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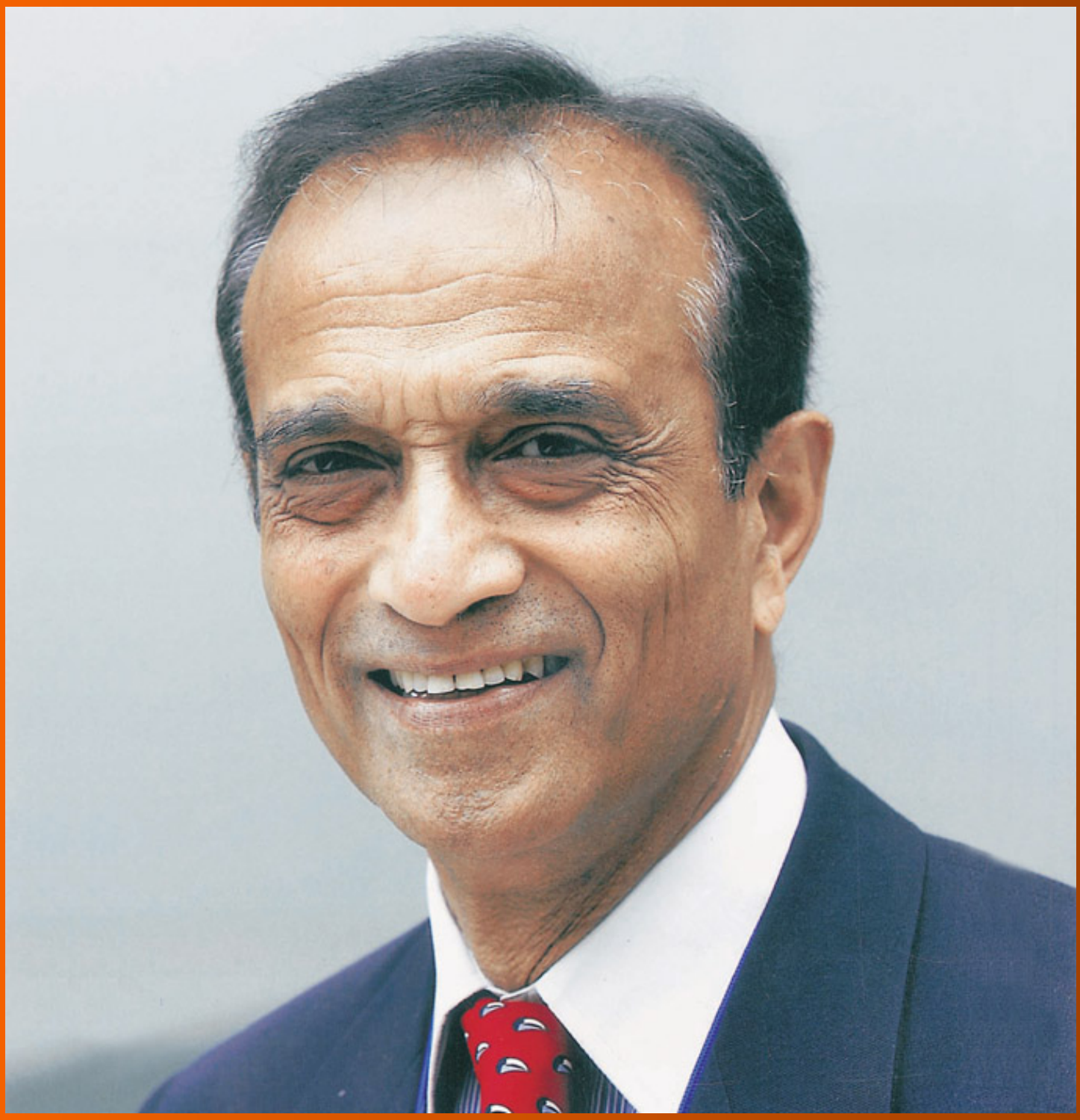

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MINIREVIEWS

Current approaches to the management of patients with cirrhotic ascites

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Abstract

This review describes current approaches to the management of patients with cirrhotic ascites in relation to the severity of its clinical manifestations. The PubMed database, the Google Scholar retrieval system, the Cochrane Database of Systematic Reviews, and the reference lists from related articles were used to search for relevant publications. Articles corresponding to the aim of the review were selected for 1991-2018 using the keywords: "liver cirrhosis," "portal hypertension," "ascites," "pathogenesis," "diagnostics," and "treatment." Uncomplicated and refractory ascites in patients with cirrhosis were the inclusion criteria. The literature analysis has shown that despite the achievements of modern hepatology, the presence of ascites is associated with poor prognosis and high mortality. The key to successful management of patients with ascites may be the stratification of the risk of an adverse outcome and personalized therapy. Pathogenetically based approach to the choice of pharmacotherapy and optimization of minimally invasive methods of treatment may improve the quality of life and increase the survival rate of this category of patients.

Key words: Liver cirrhosis; Ascites; Diuretics; Large volume paracentesis; Peritoneovenous shunting; Transjugular intrahepatic portosystemic shunting

Core tip: This review describes current approaches to the management of patients with cirrhotic ascites in relation to the severity of its clinical manifestations. The literature analysis has shown that despite the achievements of modern hepatology, the presence of ascites is associated with poor prognosis and high mortality. The key to successful management of patients with ascites may be the stratification of the risk of an adverse

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outcome and personalized therapy. Pathogenetically based approach to the choice of pharmacotherapy and optimization of minimally invasive methods of treatment may improve the quality of life and increase the survival rate of this category of patients.

