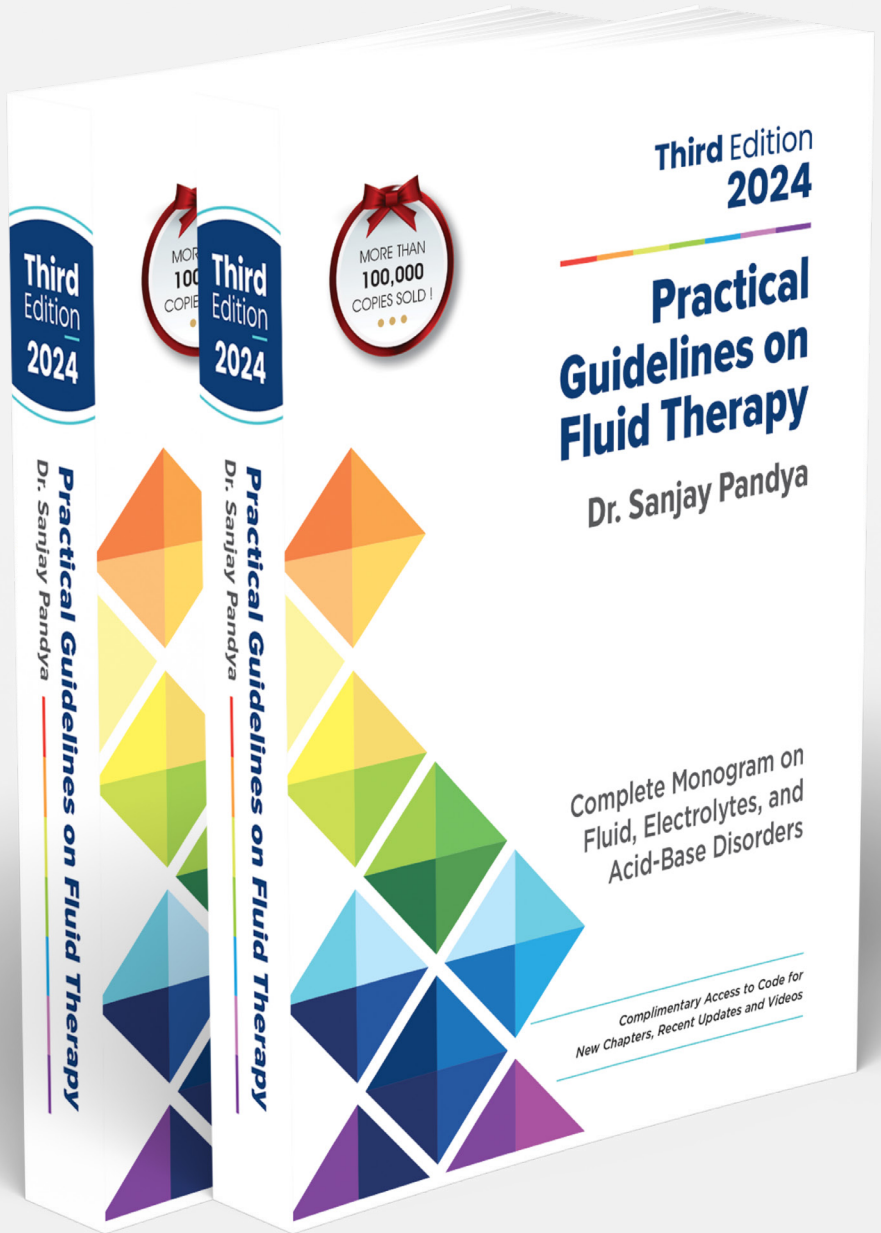
Chapter 37:
Hepatorenal Syndrome



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37 Hepatorenal Syndrome

Kidney failure is the most frequent organ failure in patients with acute or chronic liver disease, with a frequency of 20–50% in hospitalized cirrhotic patients [1–3].

