Ascites and intraabdominal infection

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Purpose of review

This review will give an overview of current trends in diagnosis, treatment, and pathogenesis of ascites and intraabdominal infection in cirrhotic and noncirrhotic critically ill patients.

Recent findings

Single clone-bacterial DNA has been found in sterile ascites and serum, proving the concept of direct translocation. Activation of mesenteric macrophages can be induced by splanchnic vasodilatation but also by hypoxia. Carbon monoxide, an end product of heme catabolism, promotes splanchnic vasodilatation, representing a possible link between gastrointestinal hemorrhage and circulatory dysfunction. Colorimetric test strips and automated counters accurately diagnose spontaneous bacterial peritonitis. Vasopressin V2-antagonists have been introduced as novel therapy for impaired water excretion in hyponatremia.

Summary

Emerging pathophysiological concepts have modified the conventional view of hydrostatic and Starling forces in the evolution of ascites. Current data indicate that the dynamic sequence of bacterial translocation, mesenteric inflammation, splanchnic vasodilatation and intrahepatic vasoconstriction determines occurrence, severity, and outcome of ascites and intraabdominal infection.

Keywords

ascites, infection, inflammation, nitric oxide, peritonitis, renal failure, vasodilatation

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Abbreviations

SBP	spontaneous bacterial peritonitis
TIPS	transjugular portosystemic stent-shunt

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Introduction

Ascites, defined as serous fluid collection in the abdominal cavity, may develop in a variety of clinical situations. In most instances, ascites formation is caused by sinusoidal portal hypertension, which results from the combination of splanchnic hyperperfusion and disturbance of liver architecture, as typically seen in cirrhosis. Alternatively, increased hydrostatic pressure caused by vascular occlusion at the level of portal vein, hepatic sinusoids and hepatic veins (Budd-Chiari syndrome), or congestive heart failure can give rise to ascites formation. In the intensive care setting, most ascitic patients are admitted because of decompensated hepatic failure or congestive heart failure, with increased probability of bacterial infections. Recent work has helped to unravel pathophysiological links between ascites, intraabdominal infection, and renal impairment, as the most important prognostic factor. The following paragraphs will summarize recent developments that may be relevant for diagnosis and treatment.

Recent developments in the management of ascites

Vasopressin V2 receptor antagonists for dilutional hyponatremia

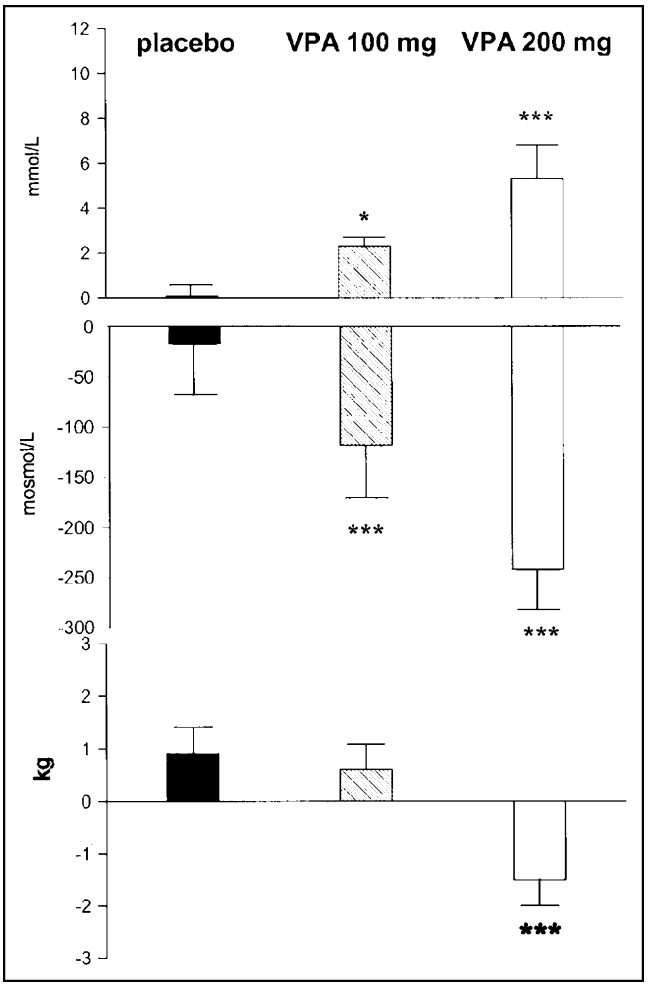
Hyponatremia in advanced cirrhosis with ascites is the result of an inappropriate nonosmotic release of vasopressin, which increases water reabsorption in the distal nephron. Hyponatremic patients have a significantly increased mortality, mainly because of progressive renal and circulatory failure [1]. Conventional treatment consisting of fluid and sodium restriction is usually insufficient in normalizing serum sodium concentrations. VPA-985 is an orally active selective vasopressin V2 receptor antagonist that decreases tubular water reabsorption. In a randomized study involving predominantly cirrhotic patients with hyponatremia (n = 33), VPA-985 produced a significant aquaretic response compared with placebo, with dose-related increases in free water clearance and serum sodium concentrations [2••]. Beneficial effects of VPA-985 on renal water excretion were maintained with continued administration for 7 days, whereas orthostatic blood pressure and serum creatinine levels were unchanged. Thirst increased with high doses, along with significant increases in plasma vasopressin levels, and half of the patients in the 250-mg group had to stop medication. The authors conclude that VPA-985 is effective in correcting abnormal renal water handling but requires close monitoring if used in higher doses. An additional randomized double-blind trial investigated 60

