Acute Renal Dysfunction in Cirrhosis

Disclosures

- I do not have (nor does any immediate family member have) a vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias my presentation
- There was no Financial Support obtained for this CPE Activity

Pharmacists Objectives

- Define the types of acute kidney injury (AKI) in patients with cirrhosis
- Describe the historical definition and reclassification of hepatorenal syndrome (HRS)
- Discuss the pharmacological treatment options for HRS-AKI

Technician Objectives

- Discuss the importance of true STAT medications
- Recall enteral, subcutaneous, and parenteral administration routes for hepatorenal syndrome (HRS) medications
- Identify common generic medications and their functions for renal and hepatic systems

Consensus Definitions of AKI

	RIFLE	AKIN	KDIGO	Conventional
Diagnostic criteria	Increase in SCr to ≥1.5 times baseline within 7 days OR GFR decrease >25% OR urine volume <0.5 mL/kg/hr for 6 hrs	Increase in SCr by ≥0.3 mg/dL within 48 hrs OR increase in SCr to ≥1.5 times baseline within 48 hrs OR urine volume <0.5 mL/kg/hr for 6 hrs	Increase in SCr by >0.3 mg/dL within 48 hrs OR increase in SCr to ≥1.5 times baseline within 7 days OR urine volume <0.5 mL/kg/hr for 6 hrs	Percentage increase in SCr by 50% or more to a final value of SCr >1.5 mg/dL
Staging	Risk: SCr increase 1.5-1.9 times baseline OR GFR decrease 25-50% OR urine output <0.5 mL/kg/hr for 6 hrs	Stage 1: SCr increase 1.5-1.9 times baseline OR SCr increase ≥0.3 mg/dL OR urine output <0.5 mL/kg/hr for 6 hrs	Stage 1: SCr increase 1.5-1.9 times baseline OR SCr increase ≥0.3 mg/dL OR urine output <0.5 mL/kg/hr for 6-12 hrs	Not provided
	Injury: SCr increase 2 to 2.9 times baseline OR GFR decrease 50-75% OR urine output <0.5 mL/kg/hr for 12 hrs	Stage 2: SCr increase 2-2.9 times baseline OR urine output <0.5 mL/kg/hr for 12 hrs	Stage 2: SCr increase 2-2.9 times baseline OR urine output <0.5 mL/kg/hr for ≥12 hrs	
	Failure: SCr increase 3 times baseline OR GFR decrease 50-75% OR SCr increase ≥4.0 mg/dL with an acute increase of 0.5 mg/dL urine output <0.3 mL/kg/hr for ≥24 hrs OR anuria for ≥12 hrs	Stage 3: SCr increase 3 times baseline OR SCr increase ≥4 mg/dL with acute increase of 0.5 mg/dL OR urine output <0.3 mL/kg/hr for >24 hrs OR anuria for ≥12 hrs	Stage 3: SCr increase 3 times baseline OR SCr increase >4 mg/dL OR initiation of renal placement therapy OR urine output <0.3 mL/kg/hr for ≥24 hrs OR anuria for ≥12 hrs	

Ameli B, et al. J Hepatol 2019;71:811-822

Prevalence and Types of AKI

- Hospitalized patients with cirrhosis
  - Chronic renal failure (1%)
  - AKI (19%)
    - Post-renal (<1%)
    - Intra-renal (32%)
    - Pre-renal (68%)
      - Volume responsive (66%)
      - Non-volume responsive
        - Hepatorenal physiology (35%)

Garcia-Tsao G, et al. Hepatology 2008;48(6):2064-2077

Renal Dysfunction in Cirrhosis

- Predictor of death in decompensated cirrhosis
- Increased frequency of complications
- Reduced survival post-transplant

D'Amico G, et al. *J Hepatol* 2006;44:217-231.
Gines P, et al. *NEJM* 2008;361(11):1279-1290.
Images from www.shutterstock.com/

Limitations of SCr in Cirrhosis

- Acute kidney injury is historically defined by a serum creatinine (SCr) concentration of >1.5 mg/dL
- SCr is influenced by
  - Body weight, race, age, and gender
  - Decreased formation of creatinine
  - Increased renal tubular secretion of creatinine
  - Increased volume of distribution
  - Increased bilirubin may interfere with SCr assays
- Overestimations of glomerular filtration rate (GFR)
  - Better to trend SCr to determine AKI versus chronic kidney disease

Arroyo V, et al. *Hepatology* 1996;23:164–176.
Salerno F, et al. *Gut* 2007;56(9):1310–1318.
Garcia-Tsao G, et al. *Hepatology* 2008;48(6):2064-2077.
Angeli P, et al. *J Hepatol* 2015;62(4):968-974.

