Sepsis and cirrhosis : many similarities

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Abstract

Sepsis and cirrhosis are both characterised by a hyperdynamic state associated with a low systemic vascular resistance, and the release of many mediators. The haemodynamic characteristics are so similar that sepsis is difficult to recognise in cirrhotic patients. Nevertheless, the occurrence of sepsis in cirrhotic patients is associated with high mortality rates. The resemblance of the two conditions may be in part related to the common translocation of bacterial products in cirrhosis.

This article reviews the similarities and differences between sepsis and cirrhosis and defines the basis for the treatment of severe sepsis in cirrhotic patients. (Acta gastroenterol. belg., **2010**, 73, **472-478**).

Key words : respiratory failure, renal failure, coagulation, encephalopathy, shock, vasopressin, corticosteroids, lactate, cardiac output, inflammation, cytokines.

Introduction

Sepsis is the systemic response to infection (1). Cirrhosis is generally classified as the end-result of chronic liver disease in which liver tissue is replaced by fibrosis and scar tissue leading to loss of liver function (2). At first glance, these two conditions may seem to have little in common, but they actually share many similarities in terms of haemodynamic characteristics and inflammatory responses. Moreover, sepsis is more common in patients with cirrhosis, and patients with cirrhosis who develop sepsis are more likely to die than their non-cirrhotic counterparts. There are relatively few data regarding sepsis in the patients with cirrhosis. Here we will highlight the ways in which these conditions resemble each other and discuss suggested management strategies for the cirrhotic patient with severe sepsis.

Pathophysiology of sepsis

The word infection refers to a microbial event involving either the invasion of sterile parts of an organism (like the blood, the cerebrospinal fluid or the ascitic fluid) by microorganisms or the invasion of a non-sterile part by pathogens (e.g., in gastroenteritis). In either case, there is usually a host response characterised by fever, tachycardia, hyperventilation and some biological alterations, like an increase in white blood cell count (WBC) or in C-reactive protein (CRP) (1).

This complex pathophysiologic state of sepsis is characterised by the release of many pro- and anti-inflammatory mediators (3). Pathogens influence intracellular function by activating cellular receptors, called pathogen recognition receptors (PRRs). Among these, Toll-like receptors (TLRs) are particularly important. TLR4 receptors are primarily stimulated by endotoxin and TLR2 by products released by Gram-positive organisms. This stimulation results in the release of pro-inflammatory cytokines (like tumour necrosis factor [TNF]) and chemokines, which in turn induce the release of secondary mediators, like platelet activating factor (PAF), and production of arachidonic acid metabolites. Damaged cells (regardless of the mechanism) also release molecular products called "alarmins" (e.g., high mobility group box1, HMGB1) that can amplify this cellular response. The coagulation system is also stimulated by the activation of tissue factor (TF), resulting in disseminated intravascular coagulation (DIC).

An anti-inflammatory response takes place simultaneously, with the release of soluble receptors and antagonists that neutralise pro-inflammatory cytokines. Anti-inflammatory cytokines (e.g., interleukin [IL]-10) are also produced and epigenetic regulations (e.g., histone acetylation/methylation and nucleosome remodelling) act to 'silence' specific pro-inflammatory genes (4). This anti-inflammatory response rapidly becomes predominant, resulting in immunosuppression and promoting the development of nosocomial infections (3). Apoptosis of immune cells (B lymphocytes, CD4 T lymphocytes and follicular dendritic cells) participates in septic immune dysfunction (5). Lymphocyte anergy is associated with increased mortality in sepsis, whereas inhibition of lymphocyte apoptosis improves survival in experimental sepsis (6).

Sepsis and organ dysfunction

The sepsis response is analogous to a battle in which the host fights against the invasion by the micro-organism. This complex pathophysiologic state is characterised by the release of many pro- and anti-inflammatory mediators. Pragmatically, the word "sepsis" is reserved for severe cases, as described by Hippocrates who already used the word, meaning "putrefaction".

