Epidemiology, Pathophysiology and Management of Hepatorenal Syndrome

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ABSTRACT

Acute kidney injury (AKI) is a common presentation in patients with advanced cirrhosis hospitalised with acute decompensation. The revised classification divides AKI in cirrhotic patients into two broad subgroups, hepatorenal syndrome AKI (HRS AKI) and non-hepatorenal syndrome AKI (non-HRS AKI). Hepatorenal syndrome AKI represents the end stage complication of decompensated cirrhosis with severe portal hypertension and is characterised by worsening of renal function in the absence of pre-renal azotaemia, nephrotoxicity and intrinsic renal disease. Non-HRS AKI may be due to pre-renal hypoperfusion, bile acid nephropathy, nephrotoxicity, acute parenchymal insult or in the setting of acute on chronic liver failure (ACLF). There have been several mechanisms to explain the pathophysiology of each type of AKI, and several markers have been recently developed to differentiate between these types, and as prognostic indicators. The standard of care management for patients with HRS-AKI is to exclude other etiologies of AKI, followed by volume expansion with human albumin solution and then the introduction of vasopressors. However, some 40% of patients treated for HRS fail to respond. In this review, we will discuss the current and recent data about classification, pathophysiology and management of AKI in general with specific insight about the treatment of HRS AKI.

KEYWORDS

Cirrhosis, Hepatorenal syndrome, Acute Kidney Injury, ACLF

INTRODUCTION

Renal dysfunction is a common finding in patients with advanced liver disease with cirrhosis and portal hypertension admitted to hospital and is associated with increased morbidity and mortality. Typically, the cause of renal dysfunction is multifactorial and as such specific management is difficult, as the exact mechanisms are not fully elucidated. Within the spectrum of acute renal dysfunction in patients with cirrhosis, hepatorenal syndrome (HRS) carries the most ominous prognosis as it usually denotes a background severe portal hypertension and circulatory dysfunction. HRS-AKI accounts for around 11% of AKI in hospitalised cirrhotic patients with refractory ascites, and is associated with a high mortality. [1,2]

In advanced cirrhosis, portal hypertension results in a profound haemodynamic derangement, which in turn causes marked splanchnic vasodilatation. This results in activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system, with intense renal vasoconstriction, which then plays a major role in the pathogenesis of HRS.[3,4] In addition, advanced portal hypertension leads to greater shear stress in the splanchnic vessels, increasing bacterial translocation from the bowel, which is associated with increased generation of nitric oxide and prostacyclins. These potent splanchnic vasodilators cause pooling of the blood and decreased effective circulating systemic blood volume.[5] Initially, these effects are compensated by a hyperdynamic circulation with increased cardiac output, stroke volume and heart rate but later in the disease course, cardiac output does not increase enough to compensate.[6 7]

Historically, most of the patients admitted with renal dysfunction in the context of chronic liver disease and ascites without evidence of intrinsic renal disease were considered as having HRS until proven otherwise. Additionally, the classification of HRS was historically subdivided into two types; type 1 where deterioration in renal function occurs over days to weeks, and type 2 where deterioration occurs over months.[8] This classification has now been abandoned because it does not accurately reflect the clinical scenario. A new classification has been proposed by the International Club of Ascites (ICA), which divides patients with cirrhosis and acute kidney injury (AKI) into distinct subgroups according to the underlying pathology.[9,1] Causes of AKI in cirrhotics other than HRS are identified in the new classification and include pre-renal causes, bile acid nephropathy and acute tubular injury.[1] This type of AKI is

collectively referred to as Non-HRS AKI. This term is different from HRS-AKI which defines a functional type of AKI in the setting of normal renal parenchyma.[1] Chronic kidney disease represents a term which includes any cause that structurally affects the renal parenchyma, including glomerulopathies, interstitial renal disease, and that associated with co-morbid diseases such as diabetes mellitus and hypertension.[1,10]

Acute on chronic liver failure (ACLF) is a recently recognised clinical entity, which occurs in patients with from acute hepatic decompensation. It is characterised by multiple organ failures and is associated with increased short-term mortality.[11,12] AKI is an important factor that defines (ACLF) and it is considered one of its major components, however the pathophysiologic mechanisms of AKI in ACLF are not fully understood.[10]

Currently, therapeutic options for HRS remain supportive and are only a bridge to liver transplantation. Despite the recent advances in scientific research in this field, the optimum management for patients with HRS-AKI remains to be established, and a better understanding of the different pathophysiologic mechanisms of HRS and non-HRS AKI is required.[13,14] In this review, we aim to discuss the recent updates in the pathogenesis, diagnosis and management of HRS in the setting of the new definitions and classification of AKI.

