REVIEW ARTICLE

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Acute Kidney Injury in Patients with Cirrhosis

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ACUTE KIDNEY INJURY (AKI) IS A COMMON CONDITION IN PATIENTS WITH cirrhosis. It occurs in up to 50% of hospitalized patients with cirrhosis and in 58% of such patients in the intensive care unit (ICU).[1-5] AKI is associated with high morbidity and mortality and an increased incidence of chronic kidney disease (CKD) after liver transplantation.[1-3,5,6] Progression to advanced stages of AKI (Table 1) portends an even worse prognosis.[1,2,5]

In general, the three main causes of AKI[11] are renal hypoperfusion (also referred to as prerenal AKI), which in most cases is due to hypovolemia; intrinsic, structural kidney injury; and postrenal injury due to urinary obstruction. A unique cause of AKI due to renal hypoperfusion in patients with cirrhosis is the hepatorenal syndrome (HRS), which is the result of renal vasoconstriction. Hypoperfusion from hypovolemia accounts for approximately half the cases of AKI in patients with cirrhosis, intrinsic causes (e.g., acute tubular necrosis) account for approximately 30% of cases, and HRS accounts for approximately 15 to 20%, with less than 1% of cases attributable to postrenal obstruction.[3]

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DEFINITION OF AKI AND HRS

Before 2012, criteria defining AKI in cirrhosis were absent, but HRS was defined as a syndrome that occurred in patients with cirrhosis and portal hypertension and was characterized by impaired kidney function (defined as a serum creatinine level of >1.5 mg per deciliter [132.6 μmol per liter]) in the absence of underlying kidney disease.[7] Clinically, HRS was divided into type 1 (HRS-1), characterized by a rapid reduction in kidney function, with an increase in serum creatinine to a level exceeding 2.5 mg per deciliter [221.0 μmol per liter] in less than 2 weeks, and type 2 (HRS-2), a more chronic deterioration in kidney function.

Over the past decade, the definitions of AKI and HRS in patients with cirrhosis have been revised (Table 1).[8-10] The new definition of AKI was harmonized with the Kidney Disease: Improving Global Outcomes definition as an increase in the serum creatinine level of 0.3 mg per deciliter (26.5 μmol per liter) or higher within 48 hours or as an increase in the serum creatinine level that is at least 1.5 times the baseline level and that is known or presumed to have occurred within the previous 7 days.[8-10,12] The new definition of HRS eliminated the threshold value for the serum creatinine level (1.5 mg per deciliter), allowing for earlier diagnosis and treatment in patients with normal serum creatinine levels but reduced kidney function, such as women, older patients, or those with sarcopenia. The acute form of HRS, HRS-1, was also renamed HRS-AKI to distinguish it from the more chronic type, HRS-2, now renamed HRS-CKD.[10] Changes in urinary output should be considered in the definition of AKI, particularly in critically ill patients with cirrhosis in whom changes in urinary output have been shown to be a sensitive,

Table 1. Definitions of Acute Kidney Injury (AKI) and the Hepatorenal Syndrome (HRS) in Patients with Cirrhosis.*

Variable or Definition	International Ascites Club, Salerno et al.[7] (2007)	Acute Disease Quality Initiative, Nadim et al.[8] (2012)	International Club of Ascites, Angeli et al.[9] (2015)	Angeli et al.[10] (2019)
Baseline serum creatinine level	—	—	Serum creatinine measured in previous 3 mo; in patients with >1 value within previous 3 mo, the value closest to time of hospital admission should be used; in patients without a previous serum creatinine value, the value on admission should be used as baseline	Similar to 2015 definition[9]
AKI	—	Increase in serum creatinine ≥0.3 mg/dl within 48 hr or increase ≥1.5 times baseline level	Increase in serum creatinine ≥0.3 mg/dl within 48 hr or increase ≥1.5 times baseline level, which is known or presumed to have occurred within previous 7 days	Absolute increase in serum creatinine ≥0.3 mg/dl within 48 hr or≥1.5 times baseline level or urinary output <0.5 ml/kg/hr in 6 hr
AKI stage	—	Stage 1: increase in serum creatinine ≥0.3 mg/dl or ≥1.5–2 times baseline level Stage 2: increase in serum creatinine >2–3 times baseline level Stage 3: increase in serum creatinine >3 times baseline level or ≥4.0 mg/dl with an acute increase ≥0.5 mg/dl or initiation of renal-replacement therapy	Similar to 2012 definition[8]	Similar to 2012 definition[8]
HRS	Cirrhosis with ascites Serum creatinine >1.5 mg/dl with no improvement (decrease ≤1.5 mg/dl) after at least 2 days of diuretic withdrawal and volume expansion with albumin (1 g/kg/day, maximum of 100 g/day) Absence of shock No current or recent treatment with nephrotoxic drugs Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria >50 red cells/high-power field, or abnormal renal findings on ultrasonography	Similar to 2007 definition[7]	Similar to 2007 definition,[7] except for removal of serum creatinine >1.5 mg/dl and inclusion of AKI diagnosis according to KDIGO serum creatinine criteria (i.e., increase in serum creatinine ≥0.3 mg/dl within 48 hr or ≥1.5 times baseline level)	Similar to 2015 definition,[9] except for addition of urinary output <0.5 ml/kg/hr for ≥6 hr as a criterion for AKI; suggestion of HRS-AKI with FeNa of <0.2% (FeNA <0.1% highly predictive)