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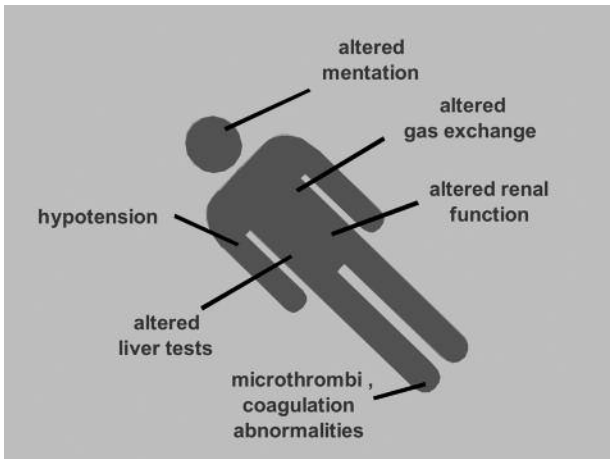

Fig. 1. — The 6 major abnormalities characterising severe sepsis.

Sepsis is considered as a "bad" host response to an infection, which occurs when the host response becomes unregulated. One would not label a flu-type reaction that prevents sufferers from going to work because of some fever and general malaise as 'sepsis'. Likewise, we would not call a patient who is admitted directly to the floor for uncomplicated pneumonia, 'septic'. In patients with sepsis, instead of fever, there may be hypothermia, which portends a worse prognosis. Likewise, there may be an acute decrease in WBC count, due to activation of leucocytes in the periphery.

There is typically some degree of organ failure attributed to sepsis (Fig. 1), which is why one commonly refers to "severe sepsis" as the condition in which there is dysfunction of at least one of 6 organs systems. As sepsis worsens, multiple organs fail and the primary cause of death of patients with sepsis is multiple organ failure. Tissue hypoperfusion and hypoxia play an important role in the development of organ failure but they are certainly not the only players. Altered microperfusion can result from decreased perfusion pressure and flow, microthrombi formation, reduced red blood cell deformability (7), blood maldistribution (8), and tissue oedema caused by increased capillary permeability. In addition, cells may be unable to properly utilise available oxygen due to impairment in mitochondrial respiration.

There are six organ systems that one can easily measure. Abnormalities within these systems can be quantified with the use of the sequential organ failure assessment (SOFA) score (Table 1) (9).

- Respiratory : There is typically an alteration in gas exchange with hypoxemia (characterised by a low PaO_2/FiO_2 ratio) and bilateral chest infiltrates in the absence of evidence of left heart failure. One speaks about acute respiratory distress syndrome (ARDS) when hypoxaemia is severe (with a PaO_2/FiO_2 ratio of less than 200 mmHg – as an example, the PaO_2 would be less than 100 mmHg under 50% oxygen by mask) or acute lung injury (ALI) when hypoxaemia is less severe (i.e., a PaO_2/FiO_2 less than 300 mmHg).
- Renal : There is oliguria (urine output less than 0.5 mL/kg/min and/or an increase in creatinine concentration.
- Haematological : In typical DIC, there is prolongation of the prothrombin time (PT) and activated partial thromboplastin time (APTT) and a decrease in thrombocyte count. The increase in D-dimers is quite non-specific, so that it is usually not included in the initial coagulation panel. Sometimes the PT and APTT are not very abnormal, so that it is the platelet count which is included as a marker of haematological dysfunction.
- Neurological : Acute deterioration of neurological status, called septic encephalopathy, is common in sepsis. This is typically characterised by altered mentation (disorientation, confusion) and obtundation (without real coma).
- Hepatic : In the acutely ill, elevation of liver transaminases is quite common, but may be of muscular origin (especially in cases of circulatory failure). Alkaline phosphatase is usually normal in the absence of biliary tract obstruction. Therefore, it is usually the increase in bilirubin concentration which is taken as an index of liver dysfunction. However, this is not optimal, as the increase in bilirubin is a relatively late signal.
- Cardiovascular : Arrhythmias are not easily quantified and do not represent a major severity index in most critically ill patients. Clearly, hypotension is a cardinal sign of cardiovascular failure in the critically ill. Shock is usually defined as hypotension associated with signs of altered tissue perfusion. One refers then to the three "windows" of acute circulatory failure : The skin (altered capillary perfusion with slow capillary refill), the kidney (decreased urine output), and the brain (altered mentation). Increased lactate levels are the best indicator of abnormal cellular oxygen metabolism. Lactate may be produced in excessive amounts in the hypoxic cell ; lactate clearance may be simultaneously reduced by the altered liver blood flow.

