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GUIDELINES

Chinese guidelines on the management of ascites and its related complications in cirrhosis

Chinese Society of Hepatology, Chinese Medical Association · Xiaoyuan Xu[1] · Zhongping Duan[2] · Huiguo Ding[3] · Wengang Li[4] · Jidong Jia[5] · Lai Wei[6] · Enqiang Linghu[7] · Hui Zhuang[8]

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Abstract

The Chinese Society of Hepatology developed the current guidelines for the Management of Ascites and Its Related Complications in Cirrhosis based on the published evidences and the panelists' consensus. The guidelines provided recommendations for the diagnosis and management of cirrhotic ascites emphasizing a step-wise approach with the first-, second-, and third-line therapy. For refractory ascites, vasoconstrictors and albumin are recommended for splanchnic vasodilation and selective vasopressin (V2) receptor antagonists for moderate-to-severe hyponatremia. For spontaneous bacterial peritonitis, empirical anti-infection treatment was recommended based on the local microbiological examination of community- or hospital-acquired infections. For hepatorenal syndrome, the administration of vasopressor terlipressin and albumin is recommended.

Keywords Liver cirrhosis · Ascites · SBP · Hepatorenal syndrome · Diagnosis · Therapy · Guidelines

Abbreviations

AASLD	American Association for the Study of Liver Disease
ACEI	Angiotensin-converting enzyme inhibitors
AKI	Acute kidney injury
ARB	Angiotensin receptor blocker
CART	Cell-free and concentrated ascites reinfusion therapy
CNNA	Culture negative neutrocytic ascites
CT	Computed tomography
EASL	European Association for the Study of the Liver
ESBL	Extended-spectrum beta-lactamase
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
eGFR	Estimated glomerular filtration rate
GRADE	Grading of recommendations assessment development and evaluation
HRS	Hepatorenal syndrome
HSA	Human serum albumin
ICA	International-Club of Ascites
IV	Intravenous
LDH	Lactic acid dehydrogenase
MDR	Multi-drug resistance
MNB	Monomicrobial non-neutrocytic bacterascities
MRI	Magnetic resonance imaging
NSAIDs	Non-steroidal anti-inflammatory drugs
PCT	Procalcitonin
PICD	Post-paracentesis circulatory dysfunction
PMNL	Polymorphonuclear leukocyte
PMN	Polymorph nuclear
RAAS	Renin angiotensin aldosterone system
RRT	Renal replacement therapy

✉ Xiaoyuan Xu
xiaoyuanxu6@163.com

Zhongping Duan
duan2517@163.com

[1] Department of Infectious Diseases, Peking University First Hospital, Beijing 100034, China

[2] Artificial Liver Center, Beijing You-An Hospital, Capital Medical University, Beijing 100069, China

[3] Center for Hepatology and Gastroenterology, Beijing You-An Hospital, Capital Medical University, Beijing, China

[4] Liver Tumor Diagnosis, Treatment and Research Center, 302 Military Hospital of China, Beijing, China

[5] Liver Research Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China

[6] Institute of Hepatology, Peking University People's Hospital, Beijing, China

[7] Department of Gastroenterology, Chinese PLA General Hospital, Beijing, China

[8] Department of Pathogen Biology, Peking University Health Science Center, Beijing, China

SAAG	Serum-ascites albumin gradient
SBP	Spontaneous bacterial peritonitis
SCr	Serum creatinine
TGFβ	Transforming growth factor beta
TIPS	Transjugular intra-hepatic portosystemic shunt
VRE	Vancomycin-resistant enterococci
WGO	World Gastroenterology Organization
XDR	Extensively drug-resistant

Introduction

Ascites is one of the most commonly observed hallmark manifestations of decompensated cirrhosis. Once ascites appears, the 1-year mortality rate is approximately 15%, with a 5-year mortality rate ranging from 44 to 85% [1, 2]. Therefore, prevention and treatment of ascites are an important clinical challenge and a key area for research.

Worldwide, a number of clinical practice guidelines have been published relating to the management of ascites [3–6]. Recommendations on guidelines for ascites in Europe and America, many of these are not suitable for clinical diagnosis and treatment of ascites in patients with hepatitis B cirrhosis in China clinical practices. The Chinese Society of Hepatology invited experts on hepatology, gastroenterology, infectious disease, clinical pharmacology, and methodology to develop the current guidelines to help clinicians make appropriate decisions on the diagnosis, treatment, and prevention of ascites and its complications. This guideline is not a mandatory standard and cannot cover or solve all of the clinical challenges in the diagnosis and treatment of cirrhotic ascites, but can be used as a preferred approach to formulate a comprehensive and yet individualized diagnosis and treatment plan.

In these guidelines, the evidences and recommendations are graded according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Table 1).

Ascites is defined as the accumulation of at least 200 mL of fluid inside the abdominal cavity as a result of a pathological state. It can be a manifestation of many diseases and can be classified by causes including: hepatic, cancerous, cardiac, vascular (vein occlusion or constriction), renal, malnutritional, and tuberculous [7]. This guideline only focuses on cirrhotic ascites and its related complications.

Cirrhotic ascites

Pathogenesis

The formation of cirrhotic ascites is a result of several factors, with portal hypertension being the main cause and initiating factor. Renin–angiotensin–aldosterone system (RAAS) imbalance and hypoproteinemia also play important roles [8, 9].

1. Portal hypertension: Cirrhosis leads to a varying degree of portal hypertension, through deformation and occlusion of intra-hepatic vessels; blockage of portal venous blood flow; an increase in both intravascular pressure in the portal venous system and capillary hydrostatic pressure, causing fluid to leak into the abdominal cavity. Ascites rarely occurs at a portal venous pressure < 12 mmHg (< 1.6 kPa). Studies show that the incidence of ascites after devascularization is considerably higher than after portosystemic shunt.
2. Enhancement of RAAS activity: Portal hypertension enhances RAAS activity by triggering splenic and systematic circulation changes, which results in sodium and water retention. This is a primary cause of ascites formation and persistence.
3. Increased secretion or enhanced activity of other vasoactive substances: During cirrhosis, there is an increase in the secretion and activity of atrial natriuretic peptide, prostaglandins, and other vasoactive peptides. This stimulates extensive dilation of the splenic arterioles and,

Table 1 Grading evidence and recommendations

Grading of evidence	
High (A)	Further research cannot change the reliability of the therapeutic efficacy evaluation results
Medium (B)	Further research might change the reliability of the therapeutic efficacy evaluation results, and might also change the evaluation results themselves
Low or extremely low (C)	Further research will likely change the reliability of the therapeutic efficacy evaluation results, and will likely also change the evaluation results themselves
Grading of recommendation	
Strong (1)	Clearly indicates that the advantages of the intervention measures are greater than the disadvantages, or that the disadvantages are greater than the advantages
Weak (2)	The advantages and disadvantages are indeterminate or the evidence, whether its quality is high or low, which indicates that the advantages and disadvantages are equivalent

hence, increases venous inflow. At the same time, there is an increase in the small intestine capillary pressure and lymph flow, which can result in increased sodium retention.

4. Hypoalbuminemia: During cirrhosis, albumin synthesis is markedly reduced, which causes a drop in the plasma colloid osmotic pressure. This promotes the leakage of fluid from the plasma into the abdominal cavity, forming ascites.
5. Obstruction of lymphatic drainage: During cirrhosis, intra-hepatic vasculature can be obstructed, while the production of hepatic lymph increases. Ascites is formed when the lymph reflux exceeds the drainage capacity of the thoracic ducts. Chylous ascites is formed if there is obstruction and rupture of the cisterna chyli.

Diagnosis, evaluation, grading, and typing

1. Diagnosis of ascites

   (1) Signs and symptoms: Patients with cirrhosis develop symptoms including fatigue and loss of appetite, and underlying symptoms may be further aggravated. Patients may also develop abdominal distension, edema in both legs, and oliguria. Symptoms such as abdominal wall varicosis or abdominal distension are observed in the physical examination. A positive test result for shifting dullness suggests that the fluid inside the patient's abdominal cavity is > 1000 mL [10]; however, a negative test result does not exclude ascites.

   (2) Imaging examinations: The most commonly used examination is abdominal ultrasound, which is simple, non-invasive, and inexpensive. An ultrasound can determine the presence and volume of ascites, and give a preliminary indication of the source and location. In addition, ultrasound can aid positioning for paracentesis. Other imaging examinations include abdominal computed tomography and magnetic resonance imaging.

2. Evaluation of ascites: After ascites is diagnosed, the nature and volume of the ascites should be evaluated, and the presence of spontaneous bacterial peritonitis (SBP) identified. The evaluation includes a medical history, physical examination, laboratory tests, abdominal imaging examination, and diagnostic paracentesis.

   (1) Paracentesis: Paracentesis is a simple and low-risk procedure used to extract a suitable amount of ascites for analysis. By analyzing the physiochemical nature, microbiology, and cytology of the ascites, it is possible to clearly determine their nature and discover latent infections at an early stage. There are relatively few contraindications for abdominal paracentesis; however, potential complications of abdominal paracentesis include hematoma of the abdominal wall, leakage at the puncture site, and intestinal perforation. The procedure should be conducted by a trained clinician and carried out using strict aseptic technique to avoid contamination.

   (2) Ascites laboratory tests and analysis: Laboratory tests for ascites are listed in Table 2.

   Ascites can be colorless and transparent (simple), turbid, purulent, hemorrhagic, or chylous. The routine laboratory tests for ascites include a differential white cell count, and quantification of albumin and total protein levels. Differential white cell counts are the primary detection indicators of ascites. The total cell count in cirrhotic ascites without complications is $< 500 \times 10^6$/L. Even when no symptoms occur in the patient, SBP should also be considered if polymorphonuclear leukocyte (PMNL) counts are $> 250 \times 10^6$/L. At this time, the PMNL proportion is > 50% of the total leucocyte count in the ascites, and if there are complications of tubercular peritonitis or a tumor, the primary manifestation is an increase in lymph cells. The positive rate of bacterial culture in ascites is low, generally about 20–40%. To improve the sensitivity, 10–20 mL of ascites should be taken at the bedside and immediately contained in a blood culture bottle. The ascites fluid should not be precipitated before culture, because this increases the chance of bacterial phagocytosis by PMNL.

