Kidney Dysfunction in the Setting of Liver Failure: Core Curriculum 2024

Swetha R. Kanduri and Juan Carlos Q. Velez

Individuals with liver disease are susceptible to pathophysiological derangements that lead to kidney dysfunction. Patients with advanced cirrhosis and acute liver failure (ALF) are at risk of developing acute kidney injury (AKI). Hepatorenal syndrome type 1 (HRS-1, also called HRS-AKI) constitutes a form of AKI unique to the state of cirrhosis and portal hypertension. Although HRS-1 is a condition primarily characterized by marked renal vasoconstriction and kidney hypoperfusion, other pathogenic processes, such as acute tubular injury and renal vein congestion, can overlap and further complicate the course of HRS-1. ALF can lead to AKI through mechanisms that involve systemic inflammation, direct drug toxicity, or bile acid-induced tubulopathy. In addition, the growing prevalence of nonalcoholic steatohepatitis is changing the spectrum of chronic kidney disease in cirrhosis. In this installment of *AJKD's Core Curriculum in Nephrology*, we explore the underpinnings of how cirrhosis, ALF, acute cholestasis, and post–liver transplantation can be associated with various forms of acute, subacute, or chronic kidney diseases. We navigate through the recommended therapies for each condition, including supportive care, pharmacological interventions, kidney replacement therapy, and organ transplantation. Finally, key acid-base and electrolyte disorders associated with hepatobiliary disease are also summarized.

Complete author and article information provided at end of article.

Am J Kidney Dis. 83(3):386-401. Published online December 7, 2023.

doi: 10.1053/j.ajkd.2023.08.013

The Core Curriculum aims to give trainees in nephrology a strong knowledge base in core topics in the specialty by providing an overview of the topic and citing key references, including the foundational literature that led to current clinical approaches.

Introduction

There is a broad spectrum of medical conditions characterized by simultaneous derangement in the function of the liver and the kidneys. The complexity and severity of coexisting liver and kidney pathologies often constitute a significant diagnostic and therapeutic challenge for the clinician. The burden of acute kidney injury (AKI) in hospitalized patients with decompensated cirrhosis—defined as an acute deterioration in liver function in conjunction with clinical complications characterized by worsening jaundice, ascites, hepatic encephalopathy, and variceal hemorrhage—is increasing and ranges between 20% and 50%. Advanced cirrhosis is associated with a unique form of AKI known as the hepatorenal syndrome (HRS-1) or HRS-AKI. However, other potential causes of AKI may affect this population (Fig 1).

In addition, patients with acute liver failure (ALF) with or without preexisting chronic liver disease (CLD) often present with concomitant AKI resulting from pathogenic processes different from that of HRS-1. The term HRS-2 has been used to refer to hepatorenal physiology-mediated kidney dysfunction that is more insidious, chronic, or persistent. HRS-2 has now been divided into HRS-AKD (acute kidney disease) and HRS-CKD (chronic kidney disease) by adhering to the KDIGO definitions. Furthermore, the changing epidemiology of CLD with an increased prevalence of metabolic (dysfunction)-associated fatty liver disease (MAFLD) and its associated metabolic disorders, including type 2 diabetes mellitus, has led to greater incidence of CKD among individuals who progress to develop cirrhosis and end-stage liver disease (ESLD).

Consequently, the evaluation of patients with decompensated cirrhosis and/or ALF who present with AKI is seldom straightforward. Herein, we review the general considerations for the evaluation of kidney function in a patient with liver disease and navigate through different clinical phenotypes and corresponding etiologies of disorders characterized by kidney dysfunction in the presence of ESLD and/or ALF as well as management recommendations. Key aspects related to acid-base and electrolyte disorders in the context of liver disease are also covered in this review.

Measurement of Kidney Function in Liver Disease

As in clinical scenarios unrelated to liver disease, a primary step to determine whether a patient has acute or chronic kidney dysfunction relies upon appropriate interpretation of laboratory values. Serum creatinine concentration is the standard test to quantify kidney function. However, utilizing serum creatinine to estimate the glomerular filtration rate (eGFR) in the context of CLD has limitations (Box 1). First, generation of creatinine from

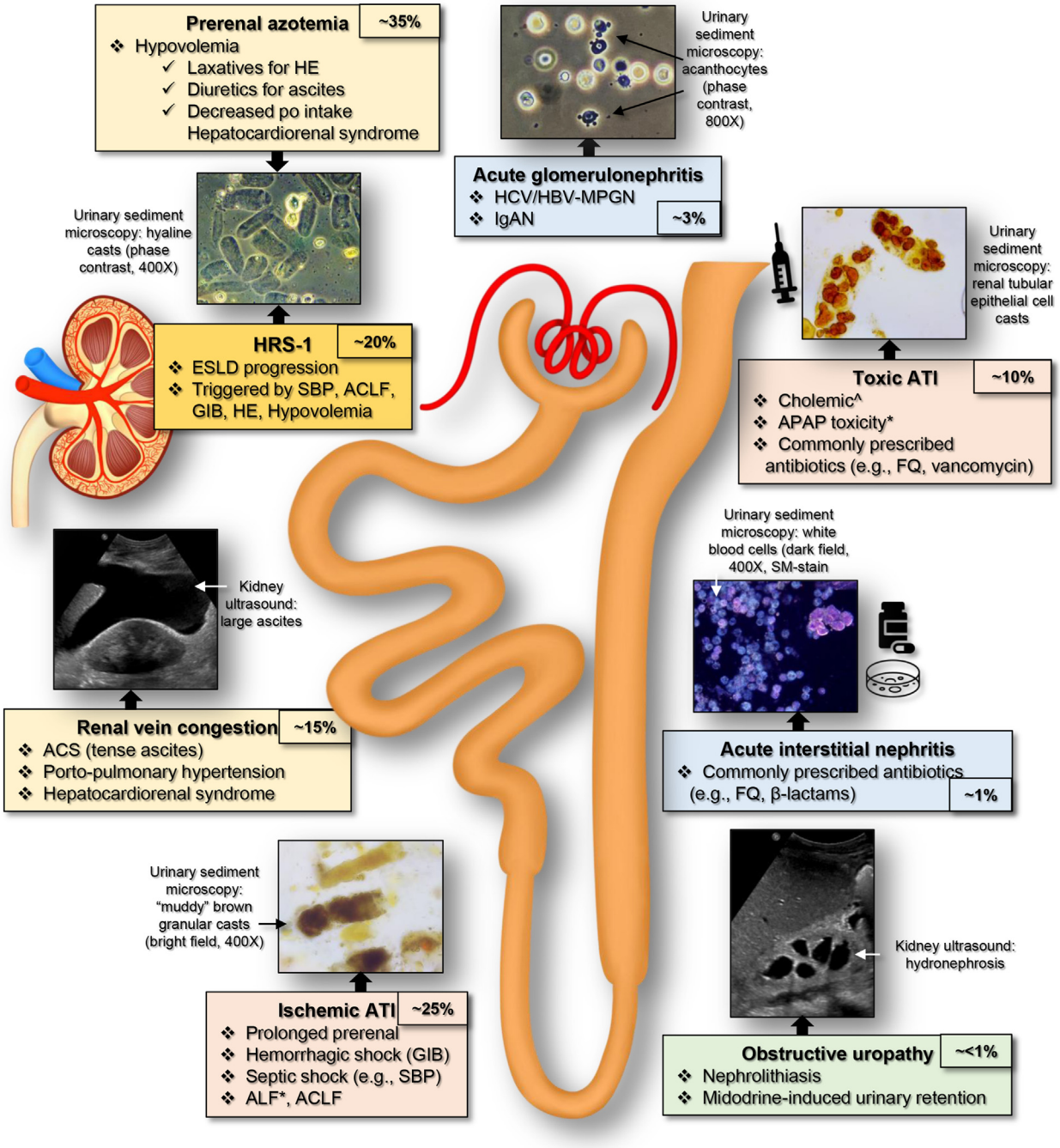

Figure 1. Etiology of AKI in patients with cirrhosis and portal hypertension or with ALF. HRS-1 (also called HRS-AKI) is a distinct cause of AKI in cirrhosis and portal hypertension. In cirrhosis, prerenal azotemia can be caused by gastrointestinal fluid losses, urinary losses or poor cardiac output. Ischemic ATI can be caused by prolonged prerenal azotemia, shock or in the setting of ALF or ACLF-associated inflammation. Toxic ATI can be caused by cholemic tubulopathy or by drugs commonly prescribed in this setting. Acetaminophen can cause ATI and ALF due to massive ingestion. Renal vein congestion can be the mechanism of AKI in ACS caused by tense ascites, right ventricular failure from portopulmonary hypertension, or cirrhotic cardiomyopathy. Acute GN can be caused by aggressive forms of cirrhosis-associated IgA nephropathy or HCV- or HBV-associated MPGN. Acute interstitial nephritis can be caused by antibiotics. Obstructive uropathy is rare in cirrhosis, but it can occur due to nephrolithiasis or by urinary retention in those treated for HRS-1 with midodrine. Percentages annotated in insets represent an approximation of the relative contribution of each etiology to the overall cases of in-hospital AKI (percentages add to >100% because of overlap). *Not specific to cirrhosis. ^Can occur with or without cirrhosis, but more commonly in cholestasis not associated with cirrhosis. Abbreviations: ACLF, acute-on-chronic liver failure; ACS, abdominal compartment syndrome; AKI, acute kidney injury; ALF, acute liver failure; APAP, acetaminophen; ATI, acute tubular injury; ESLD, end-stage liver disease; FQ, fluoroquinolones; GIB, gastrointestinal bleeding; GN, glomerulonephritis; HBV, hepatitis B virus; HCV, hepatitis C virus; HE, hepatic encephalopathy; HRS-1, hepatorenal syndrome type 1; IgAN, immunoglobulin A nephropathy; MPGN, membranoproliferative glomerulonephritis; SBP, spontaneous bacterial peritonitis.

