

Management of bacterial infections in cirrhosis

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Summary

Bacterial infections are very frequent in advanced cirrhosis and become the first cause of death of these patients. Despite numerous experimental data and significant advances in the understanding of the pathogenesis of sepsis in cirrhosis, the outcome remains poor. Classical diagnostic parameters such as C-reactive protein and SIRS criteria have less diagnostic capacity in the cirrhotic population, often delaying the diagnosis and the management of bacterial infection. Prompt and appropriate empirical antibiotic treatment of infection and early resuscitation of patients with severe sepsis or septic shock are essential in determining patient's outcome. A strategy of careful restriction of prophylactic antibiotics to the high-risk populations could reduce the spread of multidrug resistant bacteria. This review is focused on the currently recommended diagnostic, therapeutic and prophylactic strategies for bacterial infections in the cirrhotic population.

General considerations

Bacterial infection is present at admission or develops during hospitalization in about 30% of patients with cirrhosis[1]. A large proportion of these patients have ascites. Sixty percent of bacterial infections are community-acquired and 40% nosocomial. Nearly half of the infections acquired in the community are health care-related[2]. Spontaneous bacterial peritonitis (SBP) and urinary infections are the most frequent infections followed by pneumonia and cellulitis. Clinical risk factors associated with occurrence of bacterial infections in cirrhosis are high Child–Pugh score, variceal bleeding, low ascitic protein levels and prior episode of SBP[3–6].

Infection induces a systemic host response with three stages of severity called sepsis, severe sepsis (when an acute organ failure occurs), and septic shock (when hypotension does not respond to adequate fluid resuscitation). Patients with cirrhosis have increased risk to develop bacterial infection, sepsis, sepsis-induced organ failure and death[7]. The mortality of infected patients with cirrhosis reaches 38%[8]. Cirrhotic patients are 2 times more likely to die from sepsis than individuals without

cirrhosis[9]. Hospital mortality of cirrhotic patients with septic shock may exceed 70%[10].

Pathogenesis of sepsis in cirrhosis

Cirrhotic patients have an altered defense against bacteria associated with a reduced bacterial clearance. Impairment of macrophage Fcγ-receptor-mediated clearance of antibody-coated bacteria, deficiencies in the complement system, down-regulation of monocyte HLA-DR expression, depressed neutrophil phagocytic and intracellular killing contribute to this altered defense[11,12]. This immune defect facilitates bacterial translocation induced by increased intestinal permeability and gut bacterial overgrowth observed in cirrhosis[13]. Genetic immune defects could contribute to the high risk of bacterial infections in cirrhosis, particularly SBP. Cirrhotic patients carrying NOD2 (nucleotide-binding oligomerization domain containing 2) variants associated with impairment of recognition of bacterial product muramyl dipeptide have a higher risk of SBP and a reduced survival time[14]. Mannose-binding lectin deficiency, inducing a defect in opsonophagocytosis of bacteria, confers a higher risk of bacterial infections in patients with cirrhosis[15]. Toll-like receptor (TLR)2 polymorphisms are also associated with an increased susceptibility towards SBP[16].

Beside this immunodeficient state, in the early phase of bacterial sepsis, circulating levels of the pro-inflammatory cytokines tumor necrosis factor (TNF)-α and interleukin (IL)-6 are significantly higher in infected patients with cirrhosis than in those without[17]. This excessive pro-inflammatory response is recapitulated *ex vivo* with the stimulation of isolated peripheral blood mononuclear cells (PBMCs) or monocytes from patients with cirrhosis by lipopolysaccharides (LPS), part of external membrane of Gram-negative bacteria[18]. This hyper-response is at least in part explained by deficiency of negative feedbacks in TLR4 pathway (resumed in Fig. 1). This bacteria-induced 'cytokine storm' contributes to sepsis-related organ failures. Indeed, there is a relationship between high plasma and ascitic levels of TNF-α and IL-6 and occurrence of renal dysfunction in SBP[19]. Moreover, enhanced neutrophil-induced oxidative stress and elastase production observed in cirrhosis could participate to sepsis-related organ damages[20].

Today, organ support strategies are often capable to overcome the consequences of this 'cytokine storm'. Then, this pro-inflammatory phase is followed by a prolonged 'immunoparalysis', called compensatory anti-inflammatory response syn-

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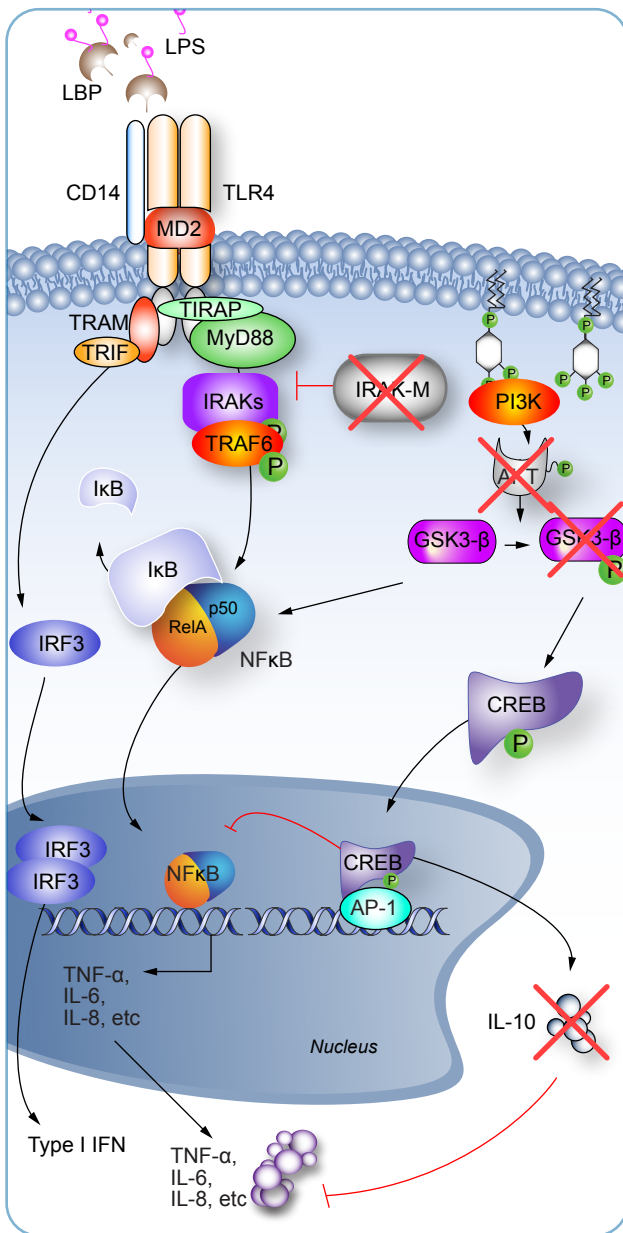