Table 2 Laboratory tests for diagnosis of ascites

Routine	Optional	Unusual
Differential white cell count	Culture (bacteria, anaerobic bacteria)	*Mycobacterium tuberculosis* smear and culture
Albumin	Glucose	Exfoliative cytology
Total protein	Lactase dehydrogenase	Bilirubin
	Amylase	Triglycerides
	Gram's stain	

If a diagnosis of cirrhotic uncomplicated ascites has already been determined, only a routine examination of the fluid is required. If the patient has a fever, abdominal pain, or hepatic encephalopathy of indeterminate cause, and an abdominal cavity infection is suspected, anaerobic bacterial culture can be carried out at the bedside with a blood culture bottle; the specimen should be obtained before antibiotics are administered to the patient and submitted for testing immediately.

(3) Common causes of ascites: cirrhosis is the most common cause of ascites. Extrahepatic diseases are the cause of approximately 15% of ascites occurrences, of which the most common are malignancies, tubercular peritonitis, chronic heart failure, and nephrotic syndrome. Some types of ascites have multiple causes. Ascites due to cirrhosis can be determined as transudate or exudate by laboratory tests, and due to portal hypertension or non-portal hypertension by serum-ascites albumin gradient (SAAG).

SAAG is defined as the difference between serum albumin and ascitic albumin, detected within the same day (SAAG = serum albumin − ascetic albumin). The albumin content indicates the osmotic pressure of ascites, so the SAAG indirectly reflects the osmotic pressure difference between the serum and the ascites. This enables determination of whether or not the ascites was caused by an increase in portal pressure [11].

There is a positive correlation between SAAG and portal pressure; the higher the SAAG, the higher the portal pressure [12]. Ascites where SAAG is ≥ 11 g/L results from portal hypertension owing to various causes [13]. Ascites where SAAG is < 11 g/L often results from non-portal hypertension, with the causes including peritoneal malignancy, tuberculous peritonitis, and pancreatic ascites. Causes of ascites in the United States are cirrhosis (approximately 85%), peritoneal malignancy (approximately 7%), heart failure (approximately 3%), and other infrequently observed causes such as tuberculous peritonitis and kidney disease [14]. SAAG can be used in combination with the ascitic total protein to determine the cause. (Table 3) [15].

3. Grading and typing of ascites: Clinically, ascites can be divided into grade 1, 2, or 3 based on the volume of fluid.

- Grade 1 ascites (small volume): ascites can only be detectable by an ultrasound examination. Patients generally have abdominal distension and tests for shifting dullness are negative; ascites detected by ultrasound are located in multiple gaps with a depth of < 3 cm.
- Grade 2 ascites (moderate volume): The patient often has moderate and symmetrical abdominal distension. Tests for shifting dullness can be negative or positive. The ascites detected by ultrasound floods the intestine, but does not cross the middle of the abdomen, and the depth is 3–10 cm.
- Grade 3 ascites (large volume): The patient has a significant bloating, tests positive for shifting dullness, and may have abdominal distension leading to umbilical hernia. The ascites detected by ultrasound occupy the entire abdominal cavity, the middle abdomen is filled with ascites, and the depth is > 10 cm.

Table 3 Common causes of ascites with different serum-ascites–albumin gradients and concentrations of ascitic total protein

	Serum-ascites–albumin gradient (g/L)	Concentration of ascitic total protein (g/L)
Liver cirrhosis	≥ 11	< 25
Heart failure	≥ 11	≥ 25
Peritoneal malignancy	< 11	≥ 25
Inflammatory ascites	< 11	≥ 25

Ascites can be clinically divided into ordinary and refractory cirrhotic ascites based on the volume of ascites, response to diuretic therapy, renal function, and presence of accompanying systemic diseases. In 2012, the refractory ascites diagnostic criteria recommended by the AASLD [4] were: (1) unresponsive (i.e., an average body weight decline of < 0.8 kg/day within 4 days, and a natriuresis of < 50 mEq/day; or a recurrence within 4 weeks of controlled ascites, and the ascites increases to at least 1 grade) to sodium-restricted (4–6 g/day) diet and high dose of diuretic treatment (spironolactone 400 mg/day; furosemide 160 mg/day) for at least 1 week OR therapeutic paracentesis (> 5000 mL per procedure); (2) development of clinically significant diuretic-induced complications or drug adverse reactions: for example, acute or chronic renal injury, uncontrollable electrolyte disorders, and gynecomastia. The inclusion of response to diuretic treatment alone as the definition of refractory ascites has long been a contentious issue.

In 2014, Chinese researchers reported the reference diagnostic criteria for refractory cirrhotic ascites: [16] (1) unresponsive to relatively high-dose diuretic therapy (spironolactone 160 mg/day, furosemide 80 mg/day) for at least 1 week OR intermittent therapeutic paracentesis (4000–5000 mL per procedure) in combination with albumin infusion (20–40 g per procedure/day) for 2 weeks; (2)

patients develop uncontrollable diuretic-induced complications or drug adverse reactions.

Treatment of ascites

Typically, a clinical decision regarding admission to hospital for treatment is based on the volume of ascites and the accompanying diseases.

Grade 1 ascites: most patients are asymptomatic; few have other complications of cirrhosis. They are sensitive to diuretic therapy, and can be treated on an outpatient basis and should be urged to schedule regular follow-up outpatient visits.

Grade 2 ascites: most patients have symptoms, accompanied by other complications of cirrhosis and require hospitalization.

Grade 3 ascites: These patients must be hospitalized for treatment (Fig. 1).

1. Principles for the treatment of cirrhotic ascites

- Treatment objectives: eliminate or control of ascites, improvement of clinical symptoms and quality of life, as well as prolonging survival time. The following sequential approaches should be adopted.
- First-line treatment: (1) etiological treatment; (2) sodium restriction (4–6 g/day) and diuretic therapy (spironolactone and/or furosemide); (3) avoid nephrotoxic drugs.

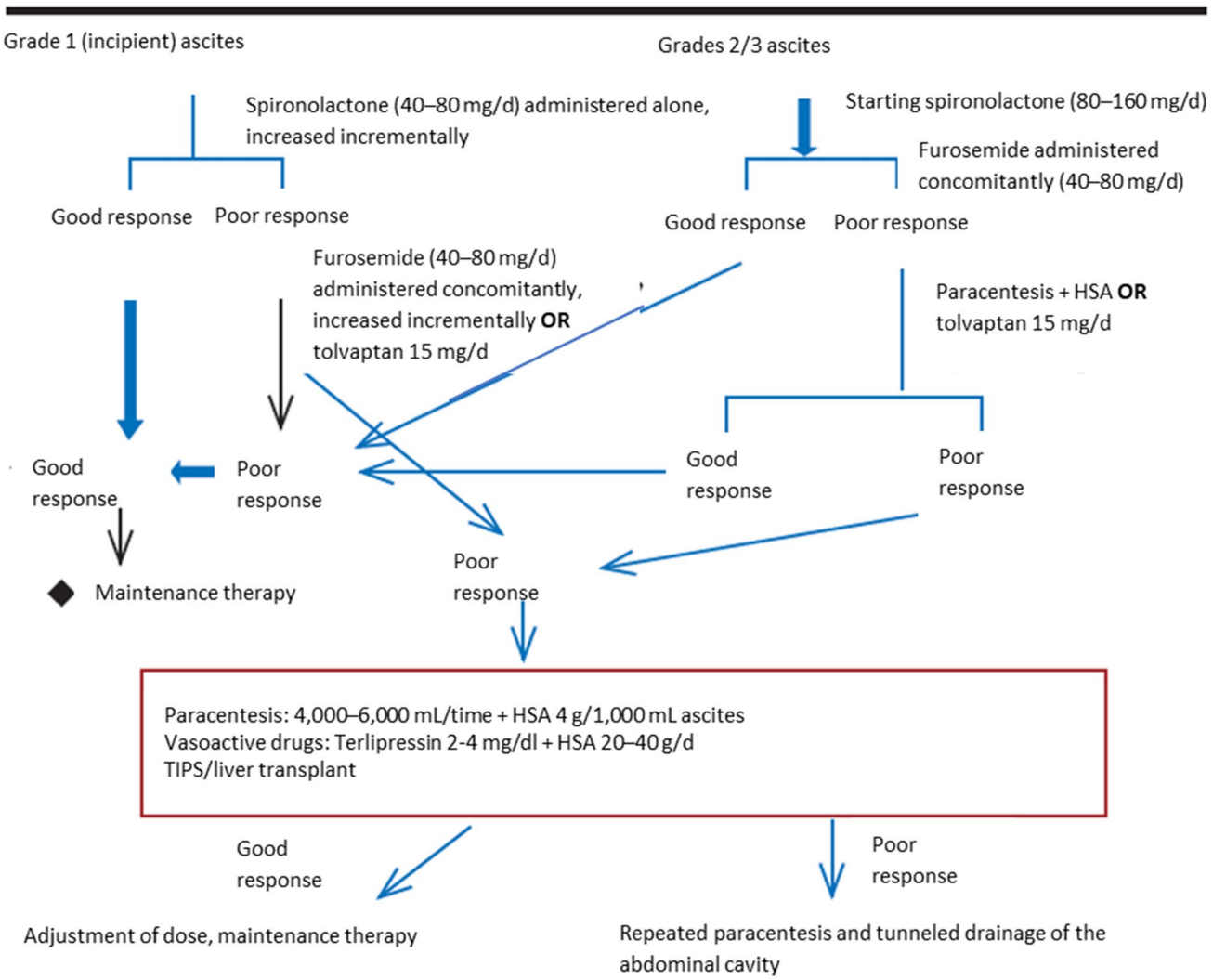

Fig. 1 Practical treatment process for ascites

- Second-line treatment: (1) administration of vasoconstrictor drugs and other diuretic/aquaretic drugs, such as terlipressin, midodrine hydrochloride, and tolvaptan; (2) large-volume paracentesis with supplement of human serum albumin (HSA); (3) transjugular intra-hepatic portosystemic shunt (TIPS); (4) discontinuation of non-steroidal anti-inflammatory drugs (NSAIDs) and vasodilators, such as angiotensin-converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARB).
- Third-line treatment: (1) Liver transplantation; (2) concentration and reinfusion of ascites into peritoneal cavity or renal replacement therapy (RRT); (3) abdominal cavity α-drainage pump or peritoneovenous Denver shunt.

