Hepatorenal Syndrome: Diagnosis, Management, and New Advances in Therapy

EDUCATIONAL OBJECTIVES
1. Review the etiology, risk assessment, and diagnostic criteria for different types of hepatorenal syndrome (HRS);
2. Describe current dosage and administration, indications, and contraindications of existing and emerging therapies for HRS;
3. Explain new advances in treatment options for HRS and the data supporting new therapeutic strategies; and
4. Discuss the clinical pharmacist’s role in the management of HRS in hospital/health care systems settings.

Posttest Questions, Answers, and Rationale

1. All of the following are typical characteristics of patients with hepatorenal syndrome (HRS), EXCEPT:
   A. Cirrhosis with ascites
   B. Serum creatinine (SCr) > 1.5 mg/dL
   C. Absence of shock
   D. Presence of parenchymal kidney disease***

Correct answer: D
Rationale: HRS is a functional renal failure occurring in patients with advanced cirrhosis. The major difference in HRS as compared with other types of acute kidney injury in patients with hepatic disease is the absence of parenchymal kidney disease.

2. Immediate discontinuation of intravenous vasoconstrictor therapy should be considered in the presence of all of the following adverse effects, EXCEPT:
   A. Myocardial ischemia
   B. Tachycardia***
   C. Digital cyanosis
   D. Mesenteric ischemia

Correct answer: B
Rationale: Adverse effects with vasoconstrictor therapy are common. Immediate discontinuation of vasopressor therapy should be considered if significant ischemia is present (myocardial, digital, or mesenteric). Extreme caution in re-initiating therapy is warranted if any of these severe adverse drug-related events occur. Dosage reduction can be considered with less severe adverse effects, such as tachycardia.
3. Which of the following is MOST likely to trigger HRS type I in a patient with severe cirrhosis and ascites:
   A. Spontaneous bacterial peritonitis
   B. Diarrhea
   C. Discontinuation of furosemide and spironolactone
   D. Propranolol prophylaxis for esophageal varices

Correct answer: A
Rationale: Bacterial infections are the most important risk factor for the development of HRS. Spontaneous bacterial peritonitis has the highest incidence of HRS, with as many as 33% of patients with the infection developing HRS. Although diarrhea can cause hypovolemia, it is less likely than spontaneous bacterial peritonitis to trigger HRS. Overuse of furosemide and spironolactone may precipitate HRS and discontinuation of drug therapy is necessary if HRS develops. Using propranolol or other beta blockers for the prophylaxis of esophageal variceal bleeding may affect blood pressure, but is not considered a usual trigger for HRS.

4. All of the following are appropriate goals for vasoconstrictor therapy in patients with HRS, EXCEPT:
   A. Increase urine output
   B. Increase mean arterial pressure by > 10 mm Hg
   C. Decrease serum creatinine to < 1.5 mg/dL
   D. Reduce Model for End-Stage Liver Disease (MELD) score to lower patients status on transplant list

Correct answer: D
Rationale: The goal of vasoconstrictor therapy is to improve urine output and decrease Scr. The initial goal for titration is to increase the mean arterial pressure by > 10 mm Hg. An unintentional consequence of treating HRS is that improving renal function decreases a patient’s MELD score, which lowers their

5. All of the following are potential roles for the clinical pharmacist in the management of HRS, EXCEPT:
   A. Identification of potentially nephrotoxic medications
   B. Discuss the potential benefits and risks of therapeutic options
   C. Determine when to initiate renal replacement therapy
   D. Outline a plan for vasoconstrictor titration and monitoring