Fig. 1. Deficiency of negative feedbacks in TLR4 pathway in cirrhotic monocytes. LPS-stimulated monocytes from patients with cirrhosis disclose a lack of interleukin-1 receptor-associated kinase (IRAK)-M induction, decrease of Akt activity, defect of glycogen synthase kinase (GSK)3 phosphorylation, and reduced expression of IL-10, contributing to the loss of counter-regulatory mechanisms of TLR4 pathway and the hyper-production of TNF- α [122–124].

drome (CARS), responsible for repeated secondary nosocomial infections and death[21]. Progressive decrease of HLA-DR on monocytes during hospitalization increases the risk of sepsis-related mortality[22].

Diagnosis of bacterial infections

Early diagnosis and treatment of infection is pivotal in the management of patients with decompensated cirrhosis. Diagnosis is nowadays based on clinical and analytical grounds.

Physical Examination

- Vital signs: body temperature (fever/hypothermia), respiratory and heart rates, mean arterial pressure
- Look for abnormal findings at examination:
 - Abdominal pain, tenderness, Blumberg sign, ileus (SBP or secondary peritonitis)
 - Respiratory signs (pneumonia/spontaneous empyema)
 - Skin inflammation (cellulitis)

Assess the Source of Infection

- Blood leukocyte cell count and culture
- Source of infection:
 - Chest X-ray
 - Ascitic/pleural fluid cell count and cultures
 - Urine sediment and culture
 - Gram staining of sputum and culture
 - Consider abdominal ultrasonography*

SIRS criteria?

When 2 or more of the following criteria are present:

- Body temperature $\geq 38^\circ\text{C}$ or $\leq 36^\circ\text{C}$
- Heart rate ≥ 90 bpm
- Respiratory rate ≥ 20 /min or arterial hypocapnia (≤ 32 mmHg)
- Blood leukocyte count $\geq 12,000$ or $\leq 4000/\text{mm}^3$ or immature neutrophils $>10\%$

Evaluate possible organ failures

- Cardiovascular system: lactate levels if severe sepsis
- Kidney: serum creatinine, electrolytes, venous blood gases
- Liver: ascites, encephalopathy, serum bilirubin
- Brain: mental status
- Coagulation: bleeding, INR, fibrinogen, platelet count
- Metabolism: serum glucose levels

Fig. 2. Suggested work-up in the diagnosis of bacterial infections in cirrhosis. Initial work-up should include a detailed physical examination and different diagnostic tests with the aim of establishing the source of the infection. *Abdominal ultrasonography should be performed in patients with severe sepsis of unknown origin and to guide paracentesis in patients with small amounts of ascitic fluid. Assessment of the severity of infection relies on the evaluation of systemic inflammatory response syndrome (SIRS) criteria and of different organ failures.

However, it must be underlined that some infected patients can be asymptomatic at initial stages[23,24]. Therefore, a complete work-up, including a diagnostic paracentesis and ascitic fluid culture, urinary sediment and culture, and chest X-ray, should be carried out at admission and whenever a hospitalized patient clinically deteriorates in order to detect and treat a possible infection (Fig. 2). This evaluation must include an electrocardiogram. Prolonged QT interval is frequently observed in patients with advanced cirrhosis, especially if treated with quinolones. This abnormality markedly increases the risk of arrhythmias[25].

Limitations of common clinical and analytical markers of infection

Infection is easier to diagnose in the presence of sepsis, the first stage of severity of the inflammatory host response to infection. Two or more of the following criteria are required to diagnose the presence of systemic inflammatory response syndrome (SIRS): 1) a core temperature $\geq 38^{\circ}\text{C}$ or $\leq 36^{\circ}\text{C}$; 2) a heart rate ≥ 90 beats/min; 3) tachypnea ≥ 20 breaths/min or partial carbon monoxide pressure (PaCO_2) ≤ 32 mmHg or the need of mechanical ventilation and 4) a white blood cell count $\geq 12 \times 10^9/\text{L}$ or $\leq 4 \times 10^9/\text{L}$ or $>10\%$ of immature neutrophils [26]. These sepsis criteria were defined in the general population but are more difficult to use and have less diagnostic accuracy in cirrhosis [27,28]. In these patients, hyperdynamic circulation leads to tachycardia in the absence of infection, patients receiving beta-blockers have a reduced heart rate, hepatic encephalopathy courses with tachypnea, and hypersplenism decreases white blood cell count. All these factors decrease the value of SIRS criteria for the detection of sepsis in cirrhosis. In fact, SIRS is present in 10–30% of decompensated cirrhotic patients without infection and in 57–70% of infected patients, which suggests that SIRS is not the best marker of infection in the cirrhotic population. The presence of SIRS at admission or during hospitalization in infected and non-infected cirrhotic patients constitutes, however, a useful prognostic parameter since it is associated with a higher probability of portal hypertension-related complications and death [27,28].

