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Review

OVERVIEW OF HEPATORENAL SYNDROME

HEPATORENAL SENDROMA GENEL BAKIŞ

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ABSTRACT

Hepatorenal syndrome (HRS) is a severe complication of advanced cirrhosis associated with high mortality. Since no specific diagnostic test exists, the diagnosis is primarily based on exclusion. It should be particularly considered in cirrhotic patients who develop new-onset renal dysfunction. The pathophysiology of HRS is highly complex; cirrhosis-related hemodynamic alterations, vascular dysregulation, and impairment of antioxidant defense mechanisms contribute to its development. Therapeutic approaches are likewise multifaceted. The initial step involves the correction of precipitating factors. Albumin administration and vasoconstrictor therapy represent the cornerstone of current management strategies. However, once HRS develops, it is often difficult to treat and is associated with poor outcomes. Therefore, recognizing risk factors, identifying preventable causes at an early stage, and promptly implementing appropriate supportive measures are of critical importance. Current evidence indicates that many aspects of HRS pathophysiology and treatment remain unclear. Given its high mortality rate and therapeutic challenges, improved understanding and management of this syndrome by clinicians are essential for optimizing patient care. This review also highlights practical diagnostic challenges and emerging biomarker-based approaches, emphasizing future directions for improved management of HRS-AKI.

Keywords: acute kidney injury, kidney, hepatorenal syndrome, liver, cirrhosis

ÖZET

Hepatorenal sendrom (HRS), ileri evre sirozda görülen ve yüksek mortalite ile seyreden ciddi bir komplikasyondur. Spesifik bir tanı yöntemi bulunmadığından, tanı, çoğunlukla dışlama esasına dayanır. Özellikle yeni gelişen böbrek fonksiyon bozukluğu olan siroz hastalarında klinik olarak akılda bulundurulması gereken bir durumdur. HRS'nin patofizyolojisi oldukça karmaşıktır; siroza bağlı hemodinamik değişiklikler, vasküler disregülasyon ve antioksidan savunma mekanizmalarındaki bozulmalar bu sürece katkıda bulunmaktadır. Tedavi yaklaşımları da benzer şekilde çok boyutludur. Öncelikli olarak kolaylaştırıcı faktörlerin ortadan kaldırılması esastır. Albümin replasmanı ve vazokonstriktör ajanların kullanımı güncel tedavi stratejilerinin temelini oluşturmaktadır. Ancak sendrom geliştiğinde, yönetimi zor ve sıklıkla yetersiz kalan bir klinik tablo ile karşılaşılmaktadır. Bu nedenle, risk faktörlerinin iyi anlaşılması, önlenebilir nedenlerin erken dönemde tanımlanarak ortadan kaldırılması ve uygun destek tedavilerinin zamanında uygulanması büyük önem taşımaktadır. Mevcut bilgiler HRS'nin patofizyolojisi ve tedavisinde birçok bilinmeyen olduğunu göstermektedir. Yüksek mortalite oranı ve tedavi güçlükleri göz önünde bulundurulduğunda, bu sendromun klinisyenler tarafından daha iyi anlaşılması ve yönetilmesi klinik pratik açısından kritik öneme sahiptir. Bu derleme ayrıca HRS-AKI'nin tanısındaki pratik zorluklara ve biyobelirteç temelli yeni yaklaşımlara dikkat çekmekte, gelecekteki yönetim stratejilerinin geliştirilmesine yönelik olası yönelimleri vurgulamaktadır.

Anahtar Kelimeler: akut böbrek hasarı, böbrek, hepatorenal sendrom, karaciğer, siroz

Introduction

Hepatorenal syndrome (HRS) represents a serious complication of advanced liver cirrhosis, marked by a progressive reduction in glomerular filtration rate (GFR) (1). Unlike intrinsic kidney diseases, HRS develops without proteinuria, hematuria, or structural changes on renal imaging, even though GFR is significantly reduced (2). In patients admitted with acute decompensated cirrhosis, acute kidney injury (AKI) occurs in roughly one-fifth to one-half of cases, highlighting its frequent and severe impact (3–5). The appearance of AKI in cirrhotic individuals is regarded as a key predictor of poor outcome, being strongly associated with higher mortality (6). Furthermore, renal status is incorporated into prognostic models such as the Model for End-Stage Liver Disease (MELD), in which the presence of AKI or chronic kidney disease (CKD) indicates worsening disease and may prompt consideration of liver transplantation (7).