Correct answer: C
Rationale: The clinical pharmacist is responsible for identifying any medications that may be contributing to the patient’s acute kidney injury (AKI) and to provide a recommendation for discontinuing and/or changing to less nephrotoxic options. Pharmacists can help providers understand the potential risks and benefits of therapeutic options. This allows for an informed and patient specific decision to be made regarding therapy. The pharmacist’s expertise is commonly needed to assist with monitoring and optimizing vasoconstrictor therapy because it differs from the strategies typically used for vasodilatory shock. Ultimately, the nephrologist will be the person to determine whether renal replacement therapy should be prescribed.
6. Which of the following is the MOST appropriate intravenous dosing strategy for vasopressin for the treatment of HRS:
   A. Use a fixed dose of 0.04 units/min
   B. Initiate at 0.04 units/min and titrate every 30 to 60 minutes to achieve > 10 mm Hg increase in MAP from baseline***
   C. Start vasopressin at 0.8 units/min and titrate down if ischemic complications occur
   D. Vasopressin 40 unit bolus, repeat every 20 minutes as needed to maintain a MAP increase > 10 mm Hg from baseline

Correct answer: B
Rationale: See Table 3. Vasopressin at a fixed dose of 0.03 or 0.04 units/min is the recommended dose for septic shock, not HRS. Answer choice B is most consistent with current recommendations for treating HRS. Answer choice C is not preferred because it may lead to significant ischemia-related adverse events. Answer choice D is not a dosing option for HRS and is reserved for advanced cardiac life support.

7. All of the following vasoconstrictor options have demonstrated the ability to improve HRS physiology, EXCEPT:
   A. Dopamine***
   B. Terlipressin
   C. Norepinephrine
   D. Vasopressin

Correct answer: A
Rationale: Dopamine has not been shown to be effective as monotherapy and the addition of renal dose dopamine to other vasoconstrictors does not improve outcomes. Terlipressin is an emerging therapy in the United States (although it is still awaiting U.S. Food and Drug Administration [FDA] approval) and is a preferred therapy per the guidelines. Norepinephrine and vasopressin are considered appropriate alternatives if terlipressin is not available.

8. Which of the following artificial organ support systems is most effective for reversing HRS:
   A. Renal replacement therapy
   B. Molecular adsorbent recirculating system (MARS)
   C. Prometheus
   D. None of the above has demonstrated improved clinical outcomes when treating those with HRS; therefore, their routine use is not recommended***

Correct answer: D
Rationale: Artificial hepatic and renal support systems are a potential emerging therapy for the management of end-stage liver disease and HRS. However, current technology has failed to demonstrate significant improvements in mortality. Additionally, the systems are expensive and are complex to manage.
9. A recommendation to discontinue vasoconstrictor therapy when encountering futility regarding the management of those with HRS should be initiated at what time point during therapy?
   A. After 4 days of appropriately titrated therapy with no response in SCr***
   B. After 10 days of appropriately titrated therapy with no response in SCr
   C. After 14 days of appropriately titrated therapy with no response in SCr
   D. Therapy should be continued until liver transplant, regardless of SCr

Correct answer: A
Rationale: Therapy should be discontinued after 4 days if no change in SCr is observed, even with adequate dosage titration, because the likelihood of response to therapy is low at this point. Continuation beyond 4 days for nonresponders only results in an increase in both the cost and the risk of adverse events. There is no post-transplant benefit for nonresponders if therapy is continued until the time of liver transplantation.

10. All of the following are considered an appropriate use of albumin for patients who are at risk for HRS or those who already have HRS, EXCEPT:
   A. Adjunctive administration during vasoconstrictor therapy
   B. To determine the diagnosis of HRS
   C. To prevent HRS in patients with spontaneous bacterial peritonitis
   D. To supplement serum albumin to achieve a concentration > 4 g/dL***

Correct answer: D
Rationale: Albumin is the preferred intravascular volume expander for patients with HRS and its combined use with vasoconstrictors may improve response. The administration of albumin is preferable to normal saline volume resuscitation when establishing the diagnosis of HRS. Albumin administration on days 1 and 3 of spontaneous bacterial peritonitis can reduce HRS and mortality. Administering albumin to achieve a specified serum concentration has not been studied and should not be routinely recommended.