Conflicting results exist regarding threshold values and diagnostic accuracy of C-reactive protein (CRP) and procalcitonin (PCT) in patients with cirrhosis. These two acute-phase serum proteins are commonly used as early markers of infection in the non-cirrhotic population [29]. While CRP is produced predominantly by hepatocytes [30], in septic patients PCT is produced ubiquitously by thyroidal and extra-thyroidal tissues including the liver [31,32]. Patients with liver failure could present an attenuated production of acute-phase proteins, especially CRP, in response to infection. Although several studies have demonstrated that the more severe the underlying liver failure the lower the CRP levels [30,33], the diagnostic accuracy of CRP to diagnose infection seems to be still good in cirrhosis with AUC ranging from 0.64 to 0.91 [33–37]. In that sense, low CRP concentrations should be interpreted with caution in Child–Pugh C patients. The diagnostic capacity of PCT seems to be also good in the cirrhotic population (AUC: 0.68–0.89), with some studies showing a superiority of PCT over CRP and others showing similar results [32,34–36,38–40]. The cut-off value proposed for PCT in cirrhosis is identical to that used in the general population, 0.5 ng/ml [32,39]. The usefulness of CRP and PCT to guide antibiotic therapy in the cirrhotic population should be further investigated.

Diagnosis of spontaneous bacterial peritonitis

SBP is defined as the infection of a previously sterile ascitic fluid without any apparent intra-abdominal source of infection. In approximately 40–60% of the cases the organism responsible for SBP is isolated in ascitic fluid or blood cultures [1,23,24]. Abdominal pain and fever are the most characteristic symptoms, followed by vomiting, ileus, diarrhea, hepatic encephalopathy, gastrointestinal bleeding, and renal impairment. The diagnosis of SBP is based on ascitic fluid analysis obtained by paracentesis. An ascitic fluid polymorphonuclear (PMN) count ≥ 250 cells/mm³

is considered diagnostic of SBP and constitutes an indication to initiate an empirical antibiotic treatment immediately [23,41,42]. In patients with hemorrhagic ascites a subtraction of one PMN per 250 red blood cells should be made [23]. Leukocyte reagent strips have been proposed as a rapid screening test for the diagnosis of SBP at the patient's bedside [43–46]. However, its variable sensitivity, between 45% and 100%, makes this method suboptimal for the diagnosis of SBP. The determination in ascitic fluid of lactoferrin, an iron-binding protein contained in PMNs that is released on degranulation, is another theoretical alternative to ascitic fluid cell count in the diagnosis of SBP. Ascitic lactoferrin concentrations ≥ 242 ng/ml have a sensitivity of 96% and a specificity of 97% for the diagnosis of SBP [47]. Future studies are clearly needed to evaluate qualitative assays capable to determine lactoferrin levels at the patient's bedside.

Secondary peritonitis constitutes the main differential diagnosis of SBP. Although it is infrequent, accounting for 5–10% of all peritonitis in patients with cirrhosis and ascites, its mortality is much higher than that of SBP (66% vs. 10%) [48]. The measurement of glucose levels and of lactic dehydrogenase (LDH) and total protein concentrations in ascitic fluid is important to distinguish between these two entities. A secondary peritonitis is very likely when at least two of the following parameters are present in ascites: glucose levels <50 mg/dl, protein concentration >10 g/L, LDH concentration $>$ normal serum levels (Runyon's criteria) [23,41,42,48]. These criteria have a sensitivity of 67% and a specificity of 90% for the diagnosis of a secondary peritonitis. Patients with gut perforation also present with high levels of amylase and bilirubin in ascitic fluid. Gram's stain of a smear of sediment obtained after centrifugation of ascitic fluid is also helpful in the diagnosis of secondary peritonitis. It is frequently negative in SBP, as the concentration of bacteria is low, but usually shows different types of bacteria in patients with a gut perforation (polymicrobial infection) [23]. Prompt abdominal CT and early indication of surgery are also key in the management of patients with secondary peritonitis [41,42,48].

Diagnosis of infections other than spontaneous bacterial peritonitis

Diagnostic criteria of other spontaneous infections in cirrhosis are the following: spontaneous empyema: a PMN cell count in pleural fluid $\geq 250/\text{mm}^3$ in the absence of pneumonia; spontaneous bacteremia: positive blood cultures with no apparent cause of bacteremia [1]. The diagnosis of other frequent bacterial infections such as urinary infections, pneumonia, cellulitis, and secondary bacteremia (bacteremia associated with invasive procedures and catheter sepsis) is made according to conventional criteria.

Treatment of bacterial infections

Patients with cirrhosis and severe infections should receive IV antibiotics immediately after diagnosis. This recommendation is based on data coming from the general population showing that any delay in the initiation of appropriate antibiotics in patients with severe sepsis is associated with an increase in mortality [49–51]. Empirical treatment should cover all potential organisms responsible for infection without causing adverse effects. During many years, third-generation cephalosporins have been considered the gold-standard empirical antibiotic treatment of many of the infections occurring in cirrhosis since

