ISSN 2231-2218

ASIAN JOURNAL OF PHARMACEUTICAL AND BIOLOGICAL RESEARCH

AJPBR

Indexed by:

ROAD Crossref Universal Impact Factor IMPACT FACTOR SEARCH

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 12 Issue 1
JAN.-APR. 2023

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 12 Issue 1
JAN.-APR. 2023

THE CONCEPT OF HEPATORENAL SYNDROME

Jumaeva Madina Fakhritdinovna
Bukhara State Medical Institute, Bukhara, Uzbekistan

Abstract. Hepatorenal syndrome is a life-threatening complication of liver cirrhosis. 90% of patients with liver cirrhosis die within 2 months of onset hepatorenal syndrome. For many years it was accepted as the only true guide the hypothesis of the hemodynamic mechanism of the occurrence of hepatorenal syndrome, according to which compensatory systemic vasodilation in response to portal hypertension causes renal ischemia and the development of a functional special physical acute kidney injury, the so-called "hepatorenal syndroma, acute kidney injury. There are two types of HRS. Type 1 HRS is characterized by a rapidly progressive impairment of the circulatory and renal functions associated with a very poor prognosis (median survival rate lower than 2 weeks). Type 2 HRS is characterized by a steady impairment of the circulatory and renal functions with a median survival of 6 months.The mechanism of development of HRS is based on a decrease in renal glomerular blood flow and, accordingly, glomerular filtration rate due to vasoconstriction of the renal vessels during vasodilation of the vessels of the abdominal organs, which leads to azotemia and an increase in serum creatinine. HRS develops a multiple organ pathology characterized by an acute dysfunction of vital organs and systems (liver, kidneys, brain, cardiovascular system). In general, the prognosis of HRS largely depends on the course of the hepatic process. Complete regression of HRS is observed with spontaneous liver function recovery or donor liver transplantation, and survival after liver transplantation in patients with prior HRS is worse than without it.

Keywords: Hepatorenal syndrome, cirrhosis, ascites, kidney failury, vasoconstictors

Introduction. Hepatorenal syndrome (HRS) is a severe functional reversible acute renal failure (ARF) in patients with severe hepatic insufficiency and portal hypertension as a result of acute or chronic liver disease, when other causes contributing to kidney damage (reception of nephrotoxic drugs, urinary tract obstruction) have been excluded. , chronic kidney disease, etc.). At the same time, morphologically, the kidneys with HRS are almost unchanged, with the exception of a decrease in the number of mesangial cells [3]. Hepatorenal syndrome is most often complicated by cirrhosis of the liver, accompanied by ascites (primarily alcoholic), often develops with severe acute hepatitis, operations on the liver or biliary tract, obstructive jaundice (the so — called "surgical" hepatorenal
syndrome), liver tumors, as well as with a decrease in the volume of circulating blood (BCC) (overdose of diuretics, prolonged diarrhea, indomitable vomiting, removal of a

large volume of fluid during paracentesis without replacement therapy with albumin solution), in cases of the use of nonsteroidal anti-inflammatory drugs (NSAIDs), nephrotoxic drugs (aminoglycosides, cyclosporine), with blood loss (bleeding from varicose veins of the esophagus or rectum), infection, alcoholic excess.

Definition. HRS is a clinical condition that usually occurs in patients with advanced liver disease and portal hypertension that is characterized by a combination of disturbances in circulatory and kidney function [6, 16, 17, 18, 19, 20] . The major abnormality in the systemic circulation is markedly reduced total SVR, which leads to a low arterial pressure. Kidney function is markedly impaired because of a severe reduction of renal blood flow. The reduction in renal blood flow is pathogenically related to the impairment in the systemic circulatory function. HRS occurs predominantly in the setting of cirrhosis, but it may also develop in other types of severe chronic liver diseases, such as alcoholic hepatitis, or in acute liver failure [7, 8, 21, 22, 23, 24, 25] . Because of its functional nature and lack of structural changes in the kidneys HRS is, theoretically, reversible if the mechanisms leading to the active renal vasoconstriction are corrected.

Pathogenesis. The mechanism of development of GDS is based on a decrease in renal glomerular blood flow and, accordingly, the glomerular filtration rate due to vasoconstriction of renal vessels during vasodilation of vessels of the abdominal cavity, which leads to azotemia and an increase in serum creatinine. The most accepted theory on the pathogenesis of HRS *(Arterial Vasodilation Theory)* proposes that renal hypoperfusion represents the extreme manifestation of an underfilling of the arterial circulation secondary to a marked vasodilatation of the splanchnic area (fig.1) [15] At the same time, morphological changes in the renal tissue, as a rule, are absent. However, dystrophy of the epithelium of the convoluted tubules of the kidneys, focal deposition of fibrin in the renal glomeruli and peritubular capillaries may be detected [19, 26,27, 28, 29, 30, 31].

Systemic vasodilation in liver damage with portal hypertension is a long-established fact. Vascular tone decreases due to an increase in the level of vasodilators (NO, prostacyclin, glucagon) and a decrease in the activation of K+ channels. Thus, glucagon, the level of which is increased in cirrhosis of the liver, reduces the sensitivity of mesenteric arterioles to catecholamines and angiotensin-II, which causes vasodilation. This leads to a decrease in systemic arterial pressure (BP), cardiac output increases compensatorily, and vasoconstrictors (angiotensin-II) are released in the kidneys, since hypotension through baroreceptors leads to activation of the renin-angiotensin-aldosterone system (RAAS), which has a systemic effect and maintains blood pressure at a normal level due to vasoconstriction of extraperitoneal vessels (kidneys, muscles, skin, etc.) [2-4, 13]. At the same time, only in the early stages of kidney disease provide adequate organ regulation of hemodynamics due to the development of their own vasodilators. With further course or in the presence of severe complications (for example, with spontaneous bacterial peritonitis, severe liver

failure), persistent vasoconstriction in the kidneys develops (spasm of efferent glomerular arterioles), since the vicious circle mechanism is activated — when a shortage of blood supply causes an even greater release of vasoconstrictors and vasoconstriction becomes irreversible. Thus, renal ischemia leads to an increase in the synthesis of endothelin-1, leukotrienes C4 and D4, thromboxane A2, which are powerful renal vasoconstrictors and lead to a decrease in the volume of mesangial cells [1, 13, 19, 32, 33, 34, 35, 36, 37].