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INTRODUCTION

Ascites, the abnormal fluid accumulation in the abdominal cavity, occurs in about 60% of patients with compensated liver cirrhosis within 10 years after establishing the diagnosis[1]. It is associated with poor prognosis and high mortality, which reaches 40% within a year and 50% within 2 years. In the case of refractory ascites, median survival does not exceed 6 mo, which is due to the development of severe complications including hyponatremia and progressive renal failure[2]. The most unfavorable predictors are hyponatremia, arterial hypotonia, high serum creatinine, low urine sodium level[3], spontaneous bacterial peritonitis[4], low total protein concentration in the ascitic fluid (≤ 2 g/dL)[5], and the number of red blood cells in the ascitic fluid of more than 10.000/mm^3 (hemorrhagic ascites)[6].

Also, the well-known scores, namely Child-Turcotte-Pugh (CTP), Model for End-Stage Liver Disease (MELD), and its modified version MELD-Na, as well as the recently developed Chronic Liver Failure Consortium - Acute-on-Chronic Liver Failure (CLIF-C ACLF) scale, help to suggest a poor outcome for patients with cirrhosis[7].

In a retrospective, observational study by Wang *et al*[8], nosocomial mortality positively correlated with ascitic volume in patients with ascites of more than 300 mL, regardless of the CTP and MELD scores.

CAUSES AND MECHANISMS OF ASCITES DEVELOPMENT IN CIRRHOSIS

At present, the leading theory of ascites formation is the hypothesis of peripheral arterial vasodilation, the reasons for which include systemic inflammatory response syndrome (SIRS) (Figure 1).

Peripheral arterial vasodilation hypothesis

Cirrhotic ascites is caused by pathophysiological disorders typical for portal hypertension (PH). Splanchnic and systemic arterial vasodilation, along with the activation of various neurohormonal pathways, cause kidney dysfunction with sodium and water retention and a decrease in glomerular filtration rate[9]. Further systemic hemodynamic disorders lead to the progression of ascites, dilutional hyponatremia, and hepatorenal syndrome development. Conventionally, there are five phases of this process at different possible intervals[10].

During the first, preascitic phase, splanchnic arterial vasodilation does not lead to a decrease in the effective arterial blood volume due to the presence of hyperdynamic circulation accompanied with an increase in plasma volume and cardiac output. Blood pressure, kidney function, renin activity, noradrenaline level, and antidiuretic hormone concentration in plasma stay normal[11].

During the second phase, the nature of hemodynamic abnormalities caused by PH does not fundamentally change. Renal perfusion, glomerular filtration rate, free water excretion, renin activity, noradrenaline level, and antidiuretic hormone concentration in plasma stay within physiological values. Despite elevated levels of endogenous natriuretic hormones, there is a moderate decrease in sodium excretion, which has no relation to the activity of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. The reason for such a decrease in sodium excretion remains unknown and may be due to the interaction of several factors/systems including aldosterone, angiotensin II, still undefined factors that affect calcium-sensing receptors and the bumetanide-sensitive Na-K-Cl cotransporter expression, without forgetting the potential roles of the sympathoadrenergic system and

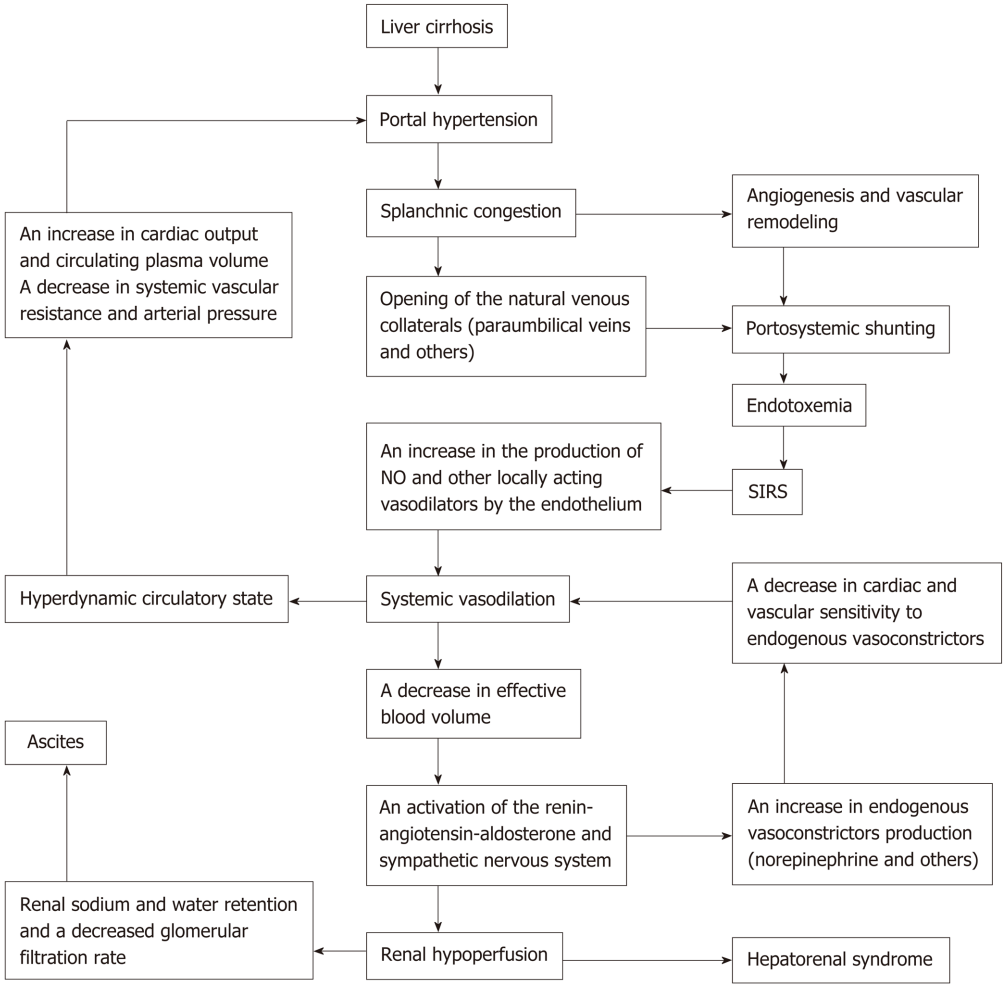

Figure 1 Potential mechanisms of ascites development in cirrhosis. SIRS: Systemic inflammatory response syndrome.

prostaglandins[12].