EPIDEMIOLOGY

AKI occurs in 25-50% of cirrhotic patients who are admitted to the hospital with an episode of acute decompensation.[15] AKI is either pre-renal, renal parenchymal or obstructive in origin. Pre-renal causes include hypovolemia and HRS-AKI, and both account for 60-70% of all causes of AKI,[16] with HRS-AKI accounting for 11-20% of all causes of AKI.[16,17] Intrinsic renal causes account for around 30% of all causes of AKI, and include ischemic injury and acute tubular necrosis, acute glomerulonephritis and acute interstitial, while post-renal (obstructive) causes are relatively uncommon (less than 1%).[16,18]

AKI increases the risk of mortality as 2-31% of hospitalised cirrhotics with AKI do not survive their admission.[19,20] One and 12-months mortality rates in these patients are 58% and 63% respectively.[21] Even those who survive their hospital admission are more prone to complications of cirrhosis including ascites and hepatic encephalopathy.[19,22]

DEFINITION AND CLASSIFICATION

In the past, all AKI episodes in the setting of advanced liver disease were thought to be HRS, but recently a new classification has emerged. HRS is now described as a more homogeneous condition with specific diagnostic features.[10] Historically, HRS was classified into two types: type 1 HRs which was defined as rapid deterioration in kidney function over the course of two weeks with a serum creatinine greater than 2.5 mg/dl, and type 2 HRS which was characterised by a progressive slower course of moderate renal failure and a serum creatinine levels between 1.5 and 2.5 mg/dl.[23] The main problem with this classification was that it mainly relied on serum creatinine as the sole factor to classify HRS irrespective of the underlying pathology or aetiology. Serum creatinine does not accurately reflect the severity of renal impairment in cirrhotic patients since it is affected by several factors including assay interference with bilirubin, and muscle wasting with sarcopenia and malnutrition .[24]

In 2007, The Acute Kidney Injury Network (AKIN) proposed a new definition of AKI,[25] which was then supported by both the Acute Dialysis Quality Initiative (ADQI) and ICA in 2011.[9] The AKIN new definition of AKI allowed the use of any increase of the absolute values of serum creatinine from a baseline by as little as 0.3 mg/dl (26.5 mmol/l), or any increase of serum creatinine by 50% above the baseline within a 48-hour period.[9] This definition was based upon new data that have been validated[19,15,26,27] (Table 1).

Recently, the International Club of Ascites (ICA) has proposed a new definition and diagnostic criteria for HRS, and the older sub-classifications of type 1 and type 2, and the time limit of 2 weeks to diagnose type 1 HRS were removed.[1] In addition, the limiting threshold of serum creatinine of 2.5 mg/dl which was the cornerstone for diagnosing HRS was removed.[1] According to this new definition, HRS-AKI is now defined as worsening kidney function in patients with advanced cirrhosis which meets the ICA-AKI

criteria (table 2); failing to respond to volume expansion, the absence of recent exposure to nephrotoxic agents (such as aminoglycosides, NSAIDs or contrast media) and no evidence of shock or signs of structural kidney disease (defined as proteinuria < 500 mg/day, and haematuria < 50 RBCs per high power field and normal renal ultrasonographic findings).[1]

The new classification describes a new phenotypic classification of AKI in cirrhotics based on pathophysiologic characteristics, Non-HRS AKI now describes other causes of AKI in cirrhotics other than HRS-AKI, including bile salt nephropathy, pre-renal hypovolemia caused by bleeding, excessive diuretic use or any excessive fluid loss, acute tubular injury, acute tubular necrosis and AKI caused by intrinsic renal causes such as acute interstitial nephritis.[1]

PATHOPHYSIOLOGY OF HRS-AKI

There have been several proposed mechanisms to explain why HRS occurs in patients with advanced cirrhosis and portal hypertension.

- **Splanchnic vasodilation:** the classic and traditional hypothesis for the development of HRS is a functional reduction in renal function caused by severe systemic vasodilation and subsequent renal vasoconstriction. Severe portal hypertension and the shear stress on the portal blood vessels causes the endothelium to produce several locally-acting vasodilators such as nitric oxide (NO) and prostanoids.[28,29] These vasodilators act locally on the splanchnic vasculature causing intense vasodilatation. In turn, the subsequent decrease in the effective mean arterial blood pressure leads to activation of the renin-angiotensin and sympathetic nervous system to increase the cardiac output and heart rate to compensate for this haemodynamic compromise.[29] Progression of liver disease results in greater splanchnic vasodilation and further renal vasoconstriction and functional impairment. (figure 1). Aldosterone causes sodium and water retention which further worsen the ascites.[30,31] The evidence that HRS is a functional disorder rather than a structural disease is the success of cadaveric transplantation of kidneys from these patients,[32] post-mortem examination[32] and resolution of HRS after liver transplantation.[33] The current treatment of HRS targets splanchnic vasodilation and effective volume depletion,

by using splanchnic vasoconstrictors and albumin. However, this treatment strategy - although improving renal function in a large percentage of patients[34,35] - is still unable to reverse HRS in around 40% of cases.[36] This indicates that patients have either been misclassified as having HRS-AKI or that other mechanisms are involved.