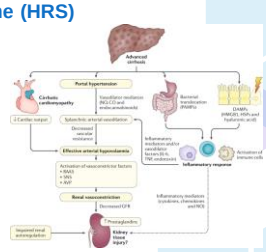
AKI in Cirrhosis and Mortality

- Mortality estimates range from 55 to 91%
- Risk of death increases with peak severity of AKI
- Model of end-stage liver disease (MELD) incorporates creatinine as a determinant of short-term mortality

Ruiz-del-Arbol L, et al. *Clin Gastroenterol Hepatol* 2013;11:1500–1508.

Hepatorenal Syndrome (HRS)

- Reduced renal perfusion
  - Hemodynamic alterations in arterial circulation
- Overactivity of endogenous vasoactive systems
- Systemic inflammation, oxidative stress, and bile salt-related tubular damage may contribute



Angeli P, et al. *J. Hepatol* 2019;71:811-822.
Angeli P, et al. *J. Hepatol* 2015;(62):968-974.
Ginès, P. et al. *Nat Rev Dis Primers* 2018;4(1):23.

Common Precipitants of HRS

- Bacterial infections
- Alcoholic hepatitis
- Lactulose-related diarrhea
- Gastrointestinal blood loss
- Over-diuresis

Angeli P, et al. *J. Hepatol* 2019;71:811-822.
Garcia-Tsao G, et al. *Hepatology* 2008;48(6):2064-2077.

Historical Classification of HRS

Type I HRS (HRS-1)

- Doubling of initial SCr to ≥2.5 mg/dL or 50% reduction of the initial creatinine clearance (CrCl) to <20 mL/min in <2 weeks
- Rapidly progressive
- Most often precipitated by bacterial infection

Type 2 HRS (HRS-2)

- Renal dysfunction that does not progress rapidly
- Can be considered chronic
- Associated with refractory ascites

Angeli P, et al. *J. Hepatol* 2015;(62):968-974.

Out with the Old, in with the New Definitions

- Defined based on changes in SCr and/or urine output (UOP)
- Diagnostic criteria aimed at excluding other causes of AKI
- Removing the SCr cut-off value
  - Initiate treatment rapidly

Angeli P, et al. *J Hepatol* 2015;62(4):968-974.

New Classification of HRS

Old Classification	New Classification	Criteria
HRS-1	HRS-AKI	• Absolute increase in SCr ≥0.3 mg/dL within 48 hours AND/OR • UO ≤0.5 mL/kg for ≥6 hours OR • Percent increase in SCr >50% using the last available SCr value outpatient within 3 months as baseline value
HRS-2	HRS-NAKI (HRS-AKD, HRS-CKD)	• eGFR <60 mL/min per 1.73m² for <3 months in the absence of other causes • Percent increase in SCr <50% using the last available value of outpatient SCr within 3 months as the baseline value • eGFR <60 mL/min per 1.73 m² for ≥3 months in the absence of other causes

Angeli P, et al. *J Hepatol* 2019;71:811-822.

Diagnostic Criteria of HRS-AKI

- Increase in SCr ≥0.3 mg/dL within 48 hours or ≥50% from baseline value and/or UO ≤0.5 mL/kg for ≥6 hours
- Lack of response after at least two days of diuretic withdrawal and volume expansion with albumin
- Absence of shock
- No current or recent treatment with nephrotoxic medications
- Absence of parenchymal disease
- Fractional Excretion of Sodium (FENa) of <0.2%

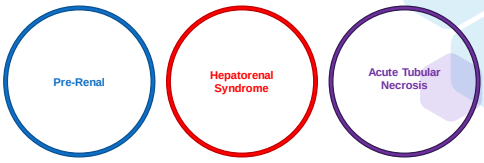
Angeli P, et al. *J Hepatol* 2019;71:811-822.

Problems with Diagnostic Criteria

- Delaying treatment for two days may impair outcomes
  - Treatment of HRS is more successful if initiated earlier, when creatinine is lower
- Patients with cirrhosis may occasionally develop volume overload
  - Albumin could add to congestive nephropathy
- Hepatorenal physiology may often co-exist with other renal insults
- Volume of fluid (albumin 1g/kg/day) used to resuscitate is fixed

Simonetto DA, et al. *BMJ*. 2020 Sep 14;370.

