



Bacterial infections in cirrhosis: A position statement based on the EASL Special Conference 2013

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We are dedicating this paper to Drs. Joan Cordoba and Andrew Burroughs in recognition of their excellent work as Doctors and Scientists. They will be remembered by many as a good friends and colleagues. Joan, Andrew may you rest in peace.

Summary

Bacterial infections are very common and represent one of the most important reasons of progression of liver failure, development of liver-related complications, and mortality in patients with cirrhosis. In fact, bacterial infections may be a triggering factor for the occurrence of gastrointestinal bleeding, hypervolemic hyponatremia, hepatic encephalopathy, kidney failure, and development of acute-on-chronic liver failure. Moreover, infections are a very common cause of repeated hospitalizations, impaired health-related quality of life, and increased healthcare costs in cirrhosis. Bacterial infections develop as a consequence of immune dysfunction that occurs progressively during the course of cirrhosis. In a significant proportion of patients, infections are caused by gram-negative bacteria from intestinal origin, yet

gram-positive bacteria are a frequent cause of infection, particularly in hospitalized patients. In recent years, infections caused by multidrug-resistant bacteria are becoming an important clinical problem in many countries.

The reduction of the negative clinical impact of infections in patients with cirrhosis may be achieved by a combination of prophylactic measures, such as administration of antibiotics, to reduce the occurrence of infections in high-risk groups together with early identification and management of infection once it has developed. Investigation on the mechanisms of altered gut microflora, translocation of bacteria, and immune dysfunction may help develop more effective and safe methods of prevention compared to those that are currently available. Moreover, research on biomarkers of early infection may be useful in early diagnosis and treatment of infections.

The current manuscript reports an in-depth review and a position statement on bacterial infections in cirrhosis.

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Introduction

Bacterial infections are very common in patients with cirrhosis and currently represent one of the most common causes of admission to hospital in these patients and a major challenge for physicians caring for patients with liver diseases. Despite the recent improvements in the knowledge of pathogenesis, prevention, and management, bacterial infections still represent a major cause of morbidity and mortality among patients with cirrhosis. On this background, the European Association for the Study of the Liver (EASL) decided to hold a Special Conference on Bacterial Infections in cirrhosis in May 2013 in Barcelona. The conference gathered a large number of clinical and basic scientists as well as clinicians with special interest on the topic who had presentations and extensive discussions on the main areas of the field. The current manuscript represents a position statement that summarizes the different areas that were discussed during the Conference and includes expert opinions on important aspects of the management of bacterial infections in cirrhosis.

Key Points

- The incidence and severity of infection in cirrhosis is greater than in the population without cirrhosis
- Infection with multiresistant organisms is common in cirrhosis and its occurrence is associated with higher mortality rates than in patients without cirrhosis
- The end-organ damaging effect of bacterial infection is greater in patients with cirrhosis due to altered sensitivity, which often culminates in acute-on-chronic liver failure
- Delays in the diagnosis and start of treatment results in higher mortality particularly in hypotensive patients with cirrhosis
- In patients with spontaneous bacterial peritonitis, the addition of albumin to antibiotics reduces mortality
- Primary prophylaxis of spontaneous bacterial peritonitis with norfloxacin is indicated in patients with variceal bleeding, severely decompensated cirrhosis, and those with ascites protein concentration of <15 g/L
- In patients with variceal bleeding, intravenous administration of 3rd generation cephalosporins improves survival
- Administration of norfloxacin to prevent recurrence of spontaneous bacterial peritonitis reduces mortality in cirrhosis
- Research into the mechanisms associated with increased risk of infection in cirrhosis, better use of current therapeutic strategies, development of rapid and accurate diagnostic tools, and development of new strategies to modulate the gut-liver interaction are urgently needed

Clinical aspects of bacterial infections in cirrhosis and the problem of multiresistant bacteria

Patients with cirrhosis have increased risk of developing bacterial infections [1,2]. Infections are present at admission or develop during hospitalization in 25–35% of patients [3,4], an incidence that is 4–5 fold higher than that observed in the general population. Spontaneous bacterial peritonitis (SBP) and urinary tract infections are the most frequent infections followed by pneumonia, skin and soft tissue infections, and bacteremia. Clinical factors associated with an increased risk of infection are poor liver function, variceal bleeding, low ascitic fluid protein levels, prior SBP and hospitalization [1,2]. Severity of infection is also higher in patients with cirrhosis who are more likely to die from sepsis than individuals without cirrhosis. Bacterial infection increases 3.75 fold the probability of death of patients with decompensated cirrhosis, reaching 30% at 1 month and 63% at 1-year (Fig. 1) [5,6].

Enterobacteriaceae and non-enterococcal streptococci cause the majority of spontaneous infections in cirrhosis. As a consequence, β -lactams and quinolones have been widely used in their treatment and prevention [1,2]. This feature and the increasing level of invasiveness to which patients with cirrhosis are currently submitted have induced important changes in the epidemiology of bacterial infections in cirrhosis. Spontaneous and secondary infections caused by non-classical pathogens or multi-drug resistant (MR) bacteria are nowadays increasingly reported in this population [1,4].

Infections by multiresistant bacteria in the general population and cirrhosis

MR bacteria are pathogens resistant to 3 or more of the main antibiotic families, including β -lactams [7]. The main MR bacteria are extended-spectrum β -lactamase-producing *Enterobacteriaceae* (ESBL), non-fermentable gram-negative bacilli such as *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia* or *Acinetobacter baumannii*, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-susceptible or resistant enterococci (VSE, VRE). Infections caused by these bacteria have increased in the general population mainly due to the dispersion of the so-called high-risk clones not only in the hospitals but also in the community. These clones are specific bacteria able to acquire several resistance mechanisms and virulence determinants. Moreover, they efficiently colonize different human niches, including the gastrointestinal tract [8].

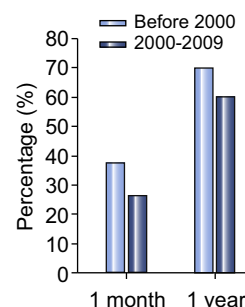


Fig. 1. Mortality rate caused by bacterial infections in cirrhosis in the last decades. 1-month and 1-year mortality rates were higher before than after 2000, although differences were not statistically significant. Modified from [6].

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Table 1. Prevalence and clinical impact of different multiresistant bacterial infections in cirrhosis in several geographical areas.

Country, yr [Ref.]	Prevalence of multiresistant bacteria	Clinical impact
Korea, 2006 [10]	29% ESBL-producing <i>Enterobacteriaceae</i> *	No impact
Spain, 2008 [11]	6% ESBL-producing <i>Enterobacteriaceae</i>	No impact
Italy, 2008 [12]	8% ESBL-producing <i>Enterobacteriaceae</i>	Higher initial treatment failure No impact on mortality
Korea, 2009 [13]	15% ESBL-producing <i>Enterobacteriaceae</i>	Independent predictor of 30-day mortality
Korea, 2009 [14, 15]	4-7.5% ESBL-producing <i>Enterobacteriaceae</i>	Higher initial treatment failure Higher hospital and 30-day mortality
Turkey, 2009 [16]	2% ESBL-producing <i>Enterobacteriaceae</i> 1% <i>Pseudomonas aeruginosa</i>	No data
France, 2009 [17]	8% MRSA** 5% VSE# 4% ESBL-producing <i>Enterobacteriaceae</i>	No data
Germany, 2009 [18]	10% VSE	Higher initial treatment failure Higher hospital mortality
Italy, 2010 [9]	20% ESBL-producing <i>Enterobacteriaceae</i> 7% MRSA	Higher hospital mortality
Spain, 2012 [19]	6% ESBL-producing <i>Enterobacteriaceae</i> 2% <i>Pseudomonas aeruginosa</i> 2% <i>Acinetobacter baumannii</i> 1% VSE	Independent predictor of mortality at 30 days
Spain, 2012 [4]	8-9% ESBL-producing <i>Enterobacteriaceae</i> 3% <i>Pseudomonas aeruginosa</i> 3-4% MRSA 3-7% VSE	Lower infection resolution Higher risk of septic shock Higher hospital mortality
USA, 2012 [20]	9% VRE [§] 6.5% ESBL-producing <i>Enterobacteriaceae</i> 5% MRSA	No data

*ESBL, extended-spectrum β -lactamase-producing *Enterobacteriaceae* (bacteria with chromosomal β -lactamases are also included).

**MRSA, methicillin-resistant *Staphylococcus aureus*.

#VSE, vancomycin-susceptible enterococci.

[§]VRE, vancomycin-resistant enterococci.

Multiple studies from very different geographical areas have recently reported an increased prevalence of infections caused by MR bacteria in cirrhosis [4,9–20]. The site of acquisition of infection determines the risk of MR bacterial infection with higher rates of MR bacteria in infections acquired in the health-care environment: 23–39% in nosocomial infections, 14–41% in healthcare-associated (HCA) episodes and 0–16% in infections acquired in the community [4,9].

Epidemiological pattern of MR bacteria differs markedly among geographical areas and even among hospitals. Regular assessment is therefore recommended [1,21]. ESBL-producing *Enterobacteriaceae* are predominant in South Europe and Asia [4,9–19], while MRSA and VRE are frequently isolated in centers from USA or South America [20].

Carbapenemase-producing *K. pneumoniae* are also being increasingly isolated in some centers in Italy [22]. Table 1 shows the different prevalence of MR bacteria in infections in patients with cirrhosis in different countries.

Clinical outcome of nosocomial and multiresistant bacterial infections in cirrhosis

Early studies reported conflicting results regarding the prognosis of nosocomial infections in cirrhosis. Some showed very high mortality rates (59–67%) while others reported figures similar to those observed in community-acquired infections (Table 1) [13,23,24]. Recent data from Spain clearly support the former contention [4]. The study included 669 infections from 2 series

(2005–2007 and 2010–2011). Hospital mortality rate of nosocomial infections (25–48% respectively) was significantly higher than that observed in health-care associated (9–23% respectively) and community-acquired episodes (7–21% respectively). The same study also demonstrated that infections caused by MR bacteria are more common among nosocomial infections, have a poorer prognosis than those caused by susceptible bacteria with higher rates of treatment failure and associated septic shock (26% vs. 10% respectively) and higher hospital mortality (25% vs. 12% respectively) [4].

Pathogenesis of bacterial infections

The following part focuses on the interaction of gut microbiota, intestinal permeability, bacterial translocation (BT) and immune deficiency which may be acquired or conferred by genetic susceptibility, acting in concert as pathophysiological culprit for most bacterial infections seen in cirrhosis (Fig. 2) [25]. BT occurs in healthy conditions but is increased in cirrhosis and hence, should be called pathological BT.

