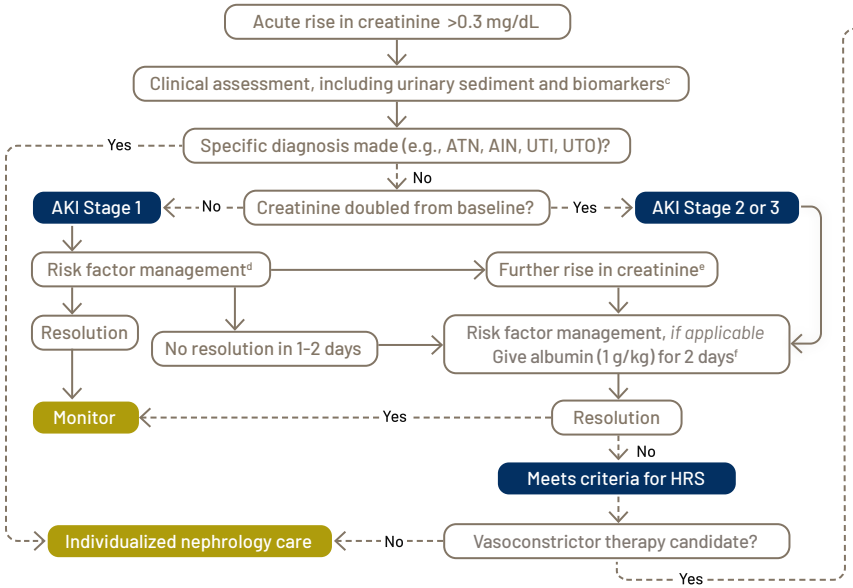
Society Guidelines and Guidance for the Treatment of HRS-AKI

Terlipressin is recommended by AASLD Guidance and ACG Guidelines for the treatment of HRS-AKI[1,2,a]

AASLD Guidance for Diagnosis[†] and Treatment of HRS-AKI



"The treatment of choice for HRS-AKI[b] is vasoconstrictor drugs in combination with albumin. **The preferred drug is terlipressin.**"

2021 AASLD GUIDANCE[1,*]

Vasoconstrictor therapy → **Treatment[1,*]:** Vasoconstrictor Therapy (in combination with albumin)

- Preferred drug: Terlipressin[a]
- In settings where terlipressin is not available, norepinephrine should be given
- If neither can be administered, a trial of midodrine in combination with octreotide may be considered
- When treating with vasoconstrictor therapy, albumin should be infused at 1 g/kg on Day 1 of therapy, then followed by 40-50 g/day and continued for the duration of therapy
- Patients should be closely monitored for side effects of vasoconstrictors and albumin, including ischemic complications and pulmonary edema
- Recurrence may occur after treatment discontinuation and should be retreated
- Decisions should be made by multidisciplinary teams when possible

Other treatment options, such as RRT and transplant, could be considered for certain patients.

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[†]AASLD criteria should be used for the diagnosis of HRS-AKI.

[a]TERLIVAZ (terlipressin) was not evaluated in comparison to other treatments in a head-to-head clinical study.

[b]Definition of kidney injury for HRS-AKI: Increase in SCr of ≥0.3 mg/dL within 48 hours or percent increase in SCr that is ≥50% of what was known or presumed to have occurred within the prior 7 days.

[c]Clinical assessment includes evaluation for prerenal (e.g., overdiuresis, dehydration) or structural (e.g., shock, nephrotoxins, obstructive uropathy) etiologies. Urinary sediments and biomarkers (particularly NGAL) may indicate ATN, whereas fractional excretion of sodium <1% may suggest HRS.

[d]Risk-factor management includes the withdrawal of nephrotoxic drugs, reduction or withdrawal of diuretics, detection, and treatment of infections, if present, and volume replacement (if severely volume-depleted) using 5% albumin or crystalloids, preferentially balanced, initially.

[e]Patients experiencing a further rise in serum creatinine despite risk factor management may immediately proceed to the next step, namely albumin challenge. Some members of the writing group advocate taking into account the absolute creatinine value in addition to the change in creatinine to expedite this step to allow earlier institution of vasoconstrictors in patients with a high (e.g., >1.5 mg/dL) creatinine.

[f]These patients are expected to have ascites, commonly refractory, and almost always hyponatremia.

[g]In the ACG Guidelines, a strength of recommendation is given as either strong (recommendations) or conditional (suggestions).