Diagnosis

The variant of hepatorenal syndrome formerly referred to as type 1 HRS presents with a sudden and marked decline in renal function, typically occurring within two weeks, during which serum creatinine levels double and exceed 2.5 mg/dL in the absence of intrinsic kidney disease (8). Under the current acute kidney injury (AKI) framework, the condition encompasses any acute reduction in renal function, identified by either a greater than 50% increase from baseline creatinine or a rise of at least 0.3 mg/dL (26.4 µmol/L) within 48 hours (9).

The diagnosis of Hepatorenal Syndrome – Acute Kidney Injury (HRS-AKI), a refined classification, requires the presence of cirrhosis with ascites, AKI stage 2 or higher, and no full or partial response after a minimum of two days of diuretic withdrawal and plasma volume expansion with albumin. Additional criteria include the absence of shock, no ongoing or recent exposure to nephrotoxic medications, and no evidence of intrinsic kidney disease. Intrinsic renal disease is ruled out by findings such as proteinuria exceeding 500 mg/day, significant microscopic hematuria (more than 50 red blood cells per high-power field), abnormal levels of urinary injury biomarkers (when available), or abnormal findings on renal ultrasound. In addition to these established diagnostic criteria, recent studies have focused on biomarkers to improve differentiation between HRS-AKI and other causes of renal dysfunction. Biomarkers have been investigated as tools to differentiate HRS-AKI from acute tubular necrosis (ATN), since traditional markers such as serum creatinine are often insufficient. Urinary neutrophil gelatinase-associated lipocalin (NGAL) is the most widely studied and is usually elevated in ATN, while remaining relatively low in HRS-AKI. This makes NGAL a potentially useful marker for differential diagnosis. However, standardized thresholds are lacking, and current international guidelines have not included NGAL or other biomarkers in routine practice. Therefore, their role remains investigational (10).

The type previously defined as HRS type 2 is characterized by a gradual decrease in renal function in the setting of chronic kidney disease (CKD). According to the new definition, HRS type 2 is a form of Hepatorenal Syndrome -non Acute Kidney Injury (HRS-NAKI) and is a type of CKD (7).

Table 1. Diagnostic criteria for HRS-AKI

Diagnostic Criteria
Cirrhosis with ascites
Diagnosis of AKI according to ICA criteria
No improvement after 2 days of diuretic withdrawal and albumin infusion (1 g/kg, max 100 g/day)
Absence of shock
No current or recent use of nephrotoxic drugs
No evidence of structural kidney injury (proteinuria >500 mg/day, microhematuria >50 RBC/hpf, abnormal renal ultrasonography)

Pathophysiology

The underlying mechanism of hepatorenal syndrome (HRS) is largely attributed to a marked reduction in effective arterial blood volume, which occurs as a consequence of pronounced splanchnic vasodilation secondary to portal hypertension — a hallmark feature of advanced cirrhosis (11). This vasodilatory state leads to arterial underfilling, triggering neurohumoral compensatory systems such as the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system, both of which promote vasoconstriction and sodium retention. In parallel, systemic inflammation and oxidative stress, driven by an imbalance between pro-inflammatory cytokine activation and antioxidant defense impairment, further worsen renal hypoperfusion and functional decline (12).

In patients with cirrhosis, intrahepatic vascular resistance rises substantially, while vasoactive substances, including nitric oxide (NO), carbon monoxide, prostacyclins, and endocannabinoids, are excessively produced within the splanchnic circulation. This overproduction causes regional vasodilation, which in turn decreases systemic vascular resistance and effective arterial volume. As a compensatory adaptation, the RAAS, sympathetic system, and arginine vasopressin pathway become activated in an effort to maintain effective arterial blood flow (EABF). Persistent activation of these mechanisms leads to renal vasoconstriction, impaired water excretion, and sodium retention, ultimately reducing renal perfusion. In the initial stages of this process, glomerular filtration rate (GFR) may remain relatively preserved owing to the vasodilatory influence of renal prostaglandins on afferent arterioles. However, as hepatic dysfunction advances or when nonsteroidal anti-inflammatory drugs (NSAIDs) are used, this compensatory balance is disrupted, predisposing the kidneys to hypoperfusion (12). Moreover, hyperammonemia, a common feature of cirrhosis, interferes with arginine metabolism, thereby impairing nitric oxide synthesis and aggravating renal circulatory dysfunction (14).