The second vasoconstrictor mechanism is a neosmolar rise in the level of antidiuretic hormone, or vasopressin. The presence of hyponatremia also has an effect through an osmolar-dependent activation mechanism. Vasopressin causes vasoconstriction through V1-receptors of vessels, and an increase in tubular reabsorption of water through V2—receptors [1, 38, 39].

In addition, the sympathetic nervous system is activated through baroreceptors, which causes vasoconstriction of afferent arterioles and leads to a decrease in glomerular filtration, an increase in reabsorption of sodium and water in the tubules. However, despite the sodium retention that occurs during GDS, its concentration in blood plasma decreases due to the existing water retention [1, 2, 13, 19, 24, 40, 41, 42, 43, 44].

In the early stages of GDS, compensation of cortical blood flow is maintained due to the production of renal vasodilators — prostaglandins [15, 45, 46, 47, 48, 49]. Thus, in cirrhosis of the liver, urinary excretion of prostaglandin E2 and prostacyclin metabolites (6-oxo-PGF1a) is usually increased. Prostaglandins play a protective regulatory role for the kidneys in a variety of situations: with dehydration, a decrease in the ejection fraction with the development of circulatory insufficiency, shock and liver failure, when the level of renin, angiotensin, norepinephrine and / or vasopressin increases in blood plasma. However, in patients with GDS, their synthesis is significantly reduced [14, 15]. Considering this, it should be remembered that the administration of cyclooxygenase inhibitors (NSAIDs) to patients suffering from cirrhosis of the liver with ascites leads to inhibition of prostaglandin synthesis, a decrease in renal blood flow and the development of renal failure, which, as a rule, disappears after discontinuation of the drug [15].

It is also assumed that adrenal insufficiency is of no small importance in the pathogenesis of GDS, which can make a significant contribution to the formation of dyscirculatory disorders. There is evidence that this can occur both as a result of regional vasoconstriction and as a result of direct inhibition of cortisol synthesis by cytokines by the adrenal glands [3, 50, 51, 52, 53].

Summarizing the data on pathogenesis, we can say that multiple organ pathology develops with GDS, characterized by acute dysfunction of vital organs and systems (liver, kidneys, brain, cardiovascular system).