Gut microbiota

The host needs to keep gut bacteria under very tight control to prevent pathological BT for which the immune system of the gut-associated lymphatic tissue plays a crucial role. On the other hand, intestinal bacteria contribute to symbiosis by educating

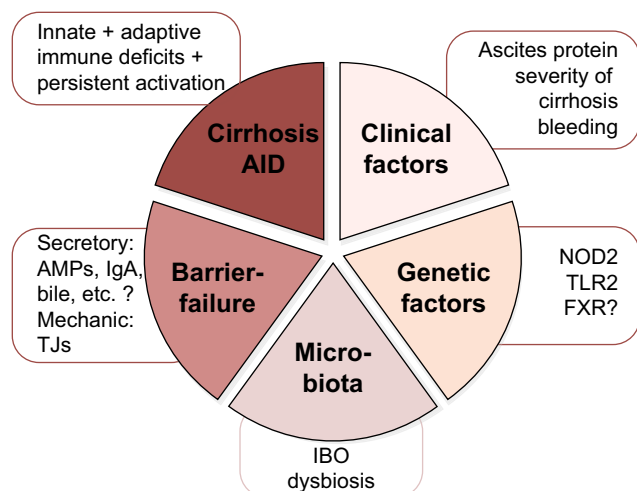


Fig. 2. Pathogenesis of bacterial infections in cirrhosis. The risk of bacterial infection in cirrhosis is due to multiple factors that include liver dysfunction, portosystemic shunting, gut dysbiosis, increased bacterial translocation, cirrhosis-associated immune dysfunction (AID) and genetic factors.

and maintaining the host immune system. A dysbalance of this delicate homeostasis between host and microbiome can lead to disease [3,26,27].

Alterations in the microbiome can either occur as quantitative (intestinal bacterial overgrowth – IBO) or qualitative (dysbiosis) changes. IBO is a common feature in patients with liver cirrhosis and occurs predominantly in the small intestine [28–30]. IBO is multifactorial, and contributing factors include modulation of gastric acid secretion, decrease in intestinal motility, lack of bile constituents and antimicrobial peptides as well as portal hypertension [31–36]. Patients with cirrhosis and IBO more frequently have SBP than patients without bacterial overgrowth [31]. Experimental IBO itself can result in microbial translocation and liver inflammation [37] emphasizing the importance of quantitative microbiome changes. Reducing the intestinal bacterial burden with antibiotics ameliorates experimental liver disease [38,39] and, decreases the liver disease severity [40,41] and infectious complications in patients with advanced cirrhosis [42]. Qualitative changes of the human microbiome have been characterized by deep pyrosequencing. Several studies described the microbial taxonomy in patients with early and end-stage liver disease [43] due to chronic hepatitis B infection [44,45], alcohol [44,46], and NAFLD/NASH [47,48]. Whether these qualitative disturbances results in factious complications will need further investigation.

Intestinal barrier dysfunction

Increased intestinal permeability has been demonstrated by complementary methods and shown to be particularly present in advanced stages of disease and septic complications. Tight junctions (TJ) between epithelial cells limit paracellular permeation and thus translocation of bacterial products. Alterations in TJ proteins are present in cirrhosis and most likely loosen TJ-function [49,50]. As for invasion of viable bacteria however, transcytosis appears to represent the major route but is poorly defined in cirrhosis. One of the key regulators modulating TJ and transcytosis is tumor necrosis factor- α , which is increased in the gut-associated lymphatic tissue in advanced cirrhosis [51,52]. Secreted mediators that limit the direct contact of intestinal bac-

teria to the epithelial surface and shown to be deficient in cirrhosis include IgA [53], biliary lipids [54], and antimicrobial peptides [35]. Compromised Paneth cell antimicrobial host defense is observed in experimental cirrhosis being associated with decreased mucosal killing activity against invading bacteria [35]. Expression of the antimicrobial protein Reg3g, which maintains a physical barrier between the epithelial cell surface and intestinal microbes [47], was suppressed in intestinal biopsies from patients with chronic alcohol abuse [38].

Genetic predisposition to bacterial infections

Extracellular bacteria are recognized by membrane-bound Toll-like receptors (TLR) and intracellular Nod-like receptors (NLR), including NOD2 and NLRP3, which lead to activation of nuclear factor NFKB and stimulate the release of antimicrobial peptides. TLR1 and TLR2 recognize tri-acylated lipoprotein from gram-positive bacteria, TLR4 detects lipopolysaccharide (LPS), and NOD2 senses muramyl dipeptide, a cell wall component of gram-negative bacteria. Of note, the presence of genetic variation in the NOD2, NLRP3, and TLR4 genes has been demonstrated to confer susceptibility to Crohn's disease [55], graft-vs.-host disease after bone marrow transplantation [56] and for mortality in patients with sepsis [57]. Interestingly, TLR4-deficient mice have less severe fulminant hepatitis and ischemic-reperfusion injury compared to normal mice [58,59]. In cirrhosis [60], carriers of NOD2 risk variants displayed a higher risk for SBP and death. This association was replicated for culture-positive SBP; an interesting finding in this study was that patients with NOD2 variants presented more often with variceal bleeding and hepatocellular carcinoma [61]. In addition, SBP was more frequent in patients with cirrhosis who carry TLR2 risk variants, which might be particularly important when gram-positive organisms, become a major cause of SBP [62]. In multivariate analysis, the simultaneous presence of variants in both NOD and TLR2 genes indicates a particularly high risk for SBP (OR = 11) and is also associated with surrogate markers for abnormal intestinal permeability and BT. Finally, in retrospective analysis, an association between a TLR4 polymorphism and increased infection rates in cirrhosis and more pronounced stimulation of cytokine expression was described [63]. These studies indicate that common gene variants linked to impaired mucosal barrier function and BT represent genetic risk factors for SBP and other infections in patients with liver cirrhosis.

Immune dysfunction

Cirrhosis associated immune dysfunction (CAID) involves a state of immunodeficiency, and in parallel a state of persistent activation of the immune system cells with production of pro-inflammatory cytokines [64–66]. Immunodeficiency affects both the innate and the adaptive arm of the immune system with a myriad of defects. Except for monocytes, cirrhosis leads to reduced numbers of circulating immune system cells, which is particularly profound for neutrophils, naïve Th- and Tc-cells, as well as CD27+ memory B-cells [64,67]. Coupled with their reduced numbers, mononuclear phagocytic cells and neutrophils show reduced abilities of phagocytosis and mobilization, T and B cells show hypo-proliferation in response to mitogens and CD40/TLR9, respectively, and NK cells display low cytotoxic activity [64,67–70]. Additionally, cirrhosis results in reticuloendothelial

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Table 2. Definition of organ failures in patients with cirrhosis. (A) Organ/systems whose functions are assessed by the Chronic Liver Failure (CLIF)-Sequential Assessment of Organ Failure (SOFA) scale (adapted from [74]). (B) Definition of the presence or absence of acute-on-chronic liver failure (ACLF) provided by the CANONIC study [76]. Organ failures shown here are those defined in panel A.

A

The CLIF-SOFA scale					
Organ/system	0	1	2	3	4
Liver					
Bilirubin (mg/dl)	<1.2	≥1.2-<1.9	≥2-<5.9	≥6-<12	≥12
Kidney					
Creatinine (mg/dl)	<1.2	≥1.2-<1.9	≥2-<3.5	≥3.5-<5	≥5
Cerebral (HE grade)	No HE	1	2	3	4
Coagulation	INR <1.1	INR 1.1-1.25	INR 1.26-1.5	INR 1.51-2.5	INR >2.5 or platelets ≤20x10 ³ /μl
Circulation					
MAP (mmHg)	≥70	<70	Dopamine ≤5 or dobutamine or terlipressin	Dopamine >5-≤15 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Lungs					
PaO ₂ /FiO ₂ or SpO ₂ /FiO ₂	>400 or >512	≤400 or >357-≤512	≤300 or >214-≤357	≤200 or >89-≤214	≤100 or ≤89

B

ACLF grade	Definition
No	<ul style="list-style-type: none"> No organ failure Single organ failure (liver, coagulation, circulation, lungs) + creatinine <1.5 mg/dl + no hepatic encephalopathy Single cerebral failure + creatinine <1.5 mg/dl
1	<ul style="list-style-type: none"> Single kidney failure Single organ failure (liver, coagulation, circulation, lungs) + creatinine 1.5-≤1.9 mg/dl and/or grade 1-2 hepatic encephalopathy Single cerebral failure + creatinine 1.5-≤1.9 mg/dl
2	<ul style="list-style-type: none"> 2 organ failures
3	<ul style="list-style-type: none"> 3 organ failures or more

The CLIF-SOFA score includes sub-scores ranging from 0 to 4 for each of six components (liver, kidneys, brain, coagulation, circulation, and lungs) with higher scores indicating more severe organ impairment. Aggregated scores range from 0 to 24 and provide information on overall severity. The use of dobutamine or terlipressin, at any dose, is sufficient to count a score of 2 for circulation. Doses of catecholamines shown in the Table are μg/kg.min.

The highlighted area in yellow shows the diagnostic criteria for organ failures [This table appears in colour on the web].

HE, hepatic encephalopathy; INR, International Normalized Ratio; MAP, mean arterial pressure; PaO₂, partial pressure of arterial oxygen; FiO₂, fraction of inspired oxygen; SpO₂, pulse oximetric saturation.

dysfunction, due to reduced number of liver reticuloendothelial mononuclear cells in liver and porto-systemic shunting, which lower the liver ability to clear intestinal bacteria, as well as decreased hepatic synthesis of molecules of the innate immune response, such as complement components and secreted-pattern recognition receptors [71]. These defects coexist with an induced expression of activation molecules on the surface of immune cells and the increased synthesis of pro-inflammatory cytokines, especially by monocytes [72,73].

CAID has a multifactorial pathogenesis, which includes continuous immune system cells stimulation by microbial- and damage-associated molecular patterns (MAMPs, DAMPs), decreased hepatic synthesis of trophic factors, hypersplenism and splenic pooling of immune system cells, and the etiological factors of cirrhosis such as alcohol or virus. Furthermore, the continuous interaction of gut bacteria with stimulation of the immune system may lead to exhaustion of the immune response and

'immune paralysis', which might further increase the risk of bacterial infections [65,74].

Consequences of bacterial infections

Bacterial infections are a common cause of acute decompensation of cirrhosis [4]. Among patients with cirrhosis and acute bacterial infections some have "mere" decompensated cirrhosis while others exhibit decompensated cirrhosis associated with newly developed liver and/or extra-hepatic organ failure(s) [2]. Patients with cirrhosis and "acute" organ failure(s) are at high risk of short-term death [74,75]. These patients are considered to have acute-on-chronic liver failure (ACLF) [74]. A large prospective observational study called CANONIC study was recently performed with the aim of establishing the diagnostic criteria of ACLF [76]. This study used the CLIF-Sequential Organ Failure

