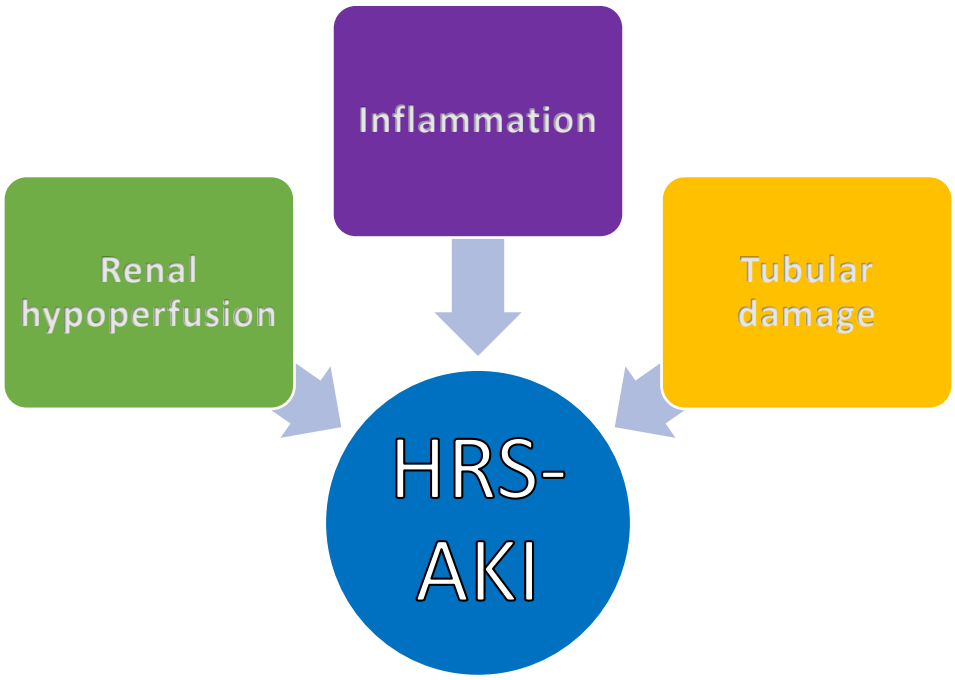
INTRODUCTION

Hepatorenal syndrome (HRS) is a serious, life-threatening complication of cirrhosis. HRS is estimated to affect 700,0000 patients annually in the United States, with a prevalence of 11.2 cases per 100,000 people, and is associated with poor outcomes and high hospital costs.[1,2] The definition HRS has evolved over the past 2 decades to now focus on the acute nature of the episode, hepatorenal syndrome – acute kidney injury (HRS-AKI). The application of the HRS-AKI definition is difficult in clinical practice, making recognition and timely treatment challenging. HRS-AKI is largely a diagnosis of exclusion, representing decreased renal function due to reduced renal blood flow. Diagnostic criteria for HRS-AKI include: cirrhosis with ascites; an acute increase in serum creatinine (SCr) ≥ 0.3 mg/dL; no improvement in SCr after at least 2 days of diuretic withdrawal and albumin administration; and the absence of shock, parenchymal pathology, and recent treatment with nephrotoxic medications.[3] Prompt diagnosis is essential so that treatment strategies can be implemented to reverse the condition and restore kidney function.[4]

SPLANCHNIC VASODILATION

Acute kidney injury due to HRS is thought to be due to splanchnic vasodilation leading to a reduction in circulating intravascular volume and compromised blood flow. The most common precipitating trigger to splanchnic vasodilation is an infectious episode resulting in an inflammatory response involving a cascade of interleukins and cytokines.[5] Cardiac output is insufficient to meet the metabolic needs of the nephron, thereby activating the renin-angiotensin-aldosterone system (RAAS) to divert blood flow to the kidney and reducing glomerular filtration rate (GFR) (Figure 1).



VASOCONSTRICTORS

Though counterintuitive to the renal vasoconstriction observed in the kidney beds, vasoconstrictors are necessary to restore perfusion in the splanchnic bed and increase blood flow to the kidneys. Vasoconstrictors can be grouped into 3 distinct categories: (1) midodrine plus octreotide (2) norepinephrine and (3) terlipressin. Midodrine exerts its effects via agonism of the α1 receptors. Octreotide exerts pluripotent activity as a somatostatin analogue. Both therapies are given together with albumin and can be administered in the general hospital care setting. Norepinephrine directly induces generalized vasoconstriction via activation of α1 receptors. Limitations to norepinephrine include its systemic effects and requirements for central venous access, restricting its use largely to critical care settings. Terlipressin is a vasopressin analogue acting directly on V1 receptors and produces a less generalized vasoconstrictive effect than norepinephrine. Additionally, terlipressin can be administered via intravenous push outside of critical care settings.

EXPERIENCE WITH TERLIPRESSIN

Terlipressin is available outside of North America, where the scientific literature and clinical experience demonstrate evidence of its efficacy to reverse HRS-AKI.[6-9] With the flexibility in dosing administration, care settings, and clinical experience, terlipressin has become a standard of care outside of North America. In the CONFIRM study (n=300 patients), a greater number of patients randomized to treatment with terlipressin and albumin achieved HRS reversal and reversal without the need for renal replacement therapy (RRT) compared to patients receiving placebo and albumin.[10] CONFIRM represents the largest study to date of terlipressin for the treatment of HRS-AKI.

	Terlipressin (n=199)	Placebo (n=101)	*P* value
Reversal of HRS	63 (32%)	17 (17%)	0.006
Reversal of HRS without RRT through 30 days	68 (34%)	17 (17%	0.001
Liver transplantation (day 90)	46 (23%)	29 (29%)	*No difference*
Death (day 90)	101 (51%)	45 (45%)	*No difference*

OTHER TREATMENT CONSIDERATIONS

Given the acuity of illness and multisystem failure, including kidneys, associated with liver disease, patients with HRS-AKI are uniquely susceptible to serious adverse events and death. In the CONFIRM trial, the most notable adverse event observed in the terlipressin group was respiratory failure, largely attributed to fluid overload.

Optimal care of the patient with acute liver disease and HRS-AKI necessitates effective collaboration among the multidisciplinary care team. Coordinating aspects of care, treatment options, and mitigating HRS-AKI before it develops, are essential to the optimal care of the patient with HRS-AKI.

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