2022 ACG GUIDELINES[2]

"In hospitalized patients with cirrhosis and HRS-AKI[b] without high grade of ACLF or disease, **we suggest terlipressin** (moderate quality, conditional recommendation[g]) or norepinephrine (low quality, conditional recommendation[g]) to improve renal function."

Additional information about TERLIVAZ® is available at **TERLIVAZ.com**

Medical judgment should be used when making individual patient treatment decisions. Please refer to the Prescribing Information for full product information.

SELECT IMPORTANT SAFETY INFORMATION

WARNING: SERIOUS OR FATAL RESPIRATORY FAILURE

- **TERLIVAZ may cause serious or fatal respiratory failure. Patients with volume overload or with acute-on-chronic liver failure (ACLF) Grade 3 are at increased risk. Assess oxygenation saturation (e.g., SpO_2) before initiating TERLIVAZ.**
- **Do not initiate TERLIVAZ in patients experiencing hypoxia (e.g., SpO_2 <90%) until oxygenation levels improve. Monitor patients for hypoxia using continuous pulse oximetry during treatment and discontinue TERLIVAZ if SpO_2 decreases below 90%.**

INDICATION AND LIMITATION OF USE

TERLIVAZ is indicated to improve kidney function in adults with hepatorenal syndrome with rapid reduction in kidney function.

- Patients with a serum creatinine >5 mg/dL are unlikely to experience benefit.

Please see additional Important Safety Information on page 2, and full Prescribing Information, including Boxed Warning.

SELECT IMPORTANT SAFETY INFORMATION

Contraindications

TERLIVAZ® is contraindicated:

- In patients experiencing hypoxia or worsening respiratory symptoms.
- In patients with ongoing coronary, peripheral, or mesenteric ischemia.

Warnings and Precautions

- **Serious or Fatal Respiratory Failure:** Obtain baseline oxygen saturation and do not initiate TERLIVAZ in hypoxic patients. Monitor patients for changes in respiratory status using continuous pulse oximetry and regular clinical assessments. Discontinue TERLIVAZ in patients experiencing hypoxia or increased respiratory symptoms.

  Manage intravascular volume overload by reducing or discontinuing the administration of albumin and/or other fluids and through judicious use of diuretics. Temporarily interrupt, reduce, or discontinue TERLIVAZ treatment until patient volume status improves. Avoid use in patients with ACLF Grade 3 because they are at significant risk for respiratory failure.
- **Ineligibility for Liver Transplant:** TERLIVAZ-related adverse reactions (respiratory failure, ischemia) may make a patient ineligible for liver transplantation, if listed. For patients with high prioritization for liver transplantation (e.g., MELD ≥35), the benefits of TERLIVAZ may not outweigh its risks.
- **Ischemic Events:** TERLIVAZ may cause cardiac, cerebrovascular, peripheral, or mesenteric ischemia. Avoid use of TERLIVAZ in patients with a history of severe cardiovascular conditions or cerebrovascular or ischemic disease. Discontinue TERLIVAZ in patients who experience signs or symptoms suggestive of ischemic adverse reactions.
- **Embryo-Fetal Toxicity:** TERLIVAZ may cause fetal harm when administered to a pregnant woman. If TERLIVAZ is used during pregnancy, the patient should be informed of the potential risk to the fetus.

Adverse Reactions

- The most common adverse reactions (≥10%) include abdominal pain, nausea, respiratory failure, diarrhea, and dyspnea.

Please see full Prescribing Information, including Boxed Warning.

AASLD, American Association for the Study of Liver Diseases; ACG, American College of Gastroenterology; ACLF, acute-on-chronic liver failure; AIN, acute interstitial nephritis; AKI, acute kidney injury; ATN, acute tubular necrosis; HRS, hepatorenal syndrome; NGAL, neutrophil gelatinase-associated lipocalin; RRT, renal replacement therapy; SCr, serum creatinine; UTI, urinary tract infection; UTO, urinary tract obstruction.

References: 1. Biggins SW, Angeli P, Garcia-Tsao G, et al. 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. *Hepatology*. 2021;74:1014-1048. **2.** Bajaj JS, O'Leary JG, Lai JC, et al. Acute-on-chronic liver failure clinical guidelines. *Am J Gastroenterol*. 2022;117:225-252.

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Terlivaz® terlipressin for injection