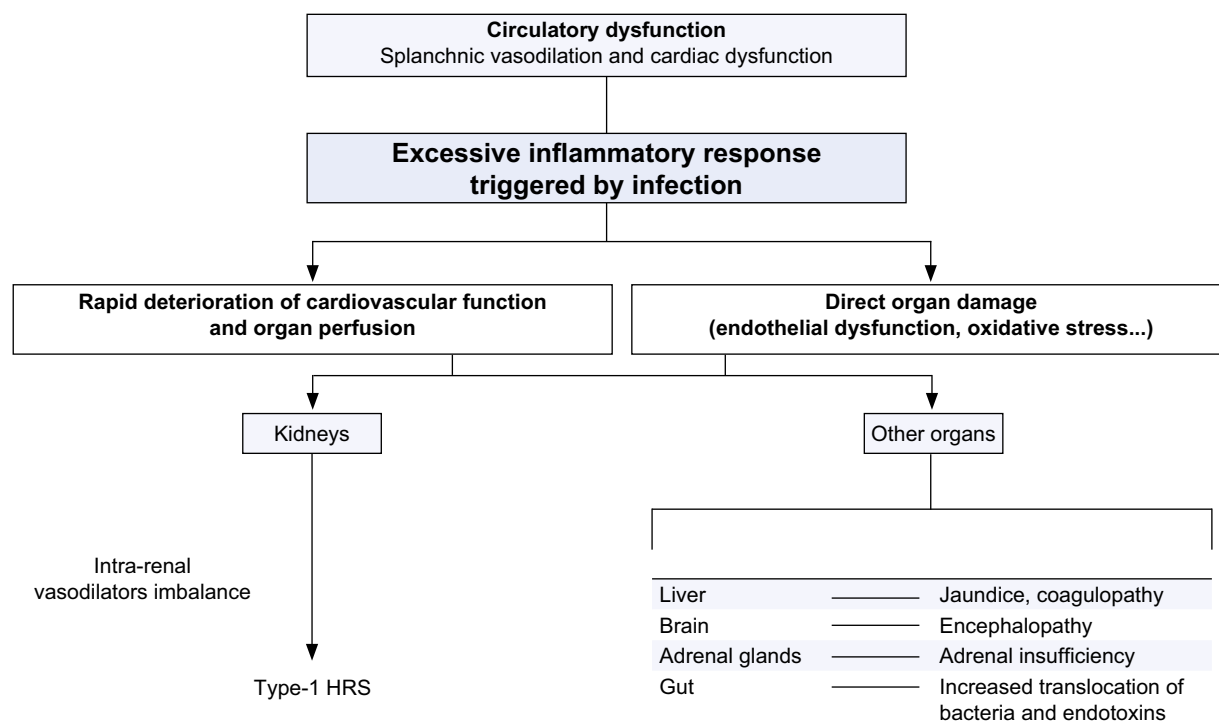


Fig. 3. Pathophysiological basis of acute on chronic liver failure and end-organ dysfunction in cirrhosis precipitated by infection.

Assessment (SOFA) score to recognize organ failures. The CANONIC study provided a robust definition of ACLF into three ACLF grades, with increasing risk of short-term death from grade 1 (22%) to grade 3 (77%) [76]. Table 2A and B describe the scoring system used and also the diagnostic criteria. Bacterial infection was the most common precipitating event of ACLF (33%) [76]. Among patients with bacterial infection, ACLF was more common in patients with SBP or pneumonia than in those with infections at other sites [9,76]. The pathophysiology and manifestations of infection-induced organ failure is incompletely understood [2]; the following mechanisms have been suggested (Fig. 3).

Inflammation

Bacterial components (e.g., lipopolysaccharide (LPS) a Gram-negative bacteria byproduct) may cause an excessive pro-inflammatory response of the host immune system resulting in tissue damage (a process called immunopathology) and organ failure [77]. An excessive production of pro-inflammatory molecules has been shown to occur *in vivo* and *ex vivo* in patients [78–87] and animals [88–90] with cirrhosis. Among infected patients, systemic inflammation is more marked in patients with ACLF than in those without [76]. The susceptibility to LPS-induced liver injury (assessed by the degree of hepatocyte apoptosis and necrosis) is higher in animals with cirrhosis than in normal animals [89,90]. This higher susceptibility in cirrhosis decreases when high-density lipoprotein administration is used to neutralize LPS [90,91]. However, infection-induced organ failure may not be entirely explained by an increased production of pro-inflammatory molecules (see below).

Several mechanisms related to bacterial infections may lead to cell necrosis [77]. Dying cells are known to release nuclear

molecules (called danger-associated molecular patterns, DAMPs), which are able to stimulate the innate immune system through different receptors and trigger inflammation [77]. The role of DAMPs in ACLF-associated inflammation requires to be investigated.

Organ damage

Infection-induced tissue damage may depend not only on the intensity of the inflammatory response per se but also on the intrinsic capacity of host organs to tolerate (i.e., endure) the effects of the inflammatory response [77]. The capacity of tolerance of each organ depends on inducible mechanisms such as anti-apoptotic pathways, among others [77]. In the context of Gram-negative infections, normal livers are protected against LPS-induced, TNF- α -mediated apoptosis because of simultaneous induction of nuclear factor- κ B (NF- κ B)-dependent anti-apoptotic molecules [89]. In contrast, cirrhotic livers are abnormally susceptible to LPS-induced, TNF- α -mediated apoptosis because NF- κ B-target anti-apoptotic molecules cannot be properly induced [89]. Therefore, in cirrhosis, infection-induced liver failure may be related not only to an excessive pro-inflammatory response but also to a decrease in the hepatic capacity of tolerance. The role of the alteration of tolerance mechanisms in the development of infection-induced extra-hepatic organ failures should be investigated in patients and animals with ACLF.

Kidney failure

Bacterial infections [79,92] are well-established triggers of kidney failure in cirrhosis. Patients with SBP without shock who exhibit the highest pro-inflammatory response are those who

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are at risk of developing kidney failure [79]. Of note, in these patients, kidney failure frequently develops while resolution of infection has been obtained by antibiotic therapy [93] suggesting that organ failure does not result from intrinsic virulence (i.e., tissue damage directly caused by bacteria) but rather extrinsic virulence (i.e., caused by the excessive inflammatory response of the host) or sepsis-related alterations in hemodynamics [93]. A potential role for alterations of tolerance mechanisms in the development of kidney failure [94] has not yet been investigated.

Brain failure

Bacterial infections are common triggers of hepatic encephalopathy [95]. Clinical and experimental data show that infections may result in brain oedema in patients with cirrhosis. It is currently uncertain whether this water accumulation is predominantly intracellular or extracellular. There is some evidence that both mechanisms combine to cause brain edema and hepatic encephalopathy (HE) [96].

Coagulation failure

Among infected patients with cirrhosis, disseminated intravascular coagulation (DIC, which can be activated by pro-inflammatory cytokines) is more frequent in patients with ACLF than in those without [75]. Thrombi in the microvasculature of a vital organ may play a role in tissue hypoxia [77]. Of note, activation of coagulation may stimulate inflammation [77].

Variceal bleeding

Variceal hemorrhage is a well-established risk factor for bacterial infection in patients with cirrhosis [97]. Moreover, it has been suggested that conversely bacterial infection might increase the risk of variceal hemorrhage [98]. This hypothesis needs to be confirmed by future studies.

Adrenal insufficiency

Patients with cirrhosis and septic shock (most often classified as ACLF grade 3 patients) may have high incidence of relative adrenal insufficiency (RAI, 51–77%) [99]. The presence of RAI seems to be associated with poor liver function, kidney failure, refractory shock and hospital mortality [100]. RAI could result in decreased corticosteroid-related anti-inflammatory mechanisms and consequently unrestricted infection-induced production of pro-inflammatory molecules. In addition, under stress conditions, defective corticosteroid production could be associated with decreased capacity of tolerance of vital organs [77,78].

Recent but limited data suggest that RAI can also occur in non-critically ill patients with cirrhosis. The reported prevalence of this entity ranges between 7% and 49% depending on the methodology used for RAI diagnosis [99]. Since serum total cortisol overestimates the prevalence of RAI in cirrhosis due to low transcortin and albumin concentrations, free cortisol levels have been suggested as the preferred method for the diagnosis of RAI in this population [101,102]. Delta total cortisol values, a dynamic diagnostic criteria of RAI not affected by changes in transcortin or albumin levels, can also be used for its diagnosis [103]. In a recent study involving non-critically ill patients with cirrhosis, RAI was associated with greater impairment of circulatory and renal func-

tion, higher probability of severe sepsis and type-1 HRS and higher short-term mortality [103]. By contrast, another study reported a higher risk of death in patients with high free cortisol levels [102].

Early diagnosis and biomarkers

Early diagnosis of bacterial infections is a crucial step in the management of patients with cirrhosis. Since the presentation and the initial course of a bacterial infection in some patients with cirrhosis may be subtle and not very specific, clinical suspicion is important. Indeed, all hospitalized patients with cirrhosis should be considered as potentially infected until proven otherwise. Therefore, a complete work-up should be carried out at admission and on clinical deterioration of a hospitalized patient in order to detect a possible infection [1,4]. In addition, a close microbiological surveillance, is needed in patients who are at risk for the development of infections caused by MR organisms [1,22,104,105]. It is well known that bacterial infections can induce systemic inflammatory response (SIRS). On the basis of conventional criteria [106], SIRS has been described in 57–70% of infected patients with cirrhosis [81,107], but these data may underestimate the rate of SIRS since these patients may have a low heart rate due to the use of beta blockers and may present an apparently normal white blood cell count due to hypersplenism. On the other hand, SIRS may be diagnosed in patients with cirrhosis in the absence of bacterial infection since the hyperdynamic circulation, hepatic encephalopathy, tense ascites and hypersplenism may alter heart and respiratory rate, temperature and white-cell count. SIRS has been described in 10–30% of patients with decompensated cirrhosis without bacterial infection [83,107]. The evident lack of sensitivity and specificity of the conventional parameters for the definition of SIRS [105,106] makes it difficult to diagnose sepsis in these patients. Thus, new tools for the diagnosis of bacterial infections are clearly needed. In this context, it should be mentioned that a recent study reported that persistently high levels of CRP in patients with decompensated cirrhosis are associated with increased short-term mortality. The predictive value of CRP was independent from relevant predictive factors, such as MELD score, and was better than that of SIRS diagnosed by conventional criteria [108]. Although not demonstrated, it is likely that the high levels of CRP may indicate a systemic inflammatory reaction linked to hidden bacterial infections and/or persistent bacterial translocation.

New tools for early detection of the presence and of the severity of bacterial infections

From a pathophysiological perspective, pathological BT, altered host response to injury, and impairment in the ability of the innate immune system to adequately fight off infections are important [1]. Therefore gut permeability, gut flora, bacterial products, acute phase proteins, the function of innate immune cells, cellular receptors and cellular products and molecules involved in endotoxin presentation and removal are likely targets for such biomarkers.