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 12 Issue 1
JAN.-APR. 2023

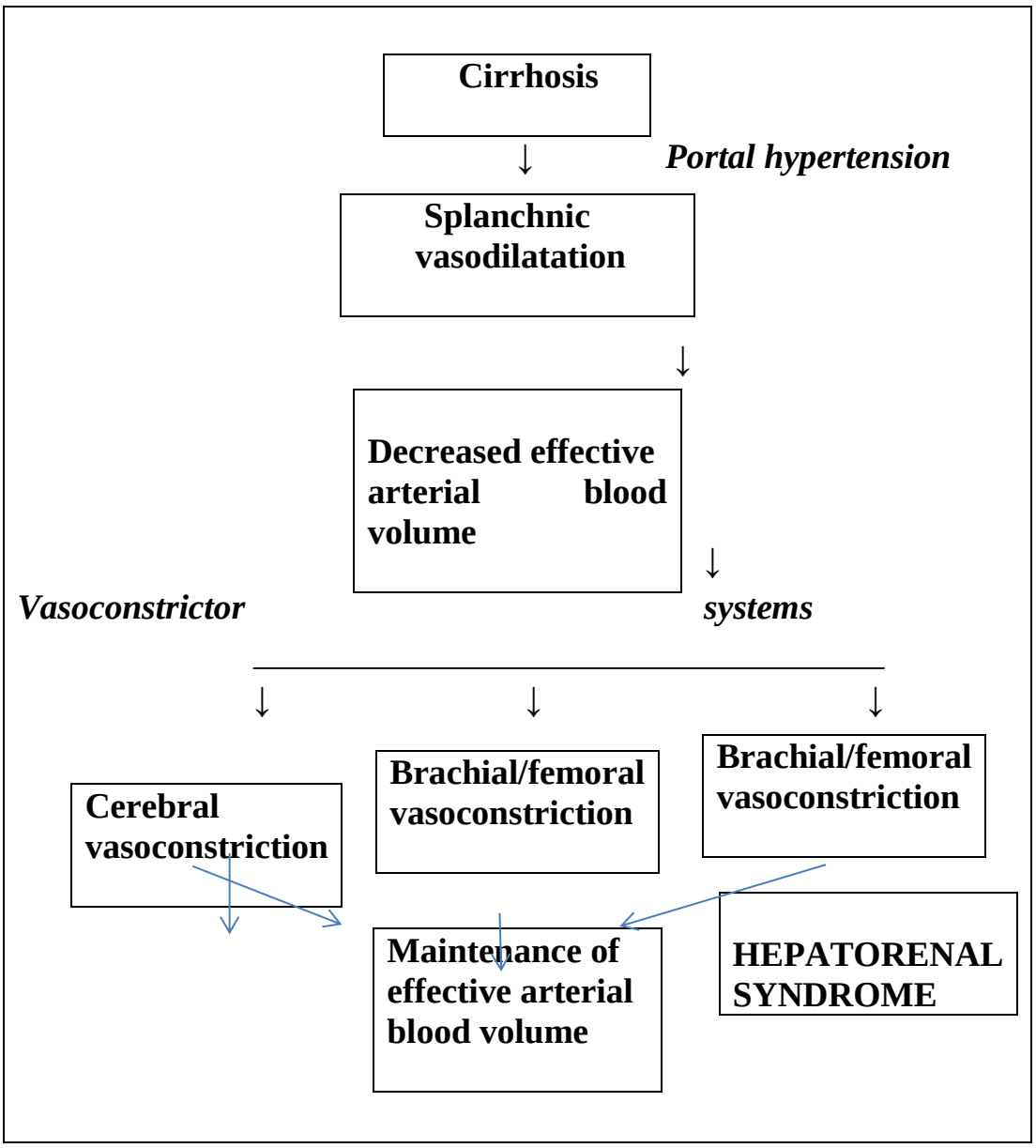
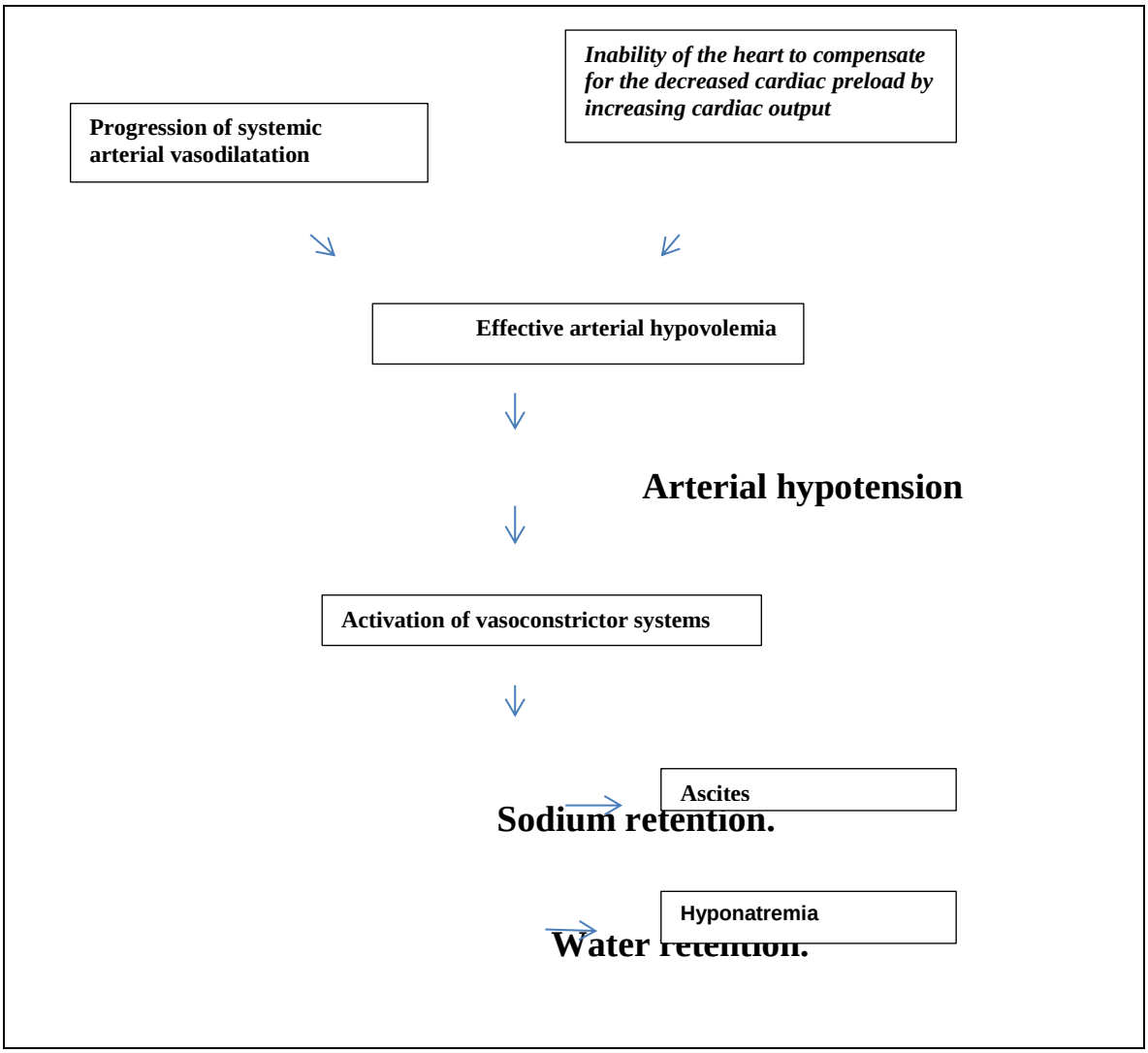


Fig.1. Pathogenesis of HRS according the Vasodilation Theory.