Box 1. Factors Affecting the Measurement of Kidney Function Specific to Patients With Liver Disease

Measurement of serum creatinine
- Decreased generation of creatinine secondary to sarcopenia
- Interference with colorimetric assay of creatinine due to elevated bilirubin

Measurement of serum urea nitrogen (SUN)
- Decreased protein metabolism and SUN generation secondary to liver disease

creatine is affected by sarcopenia, (ie, low muscle mass). Thus, the degree of loss of GFR can be underappreciated in patients with CLD. Secondly, elevated bilirubin levels can cause interference with a colorimetric laboratory assay of creatinine leading to a variability in serum creatinine readings. In addition, a rise in serum urea nitrogen (SUN) may also be inaccurate as a surrogate of loss of GFR because generation of urea is intimately related to protein synthesis and metabolism, processes that are diminished in the context of CLD.

As a potential way to circumvent these limitations, serum cystatin C concentration has been proposed as a better filtration marker. Unlike serum creatinine, cystatin C is less affected by age, muscle mass, and liver function abnormalities and may be a more accurate surrogate of eGFR. In a cross-sectional observational study comparing the performance of 3 CKD Epidemiology Collaboration eGFR equations in patients with liver cirrhosis, the CKD-EPI Cys and CKD-EPI cr-cys exhibited greater accuracy as compared with CKD-EPI cr. Although the availability of cystatin C is increasing across hospital and commercial laboratories, the turnaround time in obtaining the results remains a limiting factor for its widespread use; hence, we continue to heavily rely on serum creatinine and SUN to assess kidney function in patients with ESLD or ALF. Importantly, despite the limitations of absolute value of serum creatinine, changes in serum creatinine from day to day in AKI do correlate fairly well with changes in kidney function and remain a valid clinical tool.

Additional Readings

- Regner KR, Singbartl K. Kidney injury in liver disease. *Crit Care Clin.* 2016;32:343-355. doi:10.1016/j.ccc.2016.03.005 ★ESSENTIAL READING
- Sansoe G, Ferrari A, Nives-Castellana C, Bonardi L, Villa E, Manenti F. Cimetidine administration and tubular creatinine secretion in patients with compensated cirrhosis. *Clin Sci.* 2002;102:91-98. doi:10.1042/CS20010122
- Torre A, Aguirre-Valadez JM, Arreola-Guerra JM, et al. Creatinine versus cystatin C for estimating GFR in patients with liver cirrhosis. *Am J Kidney Dis.* 2016;67(2):341-347. doi:10.1053/j.ajkd.2015.09.022
- Woitas RT, Stoffel-Wagner B, Flommersfeld S, et al. Correlation of serum concentrations of cystatin C and creatinine to inulin clearance in liver cirrhosis. *Clin Chem.* 2000:46:712-715. doi:10.1093/clinchem/46.5.712

Acute Kidney Injury in Cirrhosis

Case 1: *A 42-year-old woman is evaluated for AKI and a 2-week history of worsening fatigue. She has alcoholic cirrhosis and reports decreased appetite and diarrhea for the prior 2 weeks. Her current medications include lactulose, carvedilol, furosemide, spironolactone, and aspirin. The dose of lactulose was recently increased. Her temperature is 36.3°C (98.5°F), pulse is 108/min, respirations are 20/min, and blood pressure is 95/50 mm Hg. Physical examination discloses dry mucous membranes and no edema on upper and lower extremities. No jugular venous distention is noted. Auscultation of the chest discloses normal heart and breath sounds. The abdomen is soft, nontender, and no ascites are noted. The laboratory studies show sodium, 140 mEq/L; potassium, 4.3 mEq/L; chloride, 95 mEq/L; serum creatinine, 2.3 mg/dL (baseline, 0.8 mg/dL); and SUN, 50 mg/dL. The urinalysis reveals specific gravity, 1.030; and no hematuria or proteinuria. No casts are identified on urine microscopy. Her urine sodium is <10 mEq/L, and urine creatinine is 100 mg/dL.*

Question 1: What is the most likely etiology of this AKI?

(a) Acute interstitial nephritis
(b) Acute tubular injury
(c) Hepatorenal syndrome
(d) Obstructive uropathy
(e) Prerenal azotemia

For the answer to the question, see the following text.

Volume depletion is commonly encountered in patients with decompensated cirrhosis, accounting for approximately 30%-40% of the cases of AKI. Patients with cirrhosis are prone to volume depletion and prerenal azotemia secondary to diarrhea from laxatives prescribed for prophylaxis of hepatic encephalopathy, poor oral intake in the context of infections, gastrointestinal hemorrhage from esophageal varices, or urinary losses from diuretics prescribed for ascites, among other factors. In addition, hypoalbuminemia and low effective arterial blood volume (EABV) constitute features inherent to cirrhosis that make patients more vulnerable to prerenal azotemia.

This patient has a history suggestive of gastrointestinal fluid losses. Lack of edema in patients with cirrhosis should trigger suspicion for volume depletion because chronic peripheral edema is common in this setting. The bland urinary sediment and low urine sodium concentration are in agreement with a prerenal cause of AKI, answer (e). Importantly, in the context of prerenal azotemia, medications including diuretics and antihypertensives should be held.

With regards to management of patients with hypovolemic AKI, intravenous volume expansion is the cornerstone. In patients with cirrhosis, intravenous albumin is preferred for fluid resuscitation because it is more effective than intravenous normal saline solution in restoring EABV, given its initial restriction to the intravascular space. Albumin has been shown to be superior to normal saline in reducing postparacentesis circulatory dysfunction when greater than 6 L of ascitic fluid were drained. In a study in patients with spontaneous bacterial peritonitis (SBP), coadministration of albumin along with antibiotics led to a greater reduction in the incidence of AKI as compared with placebo and antibiotics. More recently, the ALPS trial showed that albumin provided faster improvement in hemodynamics and lactate clearance than a balanced solution in patients with cirrhosis and sepsis-induced hypotension. Therefore, albumin should be used as the first-line treatment of hypovolemia in patients with cirrhosis.

Regarding the concentration, 25% albumin is the recommended formulation. Although there are no controlled studies comparing 5% versus 25% albumin in patients with cirrhosis, a randomized controlled trial in an intensive care unit targeting cardiac index of 2.2 L/min/m^2 reported that patients assigned to 5% albumin received 3 times more cumulative volume as compared with the 25% albumin group, which could potentially lead to undesired hypervolemia. Notably, both 5% and 25% albumin formulations administered for clinical use have a sodium concentration similar to that of normal saline (145-150 mEq/L), so they are not salt-free volume expanders. The half-life of intravenous albumin has been estimated at around 16-18 hours.

Additional Readings

- Maiwall R, Kumar A, Pasupuleti SSR, et al. A randomized-controlled trial comparing 20% albumin to plasmalyte in patients with cirrhosis and sepsis-induced hypotension [ALPS trial]. *J Hepatol*. 2002;77(3):670-682. doi:10.1016/j.jhep.2022.03.043
- Sola-Vera J, Minana J, Ricart E, et al. Randomized trial comparing albumin and saline in the prevention of paracentesis-induced circulatory dysfunction in cirrhotic patients with ascites. *Hepatology*. 2003;37(5):1147-53. doi:10.1053/jhep.2003.50169
- Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *New Engl J Med*. 1999;341(6):403-409. doi:10.1056/NEJM199908053410603 ★ESSENTIAL READING
- Wong PY, Carroll ER, Lipinski TL, Capone RR. Studies on the renin-angiotensin-aldosterone system in patients with cirrhosis and ascites: effect of saline and albumin infusion. *Gastroenterology*. 1979;77(6):1171-1176. doi:10.1016/0016-5085(7990153-7)

Case 2: *A 55-year-old man with a history of decompensated cirrhosis due to nonalcoholic steatohepatitis (NASH) is admitted for abdominal pain and weakness. His current medications include omeprazole, rifaximin, furosemide, and spironolactone. His temperature is 37.5°C, pulse is 75/min, respirations 20/min, and blood pressure 105/53 mm Hg (mean arterial pressure [MAP] of 70 mm Hg). The physical examination reveals jaundice, ascites with diffuse tenderness over the abdomen, and 2+ pitting lower extremity edema. Laboratory studies show sodium, 130 mEq/L; potassium, 4.0 mEq/L; serum creatinine, 1.8 mg/dL (baseline, 0.7 mg/dL); SUN, 35 mg/dL; and serum bilirubin, 8.1 mg/dL. The urinalysis reveals no blood or protein. Bilirubin-stained hyaline casts are identified by urine microscopy. His urine sodium is <10 mEq/L, and urine creatinine is 100 mg/dL. The patient receives intravenous albumin, 25 g every 6 hours. The next morning the patient exhibits worsening ascites, oliguria, and a further rise in serum creatinine to 2.2 mg/dL. A diagnosis of HRS-1 is made. The patient continues to exhibit worsening ascites, and a large volume paracentesis is planned. His central venous pressure is recorded at 10 mm Hg.*

Question 2: What is the most appropriate next step in the management of this patient?

(a) Begin intravenous furosemide.
(b) Cancel large volume paracentesis.
(c) Continue albumin for additional 48 hours.
(d) Initiate vasoconstrictor therapy.
(e) Schedule a transjugular intrahepatic portosystemic shunt (TIPS).

For the answer to the question, see the following text.

HRS-1 is a distinct form of AKI that affects individuals with decompensated cirrhosis. Predominance of endogenous vasoconstrictors, elevated hepatic sinusoidal pressure, and profibrotic pathways in the damaged liver with cirrhosis trigger maladaptive splanchnic and peripheral vasodilation, which in turn causes a fall in EABV, leading to overactivation of renin-angiotensin system (RAS) and sympathetic nervous system (SNS). The resulting hormonal RAS and SNS activation thereby impairs renal autoregulation and causes profound renal arterial vasoconstriction, acute reduction in GFR and AKI. Direct communication between the hepatic SNS and the renal SNS is known as the hepatorenal reflex, which may further potentiate renal hypoperfusion, independent of the maladaptive systemic vasodilation (Fig 2).

