Chapter 6
Sepsis and Septic Shock in Cirrhotic Patients

Antonios Katsounas

Introduction

Patients with liver cirrhosis are considered to be more susceptible to both spontaneous and healthcare-associated (HCA) infections. It is likely that the cause of this phenomenon is excessive pro-inflammatory cytokine responses, which play a fundamental role in the development of severe liver dysfunction with subsequent multiorgan failure. Effective prevention and early detection strategies, as well as proper clinical management, are of crucial importance for the reduction of morbidity and mortality in this very vulnerable population. This chapter expands on and summarizes the current published literature, which pays particular attention to sepsis-related organ dysfunction in patients with chronic liver diseases.

Immune Dysfunction, Gut Barrier Disruption, and Vasoplegia in Patients with Liver Cirrhosis

Overall, prior to admission to clinical facilities, 25–35% of cirrhotic patients acquire infections that persist during hospitalization, and this trend has increased over the last 5 years. Infections occur 4–5× more frequently in hospitalized patients with cirrhosis in comparison to those without this disease [1]. The risk of infection is more serious in patients with decompensated cirrhosis than in those with stable liver disease [1]. Around 40–60% of cirrhotic patients experiencing gastrointestinal bleeding during hospitalization develop infections [2]. Further, bacterial infections are considered a cause of death in up to 50% of all fatal outcomes in patients with

A. Katsounas (✉)
Division of Infectious Diseases, Department of Gastroenterology, Hepatology and Infectious Diseases, University Hospital Magdeburg, Magdeburg, Germany
e-mail: antonios.katsounas@med.ovgu.de

D. Bezinover, F. Saner (eds.), *Critical Care for Potential Liver Transplant Candidates*,
https://doi.org/10.1007/978-3-319-92934-7_6

cirrhosis [3]. This is not surprising because chronic liver disease is responsible for increased susceptibility to infections.

The molecular mechanisms of this phenomenon may involve compromised macrophage Fc_{γ}-receptor-mediated neutralization of antibody-coated bacteria, functional deficiencies of the complement factors C3 and C4, and impaired antigen presentation ability resulting from the downregulation of monocyte human leukocyte antigen–DR expression [4]. Furthermore, neutrophil cells with downregulated phagocytic killing behavior against germs like *Escherichia coli* or *Staphylococcus aureus* have been identified in patients with alcohol-related cirrhosis [5]. In the presence of portal hypertension, this state of immune dysfunction alters the composition of gut microbiota with a subsequent increase in bacterial translocation from the gastrointestinal tract to the extraintestinal sites. Portal hypertension also leads to hypersplenism, which, in turn, results in a more advanced attenuation of an antimicrobial defense capacity through over-elimination of circulating immune cells. In addition, cirrhotic patients show a diminished synthesis of bile fluid and a prolonged intestinal transit time. These two factors in combination with abnormal production of antibacterial peptides, along with an attenuated secretion of gastric acid, favor intestinal microbial overgrowth. Translocation of bacteria through a "leaky gut" along with decreasing hepatic clearance of bacterial antigens (lipopolysaccharides (LPS) or endotoxins) may lead to a systemic overload of toll-like receptor TLR-ligands and (through activation of TLR pathways) to a massive production of cytokines, which further enhances inflammatory activity [6]. This, in turn, favors a systemic cytokine "blast" and a further secretion of reactive oxygen species (ROS) in large amounts, which accelerates the development of increased intestinal permeability and leads to the formation of a "circulus vitiosus" [7, 8]. There is substantial evidence for the regulatory potential of the C-X3-C Motif Chemokine Receptor 1 (CX3CR1) in intestinal macrophages with regard to maintaining the integrity of the gut barrier [9]. Damage to this barrier (favoring bacterial translocation and, thus, hepatic inflammation/dysfunction) can lead to enhanced splanchnic vasodilation with subsequent further intestinal injury. Indeed, uncontrolled release of vasodilatory inflammatory mediators in combination with endothelial damage and an arginine-vasopressin system dysfunction may cause a vasoplegic syndrome. Nitric oxide (NO) induced by $Ca2^{+}$-independent isoforms of nitric oxide synthase (iNOS) activates soluble guanylyl cyclase (sGC). In turn, sGC is responsible for increasing intracellular cyclic guanosine monophosphate (cGMP) production, which leads to the relaxation of vascular smooth muscles and vascular unresponsiveness along with hypotension. In this setting, it is much more challenging to improve microcirculation and tissue perfusion than it is to solely increase blood pressure using vasopressors. To this end, sufficient support with fluids along with albumin is fundamental. Recent studies have shown that reversing the endothelial nitric oxide synthase (eNOS) uncoupling reaction can diminish ROS levels, increase NO bioavailability, and, thus, attenuate the endothelial "functio laesa" [10]. However, it is very likely that vascular failure during sepsis has a multifactorial background, especially in patients with end-stage liver disease. A concerted research effort focused on the underlying molecular mechanisms for vasoplegia could make a significant contribution to a more meaningful selection of therapeutic targets in this highly vulnerable patient group.