Hepatorenal syndrome (HRS) is a life-threatening complication and one of many causes of acute kidney injury in patients with acute or chronic liver disease. HRS frequently occurs in hospitalized patients and is associated with a high mortality rate (about 32 to 37%) [4–6], readmission rate (about 23%) [5], hospital and health care costs [6, 7], and longer stay in hospital [4].

The most common precipitating factors of HRS are gastrointestinal bleeding, large volume paracentesis, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), spontaneous bacterial peritonitis, and other infections [5, 8].

DEFINITIONS AND TYPES OF HEPATORENAL SYNDROME

Hepatorenal syndrome is a specific cause of acute kidney injury (AKI) frequently encountered in advanced cirrhosis characterized by rapidly progressive renal failure, which occurs without apparent pathologic abnormalities in the kidneys [9].

Hepatorenal syndrome is traditionally classified into Type 1 and Type 2 HRS based on the severity of diseases reflected by the rapidity of decline in kidney function [10]. Type 1 (HRS-1) is a serious form of AKI that occurs in advanced cirrhosis with ascites.

Type 1 HRS is characterized by a rapid and progressive reduction in renal function (a 2-fold increase of serum

creatinine to at least 2.5 mg/dL or a decrease of creatinine clearance by 50% to less than 20 mL/min within 2 weeks) [11], and has a poor prognosis (median survival only 8 to 12 weeks) [12]. Type 2 HRS is a less severe form of kidney function impairment that is slowly progressive and clinically characterized by ascites resistant to diuretics [11] and has a median survival of about 6 months [12].

The traditional classification of HRS-1 and HRS-2 has recently been reclassified (Type 1 HRS renamed as HRS-acute kidney injury (HRS-AKI), and HRS-2 renamed as HRS-NAKI (that is, non-AKI) [13–15]. Diagnostic features of HRS-AKI as recommendations by the International Club of Ascites (2019) are summarized in Table 37.1 [13].

PATHOGENESIS

The pathogenesis of HRS is multifactorial, complex, and poorly understood. However, two major mechanisms that interact and contribute to the development of HRS-AKI are the combination of hemodynamic abnormalities and systemic inflammation [3].

Table 37.1 Diagnostic criteria of HRS-AKI

1. Presence of cirrhosis and ascites
2. Presence of AKI (increase in serum creatinine >0.3 mg/dL within 48 hours, or >50% increase in serum creatinine from baseline in 3 months)
3. Lack of improvement of serum creatinine (decrease of creatinine ≤0.3 mg/dL of baseline) after at least 48 hr of diuretic withdrawal and volume expansion with albumin (1 gm/kg body weight/day for 2 d)
4. Absence of shock (septic, cardiogenic, distributive)
5. Exclusion of current or prior treatment with nephrotoxic drugs
6. Absence of proteinuria ≥500 mg/day, microhematuria, or structural abnormalities on ultrasonography

A. Hemodynamic abnormalities: The "splanchnic arterial vasodilation theory" is the main hypothesis in the pathophysiology of HRS [16]. Essential components of the pathogenesis of neurohormonal cascade in HRS are:

- **Vasodilatation:** In portal hypertension, increased intrahepatic vascular tone promotes the release of vasodilatory substances like nitric oxide and prostaglandins, which cause arterial vasodilatation in the splanchnic and systemic circulation.
- **Activation of vasoconstrictors:** Systemic and splanchnic vasodilatation reduces effective arterial blood volume and systemic arterial pressure, which triggers the carotid and aortic arch baroreceptors and activates three powerful vasoconstrictor systems (renin-angiotensin-aldosterone system, vasopressin release, and activation of the sympathetic nervous system).
- **Renal vasoconstriction:** Activation of vasoconstrictor systems increases arterial pressure and kidney vasoconstriction. In advanced stages of cirrhosis, synthesis of vasodilator factors is more pronounced with further vasodilatation of systemic and splanchnic and resultant worsening of hypotension [17]. Vasoconstrictor systems are further activated [18] to combat severe hypotension and achieve optimal arterial pressure, which is compatible with life. As renal circulation is very sensitive to the vasoconstrictive effects of these vasoconstrictors, it causes a marked reduction in renal perfusion and the development of HRS-AKI [19].
- **Cardiac dysfunction:** In cirrhotic patients with systemic vasodilation, cardiac output increases initially. But

with the progression of liver disease, cardiac output decreases, further reducing impaired renal blood flow and contributing to the development of hepatorenal syndrome [20, 21].