patients with cirrhosis and dilutional hyponatremia on 1000-mL daily fluid restriction [3••]. VPA-985 increased urinary volume and weight loss in both spontaneous and diuretic-induced hyponatremia (Fig. 1). Serum sodium concentration increased by at least 5 mmol/L in 67% of patients receiving 200 mg, in 45% of patients receiving 100 mg, but only in 5% of patients receiving placebo. Serum sodium levels normalized in 50%, 27%, and 0%, respectively, demonstrating low efficacy of conventional treatment. Notably, incidence of renal failure and encephalopathy were not increased despite a negative fluid balance in both studies.

Transjugular portosystemic stent-shunt for refractory ascites

Diagnostic criteria of refractory ascites have been refined by a recent consensus conference (Table 1 [4••]).

Figure 1. Effects of placebo, VPA-985 100 mg/d, and VPA-985 200 mg/d on serum sodium concentration, urine osmolality, and body weight in patients with cirrhosis, ascites, and hyponatremia



Effects of placebo (n = 20), VPA-985 100 mg/d (n = 22), and VPA-985 200 mg/d (n = 18) on serum sodium concentration (upper panel), urine osmolality (middle panel), and body weight (lower panel) in patients with cirrhosis, ascites, and hyponatremia. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ versus placebo. Reproduced with permission [3••].

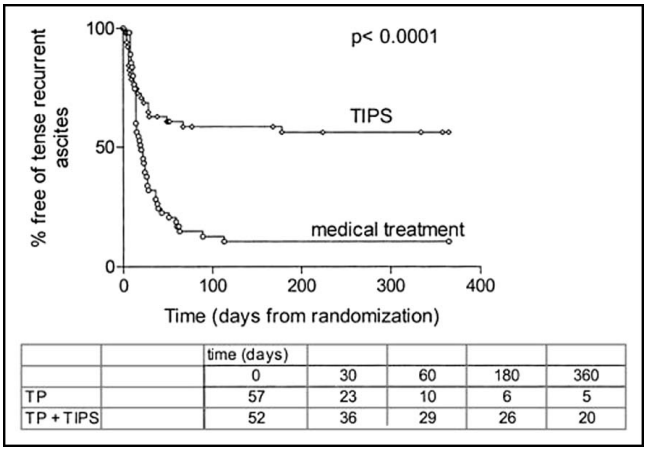
Table 1. Revised diagnostic criteria of refractory ascites

1. Treatment duration: Patients must be on intensive diuretic therapy (spironolactone 400 mg/d and furosemide 160 mg/d) for at least 1 week and on a salt-restricted diet of less than 90 mmoles or 5.2 g of salt/d.
2. Lack of response: Mean weight loss of <0.8 kg over 4 days and urinary sodium output less than the sodium intake.
3. Early ascites recurrence: Reappearance of grade 2 or 3 ascites within 4 weeks of initial mobilization.
4. Diuretic-induced complications: Diuretic-induced hepatic encephalopathy is the development of encephalopathy in the absence of any other precipitating factor. Diuretic-induced renal impairment is an increase of serum creatinine by >100% to a value >2 mg/dL in patients with ascites responding to treatment. Diuretic-induced hyponatremia is defined as a decrease of serum sodium by >10 mmol/L to a serum sodium of <125 mmol/L. Diuretic induced hypo- or hyperkalemia is defined as a change in serum potassium to <3 mmol/L or >6 mmol/L despite appropriate measures.