HRS-1 may account for up to 15%-20% of the cases of AKI in hospitalized patients with advanced cirrhosis. As liver disease progresses, the likelihood of developing HRS-1 increases. SBP is the most common precipitating factor. A study of 197 patients with cirrhosis and SBP reported that about one-third (33%) subsequently developed HRS-1 during the same hospitalization. Other infections or other acute complications of cirrhosis, such as

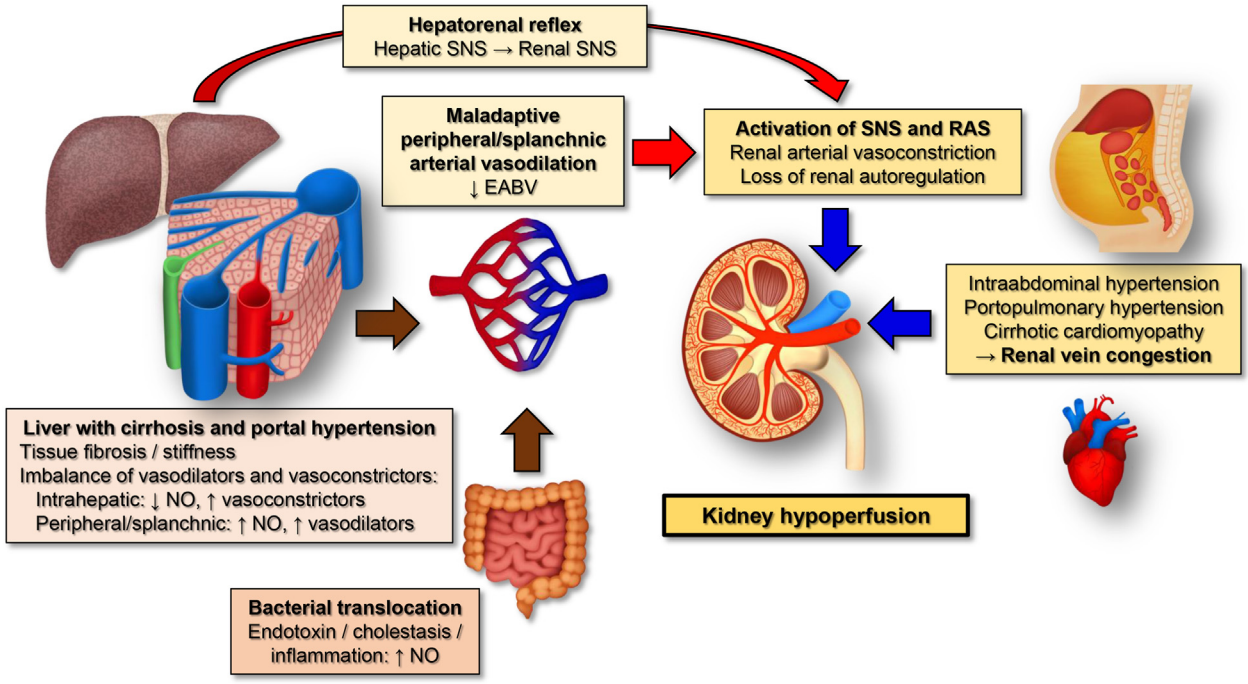

Figure 2. Pathogenesis of hepatorenal syndrome type 1, so-called hepatorenal physiology, illustrating the hemodynamic mechanisms that cause kidney hypoperfusion in decompensated cirrhosis. Abbreviations: EABV, effective arterial blood volume; NO, nitric oxide; RAS, renin angiotensin system; SNS, sympathetic nervous system.

gastrointestinal bleeding or hepatic encephalopathy, have also been linked to potentially precipitating HRS-1.

Currently, there is no gold standard to establish the diagnosis of HRS-1. Thus, the standard approach is primarily directed at excluding other causes of AKI. After multiple iterations and revisions conducted over time (Table 1), the current International Club of Ascites (ICA) diagnostic criteria for HRS-1 (HRS-AKI) include (1) diagnosis of decompensated cirrhosis with ascites; (2) AKI according to the Acute Kidney Injury Network criteria; (3) lack of improvement in serum creatinine after 2 consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g/kg of body weight per day; (4) absence of shock; (5) no recent exposure to nephrotoxic medications; and (6) no evidence of structural parenchymal kidney injury (Table 1). Urinary sodium concentration or fractional excretion of urinary sodium (FENa) were part of earlier ICA criteria. More recently, it has been recognized that lowering the FENa cutoff from <1% to a more stringent <0.2%-0.5% may add specificity to identify cases of HRS-1.

This patient has met all the ICA criteria for HRS-1. The low-grade fever and abdominal tenderness strongly suggest that SBP is present and may have triggered the onset of HRS-1. Oliguria, blood pressure in the lower end of the normal range, hyponatremia, extremely low FENa (0.1%), and absence of muddy brown granular casts in the urinary sediment are important additional phenotypical elements that, although they are not included in the ICA criteria, are clearly consistent with HRS-1. Urinary neutrophil gelatinase-associated lipocalin (NGAL) has shown potential utility as a biomarker to aid in distinguishing HRS-1 from acute tubular injury (ATI), with high values suggestive of the latter. However, overlap may still occur. NGAL is not currently available for clinical use in the United States.

The cornerstone of the management of AKI secondary to HRS-1 is the combination of vasoconstrictor therapy and intravenous albumin, so the correct answer is (d). The mechanistic target is to induce systemic and splanchnic vasoconstriction in order to increase MAP and restore renal perfusion (Table 2). Typically, the ICA recommends intravenous albumin administration at a rate of 1 g/kg per day (100 g maximum) for at least 24-48 hours along with the vasoconstrictor therapy, followed by 25 g daily thereafter. Cumulative clinical evidence suggests that terlipressin and norepinephrine are the most effective vasoconstrictors for the treatment of HRS-1. Terlipressin is a synthetic vasopressin V1 receptor agonist recently approved in United States by the Food and Drug Administration (FDA) for the management of HRS-1. Terlipressin has been the first-line therapy for HRS-1 in Europe, Oceania, Asia, and Central America for the last 15-20 years.

The efficacy of terlipressin and albumin was studied in multiple small-to-mid-size clinical trials with favorable outcomes. However, the 3 largest randomized clinical trials have been conducted in North America: OT-0401, REVERSE, and CONFIRM. In the most recent, CONFIRM,

Table 1. Evolution of ICA Diagnostic Criteria for HRS-1

Category	1979	1996	2007	2015, 2019
Major				
	Presence of severe liver disease	ESLD or ALF with portal hypertension	ESLD with ascites	ESLD with ascites
	Scr > 1.5 mg/dL over days or weeks	Scr > 1.5 mg/dL or CL_{cr} < 40 mL/min	Scr > 1.5 mg/dL	Stage 1 AKI (increase in Scr ≥ 0.3 mg/dL or >1.5× ↑ in Scr or urine output < 0.5 mL.kg/h in 6 h) Stage ≥ 2 AKI (>2.0× ↑ in serum creatinine)
		Doubling of Scr to >2.5 mg/dL in <2 wk	Doubling of Scr to >2.5 mg/dL in <2 weeks	
	No improvement with expansion of intravascular space to achieve a central venous pressure of 10 cm H_2O	No sustained improvement in kidney function after 1.5 L of IV volume expansion with normal saline and diuretic withdrawal	No sustained improvement in kidney function after 2 days of IV volume expansion with albumin (1 g/kg/d) and diuretic withdrawal	No sustained improvement in kidney function after 2 days of IV volume expansion with albumin (1 g/kg/d) and diuretic withdrawal
		Absence of shock or ongoing bacterial infection	Absence of shock	Absence of shock
	Absence of recognized nephrotoxic agents	Absence of exposure to nephrotoxin	Absence of exposure to nephrotoxin	Absence of exposure to nephrotoxin
	U/P Osm >1.0		Absence of overt hematuria (<50 RBC/HPF)	Absence of overt hematuria (<50 RBC/HPF)
	U/P creatinine >30	Absence of overt proteinuria (<500 mg/d)	Absence of overt proteinuria (<500 mg/day)	Absence of overt proteinuria (<500 mg/d)
	Urine sodium < 10 mEq/L	Normal kidney ultrasound	Normal kidney ultrasound	Normal kidney ultrasound
Minor				
	May or may not contain trace amounts of protein and sediment may or may not contain hyaline and/or granular casts	Urine sodium < 10 mEq/L		
	Urine volume < 800 mL/d	Urine volume < 500 mL/d		
	Onset may be spontaneous or may be associated with infection, bleeding, paracentesis, diuretic therapy, or other forms of volume loss	Urine osmolality > plasma osmolality		
	Initial characteristics may be followed in several days by tubular dysfunction characterized by isotonic urine, increased urine sodium and a fall in U/P creatinine, these changes may be accompanied by an accelerated rise in creatinine	Absence of overt hematuria (<50 RBC/HPF)		

(Continued)

Table 1 (Cont'd). Evolution of ICA Diagnostic Criteria for HRS-1

Category	1979	1996	2007	2015, 2019
	Postmortem renal histology is variable, nonspecific and may be normal	Serum sodium < 130 mEq/L		
Newer				
				Introduction of the terms HRS-AKI, HRS-AKD, HRS-CKD terminology (replacing HRS-1 and HRS-2) by applying KDIGO definitions FENa < 0.3% highly predictive

Abbreviations: AKD, acute kidney disease; AKI, acute kidney injury; ALF, acute liver failure; CKD, chronic kidney disease; CL_{cr}, creatinine clearance; ESLD, end-stage liver disease; FENa, fractional excretion of urinary sodium; HPF, high-power field; HRS-1, hepatorenal syndrome type 1; HRS-AKD, hepatorenal syndrome–acute kidney disease; HRS-AKI, hepatorenal syndrome–acute kidney injury; HRS-CKD, hepatorenal syndrome–chronic kidney disease; ICA, International Ascites Club; IV, intravenous; RBC, red blood cells; Scr, serum creatinine; U/P, urine/plasma.

treatment with terlipressin was associated with greater rate of HRS-1 reversal as compared with the placebo (32% vs 17%, $P = 0.006$) and reduction in kidney replacement therapy (KRT) by day 14 and by day 30. However, from a safety standpoint, treatment with terlipressin was associated with greater risk for respiratory failure (10% vs 3%). Respiratory failure events represented a greater risk among patients with serum creatinine ≥ 5 mg/dL or acute-on-chronic liver failure (ACLF) grade 3 at enrollment. This adverse effect may relate to an effect of terlipressin on cardiac afterload and possibly on the pulmonary vasculature in the presence of a large cumulative dose of albumin administered in the trial.