B. Systemic inflammation: According to this new theory, in portal hypertension, gut permeability increases, causing bacterial translocation from the gut to mesenteric lymph nodes, which triggers a systemic inflammatory response with the release of pro-inflammatory cytokine [18]. Three different mechanisms by which systemic inflammation causes organ dysfunction, and failure are [22–24]: (1) Nitric oxide production in splanchnic arterioles due to systemic inflammation accentuates the preexisting splanchnic vasodilation and stimulates endogenous vasoconstrictor systems causing renal hypoperfusion; (2) Activation of immune cells resulting in tissue damage; and (3) Metabolic alterations.

DIAGNOSIS

In patients with cirrhosis, renal dysfunction can occur due to HRS and many other causes for the development of AKI in cirrhotic patients, such as hypovolemia (gastrointestinal [GI] bleeding, use of diuretics or GI losses), medications (drug-induced or contrast-induced nephropathy), infections, intrinsic renal disease, and obstructive uropathy [25]. In cirrhotic patients with HRS, multiple causes that can potentially lead to AKI can coexist and overlap [26].

While evaluating AKI in patients with liver disease, it is important to remember that hepatorenal syndrome is the cause of AKI in about 15–43% [27, 28], AKI frequently occurs due to hypovolemia in 27–50% of all cases, and acute tubular necrosis (ATN) in about 14–35%.

As hepatorenal syndrome (HRS-AKI) is a diagnosis of exclusion, it is essential to exclude other potential causes of kidney injury in patients with liver disease [15, 18]. So detailed history, clinical assessment, laboratory assessments, and abdominal imaging should be performed to exclude different causes of AKI, such as prerenal AKI (hypovolemia), acute tubular necrosis (hypovolemic shock, infection, or nephrotoxic agents), and other causes (abdominal compartment syndrome, glomerulonephritis, acute interstitial nephritis, and obstructive uropathy) [29, 30]. Differentiating ATN and HRS-AKI may be difficult, and in such patients, the role of urinary biomarkers is promising and may prove helpful [31, 32].

PREVENTION

As HRS carries a poor prognosis, it is better to prevent than treat it. Measures to prevent HRS are:

- Avoid using nephrotoxic drugs (such as NSAIDs, aminoglycosides, amphotericin, ACE-I, angiotensin receptor blockers, or radiographic dye), and use diuretics and laxatives judiciously.
- Early detection and prompt treatment of coexisting infections and antibiotic prophylaxis in patients with increased risk of spontaneous bacterial peritonitis are effective measures to prevent AKI-HRS [28].
- Correct intravascular volume depletion, which may occur due to excessive diuretic use, diarrhea due to lactulose, variceal bleeding, and large volume paracentesis without albumin administration).
- IV albumin infusion: In patients with spontaneous bacterial peritonitis, the IV administration of albumin reduces the risk of both kidney function impairment and mortality [33–35].
- In patients with spontaneous bacterial peritonitis, albumin is started

together with antibiotics. The recommended dose of IV albumin to prevent HRS is 1.5 gm/kg within 6 hours of detection of infection (on the first day) and a second dose of 1 gm/kg after 48 hours of the first dose (on the third day).