Both insufficient and excessive NO production can impair renal blood flow. Inadequate NO availability is believed to result from elevated levels of dimethylarginines, particularly symmetric (SDMA) and asymmetric dimethylarginine (ADMA). In advanced stages of liver disease, ADMA levels rise, leading to inhibition of NO synthesis. Similarly, elevated SDMA concentrations are associated with reduced NO production, ultimately contributing to diminished renal perfusion (1). Due to this relationship, SDMA has been proposed as a potential biomarker for identifying HRS in patients with cirrhosis (15).

Another key mechanism involves bacterial translocation resulting from increased intestinal permeability associated with cirrhosis. This allows bacteria and their products to enter the splanchnic circulation, promoting both splanchnic and systemic vasodilation. In response, the body initiates compensatory vasoconstrictive systems, most notably the RAAS, which ultimately leads to renal vasoconstriction (16). A well-recognized example of this pathway is the role of systemic inflammation in the development of AKI in cirrhotic patients. Notably, up to one-third of individuals with HRS-AKI exhibit signs of inflammation in the absence of overt infection. This inflammatory response may be triggered by sterile conditions such as alcoholic hepatitis or drug-induced liver injury, or by infectious processes like bacterial infections. In both cases, either damage-associated molecular patterns (DAMPs) from hepatocellular injury or pathogen-associated molecular patterns (PAMPs) from microbes stimulate immune activation. This leads to elevated production of cytokines and chemokines. These inflammatory mediators can contribute to renal dysfunction by promoting microthrombus formation in the renal microcirculation, largely through immune mechanisms and activation of leukocytes and platelets, thereby directly injuring renal tubular cells (17,18). This inflammatory cascade is illustrated in Figure 1.

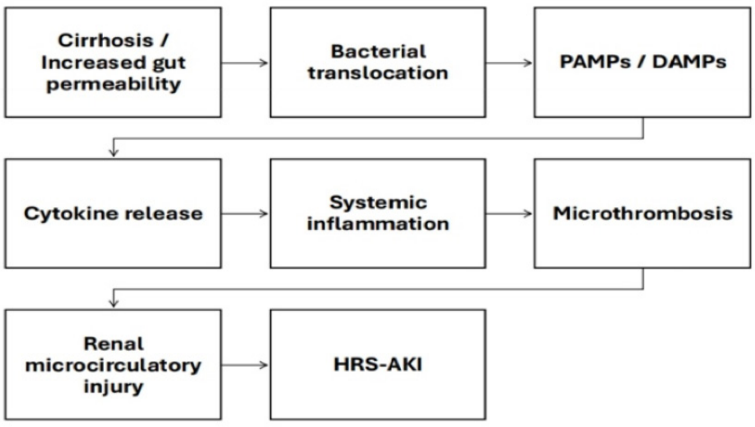

Figure 1. Inflammatory pathways linking cirrhosis, bacterial translocation, and renal dysfunction in HRS-AKI.

In addition to these, several other mechanisms are associated with HRS. It has been suggested that intra-abdominal pressure from refractory ascites may lead to HRS, and the improvement in AKI after paracentesis to reduce intra-abdominal pressure supports this mechanism (19). The probability of relative adrenal insufficiency is high in patients with decompensated ascites, and it is thought that this may lead to HRS (20,21).

Acute-on-Chronic Liver Failure (ACLF) represents an acute decline in hepatic function occurring in individuals with pre-existing chronic liver disease and is closely linked to systemic inflammation and multiple organ dysfunction. With increasing ACLF grades, both the likelihood and severity of HRS-AKI rise, and this progression is associated with higher short-term mortality (3,22).

Treatment

The initial approach to the management of HRS involves addressing precipitating factors to prevent further deterioration of renal function. In cirrhotic patients with AKI, general measures include withdrawal of diuretics, careful adjustment of agents such as lactulose when diarrhea-induced dehydration is present, avoidance of nephrotoxic medications, and correction of underlying causes of intravascular volume depletion, such as gastrointestinal bleeding. By definition, HRS-AKI is characterized by the absence of renal recovery despite these corrective interventions. Therefore, implementation of these supportive measures is essential before establishing the diagnosis of HRS-AKI in patients with cirrhosis (22,23).