During the third phase, sodium retention is caused by the activation of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system as a result of progressive splanchnic arterial vasodilation. Despite an increase in plasma renin activity and plasma noradrenaline concentration, plasma volume remains unchanged. Cardiac output decreases, although it exceeds the average level. Blood pressure parameters during this period mostly depend on the activity of the RAAS and sympathetic nervous system. High peripheral vascular resistance leads to a reduction in cerebral and muscular blood flow. However, renal perfusion and glomerular filtration rate are not affected or are moderately reduced due to renal prostaglandins, which counter angiotensin and catecholamines. Besides, prostaglandins inhibit the effect of antidiuretic hormone and prevent the development of significant hyponatremia[13].

During the fourth phase, renin activity, noradrenaline level, and antidiuretic hormone level in plasma increase significantly, so renal perfusion and glomerular filtration rate reduce. The reduced ability of kidneys to excrete osmotically free water leads to dilutional hyponatremia[14].

During the fifth phase, patients with cirrhosis present with type 2 hepatorenal syndrome, which develops as a result of left ventricular systolic dysfunction accompanied by cardiac output decrease and severe systemic vasodilation. The extreme activity of the RAAS and sympathetic nervous system induces vasopressin production. Secondary hyperaldosteronism and tubular hypersensitivity to aldosterone increase sodium reabsorption in the distal parts of the nephron, whereas the sympathetic nervous system stimulates sodium reabsorption in proximal tubules and Henle's loop. Angiotensin II-induced spasm of predominantly efferent arterioles significantly reduces glomerular filtration rate leading to a further decrease in sodium excretion, even if blood pressure is stable[15].

Systemic inflammatory response syndrome

Recently, SIRS was noted to play an important role in the development of ascites and other complications of PH in cirrhosis, even in the absence of bacterial infection. The main mechanism of its development is the translocation of viable microorganisms, mainly gram-negative microflora, from the intestinal lumen to the mesenteric lymph nodes and other organs and tissues. Bacterial products or pathogen-related molecular structures interact with the corresponding receptors and promote the formation and release of pro-inflammatory cytokines. Subsequent inflammatory response increases the production of nitric oxide, aggravating the existing vasodilation[16]. In particular, it was shown that pro-inflammatory cytokines and chemo-attractant elements are increased in cirrhosis in comparison with healthy subjects and display higher values concomitantly with cirrhosis progression[17].

The reasons for bacterial translocation from the intestinal lumen in liver cirrhosis include a violation of local immunity, changes in the composition of bacterial flora due to decreased motility and the development of bacterial overgrowth syndrome, and increased permeability caused by mucosal damage due to oxidative stress[18]. A high level of endotoxemia may serve as an indirect confirmation of bacterial translocation in those patients with liver cirrhosis, who have acute bleeding from esophageal varices[19]. The role of bacterial translocation is also indirectly evidenced by the positive effect of drugs, which normalize the intestinal microflora and prevent bacterial translocation, on portal hypertension[20].

ASCITIC FLUID ANALYSIS

In order to determine the cause of ascites formation, diagnostic paracentesis with the ascitic fluid analysis is recommended for all patients with cirrhosis and first diagnosed ascites of the second or third stage in the case of ascites progression. Ascitic fluid analysis is also recommended for patients hospitalized because of other complications of cirrhosis, in particular, suspected spontaneous bacterial peritonitis[21]. Moreover, it is necessary for differential diagnosis between spontaneous bacterial peritonitis and peritonitis caused by acute surgical diseases of the abdominal cavity (Figure 2).

If ascites is due to PH, serum-ascites albumin gradient, which shows the difference in the levels of serum and albumin contained in the ascitic fluid, exceeds 1.1 g/dL[22]. This parameter inversely correlates with ascitic fluid viscosity, the increase of which indicates the threat of acute kidney injury development[23].

The concentration of total protein in the ascitic fluid of less than 1 g/dL and that of glucose exceeding 500 mg/L indicate an increased risk of spontaneous bacterial peritonitis, and the number of neutrophils in the ascitic fluid exceeding 250 cells/mm^3 (0.25 × 10^9/L) is the diagnostic criterion for it[24]. It should be noted that the prophylactic prescription of antibiotics may be helpful in patients with cirrhosis, who have low total protein concentration in the ascitic fluid (< 1.5 g/dL) and severely impaired liver (CTP class C, bilirubin level > 3 mg/dL) and renal (serum creatinine level > 1.2 mg/dL, urea nitrogen > 25 mg/dL, or sodium < 130 mEq/L) function. Antibiotics can significantly reduce the possibility of spontaneous bacterial peritonitis and hepatorenal syndrome and increase 1-year survival rate[25].

In patients with cardiac pathology, cardiac cirrhosis can be suspected if total protein concentration in ascitic fluid is less than 4.3 g/dL and if other predisposing factors for liver damage are excluded[26].

The signs of chylous ascites include cloudy, milky ascitic fluid containing a large number of lymphocytes (> 500/mL). The concentration of triglycerides in the chylous ascitic fluid exceeds 200 mg/dL (often > 1000 mg/dL), the total protein level is between 2.5 and 7.0 g/dL, the level of glucose exceeds 100 mg/dL, the lactate dehydrogenase activity is between 110 and 200 IU/L, the serum-ascites albumin gradient is less than 1.1 g/dL, and the cholesterol concentration gradient between ascitic fluid and serum is less than 1[27].

