Introduction

Ascites is the most common complication of liver cirrhosis and portal hypertension, with the incidence of approximately 60% within 10 years of diagnosis of cirrhosis. The appearance of ascites represents the onset of decompensation and is associated with poor prognosis with a mortality rate of 20% per year. The development of ascites is related to the splanchnic vasodilatation followed by a decrease in effective blood volume and activation of vasoconstrictor system such as renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (SNS), which induce renal sodium and water retention and fluid accumulation in the peritoneal cavity. With progression of the disease, these hemodynamic alterations lead to hypersecretion of anti-diuretic hormone (arginine vasopressin, AVP) and development of hyponatremia, which is considered as one of the important prognostic factors in patients with liver cirrhosis. Despite of these efforts to compensate hypovolemia, hypovolemia due to further splanchnic vasodilatation leads to decrease in the blood flow to the kidney, and eventually renal vasoconstriction, and development of renal dysfunction, including acute kidney injury (AKI) and hepatorenal syndrome (HRS), which are associated with poor prognosis in these patients.

Definition

Renal dysfunction is usually classified to AKI, chronic kidney disease (CKD), and acute on CKD according to the acuity of presentation. AKI is defined as a rise in serum creatinine (Cr) of more than 50% from baseline or an increase in Cr of at least 0.3 mg/dL in less than 48 h, and CKD is defined as eGFR of less than 60 mL/min for more than 3 months. Acute on CKD is defined as the increase in serum Cr of at least 50% from baseline or the increase in Cr by at least 0.3 mg/dL in less than 48 h in a cirrhotic patients with GFR below 60 mL/min for more than 3 months. There was significant changes in the definition of AKI compared to the previous conventional definition of increase in serum Cr level of more than 50% to a final value of serum Cr level >1.5 mg/dL in terms of addition of absolute increase in serum Cr of ≥ 0.3 mg/dL and deletion of cut-off serum Cr level of 1.5 mg/dL, because minor increases in serum Cr is clinically relevant and adversely affect survival in patients with cirrhotic ascites.

HRS is the most severe form of functional renal disorder which is not responsive to volume challenge. HRS is divided into two types based on prognosis and clinical characteristics: type 1 HRS (HRS1) is the rapid onset of renal
failure that occurs in patients with rapid hepatic decompensation and type 2 HRS (HRS2) is the renal impairment that progress gradually over a relatively long period of time. HRS1 is regarded as a specific form of AKI, while HRS2 is included in CKD. The definition of HRS was also recently updated as no improvement in serum Cr after at least 2 days of diuretic withdrawal and volume expansion with albumin in patients with cirrhotic ascites and AKI. Therefore, patients could be diagnosed as and treated for HRS1 before resolution of bacterial infection and without delay until rise in serum Cr level up to 2.5 mg/dL. Considering that rapid treatment for HRS1 with vasoconstrictors plus albumin improves treatment response and prognosis, this revision of the definitions for HRS1 would be helpful for these patients.

Prevalence & precipitating factors

AKI is the most common form of renal dysfunction in patients with liver cirrhosis. In patients with liver cirrhosis and renal dysfunction, 70%, 17%, and 13% of the patients had AKI, acute on CKD, and CKD, respectively. In addition, AKI is a common complication in patients with liver cirrhotic ascites and it develops in 19% of these patients admitted to hospital. Renal function can be improved with volume replacement in about 70% of patients with AKI, while renal dysfunction does not respond to volume challenge in the remaining 30% of these patients. A previous study suggested that the incidence of HRS in patients with cirrhotic ascites at 1 and 5 years are 18% and 39%, respectively.

Precipitating factors can be identified in most cases of AKI (85%). Most common precipitating factors are bacterial infection, large volume paracentesis, gastrointestinal bleeding, diarrhea, and overdoses of diuretics, which are very similar with those for HRS. Use of vasodilators, and renal vasoconstriction due to nonsteroidal anti-inflammatory drugs (NSAIDs) or intravenous contrast agents could also precipitate the development of AKI. Similarly, precipitating factors can be identified in almost half of patients with HRS, and bacterial infection, gastrointestinal bleeding, and large volume paracentesis were the most common precipitating factors for HRS.

Prognosis

The development of AKI in patients with cirrhotic ascites is associated with increase in mortality and development of complications such as variceal bleeding and spontaneous bacterial peritonitis (SBP). In a recent study suggest that AKI in patients with liver cirrhosis is frequently progressive and independently associated with mortality in a stage-dependent fashion. Although recent studies suggested that vasoconstrictors or liver transplantation can improve survival in these patients, HRS still represents one of the most serious complications of liver cirrhosis. Median survival of patients with HRS1 is less than 2 weeks, if untreated. Median survival of patients with HRS2 is 6 months.
Treatment

A previous prospective observational study suggested that AKI in patients with liver cirrhosis is frequently progressive and associated with mortality in a stage-dependent fashion. Furthermore, HRS may be reversed with restoration of renal blood flow by vasoconstrictors plus IV albumin or liver transplantation. Therefore, the early identification and treatment of its cause are very important. At first, NSAIDs and diuretics should be discontinued and, in patients with hypovolemia due to bleeding, aggressive volume expansion and prompt treatment for hemostasis should be performed. If renal dysfunction does not respond to these management, patients could be treated as HRS with vasoconstrictors plus albumin.

Terlipressin, an analogue of vasopressin, is the firstly recommended vasoconstrictors for HRS treatment. Terlipressin, by stimulating vasopressin receptors in the vascular smooth muscle cells, induce splanchnic vasoconstriction, which in turn, reduce portal blood flow and portal pressure. In addition, albumin increases effective arterial volume and lead to increase in preload to the heart, cardiac output, and mean arterial pressure. Terlipressin plus albumin treatment improves renal function in 40-50% of patients with HRS. This treatment is considered effective if serum Cr is reduced at least 25% within 3 days after initiation of treatment and should be continued until serum Cr level reduce below 1.5 mg/dL. After withdrawal of treatment, HRS recurs in about 20%, however, it usually responds well to retreatment. However, survival benefit of this treatment in patients with HRS have not been confirmed yet.

Both midodrine, an a1-adrenergic agonist, and octreotide, a somatostatin analogue, are known to cause splanchnic vasoconstriction. Therefore, several uncontrolled studies evaluated the treatment efficacy of midodrine, octreotide, and albumin for HRS and reported HRS reversal rate of about 40%. However, a very recent randomized controlled trial showed conflicting results: terlipressin plus albumin was significantly more effective than midodrine and octreotide plus albumin in improving renal function in patients with HRS (complete response rate, 55.5% vs. 4.8%).

Because transjugular intrahepatic portosystemic shunt (TIPS) improves hypovolemia and overactivation of vasoconstrictor systems by reducing portal pressure and increasing systemic venous return, it could be a treatment option for HRS. Consistently, several studies suggested that TIPS was effective for improving renal function as well as survival in patients with HRS. However, unfortunately, TIPS is contraindicated in most patients with HRS. In addition, TIPS can induce severe complications, including aggravation of liver dysfunction and hepatic encephalopathy. Therefore, TIPS is not considered as first-line treatment for HRS.

Conclusions

AKI is a frequent complication and associated with poor prognosis in patients with liver cirrhosis, especially in patients with cirrhotic ascites. Recently, definitions for AKI and HRS were revised to facilitate prompt diagnosis and treatment in these patients, because prompt diagnosis and rapid initiation of appropriate treatment is very important, considering poor prognosis in these patients. In patients with AKI, sufficient volume replacement with intravenous albumin as well as withdrawal of potentially nephrotoxic drugs are recommended. Patients whose renal dysfunction
does not respond to volume replacement could be diagnosed as HRS and treatment with vasoconstrictors and albumin should be considered.

References