In patients diagnosed with HRS-AKI, initial management involves intravenous (IV) albumin at a dose of 1 g/kg/day for the first two days, along with discontinuation of diuretics. This approach also helps rule out prerenal azotemia. At this point, nonselective beta-blockers should be temporarily withheld due to their negative effects on cardiac contractility (24). Albumin plays a central role in the treatment of HRS and is typically used in combination with vasoconstrictors to maintain EABF and enhance cardiac output. Its efficacy, particularly when combined with the vasoconstrictor terlipressin, has been well established through multiple studies (25). After the initial loading dose, the usual maintenance dose is 20–40 g IV once daily (26,27). In addition to its volume-expanding properties, albumin also contributes to HRS treatment through its antioxidant and anti-inflammatory actions (28).

Vasoconstrictor agents used in the management of HRS-AKI include terlipressin, norepinephrine, octreotide, and midodrine. Among these, terlipressin remains the most extensively studied and has demonstrated the highest efficacy in improving renal function. Clinical evidence suggests that continuous intravenous infusion of terlipressin provides a more favorable safety profile and greater effectiveness compared with intermittent bolus administration (29–32). When used in combination with albumin, terlipressin enhances circulatory stability and increases the likelihood of renal function recovery. Nevertheless, clinicians should be aware of its potential adverse effects, including angina, arrhythmia, syncope, and peripheral ischemia involving areas such as the bowel, digits, or scrotum. Accordingly, it is contraindicated in patients with ischemic cardiomyopathy or peripheral vascular disease (33). The primary therapeutic mechanism of terlipressin is reducing splanchnic vasodilation, thereby improving effective arterial blood volume. The usual starting regimen involves intravenous bolus doses of 0.5–1 mg every 4–6 hours. If serum creatinine fails to decrease by at least 25% within three days and no significant side effects are observed, the dose may be gradually increased up to 2 mg every 4 hours, not exceeding a maximum treatment duration of 14 days. Therapy is generally discontinued once serum creatinine falls below 1.5 mg/dL or returns to baseline. As noted earlier, continuous infusion is preferred over bolus therapy due to better tolerance and hemodynamic control (34,35). Additionally, terlipressin may exert vasopressin-mediated anti-inflammatory effects, contributing to reduced systemic inflammation in cirrhosis-associated kidney injury (36). Despite these benefits, terlipressin has not been shown to improve overall survival, and respiratory failure remains a recognized complication, particularly among patients with advanced liver disease or fluid overload (3,10).

Emerging evidence suggests that continuous infusion regimens may be better tolerated and associated with fewer adverse events compared to bolus administration. Nevertheless, these regimens remain off-label and are not yet incorporated into major guideline recommendations (3).

Norepinephrine and midodrine are vasoconstrictive agents that exert their effects through stimulation of α-1 adrenergic receptors. Norepinephrine, similar to vasopressin, shows enhanced efficacy and safety when administered alongside albumin. However, its use requires close monitoring due to potential cardiac side effects, including both tachyarrhythmias and bradyarrhythmias (37). Midodrine is frequently used in the management of HRS-AKI, especially in regions such as North America, where terlipressin is not readily available. By inducing systemic vasoconstriction, it raises mean arterial pressure, which in turn improves renal perfusion and increases renal blood flow. In clinical practice, midodrine is typically combined

with octreotide and albumin for treating HRS-AKI. Octreotide acts as a non-specific inhibitor of various splanchnic vasodilators, particularly glucagon. It has minimal efficacy when used as monotherapy in HRS-AKI. Nonetheless, the therapeutic effectiveness of the midodrine–octreotide–albumin regimen is generally considered inferior to that of terlipressin (38,39).

The combination of midodrine, octreotide, and albumin has been evaluated as an alternative therapy. Although it may offer modest hemodynamic improvement, it is clearly less effective than terlipressin or norepinephrine and should be considered only in settings where these agents are unavailable (10).

Therapeutic plasma exchange is an effective treatment for acute liver failure. It is beneficial because it reduces inflammatory mediators and removes toxic substances. Although preliminary data are encouraging, the evidence remains insufficient to recommend routine use in HRS-AKI (40).

Renal replacement therapy (RRT) is used in conditions such as severe acidosis, hyponatremia, treatment-unresponsive hyperkalemia, and severe hypervolemia. Continuous RRT is used in patients with hemodynamic impairment. However, patients with HRS who start RRT generally have a worse prognosis (41).