The high levels of C-reactive protein and insulin-like growth factor-1 in ascitic fluid make it possible to suspect malignant ascites[28], and a cholesterol level of more than 45 mg/100 mL in combination with cytology and carcinoembryonic antigen determination have diagnostic value[29]. Malignant ascites can also be assumed if there is a high level of C-reactive protein both in ascitic fluid and blood serum[30].

The values of adenosine deaminase activity and results of the Quantiferon test (QuantiFERON-TB Gold) can be used for the rapid diagnosis of tuberculous peritonitis with high sensitivity and specificity[31].

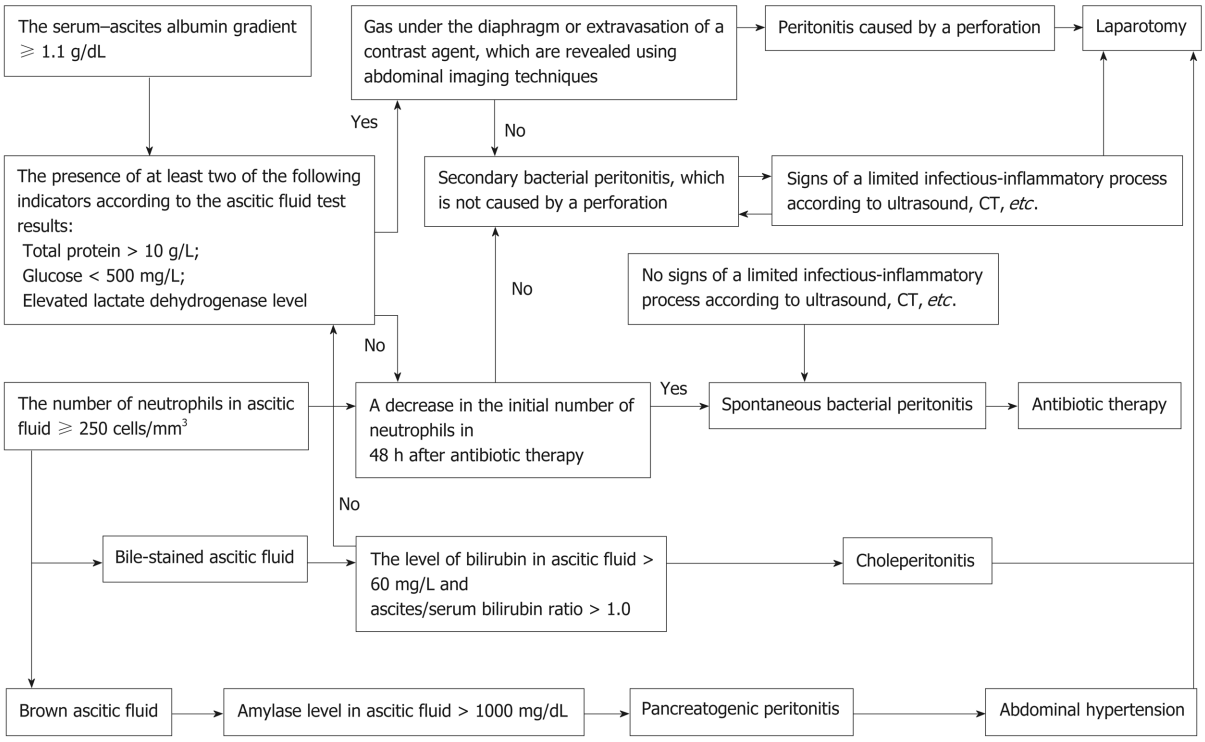

Figure 2 The algorithm for the differential diagnosis between ascites caused by portal hypertension, spontaneous bacterial peritonitis, and peritonitis caused by acute surgical diseases of the abdominal organs. CT: Computed tomography.

CLASSIFICATION OF CIRRHOTIC ASCITES

By the recommendations of the International Club of Ascites, ascites is classified into uncomplicated and refractory in patients with cirrhosis[32]. Ascites is considered uncomplicated if it is not accompanied by infection or hepatorenal syndrome. It is divided into three grades: Grade 1: mild ascites, which can be diagnosed only by ultrasound; Grade 2: moderate ascites, which is presented with a slight symmetrical stretching of the abdomen; and Grade 3: massive, tense ascites.

Refractory ascites is defined as ascites that does not recede to at least grade 1 with the use of diuretic treatment and dietary sodium restriction or the early recurrence of which after large volume paracentesis (LVP) cannot be satisfactorily prevented by medical therapy. It has two subtypes: *diuretic-resistant* and *diuretic-intractable*. In the first case, there is a resistance to optimal doses of diuretics. In the second case, the lack of effect is due to the insufficient dosage of diuretics conditioned by the threat of diuretic-induced complications[33].

TREATMENT OF ASCITES IN PATIENTS WITH CIRRHOSIS

Management of uncomplicated ascites

According to the clinical guidelines of the European Association for the Study of the Liver (EASL), the management of uncomplicated ascites depends on the severity of its clinical manifestations[34].

Patients with cirrhosis and *grade 1* ascites do not need diuretics and a low sodium diet. Patients with *grade 2* ascites can be treated in an outpatient center. Since sodium excretion is low (although not significantly) in most of them, therapy aims at reducing sodium consumption and stimulating its excretion by using diuretics and maintaining a usual drinking regimen. Sodium intake should be reduced to 80-120 mmol/d, which corresponds to 4.6-6.9 g of salt per day. Greater restrictions are undesirable, as the deterioration of food taste can lead to anorexia. Ideally, sodium balance in patients with cirrhosis and ascites should be changed on an individual basis by a hepatologist and nutritionist[35]. Due to the lack of reliable evidence for the negative effect of vertical posture on the activation of sodium retention systems and renal perfusion, bed rest prescription is unnecessary. Moreover, it is not recommended because already existing muscular atrophy may progress[36].