Further illustrating the potential role of albumin in hypervolemia in cirrhosis, a recent trial (ATTIRE) assessing the effect of proactive administration of albumin in cirrhosis demonstrated not only a lack of benefit of normalization of serum albumin concentration but an increased risk for pulmonary edema associated with the intervention. Therefore, routine administration of volume expanders in HRS-1 without careful consideration of volume status may introduce a risk of pulmonary edema. Assessment of volume in patients with cirrhosis is often challenging. A combination of history, physical examination, laboratory data, and noninvasive modalities, such as point-of-care ultrasound, might be beneficial tools for this purpose.

Norepinephrine administered as a continuous infusion has demonstrated comparable efficacy to that of terlipressin in several small-scale clinical trials in patients with HRS-1. The advantages of its use include the ease of dose titration to a desired MAP goal and the relatively low cost of norepinephrine compared with terlipressin. The drawbacks regarding the use of norepinephrine include requirement of a central line and admission to an intensive care unit (ICU). The most limiting side effect of norepinephrine is tachycardia, but generally it is well-tolerated.

The combination of midodrine and octreotide has been advocated for the treatment of HRS-1. However, evidence supporting its use is sparse. When compared against either terlipressin or norepinephrine, midodrine/octreotide is less effective. Midodrine is an α1-receptor agonist, and octreotide is a somatostatin analog. Both drugs are intended to induce splanchnic arterial vasoconstriction. Because of their relatively benign side-effect profile and ease of administration, they are often used in general wards. However, because of their limited efficacy, midodrine/octreotide should no longer be used as first-line vasoconstrictor therapy.

Regardless of the vasoconstrictor employed, its therapeutic efficacy is directly related to the achieved increase in MAP. The greater the increase in MAP, the greater the probability of observing a reduction on serum creatinine. Although a defined MAP target has not been fully elucidated, the recommendation is to seek an increase in MAP of ≥15 mm Hg from baseline.

As previously mentioned, a vasoconstrictor can be used in combination with intravenous albumin. In the study design of virtually all clinical trials evaluating the efficacy of vasoconstrictor therapy, albumin was either given concomitantly by trial protocol or was highly recommended. The argument for its added benefit has relied on a study that reported a greater rate of HRS-1 reversal when albumin was combined with terlipressin, compared with terlipressin alone. However, the study was small and included both HRS-1 and HRS-2. Furthermore, patients treated with terlipressin alone did not achieve an increase in MAP. Therefore, it could be argued that the benefit of addition of albumin to vasoconstrictors has not been clearly demonstrated in the context of effectively used vasoconstrictor therapy. As previously mentioned pertaining to CONFIRM and ATTIRE, the detrimental consequences of overzealous administration of albumin may not be trivial. Therefore, adding albumin to a vasoconstrictor should be implemented with caution and with proper individual assessment of volume status. In fact, administration of diuretics may be appropriate as adjuvant therapy in some patients with HRS-1 and hypervolemia.

Transjugular intrahepatic portosystemic shunt (TIPS) has been studied as treatment for HRS-1 and may be associated with renal recovery in some cases. However, these reports are from retrospective, uncontrolled, cohort studies, and it may increase the risk for hepatic

Table 2. Properties of Vasoconstrictors for the Treatment for HRS-1 (HRS-AKI)

	Receptor Agonism to Mediate Vasoconstriction	Route of Administration	Hemodynamic Effect	Advantages	Adverse Effects	Disadvantages
Midodrine and octreotide	α_1-Adrenergic[a] and somatostatin receptor type 2[b]	Oral[a] and SC[b]	Increase in MAP	• No need for IV • Low cost	• Urinary retention[a] • Bradycardia[a,b] • Glycemia ↑↓[b]	Limited efficacy
Terlipressin	V1a	IV	Increase in MAP	• Proven efficacy[c] • No need for ICU • V1a over V2 receptor selectivity • Divided IV doses, no infusion needed	• Abdominal pain • Ischemia • Respiratory failure	Cost
Vasopressin	V1a	IV	Increase in MAP	• Potentially effective	• Bradyarrhythmia • Hyponatremia • Ischemia	Need for ICU
Norepinephrine	α_1-Adrenergic	IV	Increase in MAP Increase in cardiac contractility[d]	• Proven efficacy • Titratable	• Tachyarrhythmia[d] • Restlessness	Need for ICU

Abbreviations: ICU, intensive care unit; IV, intravenous; MAP, mean arterial pressure; SC, subcutaneous.
[a]Midodrine.
[b]Octreotide.
[c]Drug with evidence from randomized placebo-controlled trials.
[d]β_1-Adrenergic effect.

encephalopathy. Therefore, the therapeutic advantage of TIPS in HRS-1 remains speculative.

Other therapeutic maneuvers as part of supportive care must be considered in HRS-1 and for any patient with cirrhosis and AKI. Medications such as lactulose and diuretics can lead to gastrointestinal and urinary losses and should be withheld, when applicable, although withholding lactulose may not be feasible in patients at considerable risk for hepatic encephalopathy. Nonsteroidal anti-inflammatory agents (NSAIDs) can precipitate AKI and should be always avoided. β-Blockers, often used for variceal bleeding prophylaxis, may lower the MAP and increase the risk for precipitating HRS-1, so they should be avoided as well. In addition, it is important to recognize prevention of SBP as a preventive measure for HRS-1. In a randomized placebo-controlled trial for primary prophylaxis of SBP in patients with cirrhosis, norfloxacin was associated with a reduced 1-year probability of developing SBP (7% vs 61%, $P < 0.001$) as well as HRS-1 (28% vs 41%, $P = 0.02$), thus highlighting SBP as triggering event for HRS-1.

Additional Readings

- Alsaad AA, Wadei HM. Fractional excretion of sodium in hepatorenal syndrome: clinical and pathological correlation. *World J Hepatol*. 2016;8:1497-1501. https://doi.org/10.4254/wjh.v8.i34.1497 ★ESSENTIAL READING
- Angeli P, Garcia-Tsao G, Nadim M, Parikh C. News in pathophysiology, definition, and classification of hepatorenal syndrome: a step beyond the International Club of Ascites (ICA) document. *J Hepatol*. 2019;71:811-822. doi:10.1016/j.jhep.2019.07.002
- Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *Gut*. 2015;64(4):531-537. doi:10.1016/j.jhep.2014.12.029 ★ESSENTIAL READING
- Boyer TD, Sanyal AJ, Wong F, et al. Terlipressin plus albumin is more effective than albumin alone in improving renal function in patients with cirrhosis and hepatorenal syndrome type 1. *Gastroenterology*. 2016;50(7):1579-1589.e2. doi:10.1053/j.gastro.2016.02.026
- China L, Freemantle N, Forrest E, et al. A randomized trial of albumin infusions in hospitalized patients with cirrhosis. *New Engl J Med*. 2021;384(9):808-817. doi:10.1056/NEJMoa2022166 ★ESSENTIAL READING
- Follo A, Llovet JM, Navasa M, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. *Hepatology*. 1994;20:1495-1501. doi:10.1002/hep.1840200619
- El-Desoki ME, Abdelaziz DH, Abd-Elsalam S, Mansour NO. Norepinephrine is more effective than midodrine/octreotide in patients with hepatorenal syndrome-acute kidney injury: a randomized controlled trial. *Front Pharmacol*. 2021;12:675948. doi:10.3389/fphar.2021.675948

- Nassar-Junior AP, Queiroz-Farias A, Carneiro-D'Albuquerque LA, et al. Terlipressin versus norepinephrine in the treatment of hepatorenal syndrome: a systematic review and meta-analysis. *PLoS One*. 2014;9:e107466. doi:10.1371/journal.pone.0107466
- Regner KR, Kanduri SR, Velez JCQ. Management of AKI in patients with cirrhosis. *Curr Treat Options Gastroenterol*. 2022;20:295-316. doi:10.1007/s11938-022-00398-7
- Velez JCQ, Nietert PJ. Therapeutic response to vasoconstrictors in hepatorenal syndrome parallels increase in mean arterial pressure: a pooled analysis of clinical trials. *Am J Kidney Dis*. 2011;58(6):928-938. doi:10.1053/j.ajkd.2011.07.017 ★ESSENTIAL READING
- Velez JCQ, Therapondos G, Juncos LA. Reappraising the spectrum of AKI and hepatorenal syndrome in patients with cirrhosis. *Nat Rev Nephrol*. 2020;16(3):137-155. doi:10.1038/s41581-019-0218-4 ★ESSENTIAL READING
- Wong F, Pappas SC, Curry MP, et al. Terlipressin plus albumin for the treatment of type 1 hepatorenal syndrome. *New Engl J Med*. 2021;384(9):818-828. doi:10.1056/NEJMoa2008290 ★ESSENTIAL READING

Case 3: *A 40-year-old man with history of decompensated cirrhosis presents with hematemesis. He has history of portal hypertension and variceal bleeding. His current medications are nadolol and norfloxacin. His blood pressure is 85/45 mm Hg, heart rate is 110/min, and urine output is 15 mL/hour. The physical examination reveals jaundice, yellowish skin discoloration, spider angioma, hepatomegaly, and ascites. The laboratory studies reveal hemoglobin, 6.6 g/dL; serum sodium, 128 mEq/L; potassium, 5.4 mEq/L; serum creatinine, 3.0 mg/dL (baseline of 0.9 mg/dL); SUN, 85 mg/dL; and serum bilirubin, 10.5 mg/dL. Urinalysis reveals no blood or protein. Urine sediment microscopy reveals muddy brown granular casts and leucine crystals. His urine sodium is 20 mEq/L, and urine creatinine is 80 mEq/L.*

Question 3: What is the most likely etiology of AKI?