- During large volume paracentesis, replacing 6–8 gm of albumin for every liter of ascites removed reduces the risk of HRS-AKI [14, 30, 36, 37].
- Antibiotics prophylaxis: In patients with advanced cirrhosis, administration of oral norfloxacin (or alternative trimethoprim-sulfamethoxazole if norfloxacin is unavailable) decreases the one-year probability of spontaneous bacterial peritonitis, delays the development of HRS, and improves survival [38]. Rifaximin also reduced the incidence of HRS-AKI in cirrhotic patients [39, 40].
- Early diagnosis and prompt management of gastrointestinal bleeding.
- Pentoxifylline: Due to its protective effect against oxidative renal cell injury, pentoxifylline (1200 mg/day) is found to reduce the risk of HRS-AKI in alcoholic hepatitis and may be an effective prophylaxis [41–44]. However, larger studies are needed to validate the efficacy [45, 46].
- As HRS is a common complication in acute alcohol hepatitis, early detection and treatment of alcoholic hepatitis, alcohol abstinence, and proper nutritional supplementation are essential [47].

MANAGEMENT

HRS requires early and aggressive therapy because, besides all therapeutic advances, the outcome of HRS is poor.

The goals of management of hepatorenal syndrome are:

- Identify and treat reversible factors.
- To correct hypovolemia and avoid volume overload.
- To achieve a higher mean arterial blood pressure (rise in MAP ≥10–15 mmHg from baseline) is the most effective approach for better perfusion of the kidneys [29, 48, 49].
- Reversal of hemodynamic disturbances and acute kidney injury.
- To stabilize the patient, provide renal replacement therapy if necessary, and prolong survival until candidates undergo liver transplantation.

Three primary treatment options for managing HRS are general measures, pharmacological therapy, and non-pharmacological therapy.

A. General measures

- Meticulous evaluation to diagnose underlying precipitating factors and their early treatment.
- Volume expansion. The first step in managing AKI in cirrhosis is volume expansion (with crystalloids or intravenous albumin). As prerenal AKI is the most common cause of renal failure in cirrhotic patients, it is essential to correct hypovolemia immediately by replacing fluids, considering the cause and severity of the fluid loss [14, 18, 50]. Normal saline infusion is preferred to correct hypovolemia due to vomiting or the excess dose of diuretics. Blood or blood products effectively correct hypovolemia and anemia due to gastrointestinal bleeding. The reversal of AKI in 48 hours with volume expansion favors prerenal AKI [50].
- Assessing the volume status of cirrhotic patients can be challenging due to the complexity of the condition. At times it can be challenging to correct hypovolemia optimally in these patients because they may

have intravascular volume depletion despite the presence of ascites or peripheral edema. Additionally, over-infusing fluids can worsen existing conditions such as ascites, pleural effusion, heart failure, or respiratory failure [51].

- To determine the best approach for volume assessment and fluid management, a careful history, detailed clinical examination, laboratory tests, X-ray-based imaging, and point-of-care ultrasound should be used [52].
- Stop β-blockers in patients with low or borderline blood pressure [14]. Discontinue nephrotoxic drugs (as discussed in prevention).
- Stop diuretics and avoid the temptation to use diuretics to increase urine output in severe AKI in HRS [14]. Diuretic therapy in HRS can lead to volume depletion and further reduction of effective circulating volume, which can aggravate renal hypoperfusion and may trigger or worsen HRS [53, 54]. In addition, it is essential to discontinue spironolactone in HRS as it carries the risk of life-threatening hyperkalemia.
- As spontaneous bacterial peritonitis is a main triggering factor of AKI-HRS, its prompt treatment with albumin and antibiotics helps in preventing AKI-HRS [28, 33, 34]. But the administration of albumin is not recommended in patients of HRS with non-spontaneous bacterial peritonitis infections [55, 56].
- Always search for the presence of electrolyte disorders (such as hyponatremia, hyperkalemia, hypokalemia, etc.) or acid-base disorders (such as respiratory alkalosis, metabolic alkalosis, and metabolic acidosis) and treat them [51].
- Etiology-driven management of AKI.
- Measure vitals, urine output, fluid balance, and daily weight and closely monitor patients.

B. Pharmacological therapy

Combined therapy with albumin and a vasopressor is recommended as the first line of treatment for HRS-AKI and should be started as soon as possible [14, 18, 30, 57].

1. Albumin

In cirrhotic patients with AKI, administering albumin is important for both diagnostic and therapeutic purposes [18, 58].