Expectation (Literature) Versus Reality



Prevention of HRS

- Avoid nephrotoxins in patients with advanced cirrhosis
  - NSAIDs
  - ACE inhibitors
  - ARBs
- Albumin administration
  - Large volume paracentesis
  - Spontaneous bacterial peritonitis

Ginès P, et al. *Gastroenterology*. 1988 Jun;94(6):1493-502.

Management of HRS

Non-pharmacologic

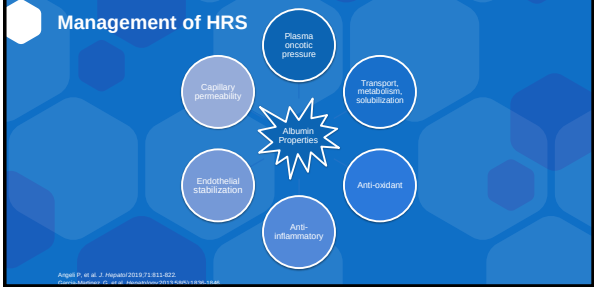
- Treat infections
- Avoid nephrotoxic medications
  - NSAIDs
  - Diuretics
  - Vasodilators
  - Some antibiotics

Pharmacologic

- Volume expansion with concentrated albumin AND
- Vasoconstrictor therapy
  - Midodrine or Norepinephrine
  - Octreotide
  - Terlipressin

Angeli P, et al. *J. Hepatol* 2019;71:811-822.
Angeli P, et al. *J. Hepatol* 2015;62(4):968-974.

Management of HRS



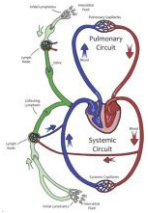
Angeli P, et al. *J. Hepatol* 2019;71:811-822.

The Most Misunderstood Drug in the World: Albumin

	Incorrect Logic	Correct Logic	Comments
Intravascular fluid	Albumin increases oncotic pressure and draws fluid intravascular	The lymphatic system is responsible for returning intravascular fluid	
Albumin location	Albumin remains intravascular	40% initially remains intravascular	~5% per hour transescapes to extravascular space
Albumin ADRs	There are none	Albumin is mixed with 0.9% normal saline	(ab)normal saline has been associated with hypernatremia and hyperchloremic acidosis

5 Human Albumin. Transfus Med Hemother. 2009;36(6):399-407.

Lymphatic System



- Return fluid from leaky capillary walls (i.e. third spaced fluids)
- Fluid returns to the veins to maintain fluid balance
- DOES NOT rely on albumin

Moore JE Jr, et al. Annu Rev Fluid Mech. 2018 Jan;50:459-482.

Albumin Dosing for HRS

Diagnostic Challenge

1 gram/kg daily (maximum of 100 grams) for two days

Maintenance Treatment

20 to 40 grams daily

Angeli P, et al. *J. Hepatol* 2019;71:811-822.

Midodrine and Octreotide

	Midodrine	Octreotide
Mechanism of action	α-1 agonist	Somatostatin analogue
Starting dose	10 mg PO q8hr	100 mcg subQ q8hr
Max dose	15 mg PO q8hr	200 mcg subQ q8hr
Titration parameter	Increase in mean arterial pressure (MAP) by 15 mmHg from baseline	
Adverse reactions	Supine hypertension, bradycardia, pruritus	Bradycardia, peripheral edema, hyperglycemia, abdominal pain, nausea

Midodrine. Package insert. Eon Labs, 2019.
Octreotide. Package insert. Mylan Institutional LLC, 2019.
Angeli P, et al. *Hepatology* 1999;29(6):1690-1697.

Norepinephrine

	Norepinephrine
Mechanism of action	Stimulates β1 adrenergic receptors and α-adrenergic receptors causing vasoconstriction
Dosing range	0.3 mg/hr to 3 mg/hr
Titration	Titrated every 4 hours by a dose of 0.5 mg/hr
Titration parameter	Increase in MAP by a minimum of 10 mmHg from baseline or an increase in 4 hour urine output by more than 200 mL
Adverse reactions	Cardiac arrhythmias, peripheral vascular insufficiency

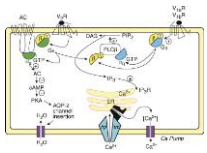
Norepinephrine. Package insert. Bader Healthcare Corporation. 2019.
Singh V, et al. *J. Hepato*l 2012;56(6):1293-1298.
Sharma P, et al. *Am. J. Gastroenterol* 2008;103:1689-1697.
Gupta K, et al. *Clin Exp Gastroenterol* 2018;11:317-324.