HRS type 1	Rapid, progressive renal failure, defined by doubling of initial serum creatinine (to a level >2.5 mg/dl) in <2 wk	A specific form of AKI	—	HRS-AKI: absolute increase in serum creatinine ≥0.3 mg/dl within 48 hr or increase in serum creatinine >1.5 times baseline level; or urinary output <0.5 ml/kg/hr for 6 hr
HRS type 2	Serum creatinine increased from 1.5 to 2.5 mg/dl, with steady or slowly progressive course; typically associated with refractory ascites	A specific form of CKD	—	HRS-CKD: eGFR <60 ml/min/1.73 m^2 for ≥3 mo in the absence of other (structural) causes HRS-AKD: eGFR <60 ml/min/1.73 m^2 for <3 mo in the absence of other (structural) causes or <50% increase in serum creatinine with last outpatient value within previous 3 mo as baseline level
Response to therapy	Complete response (reversal of HRS): decrease in serum creatinine to <1.5 mg/dl Partial response: decrease in serum creatinine ≥50% of pretreatment level, without reaching level of <1.5 mg/dl No response: no decrease in serum creatinine or decrease to <50% of pretreatment level, with final level >1.5 mg/dl Relapse: increase in serum creatinine >1.5 mg/dl after discontinuation of therapy	—	Full response: return of serum creatinine to a level within 0.3 mg/dl of baseline level Partial response: regression of AKI stage, with reduction of serum creatinine to ≥0.3 mg/dl above baseline level No response: no regression of AKI	Similar to 2015 definition[9]

* To convert values for creatinine to millimoles per liter, multiply by 88.4. CKD denotes chronic kidney disease, eGFR estimated glomerular filtration rate, FeNa fractional excretion of sodium, and KDIGO Kidney Disease: Improving Global Outcomes.

early marker of AKI and are associated with worse outcomes (Table 1).[5,10,13] One of the major limitations of the definition of HRS is the exclusion of underlying parenchymal kidney disease. In an era marked by an increasing incidence of nonalcoholic steatohepatitis, the presence of underlying CKD due to diabetes mellitus, hypertension, or both is also increasing. In patients with preexisting CKD, the prognostic and therapeutic implications of HRS-AKI have yet to be determined, and these implications will probably differ from those in patients with HRS-AKI that progresses to HRS-CKD.[8,10]

PATHOPHYSIOLOGY

Patients with cirrhosis, particularly those with ascites, have an increased susceptibility to AKI because of the hemodynamic alterations that result from portal hypertension (Fig. 1).[14,15] The initial mechanism in the pathogenesis of portal hypertension is increased intrahepatic resistance due to distortion of the liver architecture (fibrosis and nodules) and an increase in intrahepatic vascular tone. Subsequent activation of vasodilators in the splanchnic circulation (the most important being nitric oxide) leads to progressive splanchnic and systemic vasodilatation. Increased translocation of bacteria and bacterial products due to intestinal dysbiosis, bacterial overgrowth, and altered tight-junction proteins contributes further to vasodilatation, resulting in a reduction in the effective arterial blood volume that will activate the neurohumoral systems (the renin–angiotensin–aldosterone, sympathetic, and arginine–vasopressin systems) leading to sodium and water retention and ascites formation.[16,17] In advanced stages of cirrhosis, progressive vasodilatation leads to more avid retention of sodium and water, resulting in refractory ascites and dilutional hyponatremia, respectively (Fig. 1).

With progressive vasodilatation, vasoconstrictive systems (mainly renin and angiotensin) are activated, resulting in renal vasoconstriction and decreased renal blood flow. In addition, a relative decrease in cardiac output in this high-output state of cardiac failure (so-called cirrhotic cardiomyopathy) may further contribute to decreased renal perfusion.[18-20] The reduced renal blood flow results in a decrease in the glomerular filtration rate (GFR) and a prerenal type of kidney injury that does not respond to volume expansion — that is, HRS-AKI. Renal vasoconstriction in patients with cirrhosis is not countered by the release of vasodilatory substances (e.g., prostaglandins) because of a decrease in their production and local release of vasoconstrictors such as endothelin.