- **Cardiac dysfunction:** cirrhotic cardiomyopathy is a term describing the abnormalities detected in the cardiac response and function of cirrhotic patients, can affect as many as 50% patients.[6] It is marked by the abnormal response to both physiologic and pathologic stresses, with patients having a relatively low cardiac output for the degree of systemic vasodilatation. Low cardiac output states in patients with cirrhosis and refractory ascites are found to be a predictor of HRS and is associated with worse prognosis. Beta-blockers prescribed to patients with ascites have been reported to cause further deterioration in HRS patients,[37,38] most probably due to their hypotensive effects.
- **Adrenal insufficiency:** adrenal insufficiency is reported to affect about 25% of patients with decompensated cirrhosis.[39] It causes further deleterious effects on the heart by down-regulating beta-adrenergic receptors and modulating the effects of catecholamines on the myocardial contraction and vascular responsiveness.[40] These effects add to the haemodynamic compromise.
- **Inflammation:** systemic inflammation is a key factor that predisposes to AKI in advanced cirrhotic patients, especially in association with ACLF.[41] Inflammation is more likely to cause Non-HRS AKI rather than HRS-AKI. Mortality rates are more than twice as high in patients with cirrhosis and renal failure who have a systemic inflammatory response than those without.[42] Patients with SBP were observed to have higher levels of pro-inflammatory cytokines (including interleukin-6 and tumour necrosis factor-α) when compared to patients with AKI but without SBP.[43]

PATHOPHYSIOLOGY OF NON-HRS-AKI

Non-HRS AKI encompasses all the other causes of AKI in the setting of decompensated cirrhosis other than HRS. This includes pre-renal causes which lead to hypovolemia, such as excess diuretic use, upper gastrointestinal bleeding and any other form of severe fluid loss, bile acid toxic effects in the

context of severe hyperbilirubinemia and other intrinsic renal causes such as acute tubular injury and necrosis (ATN) and acute interstitial nephritis.

Systemic inflammation and bacterial translocation have been proposed as one of the crucial mechanisms to explain Non-HRS AKI in advanced cirrhosis. It has been recently described and suggested to a key factor for development of AKI in the setting of ACLF. AKI in patients with ACLF is a heterogeneous disorder initiated by multiple factors including infection and associated with varying degrees of systemic inflammation that leads to multiple organ failures.[44] In the CANONIC study, patients with renal failure (defined as serum creatinine ≥ 2 mg/dl) had 20% mortality and is a diagnostic criteria for ACLF. This mortality was found to be significantly higher if the renal failure was associated with other organ failures.[11] Lack of response to treatment with albumin and terlipressin was associated with higher CLIF-OF scores, worsening bilirubin levels and non-resolving infections.[45,46] In a recent study, various markers of inflammation including nonmercaptalbumin 2 were measured in both ACLF and Non-ACLF patients, and it was found that the levels of inflammatory markers were markedly and significantly increased in ACLF patients compared to the Non-ACLF group.[47] Interestingly, the presence of renal impairment correlated with markers of inflammation (Interleukin-6, interleukin-8 and human nonmercaptalbumin 2), but not with plasma renin concentration, a marker of circulatory dysfunction.[47] These findings strongly suggest that AKI in cirrhotic patients is strongly linked to systemic inflammation, especially those with ACLF, rather than the more traditional hemodynamic dysfunction hypothesis.

In a retrospective study, renal biopsies from 65 cirrhotic patients with unexplained renal dysfunction, defined as serum creatinine above 1.5 mg/dl were studied., 28% of patients who had no evidence of structural renal disease (defined as no haematuria, no proteinuria and with a normal ultrasound scan), were found to have structural changes on their renal biopsies including chronic tubulointerstitial injury, glomerular and vascular injury. This finding is of particular importance as it demonstrates that patients who appear to have functional renal impairment may also have parenchymal lesions.[48] Another finding in of these studies was the increased renal tubular expression of Toll-like receptor (TLR4) and caspase-3 in renal biopsies from patients with Non-HRS AKI and ACLF (5 patients), a finding which was not present in patients with HRS-AKI and ACLF.[48] This suggests that Non-HRS AKI, unlike HRS-AKI, is

associated with acute tubular injury, as evidenced by tubular cell death and increased TLR4 expression. These data can be reproduced in animal models by administering endotoxin to bile-ligated rat models of cirrhosis.[49]

Gut bacterial translocation increases proinflammatory cytokines and lipopolysaccharides, which directly cause renal tubular cell apoptosis through the caspase-mediated pathway.[50] This renal tubular injury can be markedly attenuated by norfloxacin administered prior to endotoxin exposure to l in cirrhotic animal models.[49] In humans, use of norfloxacin as a primary prophylaxis for spontaneous bacterial peritonitis (SBP) was found to delay the onset of occurrence of HRS-AKI with an improved 1-year survival.[51] Rifaximin also reduces the incidence of AKI, including HRS-AKI[52]. In a retrospective analysis of data from 4 cohorts of patients treated for HRS, it was found that ACLF grade was the largest determinant of response to terlipressin and albumin and the ACLF grade affects survival independently of response to treatment.[53]