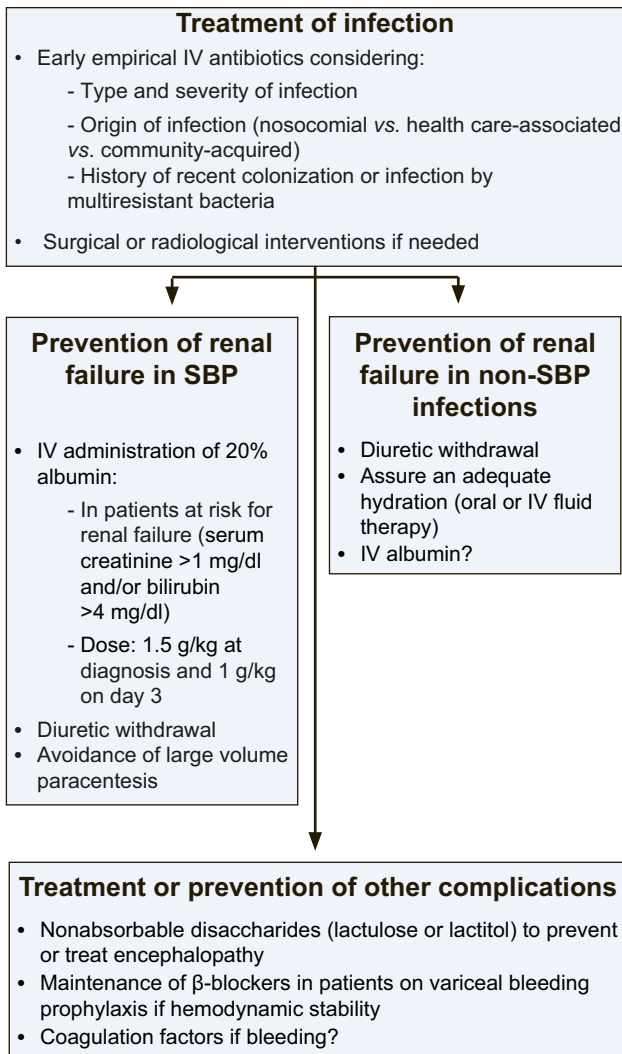


Fig. 3. Integrated treatment of bacterial infections in cirrhotic patients. Recommended strategy is based on the early administration of appropriate broad-spectrum antibiotics considering not only the type of infection but also epidemiological factors such as the site of acquisition of the infection and previous history of multiresistant infection. Prevention and treatment of renal failure and other complications of cirrhosis is also essential in the management of these patients.

they are active against Enterobacteriaceae and non-enterococcal streptococci and are well tolerated [23,41,42]. However, recent studies show an increasing prevalence of infections caused by multiresistant bacteria, especially in nosocomial episodes [52–56]. Patients with community-acquired infections but recent hospitalization or contact with the health care system (day hospital, day surgery, dialysis, intravenous therapy ...) also show a high rate of antibiotic resistance. Prognosis of these infections seems to be similar to that of nosocomial origin [2,57]. Empirical antibiotic therapy should therefore be selected according not only to the type and severity of infection, but also to the presence or absence of epidemiological risk factors for the development of bacteria resistant to β -lactams, especially the site of acquisition of the infection. Measures aimed at preventing other complications frequently triggered by infection such as renal failure are also essential in the management of infected patients with advanced

cirrhosis (Fig. 3) [23,41,42]. In that sense, aminoglycosides should not be used in cirrhosis, even if effective, because of the high risk of renal failure [58].

Empirical antibiotic treatment of community-acquired infections

Third-generation cephalosporins are the recommended empirical treatment of community-acquired SBP. Regrettably, this recommendation is often based on the results of unpowered trials [23,41,42]. Amoxicillin–clavulanic acid or ciprofloxacin show similar results and cost (Tables 1 and 2) [59–61]. The use of oral highly bioavailable quinolones (ofloxacin) has been suggested in patients with uncomplicated SBP (absence of all of the following: ileus, gastrointestinal bleeding, septic shock, grade 2–4 hepatic encephalopathy or serum creatinine >3 mg/dl) [62]. However, quinolones are not recommended in patients submitted to long-term norfloxacin prophylaxis or in geographical areas with a high prevalence of quinolone-resistant bacteria [42]. Third-generation cephalosporins are also the first option in the treatment of spontaneous bacteremia and empyema. The duration of antibiotic treatment for all these spontaneous infections ranges between a minimum of 5 days and 8 days, the median time for SBP resolution in clinical trials. The response to treatment in patients with SBP should be assessed by at least one follow-up paracentesis after 2 days of antibiotic therapy. A reduction in the ascitic fluid PMN count $<25\%$ with respect to pre-treatment values is arbitrarily considered as suggestive of treatment failure [23,41,42].

Empirical treatment of urinary infections acquired in the community in patients with cirrhosis includes third-generation cephalosporins, amoxicillin–clavulanic acid, quinolones or trimethoprim–sulfamethoxazole (Table 1) [7]. Uncomplicated infections can be treated with oral antibiotics. Again, quinolones are not recommended in patients submitted to long-term norfloxacin prophylaxis or in regions with a high prevalence of quinolone-resistant bacteria in the general population. Since cross-resistance between quinolones and trimethoprim–sulfamethoxazole is frequent, this latter antibiotic does not constitute a real alternative to quinolones in cirrhosis [1].

Treatment of community-acquired pneumonia in the cirrhotic population does not differ from that recommended in non-cirrhotic patients and should cover typical and atypical bacteria. Currently recommended empirical antibiotic treatment consists of oral or IV levofloxacin (500 mg/d) or moxifloxacin (400 mg/d) or of the association of third-generation cephalosporins or amoxicillin–clavulanic acid plus a macrolide (clarithromycin or azitromycin). IV amoxicillin–clavulanic acid or third-generation cephalosporins plus cloxacillin are the empirical antibiotic strategies recommended for patients with cellulitis acquired in the community (Table 1) [7].

Empirical treatment of nosocomial infections

Current guidelines for the treatment of SBP and other infections in cirrhosis do not distinguish between community-acquired and nosocomial episodes [23,41,42]. However, bacteria isolated in nosocomial SBP or spontaneous bacteremia are frequently resistant to β -lactams (33–78%) [52–56]. Recent studies confirm this feature and show an increasing prevalence of multiresistant bacteria, mainly extended-spectrum β -lactamase-producing Enterobacteriaceae, in nosocomial infections in cirrhotic patients, ranging from 22% in SBP to 57% in urinary in-

Table 1. Empirical antibiotic therapy for community-acquired and nosocomial bacterial infections in cirrhosis.