It is essential to differentiate AKI-HRS from prerenal AKI because AKI occurs due to prerenal AKI in about half of patients with AKI in cirrhosis.

Renal recovery within 48 hours after administration of albumin (along with removing risk factors and discontinuing diuretics) favors the diagnosis of prerenal AKI, and failure in improvement in renal function suggests the diagnosis of AKI-HRS [15].

IV Albumin is recommended for volume resuscitation in prerenal AKI regardless of the etiology or severity of prerenal azotemia [52].

Effects: Albumin infusion increases oncotic pressure, effectively expands circulating volume, improves hemodynamics and cardiac output, increases renal perfusion, and enhances renal recovery.

In addition to volume expanding effects in HRS, other benefits of albumin proposed in current literature are [37, 58, 59] antioxidant and anti-inflammatory effects [60, 61], positive cardiac inotropic effects [62], improvement in the autoregulation of renal perfusion [63], preservation of the integrity of endothe-

lial glycocalyx [64], and stabilization of endothelial function [65].

Dose: Recommended dose of albumin is 1 gm/kg/d (up to 100 gm/d) for two consecutive days, preferably given in divided doses (e.g., 25 gm every 6 hourly) [13, 14]. Subsequently, the dose may decrease to 20–40 gm daily. However, as per the recent ATTIRE trial (2021), tailoring albumin therapy to raise serum albumin to 3.0 gm/dL or more is not beneficial in reducing infection, kidney dysfunction, or death [66].

Combination therapy: It is important to remember that instead of albumin alone, combination therapy of albumin with vasoconstrictor therapy is more effective [67–70]. Therefore all guidelines recommend albumin with vasoconstrictor, the adjunct therapy for HRS-AKI [3, 14, 30, 57]. This combination therapy significantly improves renal function in HRS and reduces mortality compared with no treatment or albumin alone [15, 71, 72].

Duration of treatment: Albumin plus vasoconstrictor therapy should be continued until serum creatinine reduces to a value within 0.3 mg of the baseline value of serum creatinine [15].

Combination therapy is discontinued within 14 days if patients do not respond or respond partially [15].

Adverse effect: The major concern of albumin infusion in HRS is the significant risk of volume overload, especially pulmonary edema [66, 70].

So, before administration, it is essential to assess volume status and avoid albumin infusion in patients with volume overload.

As albumin increases preload and terlipressin increases afterload, the combined treatment carries the risk of precipitation of pulmonary edema [29].

2. Vasoconstrictors

Administration of IV albumin, combined with vasoconstrictors such as IV terlipressin, noradrenaline, or oral midodrine plus octreotide initiated as soon as the diagnosis of HRS is suspected. The combination therapy helps in the reversal of hemodynamic disturbances, restoration of effective circulating volume, and improvement in renal perfusion.

a. Terlipressin

According to international guidelines, terlipressin, a synthetic vasopressin analog, is recommended as the first and most preferred vasoconstrictor for managing HRS [14, 18, 25, 30, 57, 73, 74]. This is because it has been shown to improve renal function in 24–44% of patients in various studies [68–70, 75–79] and meta-analyses [69, 71, 72, 80–83], making it an effective treatment option for HRS. In addition, potent vasoconstrictor terlipressin is also found to reduce short-term mortality and hospital cost in various studies [71, 72, 81, 84, 85]. But the effect on mortality is controversial as survival benefits are lacking in other literature [69, 70, 76, 80].

Mechanism of action: Terlipressin has a high affinity for V1 receptors. V1 receptors are predominantly located in the splanchnic bed and systemic vascular smooth muscle, while V2 receptors are found more commonly in the kidney. Because of its selective effect, terlipressin causes splanchnic vessels and extrarenal vasoconstriction, which improves effective circulating volume and renal perfusion pressures.

Indications: In HRS, initiate terlipressin at early stages of AKI (i.e., serum creatinine >1.5 mg/dL), as there is a higher likelihood of a positive response to treatment when initiated at an earlier stage. However, avoid using terlipressin in milder forms of HRS-AKI (i.e., serum

creatinine <1.5 mg/dL) as they are typically benign and potentially reversible with fluid expansion alone. Terlipressin should also be avoided in patients with advanced renal dysfunction (i.e., serum creatinine >5.0 mg/dL or higher).

Dose: Initial dosage of terlipressin in HRS is 1–2 mg/12 h by continuous IV infusion or 0.5–1.0 mg/4–6 h by IV boluses, and the dose is progressively increased as per need [14]. In the absence of response, the dose of continuous IV terlipressin infusion should be increased stepwise from 2 mg/day to a maximum of 12 mg/d according to the change in urine output and serum creatinine [74, 86]. One ampoule (8.5 ml solution) contains 1 mg terlipressin acetate.

Route: Administration of terlipressin by continuous IV infusion is preferred over IV boluses because infusion is better tolerated, and the requirement of effective doses is lower [87].

Poor response: Response to terlipressin is poor in HRS-AKI patients with higher total serum bilirubin [88], higher serum creatinine [89], underlying chronic kidney disease (CKD) with significant structural kidney injury, presence of severe bacterial infections [90], and failure to achieve an increase in the mean arterial pressure and cardiac output [73].

Contraindications: As terlipressin causes extrarenal vasoconstriction, it is usually avoided in HRS patients with coronary artery disease, cerebral or peripheral vascular diseases, cardiac arrhythmias, asthma, chronic obstructive pulmonary disease, and elderly patients [91].

Adverse effects: Common adverse effects of terlipressin are abdominal pain, nausea, diarrhea (due to gastrointestinal smooth muscle spasm), coronary or peripheral vascular ischemic complications, and respiratory adverse events. Serious side effects like dyspnea and respiratory distress occur because of terlipressin-induced pulmonary vasoconstriction and cardiac overload because of increased afterload due to terlipressin and preload due to albumin [74, 92].

Measures suggested to reduce respiratory adverse events of terlipressin are judicious use of albumin and careful attention to respiratory distress, monitoring pulse oximetry, and frequent chest radiographs or point of care ultrasound [93].

Terlipressin was introduced first time in the year 1990 and was widely used worldwide subsequently. But due to respiratory adverse events [70] and the lack of mortality benefits [94], it was not approved by the FDA and therefore was unavailable. However, recently, in September 2022, the US FDA approved the use of terlipressin for the treatment of hepatorenal syndrome in adults [95].

b. Norepinephrine (Noradrenaline)

In a country like the USA, where terlipressin was unavailable till recently (September 2022), norepinephrine (plus albumin) was a preferred agent and considered a first-line treatment for HRS [52]. Early studies and meta-analyses have shown equal effectiveness of terlipressin plus albumin and norepinephrine plus albumin in reversing HRS [96–101], but in a recent study, terlipressin plus albumin was associated with a higher HRS reversal rate in patients with acute on chronic liver failure [102].

The advantages of norepinephrine are that it is significantly cheaper than terlipressin and is widely available with fewer side effects [78, 96, 100, 101, 103]. In addition, physicians use norepinephrine routinely and are very familiar with its use because it is the most standard drug for augmenting sepsis circulation.

But the requirements of the central venous catheter for its administration and the need for ICU or close monitoring

for potential adverse effects such as arrhythmia and ischemia may offset the cost-benefit of this drug [103–105].

Mechanism of action: Alpha-adrenergic agonist norepinephrine by nonselective systemic vasoconstriction improves the mean arterial pressure and renal perfusion in HRS.

Dose: The dose of norepinephrine varies from 0.5 to 3 mg/h in HRS. Norepinephrine is usually started at an initial dose of 1 mg/hour by continuous infusion and is gradually increased to maintain the mean arterial blood pressure to ensure renal perfusion [106].

c. Midodrine and octreotide

In the USA, until now, the combination of midodrine and octreotide is routinely used to treat HRS-1 in general wards because terlipressin was not available in the USA, and norepinephrine cannot be administered outside of the intensive care unit [52]. But as compared to terlipressin and norepinephrine, the combination of midodrine and octreotide has shown low rates of renal recovery in HRS [72, 107, 108].

