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PUTTING GUIDELINES INTO PRACTICE: Expert Insights on Early Identification of Acute Kidney Injury and Initiation of Treatment in Hepatorenal Syndrome Type 1

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Topic Highlights

- Hepatorenal Syndrome Type 1 (HRS-1) is a rapidly progressing and life-threatening form of acute kidney injury (AKI) in patients with advanced liver disease[1]
- Among the various forms of renal dysfunction in patients with cirrhosis, HRS-1 is associated with poor outcomes, including death, dialysis, multiorgan failure, and the need for a kidney or liver transplant[1]
- An increase of serum creatinine (SCr) by at least 0.3 mg/dL within the first 48 hours of hospitalization was shown to be the greatest predictor of mortality risk among hospitalized patients with cirrhosis[2]
- The key differences between the current International Club of Ascites (ICA) recommendations and the conventional criteria for patients with HRS-1 include[3]:
  - When defining AKI as part of an HRS-1 differential, use an increase from baseline SCr of 0.3 mg/dL or greater, as opposed to an absolute threshold of SCr ≥1.5 mg/dL; this allows for a shortened time frame for changes in SCr to become evident and an earlier diagnosis
  - Determining progression or regression of the stage of kidney injury is based on the change in SCr that has occurred (or is thought to have occurred) within the prior 7 days (compared with 48 hours). If no values in this time period are available, a SCr within 3 months can be used to define baseline, and then relate it to the current change on presentation of AKI
- Considering that the SCr at baseline prior to therapy is a predictor of HRS reversal and improved survival, using revised ICA AKI-HRS diagnostic criteria could lead to earlier treatment, which may help prevent progression and potentially improve patient outcomes[4,5]

Question & Answer

What is HRS-1 and what are some of the challenges to diagnosis?

HRS-1 is a rapidly progressing and life-threatening form of AKI in patients with advanced liver disease.[1] The susceptibility of kidney dysfunction develops as a result of both cirrhosis-induced circulatory dysfunction and maladaptive kidney perfusion.[6] Patients with advanced liver disease can develop portal hypertension, which may lead to peripheral vasodilation. To maintain blood pressure, the kidneys retain extra fluid, which can gradually lead to ascites. Over time, vasodilation throughout the body results in reduced renal perfusion and the subsequent development of kidney dysfunction.[6]

In addition to a unique pathogenic process that leads to a hemodynamic form of AKI—ie, HRS-1—patients with cirrhosis are also vulnerable to develop standard forms of AKI, such as prerenal azotemia and acute tubular necrosis (ATN). Furthermore, other pathological processes that may lead to renal dysfunction in patients with HRS-1 also can be present. These include cirrhotic cardiomyopathy, porto-pulmonary hypertension, abdominal compartment syndrome, and cholemic nephropathy (a form of kidney dysfunction observed during hyperbilirubinemia, presumably caused by bile acids). In addition, acute glomerulonephritis and/or acute interstitial nephritis can also be a cause of AKI in patients who are cirrhotic. Moreover, some of these individual entities may coexist.[6] As a result, it is imperative to conduct a careful assessment of these patients when they present with AKI.

One of the most common precipitating events for HRS-1 is spontaneous bacterial peritonitis (SBP). A decline in renal function in the presence of SBP should raise clinical suspicion for HRS-1.[6] In other situations, the differentiation between AKI and HRS-1 may not be as clear. Other causes for kidney dysfunction may be due to volume depletion, such as gastrointestinal hemorrhage, overdiuresis, and diarrhea (ie, after treatment with lactulose for hepatic encephalopathy).[6]

How should SCr assessments be used to achieve earlier diagnosis of HRS-1?