Recently, a new concept has been introduced as contributing factor in the development of HRS. In this sense it has been hypothesized that if circulatory dysfunction in cirrhosis was solely due to the progression of splanchnicarterial vasodilation and the hyperdynamic circulation, a compensatory mechanism of this disorder, cardiac output, should increase with the progression of the disease as it occurs with other homeostatic mechanism of effective arterial blood volume, such as

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 12 Issue 1
JAN.-APR. 2023
the overactivity of the renin-angiotensin and sympathetic nervous system. However, this is not the case. Despite the progressive increase in the plasma levels of renin and norepinephrine during the course of cirrhosis, indicating an accentuation of arterial vasodilation, cardiac output is similar in patients
with compensated cirrhosis, nonazotemic cirrhotic patients with ascites and normal or increased plasma levels of renin and norepinephrine and patients with type 2 HRS. The heart rate also does not increase despite the progressive stimulation of the sympathetic nervous system. This feature suggests that circulatory dysfunction in cirrhosis is related not only to a progression of arterial vasodilation but also to an inability of the heart to increase the cardiac output in response to a decrease in cardiac preload (fig.2). The recent demonstration in nonazotemic patients with cirrhosis and spontaneous bacterial peritonitis that the development of type 1 HRS occurs in the setting of a significant decrease in cardiac output further supports that cardiac dysfunction is an important event in the pathogenesis of the impairment in circulatory and renal function in decompensated cirrhosis [15, 54, 55, 56] .



Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 12 Issue 1
JAN.-APR. 2023

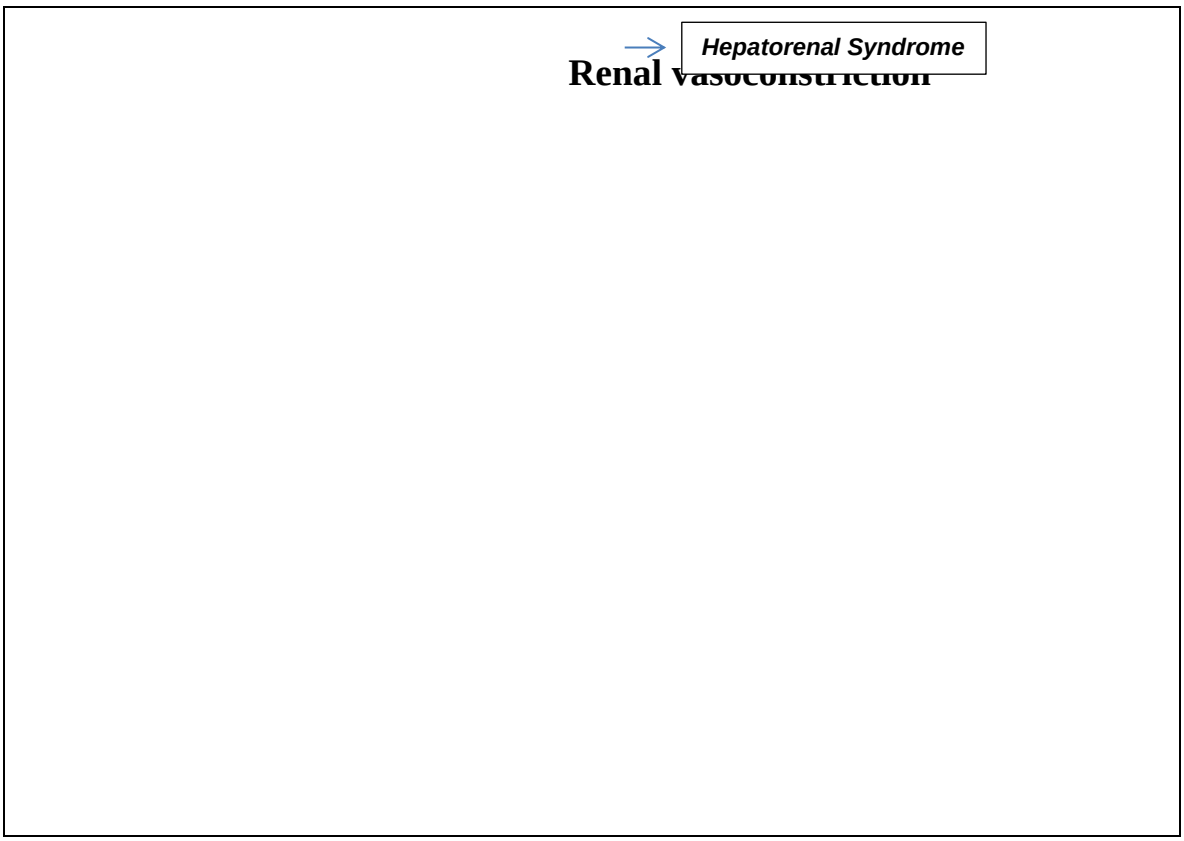


Fig.2. Pathogenesis of HRS according the Cardiocirculatory Theory.

Diagnosis. HRS is the last clinical spectrum of abnormalities of renal function in patients with cirrhosis and ascites. HRS may occur in two different clinical patterns [10, 57].

Two types of hepatorenal syndrome may develop. Type 1 HRS proceeds with rapid decompensation, the serum creatinine level usually exceeds 2.5 mg/dl. This syndrome occurs more often against the background of SBP, alcoholic hepatitis or performing volumetric paracentesis without subsequent replenishment with albumin. Without treatment or liver transplantation, patients with type 1 HRS live no more than 2 weeks. Type 2 HRS develops in patients with decompensated liver disease and is closely associated with resistant ascites. It is characterized by a slow course, less severity of renal insufficiency (serum creatinine does not exceed 1.5— 2.5 mg / dl).

Because of the lack of specifi c diagnostic tests, the diagnosis of HRS is currently made according to several criteria, as proposed by the International Ascites Club, which are based on demonstration of a marked reduction in GFR (serum creatinine 1 1.5 mg/dl in the absence of diuretic therapy) and the exclusion of other causes of renal failure that may occur in patients with cirrhosis [11] (table 1). For many years, no effective therapy existed for patients with HRS, except for liver transplantation. Recently, several effective new interventions have been introduced.