Sodium retention associated with ascites in patients with cirrhosis occurs mainly

due to reabsorption increase in renal tubules. Moreover, the mechanism of sodium reabsorption in proximal tubules is not fully established, whereas sodium reabsorption in distal tubules is mainly associated with hyperaldosteronism. Considering this, diuretic agents of choice for ascites treatment are aldosterone antagonists (spironolactone, canrenone, potassium canrenoate, *etc*.), which not only inhibit the retention of sodium and water but also suppress the potassium-excretory effect of sodium and reduce the synthesis of permeases in the aldosterone-dependent part of the collecting tubules and distal tubules. Also, loop diuretics are used. For example, furosemide can inhibit sodium reabsorption throughout the ascending limb of Henle's loop. However, due to lower efficacy and a greater number of complications in comparison with aldosterone antagonists, loop diuretics are not recommended as monotherapy[37].

The optimal variants are the sequential administration of aldosterone antagonists and loop diuretics at the initial stage of ascites treatment and the combination of these drugs if recurrence occurs. In the first case, treatment begins with the administration of spironolactone at 100-200 mg/d, then, in the absence of an effect, furosemide is added at 20-40 mg/d within two weeks. In the following, their daily dosage can be increased to 400 and 160 mg respectively. The second method suggests the combined use of diuretic agents from the very beginning, with a gradual increase in the dose of spironolactone up to 400 mg/d and furosemide up to 160 mg/d[38,39]. For the prevention of hypovolemia and eventually occurring acute kidney injury and hyponatremia, it is necessary to control daily diuresis and body weight during treatment. The decrease of body weight should not exceed 500 g/d in patients without peripheral edema and 1000 g/d in patients with it[40].

The combination of rational diuretic therapy and a low sodium diet makes it possible to achieve success in 90% of patients with cirrhosis and with uncomplicated grade 2 ascites. The effect is considered sufficient even if a small amount of fluid stays in the abdominal cavity, but there should be no peripheral edema. After achieving a positive result, diuretic agents should be reduced to a minimum, down to a complete withdrawal[41].

Side effects associated with diuretics may occur during the first weeks of treatment and are usually caused by impaired water-electrolyte balance. They mainly include dehydration, hypovolemic hyposmolar hyponatremia, and hypo- or hyperkalemia. Besides, possible complications include hepatic encephalopathy, gynecomastia, muscle cramps, and acute kidney injury.

The unreasonable intake of aldosterone antagonists may contribute to hypovolemic hyposmolar hyponatremia, although it mostly occurs because of the unreasonable use of thiazides in patients with cirrhosis and ascites, especially in the elderly. Agents of this group inhibit the reabsorption of sodium and chloride in distal convoluted tubules, act in the cortical thick ascending limb of Henle's loop and block the processes of urine osmotic dilution. Hypovolemic hyposmolar hyponatremia is characterized by a serum sodium level of less than 130 mmol/L, low plasma osmolarity, and a simultaneous decrease of extracellular fluid volume. Its main clinical presentations are a weakness, apathy, irritability, dizziness, arterial (including postural) hypotension, nausea, vomiting[42]. The development of severe hyponatremia (serum sodium level < 125 mmol/L), the worsening of hepatic encephalopathy, the presence of muscle cramps, and the signs of acute kidney injury require the withdrawal of the drugs causing them.

Hypokalemia is possible during the administration of loop diuretics, while hyperkalemia may be caused by aldosterone antagonists. Respectively, these drugs should be withdrawn when the level of serum potassium is less than 3 mmol/L or more than 6 mmol/L.

In spite of the fact that the nature of hepatic encephalopathy during treatment with diuretic agents is not fully understood, it is suggested to be caused by hyponatremia, which leads to brain cell swelling in the case of a rapid decrease in the level of serum sodium. In the case of a chronic process, hyponatremia may cause osmotic myelinolysis[43].

The long-term use of spironolactone in men is often accompanied by gynecomastia. However, spironolactone may be replaced with potassium canrenoate or amiloride only if breast pain appears[44].

Diuretic-induced hypovolemia may cause muscle cramps that are eliminated by decreasing the dose of diuretics or their complete withdrawal. In small uncontrolled studies, vitamin E, albumin, zinc, taurine, eperisone hydrochloride, and branched-chain amino acids have shown some efficacy[45]. In a randomized controlled trial (RCT) by Elfert *et al*[46], baclofen (centrally acting muscle relaxant) was successfully applied at 10 mg/d with a weekly increase up to 30 mg/d.

In addition to an intravascular volume decrease caused by the unreasonable use of diuretics, acute kidney injury may develop if they are combined with nonsteroidal

anti-inflammatory drugs[47], ACE inhibitors[48], angiotensin II receptor antagonists[49], α1-adrenergic blockers[50], aminoglycosides[51], dipyridamole[52], and contrast agents[53].

In patients with cirrhosis and massive, tense ascites (*grade 3*), the method of choice is LVP allowing simultaneous removal of more than 5-6 L of the ascitic fluid. It is then followed by the administration of diuretic agents and a low sodium diet[54]. Recent studies have shown the reduction in short-term mortality and an increase of hospitalization period in patients who underwent LVP[55], as well as the high probability of their repeated hospitalization within 30 d[56].

LVP is a relatively safe procedure. Even elevated creatinine level, hepatic encephalopathy, hypotension, and severe jaundice are not absolute contraindications for it[57]. However, LVP should be performed only by experienced specialists[58], preferably with a 15 or 16-gauge needle and under ultrasound control in order to prevent damage to venous collaterals and other vital structures[59].

The frequency of severe intra-abdominal bleedings during LVP does not exceed 1%[60]. Therefore, the use of fresh frozen plasma or platelet concentrate can be recommended only in certain clinical cases and not as standard therapy[61]. For example, they could be used in the case of severely impaired liver function assessed using the CTP and MELD scores[62] and in patients with severe thrombocytopenia[63]. In this regard, it may be useful to do a bedside hemostatic test for determining the activated clotting time, as well as to perform thromboelastometry/ thromboelastography (thromboelastography-guided transfusion strategy)[64]. Bacterial infection (sepsis) is an important risk factor for hemorrhagic complications in patients with cirrhosis[65]. However, in a recent retrospective single-center case-controlled study, it was shown that acute kidney injury is the most significant predictor for such complications after LVP[66].

