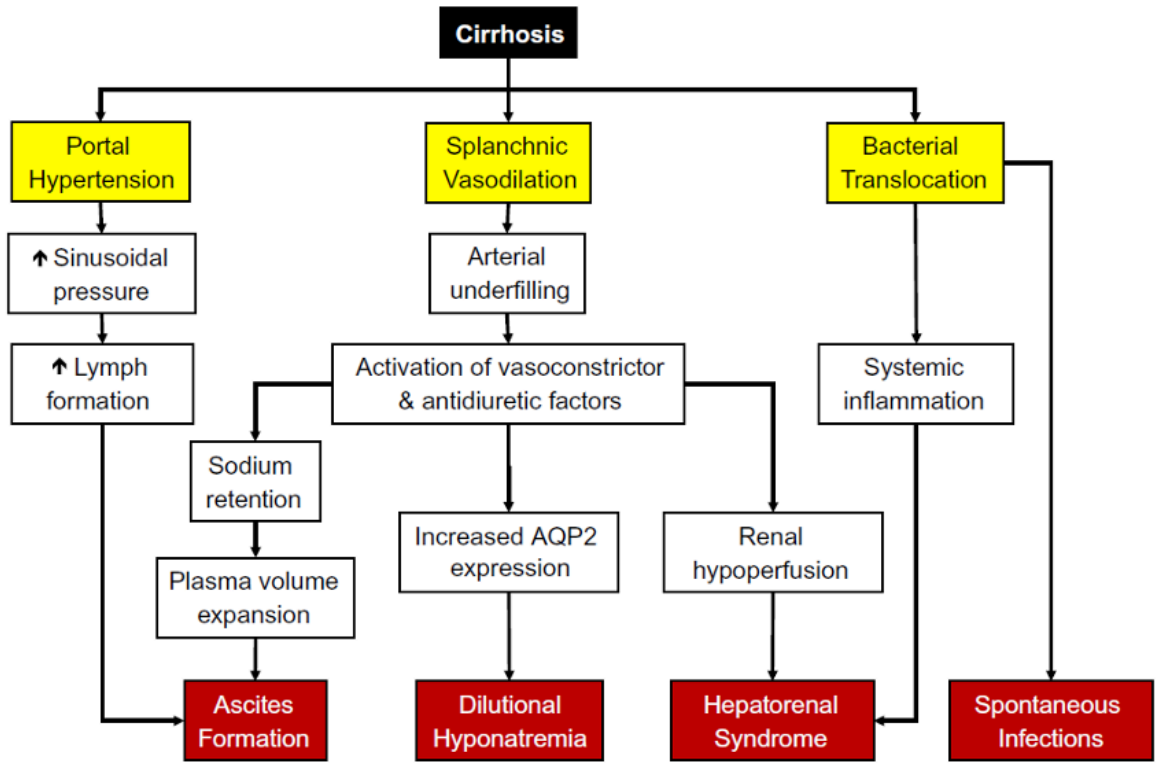
Expert Perspectives from the Chronic Liver Disease Foundation (CLDF) on the 2021 AASLD Cirrhosis Guidance

Hepatorenal Syndrome

Introduction

The "Diagnosis, Evaluation, and Management of Ascites, Spontaneous Bacterial Peritonitis and Hepatorenal Syndrome: 2021 Practice Guidance by the American Association for the Study of Liver Diseases" is a comprehensive guidance on the diagnosis, evaluation, and management of the aforementioned complications of cirrhosis. It serves to replace the prior AASLD guideline on the same topics published in 2012. The Chronic Liver Disease Foundation (CLDF) is a nonprofit 501(c)(3) educational organization dedicated to raising awareness of liver disease. Members of the CLDF cirrhosis committee, actively involved in the management and treatment of patients with advanced liver disease, cirrhosis, and its complications, have provided their expert perspectives on this updated guidance. The result is this summary, which provides a streamlined version of the practical recommendations set forth in the guidance to facilitate their use in clinical practice.