From a pathophysiological point of view, the degree of inflammation markedly affects the outcomes of cirrhotic patients with bacterial infections and sepsis. This is

strongly supported by recent findings clearly identifying C-reactive protein (CRP) and white blood cell (WBC) count as independent predictive factors of in-hospital survival [11, 12].

Sepsis in Patients with Liver Cirrhosis

Epidemiological Data on Infections in Patients with Liver Cirrhosis

Infections and immune dysfunction are common etiologies for prolonged liver injury and terminal organ failure [13]. Many patients experience repeated episodes of systemic infections that gradually impair intrinsic liver function before leading to end-stage disease. During the last decade, liver cirrhosis itself has been identified as a risk factor for hospitalization due to severe infection and sepsis-related mortality [14]. Early and accurate detection of infections and identification of their primary source are considered to be essential for targeted therapy, which, in turn, has a significant impact on patient survival (Table 6.1) [15].

According to current studies, spontaneous bacterial peritonitis, urinary tract infections, and pneumonia are the most common bacterial diseases in cirrhotic patients [11]. The origin of infections, i.e., hospital-acquired (HA) vs. community-acquired (CA), and the bacterial types, i.e., Gram-positive and Gram-negative strains, demonstrate a balanced distribution [11]. *Escherichia coli*, *Enterococcus faecium*, and *Klebsiella pneumoniae* count as the most frequently isolated microbial pathogens that cause spontaneous bacterial peritonitis (SBP). Among all patients with SBP, 30–35% of cases are caused by multidrug-resistant (MDR) bacteria [11].

Table 6.1 Site and type of infections in patients with liver cirrhosis

Sites of Infection	Type of isolated bacteria
1. Spontaneous Bacterial Peritonitis	1. Escherichia coli
2. Urinary Tract Infection	2. Enterococcus faecium
3. Pneumonia	3. Klebsiella pneumoniae
4. Primary bacteremia	4. Enterococcus faecalis
5. Skin	5. Fungi
6. Soft tissue	6. Staphylococcus aureus

Definition: Sepsis, Septic Shock, and Applicable Prognostic Scores in Patients with Liver Cirrhosis

Based on the Sepsis-3 criteria, sepsis is defined as a life-threatening organ dysfunction triggered by a dysregulated host response to infection [16–18]. Organ dysfunction can be determined by an increase in the total Sequential Organ Failure Assessment (SOFA) score of ≥ 2 points (i.e., Delta SOFA ≥ 2 points) due to an infection [16–18] (Table 6.2). The baseline SOFA score can be set to zero unless the patient is known to have a preexisting (acute or chronic) organ dysfunction before the onset of infection [16–18].

There are significant differences between the SOFA score and the Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA) score. CLIF-SOFA (Table 6.3) was developed to assess 30-day mortality rates in patients with acute decompensation of cirrhosis – defined by the development of complications (e.g., bacterial infection, hepatic encephalopathy, gastrointestinal bleeding, and ascites). However, CLIF-SOFA differs from the SOFA score in the consideration of two parameters: coagulation and the Glasgow Coma Scale (GCS) score [20].