The pathogenesis of renal vasoconstriction and decreased renal blood flow in cirrhosis ("hepatorenal physiology") represents a continuum of the mechanisms that initially lead to ascites. Thus, patients with cirrhosis who have ascites, particularly those with refractory ascites, are at the highest risk not only for the development of AKI but also for its most severe clinical form, HRS-AKI (Fig. 1). Although HRS-AKI can occur in the absence of a precipitating factor, it is more commonly precipitated by factors that cause a decrease in effective arterial blood volume. These factors include rapid fluid loss (e.g., excessive diuresis or gastrointestinal bleeding), worsening vasodilatation induced by drugs (e.g., angiotensin-converting–enzyme inhibitors), and a systemic inflammatory response (e.g., infection) (Fig. 1). Not all cases of AKI in patients with cirrhosis result from renal hypoperfusion; some cases may result from structural kidney injury. However, renal hypoperfusion may lead to structural kidney injury when prolonged or when coupled with a "second hit," such as exposure to nephrotoxic medications, resulting in a delay in renal recovery.

ASSESSMENT OF KIDNEY FUNCTION

Evaluation of kidney function in patients with cirrhosis remains critically important and a challenging problem. The serum creatinine level, which is the most practical and commonly used marker of kidney function and the measure used in the Model for End-Stage Liver Disease (MELD) score to prioritize candidates for liver transplantation, overestimates the GFR in patients with cirrhosis because of a combination of decreased creatinine production due to liver disease, protein calorie malnutrition, and muscle wasting. In addition, in patients with AKI and fluid overload, an increase in the serum creatinine level can lag by several hours to days, despite a decrease in the GFR.[21,22] Exogenous clearance markers such as inulin and iothalamate are not

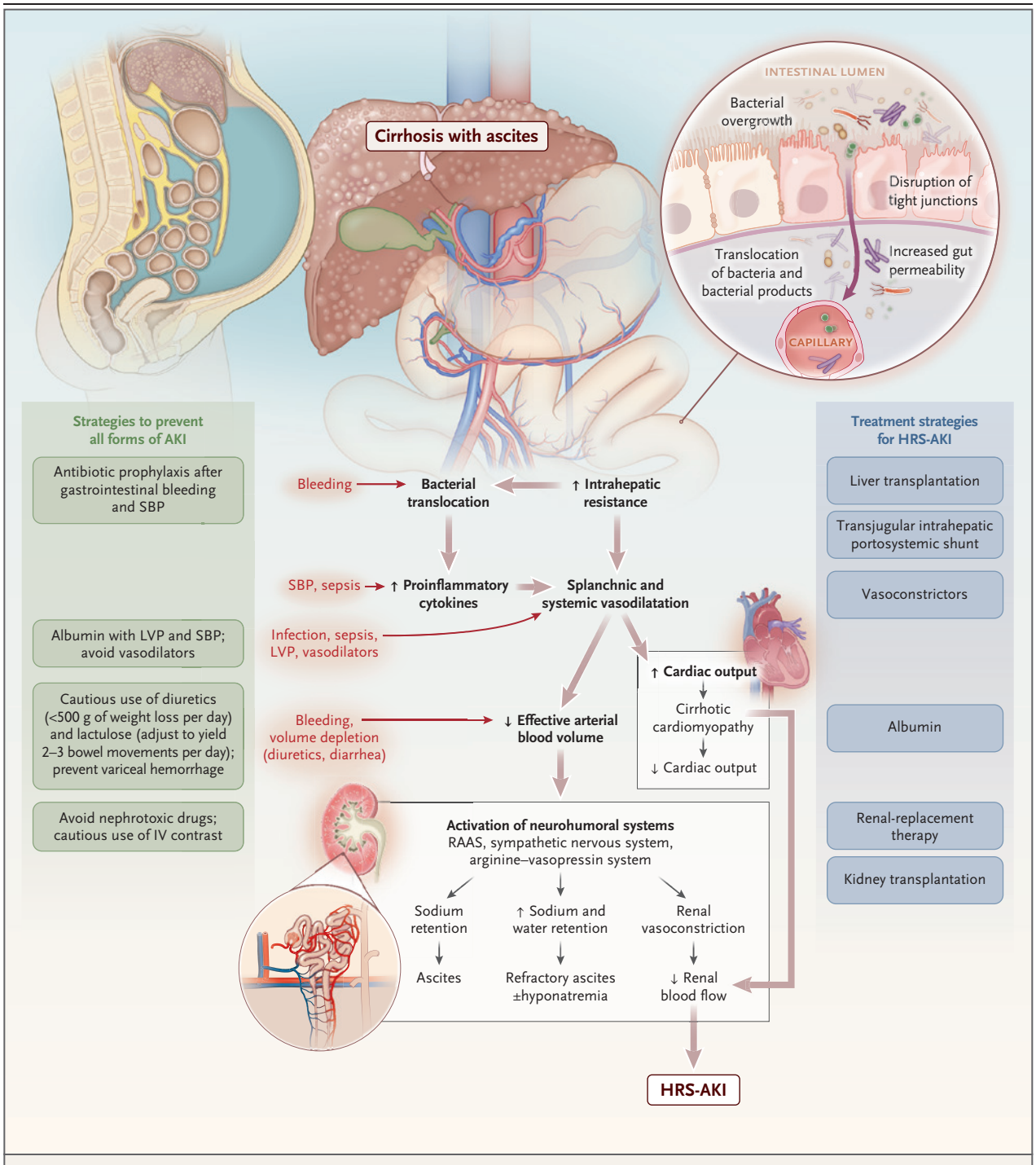


Figure 1. Pathophysiology of the Hepatorenal Syndrome and Acute Kidney Injury (HRS-AKI) in Patients with Cirrhosis.