Measuring SCr, and more specifically, monitoring serial changes in SCr, remains the primary clinical approach to assessing kidney function in patients with cirrhosis.[6] HRS-1 is associated with a significant reduction in glomerular filtration rate (GFR) and an increase in SCr.[3] However, in patients with cirrhosis, absolute SCr levels may actually be decreased due to low protein intake, loss of muscle mass, decreased formation of creatinine due to muscle wasting, increased secretion of creatinine by the kidney, and enlarged volume of distribution.[3,6,7] Therefore, the relative changes in SCr levels in these patients may not accurately indicate the degree of kidney dysfunction. Another factor to consider is that increased bilirubin levels may interfere with assays that measure SCr.[3,6] In addition, women tend to have a lower SCr level than men with the same GFR.[8] These factors, which can lead to decreased SCr levels independent of renal function, may overestimate GFR.[7]

Historically, the most commonly accepted definition for kidney injury that was suggestive of HRS-1 and warranted further investigation was increased SCr above a threshold of 1.5 mg/dL to >2.5 mg/dL.[3] However, the traditional definition of HRS-1 based on a SCr ≥1.5 mg/dL may delay the diagnosis, and thus may not detect patients with earlier stages of AKI within the context of HRS-1.[7] Based on these definitions, a SCr of 1.5 mg/dL in patients with cirrhosis oftentimes can be indicative of a more moderate to severe form of HRS-1. By the time treatment for HRS-1 is started in patients with this degree of renal dysfunction, their disease had already progressed and is potentially more refractory to therapy. Recent evidence suggests that even earlier changes in SCr, below the 1.5 mg/dL level, are prognostic indicators for patient outcomes.[3]

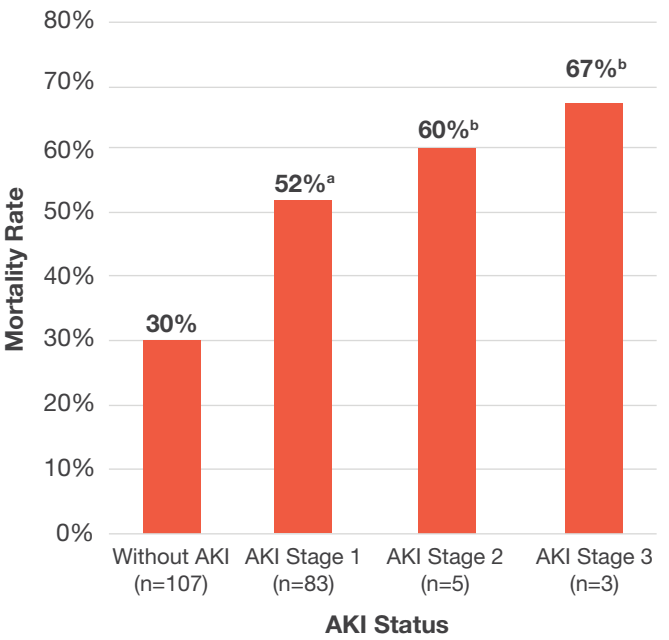
What evidence shows that the presence and severity of AKI is linked to poorer patient outcomes? Therefore, why is prompt identification of patients at risk for HRS-1 critical?

Renal dysfunction is common in patients with advanced liver disease (cirrhosis with ascites) admitted to the hospital and is associated with significant morbidity and mortality.[7] Results from a prospective, multicenter, observational cohort study demonstrated that the severity and progression of kidney injury staging is associated with increased risk of dialysis and mortality. Additionally, severity of AKI was associated with an increased likelihood for admission to an intensive care unit (ICU), mortality prior to transfer out of the ICU, and mortality prior to discharge.[4]

Among the various forms of renal dysfunction in patients with cirrhosis, HRS-1 is associated with poor outcomes, including death, dialysis, multiorgan failure, and the need for a kidney or liver transplant.[1] However, Alleghretti et al recently reported similar outcomes for HRS-1 and ATN.[9] Studies have shown a median survival time of <2 to 4 weeks and 80% mortality within 3 months.[10,11] The overall estimated mortality rate in patients with HRS-1 ranges from 55% to 91%.[7] Less severe ("earlier") forms of AKI are associated with an increased risk of death. Waiting to diagnosis HRS-1 after a significant decrease in GFR has been associated with a poorer prognosis.[1]