Bile acids and increased levels of serum bilirubin have been found to play a role in the pathogenesis of AKI through their direct toxic effects on the renal tubules.[54] Tubular bile casts were found in the renal biopsies of patients with HRS-AKI,[54] which may be a contributing factor to the deterioration observed in AKI cirrhotics with high bilirubin and could explain why higher bilirubin levels are associated with worse outcomes and reduced response to terlipressin therapy in HRS-AKI patients.[46] This hypothesis is supported by animal data, which showed that the use of nor-ursodeoxycholic acid may help decrease renal injury in rat models.[55]

Even though HRS-AKI and non-HRS AKI have different pathogenic mechanisms, and are considered different subtypes of AKI, they also have overlapping characteristics. The fact that only 40% of patients with HRS-AKI respond to treatment with terlipressin and albumin, and that this unresponsiveness increases with time raise the possibility that even if HRS-AKI was correctly diagnosed, HRS-AKI may evolve to non-HRS AKI. Despite an initial response, 80% of patients of HRS-AKI die within 3-months

and patients who develop HRS-AKI for more than 6-weeks typically fail to recover residual renal function even with liver transplantation.[10]

It should be noted that in patients with chronic co-morbid conditions, such as diabetes mellitus and systemic hypertension as well as patients with non-alcoholic fatty liver disease and chronic viral hepatitis B or C, or alcohol associated IgA nephropathy there may a certain degree of background parenchymal renal injury irrespective of the degree of liver dysfunction. Patients with chronic kidney disease are much more susceptible to developing AKI when exposed to any acute renal compromise.[10]

BIOMARKERS IN AKI

Early treatment of AKI is crucial for determining outcome, and therefore it is important to differentiate HRS-AKI from non-HRS-AKI. Biomarkers have been used for both identifying aetiology and determining prognosis. In some cases, biomarkers can be used to determine which patients are suitable for specific therapies.

Serum creatinine has been used to diagnose and assess the severity of AKI in routine clinical practice. However, serum creatinine is not only determined by renal function, but also dietary protein intake, muscle mass and activity and non-renal clearance..[57] Moreover, most patients with advanced decompensated cirrhosis have ascites and fluid overload, which also affects the accurate measurement of serum creatinine concentration.[58] High bilirubin levels also may affect the accuracy of serum creatinine in plasma samples due to spectral effects and reacting with the assay reagents.[59] Therefore, alternative enzymatic methods to measure creatinine in patients with high bilirubin levels are preferred to the colorimetric assays.

Fractional excretion of urinary sodium (FENa) of less than 1% has been widely used to differentiate patients with pre-renal AKI from patients without, but patients with HRS-AKI may also have reduced

FENa. Urinary sodium excretion can be affected by diuretics and sepsis, thus, its use in this clinical setting has largely diminished.[60]

There has been renewed interest in measuring the fractional excretion of urea (FEUrea) as a marker to differentiate between renal hypoperfusion and tubular injury.[61] Urea is filtered by the glomeruli and reabsorbed in the proximal renal tubules and concentrated in the inner medulla to generate a concentration gradient,[62] so, any renal hypoperfusion should decrease its fractional excretion, whereas any tubular injury should cause an increase in its fractional excretion. As diuretics predominantly affect the ascending loop of Henle and distal tubule, urea is less affected by the action of diuretics.[60] In a recent cohort study performed on 50 patients with cirrhosis and ascites admitted with AKI, FEUrea was found to be a promising tool to differentiate AKI caused by different causes of AKI including HRS, pre-renal azotaemia and tubular injury.[61]

Recently, different studies have suggested serum cystatin C level to be an alternative to serum creatinine for assessing renal function and more importantly predicting prognosis. Cystatin C is secreted from all nucleated cells in the body and freely passes through the glomeruli, therefore, it is exclusively removed through the kidney.[63] A recent study which included 350 patients with cirrhotic ascites showed that serum cystatin C is an independent predictor of mortality and HRS in patients with cirrhotic ascites when compared to serum creatinine.[64] However, cystatin C is increased in inflammatory conditions, and older studies have noted a progressive rise between patients with Child Turcott Pugh grades from A to C. There has now been standardisation of cystatin C assays, increasing reliability of measurement.

Serum neutrophil gelatinase-associated lipocalin (NGAL) has been the most widely investigated marker among the newer biomarkers. NGAL is a predominantly synthesised in the liver but is also expressed by the renal tubules following an inflammatory insult, be it ischemic, toxic or infective. Although some studies have suggested that it differentiates HRS-AKI, pre-renal azotaemia and acute intrinsic kidney disease, the main limitation is the significant overlap of NGAL values in different types of AKI.[65] Similarly other urinary biomarkers; interleukin 18, kidney injury molecule -1, hepatic fatty acid binding protein,

insulin-like growth hormone 1, tissue inhibitor of metallo-proteinase 2 have not been shown to clearly separate AKI-HRS and non-HRS-AKI.