Terlipressin

	Terlipressin
Mechanism of action	Synthetic vasopressin analogue that binds vascular V1 receptors to cause systemic vasoconstriction
Starting dose	Bolus: 0.5 – 1 mg IV q4-6hrs Continuous: 2mg IV per day
Max dose	Bolus: 2 mg IV q4hrs Continuous: 12 mg IV per day
Titration parameter	SCr decrease by <30% of pretreatment SCr
Adverse reactions	Abdominal ischemia, peripheral ischemia, angina pectoris, circulatory overload, diarrhea

Boyer T, et al. *Gastroenterology* 2016;150:1579-1589.
Appeli E, et al. *J Hepatol* 2019;71:911-922.

Terlipressin Mechanism of Action



- Synthetic analogue of vasopressin with higher affinity for V_1 than V_2
- Vasoconstriction (V_1) and H_2O retention (V_2)

Swasti Tiwari, Carolyn A. Ecelbarger, Chapter 17 - Molecular Biology and Gene Regulation of Vasopressin, Editor(s): Ajay K. Singh, Gordon H. Williams, Textbook of Nephro-Endocrinology, Academic Press, 2009, Pages 225-248

Terlipressin Versus Midodrine and Octreotide

Design	Randomized comparative study following 48 hours of albumin
Study Population	**Inclusion:** diagnosed cirrhosis, HRS-I or severe HRS-II, age 18-75 years old **Exclusion:** hepatocellular carcinoma, septic shock, cardiac or respiratory failure, stroke, or coronary artery disease
Primary Outcome	Complete response in the treatment of HRS
Results	• Improvement in renal function favored terlipressin (p=0.01) • Reduction of SCr in all responders favored terlipressin (p< 0.001)
Conclusion	Terlipressin plus albumin is more effective in improving renal function and survival in patients with cirrhosis and HRS compared to midodrine and octreotide plus albumin

Intervention: Terlipressin + Albumin

Control: Midodrine + Octreotide + Albumin

Cavallo M, et al. *Hepatology* 2015;62(2):567-574.

REVERSE Trial

Design	Multicenter, randomized, double-blind, placebo-controlled trial conducted at 50 sites in USA and 2 in Canada
Study Population	**Inclusion:** >18 years old with cirrhosis, ascites, and HRS-1 **Exclusion:** SCr > 7mg/dL, MAP <70 mmHg with hypoperfusion, sepsis, untreated infection, <48h since vasopressors (including midodrine and octreotide) or evidence of intrinsic renal disease
Primary Outcome	Percent of patients with HRS reversal without need of RRT or liver transplant
Secondary Outcomes	Survival, change in renal function, and ADRs

Intervention: Terlipressin

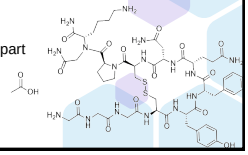
Control: Placebo

Boyer T, et al. *Gastroenterology* 2016;150:1579-1589.

REVERSE Trial: Intervention

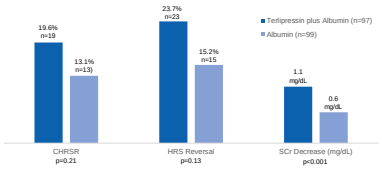
Terlipressin

- Starting dose: 1 mg IV q6hr + albumin 20-40 gm daily
- Increased to 2mg IV q6hr if <30% decrease in SCr
- Duration of treatment
  - Treatment for 14 days
  - Two SCrs ≤1.5 mg/dL drawn 48 hours apart



Boyer T, et al. *Gastroenterology* 2016;150:1579-1589.
Image: www.medkoo.com/product/product/Terlipressin_acetate/Image/Terlipressin_acetate.gif

