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Hepatorenal syndrome: historical perspectives on the recognition of the problem. Review

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Hepatorenal syndrome (HRS) is a severe functional complication of portal hypertension and liver cirrhosis, characterized by profound renal hemodynamic dysfunction in the absence of significant structural kidney damage and associated with high mortality. Recent studies report a 90-day mortality of 40–60 %, depending on disease severity and therapeutic interventions. The pathophysiology of HRS is primarily driven by marked splanchnic vasodilation, resulting in reduced effective arterial blood volume, renal vasoconstriction, and a decline in glomerular filtration rate. The association between advanced liver disease and renal dysfunction was first recognized in the 19th century, whereas a clear clinical definition of HRS emerged in the mid-20th century. Subsequent advances led to the classification of HRS into two major types: type I, an acute, rapidly progressive form with a very poor prognosis, and type II, a more indolent form commonly associated with refractory ascites. Therapeutic strategies focus on restoring effective arterial circulation. The most evidence-based pharmacological treatment is the combination of vasoconstrictors, particularly terlipressin, combined with albumin. Invasive approaches, including transjugular intrahepatic portosystemic shunt (TIPS), peritoneovenous shunting, albumin-based extracorporeal liver support systems, and renal replacement therapy, are considered as supportive or bridging options in selected patients, especially those awaiting liver transplantation. Prevention of HRS is based on early infection control, avoidance of nephrotoxic agents, adequate correction of hypovolemia, and routine administration of albumin after large-volume paracentesis. Overall, HRS represents a hallmark of advanced hepatic decompensation and requires early recognition and a multidisciplinary therapeutic approach.

Keywords
hepatorenal syndrome, liver cirrhosis, portal hypertension, terlipressin, albumin, variceal bleeding, ascites.

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Hepatorenal syndrome (HRS) is a severe complication of portal hypertension (PH) [43] and is associated with high morbidity and mortality. Recent case series and meta-analyses report 90-day mortality rates of 40–60 % in patients with HRS, which vary by disease severity and available treatments [30]. The syndrome involves disruptions of renal circulation that outweigh physiological compensatory mechanisms, leading to reduced glomerular filtration rate. Restoration of adequate renal perfusion improves kidney function and can be achieved through liver transplantation [30] or the administration of vasoconstrictor agents. Over the past decade, the terminology, diagnostic criteria, and classification of HRS have undergone substantial revisions, driven by updated approaches to diagnosing and stratifying acute kidney injury (AKI). This review highlights key contemporary advances that have shaped current understanding, diagnostic criteria, and therapeutic strategies for HRS [42].

Historical development of the concept of hepatorenal syndrome

The association between renal dysfunction and progressive liver disease was recognized as early as the late 19th century. This relationship was first described independently by the German clinician and pathologist Friedrich Theodor von Frerichs in 1861 and the American physician Austin Flint in 1863, both of whom reported oliguria in patients with liver cirrhosis and ascites [14].

As the kidney began to be regarded as an independent organ capable of primary pathological involvement, researchers increasingly considered the potential link between renal impairment and liver disease. This pathological process was later

designated as hepatorenal syndrome. Early medical literature already contained isolated reports of concurrent liver and kidney involvement, particularly in studies focused on ascites. Richard Bright laid the foundations of nephrology as a distinct medical discipline. In his seminal «Reports of Medical Cases» published in 1827, Bright described seven cases of ascites etiologically associated with liver disease. In his introductory remarks, he noted that in cases of ascites caused by renal pathology, the liver was «rarely absolutely healthy», although deviations from normal structure were often subtle and manifested as a tendency toward morphological alteration. In patients with liver disease complicated by ascites, he observed a tendency toward oliguria preceding death. Macroscopically, urine was described as «brightly colored» or containing a «pink sediment» that did not coagulate upon heating. Morphologically, in 26 cases in which ascites was attributed to liver disease, the kidneys were described as «rather pale, with uneven vascularity but normal structure», whereas in 29 cases they were characterized as «large and unhealthy» [52].