In a recent study, high levels of microRNA-21 and low levels of microRNA 146a and 210 were observed in both ATN and HRS patients compared to controls with a statistically significant difference between ATN and HRS. These preliminary results reported that different microRNAs can potentially be used to differentiate between ATN and HRS, but require further evaluation.[66]

TREATMENT

Early diagnosis and rapid medical treatment is crucial in HRS, as AKI-HRS may progress to non-HRS-AKI. The standard of care in the management of HRS is based on the understanding of the hemodynamic dysfunction, which underpins its pathogenesis. Patients suffering from cirrhosis, ascites, and AKI should be managed according to the International Club of Ascites recommendations.[67] Optimised biomarkers to differentiate HRS 1 from structural kidney injury and renal function algorithm, including the Royal Free Hospital cirrhosis glomerular filtration rate equation, may help to refine management.[68]

Volume expansion and removing nephrotoxic agents: initially, any potential nephrotoxic drugs (i.e., NSAIDs, diuretics, angiotensin-converting enzyme inhibitors, antibiotics, etc.) should be minimized or stopped, and any element of hypovolemia corrected (figures 2,3).[69] Intravascular volume assessment is an initial key step to ensure that hypovolemia is adequately managed. Accurate volume assessment in cirrhotic patients in terms of the hyperdynamic circulation and decreased systemic vascular resistance and in association with commonly encountered ascites is very challenging.[10] Unfortunately, monitoring central venous pressure has a limited role, as it poorly correlates with the intravascular response to fluid challenge. Additionally, the presence of ascites leads to increased central venous pressure without a correspondingly high ventricular preload.[70]

A meta-analysis of 38 trials comparing the use of hydroxyethyl starch (HES), crystalloids, albumin, and gelatin in intensive care patients with AKI showed that volume resuscitation with albumin in comparison to crystalloids does not reduce mortality, while hydroxyethyl starch was associated with a significantly increased risk of AKI and mortality.[71] Although another study showed no significant difference in 90-day mortality after resuscitation with 6% HES or saline, patients resuscitated with 6% HES were more likely to require renal replacement therapy.[72]

Vasoconstrictors and albumin: Guidelines recommend using vasoconstrictors in combination with albumin as first-line treatment for HRS-AKI[73] to counteract splanchnic arterial vasodilation.[74] The goal of using albumin is to combat the hemodynamic dysfunction by antagonising the decreased effective circulating volume and increasing the mean arterial pressure (MAP).

Most commonly used vasoconstrictors are noradrenaline, vasopressin analogues (terlipressin), somatostatin analogues (octreotide), and midodrine.[75] Terlipressin is the most extensively studied vasopressor of this group,[76] and is now considered as the first line of treatment of choice in treating HRS-AKI patients in Europe. This is because it has a greater affinity for vasopressin 1 (V1) receptors in splanchnic beds rather than V2 receptors in the kidneys, thus exerting its vasoconstrictor effects on the splanchnic viscera without causing equal renal vasoconstriction.[76] Even terlipressin is a powerful vasoconstrictor and can cause ischemia, so should not be used in patients with symptomatic ischemic heart disease, peripheral vascular disease or recent stroke. Terlipressin is not approved by the Food and Drug Administration for use in the USA or Canada as some recent large RCTs failed to show a clear benefit for terlipressin in treating HRS type1.[77]

Numerous studies and meta-analyses have been conducted to investigate the use of different vasopressors and albumin in managing HRS (table 3).[78,79] A network meta-analysis including 16 randomized controlled clinical trials (RCTs) of patients with HRS reported that the combination of terlipressin and albumin, noradrenaline and albumin, or continuous infusion of terlipressin and albumin were all more effective than albumin alone to achieve a complete reversal of HRS, and that the

combination of octreotide and albumin or midodrine and albumin failed to show superior effects than using albumin alone.[80] There was no significant difference between different regimens in terms of HRS recurrence, other adverse events, or mortality, as reported in previously conducted meta-analyses.[80]

Comparator studies suggest that noradrenaline is an attractive alternative to terlipressin in the treatment of HRS, and may be associated with fewer adverse events,[81,82] while other studies demonstrated that administering terlipressin by a continuous infusion instead of intermittent boluses is better tolerated.[76,83] A recent prospective study explored safety and efficacy of terlipressin infusion at 2 mg/day versus bolus dose starting at 0.5 mg, 4 hourly in patients with HRS, and showed significantly fewer adverse events in the infusion group in comparison with bolus administration.[84] In preliminary studies, terlipressin has been given to outpatients and reported to be safe, well tolerated, and an effective option for the treatment of HRS as a bridge to transplant.[85,86]