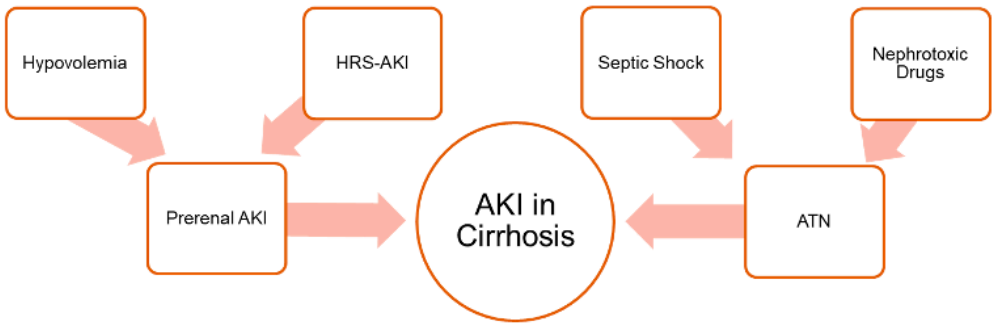
Cirrhosis directly results in the development of splanchnic vasodilation, portal hypertension, and bacterial translocation. Specifically, splanchnic vasodilation leads to effective arterial underfilling associated with the activation of vasoconstrictor (e.g., renin-angiotensin) and antidiuretic (e.g., arginine vasopressin) factors. Both portal hypertension (increases sinusoidal hydrostatic pressure) and bacterial translocation (because of gut permeability) contribute to the pathogenesis of **complications associated with ascites, including hyponatremia, acute kidney injury, hepatorenal syndrome, and spontaneous bacterial infections.**



Hepatorenal Syndrome

Defining HRS-AKI

Acute kidney injury (AKI) is diagnosed by an increase in serum creatinine (SCr) ≥ 0.3 mg/dL within 48 hours or a ≥ 50% increase in SCr that is known or presumed to have occurred within the preceding 7 days. AKI in cirrhosis is mainly caused by prerenal AKI or acute tubular necrosis (ATN). The two main causes of prerenal AKI are hypovolemia and **hepatorenal syndrome (HRS).**



AKI, acute kidney injury; ATN, acute tubular necrosis; HRS, hepatorenal syndrome

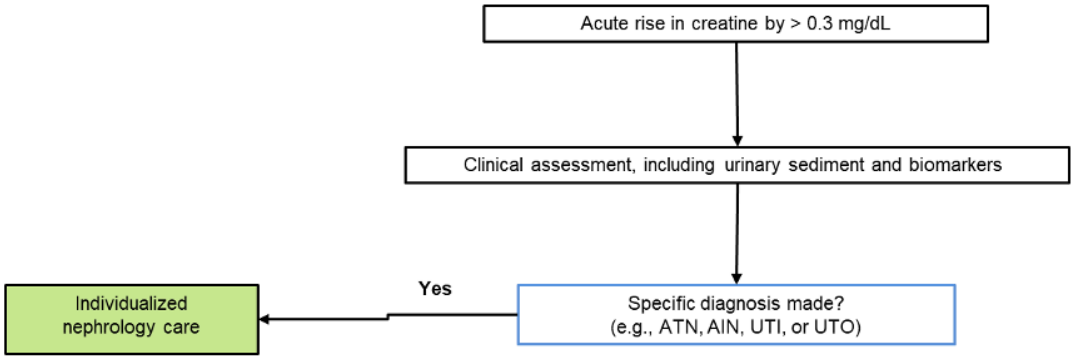
AKI commonly occurs in cirrhosis, and its causes must be evaluated before HRS is diagnosed. AKI must be differentiated from HRS. HRS, a type of AKI known as **HRS-AKI** under the current terminology, is unique to patients with cirrhosis and occurs in the absence of hypovolemia or significant abnormalities in kidney histology. HRS almost always occurs in patients with cirrhosis who also have ascites and hyponatremia, not compensated disease. Before the development of the new AKI criteria, patients with HRS were classified according to two clinical patterns. The first pattern, known as type-1 HRS and defined by an abrupt decline in kidney function, falls under the current criteria of AKI (100% increase in SCr to a value greater than 2.5 mg/dL). The second pattern, previously known as type-2 HRS, falls into the current definition of chronic kidney disease.