Markers of gut barrier dysfunction/bacterial translocation

Increased intestinal permeability is predictive for infection after variceal haemorrhage [107] and calprotectin levels have been

Table 3. Potential tools for early detection. (A) Potential tools for early detection of the presence and the severity of bacterial infections. (B) Potential tools for an early identification of the pathogen and of its susceptibility to antibiotics.**A**

Tool	Potential usefulness	Limitations
CRP	For a cut off value ≥ 10 ng/ml it has proved to be a useful marker to predict the likelihood of clinically significant bacterial infections in patients with cirrhosis without overt infections For cut off values of 24.7 ng/ml of CRP the area under the ROC curve for predicting sepsis was 0.811 in patients with cirrhosis	Patients with cirrhosis may present reduced CRP in response to infection. Up to 14.8% of patients with cirrhosis and bacterial infection may have a baseline CRP < 10 mg/L. Infection independent factors like inflammation and bacterial translocation are potentially able to induce the synthesis of CRP CRP levels could remain elevated over time despite the resolution of bacterial infection in the majority (62.5%) of patients
PCT	For cut-off values of 0.49 of PCT the area under the ROC curve for predicting sepsis was found to be 0.89 in patients with cirrhosis	Infection independent factors like inflammation and bacterial translocation are potentially able to induce the synthesis of PCT
CRP and PCT	In patients with cirrhosis the combination of PCT and CRP increased the sensitivity and negative predictive value in the detection of infections, compared with CRP on its own, by 10 and 5% respectively	The superiority of PCT over CRP in the detection of bacterial infections and in the diagnosis of sepsis remains controversial and is still a matter of debate in patients with cirrhosis

B

Tool	Potential usefulness	Limitations
Real time PCR assays	Methods for early detection of infection based on multi-pathogen probe-based real-time PCR system targeting DNA sequences of bacteria and fungi directly from whole blood sample, without prior incubation or culture steps in less than 6 hours Their sensitivity and specificity for detecting bacterial DNA from ascitic fluid in patients with cirrhosis compared with those of standard cultures were 100% and 91.5%, respectively	Concordance with ascitic cultures for species identification in patients with cirrhosis was 70.6%. They provide information not entirely interchangeable with cultures for pathogen identification Frequent detection of environmental organisms of undetermined pathogenicity is currently a limitation. They are not superior to blood cultures for pathogen identification, in an unselected patient population with suspected sepsis They are expensive and time-consuming and they need special equipment and technical expertise for DNA extraction
DST	Methods (based on MALDI-TOF) for early detection of resistant bacteria and testing their antibiotic susceptibility from blood cultures or other body-sterile fluids cultures. The reporting time for the direct testing of susceptibility for blood cultures by the system ranged from 3.3 to 17.5 h compared with conventional methods that require 1 or 2 days	Results still need to be confirmed by conventional methods and DST cannot be done or results are not reliable in mixed infections (Gram-positive and Gram-negative) or infections caused by yeasts

CRP, C reactive protein; PCT, procalcitonin; DST, direct susceptibility tests; MALDI-TOF, matrix assisted laser desorption ionization – time of flight.

shown to correlate with BT [109]. Markers of BT such as endotoxin, D-lactate, peptidoglycan and bacterial DNA are elevated in the serum of patients with cirrhosis [110–112] and may predict mortality [113–115]. However, bacterial DNA does not correlate with infection [113].

Markers of innate immune response

Neutrophil function is impaired in cirrhosis, displaying an inadequately increased resting oxidative burst with a defect in phagocytosis and killing. This is associated with an increase in mortality and an increased rate of infections. [64,114]. Similar functional defects have been shown for monocytes and macro-

phages [65,115–119]. Whether they can be used as indicators of susceptibility needs to be tested.

Markers of inflammatory response

Procalcitonin (PCT) and C-reactive protein (CRP) are two acute-phase serum proteins, which are commonly used as early markers of infection in general population [119]. CRP is mainly produced by the hepatocytes while PCT is produced ubiquitously including the liver [119]. Although there is evidence that serum levels of these acute-phase proteins are not significantly lower in patients with cirrhosis than in other patients [120], patients with cirrhosis may present reduced CRP and PCT levels, particularly

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Table 4. Recommended empirical antibiotic treatment for community-acquired and nosocomial bacterial infections in cirrhosis.

Type of infection	Community-acquired infections	Nosocomial infections*
SBP, SBE and spontaneous bacteremia	Cefotaxime or ceftriaxone or amoxicillin/clavulanic acid	Piperacillin/tazobactam ^Δ or meropenem [§] ± glycopeptide [#]
Urinary infections	Uncomplicated: ciprofloxacin or cotrimoxazole If sepsis: cefotaxime or ceftriaxone or amoxicillin/clavulanic acid	Uncomplicated: nitrofurantoin or fosfomycin If sepsis: piperacillin/tazobactam ^Δ or meropenem [§] ± glycopeptide [#]
Pneumonia**	Amoxicillin/clavulanic acid or ceftriaxone + macrolide or levofloxacin or moxifloxacin	Piperacillin/tazobactam ^Δ or meropenem/ceftazidime + ciprofloxacin ± glycopeptide [#] should be added in patients with risk factors for MRSA [‡]
Cellulitis	Amoxicillin/clavulanic acid or ceftriaxone + oxacillin	Meropenem/ceftazidime ^Δ + oxacillin or glycopeptides [#]

SBP, spontaneous bacterial peritonitis; SBE, spontaneous bacterial empyema; MRSA, methicillin-resistant *Staphylococcus aureus*.

Dosages of antibiotics have not been formally investigated or defined in cirrhotic population and it is advisable to follow standard recommended dosages.

*Recommended empirical treatment also for health-care associate (HCA) urinary infections and pneumonia. Empirical antibiotic treatment of HCA spontaneous infections and cellulitis will be decided on the basis of the severity of infection (patients with severe sepsis should receive the schedule proposed for nosocomial infections) and on the local prevalence of multiresistant bacteria in HCA infections.

^ΔIn areas with a low prevalence of multiresistant bacteria.

[§]To cover extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*.

[#]IV vancomycin or teicoplanin in areas with a high prevalence MRSA and vancomycin-susceptible enterococci (VSE). Glycopeptides must be replaced by IV linezolid in areas with a high prevalence of vancomycin-resistant enterococci (VRE).

**Liver disease is considered as severe comorbidity for community-acquired pneumonia in guidelines.

[‡]Antibiotics active against *Pseudomonas aeruginosa*.

[†]Ventilator-associated pneumonia, previous antibiotic therapy, nasal MRSA carriage.

CRP, in response to infection [121]. Despite these potential limitations, the predictive power of CRP and PCT for detecting infection has been found to be similar in patients with and without cirrhosis (Table 3A) [122–124]. However, as mentioned before it should be emphasised that CRP levels could remain elevated over time despite the resolution of bacterial infection in a large percent of patients with cirrhosis [108]. As far as the definition of the severity of the infection, elevated serum levels of PCT and CRP are correlated with the presence, course, and outcome of sepsis in patients with cirrhosis (Table 3A) [26] as in the general population [125]. Finally, randomized-controlled trials have shown a benefit from the use of PCT algorithms to guide decisions about the initiation and/or discontinuation of antibiotic therapy in patients with some types of infections in the intensive care unit [126] but its usefulness in patients with cirrhosis has yet to be investigated.

The role of other acute phase proteins (lipopolysaccharide binding protein, sCD14) in the early diagnosis as well as in the definition of infections in patients with cirrhosis is still unclear, even though they are useful predictors of mortality in cirrhosis [127] mainly when they are used in combination with CRP and PCT [123]. Recently, mid region-proadrenomedullin has been shown to provide potentially differential information in infected patients with cirrhosis compared to CRP [128].

New tools for early identification of the pathogen

With regard to the identification of the pathogen, real time PCR assays [129,130] were shown to have potential utility compared with standard culture techniques for the diagnosis of SBP in patients with cirrhosis [131]. However, they provide information not entirely interchangeable with cultures for pathogen identifi-

cation [131] (Table 3B). In addition, these molecular assays are expensive and time-consuming and they need special equipment and technical expertise for DNA extraction. Considering all these limitations they may not be suitable as a replacement of cultures for routine use in clinical practice. Recently, the application of a direct susceptibility testing (DST) based on a Matrix Assisted Laser Desorption Ionization – Time of Flight (MALDI-TOF) from positive blood cultures has been proposed for early detection of resistant bacteria and their antibiotic susceptibility (Table 3B) [132,133].

Treatment of bacterial infections in cirrhosis

Antibiotic treatment

Early diagnosis and prompt initiation of adequate antibiotic therapy is essential in the management of patients with cirrhosis and bacterial infections [1,134] as delays and inappropriate therapy is associated with increased mortality [135]. The choice of initial empirical antibiotics should be based on the type, severity and origin of infection (community-acquired, nosocomial or health care-associated; HCA) and on the local epidemiological data about antibiotic resistance. In general, third-generation cephalosporins continue to be the gold-standard antibiotic treatment of many of the infections acquired in the community [136,137]. By contrast, the empirical treatment of nosocomial and health-care associated infections should be tailored according to the local epidemiological pattern of MR bacteria (Table 4) [1,138]. The failure of response to empirical antibiotics is due to inappropriate choice of initial antibiotics, MR bacterial infections and delayed start of appropriate antibiotics [135,138]. If the causative

Table 5. Current indications of antibiotic prophylaxis in cirrhosis.

Indication	Antibiotic and dose
Gastrointestinal bleeding	Preserved liver function: norfloxacin 400 mg/12h PO for 7 days Patients with advanced cirrhosis (at least 2 of the following: ascites, jaundice, hepatic encephalopathy and malnutrition): IV ceftriaxone 1 g/d during 7 days
Primary prophylaxis of SBP in patients with low protein ascites (<15 g/L)	Norfloxacin 400 mg/d PO or ciprofloxacin 500 mg/d until liver transplantation or death in patients with advanced cirrhosis: - Child-Pugh score ≥ 9 points with serum bilirubin ≥ 3 mg/dl and/or - Renal dysfunction (serum creatinine ≥ 1.2 mg/dl, BUN ≥ 25 mg/dl and/or serum sodium ≤ 130 mEq/L)
Secondary prophylaxis of SBP	Norfloxacin 400 mg/d PO until liver transplantation, death, resolution of ascites or improvement in liver function to a compensated status

organism is identified (about 50% of cases), antibiotic regimen should be narrowed to decrease the likelihood of emergence of antibiotic resistance. Duration of antimicrobial treatment has not been formally investigated or defined in cirrhosis, except for SBP with a minimum of 5 days [139]. In SBP, response to antimicrobials, arbitrarily defined by a $\geq 25\%$ reduction of ascitic polymorphonuclear count, should be assessed by follow-up paracentesis 48 h after initial diagnosis [138]. In the case of failure of response, initial antibiotics should be changed.

Intravenous albumin

In patients with cirrhosis and SBP without shock treated with cefotaxime, an open-label randomized clinical trial (RCT) showed that the IV administration of 20% albumin reduced the incidence of renal failure and decreased mortality rates from 29% to 10% [93]. The mechanisms by which albumin improved hemodynamics could be related to its oncotic properties but also to the immunomodulation, antioxidant and endothelium stabilization capacity [140]. This effect was not observed in patients with low risk of mortality (total bilirubin <4 mg/dl and creatinine <1 mg/dl) [141,142]. In a recent randomized study, the administration of albumin in unselected patients with cirrhosis and non-SBP infections was not associated with improved overall survival but albumin administration was an independent predictor of survival after adjustment for other prognostic factors [143]. A large study is currently being planned.

Management of severe sepsis and septic shock

At this time, due to lack of data in cirrhosis, current guidelines defined in the general population should be followed [144]. Although therapeutic goals for severe sepsis and septic shock in patients with cirrhosis have not been defined, a prompt (within the 6 first hours) protocolized resuscitation of sepsis-induced hypoperfusion with pre-defined targets (central venous pressure 8–12 mmHg, urine output ≥ 0.5 ml/kg.hr and superior vena cava or mixed venous saturation 70% or 65% respectively) and normalization of increased lactate levels is recommended. Studies specifically investigating the ideal target level of mean arterial pressure in these patients have not been performed. However, it appears reasonable to state that arterial pressure should be increased to a level close to the baseline of each patient, if known. If not known, it should be at least of 65 mmHg. The balance between fluid therapy (crystalloids and albumin) and vasopressor administration in the hemodynamic support of cirrhotic patients

is undefined. A strict monitoring of patients' responsiveness to fluid replacement (i.e., pulse pressure variation and stroke volume variation in sedated patients) is necessary to avoid fluid overload, peripheral edema and abdominal compartment syndrome.

Current guidelines only recommend stress dose steroids in patients with vasopressor-unresponsive septic shock in the general population [145]. Data in patients with cirrhosis is scant and controversial [146,147]. A large double-blind European RCT is currently underway to address this topic.

