HRS is a severe complication of cirrhosis. This review will follow the journey of a patient with nonalcoholic steatohepatitis (NASH)-related cirrhosis and HRS from the outpatient setting, to becoming critically ill in the hospital setting, to receiving a LT, to recovery and transitioning back to the outpatient setting.

THE OUTPATIENT SETTING
Ms. Miller is a 65-year-old woman who came to an academic medical transplant center for LT evaluation. Complications of her liver disease include ascites, fluid retention, lower extremity edema, hepatic encephalopathy, grade 2 esophageal varices, and moderate hepatopulmonary syndrome. Her comorbidities are significant for type 2 diabetes mellitus, asthma, and chronic kidney disease (baseline creatinine of 1.3-1.5 mg/dL). She underwent workup for LT, and the selection committee deemed her an acceptable candidate for LT. At that time, her Model for End-Stage Liver Disease With Sodium (MELD-Na) score was 25 (Table 1). Evaluation findings were as follows:

- Magnetic resonance imaging (MRI) abdomen: cirrhosis with portal hypertension; no focal suspicious liver lesions
- Doppler Ultrasound Abdomen: cirrhotic liver morphology with evidence of portal hypertension, including splenomegaly, patent large paraumbilical vein, and moderate ascites.
- Echocardiogram: moderate to severe intrapulmonary shunt, Ejection Fraction: 75%
- Transplant nephrology consultation: MRI abd showed normal kidneys; ultrasound abd showed 10- and 10.4-cm kidneys, which are unremarkable; 24-hour creatinine clearance 31, protein 56 mg – 600 mL; iothalmate clearance was 24. Diagnosis: chronic kidney disease, stage 2-3, baseline creatinine (Cr) 1.53 mg/dL. Suspect patient is clinically dry; question of hepatorenal component. No need for kidney transplant or immediate need for dialysis.

Abbreviations: AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CRRT, continuous renal replacement therapy; CTAB, clear to auscultation bilaterally; GI, gastrointestinal; HEENT, head, eyes, ears, nose, and throat; HR, heart rate; HRS, hepatorenal syndrome; ICU, intensive care unit; INR, international normalized ratio; LT, liver transplant; MAP, mean arterial pressure; MELD-Na, Model for End-Stage Liver Disease With Sodium; MRI, magnetic resonance imaging; Na, sodium; NASH, nonalcoholic steatohepatitis; RBC, red blood cell; RR, respiratory rate; RRR, Regular rate and rhythm; Sat, saturation; TB, total bilirubin; VS, vital signs.
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Ms. Miller was followed closely as an outpatient and was listed for LT at our center. For her ascites/fluid retention, she was placed on a low-sodium diet and prescribed diuretics (furosemide 80 mg daily/spironolactone 200 mg daily). Her last esophagogastroduodenoscopy was 1 month prior, and she was placed on propranolol for known esophageal varices. Intrapulmonary shunt was noted, and her PaO₂ (partial pressure of arterial oxygen) was 63.5 on room air. It was planned to have an arterial blood gases recheck in 4 weeks. She had diabetes, and her insulin regimen was providing optimal control of her blood sugars. Nutrition was consulted, and she was advised of her risk for malnutrition and counseled to follow a high-protein, low-sodium diet.

OUTPATIENT MANAGEMENT: HRS PREVENTION

Prevention of HRS-AKI is important to optimize patient survival. According to the American Association for the Study of Liver Diseases practice guidelines for ascites, diuretics used can be furosemide 40 mg daily and spironolactone 100 mg daily.¹ Dosages can be increased every 3 to 5 days up to a maximum of 160 mg:400 mg.¹ A single morning dose schedule assists with a more simplistic medication regimen.¹ Paracentesis is frequently needed, many times more than once per month. Albumin replacement has been shown to decrease the incidence of AKI in this patient population and is recommended after large-volume paracentesis.² For patients with gastrointestinal (GI) bleed, hepatic encephalopathy, and signs of infection (i.e., spontaneous bacterial peritonitis), hospital admission is recommended and diuretics should be held.³ In addition, diuretics should be held if creatinine is increasing (>2 mg/dL) or hyponatremia is noted (Na < 120 mEq/L).³ Patients should be educated regarding prevention measures, including optimal control of diabetes and hypertension, avoidance of certain medications (including nonsteroidal antiinflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and propranolol), and nutrition counseling (high-protein, low-sodium diet, fluid restriction, renal or diabetic diet, if required).³ Laboratory tests should be obtained on a weekly basis, or more frequently if closer monitoring is required. The patient should have a return visit every 1 to 2 weeks, based on clinical presentation and/or laboratory findings that are concerning.

THE INPATIENT SETTING

Ms. Miller had a brief hospitalization for hepatic encephalopathy approximately 1 month after her earlier outpatient visit. She recovered and was discharged home. She had weekly laboratory tests and was informed by her nurse coordinator that her creatinine concentration had increased from 1.53 mg/dL (baseline) to 3.49 mg/dL. She was instructed to come to the emergency department for further evaluation. On examination, the patient reported fatigue and weakness, which had been progressively getting worse over the past week. She had no appetite and reported many bowel movements in the past 3 days (7-10 stools each day). See Figures 1 and 2 for physical examination.