(a) Acute interstitial nephritis
(b) Bile cast nephropathy
(c) Hepatorenal syndrome
(d) Ischemic acute tubular injury
(e) Prerenal azotemia

For the answer to the question, see the following text.

The patient is most likely developing hemorrhagic shock secondary to gastrointestinal bleeding from esophageal varices, leading to ischemic ATI; so the correct answer is (d). The history, hemodynamic instability, and severe acute anemia are strong indicators of the likely etiology of AKI. The presence of muddy brown granular casts in the urine sediment strongly points toward ATI and eliminates the possibility of HRS-1 as a primary etiology. FENa 0.58% does not exclude ATI in this context.

The patient is taking norfloxacin for SBP prophylaxis. Fluoroquinolones can cause acute interstitial nephritis (AIN), but the absence of fever, rash, and leukocyturia points against AIN. In addition, fluoroquinolones can cause crystalline tubulopathy. However, only leucine crystals were found by urine microscopy, a common finding in liver disease that does not reflect any specific type of kidney injury. Bile cast nephropathy is rarely seen when the serum bilirubin is <15 mg/dL.

In hemorrhagic shock, volume resuscitation with blood products and identification and ligation/cauterization of bleeding blood vessels should be done promptly. However, if ischemic ATI is already established, those measures are intended to prevent further insult rather than revert it. Ischemic ATI can also be encountered in patients with cirrhosis with septic shock from serious infections such as SBP. In addition, other commonly prescribed antibiotics, such as vancomycin can cause toxic ATI.

Case 4: *A 60-year-old man is admitted for progressive weight gain and dyspnea. He has advanced cirrhosis and refractory ascites requiring frequent paracentesis. His current medications are aspirin, omeprazole, and spironolactone. His blood pressure is 115/55 mm Hg and heart rate is 90/min. The physical examination reveals yellowish skin discoloration, spider angiomas, dullness to percussion at the right lower lung field, tense ascites, and 3+ pitting edema to the hips. The laboratory studies reveal hemoglobin, 9.6 g/dL; serum sodium, 128 mEq/L; potassium, 4.5 mEq/L; serum creatinine, 3.2 mg/dL (baseline of 1.2 mg/dL); SUN, 60 mg/dL; and serum bilirubin 2.5 mg/dL. The urinalysis shows no blood or protein. Urine microscopy reveals a bland sediment. His urine sodium is 15 mEq/L, and urine creatinine is 80 mEq/L. An echocardiogram reveals left ventricular ejection fraction 60%, estimated pulmonary artery systolic pressure 50 mm Hg, and central venous pressure of 15 mm Hg. His bladder pressure is estimated at 27 mm Hg.*

Question 4: Which of the following mechanisms most likely plays a key role in the pathogenesis of AKI in this patient?

(a) Decreased cardiac contractility
(b) Extrinsic compression of the kidneys
(c) Ischemic tubular insult
(d) Hypovolemia
(e) Renal vein congestion

For the answer to the question, see the following text.

Tense ascites in patients with decompensated cirrhosis and portal hypertension has been recognized as a potential cause of intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS). Increased abdominal pressure translates into elevated renal vein pressure, renal venous congestion, and impaired renal perfusion; so the correct answer is (e).

Additionally, IAH reduces inferior vena cava venous return and reduces preload and thereby cardiac output. IAH also increases intrathoracic pressure and reduces right ventricular contractility, perpetuating reduced right ventricular and cardiac output, leading to decreased renal

perfusion. In such cases, large volume paracentesis (LVP) has been associated with short-term improvement in kidney function. Although LVP has been traditionally listed as an event that can precipitate HRS-1, the evidence supporting that contention is lacking. Conversely, a recent report showed that improvement in kidney function rather than AKI is the kidney-related consequence more likely to occur within 48 hours after LVP.

In addition, the prevalence of pulmonary hypertension, known as portopulmonary hypertension (PoPHTN), is increased in cirrhosis. PoPHTN can precipitate right-sided heart failure, increase renal venous congestion, and thus precipitate AKI or worsen its course. In this case, it is conceivable that PoPHTN (based on echocardiography) exacerbated underlying portal hypertension-induced ascites and precipitated ACS and renal congestion.

Advanced cirrhosis can be associated with electrical and mechanical alterations in cardiac function characterized by progressive fall in cardiac output and known as cirrhotic cardiomyopathy, a condition that can limit renal perfusion and aggravate hypervolemia and renal congestion. Moreover, alcohol-dependance is associated with dilated cardiomyopathy. Therefore, individuals with hemodynamic or cardiac alterations associated with hypervolemia and renal venous congestion may not benefit from albumin administration and can be vulnerable to the detrimental effects of volume expansion. Decongestion must be attempted in this scenario with LVP and/or diuretics. Importantly, ACS and PoPHTN may coexist with HRS-1. Thus, diuretic therapy may be ineffective unless hemodynamics are improved by increasing the MAP with a vasoconstrictor, thus enabling effective use of diuretics.

Additional Readings

- Molitoris BA. Low-flow acute kidney injury the pathophysiology of prerenal azotemia, abdominal compartment syndrome, and obstructive uropathy. *Clin J Am Soc Nephrol*. 2022;17:1039-1049. doi:10.2215/CJN.15341121
- Pereira R, Buglevski M, Perdigoto R, et al. Intra-abdominal hypertension and abdominal compartment syndrome in the critically ill liver cirrhotic patient—prevalence and clinical outcomes. A multicentric retrospective cohort study in intensive care. *PLoS One*. 2021;16(5):e0251498. doi:10.1371/journal.pone.0251498
- Seethapathy H, Sharma S, Zhao S, et al. Acute kidney injury following paracentesis among inpatients with cirrhosis. *Kidney Int Rep*. 2020;5(8):1305-1308. doi:10.1016/j.ekir.2020.05.014 ★ESSENTIAL READING
- Umgelter A, Reindl W, Franzen M, Lenhardt C, Huber H, Schmid RM. Renal resistive index and renal function before and after paracentesis in patients with hepatorenal syndrome and tense ascites. *Intensive Care Med*. 2009;35(1):152-156. doi:10.1007/s00134-008-1253-y ★ESSENTIAL READING
- Velez JCQ, Petkovic B, Karakala N, Huggins JT. Point-of-care echocardiography unveils misclassification of acute kidney injury as hepatorenal syndrome. *Am J Nephrol*. 2019;50(3):204-211. doi:10.1159/000501299 ★ESSENTIAL READING
- Wiese S, Hove JD, Bendtsen F, Moller S. Cirrhotic cardiomyopathy: pathogenesis and clinical relevance. *Nat Rev Gastroenterol Hepatol*. 2014;11:177-186. doi:10.1038/nrgastro.2013.210
- Zardi EM, Zardi DM, Giorgi C, Chin D, Dobrina A. Portopulmonary hypertension and hepatorenal syndrome. Two faces of the same coin. *Eur J Intern Med*. 2017;43:22-27. doi:10.1016/j.ejim.2017.05.028

Acute Kidney Injury in Acute Cholestasis

Case 5: *A 55-year-old man with recently diagnosed pancreatic cancer is admitted with new-onset jaundice and abdominal pain. His blood pressure is 138/79 mm Hg, and heart rate is 75/min. The physical examination reveals jaundice and diffuse abdominal tenderness. Laboratory data reveal a serum bilirubin of 44.2 mg/dL; hemoglobin, 8.6 g/dL; serum sodium, 130 mEq/L; potassium, 5.0 mEq/L; serum creatinine, 4.5 mg/dL (baseline of 1.1 mg/dL); and SUN, 70 mg/dL. The urinalysis shows 2+ bilirubin, trace protein, and no blood. Urine microscopy reveals abundant renal tubular epithelial cell casts and scattered granular casts. His urine sodium is 35 mEq/L and urine creatinine is 70 mEq/L. Kidney ultrasound shows no hydronephrosis.*

Question 5: Which of the following is the most likely cause of AKI?

(a) Hepatorenal syndrome
(b) Ischemic acute tubular injury
(c) Obstructive uropathy
(d) Prerenal AKI
(e) Toxic acute tubular injury

For the answer to the question, see the following text.

Cholemic tubulopathy, also termed cholemic nephrosis, obstructive jaundice-induced AKI, or bile cast nephropathy, refers to a condition characterized by impaired kidney function in the setting of cholestasis. This form of toxic ATI was originally described in individuals with obstructive jaundice, such as those with cholangiocarcinoma or pancreatic masses obstructing the biliary tree. Reports of drug-induced, infectious, and alcohol-induced acute cholestatic hepatitis causing cholemic tubulopathy have subsequently emerged.