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 12 Issue 1
JAN.-APR. 2023

Table 1. Diagnostic criteria of HRS – major and additional criteria

Major criteria
1 Low glomerular fi ltration rate, as indicated by serum creatinine greater than 1.5 mg/dl or 24-hour creatinine clearance lower than 40 ml/min
2 Absence of shock, ongoing bacterial infection, fl uid losses and current treatment with nephrotoxic drugs
3 No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dl or less or increase in creatinine clearance to 40 ml/min or more) following diuretic withdrawal, and expansion of plasma volume with 1.5 liters of a plasma expander
4 Proteinuria lower than 500 mg/day and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease
Additional criteria
1 Urine volume lower than 500 ml/day
2 Urine sodium lower than 10 mmol/l
3 Urine osmolality greater than plasma osmolality
4 Urine red blood cells less than 50 per high-power fi eld
5 Serum sodium concentration lower than 130 mmol/l
All major criteria must be present for the diagnosis of hepatorenal syndrome. Additional criteria are not necessary for the diagnosis, but provide supportive evidence.

Treatment of HRS. Turning to the treatment of patients with GDS, it should be noted that drug therapy is quite ineffective.

A radical method of treating hepatorenal syndrome is to perform albumin dialysis on an artificial liver device (MARS therapy) with subsequent liver allotransplantation [9, 12, 16, 21, 25].

First of all, treatment should be aimed at preventing the progression of HRS — as soon as HRS is recognized or suspected, it is necessary to cancel nephrotoxic drugs, start therapy for intercurrent infections (the use of antibiotics with minimal hepatotoxicity and nephrotoxicity), correct hypoalbuminemia (intravenous infusion of albumin solution depending on the severity of hypoalbuminemia), limit intake liquids, sodium, potassium and protein, eat easily digestible food with the use of enzymatic preparations. If possible, paracentesis should be avoided [2, 8, 16].Normalization of hemodynamics is of key importance in the treatment of GDS. The task of treatment is to expand the renal and narrow the systemic vessels. For this purpose, any drug from the group of vasoconstrictors (vasopressin, terlipressin,

norepinephrine, dopamine, octreotide, etc.) is used. The administration is carried out for 1-3 weeks [1, 3, 16, 20].

It should be noted that the greatest experience in the use of vasoconstrictors is available for terlipressin. Terlipressin is a synthetic analogue of vasopressin. The drug forms active metabolites and has a vasoconstrictive effect. It is contraindicated in epilepsy, coronary heart disease, arterial hypertension, arrhythmias, bronchial asthma, in the early stages of pregnancy.

In recent years, good results have been obtained with the combined use of albumin and terlipressin (0.5–2 mg IV for 4-6 hours 2 times a day for 2 weeks) [18, 24]. Terlipressin is started with a dose of 0.5 mg every 4 hours. In the absence of an effect, i.e. a decrease in creatinine levels, the dose increase is carried out stepwise: after 2-3 days to 1 mg / 4 h. Then, if necessary, after 2-3 days, the dose of terlipressin is increased to 2 mg / 4 h [13]. The probability of survival increases with a daily dose of terlipressin more than 3 mg. Usually, the administration of terlipressin is continued with serum creatinine above 1.5 mg / 100 ml (0.125 mmol / L), but only in those patients who have positive dynamics during treatment, the duration of administration of the drug is no more than 15 days [16,22]. The introduction of terlipressin reduces the initial vasodilation of the arterioles of the mesenteric system, resulting in improved renal perfusion with arterial blood and, ultimately, glomerular filtration. Side effects (headache, pallor, difficulty breathing, increased blood pressure, myocardial ischemia, increased intestinal motility, uterine contraction) are usually observed at a dose of more than 2 mg / 4 h. At the usual dosage, adverse ischemic reactions after administration of terlipressin are observed in less than 5% of cases [13].With effective treatment with albumin and vasoconstrictors, the blood pressure level increases by 10 mmHg and higher, and there is also a decrease in serum creatinine to 0.125 mmol / l and lower. If serum creatinine does not decrease during the first 2 days of treatment, the dose of vasoconstrictors should be increased, even if there was a slight increase in blood pressure.Usually, conservative treatment is continued for 1-2 weeks.

A positive effect, especially when combined with arterial hypotension, can be provided by infusion of "renal" doses of dopamine (2-4 mcg / min per 1 kg of body weight), preferably in combination with albumin. However, the effectiveness of dopamine is significantly inferior to terlipressin, since dopamine itself restores renal function only in 5% of patients. If, under the influence of dopamine, diuresis does not increase within 12 hours, further administration of the drug is hopeless [1].There are reports of successful treatment of patients with type I HRS by intravenous administration of norepinephrine (0.5–3 mg / h, titration until the average blood pressure rises by 10 mmHg, continuous administration) in combination with albumin and furosemide in various doses that maintain central venous pressure at 4-10 mmHg. and diuresis of 100 ml/h. The duration of treatment is up to 15 days. The possibility of an "ischemic" side effect of norepinephrine should be taken into account [7, 16].It

is considered promising, but not yet studied, treatment of patients with HRS with endothelin antagonists and NO-inhibitors, and researchers are trying to use prostaglandins A1 and E as renal vasodilators [2].