2. Diuretics and other related drugs

Diuretic drugs are the primary method for treating cirrhotic ascites. The most commonly used diuretics are aldosterone antagonists, loop diuretics, and vasopressin V2 receptor antagonists.

(1) Aldosterone antagonists: the most widely used aldosterone antagonists include spironolactone and eplerenone. The primary cause of sodium and water retention in patients with cirrhotic ascites is an increase in sodium reabsorption by the proximal and distal convoluted renal tubules. Spironolactone is a competitive inhibitor of aldosterone, and it acts on the distal convoluted renal tubule and collecting tubule to block sodium–potassium and sodium–hydrogen exchange, resulting in an increase in the excretion of sodium and water.

Adverse reactions to aldosterone antagonists include hyperkalemia, gynecomastia, amenorrhea, and uncoordinated walking. Eplerenone is primarily used in the treatment of hypertension, but there is a lack of evidence regarding its clinical efficacy and safety in the treatment of cirrhotic ascites.

(2) Loop diuretics: furosemide is the most widely used loop diuretic. Furosemide primarily inhibits the spontaneous reabsorption of NaCl by inhibiting the Na^+/K^+ ATP enzymes related to Na^+- and Cl^--paired transport in the medullary thick ascending limb of the loop of Henle. This results in an increase in sodium and water excretion. A substantial dose–effect relationship exists for furosemide; as the dose increases, the diuretic effects are markedly strengthened, and the range of tolerated doses is relatively large. The bioavailability of oral furosemide is relatively good, while intravenous (IV) administration is even better. For patients experiencing a recurrence of ascites or refractory ascites, the therapeutic efficacy and safety of loop diuretics combined with spironolactone are superior to those of spironolactone alone [17]. Adverse reactions include postural hypotension, low potassium, low sodium, and arrhythmia.

(3) Highly selective V2 receptor antagonists: activation of vasopressin-2 receptors primarily mediates vasopressin activation of aquaporin-2 in the collecting duct, which results in an increase in water reabsorption. V2 receptor antagonists can competitively bind to V2 receptors on renal collecting duct principal cells and reduce water reabsorption; this improves cirrhotic ascites, diluted hyponatremia, and edema in surrounding tissues, while having a negligible effect on heart and renal function. V2 receptor antagonists may become a new therapy option for treating cirrhotic ascites, particularly in patients with accompanying hyponatremia.

V2 receptor antagonists include tolvaptan, satavaptan, and lixivaptan. One study reported a significant decrease in abdominal girth and more weight reduction with satavaptan, but, because the follow-up duration was very short (14 days), more studies are needed to validate this drug [18]. Tolvaptan has relatively good therapeutic efficacy and safety for patients with cirrhotic ascites and/or hyponatremia, late-stage liver disease complicated by ascites or refractory ascites [16, 19]. Short-term (less than 30 days) administration of tolvaptan is well tolerated and effective in treating patients with cirrhotic ascites and/or hyponatremia. Tolvaptan significantly increases the survival rate of patients by correcting serum sodium levels [20]. The initial dosage is 15 mg/day, which can be adjusted based on the patient's serum sodium concentration and urine volume at 8 h and 24 h after administration. The maximum dosage is 60 mg/day, and the duration of treatment should not exceed 30 days. Tolvaptan is contraindicated in patients with hypovolemic hyponatremia. The common adverse reactions to tolvaptan include thirst, hypernatremia, and renal failure. Serum sodium and hepatic function should be closely monitored in all patients administered tolvaptan [21]. The diuretics, except for tolvaptan, clinical studies have shown that diuretics cannot increase the urine volume in patients with HRS, and may even increase renal injury. Tolvaptan does not affect renal function or increase the incidence of hepatic encephalopathy, HRS or rupture, and bleeding of esophagogastric varices [22]. What time to administer V2 receptor antagonists

in patients with ascites? It is not recommended to administer tolvaptan for patients with grade 1 ascites. For patients with grade 2/3 ascites or recurrent ascites who have poor therapeutic response to routine diuretics (furosemide 40 mg/day and spironolactone 80 mg/day), tolvaptan can be administered [16, 23].

(4) Other diuretic drugs: these include amiloride and triamterene.

Amiloride and triamterene: Both are potassium-sparing diuretics and synergistic with thiazide or loop diuretics. If a patient cannot tolerate spironolactone, amiloride can be used at a dose of 10–40 mg/days.

(5) Vasoconstrictors:

a. Terlipressin: visceral vasodilation is a key factor in the occurrence of ascites, particularly for refractory ascites, or post-paracentesis circulatory dysfunction (PICD) after large-volume paracentesis [24]. Administering terlipressin (6–12 mg/day) in combination with HSA (1 g/kg/day) after large-volume paracentesis can effectively prevent PICD and HRS [25]. Compared with HSA alone, terlipressin combined with HSA could significantly improve the renal function in patients with type 1 HRS and systemic inflammatory response syndrome. Terlipressin can also be used in the treatment of refractory ascites and HRS in patients with cirrhosis [26]. Terlipressin is contraindicated in pregnant women and people with uncontrolled hypertension. Relative contraindications include ischemic cardiovascular diseases. Possible adverse reactions include abdominal colic, increased defecation frequencies, headache, and arterial hypertension. These reactions are related to the dose and the IV infusion rate.

Usage: it can be given intravenously at a slow rate (for at least 15 min) or infused continuously at 1–2 mg/every 12 h; if there is a therapeutic response, it can be used for 5–7 days. If there is no response, the dose can be increased to 1–2 mg/every 6 h; if therapeutic response is produced, it can be used for 5–7 days. If clinical relapse occurs after stopping this drug, the same or increased dose can be used again, with a maximum dose of 12 mg/day.

b. Midodrine: This is an α-1 receptor agonist frequently used to treat hypotension, which can increase the 24-h urine volume and sodium excretion of patients with refractory cirrhotic ascites. It also has good therapeutic efficacy for patients with non-azotemic cirrhotic ascites [27]. Usage: 12.5 mg, three times a day, p.o. In China, there are a lack of data and experience regarding the clinical administration of midodrine.

Indicators of therapeutic responses to active vasoconstrictors [28]:

- Full response: within 72 h, the serum creatinine (SCr) level decreases to below the baseline value of 0.3 mg/dL (26.5 μmol/L) or by > 50% compared with before administration.
- Partial response: within 72 h, acute kidney injury (AKI) stage improvement and SCr level decrease to baseline value of 0.3 mg/dL or by > 25% compared with before administration.
- No response: no improvement in AKI.

3. Diuretic drugs and dose selection: randomized-controlled studies are lacking for both the recommended dose of furosemide and spironolactone and the course of treatment for patients with cirrhotic ascites [29]. Therefore, diuretic drug and dose should be chosen based on physician experience and expert opinions, including clinical and pharmaceutical experts.

- Grade 1 (incipient) ascites: spironolactone is administered alone; the recommended initial dose is 40–80 mg, 1–2 times/day, p.o. If there is no response to therapy, spironolactone can be increased by 40 mg over 3–5 days or co-administered with furosemide. The upper limit of the routine dosage of spironolactone is 100 mg/day with a maximum dosage of 400 mg/day. The recommended initial dose of furosemide is 20–40 mg/day and can be increased by 40 mg over 3–5 days. The upper limit of the routine dosage of furosemide is 80 mg/day up to a maximum of 160 mg/day.
- Grade 2/3 (recurrent) ascites: spironolactone combined with furosemide is markedly higher in therapeutic efficacy than that of either sequential treatment or dose escalation of spironolactone alone, and lowers the incidence rate of hyperkalemia [30]. Therefore, it is recommended to use a combination of spironolactone and furosemide. The initial dosage of spironolactone and furosemide should be 80 mg/day and 40 mg/day, respectively; the doses of both can be increased incrementally for 3–5 days until the maximum dose is reached. If it was failure, tolvaptan was recommended.

Diuretic-related complications mostly occur within the first week of treatment. Therefore, the SCr, serum sodium, and potassium ion concentration

should be monitored within 3 days of administration. By randomly monitoring the urinary sodium/potassium ratio, it is possible to assess the treatment response to diuretics [31]. A clinical response to diuretics is indicated if the urinary sodium/potassium ratio is > 1 or the natriuresis is > 50 mEq/day.

4. Incompatibility of diuretics: several guidelines have recommended that patients with cirrhotic ascites should be cautious in the use of NSAIDs, such as ibuprofen and aspirin [3, 4, 32]. NSAIDs can lead to renal prostaglandin synthesis, which reduces renal perfusion, and increases the risks of acute renal failure and hypokalemia. ACEIs and ARBs can cause a fall in blood pressure and renal function injury [33]. The sole use of aminoglycoside antibiotics or in combination with antibiotic drugs such as ampicillin, mezlocillin, or cephalosporins, can increase renal toxicity. Note that contrast agents may increase the risk of renal function injury in patients with abnormal renal function [34].
5. Assessment of response to diuretic treatment and the timing of drug discontinuation:

(1) Assessment of response to diuretic treatment [16, 35]: The diuretic response to treatment (Markedly effective, Effective, or Ineffective) is comprised of three main indicators including 24-h urine volume, edema in the legs, and abdominal circumference.

- 24-h urine volume:

– Markedly effective: an increase of > 1000 mL from baseline.
– Effective: an increase of 500–1000 mL from baseline.
– Ineffective: an increase of < 500 mL from baseline.

- Edema in the legs: assessment of the tibial crest or dorsum of the foot with more severe edema.

– Markedly effective: no indentations are visible at all, and there is no edema.
– Effective: indentations are visible, and there is mild edema.
– Ineffective: there are clear indentations, and there is severe edema.

- Abdominal circumference: the patient lies in supine position for horizontal measurement of the abdominal circumference at the level of the umbilicus.

– Markedly effective: the abdominal circumference is reduced by ≥ 2 cm from baseline.
– Effective: the abdominal circumference is reduced by 0–2 cm from baseline.
– Ineffective: The abdominal circumference does not change from baseline.

(2) Assessment of non-response to ascites treatment:

- Body weight declines < 0.8 kg/day on an average within 4 days and natriuresis is < 50 mEq/day, or controlled ascites recurs within 4 weeks and ascites worsens by at least one grade.
- Uncontrollable complications or adverse reactions to diuretics.
- Poor response in a patient with grade 1 ascites was defined as the ascites still existed by ultrasound examination.