Frerichs proposed that oliguria resulted from inadequate filling of the systemic circulation due to blood pooling within the splanchnic vascular bed. However, a detailed clinical characterization of the syndrome was not provided until the late 1950s, when Hecker and Sherlock, as well as Papper [32], published comprehensive analyses of two cohorts of patients with cirrhosis complicated by renal failure. The key findings of these studies, which formed the basis of the modern understanding of acute HRS, can be summarized as follows: (1) renal failure typically demonstrates rapid progression and, in some cases, develops after identifiable precipitating factors such as minor gastrointestinal bleeding, paracentesis without adequate plasma volume expansion, or surgical intervention; (2) arterial hypotension is observed in the majority of patients, indicating that the reduction in glomerular filtration rate is driven by systemic hemodynamic disturbances; (3) despite the severity of renal failure, morphological changes in the kidneys are absent or minimal; and (4) prognosis remains extremely poor, with most patients dying within the first month after diagnosis [8].

Even as recently as two decades ago, the pathogenesis of HRS had not been fully elucidated, although it was already hypothesized to represent an extreme manifestation of arterial underfilling caused by predominant arterial vasodilation within the splanchnic circulation [5]. Nevertheless, the mechanisms underlying renal vasoconstriction remained poorly understood [42].

Classification of hepatorenal syndrome

As HRS research progressed, it became evident that two fundamentally distinct clinical types exist. The introduction of HRS classification into type I and type II enabled significant improvements in the principles of diagnosis, treatment, and prevention of this syndrome [11]. A hallmark of HRS is the presence of peripheral vasodilation accompanied by marked renal vasoconstriction [19, 21].

HRS is traditionally classified into type I and type II. Type I HRS is characterized by rapidly progressive renal failure, defined by a doubling of serum creatinine to > 2.5 mg/dL (221 μmol/L) or a creatinine clearance < 20 mL/min within two weeks. The prognosis of type I HRS is extremely poor: approximately 80 % of patients die within two weeks, and only about 10 % survive longer than three months. In contrast, type II HRS is defined by a serum creatinine level > 1.5 mg/dL (132.6 μmol/L) and/or a creatinine clearance < 40 mL/min; however, renal function deteriorates more slowly, and the prognosis is comparatively better [1, 7, 47].

Additional diagnostic criteria for HRS include urine output < 500 mL/day, urinary sodium concentration < 10 mmol/L, urine osmolality exceeding plasma osmolality, fewer than 50 erythrocytes per high-power field in the urine sediment, and a serum sodium concentration < 130 mmol/L. There should be no evidence of shock, ongoing bacterial infection, or current or recent exposure to nephrotoxic drugs. Gastrointestinal fluid losses must be excluded, defined as weight loss > 500 g/day over several days in patients with ascites without peripheral edema or ≥ 1000 g/day in patients with peripheral edema. Furthermore, there should be no sustained improvement in renal function, defined as a decrease in serum creatinine to ≤ 1.5 mg/dL (132.6 μmol/L) or an increase in creatinine clearance to ≥ 40 mL/min [1, 42].

Therapeutic management of hepatorenal syndrome

In 2000, terlipressin therapy was first introduced for the treatment of patients with HRS [46]. Terlipressin is a synthetic analogue of vasopressin, a naturally occurring hormone secreted by the posterior pituitary gland. Its most prominent pharmacological effects include potent vasoconstrictor and antihemorrhagic actions. Of particular importance is the reduction in blood flow within the splanchnic circulation, leading to decreased hepatic blood flow and lower portal venous pressure [4].

In 2000, Mark G. Hamilton (Calgary, Canada) reported regression of HRS in seven of nine treated patients [16]. Treatment was associated with

a significant improvement in mean arterial pressure (from 68 ± 2 to 80 ± 4 mm Hg) and suppression of vasoconstrictor activity, evidenced by reductions in plasma renin activity and plasma norepinephrine levels. No signs of ischemia were observed in any patient. Therapy was discontinued in one patient on the fifth day due to the development of acute pancreatitis [4]. At that time, terlipressin was already being used in the symptomatic management of portal hypertension complicated by bleeding from esophageal and gastric varices [34].

It has been demonstrated that the combination of terlipressin and albumin is effective in the treatment of HRS [20, 29]. The majority of studies have shown a favorable therapeutic response to combined terlipressin and albumin therapy, characterized by an increase in mean arterial pressure and a reduction in serum creatinine to levels below 1.5 mg/dL (132.6 μmol/L) [31, 35, 51].