Type of infection	Responsible bacteria	Recommended empirical antibiotics
SBP, SBE and spontaneous bacteremia	<i>E. coli</i> , <i>K. pneumoniae</i> , <i>Enterobacter spp.</i> , <i>S. pneumoniae</i> , <i>S. viridans</i>	First-line therapy: cefotaxime 2 g/12 h IV or ceftriaxone 1 g/12-24 h IV or amoxicillin-clavulanic acid 1-0.2 g/6-8 h IV Other options: 1) Ciprofloxacin 200 mg/12 h IV or ofloxacin 400 mg/12 h PO (in uncomplicated SBP)* 2) Meropenem (1 g/8 h IV) in nosocomial infections in areas with a high prevalence of ESBL-producing Enterobacteriaceae
Urinary tract infections	<i>E. coli</i> , <i>K. pneumoniae</i> , <i>E. faecalis</i> , <i>E. faecium</i>	First-line therapy: cefotaxime 2 g/12 h IV or ceftriaxone 1 g/12-24 h IV or amoxicillin-clavulanic acid 1-0.2 g/6-8 h IV in patients with sepsis. Ciprofloxacin 500 mg/12 h PO or cotrimoxazole (160-800 mg/12 h PO) in uncomplicated infections* Other options: In geographical areas with a high prevalence of ESBL-producing Enterobacteriaceae, nitrofurantoin (50 mg/6 h PO) in uncomplicated infections and carbapenems in patients with nosocomial infections and sepsis**
Pneumonia	<i>S. pneumoniae</i> , <i>M. pneumoniae</i> , <i>Legionella spp.</i> , <i>H. influenzae</i> , <i>K. pneumoniae</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i>	Community-acquired infections: ceftriaxone 1 g/12-24 h IV or amoxicillin-clavulanic acid 1-0.2 g/6-8 h IV and a macrolide or levofloxacin (500 mg/24 h IV or PO) Nosocomial and health care-associated infections [§] : meropenem (1 g/8 h IV) or ceftazidime (2 g/8 h IV) + ciprofloxacin (400 mg/8 h IV). IV vancomycin or linezolid should be added in patients with risk factors for MRSA [¶]
Soft tissue infections	<i>S. aureus</i> , <i>S. pyogenes</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i>	Community-acquired infections: amoxicillin-clavulanic acid 1-0.2 g/6-8 h IV or ceftriaxone 1 g/12-24 h IV + cloxacillin (2 g/6 h IV) Nosocomial infections [§] : meropenem (1 g/8 h IV) or ceftazidime (2 g/8 h IV) + a glycopeptide

*Quinolones should not be used in patients submitted to long-term norfloxacin prophylaxis or in geographical areas with a high prevalence of quinolone-resistant Enterobacteriaceae.

**In patients with severe sepsis or septic shock a glycopeptide should be added to cover *E. faecium*.

[§]Empirical antibiotic therapy for nosocomial infections should be adapted to the local epidemiological pattern of resistant bacteria.

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

SBP, spontaneous bacterial peritonitis; SBE, spontaneous bacterial empyema; ESBL, extended-spectrum β-lactamase-producing Enterobacteriaceae; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 2. Cost of antibiotic therapy and outcome in spontaneous bacterial peritonitis*.

Antibiotic [Ref.]	Resolution rate (%)	Cost**
Cefotaxime 2 g /12 h IV [125]	79	37.8
Ceftriaxone 2 g followed by 1 g/24 h IV [56, 82]	67-80	36.4
Amoxicillin-clavulanic acid 1-0.2 g/8 h IV [59]	83	20.2
Ciprofloxacin 200 mg/12 h IV [61]	76	62.7
Ofloxacin 400 mg/12 h PO [62]	84	9.4

*Studies included mainly community-acquired infections.

**Estimated cost in Euros for 5 days of treatment.

fections [56]. β-Lactamase hydrolyzes cephalosporins, aztreonam, and extended-spectrum penicillins, rendering these antibiotics clinically ineffective. Extended-spectrum β-lactamase-producing Enterobacteriaceae have been described in patients with SBP in different geographical areas such as Spain, Italy, Turkey, Korea and France (Table 3) [52,55,56,63-69]. These data suggest that third-generation cephalosporins or amoxicillin-clavulanic acid may be ineffective in the treatment of a relevant proportion

of nosocomial infections in cirrhosis. Recent studies show that current guidelines for the treatment of SBP fail in 26–41% of patients [65,66,70].

Empirical antibiotic strategies for the treatment of nosocomial infections in cirrhosis should consider the local epidemiological patterns of multiresistance. In areas with a high prevalence of extended-spectrum β-lactamase-producing Enterobacteriaceae, carbapenems should be used in the empirical treatment of nosocomial episodes of SBP and spontaneous bacteremia. Although tigecycline is a potential alternative, it is currently not recommended as first-line therapy in the general population in the light of recent studies showing increased mortality related to its low clinical efficacy [71]. Oral nitrofurantoin or fosfomycin (in uncomplicated infections) and carbapenems plus glycopeptides should be used in the treatment of nosocomial urinary infections with sepsis (Table 1). Empirical treatment of other nosocomial infections such as pneumonia [72] or cellulitis should follow the local recommendations for the general population. Moreover, an appropriate control of infection (isolation of patients with multiresistant bacterial infection during hospitalization) and antibiotic management strategies (restrictive use of third-generation cephalosporins and of long-term quinolone prophylaxis) are needed to prevent the spread of multiresistant bacteria and *Clostridium difficile* infections in the cirrhotic population [73]. In addition, early de-escalation to the

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Table 3. Prevalence and risk factors of extended-spectrum β -lactamase-producing (ESBL) Enterobacteriaceae in spontaneous bacterial peritonitis (SBP).

Author [Ref.]	Year	Country	Prevalence	Risk factors
Fernandez [1]	2002	Spain	1.5%	No data
Park [63]	2003	Korea	7% in 1995, 28% in 1999	Previous exposure to quinolones or β -lactams Current or recent hospitalization
Song [55]	2006	Korea	14% in community-acquired SBP and 67% in nosocomial infections	No data
Cereto [64]	2008	Spain	6%, 13% in patients on quinolone prophylaxis	Norfloracin prophylaxis
Angeloni [65]	2008	Italy	8%	Health care-related infections
Cheong [52]	2009	Korea	6%	Previous exposure to β -lactams Nosocomial infection
Acevedo [56]	2009	Spain	2% in community-acquired SBP and 16% in nosocomial infections	Nosocomial infection Previous exposure to β -lactams (3 months) Norfloracin prophylaxis
Yakar [66]	2009	Turkey	18%	No data
Song [67]	2009	Korea	7.5%	Previous exposure to antibiotics Recent hospitalization
Heo [68]	2009	Korea	11%	No data
Piroth [69]	2009	France	5%	No data

most appropriate antibiotic should be done after microbiological results have become available [49].