The mean serum bilirubin in a cohort of patients with biopsy-proven cholemic tubulopathy was 27 (± 12) mg/dL. Experimental evidence suggests that bile acids, rather than bilirubin, are potentially toxic to the renal tubules. In addition, bile acids may lead to renal hemodynamic derangements and cardiac output compromise, causing renal hypoperfusion. The presence of intratubular bile casts in

kidney biopsy specimens and autopsies in affected patients further supports the injurious role of bile acids. However, within the context of cirrhosis, it remains unclear whether the presence of intratubular bile casts merely reflects reduced GFR and tubular stasis characteristic of HRS-1 or signifies a potential role in inducing tubular injury.

Notably, identification of renal tubular epithelial cell casts on urine microscopy has been described in patients with severe hyperbilirubinemia and suggests cholemic tubular injury. However, those casts can be found in the absence of AKI, so their clinical significance remains unclear. Interestingly, greater severity of hyperbilirubinemia has been associated with attenuated response to vasoconstrictors in HRS-1, suggesting that parenchymal mechanisms might complicate those cases. Therefore, although it remains unclear whether cholemic tubulopathy could contribute to AKI in patients with decompensated cirrhosis, it could potentially play a contributary role in some cases, particularly in those with severe hyperbilirubinemia.

In this case, the patient does not have cirrhosis but presented with obstructive jaundice with extreme hyperbilirubinemia. Findings in the urinary sediment and a FENa 1.7% both suggest a tubular insult. Therefore, cholemic tubulopathy is the most likely cause of AKI in this case, and the correct answer is (e). Prompt resolution of biliary obstruction can improve the AKI, depending on the duration and severity of the AKI.

Additional Readings

- Brasen JH, Mederacke YS, Schmitz J, et al. Cholemic nephropathy causes acute kidney injury and is accompanied by loss of aquaporin 2 in collecting ducts. *Hepatology*. 2019;69:2107-219. doi:10.1002/hep.30499 ★ESSENTIAL READING
- Fickert P, Krones E, Pollheimer MJ, et al. Bile acids trigger cholemic nephropathy in common bile-duct–ligated mice. *Hepatology*. 2013;58:2056-2069. doi:10.1002/hep.26599
- Foshat M, Ruff HM, Fischer WG, et al. Bile cast nephropathy in cirrhotic patients: effects of chronic hyperbilirubinemia. *Am J Clin Pathol*. 2017;147:525-535. doi:10.1093/ajcp/aqx030
- Van Slambrouck CM, Salem F, Mehhan SM, Chang A. Bile cast nephropathy is a common pathologic finding for kidney injury associated with severe liver dysfunction. *Kidney Int*. 2013;84:192-197. doi:10.1038/ki.2013.78
- Wait RB, Kahng KU. Renal failure complicating obstructive jaundice. *Am J Surg*. 1989;157(2):256-263. doi:10.1016/0002-9610(8990540-0) ★ESSENTIAL READING

Acute Kidney Injury in Acute Liver Failure

Case 6: *A 29-year-old woman is brought to the emergency department with altered mental status. She was last seen completely awake 36 hours ago. She was recently evaluated by her psychiatrist for depression. On examination, she was lethargic, oriented only to person, and reported abdominal pain and three episodes of vomiting. Her medical history was only pertinent for depression. Her temperature was 37.5°C (99.5°F), pulse was 88/min, respirations were 20/min, and blood pressure was 105/53 mm Hg. The physical examination showed jaundice. Palpation of the abdomen disclosed mild epigastric tenderness. The laboratory studies revealed hematocrit, 32%; leukocyte count, 9,020/mm³; prothrombin time, 24 seconds (international normalized ratio [INR], 2.7); serum sodium, 140 mEq/L; potassium, 3.7 mEq/L; SUN, 34 mg/dL; creatinine, 3.8 mg/dL (baseline of 0.9 mg/dL); total bilirubin, 8.3 mg/dL; aspartate aminotransferase (AST), 3,913 IU/L; and alanine aminotransferase (ALT), 1,795 IU/L. The urinalysis showed 1+ protein; her red blood cell count (RBC) is 1-4/high-power field (HPF); and white blood cell count (WBC) is 0-2/HPF. Her urine sodium is 25 mEq/L, and urine creatinine is 50 mg/dL. Urine sediment microscopy reveals dark granular and waxy casts.*

Question 6: What is the likely cause of AKI here?

(a) Acetaminophen-induced tubular injury
(b) Cholemic tubulopathy
(c) Hepatorenal syndrome
(d) Ischemic acute tubular injury
(e) Prerenal azotemia

For the answer to the question, see the following text.

AKI is encountered in about 2%-10% of individuals with ALF due to acetaminophen intoxication, answer (a). The rise in serum creatinine is typically seen 1-5 days after the ingestion. A retrospective cohort study including 2,914 patients with acetaminophen intoxication reported that the overall risk of developing AKI was 2.4-fold higher than in an age/sex-matched control group. Massive ingestion of acetaminophen leads to accumulation of a highly reactive intermediate metabolite N-acetyl-p-benzoquinone imine (NAPQI). Although intracellular glutathione assists in detoxifying the toxic compounds, excessive production of the toxic intermediate molecules can deplete intrahepatic glutathione stores and increase the levels of NAPQI. Excessive levels of NAPQI are toxic to renal tubular cells and can precipitate AKI. Management is typically supportive. Intravenous administration of N-acetyl cysteine (NAC) is recommended until the INR is <1.5, although there is no clear evidence demonstrating that NAC promotes renal recovery.

Acute alcoholic hepatitis can be associated with concomitant AKI. In a retrospective study evaluating patients with ALF due to biopsy-proven alcoholic hepatitis, 28% developed AKI during the hospitalization. Ninety-day mortality was higher among patients with AKI (65%) as compared with those without AKI (7%). The presence of systemic inflammatory response syndrome (SIRS), elevated serum bilirubin, and elevated INR at admission were predictors of AKI. In the context of SIRS, ischemic ATI may

represent the predominant pathogenic process for most cases of AKI from acute alcoholic hepatitis. In addition, reports of cholemic tubulopathy have emerged and may explain a fraction of the AKI cases, particularly for those with severe hyperbilirubinemia.

Besides supportive care and abstinence from alcohol, some evidence suggests a therapeutic role of pentoxifylline. In cases of acute alcoholic hepatitis superimposed to cirrhosis, coexisting hepatorenal physiology may be present and add complexity for diagnosis and management.

Additional Readings

- Altamirano J, Fagundes C, Dominguez M, et al. Acute kidney injury is an early predictor of mortality for patients with alcoholic hepatitis. *Clin Gastroenterol Hepatol*. 2012;10(1):65-71.e3. doi:10.1016/j.cgh.2011.09.011
- Chen YG, Lin CL, Dai MS, et al. Risk of acute kidney injury and long-term outcome in patients with acetaminophen intoxication. *Medicine (Baltimore)*. 2015;94:e2040. doi:10.1097/MD.0000000000002040 ★ESSENTIAL READING
- Ghannoum M, Kazin S, Grunbaum AM, Villeneuve E, Gosselin S. Massive acetaminophen overdose: effect of hemodialysis on acetaminophen and acetylcysteine kinetics. *Clin Toxicol (Phila)*. 2016;54:519-522. doi:10.1080/15563650.2016.1175006

Dialysis in Advanced Cirrhosis

Patients with decompensated cirrhosis and AKI may rapidly deteriorate to need KRT. Continuous kidney replacement therapy (CKRT) is the modality of choice for hemodynamically unstable patients, and intermittent hemodialysis can be attempted in more stable patients. Intraoperative CKRT can be performed during liver transplantation to manage perioperative volume overload and acid-base and electrolyte abnormalities.

The decision to initiate KRT in this context is complex and depends on multiple factors including eligibility for liver transplant, the patients' goals of care, and potential risks and benefits of initiating KRT. The mortality associated with HRS-1 requiring KRT is comparable to that of ATI requiring KRT, so the etiology of AKI should not be a decisive factor in offering KRT. When considering KRT in patients with cirrhosis, the potential complications are significant. Thrombocytopenia and coagulopathy may increase the risk of bleeding, especially during placement of central venous catheters for hemodialysis. Because the use of systemic anticoagulation is contraindicated with ongoing gastrointestinal bleeding and because impaired hepatic citrate metabolism limits the use of regional citrate anticoagulation, dialysis filter clotting may reduce the effectiveness of KRT. For patients who are eligible for liver transplantation, KRT should be offered until kidney function recovers. For patients who are being evaluated for liver transplantation and their disposition is unclear, palliative care consultation is recommended to clarify the goals of care. Short-term nonrenal prognosis should be assessed. When feasible, a time-limited trial of KRT can be considered. For patients who are ineligible for liver transplantation, a multidisciplinary approach that includes patients and their families is necessary, weighing the potential risks and benefits. With no signs of AKI reversibility and multiorgan failure in an intensive care setting, offering KRT could be deemed futile.

Additional Readings

- Allegretti AS, Vela-Parada X, Eneanya ND, et al. Prognosis of patients with cirrhosis and AKI who initiate RRT. *Clin J Am Soc Nephrol*. 2018;13(1):16-25. doi:10.2215/CJN.03610417 ★ESSENTIAL READING
- Velez JCQ. Patients with hepatorenal syndrome should be dialyzed? Pro. *Kidney360*. 2020;2(3):406-409. doi:10.34067/KID.0006952020
- Wadei H. Patients with hepatorenal syndrome should be dialyzed? Con. *Kidney360*. 2020;2(3):410-412. doi:10.34067/KID.0006872020

Liver Transplantation and Combined Liver and Kidney Transplantation

Liver transplantation is the definitive treatment for HRS-1, with an estimated 65%-75% of patients achieving recovery from AKI after liver transplantation. Resolution of AKI due to HRS-1 is expected shortly after liver transplantation. However, the probability of renal recovery diminishes for those who require KRT before transplantation. Specifically, AKI requiring KRT for longer than 4-6 weeks is associated with a lower probability of renal recovery. Therefore, those patients should be considered for eligibility for a combined liver and kidney transplantation. Advanced CKD is also an indication for combined liver and kidney transplantation (Box 2). Notably, the complex surgical procedure required for liver transplantation is associated with inevitable blood losses and intraoperative hemodynamic instability. Thus, patients with AKI at the time of transplantation are vulnerable to additional insults from ischemic ATI. As a result, the length of KRT required after liver transplantation may depend on preoperative and intraoperative factors. Furthermore, lower postoperative MAP (below 90 mm Hg) has been associated with approximately double the risk of AKI after liver transplantation. Nonetheless, whether pharmacologically mediated increase in MAP may reduce postoperative AKI is not known and would require further study.