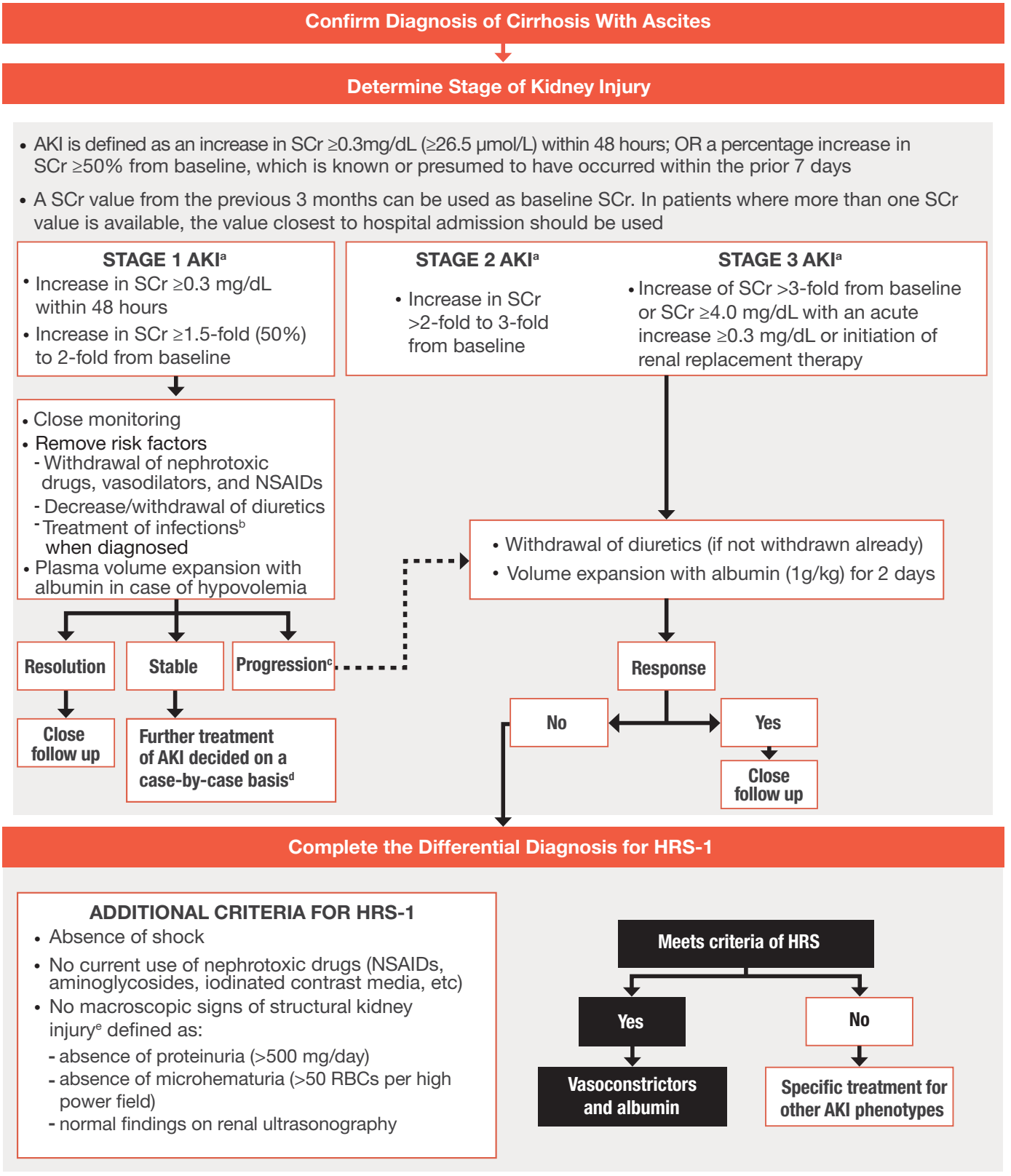
In a retrospective study of 198 hospitalized patients with cirrhosis, mortality rates were higher in 91 patients with AKI, and those with more severe stages of AKI had an increased risk of mortality (Figure 1). An increase of SCr by 0.3 mg/dL within the first 48 hours of hospitalization was shown to be the best predictor of mortality risk among hospitalized patients with cirrhosis.[2] By delaying diagnosis, SCr levels will likely continue to increase, and patients will be more susceptible to progress to more severe stages of AKI. Patients with Stage 1 disease were at risk for death, but if they did not progress, they generally did well. However, progression of their kidney injury was accompanied by a dramatic increase in risk of death. These data emphasize the importance of early identification and subsequent management of kidney injury in patients with cirrhosis.

