CHAPTER

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Approach to Hepatorenal Syndrome

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INTRODUCTION

Acute kidney injury (AKI) is common in cirrhosis but functional renal failure defined as Hepatorenal syndrome (HRS) accounts for 20% of AKI. HRS is reversible syndrome in patients with cirrhosis and ascites can appear spontaneously or follow precipitating event. HRS can be defined as presence of cirrhosis with ascites with serum creatinine more than 1.5 mg/dl, no improvement of serum creatinine (=/> 1.5mg/dl) after at least 48 hours of diuretic withdrawal and volume expansion with albumin 1gm/kg body weight per day for two days, absence of hypovolumic shock or severe infection requiring vasoactive drugs to maintain the arterial pressure, no current or recent treatment with nephrotoxic drugs, proteinuria less than 500 gms/day and no micro hematuria. Evolving concepts of renal dysfunction in cirrhosis have been discussed by various international groups in the recent past. International ascites club defined HRS in 1996, 2007 and 2015 while kidney associations which defined renal failure in other instances also defined kidney failure in cirrhosis. KIDGO (kidney disease improving global outcome), RIFLE (risk, injury, failure, loss of function, end stage renal disease), AKIN (acute kidney injury network) and ADQI (acute dialysis quality initiative) are important amongst them.

Table 1: Diagnosis of AKI in Cirrhosis

Parameter	Definition
Base line Serum Creatinine	Stable SCr ≤3 months If not available, a stable SCr closest to the current one If no previous SCr at all, use admission SCr
Definition of AKI	Increase in SCr ≥ 26.5 umol/l (0.3mg/dL) ≥ 48 hours, or Increase 50% from baseline
Staging	Stage 1 : Increase SCr ≥ 26.4 umol/L (0.3mg/dL) or Increase SCr ≥ 1.5 – 2.0 x from baseline Stage 2: Increase SCr > 2 – 3.0 x from baseline Stage 3: SCr > 3.0 x from baseline or SCr ≥ 352 umol/L (4,0mg/dL) with an acute increase of ≥ 26.4 umol/L (0.3mg/dL) or Initiation of renal replacement therapy

DIAGNOSIS OF HRS (TABLE 1)

It is based on AKI stage 2 or 3 with already mentioned criteria remaining same. Diagnosis of chronic kidney disease in cirrhosis is based on criteria: GFR less than 60 ml/minute calculated using MDRD six formula. HRS type II is defined as a specific form of chronic kidney disease. As many of the cirrhotics have GFR less than 60 ml/minute with serum creatinine levels being normal. Acute on chronic kidney disease is defined as rise in serum creatinine 50% from the baseline or a rise of serum creatinine more than 0.3mg/dL in less than 48 hours in patients with cirrhosis with GFR less than 60 ml/minute for more than three months calculated by MDRD six formula.

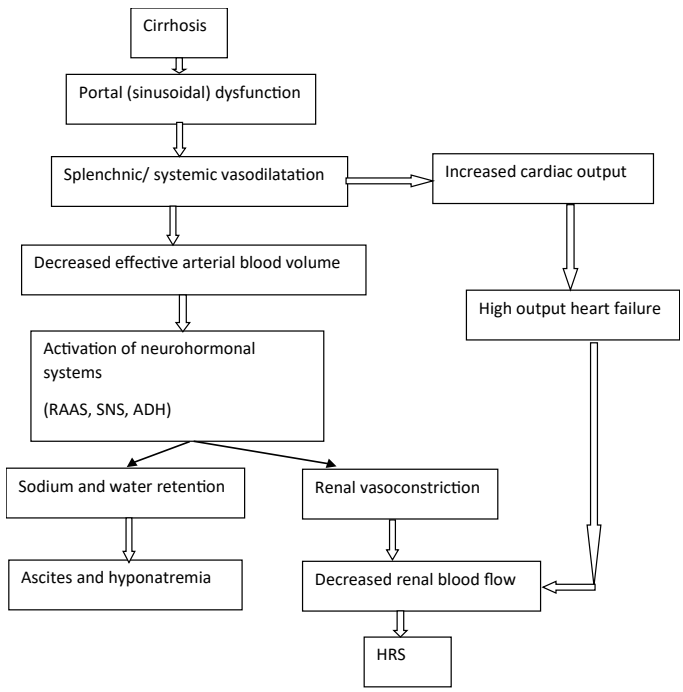

Fig. 1: Pathophysiology of HRS

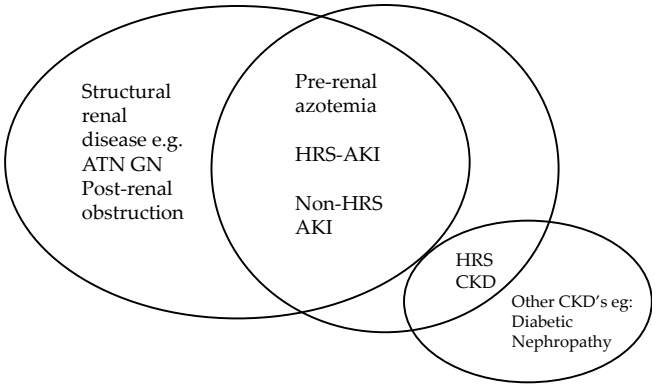

Fig. 2: Renal dysfunction in cirrhosis

PATHOPHYSIOLOGY OF HRS (FIGURE 1)