Prophylaxis of bacterial infections

Since most episodes of spontaneous bacterial infections in cirrhosis are the result from the translocation of enteric gram-negative bacilli, prophylactic agents should be effective at decreasing the concentration of these bacteria in the gut while preserving the protective anaerobic flora. Norfloxacin, a poorly absorbable quinolone that eliminates gram-negative bacilli selectively from the intestinal flora, has been used in the prophylaxis of bacterial infections in cirrhosis. However, given the risk of developing resistant organisms, the use of prophylactic antibiotics must be strictly restricted to patients at high risk of bacterial infections such as patients with upper gastrointestinal bleeding, patients with advanced cirrhosis and low total protein content in ascitic fluid and patients with a previous history of SBP (Table 5) [135,136,138,148,149].

Gastrointestinal bleeding

Forty-five to 66% cirrhotic patients with upper gastrointestinal bleeding develop bacterial infection within the first 5–7 days of the bleeding episode [150,151]. The administration of oral or systemic antibiotics (penicillins, cephalosporins, and quinolones) decreases the incidence of bacterial infections to 10–20%, [152–154] improves control bleeding, prevents rebleeding and improves survival [152]. Oral norfloxacin (400 mg/12 h for 7 days) is the gold standard prophylaxis in patients with preserved liver function. Nevertheless, patients with advanced cirrhosis (at least two of the following: ascites, severe malnutrition, encephalopathy or jaundice) should receive IV ceftriaxone (1 g/day for 7 days) [1]. In a RCT, the probability of developing proven infection was significantly lower in patients receiving ceftriaxone iv than in those receiving norfloxacin per os (11% vs. 26%, $p = 0.03$) [152]. In patients with recent infection with extended-spectrum β -lactamase-producing *Enterobacteria-*

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ceae (3–6 months), antibiotics such as oral nitrofurantoin or ertapenem should be used. Antibiotic prophylaxis should ideally be given before or immediately after endoscopy [153].

Primary prophylaxis in advanced cirrhosis

Patients with low protein ascites (10–15 g/L), liver failure (serum bilirubin >3.2 mg/dl) and low platelet count ($<98,000 \times \text{mm}^3$) have a high risk of developing the first episode of SBP [1,3,135,150,155]. A RCT evaluated the impact of primary prophylaxis with norfloxacin in cirrhotic patients at high risk of developing SBP and hepatorenal syndrome. Patients with low protein ascites ($<15 \text{ g/L}$) and advanced liver failure (Child-Pugh score ≥ 9 points with serum bilirubin $\geq 3 \text{ mg/dl}$) or impaired renal function (serum creatinine $\geq 1.2 \text{ mg/dl}$, BUN $\geq 25 \text{ mg/dl}$ or serum sodium $\leq 130 \text{ mEq/L}$) were randomized to receive norfloxacin (400 mg/d for 1 year) or placebo. Norfloxacin reduced the 1-year probability of developing SBP (7% vs. 61%) and hepatorenal syndrome (28% vs. 41%, $p = 0.02$) and improved 3-month survival (94% vs. 62%) [154]. Long-term norfloxacin administration is therefore indicated in this specific subpopulation of patients with advanced cirrhosis, particularly if they are awaiting liver transplantation. Oral ciprofloxacin 500 mg/d is an alternative option to norfloxacin [1].

Secondary prophylaxis

Patients who recover from a previous episode of SBP are at a very high risk of SBP recurrence in the absence of antibiotic prophylaxis. Long-term norfloxacin administration (400 mg/d PO) is effective in the prevention of SBP recurrence. Long-term norfloxacin prophylaxis was shown to decrease the overall probability of SBP recurrence at 1 year from 68% in the placebo group to 20% and from 60% to 3% respectively if analysis was restricted to SBP caused by gram-negative bacilli [155]. After an episode of SBP, liver transplantation must be considered [1].

Infections caused by multiresistant bacteria. The need for alternative strategies

Prolonged antibiotic administration leads to the emergence of resistant bacteria. Epidemiological studies have demonstrated that long-term norfloxacin prophylaxis increases the risk of infections caused by quinolone-resistant, trimethoprim-sulfamethoxazole-resistant and ESBL-producing strains in cirrhosis [4,20]. Long-term norfloxacin prophylaxis increases 2.7 fold the risk of developing MR bacterial infections and almost 4 fold the risk of infections caused by ESBL-producing *Enterobacteriaceae* [3,4,20].

Rifaximin, an antibiotic with broad-spectrum antimicrobial activity that eliminates intestinal flora non-selectively [156], has been suggested as a potential alternative to norfloxacin in the prophylaxis of bacterial infections in cirrhosis. Its administration in patients with hepatic encephalopathy is not associated with the development of infections by MR bacteria [157]. Three main characteristics of rifaximin can explain this finding: (1) it reaches high fecal concentrations but is virtually non-absorbed (bioavailability in blood after oral administration $<0.4\%$); (2) it reduces the expression of bacterial virulence factors and compromises plasmid transfer, an important mechanism of multiresistance; (3) despite high gut concentrations and its broad spectrum of activity, rifaximin produces minimal alterations in

the intestinal microflora (1 log reduction in intestinal coliforms per gram of stool after 2 weeks of treatment) [156–158]. A case-control study has recently found a significant benefit for rifaximin for prophylaxis of SBP when used in patients with encephalopathy [157]. Risk of *Clostridium difficile* was not increased [157]. Despite these data, real efficacy and safety of rifaximin in the prevention of spontaneous bacterial infections in cirrhosis remains to be explored. Nevertheless, it should be emphasized that there are no studies comparing rifaximin vs. norfloxacin in the prevention of SBP.

Non-antibiotic strategies have been studied as a potential alternative to quinolones in the prophylaxis of bacterial infections in cirrhosis but evidence published so far is still limited [159–161,54,162]. Although these strategies seem to prevent bacterial translocation and SBP in experimental models, none of them has been compared with norfloxacin in the prevention of SBP in RCT in patients with cirrhosis.

Future research and conclusions

It has become clear that cirrhotic patients are susceptible to bacterial infections due to a variety of possible pathogenic mechanisms as highlighted. In a recent study, the occurrence of infection in a cirrhotic patient was suggested to represent a critical step in the progression of cirrhosis [6]. Gut dysbiosis, increased bacterial translocation and cirrhosis-associated immune dysfunction play important roles. The main research efforts will be the generation of models and possible biomarkers to identify high-risk patients and the associated mechanisms to allow preventative strategies. The cirrhotic patient with superimposed infection is more susceptible to its effects with increased risk of end-organ dysfunction and mortality. Future research should try to dissect the associated mechanisms and devise strategies to reduce this end-organ sensitivity while maintaining immune competence. The diagnosis of infection in cirrhosis is difficult because of the co-incident systemic inflammatory response that may exist due to the disease process itself rendering current markers ineffective resulting in delayed diagnosis. Development of biomarkers that can be used early will result in a reduction in the morbidity and mortality. Infection with multi-drug resistant bacteria is increasing possibly due to reduced immune surveillance and inappropriate use of broad-spectrum antibiotics. Newer tools to detect the kind of infection will limit the use of broad-spectrum antibiotics and possibly reduce the incidence of multi-resistant bacterial infections. Better selection of patients for antibiotic prophylaxis and development of non-antibiotic strategies will be the key to improving the outcome of patients. Management of the acute episode of infection and use of albumin has already yielded good results in spontaneous bacterial peritonitis, and trials will be needed for other infections. It is clear that a concerted program of activity is necessary to address these pending questions.

Conflict of interest

RJ received research funding from Vital Therapies, has served on Scientific Advisory Board for Conatus Pharma, received lecture fees from Gambro, has on-going research collaboration with Gambro, Grifols and is the PI of an Industry sponsored study

(Sequana Medical). He is also the inventor of a drug, L-ornithine phenylacetate, which UCL has licensed to Ocera Therapeutics.

PG has received a research grant and lecture fees from Grifols International and a research grant from Sequana Medical AG.