Old classification	New classification		Criteria
HRS-1	HRS-AKI		a) Absolute increase in sCr ≥ 0.3 mg/dL within 48 h AND/OR b) Urinary output ≤ 0.5 mL/kg body weight ≥ 6 h OR c) Percent increase in sCr ≥ 50% using the last available value of outpatient sCr within 3 months as the baseline value
HRS-2	HRS-NAKI	HRS-AKD	a) eGFR <60 ml/min per 1.73 m^2 for < 3 months in the absence of other (structural) causes OR b) Percent increase in sCr < 50% using the last available value of outpatient sCr within 3 months as the baseline value
		HRS-CKD	a) eGFR < 60 mL/min per 1.73 m^2 for ≥ 3 months in the absence of other (structural) causes

HRS, hepatorenal syndrome; HRS-AKI, acute kidney injury type of HRS; HRS-NAKI, non-acute kidney injury type of HRS; HRS-AKD, HRS acute kidney disease; HRS-CKD, HRS chronic kidney disease

Streamlining the Diagnostic Algorithm

- **Acute rise in SCr is detected:** Per the definition of AKI, an increase in SCr ≥ 0.3 mg/dL within 48 hours or a ≥ 50% increase in SCr that is known or presumed to have occurred within the preceding 7 days should lead to suspicion of AKI.



AIN, acute interstitial nephritis; ATN, acute tubular necrosis; UTI, urinary tract infection; UTO, urinary tract obstruction

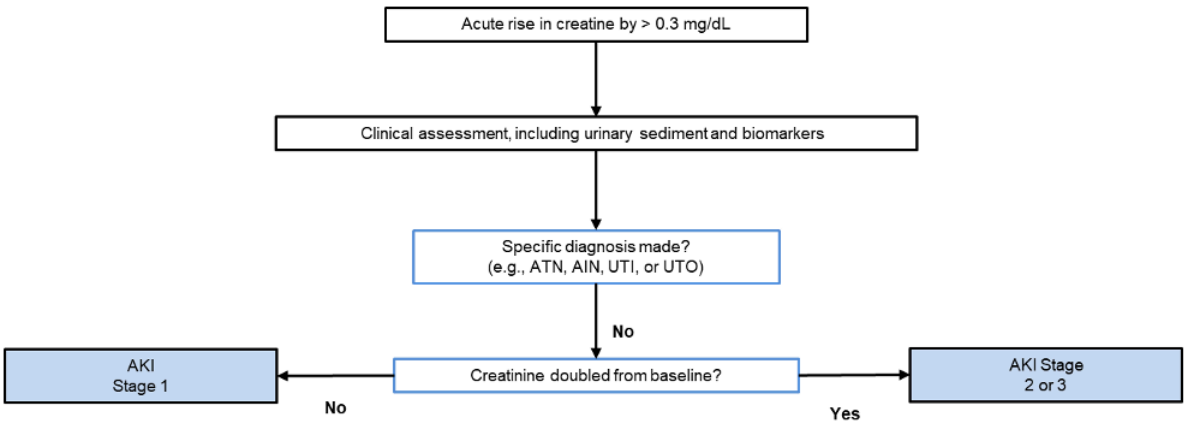
- **Clinical assessment and serum and urine tests:** Assess for the following:

Serum tests	**Elevations seen in hemoglobin/hematocrit, total protein/albumin, calcium bicarbonate, or uric acid**
Urine tests	**Decreased urine volume (< 500 mL/day), urine specific gravity > 1.105, urine sodium < 20 mEq/L, fractional excretion of Na < 1%, fractional excretion of urea < 35%*, or fractional excretion of uric acid < 10%***

*Not affected by diuretic use
Na, sodium

- **If, a specific diagnosis is made, other than AKI:** (e.g., ATN, acute interstitial nephritis (AIN), urinary tract infection (UTI), urinary tract obstruction (UTO)), individualized nephrology care is recommended.