(3) When to discontinue diuretic treatment: In theory, long-term maintenance therapy with diuretics is required for patients with cirrhotic ascites to avoid recurrence of ascites. So far, there is still not consensus on when to stop diuretics after control of ascites at any guidelines. Generally speaking, in Child A/B patients, if the ascites disappears and no ascites recurrence during a maintain treatment of 3–6 months, the diuretic drug can be stopped. In patients with Child C or chronic liver failure with refractory ascites, it is difficult to completely eliminate ascites. These patients need long-term diuretics treatment. This is particularly true in the case of patients with Child–Pugh grade B/C cirrhosis. Discontinuing the administration of diuretics during HRS is contentious; there is currently no evidence assessing the safety of furosemide administration for type 1 HRS, but diuretics can help to maintain an adequate urine volume [36].

6. Nutritional support and sodium restriction

(1) Reasonable sodium restriction: sodium supplementation and sodium restriction have always been controversial in the treatment of cirrhotic ascites. Sodium restriction refers to a sodium intake of 80–120 mmol/day (4–6 g/day) [3, 4]. Further sodium restriction might significantly relieve ascites, and reduce sodium and water retention in 10–20% of patients with incipient ascites, decreasing the risk of ascites recurrence. However, long-term sodium restriction is likely to lead to loss of appetite, hyponatremia, and exacerbation of malnutrition. Furthermore, RAAS activ-

ity is enhanced and natriuresis is reduced when sodium restriction is strictly conducted and the plasma sodium level is low, leading to a vicious cycle that is hard to correct. Research indicates that treatment of cirrhotic ascites with short-term large doses of diuretic drugs and appropriate sodium supplementation is effective and well tolerated [37]. Therefore, many scholars believe that it is not necessary to severely restrict sodium for cirrhotic ascites.

Patients with cirrhosis should consume ≥ 2000 calories/day, mainly derived from carbohydrate, to ensure that blood glucose levels are maintained [38, 39]. Patients with cirrhosis and hypoalbuminemia should consume 1–1.2 g/kg/day of high-quality protein and receive vitamin supplementation. Patients with obvious hepatic encephalopathy should limit protein intake to < 0.5 g/kg/day, along with appropriate nutritional supplements according to guidelines [40]. If nutritional supplementation is given over 3 months in patients with cirrhosis, the serum albumin level and nitrogen balance could return to normal in most patients.

(2) Managing hyponatremia: there is no need to restrict fluid for most patients with cirrhotic ascites, but appropriate fluid restriction is recommended if serum sodium is < 125 mmol/L. Isovolemic or hypervolemic hyponatremia is present in about 60% of patients with cirrhotic ascites in clinical practice. Cirrhotic hyponatremia commonly develops slowly and it is often concealed by the other symptoms of cirrhosis. Administration of hypertonic saline can rapidly correct hyponatremia, but may itself result in greater water and sodium retention; therefore, this approach is generally not recommended. If a patient with cirrhotic ascites experiences severe hyponatremia (serum sodium < 110 mmol/L) or develops hyponatremic encephalopathy, IV 50–100 mL of 3–5% sodium chloride solution could be appropriately supplemented. Tolvaptan can also be used to correct hyponatremia. While the patient is receiving tolvaptan, urine volume, vital signs, and electrolytes should be closely monitored, and 24-h serum sodium levels kept below 12 mmol/L to avoid aggravating circulatory load or damage to the nervous system due to demyelination.

(3) HSA and fresh plasma: HSA possesses important physiological functions [41]. In the treatment of patients with cirrhotic ascites, particularly those with refractory ascites and HRS, supplementation of HSA is important for improving patient prognosis and improving the efficacy of diuretics and antibacterials [42]. International guidelines recommend [3, 4] 6–8 g albumin which should be administered for each 1000 mL of ascites removed, which can prevent PICD and increase survival rates. Clinical trials have shown that the incidence of PICD is similar when doses of 8 g or 4 g HSA per 1000 mL are administered immediately following paracentesis of ascites by abdominal puncture [43]. For patients with cirrhotic ascites accompanied by SBP, 1.5 g/kg HSA is administered on Day 1 and then 1 g/kg on days 2–5. There was a marked decline in the incidence of renal failure, mortality during hospitalization, and 3-month mortality in patients with cirrhosis who received HSA compared with those who did not (4.7, 3.1, and 7% compared with 25.6, 38.2, and 47%, respectively) [44]. In recently ANSWER study, long-term HA (40 g twice weekly for 2 weeks, and then 40 g weekly for up to 18 months) administration prolongs overall survival and might act as a disease modifying treatment in patients with decompensated cirrhosis [45].

The therapeutic efficacy and safety of HSA are superior to those of other expanders, such as dextran and polygeline [46]. In China, most inpatients with cirrhosis present with serious comorbidities. For patients undergoing large-volume paracentesis (> 5 L) or whose ascites is accompanied by SBP, there is insufficient clinical evidence for supplemented doses of HSA. Experts have not reached consensus and further studies are warranted.

7. Abdominal paracentesis: abdominal paracentesis is still an effective treatment for refractory ascites and rapidly relieves bloating [47]. Common complications of large-volume paracentesis include hypovolemia, kidney injury, and PICD. Studies have confirmed that continuous large-volume paracentesis (4–6 L/day) with HSA supplementation (8 g/1000 mL ascites) is more effective than administering a diuretic alone, with fewer complications. For patients who have a large volume or tension ascites, large-volume paracentesis in combination with HSA therapy can substantially relieve symptoms. Large-volume paracentesis at an early stage in patients with cirrhotic refractory ascites can markedly reduce 30-day rehospitalization rates and 90-day mortality rates [48]. Currently, most reports related to paracentesis of ascites by placing a drainage tube in the abdominal cavity involve cancer-related ascites. The only advantage of placing a drainage tube in the abdominal cavity compared with repeated para-

centesis (interval 10 days, 5000 mL per procedure) is a cost reduction for patients undergoing more than nine paracentesis procedures with a predicted survival time < 90 days [49]. Therefore, even in the case of cancer-related ascites, if the patient's expected survival time exceeds 90 days, use of a drainage tube in the abdominal cavity is not recommended [50].

8. TIPS: TIPS is an effective method for treating refractory ascites [51]. So far, however, there is still no consensus on whether an early or late TIPS should be used for treatment refractory ascites. It can serve as transition therapy for patients who require regular paracentesis, frequent hospitalization (≥ 3 times/month), or a liver transplant. TIPS can also relieve the symptoms of 60–70% of patients with refractory hepatic hydrothorax [52]. Research has demonstrated that TIPS lowers portal pressure, relieves ascites, and improves natriuresis and kidney function. However, the incidence of hepatic encephalopathy after TIPS is 25–50%, with a higher risk in patients ≥ 60 years. Therefore, hepatic encephalopathy, cardiopulmonary disease, liver failure (bilirubin ≥ 5.8 mg/dL), and pyemia are regarded as absolute contraindications of TIPS. In the 2012 AASLD treatment guidelines, a Child–Pugh score of ≥ 12 points for patients ≥ 70 years is a contraindication for TIPS.
9. Reinfusion of concentrated ascites after ultrafiltration and RRT

   (1) Cell-free and concentrated ascites reinfusion therapy (CART) can be used to treat refractory ascites. CART can improve the quality of life in patients with decompensated cirrhosis and refractory ascites, as well as the symptoms in some of these patients. CART does not significantly affect renal function and can also serve as an effective palliative treatment method. However, most patients develop fever [53].
   (2) Abdominal cavity α-drainage pump: An automated ascites drainage pump system re-infuses the ascites to the bladder via an abdominal cavity tunneled drainage catheter, such as a PleurX™, allowing ascites to be eliminated through normal urination. This is an effective method for malignant ascites, but there is little experience with its application in patients with cirrhosis and refractory ascites [50].
   (3) Peritoneovenous shunt: In the 1970s, the Denver peritoneovenous shunt was a common method for treating ascites surgically [54]. However, there were more complications with peritoneovenous shunts compared with medical treatment, but no improvement in survival. Therefore, peritoneovenous shunts are not recommended.
   (4) RRT: there have been reports of bedside hemodialysis and continuous venous hemofiltration in the treatment of cirrhotic refractory ascites and HRS, but there has been no research comparing these methods with the other treatment methods such as vasoconstrictors.

10. Liver transplant: patients with Child–Pugh grade C cirrhosis with refractory ascites should be considered for liver transplantation; chronic kidney injury and infection should be controlled as much as possible prior to surgery. Patients who respond to vasoactive drug therapy may be able to delay liver transplant [25]. Does the window of opportunity open for liver transplantation? In this guideline, open window for liver transplantation were: poor response to drugs treatment in patients with refractory ascites, need frequently abdominal ascites paracentesis (more than 3 times/week); frequently hospitalizationed (more than 3/month).
11. Treatment of the cause of the disease and follow-up: the causes of cirrhotic ascites include viruses, alcohol, cholestasis, auto-immune disorders, inherited metabolism, drugs, and parasites. Treatment should focus on the primary cause and should be aggressive to alleviate fibrosis, reduce portal vein pressure, and prevent and reduce the progression of fibrosis and cirrhosis [55, 56].

    Through treatment of the cause of the disease in patients with decompensated cirrhosis, it is possible to stabilize or reverse the condition to compensate cirrhosis, or even to remove cirrhosis by liver transplantation. When patients with decompensated cirrhosis related to hepatitis B or C are given anti-viral and anti-inflammatory hepatoprotective treatment in a timely manner, liver function can be markedly improved and the occurrence of complications such as ascites can be reduced, and compensated cirrhosis can be achieved. For patients with decompensated cirrhosis in which ascites has not yet developed, treatment of the primary disease will similarly improve liver function, reverse fibrosis, and cirrhosis. This is the key to preventing the occurrence of cirrhotic decompensation and ascites. Research has shown that some traditional Chinese medicines may have protective effects against liver fibrosis and cirrhosis, such as the evidence that *anluo huaxian pills* can reverse liver fibrosis induced by carbon tetrachloride in rats. In this example, the mechanism involved may be that hepatic stellate cell activation is inhibited by affecting transforming growth factor β1 production, with the result that anti-fibrosis

action is exhibited; the traditional Chinese medicines such as *anluo huaxian pills*, *fuzheng huayu capsules*, and *biejiaruangan tablets* have also demonstrated adjuvant therapy effects for liver cancer [57–59].

For patients with stable conditions of cirrhosis and ascites, biochemical tests, routine blood tests coagulation function test, alpha-fetoprotein test, and abdominal ultrasound should be conducted every 3 months. Patients should also have gastroscopy every 12 months to check for the presence and extent of esophagogastric varices. Long-term and potentially lifelong clinical management programs for patients with decompensated cirrhosis need to be followed.

12. Prognosis: when ascites develops rapidly, there is often a clear cause and the prognosis is relatively good. If the ascites is related to portal vein pressure, a good response to treatment is typically observed. When liver failure is the cause of ascites, clinical manifestations include jaundice and hepatic encephalopathy, and the prognosis is poor. In patients with renal failure, oliguria, and azotemia, the 3-month mortality rate is 50–70%. Patients with decompensated cirrhosis have an extremely high risk of liver cancer.

- Recommendation 1: paracentesis and a routine examination for ascites, including ascites differential cell count, total protein, and albumin levels, should be conducted for patients with newly developed ascites and those whose ascites is grades 2, 3, or above. SAAG should be calculated on the same day as paracentesis. A SAAG of ≥ 11 g/L is classified as portal hypertension ascites **(B, 1)**.
- Recommendation 2: when an abdominal cavity infection is suspected, blood culture bottles can be used to culture ascites and anaerobic bacteria at the bedside. Specimens should be collected using aseptic technique prior to administering antibiotics. Approximately 10–20 mL of ascites should be decanted into the blood culture bottle at the bedside and then immediately sent for testing **(A, 1)**.
- Recommendation 3: diagnosis of refractory ascites should be based on the following observations: (1) no response after diuretic (spironolactone 160 mg/day, furosemide 80 mg/day) treatment for at least 1 week OR paracentesis (4000–5000 mL per procedure) combined with HSA (20–40 g/time/day) treatment for 2 weeks; (2) development of uncontrollable complications or adverse reactions related to diuretic drugs; note that malignant ascites and ascites caused by presinusoidal portal hypertension are excluded **(B, 1)**.
- Recommendation 4: the initial dosage of spironolactone (aldosterone antagonist) should be 40–80 mg/day; the dosage should be increased by 40 mg/day for 3–5 days. The upper limit of routine dosage is 100 mg/day, with a maximum daily dose of 400 mg.

  The initial dosage of furosemide should be 20–40 mg/day and the dosage should be increased by 40 mg/day for 3–5 days. The upper limit of the routine dosage of furosemide is 80 mg/day, with a maximum daily dose of 160 mg **(B, 1)**.
- Recommendation 5: tolvaptan (V2 receptor antagonist) is an effective drug for the treatment of cirrhotic ascites, particularly when it is accompanied by hyponatremia. The initial dosage should be 15 mg/day and the dosage should be adjusted based on the blood sodium level to avoid a too rapid elevation of the blood sodium. The minimum dosage is 3.75 mg/day and the maximum dosage is 60 mg/day **(A, 1)**.
- Recommendation 6: terlipressin (vasoconstrictor) can be used for treatment of refractory cirrhotic ascites. The dosage should be 1–2 mg once every 12 h either by one slow IV injection (at least 15 min) or continuous IV drip. If there is a treatment response, then administration should be continued for 5–7 days. If there is no response, treatment should be switched to 1–2 mg once every 6 h either by one slow IV injection or continuous IV drip. If the condition recurs after the drug is discontinued, the same dose can be repeated **(B, 1)**.
- Recommendation 7: the administration of NSAIDs and aminoglycoside antibiotics should be avoided in patients with cirrhotic ascites **(C, 1)**.
- Recommendation 8: patients with refractory ascites should be educated about sodium restriction to 4–6 g/day **(B, 1)**. If blood sodium is < 125 mmol/L, patients should restrict their fluid intake, but this is not necessary if blood sodium is ≥ 125 mmol/L **(C, 2)**.
- Recommendation 9: HSA infusions (20–40 g/day) may improve the prognosis of patients with cirrhotic ascites, especially in patients with refractory ascites and SBP **(A, 1)**.
- Recommendation 10: large-volume paracentesis (4000–5000 mL/procedure/day) combined with HSA (4 g for every 1000 mL removed) is an effective method for treating refractory ascites **(B, 1)**.
- Recommendation 11: TIPS therapy can be used for treatment of the early stage refractory cirrhotic ascites that has poor response to diuretics, as long as the patient has no contraindications **(B, 1)**.
- Recommendation 12: generally, placing a peritoneal drainage tube for paracentesis of ascites is not rec-

ommended **(B, 1)**. Patients with refractory cirrhotic ascites should be prioritized for liver transplant **(B, 2)**.

- Recommendation 13: if possible, etiological treatment should be actively applied in eligible candidates, to stabilize the patient's condition, reverse decompensated cirrhosis, achieve compensated cirrhosis, or to a state where there is no cirrhosis (e.g., by liver transplantation) **(A, 1)**.
- Recommendation 14: when necessary, it is possible to add the traditional Chinese medicines such as *anluo huaxian pills*, *fuzheng huayu capsules*, and *biejiaruangan tablets*, which may have protective effects against liver fibrosis and cirrhosis **(B, 2)**.

Spontaneous bacterial peritonitis (SBP)

Spontaneous bacterial peritonitis is an abdominal cavity infection that can develop in patients with cirrhosis and refers to peritonitis that has no obvious cause of intra-abdominal lesion, for example, intestinal perforation or abscess. It is a common complication in patients with end-stage liver disease, such as cirrhosis (40–70% of patients), and the incidence of SBP is approximately 27% for patients with cirrhosis undergoing paracentesis after hospitalization. In patients with cirrhosis and a history of SBP, the recurrence rate within 12 months is 40–70%. SBP can rapidly develop into liver and kidney failure, and is a major cause of death in patients with end-stage liver disease. In recent years, the early diagnosis and treatment with effective, well-tolerated antibiotics have reduced the mortality rate related to SBP infection from 90% in the 1970s to approximately 20–60% at present. However, in patients with SBP who have not been treated in a timely fashion, or have hospital-acquired SBP, the mortality rate approaches 50–60% [60, 61].

Clinical manifestations

SBP in patients with cirrhosis is often underdiagnosed owing to insidious onset and diverse clinical signs. Approximately one-third of patients exhibit typical signs and symptoms of peritonitis, including fever, abdominal pain or diarrhea, abdominal tenderness, and/or rebound tenderness. However, most patients do not present with typical signs and symptoms, and the disease can manifest itself as refractory ascites, shock, and hepatic encephalopathy. Risk factors for SBP include a history of SBP, > 65 years of age, diabetes, liver cancer or other tumors, use of immunosuppressive drugs, severe liver function impairment (Child–Pugh grades B/C liver failure), and history of bleeding esophageal varices.

A diagnosis of SBP should be considered in patients with ascites who exhibit fever with a suspected bacterial cause that does not improve with antibiotics; atypical symptoms of liver failure, pyemia with an unknown cause or long-term hypotension (systolic pressure < 80 mmHg for > 2 h) and do not respond to fluid resuscitation.

SBP diagnosis and differential diagnosis

The clinical presentation of SBP is not specific and it is extremely important to actively search for an additional evidence to support the diagnosis. The early diagnosis should be based on the following considerations:

1. One or more of the following signs or symptoms are present: (1) acute peritonitis: abdominal pain, abdominal tenderness or rebound tenderness, an increase in abdominal muscular tension, vomiting, and diarrhea or intestinal obstruction; (2) systemic inflammatory response syndrome: fever or normothermia, shivering, tachycardia, and tachypnea; (3) deterioration of liver function due to an unknown underlying cause; (4) hepatic encephalopathy; (5) shock; (6) refractory ascites, no response to diuretics, or renal failure; (7) acute gastrointestinal tract bleeding.
2. One or more of the following laboratory test abnormalities are present: (1) ascites polymorphonuclear (PMN) cell count $\geq 0.25 \times 10^9$/L; (2) positive ascites bacteria culture; (3) procalcitonin (PCT) > 0.5 ng/mL, and infection of other sites is excluded. Chinese reports indicate that the combination of five indices (body temperature, abdominal tenderness, peripheral blood neutrophil percentage, total bilirubin, and ascites PMN cell count) has a prognostic value for the early screening of asymptomatic SBP [62].

   Any of the following clinical presentations or laboratory abnormalities in a patient with SBP are suggestive of severe infections: (1) fever (> 39.5 °C) or chills; (2) septic shock; (3) acute respiratory distress syndrome; (4) unexplained stage 3 acute kidney failure; (5) peripheral blood leukocytes > 10×10^9/μl; (6) PCT > 2 ng/mL.

   In patients who already received antibiotics, the diagnosis of SBP could be based on the comprehensive assessment of symptoms, signs, complete blood count, ascites test, and other infection indicators such as procalcitonin.

SBP special clinical types

1. Culture-negative neutrocytic ascites (CNNA): diagnostic criteria: (1) culture-negative ascites; (2) ascitic PMN count $\geq 0.25 \times 10^9$/L; (3) secondary peritonitis excluded; (4) no antibiotic drug therapy used within 30 days.

Culture-positive SBP and CNNA have similar clinical signs and symptoms, ascites results, mortality rates, and response to antibiotic treatment. Therefore, CNNA and SBP may be variants of the same disease.

2. Monomicrobial non-neutrocytic bacterial ascites, also known as bacterial ascites: diagnostic criteria: (1) culture-positive ascites; (2) ascitic PMN count $< 0.25 \times 10^9$/L; (3) no significant intra-abdominal infection foci. It was believed that most cases of bacterial ascites were asymptomatic, therefore, there was no need for treatment and SBP or CNNA would not develop. However, recent studies have found that a considerable number of patients with bacterial ascites are symptomatic, and their clinical presentation, laboratory results, ascites examination results, and hospital mortality rates are similar to those of SBP and CNNA. It is now believed that symptomatic bacterial ascites is a variant of SBP, and its long-term prognosis is similar to that of patients with culture-positive ascites; therefore, therapy should be the same as for SBP. As patients with asymptomatic bacterial ascites are similar to those without bacterial ascites, some believe that asymptomatic bacterial ascites represent a transitory bacterial colonization. [63]

   If the ascetic cell count is high, with lymphocyte predominant but polymorph count > 250/dL, the diagnosis of SBP is still considered. However, the etiology could be a special type of SBP, such as tuberculous peritonitis or cancer-associated ascites with SBP.

Anti-infective treatment for SBP

The early diagnosis and initiation of empirical anti-infective therapy for SBP are still major clinical challenges [64]. Distinguishing between community- and hospital-acquired SBP infections is extremely important for the empirical selection of antibiotics [65]. Patients are classified as having hospital-acquired SBP if they present with cirrhotic ascites, exhibit SBP signs and symptoms, or meet the conditions for a SBP laboratory diagnosis 48 h after admission.

1. Empirical anti-infective therapy: A single broad-spectrum antibiotic can increase the culture-negative ascites rate to 86%, at which point only drug-resistant strains can be detected. As the mortality rate is high in patients with cirrhosis and SBP, appropriate early empirical use of antibiotics is important to decrease mortality risk [26].

   For community-acquired SBP, empirical treatment must cover Gram-negative *Escherichia coli*, Gram-positive cocci, and a selection of antibiotics that can cover anaerobic bacteria. When the initial treatment has achieved satisfactory clinical effects, there is no need to alter the treatment plan, even if subsequent reviews indicate the presence of uncontrollable pathogens.

   The recommended treatment for mild-to-moderate community-acquired SBP is either: monotherapy with cefoxitin, moxifloxacin, or ticarcillin/clavulanate; or cefazolin, cefuroxime, ceftriaxone, cefotaxime, or fluoroquinolones in combination with metronidazole. Treatment for severe community-acquired SBP should be either: monotherapy with imipenem/cilastatin, meropenem, biapenem, or piperacillin/tazobactam; or ceftazidime, cefepime, or fluoroquinolone in combination with metronidazole [66].

   Empirical antibiotic drug therapy for hospital-acquired SBP should be determined based on identification of the bacteria present. It is often necessary to use a multi-drug combined therapy plan to cover a broad-spectrum of Gram-negative bacteria and anaerobic bacteria; for example, imipenem/cilastatin, meropenem, biapenem, piperacillin/tazobactam, and ceftazidime or cefepime in combination with metronidazole. Treatment may also require tigecycline or mycin drugs [67].

   Drugs for treating severe community- and hospital-acquired infections should not be used in the treatment of mild or moderate community infections.

   In cases of suspected SBP, cefotaxime or a similar third-generation cephalosporin antibacterial drug can be used to cover 95% of bacteria. However, long-term empirical use of a third-generation cephalosporin will increase the risk of antibiotic resistance and may result in a relatively poor clinical prognosis [68]. Clinical studies have shown that meropenem in combination with daptomycin is more effective than cefotaxime in treating patients with cirrhotic hospital-acquired SBP [69]. Therefore, carbapenem is the first choice of empirical anti-infective therapy for hospital-acquired SBP, which can significantly reduce the mortality rate.

   Assessment of non-responsiveness to antibiotics therapy for SBP: So far, there was still not consensus on the definition of non-responsiveness to antibiotics for SBP. In general, it was defined as no significant improvement or deterioration of the symptoms and signs of peritonitis, systemic inflammatory response syndrome, or infection-related laboratory abnormalities after 72 h of antibacterial therapy. In this condition, antibiotics-resistant or mixed bacterial infection or fungal peritonitis should be suspected. For patients with positive ascites culture, high ascites neutrophil count or high ascites protein concentration, and poor response to antibiotics, secondary bacterial peritonitis should be suspected.
2. The third-generation cephalosporins in combination with HSA: some studies have shown that the mortality rate was markedly lower in patients with SBP who received 1.5 g/kg HSA within 6 h of cefotaxime fol-

lowed by 1.0 g/kg HSA on day 3 compared with cefotaxime alone. It was also possible to control the complications of cirrhosis with this treatment [70]. Antibiotics in combination with HSA could delay the occurrence of AKI in patients with cirrhotic SBP, but had no effect on the long-term prognosis [71].

3. Terlipressin and HSA in combination with the third-generation cephalosporin antibiotics: Cirrhotic SBP is a major cause of AKI and HRS. Terlipressin in combination with HSA and third-generation cephalosporins can significantly improve survival rate in patients who are hospitalized [72].
4. Targeted therapy for drug-resistant bacteria: bacterial ascites strains have evolved over time due to the widespread use of fluoroquinolones, frequent patient hospitalization, and the use of broad-spectrum antibiotics. The increased presence of drug-resistant strains, such as Gram-positive bacteria and extended-spectrum β-lactamase-producing *Escherichia coli*, is seriously impairing the effectiveness of anti-infective therapy and, therefore, the prognosis for patients [63, 73]. In China, drugs that are still effective against Gram-negative bacteria include piperacillin/tazobactam, cefoperazone/sulbactam, imipenem, meropenem, biapenem, amikacin, minocycline hydrochloride, and sulfa drugs. Effective drugs for *Staphylococcus aureus* include vancomycin, daptomycin, teicoplanin, linezolid, and rifampicin. Effective drugs for enterococcus include vancomycin, teicoplanin, linezolid, and daptomycin. Vancomycin-resistant enterococcus, mainly *Enterococcus faecium*, should be treated with daptomycin, linezolid, minocycline, or high-dose ampicillin. Drugs with a relatively low drug resistance rate in common fungi, such as *Candida albicans*, include voriconazole, fluconazole, and amphotericin B.

   The risk factors for multi-drug resistance and infection with drug-resistant pathogenic bacteria include: hospitalization, long-term prophylactic administration of fluoroquinolone drugs, infection with a drug-resistant bacterium, and recent use of a β-lactam antibiotic. Infection with these drug-resistant bacteria is associated with a high mortality rate. To reduce drug resistance, antibiotic prophylaxis should be restricted. Once the infecting strain has been identified, antibiotic administration time should be shortened and replaced with a narrow-spectrum antibiotic based on antibiotic sensitivity testing. Patients with SBP with a suspected drug-resistant infection should be treated with piperacillin/tazobactam, cefoperazone/sulbactam, or a carbapenem in combination with daptomycin, vancomycin or linezolid. Fungal peritonitis should be suspected in patients with cirrhotic ascites who do not respond to antibiotic treatment [74, 75].
5. Non-absorbable intestinal antibiotics: Rifaximin is a broad-spectrum antibiotic derivative of rifamycin. It is particularly effective against enteric bacteria, and possesses bactericidal/bacteriostatic, immunomodulatory, and anti-inflammatory activity. There is evidence that rifaximin does not interact with the intestinal microbial environment.

   Rifaximin-α is a crystal polymorph approved by the US Food and Drug Administration for treatment of hepatic encephalopathy. It reduces endotoxemia and improves the hemodynamics in patients with cirrhosis. In addition, rifaximin-α has a role in the prevention and treatment of cirrhotic SBP and refractory ascites [76].

- Recommendation 15: in patients with cirrhosis, abdominal signs, and symptoms (such as fever, abdominal pain, or tenderness) or abnormal laboratory test results of infection can serve as indicators for the early empirical anti-infective treatment **(B, 1)**.
- Recommendation 16: for patients with community-acquired mild-to-moderate SBP who have recently received a β-lactam, the first choice of treatment should be a third-generation cephalosporin **(A, 1)**. A fluoroquinolone can be used alone if patients have not previously received it **(B, 2)**.
- Recommendation 17: for patients with SBP who are either hospitalized or who have recently received a β-lactam, empirical anti-infective therapy should be based on antibiotic sensitivity testing or include a carbapenem **(A, 1)**.
- Recommendation 18: patients should receive empirical anti-infective therapy if the ascites PMN count is $< 250/mm^3$ and they are exhibiting symptoms of infection such as abdominal pain or tenderness **(B, 1)**.
- Recommendation 19: adverse reactions should be closely monitored in patients with cirrhotic ascites receiving anti-infective drugs **(C, 1)**. Rifaximin can help to prevent the recurrence of SBP **(B, 2)**.

Hepatorenal syndrome

Definitions

When renal impairment occurs in patients with cirrhosis complicated with ascites, AKI should be considered and the etiology of AKI should be investigated as early as possible, and precipitating factors of AKI should be identified and treated, including screening and treatment of infection, volume expansion when appropriate, and discontinuation of all renal toxicity drugs, such as vasodilators or NSAIDs.

On this basis, it can be diagnosed as hepatorenal syndrome according to the traditional criteria.

HRS can be classified into two types, based on disease progression and prognosis [77]:

- Type 1 HRS(HRS-AKI: rapid and progressive renal injury characterized by a doubling of the initial SCr or > 226 μmol/L (2.5 mg/dL) within 2 weeks, and an estimated GFR (eGFR) decline by more than 50% to < 20 mL/min. Patients with severe or repeated episodes of AKI have a higher risk of developing CKD. In addition, renal tubular damage can occur in patients with HRS-AKI and HRS-AKI can occur in patients with underlying CKD.
- Type 2 HRS (non-AKI-HRS, NAKI): slowly progressive renal injury, moderate kidney failure, SCr levels of 133–226 μmol/L (1.5–2.5 mg/dL), often accompanied by refractory ascites, slow renal function decline, and is often a spontaneous process, sometimes with inducing factors. Type 2 HRS now includes renal impairment which fulfills the criteria of HRS but not of AKI, namely non-AKI-HRS (NAKI), and only HRS-CKD.

Pathogenesis

The pathogenesis of cirrhotic HRS is currently unknown. It is generally believed that renal function is mainly affected by hemodynamic changes caused by severe liver dysfunction.

Severe liver dysfunction reduces the inactivation of vasoactive mediators, such as cysteinyl leukotrienes and thromboxane A2. In patients with portal hypertension, vasoactive mediators enter the circulation through a portosystemic shunt that causes vasodilation. This results in a decrease in the effective arterial blood volume and a fall in the mean arterial pressure. The decrease in the effective blood volume causes intra-renal vasoconstriction, and sodium and water retention through activation of the neurohumoral system. Activation of the sympathetic nervous system and RAAS causes changes in renal vasoconstriction and autoregulation, resulting in renal blood flow becoming more sensitive to the changes of mean arterial pressure. In addition, endotoxemia is an important risk factor for HRS in patients with severe liver disease. The detoxification function of liver cells is decreased in patients with severe liver disease, so a large number of endotoxins absorbed through the intestine may be allowed to enter into systemic circulation through the liver or collateral circulation. Endotoxins can cause constriction of both renal and peripheral blood vessels, a decrease in renal blood flow, and a decline in GFR. Ultimately, this results in oliguria and azotemia [78].

In recent years, not all patients presenting with severe liver dysfunction will develop HRS. Therefore, some suggest a "two-strike" hypothesis. The "first strike" constitutes sinus portal hypertension and hepatic function decompensation, causing systemic peripheral vasodilation and a decrease of the effective circulating blood volume. The "second strike", including any initiating factor that exacerbates hemodynamic abnormalities (e.g., upper digestive tract bleeding, excessive urination, SBP, or extraction of a large volume of ascites), promotes HRS formation [79].

Diagnosis

Diagnostic criteria for HRS: (1) cirrhosis complicated by ascites; (2) no shock; (3) rise of SCr ≥ 50% of the baseline level and > 1.5 mg/dL (133 μmol/L); (4) no sustained improvement in renal function (SCr < 133 μmol/L) in patients treated with: HSA (1 g/kg/day) until the volume expands, to a maximum of 100 g/day if a diuretic was initiated but has been discontinued for at least 2 days; (5) no previous use of nephrotoxic drugs, such as NSAIDs, aminoglycoside antibiotics, or contrast agents; (6) no renal parenchymal disease.

There is debate about the significance of urine volume in the diagnosis of HRS when cirrhosis is complicated by ascites. Patients with cirrhotic ascites often experience oliguria and severe sodium retention, but maintain relatively normal GFR values. In addition, diuretic use can lead to an increase in urine volume in some patients.

In 2015, the ICA argued that dynamic monitoring of SCr can accurately reflect the course of AKI in patients with HRS; specifically that SCr increases sharply within 48 h by > 50% of the baseline level, and finally reaches ≥ 1.5 mg/dL (133 μmol/L) [28]. There are three AKI stages. Stage 1; SCr increases by ≥ 0.3 mg/dL (26.5 μmol/L), OR SCr increases to 1.5–2.0-times the baseline value. Stage 2; either SCr increases by ≥ 2.5 mg/dL (226 μmol/L), or SCr increases to > 2.0–3.0-times the baseline value. Stage 3; SCr increases by > 3.0 times the baseline value, SCr increases to ≥ 4.0 mg/dL (353.6 μmol/L), there is an acute rise of ≥ 0.3 mg/dL (26.5 μmol/L), or sustained blood filtration is started.

Compared with HRS, AKI caused by other factors has a better prognosis and is far easier to alleviate; for example, the duration of the injury is shorter, the 30-day mortality rate is lower, and the non-transplant survival rate is higher. Therefore, the early diagnosis and intervention should be considered with even a slight elevation of SCr to prevent the occurrence of HRS.

HRS should be considered if patients present with upper digestive tract bleeding, electrolyte disorder, poor control of ascitic infection, large-volume paracentesis, polyuria, severe vomiting, and diarrhea or rapid renal

function decline. The following measures could be considered when diagnosing HRS: (1) recent medication history and a reduction or discontinuation of any diuretics, vasodilators, or NSAIDs; (2) expansion therapy such as a crystalloid fluid, HSA, or a blood product in patients with suspected hypovolemia is ineffective; (3) anti-infective therapy to treat a confirmed diagnosis of a bacterial infection is ineffective; (4) SCr continues to rise to > 50% of the baseline level and is > 1.5 mg/dL (133 μmol/L).

Treatment

The prognosis for HRS is poor, so treatment should be initiated as soon as possible following confirmation of the diagnosis to prevent the further deterioration of kidney failure.

1. Care management: patients should rest in bed and eat an easily digestible, high-calorie diet. Blood pressure, urine output, fluid balance, liver and kidney function, and the complications of cirrhosis should be monitored frequently. Excessive intake of fluids should be avoided to prevent the occurrence of fluid overload and diluted hyponatremia.
2. Drug therapy: based on the pathophysiological characteristics of HRS, therapy with vasoconstrictors aims to improve the hyperdynamic circulation and increase peripheral arterial pressure by constricting the already markedly dilated vascular bed, and thereby increasing renal blood flow and GFR. These drugs include vasopressin and its analogs (terlipressin), α-adrenergic receptor agonists (midodrine and norepinephrine), and somatostatin analogs (octreotide).

    (1) Terlipressin in combination with HSA: a meta-analysis has demonstrated that terlipressin improves the renal function of patients with type 1 HRS and has a therapeutic efficacy of approximately 40–50% [80]. A small number of randomized-controlled studies have shown that treatment with terlipressin can also improve renal function in patients with type 2 HRS. International studies have demonstrated that the effects of terlipressin in combination with HSA (1 g/kg on day 1, 20–40 g/day thereafter) are improved compared with either terlipressin or HSA alone [25, 65]. Another study showed similar results, but at a lower dose of HSA (10–20 g/day) [81].

    The initial dosage of terlipressin should be 1 mg every 4–6 h, which can be gradually increased up to a maximum of 2 mg every 4–6 h if SCr level does not decrease by ≥ 25% after 3 days of treatment. Treatment should be sustained until SCr falls to < 133 μmol/L. Treatment response is defined as a slow but progressive fall of SCr to < 133 μmol/L associated with an increase in arterial pressure, urine volume, and sodium concentration. The median time to response for terlipressin is 14 days; and treatment time decreases and response rate increases with a decrease in the patient's baseline SCr. In general, recurrence is rare after terlipressin discontinuation, but treatment can be reinitiated if HRS recurs.

    Predictive factor: in patients with type 1 HRS, the baseline serum bilirubin of < 10 mg/dL and the increased mean arterial pressure ≥ 5 mmHg after 3 days of treatment are two independent predictive factors of response to vasoconstrictors [82].

    (2) Octreotide and midodrine in combination with HSA: The treatment of type 1 HRS with octreotide in combination with midodrine and HSA is an alternative to terlipressin [83]. The initial dose for oral administration of midodrine should be 2.5–7.5 mg every 8 h, and 100 μg of octreotide should be subcutaneously injected every 8 h. If there is no improvement in renal function, the dose can be increased to 12.5 mg and 200 μg, respectively, every 8 h.

    (3) Norepinephrine in combination with HSA: In a meta-analysis, treatment with norepinephrine (0.5–3 mg/h) in combination with HSA (10–20 g/day) over the course of 7–14 days had the same results as terlipressin for patients with type 1 or type 2 HRS. However, the meta-analysis only included non-randomized-controlled studies [84]. In a non-randomized trial with a small sample number in China, norepinephrine alone had a similar effect to norepinephrine in combination with terlipressin [85].

    (4) Vasodilators: peripheral vasoconstriction is the primary mechanism that leads to cirrhotic HRS. Currently, the use of vasodilators is not recommended for cirrhotic HRS.

3. TIPS: TIPS can improve the kidney function of patients with type 1 HRS [86]. However, if patients with cirrhotic ascites develop type 1 HRS, their condition is often serious and many are contraindicated for TIPS therapy. Theoretically, TIPS can control ascites and alleviate portal pressure; therefore, it may have good therapeutic efficacy for patients with type 2 HRS [87].
4. RRT: RRT, such as hemodialysis or continuous venous hemofiltration, cannot improve the overall prognosis of patients with type 1 HRS, but it may improve renal function [88]. Therefore, RRT is only used for HRS com-

plicated by severe hyperkalemia or metabolic acidosis, and as emergency treatment for fluid overload. The Molecular Adsorbent Recirculating System (MARS®) can be effective for some patients with type 1 HRS, with a significant renal function improvement achieved in approximately 40% of patients [89].

5. Liver transplant: a liver transplant is the preferred intervention for patients with type 1 and type 2 HRS. Compared with patients with cirrhosis without HRS, the post-transplant survival rate (approximately 65%) in patients with type 1 HRS is lower, primarily due to potential renal failure [90]; however, terlipressin therapy and/or RRT after transplant can improve the survival rate. Patients with type 1 HRS have a high short-term mortality rate, so they are the preferred candidates for liver transplantation.

Prevention of HRS

In patients with cirrhotic ascites, HRS may be induced by bacterial infection, excessive use of diuretics, large-volume paracentesis, upper gastrointestinal bleeding, cholestatic jaundice, and other secondary complications.

1. Preventing infections: prophylactic antibiotics can improve the survival rate in patients with cirrhotic ascites who are susceptible to bacterial infections, such as those with variceal bleeding. Approximately 30% of cases of cirrhotic ascites with SBP can develop into HRS, with prophylactic administration of antibiotics in combination with HSA lowering this incidence to 10%. The 2009 AASLD and 2018 EASL guidelines both recommend the infusion of HSA in combination with an antibiotic to reduce the incidence of HRS and improve the survival rate [3, 5, 65].
2. Careful use of high-dose diuretics and large-volume paracentesis: the treatment of cirrhotic ascites normally consists of sodium restriction and reasonable administration of diuretics. In patients with cirrhotic ascites and hyponatremia, diuretics should be used with caution and sodium restriction is not necessary. However, patients with cirrhotic ascites and serum sodium levels in the normal range should restrict their sodium intake to avoid renal injury caused by hypernatremia.
3. Rational use of non-selective β-blockers: in patients with cirrhosis, non-selective β-blockers lower the portal venous pressure, and can reduce the risk of rupture and bleeding of varicose veins. However, the use of non-selective β-blockers can worsen hemodynamic disorders in patients with cirrhotic ascites complicated by SBP who have an arterial systolic pressure < 90 mmHg and a serum sodium < 130 mmol/L or renal dysfunction. Therefore, in this situation, non-selective β-blockers for the prevention of esophagogastric variceal rupture and bleeding should be discontinued temporarily. The use of β-blockers should be resumed after circulatory and renal function have improved [91].Therefore, it can be used as primary or secondary prophylaxis of variceal bleeding in patients with ascites but normal renal function.

Future Perspectives

The distinction between HRS-AKI and acute tubular necrosis (ATN) is difficult, because the kidney biopsy is rarely performed in the setting of AKI in clinical practice, so the diagnosis based on a combination of multiple biomarkers may be interesting but needs further evaluation. Furthermore, it is meaningful to find more effective drugs by multicenter, randomized-controlled clinical trials, especially for type 2 HRS (non-AKI-HRS).

- Recommendation 20: HRS should be considered if a patient with cirrhotic ascites presents with upper digestive tract bleeding, electrolyte disorder, ascites infection, large-volume paracentesis, polyuria, severe vomiting and diarrhea, or a rapid decline in renal function **(C, 2)**.
- Recommendation 21: diagnosis of HRS: (1) cirrhosis complicated by ascites; (2) no shock; (3) rise of SCr > 50% of the baseline level or > 1.5 mg/dL (133 μmol/L); (4) renal function is not improved after volume expansion and the withdrawal of diuretics (SCr < 133 μmol/L); (5) no recent history of nephrotoxic drug use; (6) no renal parenchymal disease **(A, 1)**.
- Recommendation 22: Type 1 HRS: rapid and progressive renal injury characterized by a doubling of the initial SCr or > 226 μmol/L (2.5 mg/dL) within 2 weeks, and an eGFR decline by > 50% to < 20 mL/min.

  Type 2 HRS: there are some characteristics including slowly progressive renal injury, SCr levels of 133–226 μmol/L (1.5–2.5 mg/dL), often accompanied by refractory ascites **(A, 1)**.
- Recommendation 23: terlipressin (1 mg every 4–6 h) in combination with HSA (20–40 g/day) can be used to treat type 1 or type 2 HRS. If, after treatment for 3 days, SCr does not decline by at least 25%, the dose of terlipressin can be gradually increased to a maximum dose of 2 mg every 4–6 h. If effective, the course of treatment is 7–14 days; terlipressin should be discontinued if treatment is ineffective over this period. If treatment is effective and the condition recurs, terlipressin treatment can be reinitiated **(A, 1)**.
- Recommendation 24: patients with HRS, refractory cirrhotic ascites, and hyponatremia can receive tolvaptan. Non-selective β-blockers should be temporarily discon-

tinued and the use of vasodilators is not recommended for HRS **(C, 2)**.

- Recommendation 25: if patients with type 1 HRS do not respond to vasoconstrictor therapy, RRT or an artificial liver support system can be used (if patients meet the criteria). Patients with type 2 HRS should not receive RRT **(B, 1)**.
- Recommendation 26: patients with type 2 HRS and a large volume of ascites who do not respond to vasoconstrictor therapy can receive TIPS therapy. TIPS therapy for type 1 HRS is not recommended. Patients with type 1 or type 2 HRS should be prioritized for liver transplant **(B, 1)**.

Topics requiring further research

1. The advancement of early stage diagnosis and rapid diagnostic methods to improve the sensitivity and specificity for detection of the pathogenic microorganisms in ascites.
2. Evaluation of dose, course of treatment, and safety of diuretics, vasoactive drugs, HSA, and the maximum volume of paracentesis during each procedure.
3. Evaluation of dose, course of treatment, and safety of empirical antibiotics.
4. New treatment programs for patients with cirrhotic ascites, such as novel diuretics and stem cell therapy.
5. Relationship between intestinal microflora and prevention or treatment of cirrhosis complications.

Acknowledgements List of Expert Group Members (in order of the pinyin Romanization of the individual's last name): Jihong An (Department of Infectious Diseases, Inner Mongolia People's Hospital), Dachuan Cai (Department of Gastroenterology, the Second Affiliated Hospital of Chongqing Medical University), Guofeng Chen (Center for the Diagnosis of Liver Fibrosis, 302 Military Hospital of China), Hongsong Chen (Institute of Hepatology, Peking University People's Hospital), Xinyue Chen (General Department of Hepatology, Beijing You-An Hospital, Capital Medical University), Huiguo Ding (Center for Hepatology and Gastroenterology, Beijing You-An Hospital, Capital Medical University), Lei Dong (Department of Gastroenterology, the Second Affiliated Hospital of Xi'an Jiaotong University), Xiaoguang Dou (Department of Gastroenterology, Sheng Jing Hospital of China Medical University), Zhongping Duan (Artificial Liver Center, Beijing You-An Hospital, Capital Medical University), Jiangao Fan (Department of Gastroenterology, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine), Xuegong Fan (Department of Infectious Diseases, Xiangya Hospital), Jianhe Gan (Department of Infectious Diseases, First Affiliated Hospital of Soochow University), Lei Gao (Department of Infectious Diseases, Peking University First Hospital), Rentao Gao (Department of Infectious Diseases, Anhui Provincial Hospital), Wuhua Guo (Department of Gastroenterology, Mengchao Hepatobiliary Hospital of Fujian Medical University), Tao Han (Department of Hepatology, Tianjin Third Central Hospital), Ying Han (Department of Gastroenterology, Xi Jing Hospital, Fourth Military Medical Hospital), Jianyu Hao (Department of Gastroenterology, Beijing ChaoYang Hospital), Jinlin Hou (Department of Infectious Diseases, Nanfang Hospital, Nanfang Medical University), Yuan Huang (Department of Hepatobiliary and Pancreatic Surgery, Beijing Tsinghua Changgung Hospital), Jidong Jia (Liver Research Center, Beijing Friendship Hospital, Capital Medical University), Huiqing Jiang (Department of Gastroenterology, Second Hospital of Hebei Medical University), Jianning Jiang (Department of Infectious Diseases, First Affiliated Hospital of Guangxi Medical University), Ying'an Jiang (Department of Infectious Diseases, Hubei Provincial People's Hospital), Yuanyuan Kong (Medical Statistics Office, Beijing Friendship Hospital, Capital Medical University), Huibo Li (Department of Pharmacology, Peking University Third Hospital), Jie Li (Department of Pathogen Biology, Peking University Health Science Center), Shuchen Li (Department of Infectious Diseases, Second Affiliated Hospital of Harbin Medical University), Wengang Li (Liver Tumor Diagnosis, Treatment and Research Center, 302 Military Hospital of China), Wu Li (Department of Infectious Diseases, First Affiliated Hospital of Kunming Medical University), Yufang Li (Department of Infectious Diseases, General Hospital of Ningxia Medical University), Shumei Lin (Department of Infectious Diseases, the First Affiliated Hospital of Xi'an Jiaotong University Medical School), Enqiang Linghu (Department of Gastroenterology, Chinese PLA General Hospital), Deliang Liu (Department of Gastroenterology, Hunan Xiangya Second Hospital), Jiyong Liu (Department of Gastroenterology, Shandong Provincial Hospital), Jingfeng Liu (Department of Hepatobiliary Surgery, Mengchao Hepatobiliary Hospital of Fujian Medical University), Xiaoqing Liu (Department of Infectious Diseases, Beijing Union Medical College Hospital), Yulan Liu (Department of Gastroenterology, Peking University People's Hospital), Lungen Lu (Department of Gastroenterology, First Hospital Affiliated to Shanghai Jiao Tong University School of Medicine), Qinghua Lu (Department of Hepatology, Qinghai Fourth People's Hospital), Xinhua Luo (Department of Infectious Diseases, Guizhou People's Hospital), Hong Ma (Hepatology Center, Beijing Friendship Hospital, Capital Medical University), Yimin Mao (Department of Gastroenterology, Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine), Zhechuan Mei (Department of Gastroenterology, the Second Affiliated Hospital of Chongqing Medical University), NAN Yuemin (Department of Traditional and Western Medicine Hepatology, Hebei Medical University), Yuqiang Nie (Department of Gastroenterology, Guangzhou First People's Hospital), Junqi Niu (Department of Infectious Diseases, First Hospital of Jilin University), Hong Ren (Department of Infectious Diseases, the Second Affiliated Hospital of Chongqing Medical University), Weihong Sha (Department of Gastroenterology, Guangdong People's Hospital), Jia Shang (Department of Infectious Diseases, Henan People's Hospital), Ziqin Sun (Department of Gastroenterology, Jinan Military District General Hospital), Hong Tang (Center for Infectious Diseases, Huaxi Hospital, Sichuan University), Hong Wei (Department of Gastroenterology, Hainan People's Hospital), Lai Wei (Institute of Hepatology, Peking University People's Hospital), Jing Wu (Department of Gastroenterology, Shijitan Hospital, Capital Medical University), Wen Xie (Center for Hepatology, Beijing Ditan Hospital Affiliated with Capital Medical University), Shaojie Xin (Liver Failure Diagnosis, Treatment and Research Center, 302 Military Hospital of China), Huichun Xing (Center for Hepatology, Beijing Ditan Hospital Affiliated with Capital Medical University), Jianming Xu (Department of Gastroenterology, First Affiliated Hospital of Anhui Medical University), Xiaoyuan Xu (Department of Infectious Diseases, Peking University First Hospital), Youqing Xu (Department of Gastroenterology, Beijing Tiantan Hospital, Capital Medical University), Jie Yan (Center for Hepatology, Beijing Ditan Hospital Affiliated with Capital Medical University), Ming Yan (Department of Gastroenterology, Qilu Hospital, Shandong University), Dongliang Yang (Department of Infectious Diseases, Xiehe Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology), Jiming Yang (Department of Infectious Diseases, Tianjin

Infectious Diseases Hospital), Shaoqi Yang (Department of Gastroenterology, General Hospital of Ningxia Medical University), Yuxiu Yang (Department of Gastroenterology, Henan People's Hospital), Hong You (Liver Research Center, Beijing Friendship Hospital, Capital Medical University), Yanyan Yu (Department of Infectious Diseases, Peking University First Hospital), Suodi Zhai (Department of Pharmacology, Peking University Third Hospital), Bin Zhang (Center for Endoscopy, China-Japan Union Hospital of Jinlin University), Chunqing Zhang (Department of Gastroenterology, Shandong Provincial Hospital), Dazhi Zhang (Department of Infectious Diseases, the Second Affiliated Hospital of Chongqing Medical University), Guoliang Zhang (Department of Gastroenterology, Tianjin First Central Hospital), Lingqi Zhang (Department of Hepatology, Lanzhou University Second Hospital), Wenhong Zhang (Department of Infectious Diseases, Huashan Hospital, Fudan University), Xinxin Zhang (Department of Infectious Diseases, Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine), Jingmin Zhao (Department of Pathology, 302 Military Hospital of China), Shousong Zhao (Department of Infectious Diseases, Bengbu Medical College Hospital), Hui Zhuang (Department of Pathogen Biology, Peking University Health Science Center), Weize Zuo (Department of Infectious Diseases, First Affiliated Hospital of Shihezi Unviersity School of Medicine). Secretaries: Xiaxia Zhang (Department of Gastroenterology, Tiantan Hospital, Capital Medical University), Ying Han (Center for Hepatology and Gastrointerology, Beijing You-An Hospital, Capital Medical University), and Hao Luo (Department of Infectious Diseases, Peking University First Hospital).

Compliance with ethical standards

Conflict of interest None to declare.

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