Therefore, midodrine and octreotide having much lower efficacy than terlipressin, are not preferred in ICU patients and are used in general wards only when terlipressin is unavailable [14, 30].

The combination of midodrine and octreotide plus albumin is the most effective therapy for increasing serum sodium in dilutional hyponatremia associated with HRS [83].

Midodrine is an orally available alpha-adrenergic agonist which causes systemic vasoconstriction and improves renal perfusion. Midodrine is usually started at a dose of 5–7.5 mg thrice daily orally, which can be increased maximum up to 15 mg three times daily as needed [109]. Synthetic somatostatin octreotide is potent splanchnic vasoconstriction which is given either as a continuous infusion (usual initial dose 50 mcg/h) or subcutaneously (usual dose 100–200 mcg/8 h) [109]. The combination of octreotide and midodrine is beneficial in HRS, but midodrine as a monotherapy does not improve renal function.

The selection of vasoconstrictors with albumin in hepatorenal syndrome based on treatment setup (in the intensive care unit or ward) is summarized in Table 37.2.

C. Non-pharmacological therapy

When patients do not respond to the above pharmacological measures, treatment options are dialysis, transjugular intrahepatic portosystemic shunt (TIPS), liver transplantation, or simultaneous liver-kidney transplantation.

1. Renal replacement therapy (RRT)

The use of RRT in patients with HRS is controversial [110–112]. HRS patients with failure of medical treatment but the possibility of improvement in kidney or liver function or patients who are eligible for liver transplantation are usually offered RRT [52]. Common indications of RRT in HRS-AKI are worsening renal function, electrolyte disturbances, or increasing volume overload besides optimum vasoconstrictor therapy [30].

2. Transjugular intrahepatic portosystemic shunt

TIPS may be used as a salvage therapy when medical management fails. When the intrahepatic stent is connected between the portal vein and the hepatic vein, it redirects portal blood into the systemic circulation, which decompresses the portal system and increases systemic

Table 37.2 Vasoconstrictor with albumin in hepatorenal syndrome				
Albumin To all patients (expands intravascular volume)				
Choice of vasoconstrictors				
	Setup	Firstline drugs	Class	Route
Terlipressin available	ICU	Terlipressin	Vasopressin analog	IV
	Wards			
Terlipressin not available	ICU	Norepinephrine	Alpha agonist	IV
	Wards	Midodrine and octreotide	Alpha agonist Somatostatin analog	Oral and SQ
Duration of therapy: About 1–2 weeks				
Goal: To raise mean arterial pressure by 10–15 mm of Hg, reduction of serum creatinine <1.5 mg/dL				

venous return leading to the return of more blood to the heart, causing increased cardiac output and improvement in arterial and renal perfusion. In a recent meta-analysis, it was found that TIPS can improve serum creatinine levels, urine volume, and urinary sodium excretion [113].

However, TIPS is not routinely recommended in patients with AKI-HRS because: (1) In clinical practice, its use is very limited (contraindicated in HRS with severe liver failure or severe hepatic encephalopathy) [14]; (2) It is associated with complications such as procedure-related bleeding, worsening of liver function, or development of hepatic encephalopathy [114]; and (3) Its role of in HRS is not precisely defined [115] and data supporting its use are insufficient [30].

3. Liver transplantation

Liver transplantation is the only curative treatment and therapy of choice for both types of HRS. But unfortunately, this most effective modality is available to a small fraction of the affected patients, and many patients die before a donor liver can be obtained.

4. Simultaneous liver-kidney transplantation (SLKT)

SLKT is usually recommended in patients with HRS-AKI when kidney function is not expected to recover post-liver transplantation (e.g., AKI associated with dialysis ≥6 weeks and glomerular filtration rate [GFR] ≤25 mL/min for more than 6 weeks or presence of underlying advanced CKD or CKD requiring dialysis) [116, 117].

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