Septic shock is defined as hypotension requiring the use of vasopressors to maintain MAP ≥ 65 mm Hg and a serum lactate level > 2 mmol/l despite adequate fluid resuscitation. For patients meeting these criteria, the hospital mortality rate exceeds 40% [16–18]. Timely and accurate identification of patients at risk for sepsis and septic shock must, therefore, be prioritized. In order to identify adult patients with a possible infection and an expected poor outcome, a new scoring tool quick SOFA (qSOFA) has been introduced. The qSOFA provides simple bedside measures and is considered to be positive when patients meet ≥ 2 of the following three criteria: alteration of consciousness, respiratory rate ≥ 22/min, and systolic blood pressure ≤ 100 mm Hg. According to recent findings [7], cirrhotic patients with a positive qSOFA score meet significantly more Sepsis-3 criteria [16–18] than do those with a negative qSOFA score [16–18].

Based on these observations, a novel algorithm focused on the implementation of Sepsis-3 criteria and the qSOFA has been proposed to assist clinicians with the management of hospitalized patients facing the challenge of concomitant liver cirrhosis and bacterial infection (Fig. 6.1).

According to this algorithm, both Sepsis-3 criteria and the qSOFA should be applied if a baseline SOFA score is unavailable. A patient who meets both screening criteria should be admitted to the ICU, due to a predicted worse outcome. On the other hand, a patient who does not meet the criteria for either scale has the best prognosis. If the situation is uncertain, the SOFA score should be closely monitored for further clinical decisions and management [7].

It has been demonstrated that the CLIF Consortium Acute Decompensation score (CLIF-CADs), used to establish a prognosis for hospitalized cirrhotic patients without acute-on-chronic liver failure, is capable of predicting mortality more

Table 6.2 SOFA score modified from Vincent et al. [19]

	Score				
System	0	1	2	3	4
Respiration					
Pap2/FIO_2, mm Hg (kPa)	≤ 400 m (53.3)	< 400 m (53.3)	< 300 m (40)	< 200 m (26.7) with respiratory support	< 100 m (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥ 150	< 150	< 100 m	< 50	< 20 m
Liver					
Bilirubin mg/dl (μmol/L)	<1.2	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	> 12.0 (204)
Cardiovascular					
	MAP ≥ 70 mm Hg	MAP < 70 mm Hg	Dopamine < 5 or dobutamine (any dose)	Dopamine 5.1–15 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1
Central nervous system					
Glasgow Coma Scale Score	15	13–14	10–12	6–9	< 6
Renal					
Creatinine, mg/dL (μmol/L)	< 1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	> 5.0 (≥ 441)
Urine output (mL/day)				< 500	< 200

Catecholamine doses are given as μg/kg/min for at least 1 h. Glasgow Coma Scale scores range from 3 to 15; higher score values indicate better neurological function

FIO_2 fraction of inspired oxygen, *MAP* mean arterial pressure, *PaO_2* partial pressure of oxygen

Table 6.3 CLIF-SOFA modified from Jalan et al. [21]

	CLIF-SOFA score				
Organ/system	0	1	2	3	4
Liver					
Bilirubin (mg/dl)	< 1.2	1.20–1.99	2.0–5.99	6.0–11.9	≥ 12.0 (204)
Kidney					
Creatinine (mg/dL)	< 1.2	1.20–1.99	2.0–3.49	3.5–4.99	≥ 5.0
Cerebral					
Hepatic encephalopathy (HE) grade	No HE	HE grade1	HE grade 2	HE grade 3	HE grade 4
Coagulation					
INR	< 1.1	1.1–1.25	1.26–1.5	1.51–2.5	> 2.5 or Platelets ≤ 20×10^3/μl
Circulation					
MAP (mmHg)	≥ 70	< 70	Dopamine < 5 or dobutamine or terlipressin	Dopamine 5.1–15 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1
Lungs					
PaO_2/FiO_2	> 400	≤ 400	≤ 300	≤ 200	≤ 100
or SpO_2/FiO_2	> 512	358–512	215–357	90–214	≤ 89

Overall, scores range from 0 to 24. The use of dobutamine or terlipressin, at any dose, is sufficient for a score of 2 for circulation. Doses of catecholamines are given as μg/kg/min

HE hepatic encephalopathy, *INR* international normalized ratio, *MAP* mean arterial pressure, PaO_2 partial pressure of arterial oxygen, FIO_2 fraction of inspired oxygen, SpO_2 pulse oximetric saturation