If Other Diagnoses Are Ruled Out and AKI Is Confirmed, Assess for Doubling of SCr:



AKI, acute kidney injury; AIN, acute interstitial nephritis; ATN, acute tubular necrosis; UTI, urinary tract infection; UTO, urinary tract obstruction

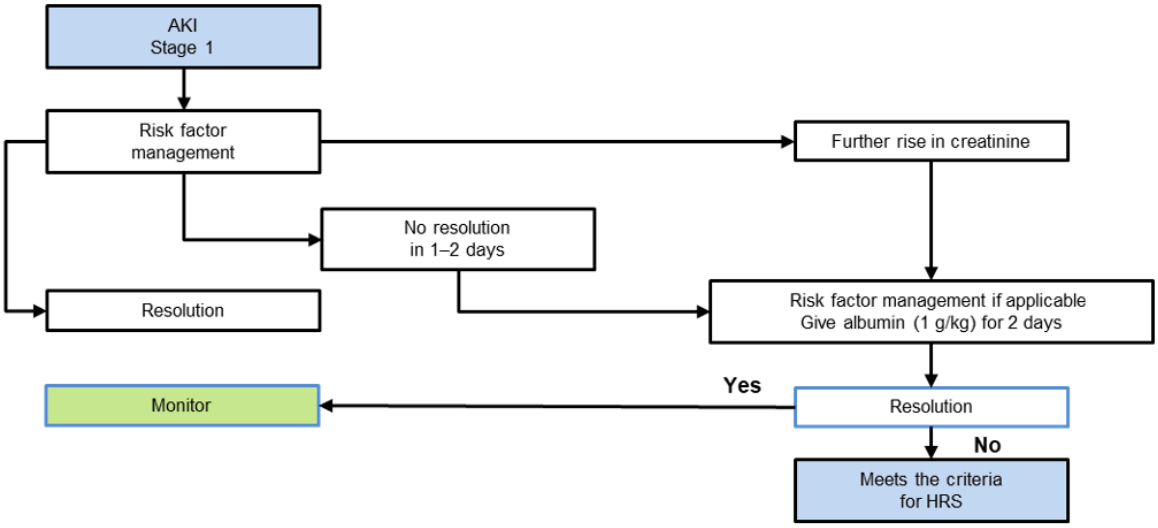
- If the SCr has not doubled, manage as **AKI Stage 1.**
- If the SCr has doubled, manage as **AKI Stage 2 or 3.**

AKI Stage	Description
1	Increase in creatinine ≥ 0.3 mg/dL up to 2-fold of baseline
2	Increase in creatinine between 2-fold and 3-fold of baseline
3	Increase in creatinine > 3-fold of baseline or creatinine > 4 mg/dL (353.6 µmol/L) with an acute increase of ≥ 0.3 mg/dL (26.5 µmol/L) or the initiation of RRT

RRT, renal replacement therapy

Managing AKI Stage 1

Although there is no specific therapy to reverse AKI, a diligent search must be conducted for treatable causes.



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- If **AKI Stage 1 is diagnosed, implement risk factor management,** which includes the following:

AKI Risk Factor Management
Withdrawal of nephrotoxic drugs
Reduction or withdrawal of diuretics
Detection and treatment of infections
Volume replacement (if severely volume depleted) initially using 25% salt-poor albumin or crystalloids, preferentially balanced

- **Assess for one of the following scenarios:**
  1. **SCr normalizes with risk factor management:** Continue to monitor.
  2. **SCr does not normalize within 1 to 2 days despite risk factor management:** Implement the albumin challenge (albumin 1g/kg for 2 days).
  3. Absolute SCr > 1.5 mg/dL should expedite the use of vasoconstrictors.