Renal vasoconstriction, oxidative stress and sluggish micro circulation are responsible for renal dysfunction. Portal hypertension leads to increase incidence of sheer stress on portal vessels. This leads to splanchnic vasodilation. Activation of various vasoconstrictor systems leads to renal vasoconstriction. Increased translocation of gut bacterial products from the bacterial infection can lead to increased vasodilators leading to splanchnic vasodilation which in turn leads to increased activation of various vasoconstrictor systems leading to renal vasoconstriction. Damage associated metabolic products (DAMS) and PAMS lead to increased oxidative stress and sluggish micro circulation leading to AKI. Infection is the most common precipitant of AKI in liver cirrhosis, while other precipitants are excessive diuretics, GI blood loss and large volume paracentesis. Inflammatory products cause changes in renal tubulus and micro vasculatures. Important amongst them are DAMS & PAMS and TNF alpha. AKI in cirrhosis have got a high mortality. 30 day mortality is around 40% while it is 5% in patients with cirrhosis who are hospitalized. 30 day mortality is increased even in patients who make complete recovery out of AKI. It holds true even in cirrhotic patients treated on outdoor basis.

MANAGEMENT OF HRS IN CIRRHOSIS

Management of AKI depends on diagnosis of AKI in cirrhotics (Figure 2). Withdrawal of diuretics and nephrotoxic drugs, treatment of infections when present, blood transfusion for GI blood loss, volume expansion with albumin should be given in AKI. With response to this treatment if AKI improves, you need to continue the treatment with close follow up. If there is no response or progression of AKI over 48 hours, it should be considered as HRS type I and should be treated with vasoconstrictors and albumin. The use of albumin in AKI has got multiple functions including oncotic pressure, capillary permeability, hemostatic effect, solubilization, transport, and metabolism, endothelial stabilization, antioxidants and immune modulators. Portal hypertension can also cause splanchnic vasodilatation which leads to endothelial dysfunction and also causes decrease extrahepatic blood volume leading to decrease capiallary permeability which in turn lead to the activation of vasoconstrictor causing renal hypo-perfusion. In recent studies Salerno demonstrated dose response curve of albumin infusion in improving survival of patients with cirrhosis. In addition to albumin, Terlipressin has shown to be effective in treatment of HRS. HRS reversal has been shown in as many as more than 30% patients. Bolus vs continuous infusion of Terlipressin has been shown to be more effective. Small dose of Terlipressin is required in these patients. Significantly less side effects are seen with 2mg Terlipressin over 24 hrs. The other option is Midodrine / Octreotide infusion has been shown to be effective, but its effectiveness is less than Terlipressin. The other option is norepinephrine which has been shown to be equally effective as Terlipressin. Meta-analysis shows equal efficacy of norepinephrine as compared to Terlipressin. Stage I AKI which reverses to normal has been shown to have 2% mortality while AKI if progresses to stage II has 29% mortality, Stage III has 50% mortality and with requirement to dialysis goes up to 55%. AKI stage II if non-progressive, has mortality of 7% while if it progress, mortality is 18% and with requirement of dialysis it goes beyond 50%. AKI stage III if does not progress, mortality is 21% while it progresses, mortality is more than 70%. Regression of stage of AKI is associated with improved survival. Continuous renal replacement therapy (CRRT) should be used with caution in patients with AKI. CRRT is preferred in the removal of inflammatory cytokines such as IL6 and TNF alpha. In type II HRS, TIPS (Transjugular intrahepatic portasystemic shunts) has been used anecdotally. Liver transplantation is definitive treatment for the AKI not responding to therapy. There is still a lot of debate as to when to perform simultaneous liver and kidney transplantation. The general consensus is to do simultaneous liver and kidney transplantation if AKI has been present for more than four weeks. For patients who receive a liver transplant alone, transient persistence of renal dysfunction post-transplant may require short term dialysis.

REFERENCES

1. Pandey CK, Karna ST, Singh A, Pandey VK, Tandon M, Saluja V. Hepatorenal syndrome: A decade later. *JAPI* 2014; 62:36-42.
2. Egerod Israelsen M, Gluud LL, Krag A. Acute kidney injury and hepatorenal syndrome in cirrhosis. *J Gastroenterol Hepatol* 2015; 30:236-43.
3. Nassar Junior AP, Farias AQ, D' Albuquerque LA, Carrilho FJ, Malbouisson LM. Terlipressin versus norepinephrine in the treatment of hepatorenal syndrome: a systematic review and meta-analysis. *PLoS One* 2014:9;9:e107466. doi:10.1371/journal.pone.0107466. eCollection 2014
4. Wong F. The evolving concept of acute kidney injury in patients with cirrhosis. *Nat Rev Gastroenterol Hepatol* 2015; 12:711-9.
5. Shah N, Kowalski A, Desai C, Lerma E. Hepatorenal syndrome. Dis Mon. 2016 Jun 29. pii: S0011-5029(16)30040-2. doi: 10.1016/j.disamonth.2016.05.009. [Epub ahead of print] Review. PubMed PMID: 27372112.
6. Angeli P, Ginès P, Wong F, Bernardi M, Boyer TD, Gerbes A, Moreau R, Jalan R, Sarin SK, Piano S, Moore K, Lee SS, Durand F, Salerno F, Caraceni P, Kim WR,
7. Arroyo V, Garcia-Tsao G. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol* 2015; 62:968-74.