There is strong data supporting the efficacy of human albumin solution (HAS) in the treatment of HRS.[87] The optimal dose of albumin used for HRS treatment remains poorly identified, and doses vary between studies. However, a recent meta-analysis including 19 clinical trials demonstrated that the most important factor in predicting a successful response to albumin therapy appears to be the cumulative dose.[35] This meta-analysis observed a dose-response relationship between the amount of infused albumin and survival, with significantly improved survival with 100-g increments, and expected 30-days survival rates among patients receiving cumulative albumin doses of 200, 400 and 600 g were 43.2 %, 51.4 %, and 59.0 %, respectively, independent of treatment duration, vasoconstrictor type, or MAP.[35]

Moreover, volume expansion using albumin during spontaneous bacterial peritonitis following large volume paracentesis, and with antibiotic prophylaxis in advanced cirrhosis with low ascitic fluid protein can help prevent HRS-AKI.[88] Albumin has many theoretical advantages in terms of its anti-inflammatory and antioxidant properties, in addition to its role in increasing oncotic pressure as a plasma protein.[87]

Liver transplantation (LT) is the best and most definitive treatment option for AKI, by curing end-stage liver disease and subsequently reversing HRS-AKI.[89] The overall 1- and 5-year survival following LT in the setting of pre-transplantation AKI were 77% and 69%, respectively.[90] The pre-transplantation renal function was shown to be an important predictor of renal dysfunction after LT, with shorter duration of HRS-AKI (<4 weeks) having more improved outcome.[91] It was found that if AKI episode persisted for longer than 6-weeks, then patients were less likely to recover renal function, and as such should be considered for combined liver-kidney transplantation.[44]

A recent retrospective study from Japan observed that preoperative renal dysfunction with a cut off GFR <40 mL/min/1.73m2 upon admission was an independent risk factor for 1-year survival after living-related transplant recipients, and the postoperative 1, 3 and 5-year survival was significantly lower in patients with preoperative HRS-AKI than in patients without HRS.[92] Although being the ideal option, liver transplantation is not available for all patients. .

Renal replacement therapy (RRT): the effect of RRT remains controversial in the management of HRS-AKI, with similar short-term (30 days) and long-term (180 days) survival compared to non-RRT treated patients suggesting that routine use of RRT may not be beneficial in HRS.[93] The Acute Dialysis Quality Initiative group recommended renal support only for patients with HRS-AKI if there was an acute potentially reversible event, or liver transplantation planned, due to the lack of any evidence for a major survival benefit for RRT in HRS-AKI.[44,93]

Trans-jugular intra-hepatic porto-systemic shunting (TIPS) is also an option for treatment of HRS-AKI, especially in patients failing to respond to pharmacological treatment, or with frequent relapses. TIPS increases the effective renal blood flow by decreasing portal pressure and redistributing regional vascular resistance.[94] A meta-analysis studied the efficacy and safety of TIPS for the treatment of HRS showed that serum creatinine, serum sodium, blood urea nitrogen, sodium excretion, and urine volume significantly improved following TIPS. The higher incidence of hepatic encephalopathy limits the standard use of TIPS as a routine therapeutic option for HRS.[95]

Experimental agents: Research is ongoing to study potential promising medications for the treatment of HRS. Seralaxin (a recombinant human relaxin-2) is a peptide with vasoprotective properties, which was studied in rat models of cirrhosis, showed an increase in renal perfusion by reducing renal vascular resistance. Studies to compare IV serelaxin infusion with terlipressin IV bolus in cirrhotic patients with renal impairment showed that serelaxin infusion increased the total renal arterial blood flow by 65% from baseline, and was safe and well tolerated, with no adverse effects related to systemic blood pressure or hepatic perfusion.[96]

Nebivolol is a third-generation vasodilator beta-blocker and has been studied in D-galactosamine-induced HRS in rats, were it was reported to have anti-oxidant, anti-inflammatory, and anti-apoptotic properties, with reno-protective and hepatoprotective effects. This potentially makes nebivolol a promising drug with a possible effect in the prevention of HRS or as an add-on medication in patients with known HRS.[97]

A randomized placebo-controlled clinical trial studied the safety of adding pentoxifylline (PTX) to albumin with midodrine and octreotide (AMO) in the treatment of HRS-1 and was shown to be safe, but further large-scale prospective studies are needed to validate the efficacy of PTX.[98]

Rifaximin therapy was investigated in the context of preventing not treating ongoing HRS, and the overall blood urea nitrogen and serum creatinine and HRS were statistically significantly lower in rifaximin group than control group.[99] Rifaximin may also decrease the levels of interleukin-6, tumour necrosis factor-α, and endotoxins, which play a crucial role in the development of SBP and HRS.

CONCLUSIONS

In conclusion, the change in the classification of AKI and further advances in understanding the pathophysiological basis of this syndrome is likely to lead to newer therapies for this terrible complication of cirrhosis, which is associated with high mortality rates.