Figure 1: Hospital Mortality According to Acute Kidney Status in Cirrhotic Patients With Ascites[2]



CI=confidence interval; NS=not significant; OR=odds ratio.
[a]OR=2.5; 95% CI=1.4-4.6; *P*=0.002.[2]
[b]*P*=NS.[2]

Figure 2: Algorithm for the Diagnosis and Treatment of HRS-1, Including AKI Based on 2015 ICA Consensus Recommendations[3]



NSAIDs=non-steroidal anti-inflammatory drugs; RBCs=red blood cells.

[a]Initial AKI stage is defined as AKI stage at the time of first fulfillment of the AKI criteria.[3] [b]Treatment of spontaneous bacterial peritonitis should include albumin infusion according to current guidelines.[3] [c]Progression of AKI to a higher stage and/or need for dialysis.[3] [d]No global consensus was reached on this point.[3] [e]Volume expansion with albumin should not be done in patients who exhibit overt signs of fluid overload affecting a major organ (lungs, heart, etc). [f]Some aspects of the HRS-1 phenotype are not included in the Additional Criteria box. For instance, hyponatremia, oliguria, blood pressure within the low-normal range, absence of abundant granular casts in the urinary sediment are also expected to be found in HRS-1. [g]Patients who fulfill these criteria may still have structural damage, such as tubular damage. Urine biomarkers will become an important element in making a more accurate differential diagnosis between HRS and acute tubular necrosis.[3]

The ICA updated its consensus recommendations on the diagnosis and management of AKI in patients with cirrhosis. What are some of the key updates in this new approach to the diagnosis and treatment of this condition?

The key differences between the current ICA recommendations and the conventional criteria for patients with HRS-1 include[3]:

1. When defining AKI as part of an HRS-1 differential, use an increase from baseline SCr of 0.3 mg/dL or greater, as opposed to an absolute threshold of SCr ≥1.5 mg/dL; this allows for a shortened time frame for changes in SCr to become evident and an earlier diagnosis
2. Determining progression or regression of the stage of kidney injury is based on the change in SCr that has occurred (or is thought to have occurred) within the prior 7 days (compared with 48 hours). If no values in this time period are available, a SCr within 3 months can be used to define baseline and then relate it to the current change on presentation of AKI

In the revised recommendations, urine output was removed as a diagnostic criterion for HRS-1, although it is generally reduced or sometimes absent in patients with cirrhosis. Figure 2 illustrates a proposed algorithm for the diagnosis of HRS-1, including AKI.[3]

To illustrate an example based on the conventional criteria, a patient with a SCr level of 1.2 mg/dL would be perceived as having a relatively normal kidney function, whereas in reality, that patient may have Stage 1 or Stage 2 AKI. In the new ICA recommendations, by removing the criteria that the SCr needs to be doubled to >2.5 mg/dL in <2 weeks, patients at risk for HRS-1 can be identified earlier. In addition to assessing serial SCr levels, other patient-specific factors are important to evaluate in order to try to elucidate whether the AKI is HRS-1 or some other pathology. Clinicians should perform a careful evaluation of volume status, ensure absence of shock, remove potential nephrotoxic medications, perform a volume expansion challenge (when appropriate), and rule out other causes of parenchymal (tubular, interstitial, or glomerular) or obstructive AKI. Although a precipitating event is not required for the diagnosis of HRS-1, the recent presence of SBP or acute-on-chronic liver failure should increase clinical suspicion for HRS-1.[6]

The ultimate goal is to be able to promptly identify and diagnose HRS-1 earlier in more patients with cirrhosis so that effective treatment can be instituted. Importantly, while the ICA criteria provide a useful foundation to narrow down the diagnosis of HRS-1, clinicians must remain cognizant of the potential pitfalls of the diagnostic criteria. Clinical judgement should be used to integrate the available clinical information and ultimately entertain the diagnosis.