The possible leaking of ascitic fluid from a puncture site is prevented by careful observance of all recommendations for the procedure[67].

The most dangerous consequence of LVP is paracentesis-induced circulatory dysfunction (PICD) which is an important independent indicator of an adverse outcome. Predisposing factors for PICD are not fully established, however, the rate of ascitic fluid removal does not play any significant role[68]. It is known that PICD occurs in the background of preexisting systemic arterial vasodilation and is accompanied by significant but ineffective RAAS activation. It is characterized by severe hemodynamic disturbances which are accompanied by increased cardiac output, decreased central venous pressure, and peripheral vascular resistance reduction[69]. Meta-analysis of seventeen RCTs including 1225 patients with cirrhosis who underwent LVP showed that PICD is associated with frequent recurrences of ascites, dilutional hyponatremia, hepatorenal syndrome development, and high mortality[70]. PICD is diagnosed considering renin concentration in blood plasma, which increases by 50% from baseline values or exceeds 4 ng/mL per hour in 5-6 d after LVP[71]. Albumin infusions in the amount of 8 g per 1 L of removed ascitic fluid may prevent this complication. The positive effect of albumin infusions is associated not only with an increase in oncotic pressure in the intravascular space but also with anti-inflammatory and antioxidant properties of albumin[72]. As an alternative to albumin infusions, Japanese authors have proposed cell-free and concentrated ascites reinfusion therapy (CART), which is aimed for maintaining serum albumin levels by filtrating and concentrating the removed ascitic fluid, followed by intravenous reinfusion of the collected proteins. In a retrospective observational study, Kozaki *et al*[73] performed 24 procedures in 11 patients with decompensated cirrhosis and showed the effectiveness and safety of CART. Even though CART reduces the need for albumin, there are problems with the high cost of equipment for it. To conduct one CART procedure, the estimated expense was ¥90500 (¥62400 for material costs and ¥28100 for technical costs).

Treatment of refractory ascites

Refractory ascites develops due to severe hemodynamic disturbances which are characteristic for decompensated cirrhosis. It should be noted that refractory ascites may be misdiagnosed and successfully corrected by eliminating its cause in the following clinical situations[57]: in patients receiving only loop diuretics, or in the case of prescribing aldosterone antagonists without taking into account the severity of hyperaldosteronism; during diuretic therapy, when increased diuresis is accompanied by the negative water balance of more than 900 mL/d and a rapid decrease in body weight that lead to hypovolemia with the development of prerenal azotemia; due to competing but potentially reversible complications that increase arterial vasodilation, and therefore worsen the discrepancy between intravascular volume and vascular capacity (dehydration caused by vomiting or diarrhea, gastrointestinal bleedings, bacterial infections); and in patients not keeping a low sodium diet.

Due to the poor prognosis, all patients with cirrhosis and refractory ascites should be considered as candidates for liver transplantation. Unfortunately, it is not possible

for many of them due to the presence of contraindications or problems related to the lack of donors[74]. In normal clinical practice, the first-line therapeutic intervention is LVP repeated every 2-3 wk in combination with albumin infusions. Moreover, diuretics are prescribed only when the concentration of sodium in urine is more than 30 mmol/d[75]. For increasing the effectiveness of therapy, it is possible to add clonidine (α2-presynaptic receptor agonist), which provides an early diuretic response with fewer complications and decreases the need for diuretics[76]. The positive effect of this drug is associated with the ability to reduce plasma norepinephrine concentration, followed by increased glomerular filtration rate, decreased sodium reabsorption in the proximal tubule, and increased sodium delivery to the distal tubule[77]. To obtain optimal results, clonidine is administered at 0.075-0.15 mg/d under the control of blood pressure, which should not be less than 135 mmHg[37].

Midodrine, an α1-adrenoreceptor agonist, can positively affect systemic and renal hemodynamics and increase sodium excretion by reducing plasma renin activity in patients with cirrhosis and refractory ascites without azotemia[78]. Its effectiveness was evaluated in the recent systematic review and meta-analysis of ten RCTs, six of which considered midodrine at 15 mg/d as a new drug for treating refractory ascites in patients with cirrhosis, and four regarded it as an alternative to albumin infusions during LVP. The results showed that midodrine is therapeutically effective and does not have a statistically significant effect on survival in comparison with placebo. Although midodrine cannot be considered as an alternative to albumin infusions during LVP, both treatment methods were equally successful in preventing PICD[79]. In an RCT by Hanafy *et al*[80], midodrine (15 mg/d) and rifaximin (1.1 g/d), which were added to diuretic agents, increased diuresis, improved systemic and renal hemodynamics, and subsequently improved short-term survival.

Despite the positive results of the aforementioned studies, the addition of clonidine or midodrine to the diuretic treatment in refractory ascites is not recommended according to current guidelines.

Terlipressin, a synthetic analog of vasopressin with longer biological activity and better safety profile, is the drug of choice for the treatment of acute bleeding from esophageal varices[81] and type 1 hepatorenal syndrome in patients with cirrhosis[82]. Terlipressin causes the contraction of arteries, in particular, arterioles of abdominal organs by stimulating specific V1 receptors on the arterial muscle cells. Reduced splanchnic vasodilation decreases portal pressure and therefore has a positive effect on hyperdynamic circulation, which in turn increases effective blood volume and renal perfusion pressure[83]. Intravenous bolus administration of 2 mg of terlipressin was found to increase glomerular filtration rate and sodium excretion in urine, and reduce renin activity and noradrenaline level in plasma of patients with cirrhosis and refractory or uncomplicated ascites[84].