A sine qua non for the development of HRS-AKI is the presence of ascites, which is often tense ascites and is often associated with hyponatremia, a low mean arterial pressure, and oliguria. Factors that can precipitate AKI in a patient with cirrhosis (even without ascites) or HRS-AKI are indicated by red arrows. Strategies to prevent all forms of AKI (including HRS-AKI) in patients with cirrhosis are shown. IV denotes intravenous, LVP large-volume paracentesis, RAAS renin–angiotensin–aldosterone system, and SBP spontaneous bacterial peritonitis.

readily available and are confounded by changes in the volume of distribution due to ascites and extracellular volume expansion. Measurements of creatinine clearance with the use of timed urinary collection (typically over 24 hours) are subject to inaccuracy because of errors in urinary collection (i.e., incomplete collection or overcollection) or increased tubular secretion of creatinine as the GFR declines.

Estimated GFR (eGFR) equations based on serum creatinine, cystatin C, or both are a simple method of determining kidney function in the general population of persons with stable serum creatinine levels. In patients with cirrhosis, however, eGFR equations tend to overestimate the true GFR by 10 to 20 ml per minute per 1.73 m^2 of body-surface area, especially in patients with a GFR of less than 40 ml per minute per 1.73 m^2, ascites, or both and should be used with caution.[23-25] The accuracy of eGFR measurements is particularly important in patients with cirrhosis because eGFR is one of the factors used to determine candidacy for simultaneous liver and kidney transplantation. The removal of race from all eGFR equations was recently recommended as an important step in efforts to eliminate disparities in the care of patients with kidney disease,[26] and this removal has been adopted within the transplantation community; however, the effect of this change in eGFR equations on candidacy for simultaneous liver and kidney transplantation remains to be adequately studied.[27]

DIAGNOSTIC WORKUP AND MANAGEMENT OF AKI

Once AKI is diagnosed, it is important to discontinue any medications that could have a role in precipitating or worsening AKI — specifically, diuretics, vasodilators, nonselective beta-blockers, nonsteroidal antiinflammatory drugs — and to rule out infection, particularly spontaneous bacterial peritonitis, which is frequently a precipitant of AKI and HRS-AKI (Fig. 2). At the same time, a diagnostic workup for AKI is essential for treating early AKI and for preventing progression, which is associated with increased mortality.[1,2,5] The cause of AKI is determined on the basis of the patient's history and physical examination, urinary tests, the response to diuretic withdrawal, and a volume challenge when clinically indicated (Fig. 2). Microscopical examination of urinary sediment is important to rule out intrinsic causes of AKI.

Measurements of fractional excretion of sodium and urea have been used by clinicians to confirm hypovolemia and HRS-AKI and to rule out acute tubular necrosis. However, patients with cirrhosis and ascites already have avid sodium retention, and fractional excretion of sodium of less than 1.0% is common in such patients, even in the absence of AKI.[28] Differentiating between HRS-AKI and acute tubular necrosis is therefore often challenging. In general, cutoff values of less than 0.1% for fractional excretion of sodium, less than 21% for fractional excretion of urea, and less than 44 mg per deciliter for urinary albumin may help to confirm HRS-AKI and rule out acute tubular necrosis.[28-30] These cutoff values should be interpreted cautiously, however, and always in the context of the patient's clinical presentation, since they are not very sensitive or specific and have not been correlated with histologic findings. Urinary neutrophil gelatinase–associated lipocalin, a marker of tubular injury, has been shown to differentiate between HRS-AKI and acute tubular necrosis. However, its use in clinical practice has been limited because of lack of standardization, uncertainty regarding the cutoff value, and the unavailability of the biomarker in many countries.[28,31-34] Kidney biopsy should be considered only if the results might change management (e.g., treatment of glomerular diseases), since biopsy is an invasive procedure and may be associated with bleeding complications.

Volume expansion is central in reversing AKI due to volume depletion, and the response to volume expansion will help to determine the cause of AKI (Fig. 2). The type of resuscitation fluid (crystalloids vs. albumin) and the amount should be individualized according to the cause of AKI and the patient's volume status (Fig. 2). Volume resuscitation is recommended for a trial period of 24 to 48 hours in patients who are clinically hypovolemic or euvolemic. However, it is important to exercise caution in administering fluids in patients with AKI in order to avoid fluid overload and pulmonary edema. Assessment of intravascular volume and volume responsiveness is desirable but has been challenging, since many of the hemodynamic tools have not been studied in patients with cirrhosis and

may be misleading because of increased intraabdominal pressures due to ascites.[13] In a small, single-center, retrospective study that assessed volume status with the use of point-of-care ultrasonography in patients with a diagnosis of HRS-AKI who were considered to have adequate volume repletion, 21% of the patients had intravascular fluid overload, and 28% continued to have intravascular volume depletion.[35] A combination of assessments, including a careful history taking and physical examination, point-of-care ultrasonography, and static and dynamic measurements, when available, should be used to evaluate volume status and fluid responsiveness.

There is insufficient evidence supporting the use of paracentesis to improve intraabdominal pressure (and theoretically, kidney function) in patients with cirrhosis and AKI. Partial ascites removal is recommended for comfort in patients with tense ascites and should be accompanied by intravenous administration of albumin to prevent circulatory dysfunction, a vasodilatory state that follows large-volume paracentesis (removal of >5 liters) and can lead to worsening kidney function.[36-38]

TREATMENT OF HRS-AKI

In patients with cirrhosis, HRS-AKI should be treated only after other causes of AKI have been investigated and excluded (Fig. 2).

PHARMACOLOGIC THERAPY

The mainstay of pharmacologic management of HRS-AKI is the use of vasoconstrictors combined with intravenous albumin (Fig. 3).[39,40] As proof of concept, changes in the serum creatinine level correlate inversely with changes in mean arterial pressure induced by vasoconstrictors.[41] Vasoconstrictors have not been shown to improve survival, so their use should be considered a bridge to transplantation rather than a cure for HRS-AKI.

Terlipressin, a vasopressin analogue, is the most common vasoconstrictor used worldwide, and both U.S.[37] and European[38] guidelines recommend it as a first-line agent for HRS-AKI. Terlipressin can be administered intravenously as a bolus or as a continuous infusion, with similar efficacy. However, the cumulative daily dose and the incidence of adverse events are lower with a continuous infusion.[42] The initial dose can be increased, maintained, or discontinued, according to the response (changes in the serum creatinine level) (Fig. 3). In a large randomized, controlled trial showing the efficacy of terlipressin in patients with HRS-AKI, which led to its approval in the United States, the agent was associated with an increased incidence of respiratory failure due to pulmonary edema.[43] Therefore, it is essential to withhold terlipressin and albumin if there is clinical evidence of intravascular volume overload (i.e., anasarca, jugular venous distention, hypoxemia, pulmonary congestion on a chest radiography, or elevated right ventricular systolic pressure on an echocardiography).

Small single-center studies have shown that the responses to norepinephrine, an alternative vasopressor, are similar to those to terlipressin. However, norepinephrine requires continuous infusion in an ICU.[39,40] The combination of octreotide and midodrine has weak vasoconstrictive activity, and a randomized, controlled trial showed that the combined treatment was inferior to terlipressin in reversing HRS-AKI.[44] Therefore, octreotide and midodrine should be used only temporarily, for 24 to 48 hours, and only if terlipressin is unavailable or contraindicated.

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT

An important therapeutic option in patients with portal hypertension is the placement of a transjugular intrahepatic portosystemic shunt (TIPS) that may improve kidney function by redistributing blood volume and reducing portal pressure.[45-48] A meta-analysis of nine small studies suggested that treatment with TIPS led to a significant improvement in kidney function, with a pooled response of 93% among patients with HRS-AKI.[49] However, there is currently insufficient evidence to recommend TIPS for HRS-AKI.

RENAL-REPLACEMENT THERAPY

Renal-replacement therapy (also known as kidney-replacement therapy) has been viewed as a bridge to liver transplantation, but renal-replacement therapy for patients with HRS-AKI who are not candidates for liver transplantation has been controversial because of high mortality.[50] However, because mortality associated with renal-replacement therapy has been shown to be similar among patients with HRS-AKI and those

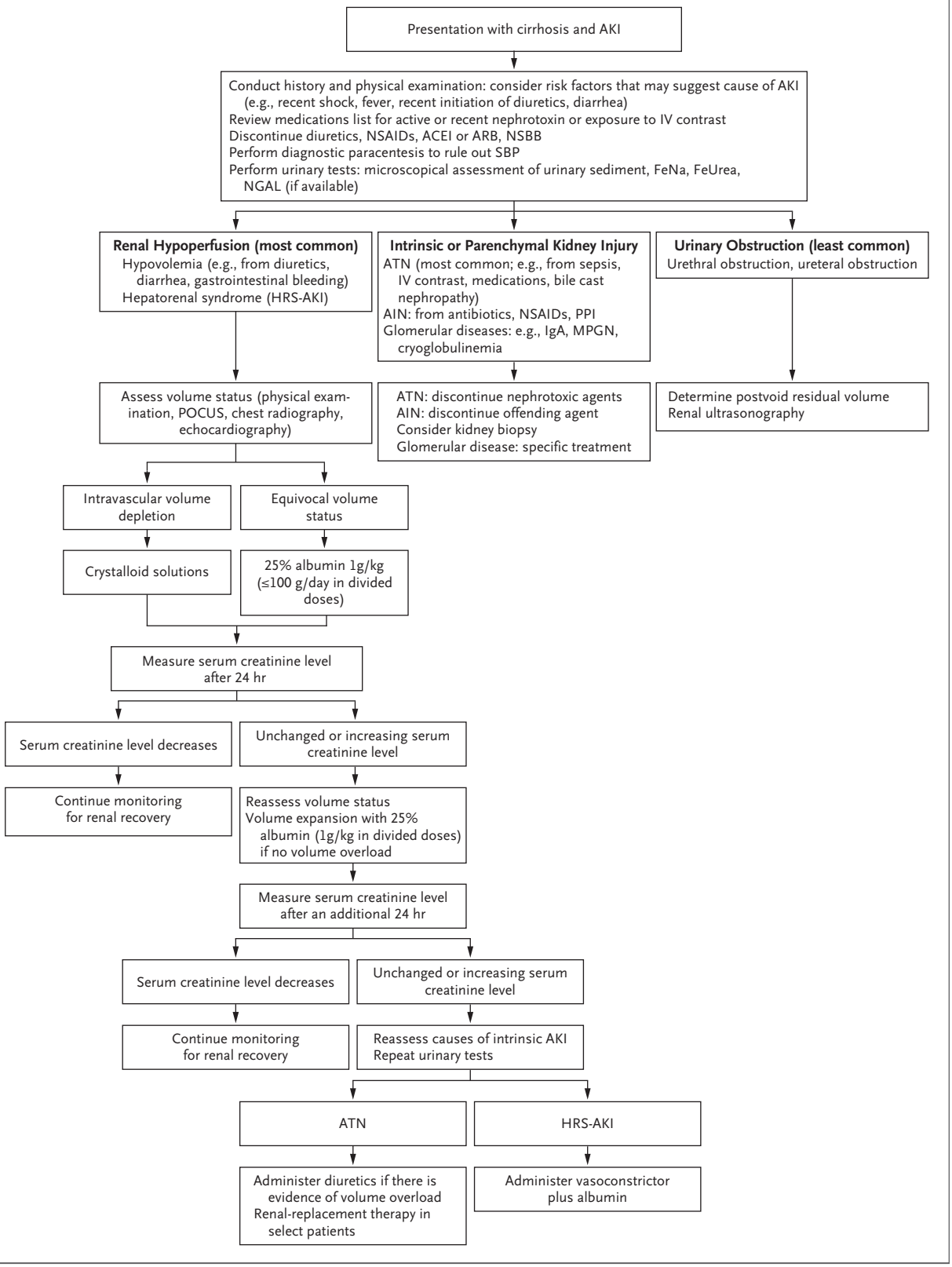


Figure 2 (facing page). Workup and Management of AKI in a Patient with Cirrhosis.

AKI is defined by a serum creatinine level that exceeds the baseline level by 0.3 mg per deciliter (26.5 mmol per liter) within 48 hours or a serum creatinine level that is at least 1.5 times the baseline level (an increase that is known or presumed to have occurred within the previous 7 days) or urinary output of less than 0.5 ml per kilogram of body weight per hour over a period of 6 hours. Urinary tests are important in differentiating between HRS-AKI and various causes of AKI that are due to intrinsic or parenchymal kidney injury. Findings suggestive of HRS-AKI include the following: normal urinary sediment, fractional excretion of sodium (FeNa) of less than 0.1%, and fractional excretion of urea (FeUrea) of less than 21%. A urinary neutrophil gelatinase–associated lipocalin (NGAL) level greater than 220 to 244 μg per gram of creatinine is suggestive of acute tubular necrosis (ATN). Volume overload is suggested by the presence of anasarca, jugular venous distention, a chest film showing pulmonary congestion, or an elevated right ventricular systolic pressure. Diuretics may need to be initiated or continued if there is evidence of volume overload. ACEI denotes angiotensin-converting–enzyme inhibitor, AIN acute interstitial nephritis, ARB angiotensin-receptor blocker, MPGN membranoproliferative glomerulonephritis, NSAIDs nonsteroidal antiinflammatory drugs, NSBB nonselective beta-blocker, POCUS point-of-care ultrasonography, and PPI proton-pump inhibitor.

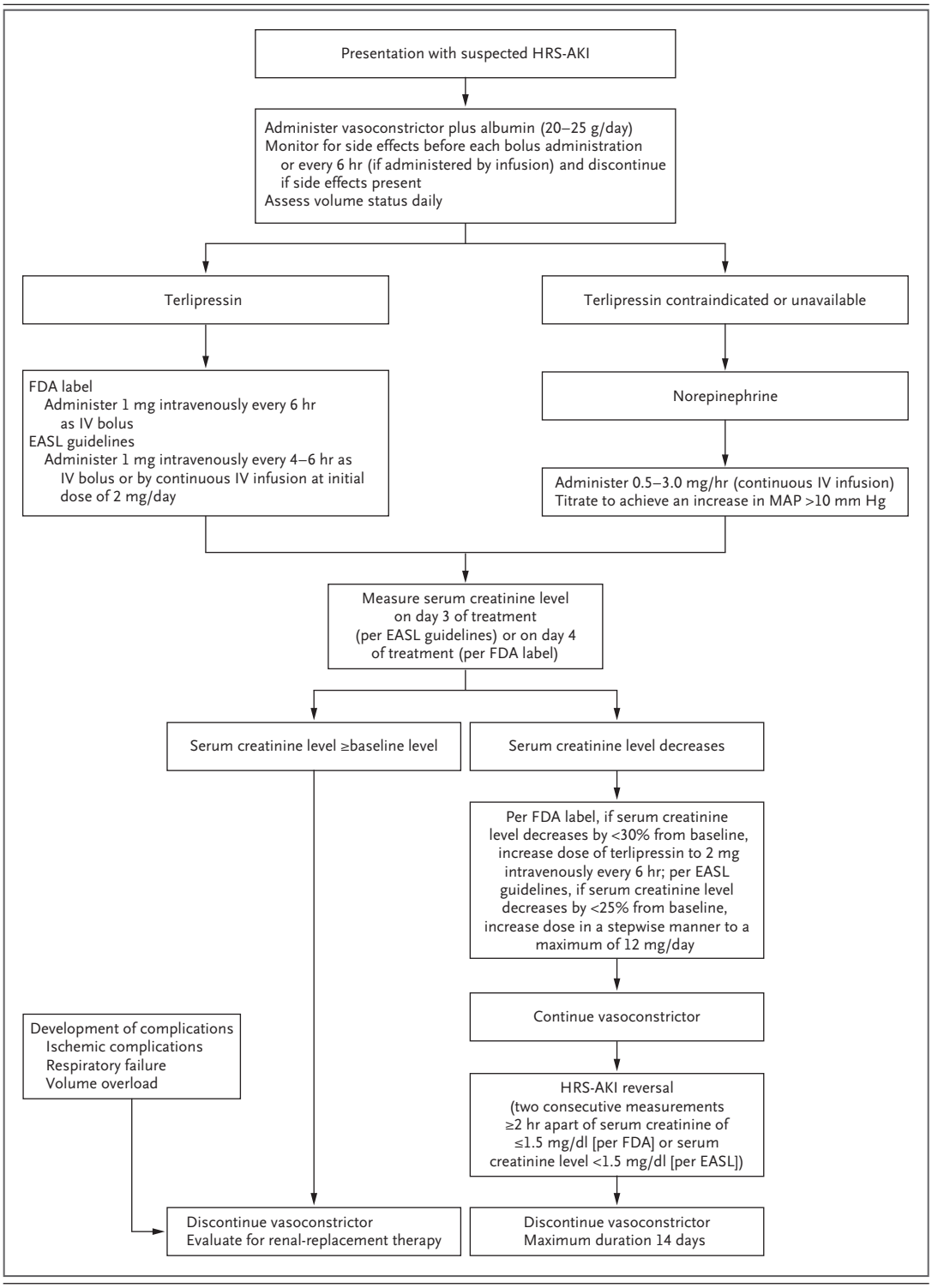
with cirrhosis and acute tubular necrosis,[51] a trial of renal-replacement therapy in selected patients with HRS-AKI could be considered.[13,37] There is no consensus on when renal-replacement therapy should be initiated in patients with cirrhosis and AKI. Although several randomized, controlled trials have not shown a benefit of early initiation of renal-replacement therapy in the general population of critically ill patients in the ICU, patients with cirrhosis were excluded or were largely underrepresented in those studies.[52-55] Therefore, in patients with cirrhosis, the decision about when to initiate renal-replacement therapy should be individualized on the basis of life-threatening indications that are refractory to medical treatment (e.g., hyperkalemia, acidosis, or fluid overload), uremic complications, the trajectory of kidney function, or the overall prognosis.[13,37,56,57]

LIVER TRANSPLANTATION

Liver transplantation is the treatment of choice in patients with HRS-AKI. Simultaneous liver and kidney transplantation is a potential therapeutic option for patients with prolonged kidney dysfunction before liver transplantation, since recovery of kidney function is less likely in these patients than in those with a shorter duration of kidney dysfunction. However, predicting the severity and duration of kidney dysfunction that make recovery unlikely remains challenging.[6,58] In 2017, the Organ Procurement and Transplantation Network set forth criteria for simultaneous liver and kidney transplantation on the basis of previous national guidelines. These criteria included factors such as prolonged duration of AKI and dialysis and the presence of CKD. The organization also implemented a safety-net policy that gave priority to patients with persistent, severe kidney dysfunction after liver transplantation to receive a kidney transplant within the first year.[59,60] Kidney biopsy may assist in establishing the diagnosis and determining the reversibility of kidney dysfunction and the need for simultaneous liver and kidney transplantation.[61] Predictors of reversibility of AKI after transplantation, such as biomarkers, are needed to guide the allocation of kidney grafts.[62,63]

PREVENTION OF AKI

The development of AKI is a common, yet severe complication in patients with cirrhosis. Therefore, it is imperative to recognize and manage events that may result in AKI, particularly in patients with ascites (Fig. 1).[64] Volume depletion should be prevented through the careful use of diuretics (with a goal of <1 lb [0.45 kg] of bodyweight loss per day), careful use of lactulose (with dose adjustment to yield two or three formed bowel movements a day), and prevention of variceal hemorrhage.[65] Intravenous albumin infusions at a dose of 4 to 6 g per liter of ascites removed have been shown to ameliorate circulatory dysfunction and prevent AKI after large-volume paracentesis (removal of >5 liters).[66] Albumin infusions have also been shown to reduce the incidence of AKI and to decrease mortality among patients with spontaneous bacterial peritonitis.[67] However, in a study involving patients with infections other than spontaneous bacterial peritonitis, intravenous albumin did not prevent AKI and was actually associated with an increased incidence of pulmonary edema.[68] The long-term use of intravenous albumin infusions (weekly or every 2 weeks) in the outpatient setting has led to controversial results. An open-



label, randomized, controlled trial showed that this approach was associated with a reduced incidence of complications of ascites (including AKI) and death,[69] whereas a randomized, placebo-controlled trial showed no significant reductions in the incidence of AKI or death with long-term

Figure 3 (facing page). Management Algorithm for Suspected HRS-AKI.

The Food and Drug Administration (FDA) label and the European Association for the Study of the Liver (EASL)[38] guidelines recommend terlipressin as first-line therapy for HRS-AKI. Side effects include myocardial infarction, peripheral or mesenteric ischemia, and pulmonary edema. Albumin infusion should be decreased, and cautious use of terlipressin is recommended in patients with evidence of intravascular volume overload. Terlipressin should be withheld if oxygen saturation (SpO_2) is less than 90%. Norepinephrine use is limited to the intensive care unit (ICU) and requires placement of a central catheter. It may be considered as an alternative if terlipressin is contraindicated or unavailable. Side effects of norepinephrine include ischemic events and cardiac dysrhythmias. The combination of midodrine (7.5 to 15 mg orally three times a day) and octreotide (100 to 200 μg subcutaneously three times a day), given over a period of 24 to 48 hours, may be considered if terlipressin is unavailable or contraindicated and a transfer to the ICU for norepinephrine infusion is not an option. Midodrine may cause bradyarrhythmias. The baseline serum creatinine level is the level determined just before the initiation of vasoconstrictor therapy. MAP denotes mean arterial pressure.

albumin infusions.[70] In a randomized, controlled trial involving hospitalized patients, an intravenous albumin infusion targeted at maintaining serum albumin levels at approximately 3 g per deciliter did not improve outcomes (one of which was the development of AKI) and was associated with an increased incidence of pulmonary edema.[71] Therefore, long-term use of albumin in the outpatient or inpatient setting is currently not recommended.

Various medications such as nonsteroidal antiinflammatory drugs and renin–angiotensin–aldosterone system blockers have direct nephrotoxic effects by impairing intrarenal blood flow. Some agents (e.g., radiocontrast dye, aminoglycosides, vancomycin, and amphotericin B) have direct renal tubule toxicity, and some (e.g., beta-lactam antibiotics and proton-pump inhibitors) cause allergic interstitial injury. Thus, kidney function should be closely monitored in patients with cirrhosis and ascites while they are receiving these medications. Data on the use of intravenous contrast material in these patients are lacking. Cautious use of intravenous contrast material is recommended, especially in patients with an eGFR of less than 45 ml per minute per 1.73 m^2.[72]

CONCLUSIONS

Advances over the past decade in the classification, pathophysiological understanding, diagnosis, and management of AKI in patients with cirrhosis will allow for earlier diagnosis and treatment of HRS-AKI. Since previous studies of the treatment of HRS-AKI used the old criterion of a serum creatinine level exceeding 2.5 mg per deciliter, it is possible that with the new definition, reversal of HRS-AKI with terlipressin and albumin may occur more frequently and with lower doses or for a shorter duration than reported in recent randomized trials. However, the extent to which the presence of systemic inflammation or underlying kidney parenchymal damage limits the efficacy of treatment in patients with HRS-AKI remains unknown. Further development of urinary biomarkers and their inclusion in the diagnostic or treatment algorithm could potentially improve the differential diagnosis of AKI, guide vasoconstrictor therapy for HRS-AKI, and assist in predicting the reversibility of AKI after liver transplantation. Additional investigations are needed to determine the amount of albumin necessary for the prevention and treatment of AKI and HRS-AKI and to support wider use of point-of-care ultrasonography to guide fluid repletion.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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