Several recent studies have addressed the role of transjugular portosystemic stent-shunt (TIPS) for the treatment of refractory ascites [5]. In a US multicenter study, 109 patients with refractory ascites were randomized to receive either medical therapy (sodium restriction, diuretics, paracentesis) or medical therapy plus TIPS [6••]. TIPS plus medical therapy was superior for the control of ascites (Fig. 2) but did not improve hospitalization rate, quality of life, or survival. The authors suggest using TIPS only as second-line therapy.

Gines *et al.* randomized patients with refractory ascites to receive TIPS (n = 35) or repeated paracentesis plus albumin (n = 35). TIPS lowered the rate of ascites recurrence and the incidence of the hepatorenal syndrome in cirrhotic patients with refractory ascites but increased the rate of severe encephalopathy and caused higher costs, without improving survival [7•]. A meta-analysis of randomized studies evaluating TIPS for refractory ascites

Figure 2. Improved control of tense ascites in patients treated with transjugular portosystemic stent-shunt compared with medical treatment



	time (days)				
	0	30	60	180	360
TP	57	23	10	6	5
TP + TIPS	52	36	29	26	20

Improved control of tense ascites in patients treated with transjugular portosystemic stent-shunt (TIPS) compared with medical treatment. Reproduced with permission [6••].

yielded 45% pooled estimates for complete response at 6 months and 63% for any response (complete or partial) [8]. Pooled 6-month mortality was 36%. The rate of new or worsening encephalopathy after TIPS was 32%, and mortality was 100% in patients with refractory encephalopathy. Risk factors for death included serum creatinine greater than 1.5 mg/dL, total bilirubin greater than 3 mg/dL, age greater than 60 years, and poor initial response to TIPS. Despite studies describing beneficial effects of TIPS in hepatorenal failure, the authors suggest alternative treatments if the above risk factors are present.

Stenosis of TIPS is a major cause of morbidity and ascites recurrence, which could be reduced by polytetrafluoroethylene (PTFE) coating. A retrospective 2-year follow-up of 508 Austrian cirrhotic patients treated between 1994 and 2002 suggests that PTFE-coated TIPS was associated with higher survival at 3 months, 1 year, and 2 years, being 93%, 88%, and 76% in the PTFE-coated compared with 83%, 73%, and 62% in the bare-stent group [9•]. Multivariate analysis confirmed that stent type, patient age, and Child-Pugh class were important predictors of survival, whereas indication for stent placement was not.

Transjugular portosystemic stent-shunt for hepatic hydrothorax

Hepatic hydrothorax is a refractory pleural effusion that occurs when ascitic fluid tracks up into the thorax via diaphragmal defects. Medical treatment is often ineffective and repeat thoracocentesis (avoiding tube thoracostomy) may be required to prevent respiratory distress. TIPS was investigated in 21 patients with hepatic hydrothorax [10]. Clinical response was complete in 63%, partial in 11%, and absent in 26% of patients, confirming results of a previous study [11]. Of the 13 patients surviving more than 30 days, 10 had a lasting response, but most of the nonresponders died within 30 days. Considering the poor outcome of alternative treatment modalities, TIPS appears to be a good option for patients with hepatic hydrothorax and relatively preserved hepatic function.

Saline or albumin to prevent paracentesis-induced circulatory dysfunction

Effects of plasma volume expansion with albumin versus isotonic saline infusion on paracentesis-induced circulatory dysfunction were prospectively compared [12•]. Overall, paracentesis-induced circulatory dysfunction occurred more frequently in the saline (33%) than in the albumin group (11%). Use of saline but not albumin caused significant increases in plasma renin activity 24 hours and 6 days after paracentesis. No difference, however, was observed if less than 6L ascites was evacuated. This study indicates that saline can be a substitute for albumin only if less than 6 L of ascitic fluid is evacuated.

Mannitol for refractory ascites

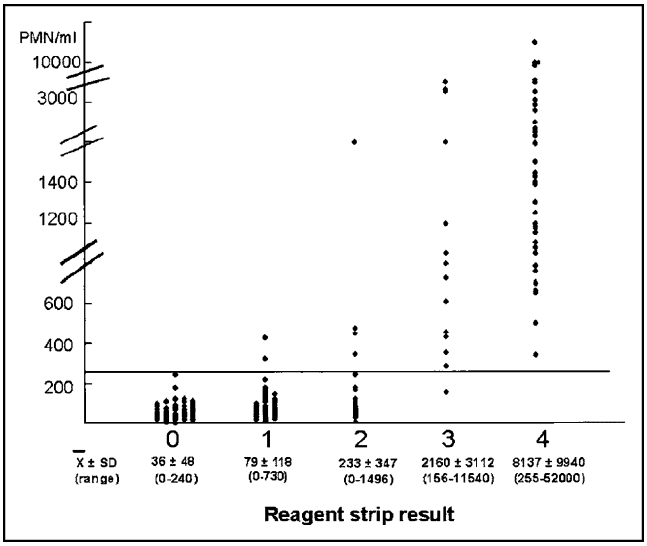
In a preliminary study, cirrhotic patients with refractory ascites were randomized to receive 100 mL of mannitol 20% solution or 5% dextrose [13]. There was a moderate increase in urine volume and natriuresis in the mannitol group. Overall, 53% of patients were classified as responders. Interestingly, baseline urinary sodium excretion and serum sodium levels were lower in patients who responded to mannitol than in those who did not, making mannitol a potential alternative in hyponatremic patients not responding to diuretics.

Management of spontaneous bacterial peritonitis

Diagnosis

Spontaneous bacterial peritonitis (SBP), defined as infection of a previously sterile ascitic fluid without apparent surgically treatable intraabdominal source of infection, is diagnosed by a polymorphonuclear count of equal or more than 250 cells per cubic millimeter [14]. Prevalence is 10 to 30% in hospitalized cirrhotic patients. Given negative ascites cultures in more than 60% of affected patients and a delay of several days for microbiologic results, early diagnosis of this life-threatening infection requires microscopic analysis of ascitic fluid. Manual counting often delays the initiation of therapy and may be not available on a 24-hour basis. Biochemical evaluation of ascitic fluid is limited by low specificity [15]. Vanbiervliet *et al.* [16•] reported 100% sensitivity and specificity of a positive WBC Multistix urine reagent strip for the correct diagnosis of SBP, although findings were limited by a low incidence of SBP. Spanish investigators compared a 5-grade colorimetric leukocyte esterase activity strip and polymorphonuclear count in 52 episodes of SBP and 5 episodes of secondary peritonitis [17••]. Considering a reagent strip result of 2 or more as positive, sensitivity was 96%, specificity was 89%, and positive predictive value was 99% for SBP diagnosis. Even patients with a high total leukocyte but a low polymorphonuclear count (chylous ascites, hematologic neoplasia, tuberculosis) were correctly classified (Fig. 3). Angeloni *et al.* [18••] compared an automated blood cell counter with the traditional microscopic method in 130 ascitic fluid samples from 74 consecutive cirrhotic patients. All but one episode of peritonitis were correctly identified, with a mean difference of only six white cells per cubic millimeter, yielding a sensitivity of 94% and a specificity of 100%. Positive and negative predictive values were 100% and 99%, respectively. Combining results from these studies, the use of automatic counters to confirm positive findings on a colorimetric test strip provides a simple, rapid, and accurate method to detect SBP, with the possible exception of tuberculous peritonitis. A large randomized study comparing clinical outcomes of reagent strip based or automated counting versus manual diagnosis is still required to be performed before manual cytology can be replaced by alternative methods.

Figure 3. Correlation of absolute polymorphonuclear count and colorimetric leukocyte esterase test strip results in cirrhotic patients with ascites



Correlation of absolute polymorphonuclear (PNM) count and colorimetric leukocyte esterase test strip results in cirrhotic patients with ascites. Reproduced with permission [17••].

Antibiotic prophylaxis and treatment of spontaneous bacterial peritonitis

Current guidelines recommend daily oral norfloxacin prophylaxis in all patients after a first episode of SBP [19], which could lead to the emergence of resistant bacteria. Temporal patterns of antimicrobial resistance and outcome were investigated in patients with end-stage liver disease and SBP evaluated for transplantation [20]. Although the frequency of multiple-antibiotic bacterial resistance increased from 8.3% between 1991 and 1995 to 38.5% between 1996 and 2001 ($P = 0.07$), mortality did not change over time (26% in both cohorts). The authors identified the severity of hepatic and renal dysfunction but not multiple-antibiotic resistance as independent determinants of outcome. In a prospective evaluation of all bacterial infections diagnosed in 405 hospitalized cirrhotics between 1998 and 2000 [21], SBP was the most frequent infection (138 cases), and gram-positive cocci were the main bacteria isolated in nosocomial infections (59%). Intensive care admission and invasive procedures increased the likelihood of gram-positive infection, whereas long-term norfloxacin increased quinolone-resistant gram-negative infections. Empirical treatment of SBP by oral ciprofloxacin was found to be as effective but less costly compared with the current standard of intravenous cefotaxime or ceftriaxone [22]. Daily norfloxacin was more effective than weekly rufloxacin in the prevention of SBP recurrence [23]. The author's concern that development of quinolone-resistant *Escherichia coli* in feces could be an important problem in patients on long-term prophylaxis seems to be confirmed by a study from Korea reporting increasing numbers of microorganisms resistant to third-generation cephalosporins and quinolones in patients with SBP. In this study, emergence of multiple-antibiotic resistance was independently associated with a worse prognosis [24]. Epidemiologic changes favoring gram-positive infections are not only related to norfloxacin prophylaxis but also to the increasing use of invasive procedures [25]. Moreover, antibiotic prophylaxis for SBP increases the risk of post-transplant invasive candidiasis by a factor of 8 [26].

Efficacy of antibiotic therapy in cirrhotic patients with SBP has been investigated by a Cochrane meta-analysis of 9 randomized trials that compared different types of antibiotics in 684 patients [27•]. Because of insufficient study design and the absence of placebo-controlled trials, the reviewers were unable to establish the optimal dose or duration of antibiotic therapy. They also found no convincing evidence that cefotaxime was more effective than ampicillin-tobramycin or that oral quinolones should be recommended for patients with less severe manifestations.

Prognostic issues in spontaneous bacterial peritonitis

Spontaneous bacterial peritonitis is an ominous prognostic sign in hospitalized cirrhotic patients, with in-hospital mortality rates of 20 to 30% and a high risk of recurrence and progressive renal failure [19]. Given 1-year survival rates of 30 to 50%, patients with ascites recovering from an episode of SBP are considered potential candidates for liver transplantation [28••]. However, does this also apply to outpatients presenting without risk factors such as gastrointestinal bleeding, hepatorenal syndrome, or hepatic encephalopathy? A study from the Mayo Clinic in Rochester, Minnesota reviewed a prospectively recorded database of all outpatients with cirrhotic ascites undergoing paracentesis during a 7-year period. The prevalence of SBP defined by neutrophil count was only 3.5% (15/427 patients). Only six of these patients had positive cultures (predominantly gram-positive bacteria), whereas eight patients had bacterial ascites without elevated neutrophil count. One-year survival was 67%, and hepatorenal syndrome did not develop in any patients. The authors conclude that SBP in outpatients with cirrhotic ascites occurs much less frequently and has a better outcome than its counterpart in hospitalized patients, obviously reflecting different disease severity and risk factors. Outcomes of nonneutrocytic and neutrocytic ascites were similar, without apparent impact of antibiotic treatment on prognosis. This suggests spontaneous recovery from infection, again unlikely in hospitalized patients. A Danish study reported an SBP rate of 27% and in-hospital mortality of 20% in hospitalized cirrhotic patients undergoing their first paracentesis [29]. Quite unexpectedly, risk of mortality in patients with SBP relative to those without SBP was 1.0 (95% CI, 0.7–1.5) after adjustment for age, gender, comorbidity, and alcohol abuse. Moreover, SBP did not affect prognosis of pa-

tients with cirrhosis if diagnosed at first paracentesis, whereas development of SBP during follow-up doubled the mortality risk, obviously because of a longer diagnostic delay. The use of reagent strip testing might therefore be appropriate in all paracenteses for rapid diagnosis of SBP.

A study from southern Brazil assessed incidence, prognosis, and predictive factors for renal impairment after SBP in cirrhotic patients [30]. Of 1030 hospitalizations of cirrhotic patients, 114 episodes of SBP were diagnosed in 94 patients. In 61% of episodes, SBP was associated with renal impairment. Mortality in patients with versus without renal impairment was 36% versus 6%, respectively ($P < 0.001$). Progressive renal impairment had 100% mortality, as opposed to 58% with steady and 2.85% with transient impairment. Creatinine levels (greater than or equal to 1.3 mg/dL) before the diagnosis of SBP and the rate of infection resolution were the only predictors of renal impairment in the multivariate analysis. A French multicenter study investigating patients with a history of variceal bleeding found that the presence and severity of ascites were the only independent predictors of bleeding-free survival, indirectly confirming the pivotal prognostic role of splanchnic vasodilatation and renal dysfunction [31].

Complications of spontaneous bacterial peritonitis

Despite rapid resolution of infection, many patients with SBP develop progressive splanchnic and systemic vasodilatation, causing hepatorenal and subsequent multiorgan failure. Bacterial translocation, by triggering nitric oxide–induced vasodilatation, plays an important role in hemodynamic deterioration [32]. Patients with advanced cirrhosis have increased local production of tumor necrosis factor-α in mesenteric lymph nodes that seems to be mainly induced by bacterial translocation and is independently associated with the presence of ascites, advanced cirrhosis, and increased systemic tumor necrosis factor-α concentrations [33]. Recent experiments have also demonstrated that hypoxia in cultured macrophages from cirrhotic patients induces release of macrophage-derived vasodilatory factors (vascular endothelial growth factor, adrenomedullin), suggesting that local reduction in oxygen tension could aggravate the circulatory disturbance of cirrhotic patients [34••]. Carbon monoxide, a product of the heme-oxygenase pathway, appears to act as a further endogenous vasoactive substance. CO concentration in exhaled air and blood carboxyhemoglobin levels were determined in 16 healthy subjects, 32 noninfected cirrhotic patients (20 with ascites), and 19 patients with SBP, all nonsmokers. Exhaled CO and carboxyhemoglobin levels were significantly higher in noninfected cirrhotic compared with healthy subjects (2.3 ppm *vs* 0.7 ppm and 1.0% *vs* 0.6%, respectively; $P < 0.05$). CO values were even higher in patients with ascites and were highest in those with SBP. They decreased after resolution of the infection, reaching values similar to those of noninfected patients 1 month after SBP. A direct correlation between CO and plasma renin activity ($r = 0.71$, $P < 0.001$) suggests that increased CO production contributed to circulatory dysfunction in cirrhosis with SBP. Cirrhotic patients with ascites and marked immune and hemodynamic derangement were also reported to have increased circulating levels of lipopolysaccharide-binding protein, which forms a complex with lipopolysaccharide that activates the CD14 receptor, greatly enhancing the effects of lipopolysaccharide [35]. Decreasing levels of lipopolysaccharide-binding protein by norfloxacin treatment suggests a causal involvement of enteric bacteria in pathogenesis, suggesting direct bacterial translocation, which already has been confirmed by the simultaneous presence of bacterial DNA in nonneutrocytic, culture-negative ascites and serum [36].

Conclusion

Advances in pathophysiology have greatly influenced our understanding of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome. Emergence of ascites in cirrhotic patients is a clear sign of impending decompensation, and there is broad consensus that these patients should be evaluated for transplantation if applicable [4••]. Bacterial translocation seems to be a key factor triggering decompensation, and SBP should be considered in all cirrhotic patients with clinical deterioration. A simple test strip appears to be sufficient for diagnosing this potentially lethal complication. As demonstrated in a landmark study by Ginès, parameters indicating vasodilatation and circulatory dysfunction more accurately predict prognosis than those reflecting hepatic function [37]. Future studies may address whether a combined approach addressing bacterial translocation (oral antibiotics, probiotics) and vasodilatation (vasopressin V1 agonists) will be beneficial.

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