A theoretical alternative to the use of carbapenems in the treatment of infections caused by extended-spectrum β -lactamase-producing *Escherichia coli*, which could favour the development of bacterial resistance to these antibiotics, is the optimization of the pharmacodynamic properties of β -lactams in terms of dosage and modality of administration or the use of penicillins with β -lactamase inhibitors (e.g., piperacillin-tazobactam). Although this strategy can be adopted in uncomplicated infections, its use in severe infections or in those caused by extended-spectrum β -lactamase-producing *Klebsiella pneumoniae* is not advised in the general population [74,75]. Moreover, the lack of data on antibiotic pharmacokinetics and pharmacodynamics (volume distribution, hepatic and renal clearance, albumin-binding and transport, tissue concentration ...) in patients with liver failure limits the use of these strategies in cirrhosis.

As stated before, health care-associated infections seem to have a microbiology that is similar to that reported for nosocomial infections [2]. If this feature is confirmed in further studies, empirical antibiotic strategies for these infections should follow that described for nosocomial infections.

Albumin administration

Bacterial infections can deteriorate the hemodynamic status of patients with cirrhosis and ascites and induce renal failure [76]. SBP is by far the most frequent infection causing hepatorenal syndrome [77,78], which can also be induced by biliary, gastrointestinal, and complicated urinary infections [79]. Treatment with IV albumin reduces the incidence of renal impairment (from 33% to 10%) and improves hospital survival (from 71% to 90%) in patients with SBP [80]. The administration of IV albumin in these patients improves systemic hemodynamics by several mechanisms. Albumin acts as a plasma expander increasing cardiac preload but also attenuates endothelial dysfunction increasing peripheral vascular resistance. This effect is not observed with synthetic plasma expanders [81,82]. Albumin is given at an arbitrary dose of 1.5 g per kilogram of body weight at the time of diagnosis, followed by 1 g per kilogram of

body weight on day 3. Patients with bilirubin >4 mg/dl or creatinine >1.0 mg/dl are at a high risk for the development of hepatorenal syndrome (incidence between 33% and 57%) and clearly benefit from volume expansion with albumin. On the contrary, renal failure is infrequent in patients with a baseline bilirubin level <4 mg/dl and a creatinine level <1 mg/dl (<8%). These low-risk patients should not receive albumin [83]. Two recent studies suggest that 1) albumin can not be substituted by artificial plasma expanders in patients with SBP [82] and 2) the administration of albumin in unselected cirrhotic patients with non-SBP infections is not associated with clinically relevant effects [84]. Further studies are needed to determine whether lower doses of albumin are also effective in patients with SBP and which kind of infections different from SBP benefit from albumin administration.

Management of severe sepsis and septic shock

Bacterial infections frequently lead to the development of severe sepsis and septic shock in the cirrhotic population. Prognosis of these entities is poor with hospital mortality rates that range from 30% to 70%. Early diagnosis and treatment are therefore essential [7,24]. The integrated strategy currently recommended in the management of these patients is discussed in depth in the article by Ginès *et al.* in this Supplement [126].

Initial resuscitation, early diagnosis, and antibiotic treatment

Patients with cirrhosis and severe sepsis or septic shock should be resuscitated following an early goal-directed therapy. It consists of a prompt and stepwise emergent resuscitation with predefined goals that must be achieved within the first 6 hours after diagnosis in order to treat sepsis-induced tissue hypoperfusion (mean arterial pressure ≥ 65 mmHg, central venous pressure between 8 and 12 mmHg, central venous oxygen saturation $\geq 70\%$ and urine output ≥ 0.5 ml·kg⁻¹·h⁻¹) [49,85]. These goals were defined in the general population and probably should be redefined in the cirrhotic population.

An early diagnosis of the infection and the initiation of IV antibiotics are essential in the management of cirrhotic

Table 4. Current indications of antibiotic prophylaxis in cirrhosis.

Indication	Antibiotic and dose	Duration
Gastrointestinal bleeding	Norfloxacin 400 mg/12 h PO IV ceftriaxone 1 g/d in patients with advanced cirrhosis (at least 2 of the following: ascites, jaundice, hepatic encephalopathy, and malnutrition)	Seven days
Primary prophylaxis in patients with low protein ascites (<15 g/L)	Norfloxacin 400 mg/d PO in patients with advanced cirrhosis: - Child-Pugh score ≥9 points with serum bilirubin ≥3 mg/dl and/or - Impaired renal function (serum creatinine ≥1.2 mg/dl, BUN ≥25 mg/dl or serum sodium ≤130 mEq/L)	Until liver transplantation or death
Secondary prophylaxis	Norfloxacin 400 mg/d PO	Until liver transplantation or death

patients with severe sepsis or septic shock as is true for the general population [49]. Broad-spectrum antibiotics should be started as early as possible and always within the first hour of recognizing severe sepsis or septic shock [49–51,85]. Initial empirical antibiotic treatment should cover all likely pathogens. De-escalation to the most appropriate single antibiotic should be done once the susceptibility profile of the responsible bacteria is known [49]. Prompt admission of the patient to the ICU is also essential in the management of these patients.

Fluid therapy and vasoactive drugs

Current guidelines recommend fluid resuscitation with either albumin, artificial colloids (gelatins or hydroxyethyl starches) or crystalloids [49]. However, resuscitation with crystalloids requires more fluid to achieve the same goals and results in more edema, especially in cirrhotic patients, who characteristically have marked hypoalbuminemia. Moreover, resuscitation with albumin seems to be associated with a decrease in mortality compared to other solutions in non-cirrhotic patients with sepsis [86]. Future RCTs should compare albumin with other plasma expanders in the fluid resuscitation of patients with cirrhosis and severe sepsis or septic shock. Norepinephrine and dopamine are considered as first-line vasopressor agents in patients with septic shock [87], vasopressin being a second-line therapy [88]. Cirrhotic patients with septic shock have vascular hyporeactivity to these vasopressor agents [7]. Inotropic drugs are not usually effective in cirrhotic patients with sepsis since they already present high cardiac outputs. A European RCT is currently evaluating the efficacy and safety of terlipressin in patients with cirrhosis and septic shock.