Additional Readings

- Kwon HM, Moon YJ, Jung KW, et al. Low mean arterial blood pressure is independently associated with postoperative acute kidney injury after living donor liver transplantation: a propensity score weighing analysis. *Ann Transplant*. 2018;23:236-245. doi:10.12659/AOT.908329

Box 2. Indications for SLK Transplantation (OPTN 2017 Criteria) Specific to Degree of Kidney Dysfunction

Sustained Acute Kidney Injury
- KRT for at least > 6 weeks
- GFR < 25 mL/min > 6 weeks, documented every 7 days in medical record
- Combination of above 2 criteria and meeting 6-week duration

Chronic Kidney Disease (GFR < 60 mL/min for > 90 days)
At least 1 of the following:
- Regularly administered dialysis as an ESKD in a hospital based or home setting
- GFR ≤ 30 mL/min at the time of registration on kidney waiting list
- GFR ≤ 30 mL/min on a date after registration on the kidney waiting list

Metabolic Disease
At least 1 of the following diagnoses:
- Hyperoxaluria
- Atypical hemolytic uremic syndrome from mutations in factor H or factor I
- Familial nonneuropathic systemic amyloidosis
- Methylmalonic aciduria

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; ESKD, end-stage kidney disease; GFR, glomerular filtration rate; KRT, kidney replacement therapy; OPTN, Organ Procurement and Transplantation Network; SLK, simultaneous liver kidney.

➢ Sharma P, Goodrich NA, Zhang M, Guidinger MK, Schaubel DE, Merion RM. Short-term pretransplant renal replacement therapy and renal nonrecovery after liver transplantation alone. *Clin J Am Soc Nephrol*. 2013;8:1135-1142. doi:10.2215/CJN.09600912
★ESSENTIAL READING
➢ Wong F, Leung W, Al Beshir M, Marquez M, Renner EL. Outcomes of patients with cirrhosis a hepatorenal syndrome type 1 treated with liver transplantation. *Liver Transplant Soc*. 2015;21:300-307. doi:10.1002/lt.24049

Subacute and Chronic Kidney Disease in Cirrhosis

Glomerular Disease in Cirrhosis

Case 7: *A 54-year-old woman with alcoholic cirrhosis is evaluated in the clinic due to worsening kidney function. She reports intermittent dark urine over the last several months but otherwise no new symptoms. She has a history of hepatitis C virus (HCV) infection (treated with sofosbuvir/velpatasvir). Her current medications are spironolactone and norfloxacin. Her blood pressure is 165/85 mm Hg and heart rate is 80/min. Physical examination reveals ascites and 1+ lower extremity edema. The laboratory studies show hemoglobin, 10.4 g/dL; serum creatinine, 1.6 mg/dL (9 months ago, 1.2 mg/dL); and serum albumin, 3.0 g/dL. The urinalysis reveals 3+ blood, 2+ protein, RBC > 100/HPF, and WBC 5-10/HPF. Her urine protein-to-creatinine measure is 2.7 g/g, and the urine sediment microscopy reveals acanthocytes and red blood cell casts. She has normal serum complements and rheumatoid factor. The laboratory results for her cryoglobulin levels and HCV RNA levels are pending.*

Question 7: What histopathological pattern would be expected on kidney biopsy?
(a) Focal segmental glomerulosclerosis
(b) IgA nephropathy
(c) Membranoproliferative glomerulonephritis
(d) Membranous nephropathy
(e) Normal renal parenchyma

For the answer to the question, see the following text.

Individuals with cirrhosis are at risk for certain forms of glomerular disease. Cirrhosis is the most common cause of IgA nephropathy secondary to a systemic condition. The clinical spectrum of IgA nephropathy in cirrhosis is quite variable. Patients can present with rather benign and nonprogressive, subtle abnormalities including hematuria, low-grade proteinuria, and mild reduction in eGFR. Some only exhibit mesangial IgA deposits at autopsy without any premortem clinical manifestations. On the other hand, others present with more substantial kidney disease including overt proteinuria, progressive CKD, or AKI and exhibit outcomes similar to those of primary IgA nephropathy. A minor proportion of patients can develop a more aggressive course with features of rapidly progressive glomerulonephritis (RPGN). It is often difficult to ascertain if the cases of RPGN are linked to underlying cirrhosis or coincidental presentation of primary IgA nephropathy of the Henoch-Schoenlein purpura spectrum. However, some histopathological features are more likely to be present in cirrhosis-associated IgA nephropathy, and those include membranoproliferative features (endocapillary proliferation, double contour) and segmental glomerulosclerosis.

Historically, alcoholic cirrhosis was felt to be the most common type of cirrhosis associated with secondary IgA nephropathy. However, those observations might have been biased by the higher prevalence of alcoholic cirrhosis relative to other causes. In the carbon tetrachloride rodent model of cirrhosis, mesangial deposition of IgA has been reported (ie, without alcohol-mediated injury). Furthermore, 1 study reported no difference in IgA glomerulonephritis between hepatitis B virus (HBV) or alcoholic cirrhosis. Therefore, this entity should be considered in patients with cirrhosis of any etiology.

Patients with viral hepatitis-associated cirrhosis may present with glomerulonephritis. Both HCV- and HBV-associated cirrhosis can be accompanied by a glomerular lesion of a membranoproliferative pattern of injury, often with cryoglobulinemia. In addition to varying degrees of proteinuria, hematuria, and "active" urinary sediment (dysmorphic erythrocytes, cellular casts),

patients may present with various degrees of kidney dysfunction ranging from mild insidious CKD to an aggressive RPGN picture. C4 hypocomplementemia is often found in cryoglobulinemic glomerulonephritis. Antiviral therapy is the cornerstone of management in this setting. However, aggressive cases may warrant immunosuppression.

In this case, the elevated arterial blood pressure and urinary sediment microscopy findings are consistent with glomerulonephritis. The most likely diagnosis is IgA nephropathy secondary to cirrhosis, answer (b). Despite the history of HCV infection, glomerulonephritis associated with HCV has become less frequent with the arrival of direct-acting antivirals. In addition, normal C4 and negative rheumatoid factor are not characteristic of HCV-associated glomerulonephritis.

Additional Readings

- Gupta A, Quigg RJ. Glomerular diseases associated with hepatitis B and C. *Adv Chronic Kidney Dis*. 2015;22(5):343-351. doi:10.1053/j.ackd.2015.06.003 ★ESSENTIAL READING
- Obrisca B, Stefan G, Gherghiceanu M, et al. Associated or secondary IgA nephropathy? An outcome analysis. *PloS One*. 2019;14(8):e0221014. doi:10.1371/journal.pone.0221014
- Pouria S, Feehally J. Glomerular IgA deposition in liver disease. *Nephrol Dial Transplant*. 1999;14:2279-2282. doi:10.1093/ndt/14.10.2279 ★ESSENTIAL READING

Hepatorenal Syndrome Type 2 (HRS-2)

HRS-2 refers to a subacute or chronic form of renal impairment in patients with cirrhosis that is presumed to also originate from the hemodynamic derangement caused by portal hypertension that leads to reduction in renal perfusion in HRS-1. Patients may develop HRS-2 when the systemic and renal maladaptive responses to portal hypertension are less pronounced and/or less rapid. Most patients with HRS-2 have refractory ascites. To provide a more precise definition, HRS-2 is now divided into HRS-CKD and HRS-AKD. The latter, HRS-AKD, refers to patients who develop AKI and remain with a >50% rise in serum creatinine from the pre-AKI value for up to 90 days (KDIGO). HRS-CKD applies to those with cirrhosis and refractory ascites with an eGFR of <60 mL/min/1.73 m^2 for >90 days in which an alternative etiology cannot be identified.

When cases of HRS-CKD were preceded by an event of HRS-1 (HRS-AKI) and resulting HRS-AKD, it is assumed that the renal impairment comes from the same pathogenesis that progressed to tubular scarring. Outside that context, the diagnosis of HRS-CKD is difficult to ascertain and distinguish from other causes of CKD in patients with cirrhosis. Illustrating this aspect, 1 study identified only 1 of 643 patients with cirrhosis (0.15%) admitted to a hospital as having HRS-CKD. By contrast, a study found that 19% of patients referred for TIPS met the definition of CKD. Importantly, estimation of the prevalence of HRS-CKD is hindered by the limitations of serum creatinine in cirrhosis.

Additional Readings

- Choi YJ, Kim JH, Koo JK, et al. Prevalence of renal dysfunction in patients with cirrhosis according to ADQI-ICA working party proposal. *Clin Mol Hepatol*. 2014;20:185-191. doi:10.3350/cmh.2014.20.2.185
- Ponzo P, Campion C, Rizzo M, et al. Transjugular intrahepatic porto-systemic shunt in cirrhotic patients with hepatorenal syndrome—chronic kidney disease: impact on renal function. *Dig Liv Dis*. 2022;54:1101-1108. doi:10.1016/j.dld.2021.09.008

Chronic Kidney Disease Associated With MAFLD

With the arrival of curative treatment for HCV and the obesity pandemic over the last few decades, MAFLD, also known as nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), is rapidly becoming the second most common cause of cirrhosis after alcoholic liver disease. MAFLD has been reported to increase the risk of development of CKD by 22%. Consequently, the overall prevalence of CKD in patients with cirrhosis is gradually increasing. Furthermore, the risk of CKD increases as the severity of MAFLD increases. In a cross-sectional study evaluating patients with MAFLD, the prevalence of CKD in patients with NASH was 21% compared with 6% in patients with MAFLD but not NASH. The mechanism of CKD in patients with MAFLD is not completely understood. It is plausible that MAFLD and CKD share common metabolic risk factors such as insulin resistance, the metabolic syndrome, diabetes, hypertension, obesity, oxidative stress, and inflammation.