Although octreotide, a synthetic analog of somatostatin that is also used to treat acute bleeding from esophageal varices, alone does not improve renal function in cirrhotic patients with ascites, its combination with diuretic treatment increases glomerular filtration rate and sodium and water excretion, mainly through the suppression of an activated renin-aldosterone axis[85].

If euvolemic or hypervolemic (dilutional) hyponatremia develops (serum sodium level < 125 mmol/L), patients with cirrhosis and refractory ascites should stop the intake of diuretic agents and limit fluid intake to 1 L/d. Hyponatremia correction is possible using tolvaptan, a selective oral vasopressin V_2-receptor antagonist. Tolvaptan inhibits the action of antidiuretic hormone, increasing free water excretion and thereby contributing to an increase in serum sodium level without significantly affecting sodium and potassium excretion[86]. However, considering that the results of phase III multicenter clinical studies are not received yet, it is recommended to use tolvaptan only when the need for treatment outweighs the risk of its use. Therapy should be carried out in a hospital, and serum sodium level should be monitored for the first 8-12 h, and then daily. Tolvaptan is administered once a day, starting with 15 mg. If necessary, this dose may be increased up to 60 mg. There is no need to correct the dosage depending on age, sex, heart, liver, or kidney function (if creatinine clearance ≥ 10 mL/min). During treatment, water restriction is not required[87].

Currently, the question remains whether it is possible to use nonselective β-adrenergic blockers in patients with decompensated cirrhosis and ascites, although they are the drugs of choice for the prevention of bleeding from esophageal varices[88]. A recent systematic review and meta-analysis of three RCTs and eight observational studies of propranolol, carvedilol, nadolol, and metoprolol, involving a total of 3145 patients with decompensated cirrhosis and ascites, revealed no reason to abandon β-adrenergic blockers[89]. However, careful monitoring of blood pressure, kidney function, and infectious screening should be conducted in order to identify cases requiring the reduction of non-selective β-blockers dose or their complete withdrawal[90].

A large number of publications have shown that refractory ascites can be successfully treated by transjugular intrahepatic portosystemic shunting (TIPS)[91]. Portal pressure reduction caused by TIPS improves the function of the cardiovascular system that contributes to increased renal blood flow and increased glomerular filtration rate[92]. At the same time, current clinical guidelines consider TIPS as a second line measure and recommend using it only in the case of frequently required LVP or its inefficiency. The reason for it is the development of TIPS-related hepatic encephalopathy and high mortality in patients with decompensated cirrhosis[93].

Nevertheless, the accumulation of experience and the development of new technologies, in particular, self-expanding polytetrafluoroethylene-covered stents, reduce the number of typical TIPS-related complications[94]. The smaller amount of complications leads to an increase in 1-year survival in patients who undergo TIPS without liver transplantation in comparison with those who receive repeated LVP in combination with albumin infusions[95]. Moreover, stents with a diameter of 10 mm control ascites better than stents with a diameter of 8 mm and do not increase the frequency of hepatic encephalopathy[96].

Also, the careful selection of candidates for TIPS among patients with cirrhosis and refractory ascites improves the results of the operation. The adverse outcome after TIPS is found in CTP class C patients[97] with the following: (1) MELD score > 25 points and a portosystemic gradient < 8 mmHg[98]; (2) INR value > 2[99]; (3) Total serum bilirubin level > 3 mg/dL and platelet count < 75 × 10^9/L[100]; (4) Serum creatinine level > 1.9 mg/dL[101]; (5) Glomerular filtration rate < 90 mL/min and platelet count < 125 × 10^9/L[102]; (6) Recurrent hepatic encephalopathy, which equals or exceeds the 2nd stage[103]; and (7) Diastolic dysfunction (E/A ratio ≤ 1)[104].

Besides, an important TIPS-related mortality risk factor is experience with its use. Mortality is lower in those hospitals, where at least 20 procedures are done per year[105].

Additionally, early stent placement turns out to be more cost-effective in those patients with cirrhosis and refractory ascites who need LVP more often than every 10 wk (> 5 LVPs per year) and are candidates for TIPS[106].

If a patient has contraindications to TIPS, implantation of a permanent Pleurx® tunneled peritoneal catheter may serve as an alternative. It is commonly used in the treatment of recurrent ascites caused by malignant neoplasms and allows to drain a small amount of ascitic fluid (< 2 L per day) in small portions even at home[107]. The first experience of using this method in a small cohort of patients with cirrhosis and refractory ascites showed its sufficient effectiveness in decreasing the need for diuretics, LVP, and albumin infusion. The procedure made it possible to avoid hyponatremia and the deterioration of renal function[108]. According to the data, 38% of patients developed spontaneous bacterial peritonitis, which was successfully treated with antibiotics[109]. CT-guided paracentesis with a pigtail catheter is a clinically effective, cheap, and safe alternative to conventional bedside paracentesis[110]. In an observational study performed by Riedel *et al*[111], the safety of Pleurx® catheter implantation almost did not differ from the standard LVP. Despite positive preliminary results, it is too early to talk about the feasibility of using these catheters in patients with cirrhosis and refractory ascites, and prospective RCTs are needed for conclusions.

In 1998, Rozenblit *et al*[112] proposed the first mechanical device designed to actively move ascitic fluid from the abdominal cavity to the bladder. However, it did not find widespread clinical use because of technical problems. A few years later, this idea was implemented by developing an automatic low-flow pump (Alfapump® system, Sequana Medical AG, Zurich, Switzerland). It consists of a subcutaneously implanted battery-operated pump connected to a catheter placed in the abdominal cavity. The pump aspirates ascitic fluid and transfers it through the second subcutaneous catheter to the bladder. The alfapump® system is equipped with internal sensors to monitor the pressure in the abdominal cavity and the bladder. They stop the pump when there is no ascites or when the bladder is full. The device is fully automated and programmed by the attending physician depending on the needs of the patient. The alfapump® system moves ascites to the bladder in small portions (usually 5-10 mL) every 5-10 min, from 0.5 to 2.5 L of ascitic fluid per day without the necessary administration of albumin. For patients' convenience, the pump is usually set to work only when they are awake[113].