How might application of the 2015 ICA Consensus Recommendations potentially improve outcomes in patients with HRS-1?

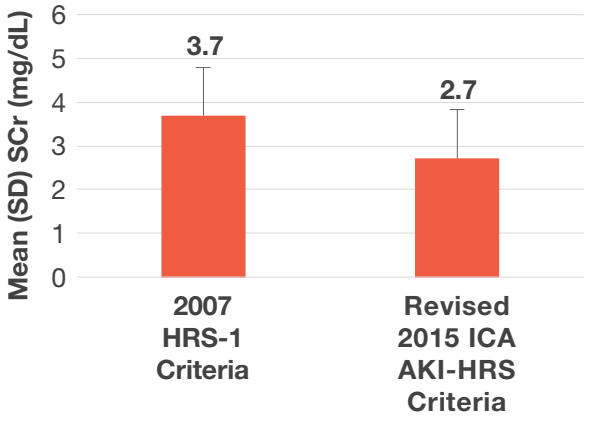
In a retrospective analysis of patients with HRS-1 enrolled in a clinical trial, mean (standard deviation [SD]) SCr level at diagnosis with the revised criteria was lower than that with the traditional criteria (Figure 3).[5]

The application of AKI criteria for diagnosis of HRS-1 and guidelines for intervention allowed for the following[5]:

- Earlier treatment by approximately 4 days
- Initiation of treatment when patient SCr levels were, on average, approximately 1 mg/dL lower
- Recommendation of treatment before a further ≥1.5-fold increase in SCr (in 47% of patients)

These data validate using the updated criteria when managing HRS-1. Considering that SCr at baseline prior to therapy is a predictor of HRS reversal and improved survival, using revised ICA AKI-HRS diagnostic criteria could lead to earlier treatment, which may help prevent progression and potentially improve patient outcomes.[4,5]

Figure 3: SCr at Diagnosis of HRS Depending on Diagnostic Criteria (N=141)[5]



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Josh Levitsky, MD, MS is a Professor of Medicine and Surgery in the Division of Gastroenterology & Hepatology at the Northwestern University Feinberg School of Medicine. Dr Levitsky received his BS from the University of Michigan and MD from the Albert Einstein College of Medicine. He then completed an Internal Medicine residency and Gastroenterology fellowship at the University of Chicago Hospitals and a Transplant Hepatology fellowship at the University of Nebraska Medical Center, receiving an American Association for the Study of Liver Diseases (AASLD) Fellowship Award. Dr Levitsky is currently certified by the American Board of Internal Medicine in Gastroenterology and Transplant Hepatology. At Northwestern, he completed a MS in Clinical Investigation, is Director of Liver Research, and is the program director for the Gastroenterology Fellowship. He has been elected to the Northwestern Feinberg Academy of Medical Educators and has received several teaching awards.

Dr Levitsky is an active member of several professional societies, including the American Society of Transplantation and International Liver Transplantation Society where he served on the executive boards, as well as the AASLD where he has served on several committees. He is Deputy Editor for the American Journal of Transplantation and on the Editorial Board for Hepatology. Dr Levitsky's academic interests are clinical and translational in nature, with a focus on liver transplant immunosuppression, tolerance, and biomarkers. He previously received an AASLD Career Development Award in Liver Transplantation and has published numerous peer-reviewed journal articles, abstracts, book chapters, and reviews on topics relevant to liver disease and transplantation. He is the principal and co-investigator for a number of National Institutes of Health, pharmaceutical, and investigator-initiated trials. His goal is to advance clinical/translational research in immune-mediated liver diseases and liver transplantation, identifying biomarkers of kidney injury and rejection and novel strategies to optimize outcomes.