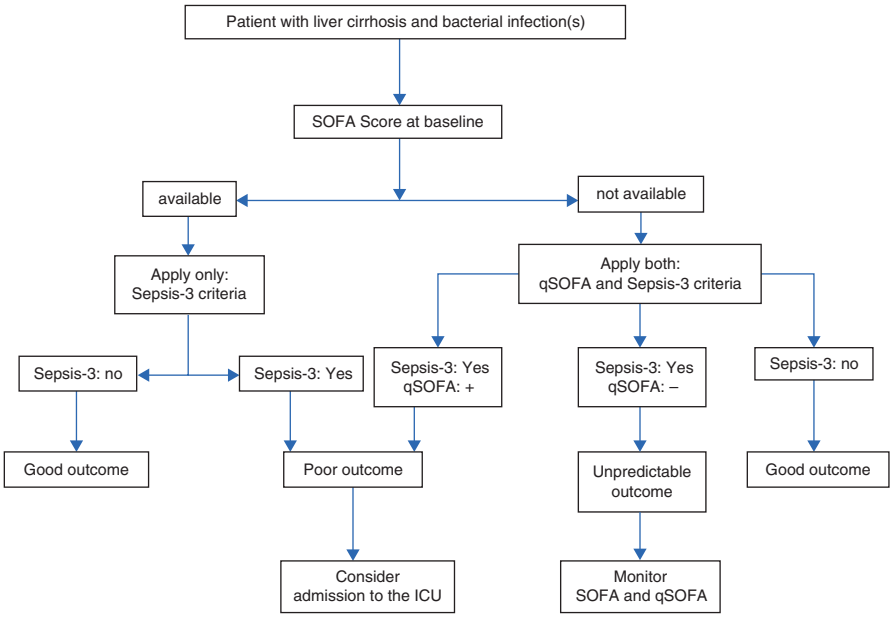

Fig. 6.1 Flowchart for the implementation of Sepsis-3 criteria in the clinical management of patients with cirrhosis and systemic infections. *ICU* intensive care unit. (Figure modified from Piano et al. [11])

accurately. This is likely because in CLIF-CADs both the organ dysfunction-specific variables (e.g., international normalized ratio, creatinine, and serum sodium concentration) and the degree of inflammation (e.g., WBC count) during systemic bacterial infections are taken into account [12].

Treatment/Hemodynamics and Sepsis-Related Complications of Cirrhosis

In patients with cirrhosis, therapy is aimed at preventing and correcting organ hypoperfusion along with fast identification and elimination of the infectious sources. Fluid substitution should be the primary therapeutic option to improve perfusion and enable the maintenance of stable function of vital organs [17]. Hypotensive patients with an adequate intravascular volume status should receive additional treatment with vasopressors to stabilize mean arterial pressure (MAP) (measured by direct arterial pressure monitoring) above 65 mmHg and urine output above 0.5 ml/kg/h [22]. Some recommendations for the management of hemodynamics are based on a measurement of central venous pressure (CVP) [22] and the goal of achieving central venous oxygen saturation (ScvO2) > 70%. Several studies have shown that albumin supplementation using a dose of 1.0–1.5 g/kg may

delay the onset of renal failure, especially in cirrhotic patients with an infection not related to SBP [23, 24]. However, these results are controversial [25–28]. In the ongoing debate on the potential beneficial effect of albumin administration in these patients, clinicians should be aware of the anti-oxidant/anti-inflammatory, immunomodulatory properties and functional role of albumin as a carrier molecule for many endogenous/exogenous substances, in addition to its physiological effect as a plasma expander [29]. Beyond that, caution should be exercised; that is, treatment with highly protein-bound antibiotics should not be initiated without considering what is likely to be the unfavorable influence of hypoalbuminemia on the pharmacokinetics of these drugs [30]. All these complications of cirrhosis, including hepatic encephalopathy [31, 32], hepatorenal syndrome [33], hepato- and porto-pulmonary hypertension [34], malnutrition and impaired gluconeogenesis [35], must be optimally managed in order to support a cirrhotic patient through sepsis [36].