When treating patients with HRS, several important nuances of therapy should be remembered:

• intravenous administration of hypertonic sodium chloride solution should not be used, as this can lead to the development of pulmonary edema and death of the patient;

• administration of mannitol can lead to acidosis;

• potassium-sparing diuretics can cause hyperkalemia;

• vasoconstrictors should be administered with caution to patients with coronary heart disease, severe atherosclerosis of the cerebral and peripheral arteries;

• in the absence of prospects for liver transplantation in patients with decompensated cirrhosis, traditional dialysis is usually not performed due to coagulopathy, hemodynamic instability and the risk of sepsis;

• if there is no response to treatment with albumin and vasoconstrictors for 4-5 days, there will be no effect from transjugular portosystemic bypass surgery;

• due to hyponatremia, dilutions are usually limited to the administration (orally and parenterally in total) of 1000 ml of liquid per day;

• to exclude subclinical hypovolemia, 1.5 liters of liquid should be injected immediately upon detection of the disease (preferably an albumin solution);

• it should be analyzed whether renal insufficiency is caused by iatrogenic hypovolemia, which develops with excessive administration of diuretics, laxatives (lactulose prescribed in connection with hepatic encephalopathy).

The most effective method of treating type I HRS is liver transplantation. A positive effect, consisting in an increase in life expectancy, is given by transjugular portosystem bypass surgery or extracorporeal albumin dialysis by a molecular absorbent recirculating system (MARS) [8, 11]. As a conservative therapy, the use of vasoconstrictors (terlipressin) and albumin is mandatory [7, 8, 20, 22, 25].In the treatment of patients with type II HRS, the effectiveness of conservative therapy with vasoconstrictors and albumin has been proven so far only in pilot studies. The main problem in this category of patients is refractory ascites. Liver transplantation can also be performed in such patients. And the available data concerning the effectiveness of transjugular portosystemic bypass surgery in patients with type II HRS do not fully answer questions about the complications of therapy and survival of patients against the background of positive ascites dynamics and a decrease in serum creatinine [5, 11].The effectiveness of conservative treatment of HRS without the use of vasoconstrictors and albumin is very low — the mortality rate is close to 100% [2, 3, 8, 25]. Satisfactory effect of albumin therapy with terlipressin occurs in 60-75% of patients with type I HRS with Child-Pugh severity class A and B on the 7th-14th day of treatment [9, 20, 25]. Similar treatment for type II disease in most cases ensures

survival.It should be remembered that the aggravation of the combination of azotemia, hyponatremia and hypotension should be regarded as a harbinger of death. And the most common cause of death in hepatorenal syndrome is not kidney failure, but hepatic coma.

In general, the prognosis of HRS largely depends on the course of the hepatic process. Complete reverse development of HRS is observed with spontaneous restoration of liver function or transplantation of a donor liver, while survival after liver transplantation in patients with previous HRS is worse than without it. The prognosis of hepatorenal syndrome against the background of acute hepatitis is quite favorable. With cirrhosis of the liver, mortality in this pathology reaches 90%. The prognosis is especially serious when the serum creatinine content exceeds 221 mmol/l and the serum sodium level is less than 120 mmol/l [1, 2, 15, 26].Given the high lethality and complexity of HRS correction, prevention of its development is life-saving for the patient.

Prevention of HRS provides for strict control of the use of diuretic drugs, evacuation of large amounts of ascitic fluid in paracentesis, prevention and emergency measures to stop bleeding, prevention of the development of infectious complications and timely adequate control of them, avoidance of prescribing nephrotoxic drugs to patients with severe liver pathology (aminoglycosides, rengtgen contrast agents, NSAIDs). It should also be borne in mind that arginine, as a constituent component of citrarginine, is a donor of nitric oxide, its use can worsen renal failure in HRS.

As mentioned above, the causes of the development of HRS are often iatrogenic in nature. Therefore, it is particularly necessary to focus on the correctness of the treatment of ascites — as a prevention of the development of HRS. As a rule, the stereotype of doctor's appointments to a patient with ascites involves parenteral administration of massive doses of furosemide. In this case, this is unacceptable — in the treatment of ascites in patients with cirrhosis of the liver, an oral route of administration and preferably spironolactone is preferred. The use of furosemide is possible, but in moderate doses and with strict control of diuresis. If diuresis under the action of diuretics in a patient who does not have peripheral edema increases by more than 700-1000 ml, there is a loss of intravascular fluid, this can provoke HRS. In addition, it should not be forgotten that diuretics themselves can cause kidney damage in patients with cirrhosis of the liver and ascites.

References

1. Jumaeva M.F., Hepatocardiorenal syndrome. Asian journal of Pharmaceutical and biological research . Volume 11 Isue 1 JAN-APR 2022 p.83-97
2. Jumaeva M.F., Hepatorenal Syndrome. Asian journal of Pharmaceutical and biological research. Volume 11 Issue 3 SEPT.-DEC. 2022 p.72-77
3. Jumayeva M.F., Predictors Of The Development Of Hepatorenal Syndrome. Problems biology and medicine. 2022 № 6 (140) p.80-82

4. Ubaydova D.S. Clinical aspects of liver damage in covid-19. Asian journal of Pharmaceutical and biological research 2231-2218. Volume 11 Issue 2 MAY-AUG 2022Pages 69-75

5. Ubaidova D.S. Non-invasive methods diagnostics of liver fibrosis in patients with diseases of the hepatobiliary system Asian journal of Pharmaceutical and biological 2231-2218 Volume 11 Issue 3 SEPT.-DEC. 2022

6. A.N. Aripov, O.A. Aripov, L.L. Akhundjanova, D.A. Nabieva Study the antifibrous efficacy of plant proanthocyanidin in rats with chronic heliotrine liver damage // Frontline medical sciences and pharmaceutical journal. 2022. Iss. 2 (5) P. 16-25

7. A.N. Aripov, O.A. Aripov, L.L. Akhundjanova, D.A. Nabieva Study the effect of yantacin on some indicators of cellular renewal and on the level of protein expression on rat hepatocytes in chronic heliotrine liver damage // International Journal of Medical Sciences And Clinical Research. 2022. Iss. 2 (5) P. 6-13

8. MM Tashpulatova, DA Nabiyeva, ER Djurayeva, NA Akhmedova Diagnostic Significance of 14-3-3 η (Eta) Protein and MRI of Joints in Early Stage of Rheumatoid Arthritis // American Journal of Medicine and Medical Sciences. 2021. 11(3). P. 165-169.