Juan Carlos Velez, MD earned his medical degree from Universidad Peruana Cayetano Heredia in Lima, Peru. He completed internship and residency in Internal Medicine at Advocate Illinois Masonic Medical Center, serving as Chief Medical Resident. Subsequently, he completed a clinical and research fellowship in Nephrology at Emory University School of Medicine. Following his training, Dr Velez joined the Division of Nephrology at the Medical University of South Carolina (MUSC). After spending 11 years of intense clinical, educational, and investigational efforts at MUSC, he was recruited by the Department of Nephrology at the Ochsner Clinic Foundation in 2016 to enhance the academic and clinical research programs of the department at the rank of Associate Professor of Medicine at Ochsner Clinical School / The University of Queensland (Brisbane, Australia). He serves as Clerkship Director for Medical Specialties at Ochsner Clinical School. He was appointed as Chair of Nephrology at Ochsner Health System in early 2019. Dr Velez also holds an appointment as Adjunct Associate Professor of Physiology at Tulane University.

Dr Velez has conducted experimental research in the area of the intrarenal renin-angiotensin system that resulted in federal funding and peer-reviewed publications. Clinically, his areas of expertise and ongoing investigation include hepatorenal acute kidney injury, hyponatremia, glomerular diseases, and renal syndromes associated with exposure to antimicrobials. Dr Velez is certified in Nephrology by the American Board of Internal Medicine in Kidney Ultrasonography by the American Society of Diagnostic and Interventional Nephrology, and as a Hypertension Specialist by the American Society of Hypertension; he is also a member of the Southern Society of Clinical Investigation. In addition, he serves in the American Society of Nephrology/National Board of Medical Examiners Fellows In-Training Examination Development Committee and has a track record of mentoring young trainees.

In summary, why is it critical to identify and diagnose HRS-1 early, and how might we be able to improve patients' prognosis and care in the future?

The latest ICA recommendations for the diagnosis and management of HRS help allow for subtle, early changes in SCr to be tracked and for appropriate intervention to be initiated. Based on the revised ICA criteria, AKI is defined as an increase in SCr ≥0.3 mg/dl (≥26.5 µmol/L) within 48 hours or a percentage increase SCr ≥50% from baseline that is known, or presumed, to have occurred within the prior 7 days (within 3 months if not known).[3]

The ICA recommendations are a reasonable guide, which are meant to be utilized in concert with clinical reasoning and decision making based on specific individual patients and their disease characteristics. In order to more quickly and accurately diagnose HRS-1 and rule out causes of parenchymal or obstructive AKI, clinicians should perform a careful evaluation of history of present illness, physical examination, laboratory data, and volume status; ensure absence of shock; remove potential nephrotoxic medications; assess the potential renal effect of antibiotics on each case of AKI; perform a volume expansion challenge when appropriate; and perform urine microscopy when feasible. Although a precipitating event is not required for the diagnosis of HRS-1, the recent presence of SBP or acute-on-chronic liver failure should increase clinical suspicion for HRS-1.[6]

HRS-1 is a rapidly progressing form of AKI with poor outcomes in patients with advanced liver disease.[1,6] To promptly diagnose a patient with HRS-1, there should be a high index of suspicion when a patient with cirrhosis presents with an elevated SCr in the absence of precipitating factors. Delaying diagnosis puts these patients at risk for experiencing continued increases in SCr levels and subsequent progression to a higher AKI stage.[2] Therefore, prompt identification of patients at risk for HRS-1 is important to help maximize the potential for improved outcomes, including increasing the chances for reversal of AKI.[1]

> *"To promptly diagnose a patient with HRS-1, there should be a high index of suspicion when a patient with cirrhosis presents with an elevated SCr in the absence of precipitating factors. Prompt identification of patients at risk for HRS-1 is important to help maximize the potential for improved outcomes."*
>
> **– Josh Levitsky, MD, MS, and Juan Carlos Velez, MD**

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