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References

- Fernandez J, Gustot T. Management of bacterial infections in cirrhosis. *J Hepatol* 2012;56:S1–S12.
- Gustot T, Durand F, Lebre C, Vincent JL, Moreau R. Severe sepsis in cirrhosis. *Hepatology* 2009;50:2022–2033.
- Fernandez J, Navasa M, Gomez J, Colmenero J, Vila J, Arroyo V, et al. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology* 2002;35:140–148.
- Fernández J, Acevedo J, Castro M, García O, de Lope CR, Roca D, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. *Hepatology* 2012;55:1551–1561.
- Foreman MG, Mannino DM, Moss M. Cirrhosis as a risk factor for sepsis and death: analysis of the National Hospital Discharge Survey. *Chest* 2003;124:1016–1020.
- Arvaniti V, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. *Gastroenterology* 2010;139:1246–1256.
- Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012;18:268–281.
- Woodford N, Turton JF, Livermore DM. Multiresistant Gram-negative bacteria: the role of high-risk clones in the dissemination of antibiotic resistance. *FEMS Microbiol Rev* 2011;35:736–755.
- Merli M, Lucidi C, Giannelli V, Giusto M, Riggio O, Falcone M, et al. Cirrhotic patients are at risk for health care-associated bacterial infections. *Clin Gastroenterol Hepatol* 2010;8:979–985.
- Song JY, Jung SJ, Park CW, Sohn JW, Kim WJ, Kim MJ, et al. Prognostic significance of infection acquisition sites in spontaneous bacterial peritonitis: nosocomial vs. community acquired. *J Korean Med Sci* 2006;21:666–671.
- Cereto F, Herranz X, Moreno E, Andreu A, Vergara M, Fontanals D, et al. Role of host and bacterial virulence factors in *Escherichia coli* spontaneous bacterial peritonitis. *Eur J Gastroenterol Hepatol* 2008;20:924–929.
- Angeloni S, Leboffe C, Parente A, Venditti M, Giordano A, Merli M, et al. Efficacy of current guidelines for the treatment of spontaneous bacterial peritonitis in the clinical practice. *World J Gastroenterol* 2008;14:2757–2762.
- Cheong HS, Kang C, Lee JA, Moon SY, Joung MK, Chung DR, et al. Clinical significance and outcome of nosocomial acquisition of spontaneous bacterial peritonitis in patients with liver cirrhosis. *CID* 2009;48:1230–1236.
- Song KH, Jeon JH, Park WB, Park SW, Kim HB, Oh MD, et al. Clinical outcomes of spontaneous bacterial peritonitis due to extended spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* species: a retrospective matched case-control study. *BMC Infect Dis* 2009;9:41–46.
- Heo J, Seo YS, Yim HJ, Hahn T, Park SH, Ahn SH, et al. Clinical features and prognosis of spontaneous bacterial peritonitis in Korean patients with liver cirrhosis: a multicenter retrospective study. *Gut Liver* 2009;3:197–204.
- Yakar T, Güçlü M, Serin E, Alişkan H, Husamettin E. A recent evaluation of empirical cephalosporin treatment and antibiotic resistance of changing bacterial profiles in spontaneous bacterial peritonitis. *Dig Dis Sci* 2009;55:1149–1154.
- Piroth L, Pechinot A, Minello A, Jaulhac B, Patry I, Hadou T, et al. Bacterial epidemiology and antimicrobial resistance in ascitic fluid: a 2-year retrospective study. *Scand J Infect Dis* 2009;37:2–8.
- Umgeleter A, Reindl W, Miedaner M, Schmid RM, Huber W. Failure of current antibiotic first-line regimens and mortality in hospitalized patients with spontaneous bacterial peritonitis. *Infection* 2009;37:2–8.
- Ariza X, Castellote J, Lora-Tamayo J, Girbau A, Salord S, Rota R, et al. Risk factors for resistance to ceftriaxone and its impact on mortality in community, healthcare and nosocomial spontaneous bacterial peritonitis. *J Hepatol* 2012;56:825–832.
- Tandon P, Delisle A, Topal JE, Garcia-Tsao G. High prevalence of antibiotic-resistant bacterial infections among patients with cirrhosis at a US liver center. *Clin Gastroenterol Hepatol* 2012;10:1291–1298.
- Acevedo J, Silva A, Prado V, Fernandez J. The new epidemiology of nosocomial bacterial infections in cirrhosis: therapeutic implications. *Hepatol Int* 2013;7:72–79.
- Piano S, Romano A, Rosi S, Gatta A, Angeli P. Spontaneous bacterial peritonitis due to carbapenemase-producing *Klebsiella pneumoniae*: the last therapeutic challenge. *Eur J Gastroenterol Hepatol* 2012;24:1234–1237.
- Campillo B, Richardet JP, Kheo T, Dupeyron C. Nosocomial spontaneous bacterial peritonitis and bacteremia in cirrhotic patients: impact of isolate type on prognosis and characteristics of infection. *CID* 2002;35:1–10.
- Bert F, Andreu M, Durand F, Degos F, Galdabart JO, Moreau R, et al. Nosocomial and community-acquired spontaneous bacterial peritonitis: comparative microbiology and therapeutic implications. *Eur J Clin Microbiol Infect Dis* 2003;22:10–15.
- Berg RD, Garlington AW. Translocation of certain indigenous bacteria from the gastrointestinal tract to the mesenteric lymph nodes and other organs in a gnotobiotic mouse model. *Infect Immun* 1979;23:403–411.
- Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. *Science* 2012;336:1268–1273.
- Littman DR, Pamer EG. Role of the commensal microbiota in normal and pathogenic host immune responses. *Cell Host Microbe* 2011;20:311–323.
- Bauer TM, Steinbrückner B, Brinkmann FE, Ditzel AK, Schwacha H, Aponte JJ, et al. Small intestinal bacterial overgrowth in patients with cirrhosis: prevalence and relation with spontaneous bacterial peritonitis. *Am J Gastroenterol* 2001;96:2962–2967.
- Morenos FC, Las Heras CG, Martín RL, López Arias MJ, Ledesma F, Pons RF. Small bowel bacterial overgrowth in patients with alcoholic cirrhosis. *Dig Dis Sci* 1995;40:1252–1256.
- Pande C, Kumar A, Sarin SK. Small-intestinal bacterial overgrowth in cirrhosis is related to the severity of liver disease. *Aliment Pharmacol Ther* 2009;29:1273–1281.
- Chang CS, Chen GH, Lien HC, Yeh HZ. Small intestine dysmotility and bacterial overgrowth in cirrhotic patients with spontaneous bacterial peritonitis. *Hepatology* 1998;28:1187–1190.
- Zhao G, Downes M, Yu RT, Shelton JM, Richardson JA, Repa JJ, et al. Regulation of antibacterial defense in the small intestine by the nuclear bile acid receptor. *Proc Natl Acad Sci U S A* 2006;103:3920–3925.
- Perez-Paramo M, Munoz J, Albillos A, Freile I, Portero F, Santos M, et al. Effect of propranolol on the factors promoting bacterial translocation in cirrhotic rats with ascites. *Hepatology* 2000;31:43–48.
- Shindo M, Ken A, Okuno T. Varying incidence of cirrhosis and hepatocellular carcinoma in patients with chronic hepatitis C responding differently to interferon therapy. *Cancer* 1999;85:1943–1950.
- Teltschik Z, Wiest R, Beisner J, Nuding S, Hofmann C, Schoelmerich J, et al. Intestinal bacterial translocation in rats with cirrhosis is related to compromised Paneth cell antimicrobial host defense. *Hepatology* 2012;55:1154–1163.
- Yan AW, Fouts DE, Brandl J, Starkel P, Torralba M, Schott E, et al. Enteric dysbiosis associated with a mouse model of alcoholic liver disease. *Hepatology* 2011;53:96–105.
- Lichtman SN, Sartor RB, Keku J, Schwab JH. Hepatic inflammation in rats with experimental small intestinal bacterial overgrowth. *Gastroenterology* 1990;98:414–423.
- Seki E, De Minicis S, Osterreicher CH, Kluwe J, Osawa Y, Brenner DA, et al. TLR4 enhances TGF-beta signaling and hepatic fibrosis. *Nat Med* 2007;13:1324–1332.
- Adachi Y, Bradford BU, Gao W, Bojes HK, Thurman RG. Inactivation of Kupffer cells prevents early alcohol-induced liver injury. *Hepatology* 1994;20:453–460.

Position Paper

- [40] Kalambokis GN, Tsianos EV. Rifaximin reduces endotoxemia and improves liver function and disease severity in patients with decompensated cirrhosis. *Hepatology* 2012;55:655–656.
- [41] Madrid AM, Hurtado C, Venegas M, Cumsille F, Defilippi C. Long-Term treatment with cisapride and antibiotics in liver cirrhosis: effect on small intestinal motility, bacterial overgrowth, and liver function. *Am J Gastroenterol* 2001;96:1251–1255.
- [42] Leber B, Spindelboeck W, Stadlbauer V. Infectious complications of acute and chronic liver disease. *Semin Respir Crit Care Med* 2012;33:80–95.
- [43] Bajaj JS, Hylemon PB, Ridlon JM, Heuman DM, Daita K, White MB, et al. Colonic mucosal microbiome differs from stool microbiome in cirrhosis and hepatic encephalopathy and is linked to cognition and inflammation. *Am J Physiol Gastrointest Liver Physiol* 2012;303:G675–G685.
- [44] Chen Y, Yang F, Lu H, Wang B, Chen Y, Lei D, et al. Characterization of fecal microbial communities in patients with liver cirrhosis. *Hepatology* 2011;54:562–572.
- [45] Vaishnava S, Yamamoto M, Severson KM, Ruhn KA, Yu X, Koren O, et al. The antibacterial lectin RegIIIgamma promotes the spatial segregation of microbiota and host in the intestine. *Science* 2011;334:255–258.
- [46] Mutlu EA, Gillevet PM, Rangwala H, Sikaroodi M, Naqui A, Engen PA, et al. Colonic microbiome is altered in alcoholism. *Am J Physiol Gastrointest Liver Physiol* 2012;302:G966–G978.
- [47] Du PJ, Vanheel H, Janssen CE, Roos L, Slavik T, Stivaktas PI, et al. Activated intestinal macrophages in patients with cirrhosis release NO and IL-6 that may disrupt intestinal barrier function. *J Hepatol* 2013;58:1125–1132.
- [48] Yoshimoto S, Loo TM, Atarashi K, Kanda H, Sato S, Oyadomari S, et al. Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. *Nature* 2013;499:97–101.
- [49] Assimakopoulos SF, Tsamandas AC, Tsiaoussis GI, Karatzas E, Triantos C, Vagianos CE, et al. Altered intestinal tight junctions' expression in patients with liver cirrhosis: a pathogenetic mechanism of intestinal hyperpermeability. *Eur J Clin Invest* 2012;42:439–446.
- [50] Assimakopoulos SF. Uncovering the molecular events associated with increased intestinal permeability in liver cirrhosis: the pivotal role of enterocyte tight junctions and future perspectives. *J Hepatol* 2013;59:1144–1146.
- [51] Genesca J, Marti R, Rojo F, Campos F, Peribanez V, Gonzalez A, et al. Increased tumour necrosis factor alpha production in mesenteric lymph nodes of cirrhotic patients with ascites. *Gut* 2003;52:1054–1059.
- [52] Munoz L, Albillos A, Nieto M, Reyes E, Lledo L, Monserrat J, et al. Mesenteric Th1 polarization and monocyte TNF-alpha production: first steps to systemic inflammation in rats with cirrhosis. *Hepatology* 2005;42:411–419.
- [53] Saitoh O, Sugi K, Lojima K, Matsumoto H, Nakagawa K, Kayazawa M, et al. Increased prevalence of intestinal inflammation in patients with liver cirrhosis. *World J Gastroenterol* 1999;5:391–396.
- [54] Lorenzo-Zuniga V, Bartoli R, Planas R, Hofmann AF, Vinado B, Hagey LR, et al. Oral bile acids reduce bacterial overgrowth, bacterial translocation, and endotoxemia in cirrhotic rats. *Hepatology* 2003;37:551–557.
- [55] Man SM, Kaakoush NO, Mitchell HM. The role of bacteria and pattern-recognition receptors in Crohn's disease. *Nat Rev Gastroenterol Hepatol* 2011;8:152–168.
- [56] Holler E, Rogler G, Herfarth H, Brenmoehl J, Wild PJ, Hahn J, et al. Both donor and recipient NOD2/CARD15 mutations associate with transplant-related mortality and GVHD following allogeneic stem cell transplantation. *Blood* 2004;104:889–894.
- [57] Brenmoehl J, Herfarth H, Gluck T, Audebert F, Barlage S, Schmitz G, et al. Genetic variants in the NOD2/CARD15 gene are associated with early mortality in sepsis patients. *Intensive Care Med* 2007;33:1541–1548.
- [58] Ben Ari Z, Avias O, Pappo O, Zilbermint V, Cheporko Y, Bachmetov L, et al. Reduced hepatic injury in Toll-like receptor 4-deficient mice following d-galactosamine/lipopolysaccharide-induced fulminant hepatic failure. *Cell Physiol Biochem* 2012;29:41–50.
- [59] Shah N, Montes de Oca M, Jover-Cobos M, Tanamoto K, Muroi M, Sugiyama K, et al. Role of toll-like receptor 4 in mediating multi-organ dysfunction in mice with acetaminophen induced acute liver failure. *Liver Transpl* 2013;19:751–761.
- [60] Appenrodt B, Grunhage F, Gentemann MG, Thyssen L, Sauerbruch T, Lammert F. Nucleotide-binding oligomerization domain containing 2 (NOD2) variants are genetic risk factors for death and spontaneous bacterial peritonitis in liver cirrhosis. *Hepatology* 2010;51:1327–1333.
- [61] Bruns T, Peter J, Reuken PA, Grabe DH, Schuldes SR, Brenmoehl J, et al. NOD2 gene variants are a risk factor for culture-positive spontaneous bacterial peritonitis and monomicrobial bacterascites in cirrhosis. *Liver Int* 2012;32:223–230.
- [62] Nischalke HD, Berger C, Aldenhoff K, Thyssen L, Gentemann M, Grunhage F, et al. Toll-like receptor (TLR) 2 promoter and intron 2 polymorphisms are associated with increased risk for spontaneous bacterial peritonitis in liver cirrhosis. *J Hepatol* 2011;55:1010–1016.
- [63] Soriano G, Sanchez E, Nieto J, Roman E, Vidal S, Oliva L, et al. Cytokine production in patients with cirrhosis and D299G and/or TLR4 polymorphisms. *J Hepatol* 2013;58(Suppl. 1):S247–S248.
- [64] Tritto G, Bechlis Z, Stadlbauer V, Davies N, Frances R, Shah N, et al. Evidence of neutrophil functional defect despite inflammation in stable cirrhosis. *J Hepatol* 2011;55:574–581.
- [65] Wasmuth HE, Kunz D, Yagmur E, Timmer-Stranghoner A, Vidacek D, Siewert E, et al. Patients with acute on chronic liver failure display "sepsis-like" immune paralysis. *J Hepatol* 2005;42:195–201.
- [66] Malik R, Mookerjee RP, Jalan R. Infection and inflammation in liver failure: two sides of the same coin. *J Hepatol* 2009;51:426–429.
- [67] Doi H, Iyer TK, Carpenter E, Li H, Chang KM, Vonderheide RH, et al. Dysfunctional B-cell activation in cirrhosis resulting from hepatitis C infection associated with disappearance of CD27-positive B-cell population. *Hepatology* 2012;55:709–719.
- [68] Tian Z, Chen Y, Gao B. Natural killer cells in liver disease. *Hepatology* 2013;57:1654–1662.
- [69] Lario M, Munoz L, Ubeda M, Borrero MJ, Martinez J, Monserrat J, et al. Defective thymopoiesis and poor peripheral homeostatic replenishment of T-helper cells cause T-cell lymphopenia in cirrhosis. *J Hepatol* 2013;59:723–730.
- [70] Laso FJ, Madruga JI, Giron JA, Lopez A, Ciudad J, San Miguel JF, et al. Decreased natural killer cytotoxic activity in chronic alcoholism is associated with alcohol liver disease but not active ethanol consumption. *Hepatology* 1997;25:1096–1100.
- [71] Gao B, Jeong WI, Tian Z. Liver: an organ with predominant innate immunity. *Hepatology* 2008;47:729–736.
- [72] Albillos A, Hera ADL, Reyes E, Monserrat J, Munoz L, Nieto M, et al. Tumour necrosis factor-alpha expression by activated monocytes and altered T-cell homeostasis in ascitic alcoholic cirrhosis: amelioration with norfloxacin. *J Hepatol* 2004;40:624–631.
- [73] Munoz L, Jose BM, Ubeda M, Lario M, Diaz D, Frances R, et al. Interaction between intestinal dendritic cells and bacteria translocated from the gut in rats with cirrhosis. *Hepatology* 2012;56:1861–1869.
- [74] Jalan R, Gines P, Olson J, Mookerjee R, Moreau R, Garcia-Tsao G, et al. Acute-on-chronic liver failure. *J Hepatol* 2012;57:1336–1348.
- [75] Plessier A, Denninger MH, Consigny Y, Pessione F, Francoz C, Durand F, et al. Coagulation disorders in patients with cirrhosis and severe sepsis. *Liver Int* 2003;23:440–448.
- [76] Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology* 2013;144:1426–1437.
- [77] Medzhitov R, Schneider DS, Soares MP. Disease tolerance as a defense strategy. *Science* 2012;335:936–941.
- [78] Byl B, Roucloux I, Crusiaux A, Dupont E, Devière J. Tumor necrosis factor alpha and interleukin 6 plasma levels in infected cirrhotic patients. *Gastroenterology* 1993;104:1492–1497.
- [79] Navasa M, Follo A, Filella X, Jiménez W, Francitorra A, Planas R, et al. Tumor necrosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis: relationship with the development of renal impairment and mortality. *Hepatology* 1998;27:1227–1232.
- [80] Devière J, Content J, Denys C, Vandenbussche P, Schandene L, Wybran J, et al. Excessive in vitro bacterial lipopolysaccharide-induced production of monokines in cirrhosis. *Hepatology* 1990;11:628–634.
- [81] Le Moine O, Marchant A, De Groote D, Azar C, Goldman M, Devière J. Role of defective monocyte interleukin-10 release in tumor necrosis factor-alpha overproduction in alcoholics cirrhosis. *Hepatology* 1995;22:1436–1439.
- [82] Tazi KA, Quioc JJ, Saada V, Bezeaud A, Lebrec D, Moreau R. Upregulation of TNF-alpha production signaling pathways in monocytes from patients with advanced cirrhosis: possible role of Akt and IRAK-M. *J Hepatol* 2006;45:280–289.
- [83] Thabut D, Massard J, Gangloff A, Carbonell N, Francoz C, Nguyen-Khac E, et al. Model for end-stage liver disease score and systemic inflammatory response are major prognostic factors in patients with cirrhosis and acute functional renal failure. *Hepatology* 2007;46:1872–1882.
- [84] Tazi KA, Quioc JJ, Abdel-Razek W, Tellier Z, Guichard C, Ogier-Denis E, et al. Protein array technology to investigate cytokine production by monocytes from patients with advanced alcoholic cirrhosis: an ex vivo pilot study. *Hepatol Res* 2009;39:706–715.
- [85] Galbois A, Thabut D, Tazi KA, Rudler M, Mohammadi MS, Bonnefont-Rousselot D, et al. Ex vivo effects of high-density lipoprotein exposure on