9. Shakhnoza Pulatova, Dildora Nabiyeva, Nargiza Abduazizova, Sevara Mukhammadiyeva, Gulnara Agzamova Clinical and pathogenetic values of disorders of mineral metabolism in ankylosing spondylitis // Tashkent medical academy repository. 2022/1/9

10. Nargiza Abduazizova Mashkura Rizamukhamedova, Dildora Nabiyeva, Elnora Dzhurayeva, Dilfuza Berdieva, Sevara Mukhammadieva "Granulomatosis with Polyangiitis: Diagnostic Difficulties and Treatment" // International Journal of Pharmaceutical Research. 2020. Iss. 2 (12) P. 745-752.

11. DA Nabieva, AN Aripov The detection of proteomic markers and immunologic profile and their relationship with metabolic parameters in patients with gout // Klinicheskaia Laboratornaia Diagnostika. 2017. Iss. 62 (8) P. 485-489.

12. DA Nabiyeva, KA Ilkhomova Renewed approach to the diagnosis and treatment of the rheumatoid arthritis in early stages // Tashkent medical academy repository. Jun-2022.

13. DA Nabieva Dyslipidaemia and cytokine profile in patients with gout: the role of il-6, il-18 and hyperuricemia in the development of metabolic disorders // Tashkent medical academy repository. 2017/1/10.

14. MZ Rizamukhamedova, DA Nabieva, NA Ganieva Efficiency of application of tutukon at patients with gouty nephropathy // O‘zbekiston terapiya axborotnomasi. P. 66

15. DA Nabieva, MZ Rizamukhamedova, CM Muhammadieva Characteristics of metabolic changes in patients with gout // Medical business. 2017. Iss. 62 (8) P. 485-489. (in Russian)

16. DA Nabieva, MZ Rizamukhamedova Relationships between hyperuricemia and hyperlipidemia in men with primary gout // Juvenis scientia. 2016. Iss. 3. P. 27-28. (in Russian)

17. GB Saidrasulova, CM Muhammadieva, RB Khuzhaev, Sh Ruzikulova Features of early clinical manifestations of ankylosing spondylitis // Botkin readings. 2018. P. 27-28. (in Russian)

18. CM Muhammadieva, DA Nabieva, GB Saidrasulova, XX Mirakhmedova Anti-inflammatory efficacy of veroxib in the treatment of ankylosing spondylitis // Botkin readings. 2020. P. 189. (in Russian)

19. DA Nabieva Immunological mechanisms of development of non-alcoholic fatty liver disease in patients with gout and pseudogout: a literature review // Scientific and practical rheumatology. 2017. Iss. 55 (5) P. 560-565. (in Russian)

20. NA Ne'matova, DR Sagatova, DA Nabieva Therapy with dolac (ketorolac tromethamine) for acute gouty arthritis // Postgraduate doctor. 2010. Iss. 39 (2) P. 91-95. (in Russian)

21. Shakhnoza Pulatova, Dildora Abdumalikovna Nabieva Evaluation of the clinical-pathogenetic significance of mineral metabolism disorders in patients with ankylosing spondyloarthritis // Journal of biomedicine and practice. 2022. Iss. 7 (5) P. 104-116. (in Russian)

22. Dildora Abdumalikovna Nabieva, Ilkhom Kobuljonovich Yusupov Informative and prognostic significance of risk factors for the development and progression of kidney damage and systemic scleroderma // Tashkent medical academy repository. 2022/10/14. (in Russian)

23. Dildora Abdumalikovna Nabieva, Ilkhom Kobuljonovich Yusupov Effect of urate-lowering therapy on quality of life in patients with gout // Tashkent medical academy repository. 2022/5/22 (in Russian)

24. AA Folatova, D Kushakov, DA Nabieva Risk factors for worsening kidney function in patients with gout // Tashkent medical academy repository. 2022/5/17 (in Russian)

25. CM Muhammadieva, DA Nabieva, MO Umbarov Atherosclerotic vascular lesions in patients with rheumatoid arthritis // Tashkent medical academy repository. 2022/5/17 (in Russian)

26. DA Nabieva, MM Tashpulatova Modern view on laboratory diagnosis of early rheumatoid arthritis // Botkin readings. 2020. P. 194. (in Russian)

27. MM Tashpulatova, DA Nabieva Clinical-immunological and instrumental changes in early rheumatoid arthritis // Days of rheumatology in saint petersburg-2021. P. 189-190. (in Russian)

28. DA Nabieva, NA Aripova, ER Juraeva, NA Ganieva To study the features of the course of reactive arthritis of yersinia etiology // Botkin readings. 2021. P. 195-196. (in Russian)

29. MM Tashpulatova, DA Nabieva Predictors of atherosclerosis in patients with early rheumatoid arthritis // Botkin readings. 2021. P. 273-274. (in Russian)

30. BS Abdullaev, DA Nabieva, MR Khidoyatova, BB Khakimov, FF Kuranbaev, UU Khoshimov Assessment of the quality of life of osteoarthritis patients after corona virus infection (COVID-19) // Botkin readings. 2021. P. 3-4. (in Russian)

31. MM Tashpulatova, DA Nabieva, ER Juraeva, KK Alieva Assessment of the functional state of the thyroid gland in patients with early rheumatoid arthritis on the background of pharmacotherapy // Botkin readings. 2021. P. 272-273. (in Russian)