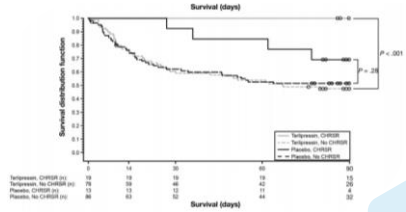
REVERSE Trial: Renal Function Outcomes



CHRSR: Confirmed HRS Reversal

Boyer T, et al. *Gastroenterology* 2016;150:1579-1589

REVERSE Trial: CHRSR Improvement



Boyer T, et al. *Gastroenterology* 2016;150:1579-1589

Confirm Trial

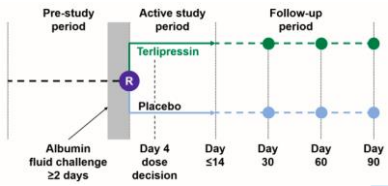
Design	Randomized, double-blind, placebo-controlled trial assigned in a 2:1 ratio for terlipressin : placebo
Study Population	**Inclusion:** Cirrhosis, ascites, HRS-1 with doubling of SCr to ≥2.25 mg/dL within 14 days before randomization **Exclusion:** >20% or decrease to below 2.25 mg/dL ≥48 hours after diuretic withdrawal and albumin infusions
Primary Outcome	Verified reversal of HRS
Secondary Outcomes	Durability of HRS reversal, HRS reversal among those with SIRS, and verified reversal without recurrence by day 30

Intervention: Terlipressin

Control: Placebo

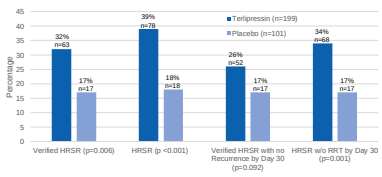
Wong F, et al. *N Engl J Med*. 2021 Mar 4;384(9):818-828.

CONFIRM Trial: Intervention



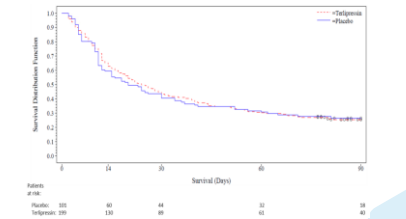
Wong F, et al. *N Engl J Med*. 2021 Mar 4;384(9):818-828.

CONFIRM Trial: Outcomes



Wong F, et al. *N Engl J Med*. 2021 Mar 4;384(9):818-828.

CONFIRM Trial: Transplant-Free Survival



Wong F, et al. *N Engl J Med*. 2021 Mar 4;384(9):818-828.

CONFIRM Trial: Adverse Events

	Terlipressin (n=199) n (%)	Placebo (n=101) n (%)
Adverse Events that Lead to Discontinuation	24 (12)	5 (5)
Abdominal Pain	10 (5)	1 (1)
Chronic Hepatic Failure	9 (4)	8 (8)
Shock	5 (2)	3 (3)
Respiratory Failure	20 (10)	3 (3)
Dyspnea	25 (13)	5 (5)
Pulmonary Edema	15 (8)	5 (5)

Wong F, et al. *N Engl J Med*. 2021 Mar 4;384(9):818-828.

CONFIRMing the Problems with Terlipressin

- Trial design
  - Did not follow consensus definition of HRS
    - SCr > 2.25 mg/dL vs. SCr rise of >0.3 mg/dL despite fluid resuscitation
    - Reversal is more likely to occur at lower pretreatment creatinine levels
- Worsened pulmonary status
  - Most common cause of death during trial: respiratory failure [6 (3%) vs 0 (0%)]

Wong F, et al. *N Engl J Med*. 2021 Mar 4;384(9):818-828.

Terlipressin Availability in the United States

- Not currently available
- Food and Drug Administration
  - September 2020 issued a response letter indicating they cannot support the New Drug Application
  - Risks > benefits at this time

Pharmaceuticals, Mallinckrodt. "Mallinckrodt Receives a Complete Response Letter from the U.S. Food and Drug Administration (FDA) for Terlipressin for the Treatment of Hepatorenal Syndrome Type 1 (HRS-1)." *Mallinckrodt Receives a Complete Response Letter from the U.S. Food and Drug Administration (FDA) for Terlipressin for the Treatment of Hepatorenal Syndrome Type 1 (HRS-1)*, 14 Sept. 2020.

Liver Transplantation

- Only definitive therapy for HRS
- Improving renal function pre-transplant has shown to improve outcomes post-transplant
- Presence of HRS may increase the possibility of obtaining an organ for transplantation
- Simultaneous liver/kidney transplant

Angeli P, et al. *J Hepatol* 2019;71:811-822.
Angeli P, et al. *J Hepatol* 2015;62(4):968-974.

Summary

- AKI in cirrhosis significantly impacts mortality
- Treatment for HRS-AKI should be timely
- Albumin is crucial for effectiveness of treatment in HRS
- Terlipressin and norepinephrine remain the vasoconstrictors of choice for HRS