Stress dose steroids

Adequate adrenal function is essential to survive critical illness. Relative adrenal insufficiency (RAI), an inappropriate adrenal response to stress, is associated to a poor prognosis in this setting. RAI is frequent in non-cirrhotic patients with septic shock and is associated with refractory shock and mortality [89]. The administration of stress dose steroids improves shock reversal. Controversial results exist regarding the effects of this treatment on survival [90]. Current guidelines only recommend stress dose steroids in patients with vasopressor-unresponsive septic shock [49,89]. RAI is also very frequent in patients with cirrhosis and severe sepsis or septic shock (51–77%) and is associated with hemodynamic instability, liver and renal failure and high mortality [91]. The clinical impact of stress dose steroids on the outcome of cirrhotic patients with septic shock is

unclear [92,93]. A large multicenter European RCT is currently underway to address this topic.

Other supportive therapies

Mechanical ventilation and renal replacement therapy modalities, sedation, and glucose control protocols and prophylactic strategies in patients with cirrhosis and severe sepsis and septic shock are discussed in the article by Ginès *et al.* in this Supplement [126].

Prevention of infection in cirrhosis

Antibiotic prophylaxis must be restricted to selected patients at a very high risk for the development of bacterial infections. This restriction to specific subpopulations is essential to prevent the development of antibiotic resistance in cirrhosis and to make these prophylactic strategies cost-effective. Current indications of antibiotic prophylaxis in cirrhosis are shown in Table 4.

Gastrointestinal bleeding

Cirrhotic patients with upper gastrointestinal bleeding are predisposed to develop SBP and other infections during or immediately after the bleeding episode. Approximately 20% of them are infected at admission and 50% develop infections during the first days of hospitalization in the absence of antibiotic prophylaxis [23,24]. The main risk period is the first 7 days after the hemorrhage, time during which antibiotic prophylaxis is recommended. Moreover, bacterial infections predict failure to control bleeding and variceal rebleeding. An increase in portal pressure and changes in hemostasis induced by infection have been suggested as possible mechanisms [94,95].

The usefulness of oral and systemic antibiotics in cirrhotic patients with gastrointestinal hemorrhage has been demonstrated in multiple controlled studies. Amoxicillin with or without clavulanic acid, cephalosporins (e.g., cefotaxime, ceftriaxone, ceftazidime, cefonicid), quinolones (eg, norfloxacin, ciprofloxacin, ofloxacin) and non-absorbable antibiotics are the prophylactic strategies evaluated in these studies [96–102]. The incidence of bacterial infections decreased in the treated groups (10–20%) in comparison to control patients (45–66%). Several meta-analyses confirm that antibiotic prophylaxis is effective in the prevention of SBP and other infections in this setting and that it improves survival [3,103]. A beneficial effect of antibiotic prophylaxis on control of bleeding and prevention of rebleeding has also been reported [103]. Current guidelines recommend antibiotic prophylaxis in all cirrhotic patients with

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gastrointestinal hemorrhage independently of the presence or absence of ascites [41,42,104]. Oral norfloxacin (400 mg/12 h) is the first choice suggested since it is simple to administer and has a low cost. However, patients with advanced cirrhosis seem to benefit from a more aggressive prophylaxis. A recent Spanish RCT indicates that IV ceftriaxone (1 g/day for 7 days) is more effective than oral norfloxacin in the prophylaxis of bacterial infections in patients with gastrointestinal bleeding and severe liver failure (at least two of the following: ascites, severe malnutrition, encephalopathy or jaundice). The probability of developing possible infections, proved infections, and spontaneous bacteremia or SBP was significantly higher in patients receiving norfloxacin (33% vs. 11%, $p=0.003$; 26% vs. 11%, $p=0.03$ and 12% vs. 2%, $p=0.03$, respectively). Type of antibiotic prophylaxis, transfusion requirements at inclusion and failure to control bleeding were independent predictors of infection [105].

Timing of antibiotic prophylaxis is also important in cirrhotic patients with gastrointestinal bleeding [106]. Baveno V consensus conference recommends that antibiotics are instituted from admission, ideally before or immediately after endoscopy [104].

Patients with low protein ascites and advanced cirrhosis (primary prophylaxis)

Patients with low protein concentration in ascitic fluid (10–15 g/L) are at risk for the development of the first episode of SBP (20% at 1 year) [5]. However, this factor is not enough to identify the subpopulation of patients that require antibiotic prophylaxis. Severe liver failure and low platelet count increase the risk of infection [107,108]. A recent study 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 g/L) and advanced liver failure (Child–Pugh score ≥ 9 points with serum bilirubin ≥ 3 mg/dl) or impaired renal function (serum creatinine ≥ 1.2 mg/dl, BUN ≥ 25 mg/dl or serum sodium ≤ 130 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 short-term survival (94% vs. 62%) [109]. Long-term norfloxacin administration is, therefore, clearly indicated in these patients, particularly if they are awaiting liver transplantation because it may increase the applicability of this procedure. Oral ciprofloxacin 500 mg/d is a valid alternative to norfloxacin [110].

Secondary prophylaxis

Patients who have recovered from a previous episode of SBP are at a very high risk of SBP recurrence in the absence of antibiotic prophylaxis [111]. Norfloxacin administration (400 mg/d) is effective in the prevention of SBP recurrence with overall rates of infection of 20–25% at 1 year (68% in the placebo group) and of 3% when the analysis is restricted to SBP caused by Gram-negative bacilli (60% in the placebo group). Daily norfloxacin is more effective than weekly quinolones in these patients [6,112]. Moreover, intermittent dosing may select resistant flora more rapidly. After SBP episode, liver transplantation must then be considered [41,42].