- the lipopolysaccharide-induced inflammatory response in patients with severe cirrhosis. *Hepatology* 2009;49:175–184.
- [86] Coant N, Simon-Rudler M, Gustot T, Fasseu M, Gandoura S, Ragot K, et al. Glycogen synthase kinase 3 involvement in the excessive proinflammatory response to LPS in patients with decompensated cirrhosis. *J Hepatol* 2011;55:784–793.
 - [87] Gandoura S, Weiss E, Rautou PE, Fasseu M, Gustot T, Lemoine F, et al. Gene- and exon-expression profiling reveals an extensive LPS-induced response in immune cells in patients with cirrhosis. *J Hepatol* 2013;58(5):936–948.
 - [88] Moreau R, Barrière E, Tazi KA, Lardeux B, Dargère D, Urbanowicz W, et al. Terlipressin inhibits in vivo aortic iNOS expression induced by lipopolysaccharide in rats with biliary cirrhosis. *Hepatology* 2002;36:1070–1078.
 - [89] Tazi KA, Bièche I, Paradis V, Guichard C, Laurendeau I, Dargère D, et al. In vivo altered unfolded protein response and apoptosis in livers from lipopolysaccharide-challenged cirrhotic rats. *J Hepatol* 2007;46:1075–1088.
 - [90] Thabut D, Tazi KA, Bonnefont-Rousselot D, Aller M, Farges O, Guimont MC, et al. HDL administration attenuates liver proinflammatory response, restores liver eNOS activity and lowers portal pressure in cirrhotic rats. *Hepatology* 2007;46:1893–1906.
 - [91] Ramírez MJ, Ibáñez A, Navasa M, Casals E, Morales-Ruiz M, Jiménez W, et al. High-density lipoproteins reduce the effect of endotoxin on cytokine production and systemic hemodynamics in cirrhotic rats with ascites. *J Hepatol* 2004;40:424–430.
 - [92] Terra C, Guevara M, Torre A, Gilibert R, Fernández J, Martín-Llahí M, et al. Renal failure in patients with cirrhosis and sepsis unrelated to spontaneous bacterial peritonitis: value of MELD score. *Gastroenterology* 2005;129:1944–1953.
 - [93] Sort P, Navasa M, Arroyo V, Aldegue X, Planas R, Ruiz-del-Arbol L, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999;341:403–409.
 - [94] Trawalé JM, Paradis V, Rautou PE, Francoz C, Escolano S, Sallée M, et al. The spectrum of renal lesions in patients with cirrhosis: a clinicopathological study. *Liver Int* 2010;30:725–732.
 - [95] Merli M, Lucidi C, Pentassuglio I, Giannelli V, Giusto M, Di Gregorio V, et al. Increased risk of cognitive impairment in cirrhotic patients with bacterial infections. *J Hepatol* 2013;59(2):243–250.
 - [96] Chavarria L, Oria M, Romero-Giménez J, Alonso J, Lope-Piedrafita S, Córdoba J. Brain magnetic resonance in experimental acute-on-chronic liver failure. *Liver Int* 2013;33:294–300.
 - [97] Bernard B, Grangé JD, Khac EN, Amiôt X, Opolon P, Poynard T. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. *Hepatology* 1999;29:1655–1661.
 - [98] Goulis J, Patch D, Burroughs AK. Bacterial infection in the pathogenesis of variceal bleeding. *Lancet* 1999;353:139–142.
 - [99] Fede G, Spadaro L, Tomaselli T, Privitera G, Germani G, Tsochatzis E, et al. Adrenocortical dysfunction in liver disease: a systematic review. *Hepatology* 2012;55:1282–1291.
 - [100] Tsai MH, Peng YS, Chen YC, Liu NJ, Ho YP, Fang JT, et al. Adrenal insufficiency in patients with cirrhosis, severe sepsis and septic shock. *Hepatology* 2006;43:673–681.
 - [101] Thevenot T, Borot S, Remy-Martin A, Sapin R, Cervoni JP, Richou C, et al. Assessment of adrenal function in cirrhotic patients using concentration of serum-free and salivary cortisol. *Liver Int* 2011;31:425.
 - [102] Thevenot T, Dorin R, Monnet E, Qualls CR, Sapin R, Grandclement E, et al. High serum levels of free cortisol indicate severity of cirrhosis in hemodynamically stable patients. *J Gastroenterol Hepatol* 2012;27:1596–1601.
 - [103] Acevedo J, Fernández J, Prado V, Silva A, Castro M, Pavesi M, et al. Relative adrenal insufficiency in decompensated cirrhosis: relationship to short-term risk of severe sepsis, hepatorenal syndrome, and death. *Hepatology* 2013;58:1757–1765.
 - [104] Bhattacharya S. Early diagnosis of resistant pathogens: how can it improve antimicrobial treatment? *Virulence* 2013;4:172–184.
 - [105] Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. ACCP/SCCM Consensus Conference Committee Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. 1992. *Chest* 2009;136:864–874.
 - [106] Cazzaniga M, Dionigi E, Gobbo G, Fioretti A, Monti V, Salerno F. The systemic inflammatory response syndrome in cirrhotic patients: relationship with their in-hospital outcome. *J Hepatol* 2009;51:475–482.
 - [107] Kim BI, Kim HJ, Park JH, Park DI, Cho YK, Sohn CI, et al. Increased intestinal permeability as a predictor of bacterial infections in patients with decompensated liver cirrhosis and hemorrhage. *J Gastroenterol Hepatol* 2011;26:550–557.
 - [108] Cervoni JP, Thévenot T, Weil D, Muel M, Barbot O, Sheppard F, et al. C-reactive protein predicts short-term mortality in patients with cirrhosis. *J Hepatol* 2012;56:1299–1304.
 - [109] Gundling F, Schmittler F, Hapfelmeier A, Schulte B, Schmidt T, Pehl C, et al. Fecal calprotectin is a useful screening parameter for hepatic encephalopathy and spontaneous bacterial peritonitis in cirrhosis. *Liver Int* 2011;31:1406–1415.
 - [110] Pelletier G, Brivet M, Ducreux M, Briantais MJ, Lemonnier A, Etienne JP. Is D-lactate assay useful for the diagnosis of ascitic infection in patients with liver cirrhosis? *Gastroenterol Clin Biol* 1993;17:304–305.
 - [111] Tas A, Akbal E, Beyazit Y, Kocak E. Serum lactate level predict mortality in elderly patients with cirrhosis. *Wien Klin Wochenschr* 2012;124:520–525.
 - [112] Zapater P, Frances R, Gonzalez-Navajas JM, Moreu R, Llanos L, Pascual D, et al. Presence of bacterial DNA is a new survival indicator in patients with cirrhosis and non-infected ascitic fluid. *Hepatology* 2007;46:A40.
 - [113] Appenrodt B, Lehmann LE, Thyssen L, Gentemann M, Rabe C, Molitor E, et al. Is detection of bacterial DNA in ascitic fluid of clinical relevance? *Eur J Gastroenterol Hepatol* 2010;22:1487–1494.
 - [114] Mookerjee RP, Stadlbauer V, Lidder S, Wright GA, Hodges SJ, Davies NA, et al. Neutrophil dysfunction in alcoholic hepatitis superimposed on cirrhosis is reversible and predicts the outcome. *Hepatology* 2007;46:831–840, [Erratum in: *Hepatology*. 2007; 46: 205].
 - [115] Berres ML, Schnyder B, Yagmur E, Inglis B, Stanzel S, Tischendorf JJ, et al. Longitudinal monocyte human leukocyte antigen-DR expression is a prognostic marker in critically ill patients with decompensated liver cirrhosis. *Liver Int* 2009;29:536–543.
 - [116] Lin CY, Tsai IF, Ho YP, Huang CT, Lin YC, Lin CJ, et al. Endotoxemia contributes to the immune paralysis in patients with cirrhosis. *J Hepatol* 2007;46:816–826.
 - [117] Holdstock G, Leslie B, Hill S, Tanner A, Wright R. Monocyte function in cirrhosis. *J Clin Pathol* 1982;35:972–979.
 - [118] Gomez F, Ruiz P, Schreiber AD. Impaired function of macrophage Fc gamma receptors and bacterial infection in alcoholic cirrhosis. *N Engl J Med* 1994;331:1122–1128.
 - [119] Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 1999;340:448–454.
 - [120] Peres Bota D, Van Nuffelen M, Zakaria AN, Vincent JL. Serum levels of C-reactive protein and procalcitonin in critically ill patients with cirrhosis of the liver. *J Lab Clin Med* 2005;146:347–351.
 - [121] Park WB, Lee KD, Lee CS, Jang HC, Kim HB, Lee HS, et al. Production of C-reactive protein in Escherichia coli-infected patients with liver dysfunction due to liver cirrhosis. *Diagn Microbiol Infect Dis* 2005;51:227–230.
 - [122] Tsiakalos A, Karatzafis A, Ziakas P, Hatzis G. Acute-phase proteins as indicators of bacterial infection in patients with cirrhosis. *Liver Int* 2009;29:1538–1542.
 - [123] Papp M, Vitalis Z, Altörjay I, Tornai I, Udvardy M, Harsfalvi J, et al. Acute phase proteins in the diagnosis and prediction of cirrhosis associated bacterial infections. *Liver Int* 2012;32:603–611.
 - [124] Li CH, Yang RB, Pang JH, Chang SS, Lin CC, Chen CH, et al. Procalcitonin as a biomarker for bacterial infections in patients with liver cirrhosis in the emergency department. *Acad Emerg Med* 2011;18:121–126.
 - [125] Wacker C, Prkno A, Brunkhorst FM, Schlattmann P. Procalcitonin as a diagnostic marker for sepsis: a systematic review and meta-analysis. *Lancet Infect Dis* 2013;13:426–435.
 - [126] Schuetz P, Albrich W, Mueller B. Procalcitonin for diagnosis of infection and guide to antibiotic decisions: past, present and future. *BMC Med* 2011;22:107.
 - [127] Albillos A, de-la-Hera A, Alvarez-Mon M. Serum lipopolysaccharide-binding protein prediction of severe bacterial infection in cirrhotic patients with ascites. *Lancet* 2004;363:1608–1610.
 - [128] Reuken PA, Kiehntopf M, Stallmach A, Bruns T. Mid-regional pro-adrenomedullin (MR-proADM): an even better prognostic biomarker than C-reactive protein to predict short-term survival in patients with decompensated cirrhosis at risk of infection? *J Hepatol* 2012;57:1156–1158.
 - [129] Sontakke S, Cadenas MB, Maggi RG, Diniz PP, Breitschwerdt EB. Use of broad range 16S rDNA PCR in clinical microbiology. *J Microbiol Methods* 2009;76:217–225.
 - [130] Rampini SK, Bloembergen GV, Keller PM, Büchler AC, Dollenmaier G, Speck RF, et al. Broad-range 16S rRNA gene polymerase chain reaction for diagnosis of culture-negative bacterial infections. *Clin Infect Dis* 2011;53:1245–1251.

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- [131] Hardick J, Won H, Jeng K, Hsieh YH, Gaydos CA, Rothman RE, et al. Identification of bacterial pathogens in ascitic fluids from patients with suspected spontaneous bacterial peritonitis by use of broad-range PCR [16S PCR] coupled with high-resolution melt analysis. *J Clin Microbiol* 2012;50:2428–2432.
- [132] Pasqualini L, Mencacci A, Leli C, Montagna P, Cardaccia A, Cenci E, et al. Diagnostic performance of a multiple real-time PCR assay in patients with suspected sepsis hospitalized in an internal medicine ward. *J Clin Microbiol* 2012;50:1285–1288.
- [133] Espinal P, Seifert H, Dijkshoorn L, Vila J, Roca I. Rapid and accurate identification of genomic species from the *Acinetobacter baumannii* [Ab] group by MALDI-TOF MS. *Clin Microbiol Infect* 2012;18:1097–1103.
- [134] Arabi YM, Dara SI, Memish Z, Abdulmajeed AA, Tamim HM, Al-Shirawi N, et al. Antimicrobial therapeutic determinants of outcomes from septic shock among patients with cirrhosis. *Hepatology* 2012;56:2305–2315.
- [135] Ginès P, Angeli P, Lenz K, Möller S, Moore K, Moreau R, et al. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol* 2010;53:397–417.
- [136] Runyon BA. AASLD Practice Guidelines Committee. Management of adult patients with ascites due to cirrhosis: update 2012. *Hepatology* 2013;57:1651–1653, [<http://www.aasld.org/practiceguidelines/Documents/ascitesupdate2013.pdf>].
- [137] Fernandez J, Arroyo V. Bacterial infections in cirrhosis – a growing problem with significant implications. *Clin Liver Dis* 2013;2:102–105.
- [138] Rimola A, Garcia-Tsao G, Navasa M, Piddock LJ, Planas R, Bernard B, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International ascites club. *J Hepatol* 2000;32:142–153.
- [139] Runyon BA, McHutchison JG, Antillon MR, Akriviadis EA, Montano AA. Short-course vs. long-course antibiotic treatment of spontaneous bacterial peritonitis. A randomized controlled study of 100 patients. *Gastroenterology* 1991;100:1737–1742.
- [140] Garcia-Martinez R, Caraceni P, Bernardi M, Gines P, Arroyo V, Jalan R. Albumin: pathophysiologic basis of its role in the treatment of cirrhosis and its complications. *Hepatology* 2013;58(5):1836–1846.
- [141] Casas M, Soriano G, Ayala E, Guarner-Argente C, Ordas I, Merce J, et al. Intravenous albumin is not necessary in cirrhotic patients with spontaneous bacterial peritonitis and low-risk mortality. *J Hepatol* 2007;76:S91.
- [142] Fernandez J, Monteagudo J, Bargallo X, Jimenez W, Bosch J, Arroyo V, et al. A randomized unblinded pilot study comparing albumin vs. hydroxyethyl starch in spontaneous bacterial peritonitis. *Hepatology* 2005;42:627–634.
- [143] Guevara M, Terra C, Nazar A, Sola E, Fernandez J, Pavesi M, et al. Albumin for bacterial infections other than spontaneous bacterial peritonitis in cirrhosis. A randomized, controlled study. *J Hepatol* 2012;57:759–765.
- [144] Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580–637.
- [145] Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med* 2008;36:1937–1949.
- [146] Fernández J, Escorsell A, Zabalza M, Felipe V, Navasa M, Mas A, et al. Adrenal insufficiency in patients with cirrhosis and septic shock: effect of treatment with hydrocortisone on survival. *Hepatology* 2006;44:1288–1295.
- [147] Arabi YM, Aljumah A, Dabbagh O, Tamim HM, Rishu AH, Al-Abdulkareem A, et al. Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. *CMAJ* 2010;182:1971–1977.
- [148] Soriano G, Guarner C, Tomás A, Villanueva C, Torras X, González D, et al. Norfloxacin prevents bacterial infection in cirrhotics with gastrointestinal haemorrhage. *Gastroenterology* 1992;103:1267–1272.
- [149] Guarner C, Sola R, Soriano G, Novella MT, Vila MC, Sàbat M, et al. Risk of a first community-acquired spontaneous bacterial peritonitis in cirrhotics with low ascitic protein levels. *Gastroenterology* 1999;117:414–419.
- [150] Blaise M, Pateron D, Trinchet JC, Levacher S, Beaugrand M, Pourriat JL. Systemic antibiotic therapy prevents bacterial infection in cirrhotic patients with gastrointestinal haemorrhage. *Hepatology* 1994;20:34–38.
- [151] Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila FI, Soares-Weiser K, Uribe M. Antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding. *Cochrane Database Syst Rev* 2010;9:CD002907.
- [152] Fernandez J, Ruiz del Arbol L, Gomez C, Durandez R, Serradilla R, Guarner C, et al. Norfloxacin vs. ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. *Gastroenterology* 2006;131:1049–1056.
- [153] de Franchis R, Baveno V faculty. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *J Hepatol* 2010;53:762–768.
- [154] Fernandez J, Navasa N, Planas R, Montoliu S, Monfort D, Soriano G, et al. Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. *Gastroenterology* 2007;133:818–824.
- [155] Ginès P, Rimola A, Planas R, Vargas V, Marco F, Almela M, et al. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. *Hepatology* 1990;12:716–724.
- [156] Koo HL, Dupont HL. Rifaximin: a unique gastrointestinal-selective antibiotic for enteric diseases. *Curr Opin Gastroenterol* 2010;26:17–25.
- [157] Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med* 2010;362:1071–1081.
- [158] Hanouneh MA, Hanouneh IA, Hashash JG, Law R, Esfeh JM, Lopez R, et al. The role of rifaximin in the primary prophylaxis of spontaneous bacterial peritonitis in patients with liver cirrhosis. *J Clin Gastroenterol* 2012;46:709–715.
- [159] Reiberger T, Ferlitsch A, Payer BA, Mandorfer M, Heinisch BB, Hayden H, et al. Non-selective betablocker therapy decreases intestinal permeability and serum levels of LBP and IL-6 in patients with cirrhosis. *J Hepatol* 2013;58(5):911–921.
- [160] Chiva M, Soriano G, Rochat I, Peralta C, Rochat F, Llovet T, et al. Effect of *Lactobacillus johnsonii* La1 and antioxidants on intestinal flora and bacterial translocation in rats with experimental cirrhosis. *J Hepatol* 2002;37:456.
- [161] Pardo A, Bartoli R, Lorenzo-Zuniga V, Planas R, Vinado B, Riba J, et al. Effect of cisapride on intestinal bacterial overgrowth and bacterial translocation in cirrhosis. *Hepatology* 2000;31:858–863.
- [162] Bauer TM, Fernández J, Navasa M, Vila J, Rodés J. Failure of *Lactobacillus* spp. to prevent bacterial translocation in a rat model of experimental cirrhosis. *J Hepatol* 2002;36:501–506.