Additional Readings

- Deng Y, Zhao Q, Gong R. Association between metabolic associated fatty liver disease and chronic kidney disease: a cross-sectional study from NHANES 2017-2018. *Diabetes Metab Syndr Obes*. 2021;14:1751-1761. doi:10.2147/DMSO.S292926
- Sinn DH, Kang D, Jang HR, et al. Development of chronic kidney disease in patients with non-alcoholic fatty liver disease: a cohort study. *J Hepatol*. 2017;67:1274-1280. doi:10.1016/j.jhep.2017.08.024 ★ESSENTIAL READING

Chronic Kidney Disease After Liver Transplantation

Ischemic ATI from intraoperative blood loss and hemodynamic instability is common immediately after liver transplantation. Such insults are often reversible, but some

individuals develop some degree of tubular scarring and residual CKD. Pre–liver transplantation AKI or CKD that does not follow with simultaneous kidney transplantation may also result in posttransplantation CKD. Patients with prolonged pre–liver transplantation AKI-KRT from any cause, including HRS-1, are at greater risk of developing CKD and qualify for kidney transplantation after liver transplantation.

Recipients of liver transplantation are chronically exposed to calcineurin inhibitors (CNI). These agents are known to induce a progressive scarring of the renal parenchyma characterized by tubulointerstitial fibrosis and subsequent glomerulosclerosis, termed CNI nephrotoxicity. Cohort studies demonstrate the risk of CKD associated with CNI after liver transplantation. It is recommended to carefully monitor kidney function in these patients. Decisions regarding discontinuation of CNI and/or transition to other immunosuppressants (eg, mycophenolate, sirolimus) must be made with caution and consideration of the overall risk of liver rejection and expected benefit of amelioration of CKD.

Additional Readings

➢ Sharma P, Sui Z, Zhang M, et al. Renal outcomes after simultaneous liver-kidney transplantation: results from the US multicenter simultaneous liver-kidney transplantation consortium. *Liver Transpl*. 2021;27:1144-1153. doi:10.1002/lt.26032 ★ESSENTIAL READING

Acid-Base and Electrolyte Disorders in Liver Disease

Hyponatremia

Individuals with cirrhosis and portal hypertension are at risk of developing hyponatremia (Box 3). Exposure to laxatives and diuretics makes them vulnerable to hypovolemic hyponatremia. In addition, the state of peripheral arterial vasodilation, poor EABV, and activation of the RAS and SNS is associated with adaptive release of arginine vasopressin (AVP) in response to diminished stretch in baroreceptors. An increase in AVP concentration leads to activation of AVP V2 receptors in the collecting duct, insertion of aquaporin 2 channels in the apical membrane, and water reabsorption. Concomitant activation of angiotensin II independently promotes proximal tubular water and sodium reabsorption. Consequently, patients with cirrhosis develop a state of high AVP characterized by hypervolemic hyponatremia. In those cases, the urine sodium concentration is typically low (<20 mEq/L), and urine osmolality tends to be elevated (>200 mOsm/kg). Water restriction, potassium supplementation, and restoration of EABV with albumin are appropriate therapeutic measures. An oral AVP V2 receptor antagonist tolvaptan can be used in refractory cases, particularly in anticipation of liver transplantation, a setting in which intraoperative hyponatremia (<120-125 mEq/L) may be associated with a high risk of rapid intraoperative correction of hyponatremia and osmotic demyelinating syndrome. In the absence of imminent liver transplantation, the risk for hepatotoxicity with tolvaptan should be considered.

Box 3. Main Acid-Base and Electrolyte Disturbances in Patients With Hepatobiliary Disease

Cirrhosis

1. Respiratory alkalosis
   (a) Progesterone-mediated central ventilatory drive stimuli
   (b) Dyspnea (eg, hydrothorax, portopulmonary hypertension, hepatopulmonary syndrome, ascites)
2. Respiratory acidosis (eg, hydrothorax)
3. Metabolic acidosis
   (a) Spironolactone
   (b) Cholestyramine in cholestatic liver disease
4. Hypokalemia
   (a) Gastrointestinal from laxatives
   (b) Renal from loop diuretics
5. Hyperkalemia
   (a) Spironolactone
6. Hyponatremia
   (a) Maladaptive high arginine vasopressin state
   (b) Depletional

Liver Transplantation

1. Hyperkalemia, type 4 renal tubular acidosis (calcineurin inhibitors)

Dyskalemia

Medications used to treat the complications of cirrhosis may alter the serum potassium (Box 3). Use of lactulose for prophylaxis of hepatic encephalopathy and as well as loop diuretics for the management of ascites increases the risk of chronic gastrointestinal and urinary losses that may exceed their oral intake of potassium, resulting in hypokalemia. Prevention of hypokalemia in the context of cirrhosis is of utmost importance given the increased risk for hepatic encephalopathy associated with hypokalemia because of increased ammoniagenesis. When spironolactone is added, hypokalemia is less common because of blockade of mineralocorticoid receptor (MR)-mediated potassium secretion in the collecting duct, whereas hyperkalemia can rarely ensue. In cholestatic states, bile acids may inhibit 11β-hydroxysteroid dehydrogenase, facilitate MR activation by cortisol, and lead to kaliuresis and hypokalemia.

CNI, commonly used after liver transplantation, impair urinary potassium excretion by activating sodium chloride cotransporters in the distal convoluted tubule, thereby reducing distal delivery of sodium to the collecting duct, causing hyperkalemia. Loop and/or thiazide diuretics can be used as treatment.

Low Serum Bicarbonate

Individuals with cirrhosis commonly develop a *respiratory alkalosis*. Hepatic metabolism of progesterone and estradiol is impaired in cirrhosis, and progesterone activates the central

ventilatory drive via GABA-mediated neurotransmission. Individuals may develop a *metabolic acidosis* in the context of AKI, lactulose use, or from spironolactone which can impair distal acidification by opposing aldosterone-mediated activation of the hydrogen ATPase in α-intercalated cells. In addition, patients with cholestatic liver disease treated with the bile sequestrant cholestyramine can develop non–anion gap metabolic acidosis caused by exchange of chloride and bicarbonate by the resin. Therefore, the serum pH should be measured in these scenarios.

Additional Readings

- Ackerman D, Vogt B, Escher G, et al. Inhibition of 11β-hydroxysteroid dehydrogenase by bile acids in rats with cirrhosis. *Hepatology*. 1999;30(3):623-629. doi:10.1002/hep.510300303
- Henriksen JH, Bendsten F, Moller S. Acid-base disturbance in patients with cirrhosis: relation to hemodynamic dysfunction. *Eur J Gastroenterol Hepatol*. 2015;27:920-927. doi:10.1097/MEG.0000000000000382
- Hoorn EJ, Walsh SB, McCormick JA, et al. The calcineurin inhibitor tacrolimus activates the renal sodium chloride cotransporter to cause hypertension. *Nat Med*. 2011;17(10):1304-1309. doi:10.1038/nm.2497 ★ESSENTIAL READING
- Kanar FB, McQuillan RF. Hyperchloremic metabolic acidosis due to cholestyramine: a case report and literature review. *Case Rep Nephrol*. 2015;2015:309791. doi:10.1155/2015/309791
- Lustik SJ, Chhibber AK, Kolano JW, et al. The hyperventilation of cirrhosis: progesterone and estradiol effects. *Hepatology*. 1997;75(1):55-58. doi:10.1002/hep.510250110
- Rondon-Berrios H, Velez JCQ. Hyponatremia in cirrhosis. *Clin Liver Dis*. 2022;26(2):149-164. doi:10.1016/j.cld.2022.01.001 ★ESSENTIAL READING

Article Information

Authors' Full Names and Academic Degrees: Swetha R. Kanduri, MD, and Juan Carlos Q. Velez, MD.

Authors' Affiliations: Department of Nephrology, Ochsner Health, New Orleans, Louisiana; and Ochsner Clinical School, University of Queensland, Brisbane, Australia.

Address for Correspondence: Juan Carlos Q. Velez, MD, Ochsner Medical Center, 1514 Jefferson Hwy, Clinic Tower, 5th Floor, New Orleans, LA 70121. Email: juancarlos.velez@ochsner.org

Support: Dr Velez was supported by funds provided by the Clinical & Translational Innovation Support Program (CRISP) at Ochsner Health.

Financial Disclosure: Dr Velez has participated in consulting, advisory board, and speaking engagements for Mallinckrodt Pharmaceuticals (maker of terlipressin), was a site investigator of the Mallinckrodt Pharmaceuticals-sponsored CONFIRM trial (terlipressin), has participated in advisory board/consulting for Travere Therapeutics, Bayer Pharmaceuticals, and Calliditas, and has been a member of a speaker bureau for Otsuka Pharmaceuticals. Dr Kanduri declares that she has no relevant financial interests.

Acknowledgements: We thank Serenella A. Velez (https://serenellavelez.wixsite.com/medicalillustrations) for generously contributing illustrations.

Peer Review: Received March 3, 2023 in response to an invitation from the journal. Evaluated by 2 external peer reviewers and a member of the Feature Advisory Board, with direct editorial input from the Feature Editor and a Deputy Editor. Accepted in revised form August 24, 2023.