Currently, three classes of vasoconstrictors are available for the treatment of HRS: vasopressin receptor agonists (vasopressin, terlipressin, and ornipressin), α-adrenergic receptor agonists (norepinephrine and midodrine), and somatostatin receptor agonists (octreotide) [19]. Among these agents, terlipressin is the most extensively studied, followed by norepinephrine, midodrine, and octreotide. A 2019 study demonstrated that the combination of terlipressin and albumin is the most effective therapeutic strategy for the management of HRS [12].

Invasive management of hepatorenal syndrome

In parallel with pharmacological therapy, several invasive and device-based treatment strategies have been used to manage HRS. These include: (1) transjugular intrahepatic portosystemic shunt (TIPS) [39]; (2) peritoneovenous shunt (PVS) [41]; (3) the Molecular Adsorbent Recirculating System (MARS) [36]; and (4) renal replacement therapy (RRT) [5, 40].

Studies indicate that early creation of an intrahepatic portosystemic shunt using the transjugular approach (TIPS) can effectively reduce portal pressure [17] and control variceal bleeding in severely ill patients with liver cirrhosis who are not candidates for surgical intervention [39, 53]. Although initial results suggest temporary shunt patency and clinical improvement, the long-term efficacy and durability of this method remain uncertain and require further evaluation in larger patient cohorts [13].

Peritoneovenous shunting as a therapeutic option for refractory ascites was first proposed by Harry H. LeVeen in 1974 [22, 24]. This technique diverts ascitic fluid from the peritoneal cavity into the venous system (most commonly the internal jugular vein) via a subcutaneously tunneled catheter equipped with a one-way valve [3]. The shunt connects the peritoneal cavity to the internal jugular vein or the superior vena cava, enabling continuous fluid drainage driven by a pressure gradient of approximately 30–50 mm H_2O (2.2–3.6 mm Hg). When the pressure falls below 30 mm H_2O (2.2 mm Hg), the valve closes, preventing retrograde blood flow [27].

Both TIPS and PVS are used in the management of medically refractory ascites [49]. Complete resolution of ascites following either procedure is uncommon. PVS provides more rapid control of ascites, whereas TIPS offers superior long-term efficacy [38]. After either shunting procedure, repeated interventions are often required to maintain shunt patency [50]. Treatment of diuretic-resistant ascites with TIPS carries a risk of early shunt-related mortality but may offer the potential for prolonged survival with sustained ascites control. TIPS implantation should therefore be considered a bridging rather than definitive therapy for persistent ascites in patients with moderate hepatic decompensation. Persistent ascites following TIPS has been identified as a strong predictor of liver transplantation and mortality [49].

The Molecular Adsorbent Recirculating System (MARS), an albumin-based dialysis device that utilizes a hybrid membrane impregnated with albumin to remove albumin-bound toxins that accumulate in liver failure, has been used clinically for more than two decades [33]. Its application in both acute and acute-on-chronic liver failure has consistently demonstrated improvements in biochemical profiles, resolution of hepatic encephalopathy, correction of hemodynamic disturbances, reduction of intracranial pressure, and partial improvement of hepatic synthetic function [26]. In several studies, albeit with small sample sizes, a survival benefit has also been observed. However, key issues such as optimal timing of initiation, duration of therapy, session frequency, and the role of adjunctive supportive treatments remain unresolved [15, 26].

The first experimental demonstration of the dialysis principle (often referred to as the concept of the «artificial kidney» or extracorporeal dialysis) dates back to 1913 and is frequently cited as the origin of RRT. Georg Haas performed the earliest documented attempts at hemodialysis in humans in Giessen between 1924 and 1928 [18]. In 1972, O. S. Better and colleagues reported a clinical case describing the successful use of concurrent hemodialysis (RRT) and massive blood transfusion in a 35-year-old patient who developed HRS following a blast-related liver injury [9]. RRT improves

short-term survival in severe acute kidney injury (AKI) and may serve as an effective bridge to transplantation or as supportive therapy in patients with acute but potentially reversible decompensation [48]. The use of RRT may be particularly beneficial in patients with HRS and AKI who are hemodynamically unstable, as well as in those at risk of elevated intracranial pressure, such as patients with acute fulminant liver failure or acute-on-chronic liver failure [25].