Treatment/Anti-infective Management

Bacterial infections may cause fatal complications such as septic and/or hepatic encephalopathy, decompensation of ascites along with hypervolemic hyponatremia, gastrointestinal bleeding, renal failure, and acute-on-chronic or acute-on-cirrhosis liver failure. In patients with SBP, ascites removal equals source control! Most importantly, after the ascetic fluid has been drained from the abdominal cavity, a blood culture evaluation should be performed immediately in order to improve diagnostic accuracy [37]. It is important to consider that antibiotics may not reach a sufficient level to treat an infection localized in the peritoneal compartment if dose administration follows standard recommendations. Therapeutic drug monitoring should be performed along with systemic substitution of albumin, as stated above. It is essential to consider the patient's previous and current antibiotic regimen. For example, if levofloxacin was used for SBP prophylaxis, it is crucial to consider that fluoroquinolones might no longer be effective as a viable therapeutic alternative. In more than 50% of cases, empirical treatment includes ≥ 2 antibiotics [11]. Quinolones, third-generation cephalosporins, carbapenems, piperacillin/tazobactam, and glycopeptides are the most frequently used substances, and empirical antibiotic treatment can be considered effective in approximately 80–85% of cases [11] (Table 6.4). While almost all of these patients achieve final resolution of infection, 15–20% develop a reinfection during hospitalization [11]. Indeed, empirical treatment should be based on valid clinical and microbiological (prognosis-related) scores and, therefore, requires good knowledge of local epidemiology including common bacterial resistance profiles and rates as well as the history of infection(s) in individual patients with chronic liver disease. With regard to the increasing prevalence of resistance to quinolones and colonization/infection with MDR bacteria, in 2014 the European Association for the Study of the Liver (EASL) published recommendations for the management of bacterial infections in cirrhotic patients [21].

Table 6.4 Common empirical antibiotic approaches for patients with severe liver disease and bacterial infection(s) modified from Gustot et al. [38]

Site/type of infection	**No severe sepsis or shock**		
	CA infections	HCA and HA infections	
		Prevalence of MDR bacteria	
		Low	High
SBP SMB UI	Third-generation Cephalosporins (i.v.)	Piperacillin/ Tazobactam (i.v.)	Meropenem (i.v.) ± Glycopeptide (i.v.)[a] or Linezolid/ Daptomycin (i.v.)[b]
PNE	Third-generation Cephalosporins (i.v.) + Macrolide (oral/i.v.) Or Levofloxacin (oral/i.v.)		Meropenem (i.v.) or Ceftazidime (i.v.) + Ciprofloxacin (i.v.) ± Glycopeptide (i.v.)[a] or Linezolid (i.v.)[a]
STI	Amoxicillin/Clavulanic Acid (i.v.)		Meropenem or Ceftazidime + Glycopeptide (i.v.)[a] or Linezolid/ Daptomycin (i.v.)[b]
Site/type of infection	**Severe sepsis or shock**		
	Empirical antibiotic treatment of severe sepsis or shock should be administered with the local rate of MDR pathogens taken into account		

MDR multidrug resistant, *CA* community-acquired, *HCA* healthcare-associated, *HA* hospital-acquired, *SBP* spontaneous bacterial peritonitis, *SBM* spontaneous bacteremia, *UI* urinary infections, *PNE* pneumonia, *STI* soft tissue infections

[a]Use of antibiotics with proven activity against methicillin-resistant *Staphylococcus aureus* (MRSA) should be considered in patients with risk factors such as previous and/or current nasal MRSA carriage, ventilator-associated pneumonia, and previous antibiotic therapy. In areas with a high prevalence of MDR *Pseudomonas aeruginosa*, the addition of nebulized colistin or amikacin should be carefully evaluated

[b]In areas with a high prevalence of vancomycin-resistant enterococci (VRE), the use of linezolid/daptomycin should be carefully evaluated

Future Challenge

Antimicrobial Resistance [39]

In patients with liver cirrhosis, the course of bacterial infections can be severe with a fourfold increase in mortality in comparison to other groups. Early and thorough administration of carefully selected anti-infective treatments is essential for the effective clinical management of these patients, especially considering that their risk of developing an MRD-associated infection is increased due to frequent hospitalization and repeated exposure to antibiotics. In order to limit the spread of MDR

organisms, rational management should be implemented to help establish an equilibrium between granting all necessary access to antimicrobial drugs and preventing both the overuse and the misuse of these:

1. For example, development of cost-efficient, bedside diagnostic tools is needed to support faster and more evidence-based decisions related to antibiotic therapies. This should help clinicians to avoid less precise empirical clinical practices.
2. It is equally important to de-escalate antibiotic regimes to single antibiotic drugs as promptly as possible. More hospital antibiotic stewardship (ABS) programs should be promoted and implemented across in-hospital settings.
3. Alternatives to antibiotics should be more intensively investigated and clinically evaluated. The paradigm of microbiota transfer via fecal transplantation as an effective technique to manage vancomycin-resistant *Clostridium difficile* infections has proven to be a true drug-free strategy for managing bacterial infections resistant to antibiotics.
4. During the last three decades, no new classes of antibiotics have been discovered and only a few novel agents are in development. Greater investment in this field is an absolute priority in order to boost basic and clinical research focused on developing new antimicrobials [40].

There is an obvious need to strengthen the understanding of antimicrobial resistance and to gain additional knowledge through focused research on diagnostic innovations, novel antimicrobials, and/or new alternative drug-free therapies.

Key Points

1. Bacterial infections are considered to be the cause of death in up to 50% of all fatalities in patients with liver cirrhosis.
2. Spontaneous bacterial peritonitis (SBP), urinary tract infections, and pneumonia are the most common bacterial infections in cirrhotic patients. *Escherichia coli*, *Enterococcus faecium*, and *Klebsiella pneumoniae* are the most frequently isolated microbial pathogens associated with SBP, which is caused by multidrug-resistant (MDR) bacteria in 30–35% of patients. In SBP, ascites removal is equivalent to source control!
3. Immune dysfunction, gut barrier disruption, and vasoplegia share common pathophysiologic mechanisms in patients with liver cirrhosis.
4. In cirrhotic patients with sepsis-related hypotension, it is very challenging to improve microcirculation and tissue perfusion based solely on administering vasopressors. Adequate fluid resuscitation including albumin is essential.
5. The SOFA score and the CLIF-SOFA score differ, as the latter includes two additional parameters: coagulation and the Glasgow Coma Scale (GCS).
6. Hospital antibiotic stewardship (ABS) programs should be promoted and implemented across in-hospital settings in order to better position clinicians to face the challenge of antimicrobial resistance.

References

1. Borzio M, et al. Bacterial infection in patients with advanced cirrhosis: a multicentre prospective study. Dig Liver Dis. 2001;33(1):41–8.
2. Bernard B, et al. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. Hepatology. 1999;29(6):1655–61.
3. Tandon P, Garcia-Tsao G. Bacterial infections, sepsis, and multiorgan failure in cirrhosis. Semin Liver Dis. 2008;28(1):26–42.
4. Wasmuth HE, et al. Patients with acute on chronic liver failure display "sepsis-like" immune paralysis. J Hepatol. 2005;42(2):195–201.
5. Rajkovic IA, Williams R. Abnormalities of neutrophil phagocytosis, intracellular killing and metabolic activity in alcoholic cirrhosis and hepatitis. Hepatology. 1986;6(2):252–62.
6. Katsounas A, et al. Altered expression of SHIP, a toll-like receptor pathway inhibitor, is associated with the severity of liver fibrosis in chronic hepatitis C virus infection. J Infect Dis. 2011;204(8):1181–5.
7. Strnad P, et al. Liver - guardian, modifier and target of sepsis. Nat Rev Gastroenterol Hepatol. 2017;14(1):55–66.
8. Prin M, Bakker J, Wagener G. Hepatosplanchnic circulation in cirrhosis and sepsis. World J Gastroenterol. 2015;21(9):2582–92.
9. Schneider KM, et al. CX3CR1 is a gatekeeper for intestinal barrier integrity in mice: limiting steatohepatitis by maintaining intestinal homeostasis. Hepatology. 2015;62(5):1405–16.
10. Sharawy N. Vasoplegia in septic shock: do we really fight the right enemy? J Crit Care. 2014;29(1):83–7.
11. Piano S, Bartoletti M, Tonon M, et al. Assessment of Sepsis-3 criteria and quick SOFA in patients with cirrhosis and bacterial infections. Gut. Published Online First: 31 Aug 2017. https://doi.org/10.1136/gutjnl-2017-314324
12. Jalan R, et al. The CLIF consortium acute decompensation score (CLIF-C ADs) for prognosis of hospitalised cirrhotic patients without acute-on-chronic liver failure. J Hepatol. 2015;62(4):831–40.
13. Scaglione S, et al. The epidemiology of cirrhosis in the United States: a population-based study. J Clin Gastroenterol. 2015;49(8):690–6.
14. Foreman MG, Mannino DM, Moss M. Cirrhosis as a risk factor for sepsis and death: analysis of the National Hospital Discharge Survey. Chest. 2003;124(3):1016–20.
15. Gustot T, et al. Severe sepsis in cirrhosis. Hepatology. 2009;50(6):2022–33.
16. Singer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–10.
17. Shankar-Hari M, et al. Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):775–87.
18. Seymour CW, et al. Assessment of clinical criteria for Sepsis: for the third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):762–74.
19. Vincent JL, et al. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707–10.
20. Moreau R, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144(7):1426–37, 1437.e1–9.
21. Jalan R, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol. 2014;60(6):1310–24.
22. Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43(3):304–77.
23. Merli M, et al. Albumin infusion in cirrhotic patients with infections other than spontaneous bacterial peritonitis: end of the story? J Hepatol. 2015;63(3):767–8.
24. Thevenot T, et al. Effect of albumin in cirrhotic patients with infection other than spontaneous bacterial peritonitis. A randomized trial. J Hepatol. 2015;62(4):822–30.