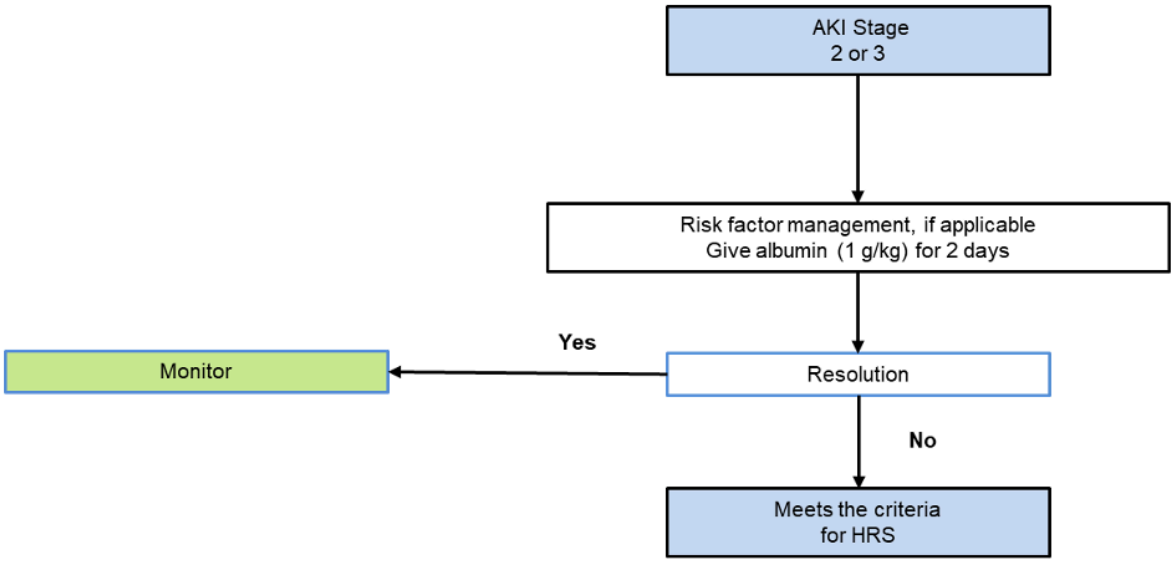
- **If there is no resolution following the albumin challenge,** refer to the HRS-AKI criteria below to diagnose HRS-AKI:

Cirrhosis with ascites
AKI according to the International Club of Ascites-Acute Kidney Injury† criteria
No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin infusion (1 g/kg body weight per day)
Absence of shock
No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, or iodinated contrast media)
No signs of structural kidney injury as indicated by proteinuria (> 500 mg per day), microhematuria (> 50 red blood cells per high-power field), and/or abnormal renal ultrasonography

†Increase in SCr ≥ 0.3 mg/dL from the baseline within 48 h or a percent increase in SCr of ≥ 50%, which is known or presumed to have occurred within the preceding 7 days

AKI, acute kidney injury; NSAIDs, nonsteroid anti-inflammatory drugs

Managing AKI Stage 2 or 3



AKI, acute kidney injury; HRS, hepatorenal syndrome

- **If AKI Stage 2 or 3 is diagnosed:**
  Implement risk factor management if applicable
  AND
  implement the albumin challenge (albumin 1g/kg for 2 days).

- **Assess for one of the following scenarios:**
  - **SCr normalizes:** Continue to monitor.
  - **There is no resolution following the albumin challenge:** Refer to the below HRS criteria to diagnose HRS.

Cirrhosis with ascites
AKI according to International Club of Ascites-Acute Kidney Injury† criteria
No response after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin infusion (1 g/kg body weight per day)
Absence of shock
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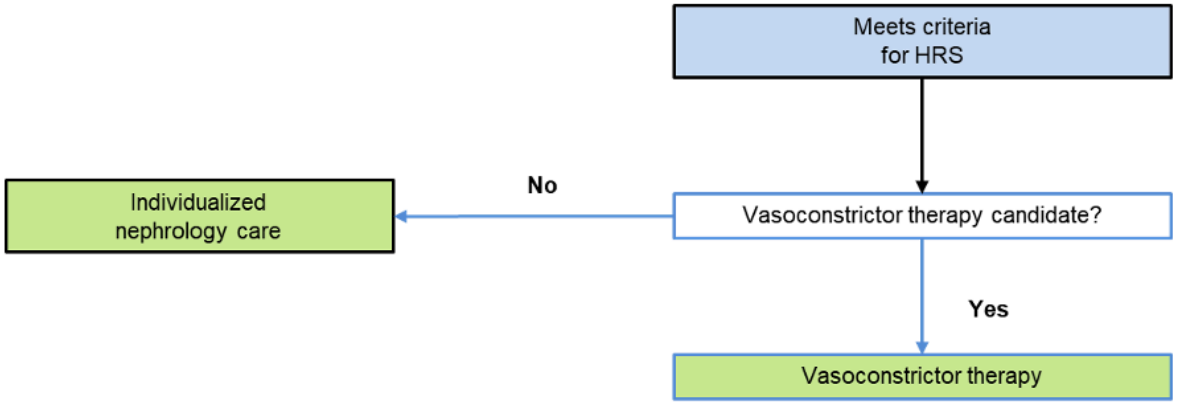
AKI, acute kidney injury; NSAIDs, nonsteroid anti-inflammatory drugs