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TABLES:

Table (1): International Club of Ascites definition and grading of AKI in patients with cirrhosis AKI: Acute Kidney Injury.

Stage of AKI	Definition
1	Increase in serum creatinine ≥0.3 mg/dl (26.5 mmol/l) or an increase in serum creatinine ≥1.5-fold to 2-fold from baseline.
2	Increase in serum creatinine >2-fold to 3-fold from baseline
3	Increase of in serum creatinine >3-fold from baseline or in serum creatinine ≥4.0 mg/dl (353.6 mmol/l) with an acute increase ≥0.3 mg/dl (26.5 mmol/l) or initiation of renal replacement therapy

Table (2): ICA diagnostic criteria of HRS-AKI. ICA: International Club of Ascites, HRS: hepatorenal syndrome, AKI: Acute Kidney Injury, RBCs: Red Blood Cells

Table 2: ICA diagnostic criteria of HRS-AKI

- Diagnosis of cirrhosis and ascites
- Diagnosis of AKI according to ICA-AKI diagnostic criteria
- No response of 48 hours of plasma volume expansion using albumin 1g/kg of body weight and withdrawal of diuretics.
- Absence of shock
- No current or recent use of nephrotoxic drugs
- No macroscopic signs of structural kidney injury defined as:
    - Absence of proteinuria (<500 mg/day)
    - Absence of microhaematuria (<50 RBCs per high power field)
    - Normal renal ultrasonography

Table (3): Randomized controlled trials of albumin and vasoconstrictors for treatment of HRS

Author	Year	Treatment/comparison	HRS %	Albumin	HRS reversal	Survival
Solanki et al	2003	Terlipressin	24 (100)	40 g/d to keep CVP 10–12	42	42
		Placebo			0	0
Alessandria et al	2007	Terlipressin	22 (41)	To keep CVP 10–15	83	92
		Norepinephrine			70	80
Neri et al	2008	Terlipressin	52 (100)	1 g/kg, then 20–40 g/d	81	42
		Placebo			19	15
Martin-Llahi et al	2008	Terlipressin	46 (56)	1 g/kg followed by 20–40 g/d	44	27
		Placebo			9	19
Sanyal et al	2008	Terlipressin	112 (100)	1 g/kg, then 25 g/d	34	13
		Placebo			13	9
Sharma et al	2008	Terlipressin	40 (100)	To keep CVP 10–12	50	45
		Noradrenaline			50	45
Singh et al	2012	Terlipressin	46 (100)	20 g/d	39	39
		Noradrenaline			43	48

Cavallin et al	2015	Terlipressin, midodrine, and octreotide	49 (92)	1 g/kg followed by 20–40 g/d	70 29	70 59

FIGURES:

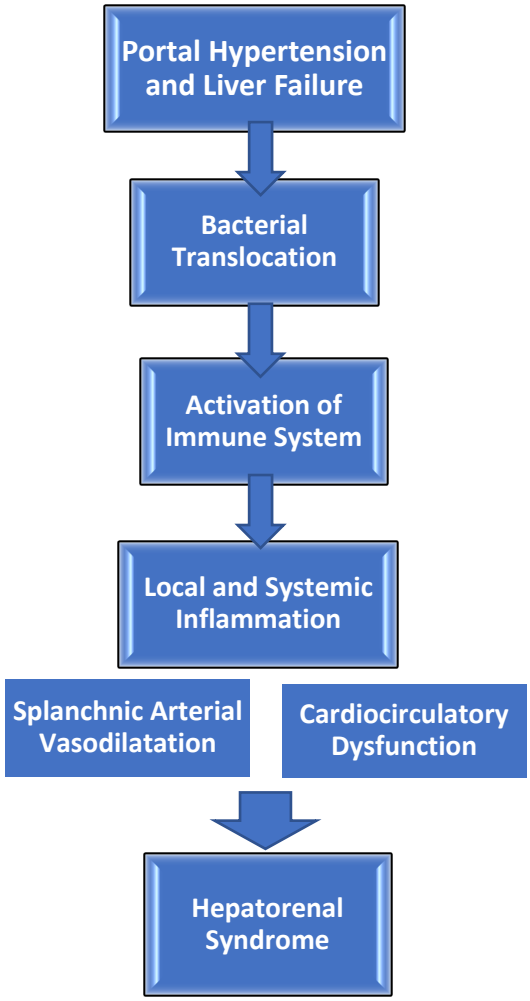

Figure 1: Pathophysiological basis of hepatorenal syndrome

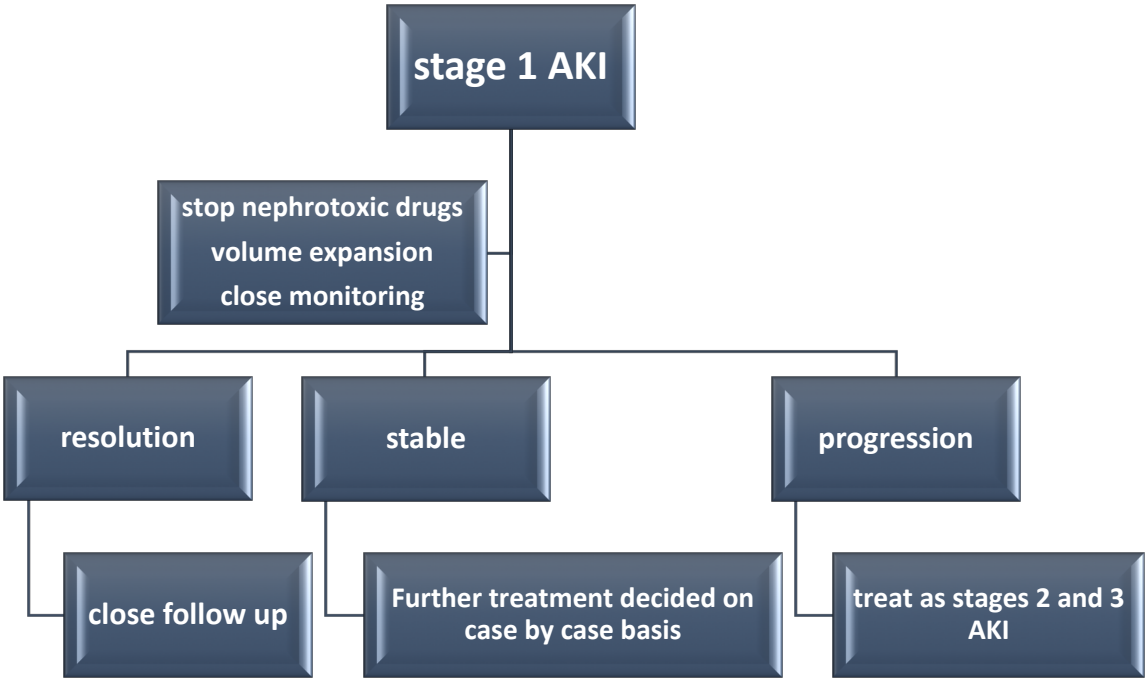

Figure 2: Management of stage 1 AKI in cirrhosis

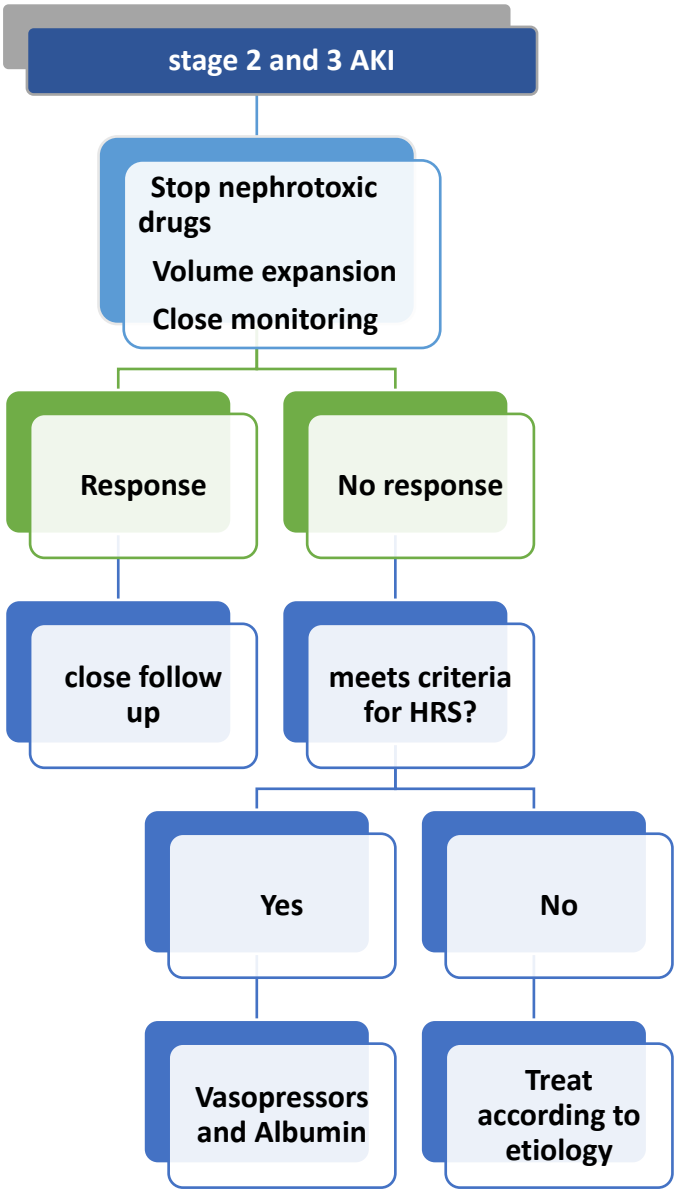

Figure 3: Management of stage 2 and 3 AKI in cirrhosis.