32. DA Nabieva, NA Ganieva, NA Aripova, SS Rakhimov Studying the clinical features and course of erythema nodosum depending on the infectious agent // Botkin readings. 2020. P. 193. (in Russian)

33. DA Nabieva, DR Sagatova, NH Abduazizova Efficiency of the application of alendronic acid in the treatment of osteoporosis in rheumatoid arthritis // Botkin readings. 2020. P. 193-194. (in Russian)

34. KK Alieva, DA Nabieva, ShB Pulatova Clinical features of gout in women // Days of Rheumatology in St. Petersburg-2019. P. 21-22. (in Russian)

35. ShB Pulatova, DA Nabieva, ER Juraeva, MB Kasimova Prevalence of osteoopenic syndrome in ankylosing spondyloarthritis // Days of Rheumatology in St. Petersburg-2019. P. 214-215. (in Russian)

36. DA Nabieva, AN Aripov Proteomic profile of blood serum of patients with gout // Gastroenterology of St. Petersburg. 2018. Iss. 2. P. 81. (in Russian)

37. MK Rakhimova, DA Nabieva Features of liver damage in psoriatic arthritis // Days of Rheumatology in St. Petersburg-2018. P. 183-184. (in Russian)

38. NH Abduazizova, DR Sagatova, DA Nabieva Rheumatoid arthritis on the background of disturbance of the respiratory system function // Botkin readings. 2018. P. 3. (in Russian)

39. DA Nabieva, DR Sagatova Evaluation of the efficacy of tenicam in rheumatoid arthritis // Botkin readings. 2018. P. 265-266. (in Russian)

40. ShB Pulatova, DA Nabieva, MB Kasimova Frequency of heart damage in ankylosing spondylitis // Days of Rheumatology in St. Petersburg-2018. P. 178-178. (in Russian)

41. KA Utkurova, DA Nabieva Liver damage in tophus gout // Botkin readings. 2018. P. 397-398. (in Russian)

42. LA Ilkhomov, SM Muhammadieva, ShB Okhunova The problem of early diagnosis of systemic lupuus erytheis in men // Botkin readings. 2018. P. 160-161. (in Russian)

43. NKh Abduazizova, KH Nazarov, DR Sagatova, SM Muhammadieva Clinical and laboratory features of psoriasis therapy // Days of Rheumatology in St. Petersburg-2018. P. 4. (in Russian)

44. LI Ilkhomov, CM Muhammadieva, NH Abduazizova Systemic lupus erythematosus: challenges in early diagnosis // Days of Rheumatology in St. Petersburg-2018. P. 82-84. (in Russian)

45. Elnara Rustamovna Juraeva, Dildora Abdumalikovna Nabieva, Maktuba Muhamadalievna Tashpulatova Modern aspects of diagnostics and treatment of early rheumatoid arthritis // Innovative approaches in industries and areas. 2017. Iss. 2 (8). P. 2-18. (in Russian)

46. MZ Rizamukhamedova, DA Nabieva Targeted biomarkers for metabolic shifts in patients with gout and assymptom hyperuricemia // Days of Rheumatology in St. Petersburg-2017. P. 209-210. (in Russian)

47. DA Nabieva, DR Sagatova Comorbidity of gout and liver pathology // Days of Rheumatology in St. Petersburg-2017. P. 171. (in Russian)

48. Dildora Abdumalikovna Nabieva, Aripov Academy of Sciences Determination of proteomic markers and immunological profile and their relationship with metabolic parameters in patients with gout // Clinical laboratory diagnostics. 2017. Iss. 62 (8) P. 485-489. (in Russian)

49. MZ Rizamukhamedova, DA Nabieva Steatohepatosis in patients with gout and ways of its correction // Journal of Theoretical and Clinical Medicine 2017. Iss. 4 P. 51-54. (in Russian)

50. DA Nabieva, MZ Rizamukhamedov Metabolic syndrome depending on the nature of liver damage in gouty arthritis // Days of Rheumatology in St. Petersburg-2016. P. 154. (in Russian)

51. DR Sagatova, DA Nabieva Effectiveness and tolerability of the drug chondrogard in patients with osteoarthritis // Days of Rheumatology in St. Petersburg-2016. P. 207-208. (in Russian)

52. MZ Rizamukhamedova, DA Nabieva Clinical forms and features of the articular syndrome in gout, according to the republican rheumatological center (RRC) of the republic of Uzbekistan // Days of Rheumatology in St. Petersburg-2016. P. 196-197. (in Russian)

53. U Sahibs, DA Nabieva, ShR Kurbonova Prediction of fracture risk in women with osteoarthritis // Days of Rheumatology in St. Petersburg-2016. P. 196-197. (in Russian)

54. DA Nabieva Pathology of the hepatobiliary system and gout // Issues of organization and informatization of healthcare. P. 2016. P. 240-243.

55. DA Nabieva, MZ Rizamukhamedov Clinical and functional features of the course of tofus gout // Journal of Theoretical and Clinical Medicine. 2016. Iss. 2 P. 23-27. (in Russian)

56. GB Rashidova, FA Burkhanova, DA Nabieva, ShS Abdullaev Evaluation of the effectiveness of synchronous intensive care in the complex treatment of patients with systemic lupus erythematosus in the conditions of the republican rheumatic center (Uzbekistan) // Scientific and practical rheumatology. 2006. Iss. 2 P. 107. (in Russian)

57. Kh T Mirakhmedova, DA Nabieva, KR Arifzhanov The role of haptoglobin phenotypes and blood groups in patients with seronegative spondyloarthritis. // Scientific and practical rheumatology. 2000. Iss. 38 (4). P. 125. (in Russian)