Prevention of hepatorenal syndrome

Preventive strategies aimed at reducing the risk of HRS include abstinence from alcohol [28], regular monitoring of serum creatinine and electrolyte levels in patients receiving diuretic therapy [2], albumin infusion during therapeutic paracentesis [10], administration of antibiotics during episodes of gastrointestinal bleeding [44], antibiotic prophylaxis against spontaneous bacterial peritonitis [45], and the use of non-selective beta-blockers [37]. The use of pharmacological agents such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and non-steroidal anti-inflammatory drugs should be avoided [1, 10]. Nephrotoxic agents, including aminoglycosides and iodinated contrast media, should be used with particular caution [36].

It has been established that plasma volume expansion, especially with albumin, significantly reduces the incidence of HRS following large-volume paracentesis – from nearly 10 % in patients who did not receive specific preventive treatment to approximately 2 % in those treated with plasma-expanding agents [6, 23].

Conclusions

Hepatorenal syndrome was first described nearly 70 years ago as a functional form of renal failure occurring in patients with cirrhosis in the absence of overt morphological kidney damage [52]. Its development is driven by profound splanchnic vasodilation, leading to renal vasoconstriction and reduced glomerular filtration. Two major clinical forms have been traditionally distinguished: an acute, rapidly progressive type (type I) and a more slowly progressive form (type II). Therapeutic strategies are primarily aimed at restoring effective circulatory volume and renal perfusion and include terlipressin in combination with albumin, TIPS, peritoneovenous shunting, and, ultimately, liver transplantation. Preventive measures focus on infection control, avoidance of nephrotoxic agents, correction of hypovolemia, and albumin administration following paracentesis.

Declaration of interests

The authors declare no conflicts of interest and no financial relationships that could be construed as a potential conflict in the preparation of this article.

Authors contributions

M. I. Tutchenko: conceptualization, study design, data analysis, methodology, and manuscript editing;
D. M. Patrakh: conceptualization, study design, data collection and processing, data analysis, methodology, and drafting of the original manuscript.

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Гепаторенальний синдром: історичні аспекти усвідомлення проблеми. Огляд

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Гепаторенальний синдром (ГРС) є тяжким функціональним ускладненням декомпенсованої портальної гіпертензії та цирозу печінки, що характеризується різким порушенням ниркової гемодинаміки без виражених морфологічних змін у нирках і супроводжується високою летальністю. Сучасні дослідження свідчать про 90-денну смертність на рівні 40—60 %, залежно від тяжкості стану та проведеної терапії. Патогенетично ГРС зумовлений спланхнічною вазодилатацією з подальшою ниркową вазоконстрикцією та зниженням швидкості клубочкової фільтрації. Історично взаємозв'язок між ураженням печінки та ниркową дисфункцією був описаний ще у XIX столітті, однак чітке клінічне окреслення синдрому сформувалося лише в середині XX століття. Подальший розвиток уявлень дозволив виокремити два типи ГРС: тип I — гострий, швидко прогресивний з вкрай несприятливим прогнозом, та тип II — хронічний, повільніший перебіг, частіше асоційований з рефрактерним асцитом. Терапевтичні підходи спрямовані на відновлення ефективного артеріального кровообігу. Найбільш обґрунтованою медикаментозною стратегією є застосування вазоконстрикторів, насамперед терліпресину в комбінації з альбуміном. Інвазивні методи, такі як трансяремне інтрапечінкове портосистемне стентування, перитонеовенозне шунтування, системи альбумінового діалізу (MARS) та замісна ниркова терапія, розглядаються як етап підготовки до трансплантації печінки або тимчасова підтримка у відібраних пацієнтів. Профілактика ГРС ґрунтується на контролі інфекцій, уникненні нефротоксичних препаратів, адекватній корекції гіповолемії та рутинному застосуванні альбуміну після великооб'ємного парацентезу. ГРС залишається маркером глибокої декомпенсації цирозу і потребує раннього розпізнавання та агресивної міждисциплінарної тактики лікування.

Ключові слова: гепаторенальний синдром, цироз печінки, портальна гіпертензія, терліпресин, альбумін, варикозна кровотеча, асцит.

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