-7 days terlipressin) 2. **Urgent metabolic complications:** - Severe hyperkalemia (K+ >6.5 unresponsive to medical management) - Severe acidosis (pH <7.1) - Pulmonary edema refractory to diuretics - Symptomatic uremia 3. **Bridge to liver transplantation** — wait list; dialysis buys time 4. **Concurrent ATN** — structural kidney damage requiring RRT

Step 4: Managing Dialysis Complications in Portal Hypertension

Portal hypertensive patients are at **high risk for problems** during dialysis:

Intradialytic Hypotension (IDH)

- **Definition:** Systolic BP drop ≥20 mmHg OR MAP drop ≥10 mmHg requiring intervention
- **Incidence in CKD:** 10-12%
- **Incidence in cirrhotic patients:** Much higher (splanchnic pooling, autonomic dysfunction)

Prevention strategies: - Smaller fluid removal per session (ultra-gradual dry-weight achievement) - **Minimal anticoagulation** or **regional anticoagulation** (citrate) — reduce bleeding risk - Cool dialysate (35-36°C) to improve hemodynamic stability - Avoid large meals before dialysis - Monitor continuously; be ready to adjust ultrafiltration rate mid-session

Variceal Bleeding Risk

- **Problem:** Dialysis causes hemodynamic fluctuations ☐ risk of variceal rupture
- **Contributing factors:** Required anticoagulation, rebound hypertension post-dialysis
- **Management:**
  - Prophylactic beta-blockers (propranolol, nadolol, carvedilol) to reduce portal pressure
  - Careful anticoagulation protocol (minimal heparin, or none)
  - Endoscopic variceal ligation if varices present
  - Close monitoring for signs of bleeding

Key Clinical Pearls

1. **Creatinine is a poor marker in cirrhosis** — muscle wasting means baseline is falsely low. Trust the *change* in creatinine, not the absolute value.
2. **HRS-AKI has high mortality even with treatment** — ~40-60% mortality at 1 year. This is a serious condition requiring ICU-level care.
3. **Terlipressin is game-changing** — FDA approval in 2023 finally gives us an agent designed specifically for HRS. Start ASAP if HRS is suspected.
4. **Dialysis is rarely "curative" for HRS** — it's a bridge therapy. Only ~11% of HRS patients recover kidney function on dialysis. The real hope is liver transplantation.
5. **Infection is a major trigger** — Many HRS cases are precipitated by spontaneous bacterial peritonitis (SBP), UTI, or pneumonia. Always look for and treat infections aggressively.
6. **Albumin is part of the regimen** — Terlipressin **without** albumin is less effective. Always give both together.
7. **Portal hypertensive patients tolerate dialysis poorly** — Expect intradialytic hypotension, need aggressive monitoring, consider peritoneal dialysis or CRRT if available.
8. **Early recognition saves lives** — The new diagnostic criteria (dynamic Cr changes) catch patients earlier than the old "Type 1/Type 2" system. Don't wait for creatinine to reach 2.0+.

Practice Questions

Question 1: Case Presentation

A 58-year-old man with biopsy-proven cirrhosis (Child-Pugh C) from alcoholic liver disease presents to the hospital with fever (38.5°C). His last creatinine 3 months ago was 0.7 mg/dL. Today it is 1.4 mg/dL. Urine output is 300 mL in the past 24 hours. Urine sodium is 8 mEq/L. Urinalysis shows no proteinuria or casts.

Which of the following is the best next step in management?

A. Start hemodialysis immediately B. Administer IV albumin challenge (500 mL normal saline) and then, if no improvement, start terlipressin + albumin C. Start furosemide to increase urine output D. Order a kidney biopsy to assess for glomerulonephritis

Answer: B. This patient has likely **HRS-AKI precipitated by infection** (fever suggests SBP or other infection). Correct approach: First, rule out volume depletion with albumin challenge and look for/treat infection. Then start terlipressin + albumin if HRS is confirmed. Dialysis is not first-line. Biopsy is unnecessary given the clinical picture (low urine sodium, no casts, typical HRS features).

Question 2: Mechanism Question

A cirrhotic patient develops HRS-AKI despite normal or low-normal systemic blood pressure. This paradoxical finding is best explained by:

A. Acute tubular necrosis from ischemia B. Splanchnic vasodilation causing "effective hypovolemia" triggering RAAS and intense renal vasoconstriction C. Direct toxic effect of ammonia on renal tubules D. Glomerulonephritis secondary to immune complex deposition

Answer: B. The key to HRS is understanding the **hemodynamic mismatch**: despite normal systemic BP, the kidneys are underperfused due to splanchnic pooling and compensatory renal vasoconstriction. This is a functional problem, not a structural one. Choice A (ATN) would show muddy casts; Choice C (ammonia) causes encephalopathy more than kidney injury; Choice D would show hematuria and RBC casts.

Question 3: Drug Therapy Question

A 65-year-old woman with cirrhosis and HRS-AKI is started on terlipressin 2 mg IV every 6 hours. After 3 days, her serum creatinine has improved from 2.8 to 1.9 mg/dL. The team considers stopping terlipressin.

Is this appropriate?

A. Yes, discontinue terlipressin immediately since creatinine is improving B. No, continue terlipressin for 5-7 days total to consolidate the response and prevent recurrence C. Yes, switch to a

beta-blocker for long-term renal protection D. No, the patient needs dialysis because creatinine is still >1.5

Answer: B. While early response is favorable, **premature discontinuation of terlipressin risks rebound worsening**. Standard practice is to continue terlipressin for 5-7 days or longer if kidney function is still improving. Short courses risk relapse.

Summary Table: HRS at a Glance

Concept	Key Point
Pathophysiology	Portal HTN ☐ splanchnic vasodilation ☐ "effective hypovolemia" ☐ RAAS activation ☐ renal vasoconstriction
Classification	HRS-AKI (rapidly progressive) vs. HRS-non-AKI (slower); no more "Type 1/Type 2"
Diagnosis	≥50% Cr increase OR ≥0.3 mg/dL rise in 48 hrs; urine Na+ <10; FENa <0.1%; no intrinsic kidney disease
Prognosis	8-12 week median survival untreated; 60% mortality at 1 year even with dialysis
First-line Rx	Terlipressin (V1 agonist) + albumin; FDA approved 2023
Dialysis Role	Bridging therapy, not primary treatment; used for refractory cases or complications
Dialysis Risks	Intradialytic hypotension (>50% in cirrhotic patients); variceal bleeding risk
Prognosis with Tx	~40-50% show improvement with terlipressin + albumin; only ~11% recover kidney function on dialysis alone

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See Also

Related Student Handouts

- Hepatology Overview
- Ammonia and Dialysis
- Hepatopulmonary Syndrome
- AKI Workup and Diagnosis
- CKD Complications

Clinical Content (01-Clinical-Medicine/Nephrology & Hepatology)

- Hepatorenal Disease Hub
- Essential Renal Laboratory Tests

Butler-COM Resources

- Butler COM - Nephrology Deep Dive

References & Further Reading

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