In a multicenter non-randomized trial, Bellot *et al*[114] evaluated the efficacy of the alfapump® system in 40 patients with cirrhosis and refractory ascites. The patients were treated in 9 hospitals, and the observational period was up to 6 months. It was noted that 40% of patients had no need for LVP after alfapump® system implantation, and 70% needed LVP less than once a month. Nevertheless, there was a high percentage of complications, which mainly involved the migration and blockage of urinary or peritoneal catheters (22.5% and 12.5%, respectively).

In a prospective observational study involving 10 European referral centers, the alfapump® system was applied for at least 12 months, and the results were evaluated in 56 patients with cirrhosis and refractory ascites. The patients had an average MELD score of 13 and CTP score of 8.9 [36 patients had CTP class B (64.3%), 15 patients had CTP class C (24.8%), and CTP class was unknown in 5 patients]. The average duration of ascites before implantation of the device was 11.0 mo. As a result, 3 patients completed the 24-mo observational period, 3 patients continued observation, 9 patients underwent liver transplantation, 17 patients were excluded from the study because of serious side effects, and 23 patients died. The most frequent technical complication was the blockade of the peritoneal catheter. During the observation, 23 reinterventions related to the pump were required (17 patients), and in 12 cases the pump was changed (11 patients). The alfapump® system was removed in 48% of patients (in 17 cases because of serious side effects, in 9 cases during liver transplantation, and in 1 case because of recovery from refractory ascites). The average frequency of LVP decreased from 2.17 to 0.17 per month[115].

An RCT by Bureau *et al*[116] showed an advantage of the alfapump® system as compared to LVP, which consisted of reducing and for the most part eliminating the need for paracentesis. The quality of life and nutritional status were also improved. Despite the higher implantation cost of the alfapump® system (£22230), there was a trend towards stabilized post-intervention costs, whereas the cost of repeated LVP steadily increased. The total number of infectious complications between groups was similar and the overall outcome was the same. However, there were significantly more cases of acute kidney injury among those who had the alfapump® system. Such a negative effect on the renal function is possibly associated with a decrease in the glomerular filtration rate and a noticeable activation of the endogenous vasoconstrictor systems, as well as in PICD[117].

Although the alfapump® system can reduce the need for paracentesis, it remains unclear whether this method has a significant advantage over LVP in improving the survival rate of patients with cirrhosis and refractory ascites. At present, it cannot be considered a standard of medical care, but theoretically, it may serve as a "bridge" to liver transplantation in patients who have contraindications to TIPS.

Peritoneovenous shunting (PVS) allows protein-rich ascitic fluid to flow from the abdominal cavity to the venous system in the positive pressure gradient, which leads to an increase in circulating plasma volume and stimulation of diuresis and natriuresis. M. de Routte, who for the first time described PVS in 1907, used a large saphenous vein for its implementation. The unidirectional movement of ascitic fluid was achieved by the ostial valve functioning. The shunt functioned for a short period because it was frequently obstructed by a thrombus or the greater omentum. Therefore, the operation was rarely used in the future. In 1962, A.N. Smith, when performing PVS, took advantage of the Holter drainage system with a slit-like valve at the distal end, previously proposed for the treatment of hydrocephalus[118]. Among the numerous modifications described subsequently, the LeVeen and Denver shunts were the most common. The initially used surgical technique was later replaced by the laparoscopic approach, which, in addition to its low invasiveness, makes it possible to histologically verify the diagnosis and determine the following therapy. At present, the development of interventional technologies and devices allows the procedure to be performed percutaneously, which is faster, cheaper, and does not require general anesthesia[119].

PVS has been reported to improve glomerular filtration rate in patients with cirrhosis and refractory ascites, and especially in those having moderate and severe renal insufficiency[120]. Ascites control was achieved faster than after TIPS. However, long-term results were worse[121]. An RCT by Ginès *et al*[122] showed an advantage of PVS over LVP with albumin infusion in reducing the incidence of ascites recurrence and the need for diuretics. However, the high frequency of shunt obstruction had a negative impact on survival, which was about the same in both groups studied.

Despite its technical simplicity, PVS can be accompanied by severe and sometimes fatal complications including infection and shunt thrombosis, disseminated intravascular coagulation of blood, air embolism, and other pathological conditions[123]. In this connection, according to the EASL guidelines, this method plays a minor role in the treatment of refractory ascites in patients with cirrhosis[34].

Numerous literature data indicate that shunt surgery is dangerous in patients with cirrhosis and refractory ascites because it has a high risk of adverse outcome. However, Orloff *et al*[124] published unique clinical and metabolic results after portocaval side-to-side shunt surgery in this category of patients. Within the group of 34 patients (CTP class A - 0, B - 23, C - 11), two died in the immediate postoperative period (the causes of death were hepatoma in one case and heart failure in the other). Long-term survival rates after 5, 10, and 15 years were 75, 74, and 73%, respectively. Due to effective diuresis and natriuresis, ascites formation was stopped in all patients

without the need for diuretics. The liver function was improved in 81% of cases, and recurrent encephalopathy was found in 6% of patients.

CONCLUSION

Patients with cirrhosis complicated by ascites constitute a sufficiently large population and are treated by doctors of different specialties. The analysis of the literature has shown that despite the achievements of modern hepatology, the presence of ascites is associated with poor prognosis and high mortality. The key to successful treatment of ascites may be the stratification of the risk of an adverse outcome and personalized therapy. Pathogenetically based approach to the choice of pharmacotherapy and optimization of minimally invasive methods of treatment may improve the quality of life and increase the survival rate of this category of patients.

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