One may try to add endocrine dysfunction to this classification, but endocrine dysfunction is much more difficult to quantify. Hyperglycaemia and insulin resistance are frequent features of sepsis and are potentially harmful, reducing neutrophil function and wound healing and by activating apoptosis and coagulation. Septic shock is frequently associated with relative adrenal insufficiency (RAI), which is implicated in a reduced response to adrenergic agents and higher mortality (10). In a double-blind randomized controlled trial (RCT) performed in patients with septic shock, Annane *et al*. showed that the administration of hydrocortisone (50 mg intravenously every 6 hours) and fludrocortisone (50 μg orally once daily) to non-responders to an adrenocorti-

Table 1. — **The sequential organ failure assessment score (9)**

SOFA score	**0**	**1**	**2**	**3**	**4**
Respiration PaO_2/FiO_2, mmHg	> 400	≤ 400	≤ 300	≤ 200 --------with respiratory support-------	≤ 100
Coagulation Platelets × $10^3/mm^3$	> 150	≤ 150	≤ 100	≤ 50	≤ 20
Liver Bilirubin, mg/dL (μmol/L)	< 1.2 (< 20)	1.2 - 1.9 (20 - 32)	2.0 - 5.9 (33 - 101)	6.0 - 11.9 (102 - 204)	> 12.0 (> 204)
Cardiovascular Hypotension	No hypotension	MAP < 70 mmHg	dopamine ≤ 5 or dobutamine (any dose)*	dopamine > 5 or adrenaline ≤ 0.1 or noradrenaline ≤ 0.1*	dopamine > 15 or adrenaline > 0.1 or noradrenaline > 0.1*
Central nervous system Glasgow coma score	15	13 - 14	10 - 12	6 - 9	< 6
Renal Creatinine, mg/dL (μmol/L) or urine output	< 1.2 (< 110)	1.2 - 1.9 (110 - 170)	2.0 - 3.4 (171 - 299)	3.5 - 4.9 (300 - 440) or < 500 mL/d	> 5.0 (> 440) or < 200 mL/d

* adrenergic agents administered for at least one hour (doses given are in μg/kg/min).

cotropic hormone (ACTH) test reduced 28-day mortality from 63 to 53% (11). However, the subsequent CORTICUS trial did not confirm these findings in patients with less severe sepsis (12) ; steroid administration was associated with a more rapid resolution of circulatory shock, but there was perhaps a greater incidence of secondary infections. Hence the administration of moderate doses of hydrocortisone is recommended in severe septic shock, but only for the duration of shock (13).

Relative arginine-vasopressin deficiency, potentially due to reduced vasopressin stores and nitric oxide (NO)-related down-regulated production by the posterior pituitary gland, is observed in septic shock and contributes to hypotension (14). Sepsis-elicited vasopressin deficiency may thus play a role in the mechanism of septic shock refractory to catecholamine administration. A double-blinded randomized controlled trial (RCT) comparing the effects of low-dose vasopressin to those of noradrenaline in patients with septic shock showed similar mortality rates in both groups (15), but lower mortality rates in patients with shock of lesser severity treated with vasopressin.

Sepsis in cirrhotic patients

Cirrhotic patients have an increased propensity to develop sepsis. Bacterial infections are much more common during hospitalization in patients with cirrhosis than in the general population, and infection is more frequent in patients with decompensated than with compensated cirrhosis (16). The mechanisms underlying these observations are not entirely clear, but immunosuppression is definitely involved (17). Deficiencies in the complement system may play a role (18). Patients with advanced, especially decompensated, cirrhosis have down-regulation of monocyte HLA-DR expression, corresponding to impaired antigen presentation ability, which may also play a role (19). Cirrhosis is also associated with impaired macrophage Fcγ-receptor-mediated clearance of antibody-coated bacteria and this defect is correlated with the occurrence of severe bacterial infections (20). Patients with alcoholic cirrhosis also have depressed neutrophil phagocytic and intracellular killing (of *Staphylococcus aureus* or *Escherichia coli*) (21). In particular, patients with alcoholic cirrhosis are at increased risk of developing severe pneumococcal infections.

In patients with decompensated cirrhosis and bacterial infection, the pro-inflammatory host response is abnormally enhanced. In the early phase of bacterial sepsis, circulating levels of both TNF-α and IL-6 are significantly higher in infected cirrhotic patients than in septic patients without cirrhosis (22). The stimulation of isolated peripheral mononuclear cells or monocytes also results in excessive cytokine release. There is a relationship with the severity of the cirrhosis, as the endotoxin-induced production of TNF-α is higher in Child C than in Child B cirrhosis (23). Mechanisms known to amplify the inflammatory response may be altered in cirrhosis. Lack of induction of the inhibitor, IRAK-M, or a defect in glycogen synthase kinase 3 phosphorylation in endotoxin-stimulated cirrhotic monocytes may be involved in the overproduction of TNF-α (24,25). Cirrhotic monocytes are also defective in endotoxin-induced production of the anti-inflammatory cytokine, IL-10 (26), and there is enhanced IL-17 production (27). DIC with increased thrombin formation, may also stimulate inflammation in these patients (28).

In infected cirrhotic patients, the most common infection is spontaneous bacterial peritonitis (SBP) followed by urinary tract infection and pneumonia (29). When cirrhotic patients develop severe sepsis, the first site of infection is the lung (30-45%) followed by the

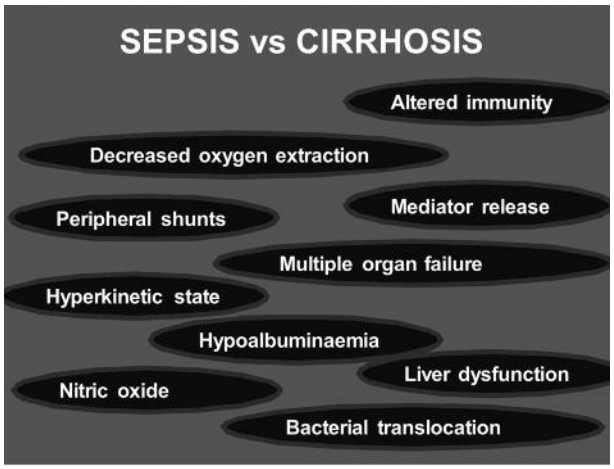

Fig. 2. — The common pathophysiologic alterations shared by sepsis and cirrhosis.

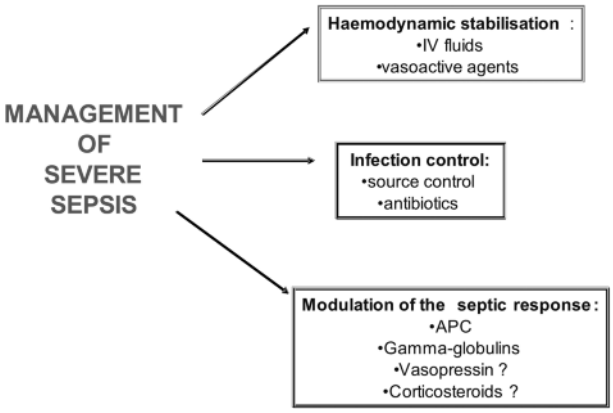

Fig. 3. — The three components of sepsis management

peritoneum (17-25%) (30). Mortality from pneumonia is very high in cirrhotic patients compared to the general population, even with 'appropriate' intensive care support and antibiotic treatment (31). Infections are culture positive in approximately 50-70% of cases. The causative organisms for community-acquired infections in cirrhotic patients are Gram-negative bacilli, especially *E. coli,* in about 60%, Gram-positive cocci in about 30%-35% and mixed in the last 5%-10%. In nosocomial infections, 60% are due to Gram-positive cocci and 30%-35% Gram-negative bacilli, largely because of previous antibiotic therapies (17).

Among patients with sepsis, the presence of cirrhosis may double the risk of death (30). Wehler *et al*. reported that cirrhotic patients with no organ failure had a hospital mortality of 6% while those with a sequential organ failure assessment (SOFA) score ≥ 3 had an almost 100% mortality rate (32). The in-hospital mortality of cirrhotic patients with septic shock exceeds 70% (30).

Organ dysfunction in the cirrhotic patient

Organ dysfunction is difficult to assess in the cirrhotic patient.

- Respiratory : Pulmonary complications are common in patients with decompensated cirrhosis. Pulmonary cellular function is altered at baseline, due to reduced alveolar macrophage antibacterial activity, alteration of T lymphocyte subsets and altered capillary permeability (33). Experimental data show that cirrhosis increases the number of pulmonary intravascular phagocytes, susceptibility to endotoxin-induced lung oedema and death (34). These factors, combined with the hyperproduction of proinflammatory cytokines and NO during infection may explain the high incidence of ARDS in cirrhosis (35). Alterations in consciousness may also increase the risk of aspiration, an important risk factor for ARDS, and tense ascites reduces expansion of the lower lobes. Patients with cirrhosis and sepsis are more likely to die with ARDS compared to individuals with ARDS who do not have cirrhosis or sepsis (36). Cirrhotic patients requiring mechanical ventilation have mortality rates well above 50% (37).
- Renal : Renal dysfunction may be related to sepsis or to a hepatorenal syndrome. Several mechanisms can account for prerenal failure in cirrhotic patients with severe sepsis (without shock) : a) Sepsis-related permeability alterations resulting in fluid extravasation causing 'hypovolaemia' ; b) relative decrease in venous return due to marked systemic vasodilatation. Both mechanisms lead to intense renal vasoconstriction and type 1 hepatorenal syndrome (38). In septic shock, cirrhotic patients rapidly develop renal failure due to ischaemic nephritis.
- Hematological : The PT may be chronically low in the cirrhotic patient. Cirrhosis is associated with impaired hepatic synthesis of zymogen forms of pro-coagulation factors (V, VII, X and prothrombin) and anticoagulant factors (protein C, protein S and antithrombin). Moreover, thrombocytopaenia is a common feature of cirrhosis because of reduced platelet survival associated with hypersplenism and/or the production of autoantibodies (39). Platelet dysfunction is also observed in vivo in cirrhosis, but may be counterbalanced by a substantial increase in von Willebrand factor expression, which increases platelet adhesion (40). The sepsis-induced TF-initiated coagulation cascade accentuates the deficiency of factors V, VII, X, prothrombin, protein C, antithrombin and thrombocytopaenia in cirrhosis (28). The reduction of protein C synthesis by the cirrhotic liver may enhance the protein C deficits in sepsis.
- Neurological : Obviously, signs of neurological dysfunction are hidden in the presence of hepatic encephalopathy. Some data suggest a degree of synergism between septic and hepatic encephalopathy. For example, endotoxin administration in cirrhotic rats alters consciousness and exacerbates brain oedema, an

effect which is not observed in control rats (41). The development of encephalopathy in cirrhotic patients with sepsis is associated with a worse prognosis.

- Hepatic : The presence of new hepatic dysfunction is difficult to assess in a cirrhotic patient with previous hyperbilirubinaemia, but it is difficult to find another reliable test of liver dysfunction.
- Cardiovascular : The cirrhotic patient has a low blood pressure associated with peripheral vasodilatation. When infection develops in patients with cirrhosis, the systemic circulation becomes even more hyperdynamic and hyporeactive to pharmacological doses of α-adrenoreceptor agonists (42). It is therefore difficult to identify any decrease in arterial pressure in the cirrhotic patient. Signs of altered organ perfusion may also be difficult to identify in the cirrhotic patient ; altered skin perfusion may be absent, decreased urine output may be due to hepato-renal syndrome, and neurological alterations due to cirrhotic encephalopathy. Even a mild increase in lactate levels can become significant in cirrhotic patients and resolution of hyperlactataemia can take long periods of time, as lactate is primarily cleared by the liver.

  Patients with decompensated cirrhosis without infection may have blunted cardiac inotropic and chronotropic responses to pharmacologic and surgical stresses, and sepsis may induce left ventricular dysfunction with cardiac dilatation thus aggravating the shock state. Thus cirrhosis and sepsis have additive, if not synergistic, effects on similar alterations, i.e., inhibition of β-adrenergic signalling, decrease in calcium availability and increase in NO production (43).
- Endocrine : Cirrhotic patients with severe sepsis and septic shock also have a high incidence of RAI, exceeding 50% (44). The incidence of RAI increases progressively with the number of organ failures. The presence of RAI is associated with high vasopressor dependency and higher mortality rates. The causes of the RAI in cirrhosis and sepsis are not well defined, but may be related to reduction in adrenal blood flow and increased cytokine release.

  Up to 80% of cirrhotic patients have impaired glucose tolerance due at least in part to insulin resistance and 10-30% of these patients develop diabetes (45). Sepsis may exacerbate the underlying insulin resistance in patients with cirrhosis. On the other hand, cirrhotic patients with septic shock are predisposed to develop hypoglycaemia due to liver failure.

  Cirrhotic patients have relatively increased arginine vasopressin levels participating in impaired water excretion and dilutional hyponatremia.

Management of sepsis in cirrhotic patients

1. *Antibiotics*

Antibiotic prophylaxis has a place in some cirrhotic patients, in particular in cases of variceal bleeding. In septic patients, the early initiation of adequate antibiotics is associated with higher survival rates (46). In cirrhosis, the beneficial effect of empiric broad-spectrum antibiotic treatment on survival has been demonstrated in SBP (without shock) (47). Undoubtedly, rapid recognition and prompt initiation of antibiotic treatment is important in all severe infections.

Source control is of paramount importance if an abscess can be drained. In catheter-related infections, the replacement of the catheter may be lifesaving.

2. *Fluid therapy*

Optimal fluid resuscitation is of great importance in severe sepsis. Currently, there is no evidence that colloids are better than crystalloids (13,48). Albumin administration may improve survival rates in patients with severe sepsis and hypoalbuminaemia (49). In cirrhotic patients, an open-label unblinded randomised trial in patients with SBP (without shock) treated with cefotaxime showed that the intravenous administration of a 20% albumin solution reduced the incidence of renal failure and decreased mortality rates (50), particularly in patients with greater disease severity.

Artificial colloids may not have the same beneficial effects. Hydroxyethyl starch (HES) can cause renal injuries resembling osmotic nephrosis (51). In a non-selected population of patients with severe sepsis, those treated with a 10% hydroxyethyl starch (HES) pentastarch solution, had higher rates of renal failure and thrombocytopaenia than patients treated with Ringer's lactate solution (52). A recent small unblinded randomised trial suggested that a 20% albumin solution improved systemic haemodynamics better than a 6% HES solution in SBP and this effect seemed to be related to a beneficial direct effect on systemic vascular tone (53).

3. *Vasopressors*

A recent RCT indicated that noradrenaline may be superior to dopamine in shock (54). In patients with septic shock, mortality is not significantly greater with adrenaline than with the combination of noradrenaline plus dobutamine (55). Nevertheless, adrenaline may reduce blood flow in the splanchnic and renal circulations and increase lactate levels (56).

4. *Immunomodulation*

The administration of recombinant human activated C protein (rhAPC) for 4 days in patients with severe sepsis significantly reduced 28-day mortality from 30.8 to 24.7% in the PROWESS study (57). This effect was more evident in patients with a high risk of death, and a subsequent RCT in patients with severe sepsis and low risk of death (APACHE II scores < 25 or single-organ failure) did not show any survival benefit (58). This drug is licensed for use in critically ill patients with sepsis and

a high risk of death, and can only be prescribed by intensivists. The principal side effect of rhAPC administration is bleeding, but its incidence is limited (severe bleeding in about 3.5% of patients). Patients with cirrhosis or portal hypertension were excluded from RCTs of rhAPC for severe sepsis because of the potential increase in the risk of severe bleeding. Nevertheless, it should be noted that patients with cirrhosis and portal vein thrombosis who are on the waiting list for liver transplantation receive anticoagulation (59), and the risk of bleeding seems fairly low in these patients. The use of rhAPC may, therefore, not be contraindicated in all patients with cirrhosis and severe sepsis.

Hydrocortisone may have a place in patients with severe septic shock. A small uncontrolled study in patients with severe cirrhosis (mean Child-Pugh scores of 11) and septic shock who were ACTH non-responders suggested that hydrocortisone at a dose of 50 mg every 6 hours could shorten the duration of shock resolution and improve survival compared with a retrospective matched cirrhotic cohort (60).

The place of vasopressin is not well defined. Whether early extracorporeal renal support may improve outcome is also uncertain, so that the routine use of these techniques is currently not recommended.

Conclusions

Sepsis and cirrhosis share many haemodynamic, metabolic, and immunological features. The prognosis of sepsis is much worse in patients with cirrhosis, suggesting that these abnormalities can exacerbate each other. The specificities of the pathogenic process of sepsis in cirrhosis have only just begun to be clarified. More effort is needed to define the specific management of sepsis in patients with cirrhosis by designing and performing specific trials in this population.

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