Transjugular intrahepatic portosystemic shunt (TIPS) can be used in the treatment of HRS by correcting the hemodynamic changes that cause it. Nevertheless, randomized controlled trial (RCT) evidence is limited, and TIPS should be reserved for carefully selected patients with preserved hepatic function and no contraindications (1,42).

Hepatorenal syndrome (HRS) serves as an important clinical marker indicating the need for liver transplantation, which remains the only curative treatment for patients with HRS-AKI. Nevertheless, renal function recovery is not always achieved following isolated liver transplantation, particularly in cases with prolonged renal hypoperfusion or structural injury. In such circumstances, simultaneous liver–kidney transplantation (SLKT) should be considered as an appropriate therapeutic strategy (43,44). The frequency of SLKT procedures has progressively increased over recent years, reflecting a growing recognition of its benefits in selected patients. Since serum creatinine constitutes a key component of the Model for End-Stage Liver Disease (MELD) score, individuals with coexisting renal impairment generally obtain higher allocation priority on transplant waiting lists (45).

Beyond therapeutic interventions, several strategies can reduce the risk of HRS development. The correction of precipitating events, particularly gastrointestinal bleeding and bacterial infections, is of primary importance. In addition, large-volume paracentesis should always be accompanied by albumin infusion, as omitting albumin replacement significantly increases the risk of circulatory dysfunction and subsequent renal impairment (27). Prophylactic use of antibiotics to prevent spontaneous bacterial peritonitis in patients with advanced liver failure has reduced the incidence of HRS (46). Regarding long-term albumin administration, the ANSWER trial demonstrated potential benefits in terms of reducing complications and improving survival in patients with decompensated cirrhosis. However, the extrapolation of these results to patients with HRS-AKI should be approached with caution, as specific evidence in this subgroup remains limited (47). In addition, close monitoring of renal functions of patients who are started on diuretics, avoiding excessive diuretic use, and avoiding the use of nephrotoxic drugs such as NSAIDs are other strategies for preventing HRS (48).

Prognosis

The prognosis of HRS-AKI is extremely poor, with median survival limited to only days or weeks in the absence of treatment (7). Transplant-free survival is significantly better in patients who respond to terlipressin compared with non-responders (49,50). Prognosis is also worse in individuals with pre-existing chronic kidney disease (51), and the severity of AKI is directly correlated with mortality (52). Furthermore, patients presenting with multiple organ failure or elevated lactate levels are at particularly high risk of adverse outcomes (53,54). A large meta-analysis including 18,747 patients with cirrhosis demonstrated that the presence of AKI increased in-hospital mortality up to sixfold, with important predictors being higher MELD scores, Child-Pugh class C, ascites, and sepsis (55). In contrast, patients with HRS-NAKI exhibit a relatively more favorable prognosis, with a median survival of approximately 6.7 months (56).

Prevention of HRS-AKI

Prevention of HRS-AKI in cirrhosis focuses on recognizing and managing triggers that impair renal perfusion. In high-risk patients, antibiotic prophylaxis for spontaneous bacterial peritonitis (SBP) helps reduce infection-related inflammation and kidney injury. During large-volume paracentesis, albumin infusion (6–8 g/L of fluid removed) is recommended to preserve circulatory stability and prevent renal dysfunction. Diuretics should be used cautiously, and nephrotoxic agents such as NSAIDs, aminoglycosides, and contrast media should be avoided to limit further

renal impairment. Together, these measures can lower the risk of HRS-AKI and improve outcomes in advanced cirrhosis (3,10,47).

Conclusion

HRS is a life-threatening complication of advanced cirrhosis, characterized by high mortality and challenging management due to its complex pathophysiology. Despite advances in supportive and pharmacological therapies, many aspects of its pathogenesis and treatment remain unclear. Clinicians should maintain a high index of suspicion for HRS, particularly in cirrhotic patients presenting with AKI or concomitant CKD. Given the poor prognosis of HRS-AKI and the limited long-term efficacy of current medical therapies, liver transplantation represents the only definitive treatment. Therefore, timely evaluation and strong encouragement of eligible patients for transplantation are essential. Increasing clinician awareness of HRS and its management is a crucial step toward reducing morbidity and mortality in patients with cirrhosis.

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