25. Guevara M, et al. Albumin for bacterial infections other than spontaneous bacterial peritonitis in cirrhosis. A randomized, controlled study. J Hepatol. 2012;57(4):759–65.
26. Sort P, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med. 1999;341(6):403–9.
27. Thevenot T, Monnet E, Di Martino V. Effect of albumin on survival in septic cirrhotic patients other than spontaneous bacterial peritonitis. The question remains open. J Hepatol. 2013;58(3):638–9.
28. Guevara M, Arroyo V, Gines P. Reply to: "effect of albumin on survival in septic cirrhotic patients other than spontaneous bacterial peritonitis. The question remains open". J Hepatol. 2013;58(3):640.
29. Caraceni P, et al. Clinical indications for the albumin use: still a controversial issue. Eur J Intern Med. 2013;24(8):721–8.
30. Roberts JA, et al. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis. 2014;14(6):498–509.
31. Iacobone E, et al. Sepsis-associated encephalopathy and its differential diagnosis. Crit Care Med. 2009;37(10 Suppl):S331–6.
32. Ferenci P, et al. Hepatic encephalopathy--definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology. 2002;35(3):716–21.
33. Tandon P, et al. Relevance of new definitions to incidence and prognosis of acute kidney injury in hospitalized patients with cirrhosis: a retrospective population-based cohort study. PLoS One. 2016;11(8):e0160394.
34. Schiffer E, et al. Hepatopulmonary syndrome increases the postoperative mortality rate following liver transplantation: a prospective study in 90 patients. Am J Transplant. 2006;6(6):1430–7.
35. Kauffmann RM, et al. Provision of balanced nutrition protects against hypoglycemia in the critically ill surgical patient. JPEN J Parenter Enteral Nutr. 2011;35(6):686–94.
36. Findlay JY, et al. Critical care of the end-stage liver disease patient awaiting liver transplantation. Liver Transpl. 2011;17(5):496–510.
37. Koulaouzidis A, et al. Spontaneous bacterial peritonitis. Postgrad Med J. 2007;83(980):379–83.
38. Gustot T, et al. Sepsis in alcohol-related liver disease. J Hepatol. 2017;67(5):1031–50.
39. Fernández J, Bert F, Nicolas-Chanoine M-H. The challenges of multi-drug-resistance in hepatology. J Hepatol. 2016;65(5):1043–54.
40. The challenge of antimicrobial resistance. The Lancet Gastroenterology & Hepatology. 1(3):173. https://www.thelancet.com/pdfs/journals/langas/PIIS2468-1253(16)30121-2.pdf