Treating HRS-AKI



HRS, hepatorenal syndrome

Vasoconstrictors, in combination with **albumin**, are effective in improving kidney function in patients with HRS-AKI. The vasoconstrictor of choice for HRS-AKI is terlipressin. In settings where terlipressin is not available, norepinephrine should be considered, typically in an intensive care setting. If neither can be administered, a trial of oral midodrine in combination with octreotide may be considered, but its efficacy is low. All vasoconstrictors should be dosed according to the table; albumin 25% should be administered in combination with each vasoconstrictor and dosed according to clinical parameters. Response to vasoconstrictor therapy is defined by SCr decreasing to < 1.5 mg/dL or returning to within 0.3 mg/dL of baseline over a maximum of 14 days. In patients whose SCr remains at or above the pretreatment level over 4 days with the maximum tolerated doses of the vasoconstrictor, therapy may be discontinued. Recurrence may occur after discontinuation of treatment, so close follow-up is warranted. If there is recurrence, patients should be retreated.

Patients with HRS-AKI have a better response to therapy if therapy is started earlier rather than later. Terlipressin, when available, should be considered the treatment of choice as response rates are better than the poor response rates of midodrine, octreotide, and albumin.

Drug	Dosing and Administration
Terlipressin	Vasoconstrictor of choice for treating HRS-AKI*
Norepinephrine	Continuous IV infusion starting at 0.5 mg/h to achieve an increase in mean arterial pressure of at least 10 mmHg or an increase in urine output of > 200 mL/4 h If at least one of these goals is not achieved, increase every 4 h in increments of 0.5 mg/h up to a maximum of 3 mg/h
Oral midodrine in combination with octreotide	Midodrine 5–15 mg po every 8 h Octreotide 100–200 µg every 8 h or 50 µg/h via IV

*Terlipressin is currently an investigational agent being evaluated for the treatment of HRS in the U.S., and its safety and effectiveness have not yet been established by the FDA.

AKI, acute kidney injury; HRS, hepatorenal syndrome

Patients on vasoconstrictors and albumin should be closely monitored for the possible development of adverse effects. Adverse effects are infrequent; are mainly related to vasoconstrictors; and include hypertension, peripheral ischemia, abdominal pain, nausea, diarrhea, headache, intestinal ischemia, and cardiac ischemia. Pulmonary edema may develop from fluid overload related to albumin infusion. Early intervention may prevent more serious consequences, and most resolve after dose reduction or discontinuation of therapy.

Additional Special Considerations in HRS Management

Transplantation	All patients with cirrhosis and AKI should be considered for urgent liver transplant (LT) evaluation given the high short-term mortality even in responders to vasoconstrictors. Simultaneous liver–kidney transplantation may be necessary for patients who are not expected to recover kidney function following transplantation.
Renal Replacement Therapy (RRT)	Use RRT in candidates for LT with worsening renal function, electrolyte disturbances, or increasing volume overload unresponsive to vasoconstrictor therapy. Initiation of RRT in patients who are not candidates for LT must be made after defining goals of care with the patient and their families.
Multidisciplinary Teams	Given the complexity of cases of patients with suspected HRS-AKI, decisions about management should be made by multidisciplinary teams. Team should include specialists in hepatology, nephrology, critical care, and transplant surgery.

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The full HRS diagnostic algorithm is shown here: