Elevated Creatinine in a Patient With Cirrhosis

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Elevation in serum creatinine is a common laboratory finding for patients with cirrhosis and can indicate the presence of either an acute kidney injury (AKI) or chronic kidney disease (CKD). However, creatinine may underestimate the actual extent of renal impairment, and both serum creatinine and creatinine-based equations for glomerular filtration rate estimation have been proven to be inaccurate for cirrhotic patients.¹ Therefore, clinicians should have a low threshold for diagnosis and treatment of kidney injury among patients with cirrhosis. Providers should be cognizant that cirrhotic patients often have lower baseline creatinine levels because of the presence of protein-calorie malnutrition, reduced muscle mass, impaired creatinine production from the liver, and increased renal tubular creatinine excretion.¹ Thus, the

clinical relevance of a single creatinine value requires a comparison with prior laboratory values and interpretation within clinical context.

For purposes of this focused review, we will concentrate on the diagnosis and management of AKI, which is the most common cause of elevated creatinine in cirrhotic patients, occurring in nearly 20% of all cirrhotic hospitalizations.² Early recognition of AKI is critical because it is associated with other complications of cirrhosis, such as spontaneous bacterial peritonitis (SBP) and variceal hemorrhage, and it is an independent predictor of mortality.³ Patients with a history of persistently elevated creatinine values or low glomerular filtration rate estimation likely have CKD and will not be addressed in this review.

Abbreviations: ADH, antidiuretic hormone; Alk phos, alkaline phosphatase; ALT, alanine aminotransferase; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; AST, aspartate aminotransferase; ATN, acute tubular necrosis; CKD, chronic kidney injury; Cr, creatinine; CX, culture; CXR, chest x-ray; Dbili, direct bilirubin; FENa, fractional excretion of sodium; GFR, glomerular filtration rate; GI, gastrointestinal; HRS, hepatorenal syndrome; INR, international normalized ratio; MAP, mean arterial pressure; MICU, medical intensive care unit; NSAID, nonsteroidal anti-inflammatory drug; PRA, prerenal azotemia; RAAS, renin-angiotensin-aldosterone system; RRT, renal replacement therapy; SBP, spontaneous bacterial peritonitis; SCr, serum creatinine; SNS, sympathetic nervous system; Tbili, total bilirubin; UNa, urine sodium; UO, urine output; UOsm, urine osmolality.

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TABLE 1. ACUTE KIDNEY INJURY NETWORK CLASSIFICATION/STAGING SYSTEM FOR ACUTE KIDNEY INJURY⁴

AKIN Stage	Serum Creatinine Criteria	Urine Output
Stage 1	Increase in SCr $\geq$ 0.3 mg/dL or increase to $\geq$ 150%-200% from baseline	UO $<$ 0.5 ml/kg/hour for $>$ 6 hours
Stage 2	Increase in SCr to $>$ 200%-300% from baseline	UO $<$ 0.5 ml/kg/hr for $>$ 12 hours
Stage 3	Increase in SCr to $>$ 300% from baseline or SCr $\geq$ 4.0 mg/dL after a rise of at least 0.5 mg/dL or treatment with RRT	UO $<$ 0.3 ml/kg/hour for 24 hours or anuria for 12 hours

Abbreviations: AKI, acute kidney injury; RRT, renal replacement therapy; SCr, serum creatinine; UO, urine output.

INITIAL EVALUATION

According to the Acute Kidney Injury Network (AKIN), the definition of AKI is an abrupt (within 48 hours) reduction in kidney function, seen by an increase in serum creatinine by at least 0.3 mg/dL or increase of at least 50% (1.5-fold) from baseline, or a reduction in urine output to less than 0.5 mL/kg/hour for more than 6 hours.⁴ There are three stages of AKI severity according to the AKIN criteria classification (Table 1). Clinicians must also be aware that patients with CKD are susceptible to a superimposed acute injury.

The three classifications of AKI in cirrhosis include²:

1. Prerenal:
- a. Renal hypoperfusion: caused by intravascular volume depletion (eg, dehydration from overdiuresis) as seen in prerenal azotemia (PRA) or cardiorenal syndrome caused by reduced cardiac output

- b. Functional renal vasoconstriction as seen in hepatorenal syndrome (HRS)
2. Intrinsic renal: ischemic or toxic injury leading to acute tubular necrosis (ATN), glomerulonephritis, or interstitial nephritis
3. Postrenal: caused by urinary tract obstruction

Initial workup includes a full assessment of renal and liver functions, as well as excluding common clinical precipitants, especially infections such as SBP (Table 2).

DIAGNOSIS

To diagnose the type of AKI, one must analyze the clinical scenario and the results of the initial evaluation. Postrenal failure is quickly identified by the presence of hydronephrosis on renal ultrasound or by resolution of urinary obstruction with placement of a urinary catheter. It is, however, more challenging to distinguish among PRA, HRS, and ATN. Table 3 outlines the key diagnostic

TABLE 2. INITIAL EVALUATION OF ACUTE KIDNEY INJURY IN CIRRHOSIS

Workup	Tests to Order
Renal function	<div><div>• Urinalysis, including urine microscopy and sediment</div><div>• Urine tests: electrolytes, osmolality, protein, albumin</div><div>• Urine output</div><div>• Renal ultrasound</div></div>
Liver function	<div><div>• Consider echocardiogram if concerned for cardiorenal process</div><div>• Liver tests: AST, ALT, Tbili, Dbili, Alk Phos, INR, albumin</div><div>• Liver ultrasound with Doppler</div></div>
Infection	<div><div>• Diagnostic paracentesis (including total protein, albumin, cell count)</div><div>• Cultures: urine, blood</div><div>• Diagnostic paracentesis (peritoneal fluid Gram stain and culture)</div><div>• Chest X-ray</div></div>

Abbreviations: Alk phos, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Dbili, direct bilirubin; INR, international normalized ratio; Tbili, total bilirubin.

TABLE 3. KEY DIAGNOSTIC FINDINGS

	PRA	HRS	ATN
Clinical characteristics	Dehydrated, aggressive diuresis, diarrhea	Advanced cirrhosis, low MAP, low serum sodium (hypervolemic hyponatremia)	Septic shock, infection, hypotension, nephrotoxins
Volume status	Dry	Overloaded (refractory ascites)	Either
UNa*	Low (<20 mEq/L)	Low (<20 mEq/L)	High (>40)
FENa*	Low (<1%)	Low (<0.1%)	High (2%)
UOsm	High (>500 mOsm/kg)	High (>500 mOsm/kg)	Low (<350 mOsm/kg)
Urine sediment	Bland	Bland	Granular casts, [†] epithelial casts

New urinary biomarkers may assist in differentiating acute kidney injury (AKI) in cirrhosis.⁶

Abbreviations: ATN, acute tubular necrosis; FENa, fractional excretion of sodium; HRS, hepatorenal syndrome; MAP, mean arterial pressure; PRA, prerenal azotemia; UNa, urine sodium; UOsm, urine osmolality.

*FENa and UNa: not interpretable in the setting of diuretics.

[†]Granular casts may be nonspecific in advanced cirrhosis and seen in both ATN and HRS.

findings as a general guideline. Dependent on the clinical setting, the use of urine electrolytes as well as the urinary sediment can potentially elucidate the diagnosis. PRA is typically responsive to volume repletion, whereas HRS is a functional type of prerenal kidney injury due to renal vasoconstriction that persists after volume challenge.² Although a type of prerenal AKI, cardiorenal syndrome (or congestive nephropathy) may worsen with volume expansion and requires evaluation with an echocardiogram to determine the presence of a decreased ejection fraction. ATN can typically be distinguished by clinical scenario and urine studies, notably with granular casts in the urine sediment; however, this finding may be nonspecific in advanced cirrhosis.

It is essential to determine the presence of HRS. There are two types of HRS (types 1 and 2), which are differentiated by timing and patient characteristics. HRS-1 is a type of AKI with sudden decline in renal function (within 2 weeks), often developing after a precipitating event such as SBP and it is associated with poor short-term prognosis. Whereas HRS-2 is more indolent, occurring slowly over time (weeks to months), and it usually presents in the outpatient setting as refractory ascites.² HRS is only considered as a possible diagnosis in patients with cirrhosis *and* ascites after other causative factors have been excluded, such as ATN, decreased cardiac outflow, shock, nephrotoxins, and parenchymal kidney disease. If there is no improvement in creatinine after at least 2 days of volume expansion (albumin 1 g/kg body weight/day), HRS is the most likely cause.^{2,5} HRS accounts for about one-sixth (17%) of all AKI cases

among hospitalized cirrhotic patients and about one-fourth (25%) of cases determined to be prerenal AKI.² The pathophysiology of HRS is illustrated in Figure 1.²

TREATMENT

The initial step in the treatment of an elevated creatinine concentration and concern for AKI in any cirrhotic patient is to discontinue potential offending agents such as diuretics, lactulose, NSAIDs, vasodilators, and other nephrotoxins. Concurrently, the patient should be evaluated for any underlying precipitants such as

FIG 1 Pathophysiology of hepatorenal syndrome (HRS). HRS is a consequence of a progressing systemic vasodilatory state related to portal hypertension that results in an overall ineffective arterial blood volume. The subsequent effect leads to hypoperfusion of the kidneys and development of renal insufficiency. Abbreviations: ADH, antidiuretic hormone; RAAS, renin-angiotensin-aldosterone system; SNS, sympathetic nervous system. Adapted with permission from *Hepatology* (Figure 2, page 2066).² Copyright 2008, American Association for the Study of Liver Diseases.

FIG 2 Proposed treatment algorithm of acute kidney injury (AKI) in cirrhosis. This proposed algorithm provides a stepwise process on the workup to diagnose and treat the common causes of AKI in patients with cirrhosis. After initial workup, including a search for possible precipitants, patients should be challenged with volume to determine whether renal function improves. However, if nonresponsive to volume and if the clinical suspicion is high, patients should then be treated for HRS with vasoconstrictor therapy, as well as referral for liver transplant evaluation. Abbreviations: ATN, acute tubular necrosis; Cr, creatinine; CX, culture; CXR, chest x-ray; GI, gastrointestinal; HRS, hepatorenal syndrome; MAP, mean arterial pressure; MICU, medical intensive care unit; NSAIDs, nonsteroidal anti-inflammatory drugs.

gastrointestinal bleeding or infection (ie, SBP). If renal function does not improve after 24 hours, patients should then be given intravascular volume repletion using albumin as the preferred agent.^{2,5} The diagnosis is likely PRA if the creatinine responds to volume. However, if the patient is unresponsive after at least 2 days of diuretic withdrawal and expansion of volume with albumin, then HRS should be strongly considered. If there is clinical suspicion for HRS (ie, ascites, low mean arterial pressure, hyponatremia), the diagnosis of HRS is assumed and the combination of albumin plus vasoconstrictors should be started immediately. According to AASLD practice guidelines, if the patient is on a medical floor,

an oral vasoconstrictor, midodrine, can be combined with octreotide, a somatostatin analogue, and albumin to initially treat HRS⁶; although recent literature has shown that this regimen is not as effective as more potent vasoconstrictors.⁷ However, when in the intensive care unit, albumin plus norepinephrine (or terlipressin if outside the United States) should be considered. All patients with HRS should be immediately referred to a liver transplant center for transplant evaluation.⁶ Refer to Figure 2 for a proposed algorithm on the treatment of AKI in hospitalized patients with cirrhosis.

CLINICAL OUTCOMES/PROGNOSIS

Patients with cirrhosis and renal failure have a poor prognosis. For all causes of renal failure, the 1-month mortality rate is near 50%, whereas the 6-month mortality rate approaches 80%.⁸ Prognosis is markedly dependent on the cause of renal injury. According to a large, single-center, prospective cohort, 3-month survival rates ranged from 73% for parenchymal disease, 46% for hypovolemia, 31% for infection-associated renal failure, and only 15% for HRS.⁹ Furthermore, type 1 HRS has a worse prognosis compared with type 2 HRS, with a median survival of only 1.0 month compared with 6.7 months, respectively.¹⁰ Given the poor short-term survival in HRS, it is crucial for these patients to be evaluated for liver transplantation, because this remains the only curative option.^{2,6,9}

KEY CLINICAL POINTS

- AKI in patients with cirrhosis is associated with poor outcomes.
- Absolute creatinine is of little utility and clinicians should evaluate the *change* in creatinine from baseline values to diagnose AKI.
- Patients with HRS should be evaluated for liver transplantation.

CORRESPONDENCE

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