Antibiotic prophylaxis and quinolone-resistant infections

Prolonged antibiotic administration leads to the emergence of resistant bacteria. Initial studies suggested that the risk of

developing SBP or other infections caused by quinolone-resistant Enterobacteriaceae in patients on long-term norfloxacin prophylaxis was low, since the majority of SBP recurrences were caused by Gram-positive cocci, mainly streptococci [113]. Subsequent studies reported a high incidence of quinolone-resistant strains of *E. coli* in stools of cirrhotic patients undergoing quinolone prophylaxis [114,115]. Several years later, the emergence of urinary infections and SBP caused by Gram-negative bacilli resistant to quinolones in patients receiving this prophylaxis was shown [1,116,117]. Fifty percent of culture-positive SBP in patients on prophylaxis was caused by such microorganisms versus 16% in patients not receiving prophylaxis. Overall, 26% of the culture-positive SBP were caused by quinolone-resistant Gram-negative bacteria [1], a prevalence that has increased to 38% in more recent studies [64,118]. These studies also reported a high rate of SBP caused by trimethoprim–sulfamethoxazole-resistant Gram-negative bacteria (44–72%), suggesting that this antibiotic is not an alternative to norfloxacin [1,118].

Areas of future research

One of the major difficulties in the management of infected patients with cirrhosis is the diagnosis of infection. Infections are culture-positive in 50–70% of cases. During decompensation of cirrhosis, classical clinical parameters do not allow to distinguish infected from non-infected patients, often delaying the diagnosis and the management of bacterial infection [119]. In doubt, broad-spectrum antibiotics are frequently started without the proof of infection in decompensated cirrhosis with an escalation in antibiotic classes in the case of clinical deterioration. We must create and/or validate new tools for diagnosis of bacterial infection in cirrhosis to help physicians to make a prompt and adequate decision (e.g., PCR assays).

Prompt and appropriate antibiotic treatment is essential in the management of cirrhotic patients with infection. While third-generation cephalosporins continue to be the gold-standard antibiotic treatment of many of the infections acquired in the community, the empirical treatment of nosocomial and possibly health care-associated infections should be adapted to the local epidemiological pattern of antibiotic resistance. Large multinational studies are required to better define the epidemiological changes that are occurring in bacterial infections in cirrhosis.

As in the general population, specific goals for early hemodynamic resuscitation should be established in cirrhotic patients with severe sepsis or septic shock [85]. Types and/or combinations of vasopressors should be defined in septic shock taking into account specificities of circulatory dysfunction in cirrhosis. The administration of recombinant human activated protein C (rhAPC) in severe sepsis improves survival but for the risk of bleeding, cirrhotic patients were excluded from this trial [120]. In the light of the low number of bleeding episodes in anticoagulated cirrhotic patients, the administration of rhAPC should be assessed in severe sepsis in cirrhosis [121]. The clinical impact of stress dose steroids in this setting should also be evaluated in appropriate RCTs.

Another key point is the prophylaxis of bacterial infections to prevent the rapid worsening of prognosis. At this time, the most studied prophylactic treatment is norfloxacin. The widespread use of quinolones and other antibiotics in cirrhotic patients leads to changes in bacterial flora and emergence of resistance. By studying pathogenesis of bacterial infection occurrence in cirrhosis, we might define new targets for

the development of “non-antibiotic” prophylaxis. An additional strategy is to characterize the high-risk population that qualifies for prophylaxis. For example, genetic susceptibilities for bacterial infection are highlighted by recent studies. In the future, we must test prophylactic management in high-risk patients guided by genetic markers.

In a long-term point of view, occurrence of bacterial infection predicts a worsening of prognosis of cirrhotic patients. Indeed, after an SBP episode, the 1-year and 2-year survival are respectively 40% and 25–30% [111]. After SBP episodes, liver transplantation must then be considered. Some cirrhotic patients enter a rapid vicious circle where bacterial infections succeed themselves with progressive liver failure. In these specific cases, not exceptional, decision between indication and contraindication of liver transplantation becomes very difficult. Tools to help decision making must be created to avoid transplantation in too sick patients and to rescue others.

Conclusions

In conclusion, bacterial infection becomes the first cause of death of cirrhotic patients. Despite numerous experimental data and significant advances in the understanding of the pathogenesis

Key Points

- Bacterial infection is one of the most frequent complications and the first cause of death in cirrhosis. Immune defects, mainly acquired but also genetic, and bacterial translocation are the main mechanisms involved in its pathogenesis
- Early diagnosis of infection is pivotal. C-reactive protein, procalcitonin and SIRS criteria have less diagnostic capacity in the cirrhotic population. New diagnostic tools are clearly needed
- Diagnosis of SBP relies on ascitic fluid analysis obtained by paracentesis. Runyon’s criteria and prompt abdominal CT scan are essential to differentiate this entity from secondary peritonitis
- Prompt and appropriate antibiotic treatment is basic in the management of cirrhotic patients with infection. While third-generation cephalosporins continue to be the gold-standard antibiotic treatment of many of the infections acquired in the community, the empirical treatment of nosocomial and possibly health care-associated infections should be adapted to the local epidemiological pattern of antibiotic resistance
- IV albumin reduces the incidence of renal impairment and improves hospital survival in patients with SBP and poor liver or renal function. Its administration in unselected cirrhotic patients with non-SBP infections is not associated to clinically relevant effects
- Resuscitation following early goal therapy and prompt broad-spectrum antibiotics and vasoactive support are key to the management of cirrhotic patients with septic shock. Specific goals for initial resuscitation should be investigated in this population
- Restriction of prophylactic antibiotics to the high-risk populations will reduce the spread of multidrug resistant bacteria in cirrhosis

of sepsis in cirrhosis, the outcome remains poor. Much effort is needed to improve prophylactic strategies against bacterial infections and to define specific management of sepsis by designing and performing the proper trials in patients with advanced cirrhosis.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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