HRS: UNDERSTANDING TWO TYPES

Our patient had a few findings that are concerning for HRS. First, she had a significant increase in her creatinine concentration from 1.53 to 3.49 mg/dL. At the time of her emergency department visit, she remained on diuretics and propranolol. She had a recent hospitalization for hepatic encephalopathy and was significantly dehydrated from frequent loose stools, ascites, and malnutrition. The classic presentation of HRS consists of three items: hypotension, hyponatremia, and oliguria.⁴ All of these were present for Ms. Miller. Also, she had physical examination findings significant for ascites and severe pitting peripheral edema (see Figs. 1 and 2), and her MELD-Na score had increased to 32.

The International Club of Ascites defined HRS as meeting the following criteria⁴:

1. “Presence of cirrhosis and ascites,
2. Serum creatinine >1.5 mg/dL (or 133 micromoles/L),
3. No improvement of serum creatinine (decrease equal to or less than 1.5 mg/dL) after at least 48 hours of diuretic withdrawal and volume expansion with albumin (recommended dose: 1 g/kg b.w. per day up to a maximum of 100 g of albumin/day),
4. Absence of shock,
5. No current or recent treatment with nephrotoxic drug, and

### TABLE 1. INITIAL LAB FINDINGS AT TIME OF EVALUATION

| Laboratory Test                  | Result                  |
|----------------------------------|-------------------------|
| Na                               | 134 mEq/L               |
| TB                               | 6.6 mg/dL               |
| INR                              | 1.6                     |
| Creatinine                       | 1.53 mg/dL              |
| Alkaline phosphatase/AST/ALT     | 107 (H)/33/20 IU/L, IU/L, IU/L |
6. Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria (>50 RBCs/high power field, and/or abnormal renal ultrasound scanning.”5

Historically, HRS was classified as type 1 and type 2. Type 1 HRS is a quickly progressive acute renal failure that can develop in a patient with cirrhosis and ascites. There is usually a trigger for acute decompensation (such as infection or GI bleeding).6 Creatinine will increase dramatically over a short period (within 2 weeks). It is associated with a poor prognosis.5 Type 2 HRS is renal failure that is gradual and usually associated with refractory ascites.

In recent years, these definitions have evolved, and now HRS-AKI is frequently seen in the literature, replacing the prior type 1 nomenclature. Current definitions are more focused on the change of creatinine in comparison with the patient’s baseline rather than the cause.7 It is believed to develop as a result of decrease in blood flow to the kidneys.7 Fluid resuscitation is attempted, but the renal function does not improve and actually worsens. Patients with HRS-AKI have a higher morbidity and mortality, and health care expenditure is significant.7

**TREATMENT FOR HRS**

In the initial 24 hours of admission, Ms. Miller was hydrated with crystalloids and albumin. Ultrasounds of liver and kidneys showed no new findings; ascites was noted. We were concerned for infection given the dramatic increase of her creatinine. Diuretics and beta blocker were held, and blood and ascitic fluid were sent for cultures to rule out infection. We checked her laboratory test results every 6 hours. She remained listed for LT. The following morning, Ms. Miller’s MELD-Na score increased to 35, her international normalized ratio (INR) increased to 2.2, creatinine increased to 4.89 mg/dL, and she became anuric. Octreotide,
midodrine, and intravenous albumin were given, and our transplant nephrology team was consulted. Within 6 hours, she became hypoxic with chest tightness and shortness of breath. She had a paracentesis with 8.5 L of fluid removed. She continued to become more hypotensive (blood pressure [BP] 90/40 and mean arterial pressure [MAP] 57) with course breath sounds. Chest radiograph revealed increased interstitial lung markings suggestive of pulmonary edema. Based on this acute decompensation, she was transferred to the intensive care unit (ICU), where she was placed on continuous renal replacement therapy (CRRT) and vasopressor support (norepinephrine), quickly requiring a second vasopressor (vasopressin). She developed acute respiratory failure requiring mechanical ventilation. On day 2 in the ICU, she received a LT. Within 2 days, she was weaned off of all pressor support and extubated; post-operative day#4 she was transitioned from CRRT to IHD intermittent hemodialysis. She remained in the hospital until POD#10.

Because HRS-AKI can rapidly progress to permanent renal damage, it is important to recognize this condition early and to provide prompt treatment. Initially, volume resuscitation is given. Many times a patient’s condition will deteriorate quickly and become severely hypotensive. Vasoconstrictors are recommended, including norepinephrine, midodrine, and somatostatin analogues (octreotide). Terlipressin is considered a first-line therapy in countries where it is available. Current clinical studies are underway to consider terlipressin as an option in the United States. LT is the only certain way to cure HRS.

POSTTRANSPLANT: OUTPATIENT MANAGEMENT

Ms. Miller returned to our clinic for her 4-month post-transplant return visit. She required intermittent hemodialysis until 8 weeks after surgery, after which time she had a full recovery of her renal function (creatinine 0.94 mg/dL). Postoperatively, she had issues with hypertension and hyperglycemia, which were promptly addressed. She had an episode of cytomegalovirus viremia and was treated with valganciclovir (adjusting for renal function). Her hepatopulmonary syndrome had resolved. Although HRS-AKI frequently is associated with a quite grim prognosis, this case study shows the story of someone who can beat the odds.

KEY POINTS

- Early identification and management of hepatorenal syndrome (HRS) is important to improved patient outcomes.
- Providers should refer to a transplant center for expedited liver transplant (LT) evaluation as soon as HRS-acute kidney injury (AKI) is suspected.
- Clinicians must be familiar with how to optimize fluid status and how to avoid triggers that can cause HRS-AKI.
- Engagement from patients and caregivers is important to be aware of early signs of acute renal failure.

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