Clinics and Research in Hepatology and Gastroenterology (2019) xxx, xxx–xxx

Available online at ScienceDirect www.sciencedirect.com

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REVIEW

Management of infections in patients with cirrhosis in the context of increasing therapeutic resistance: A systematic review

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KEYWORDS
Cirrhosis;
Bacterial infection;
Fungal infections;
Multidrug resistant bacteria

Summary Patients with cirrhosis are prone to develop bacterial infections, which consist in one of the major precursors of *Acute-on-Chronic Liver Failure* (ACLF) and are responsible for a high mortality rate. In recent years, the management of bacterial infections in patients with cirrhosis has become increasingly complicated due to a change in bacterial ecology associated with a higher rate of cocci gram positive bacteria in Europe and America along with the emergence of a multidrug-resistant (MDR) and extensively drug-resistant (XDR) bacteria leading to a decrease in the efficacy of empirical strategies based on the administration of third-generation cephalosporins. MDR and XDR now account for about 40% of the infections worldwide, and up to 70% in India. Among them, the most common ones are extended-spectrum beta-lactamase producing (ESBL-P) bacteria, carbapenem-resistant enterobacteriaceae (CRE), Methicillin-resistant Staphylococcus aureus (MRSA), and vancomycin-resistant enterococci (VRE). An early diagnosis associated to an empirical antibiotic adapted to the site of infection and potential bacterial resistance is now crucial in order to improve the chances of survival and contain the resistance phenomenon. Moreover, a fungal infection must always be discussed in these high-risks patients, especially in the absence of clinical improvement under appropriate antibiotic treatment. In this review, we will focus on the emerging threat of MDR and XDR organisms, as well as fungal infections, in order to better adapt the therapeutic management of cirrhotic patients with infections.

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https://doi.org/10.1016/j.clinre.2019.10.003
2210-7401/

Please cite this article in press as: Allaire M, et al. Management of infections in patients with cirrhosis in the context of increasing therapeutic resistance: A systematic review. Clin Res Hepatol Gastroenterol (2019), https://doi.org/10.1016/j.clinre.2019.10.003

Abbreviations

ACLF	Acute-on-Chronic Liver Failure
CRE	carbapenem-resistant enterobacteriaceae
ESBL	extended-spectrum beta-lactamase
ICU	intensive care unit
MDR	multidrug-resistant
MRSA	Methicillin-resistant Staphylococcus aureus
PMN	polymorphic nuclear
SFP	spontaneous fungal peritonitis
SPB	spontaneous bacterial peritonitis
TIPS	porto-systemic intrahepatic transjugular shunt
TLR4	Toll Like receptor 4
VSE	vancomycin-susceptible enterococci
VRE	vancomycin-resistant enterococci
XDR	extensively drug-resistant

Introduction

Bacterial infections must be systematically sought in all hospitalized cirrhotic patients, regardless of the stage of the liver disease, since they appear as a major precursor of Acute Chronic Liver Failure (ACLF) and are responsible for a high mortality rate [1—6]. In fact, patients with cirrhosis presented a risk of sepsis 2.6-fold higher than those without cirrhosis in a large American study [7]. Moreover, about half of the in-hospitalized patients for acute decompensation of cirrhosis will present bacterial infections [3,4,8—10]. In recent years, the management of bacterial infections in patients with cirrhosis has become increasingly complicated due to a change in bacterial ecology and the appearance of antibiotic resistances. In fact, the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) bacteria has led to a decrease in the efficacy of classical empirical strategies based on the administration of third-generation cephalosporins. These observations are associated with a higher mortality rate: an increased duration of in-hospital stays and higher healthcare related costs when compared to infections caused by susceptible strains [10—16]. The diagnosis of such infections can be complex but a treatment adapted to the type of infection and bacterial ecology must be started quickly, overriding the fear of drug toxicity due to the liver disease. Besides, in order to improve the chances of survival, not only bacterial infections should be sought but also fungal infections, especially in the absence of clinical improvement under appropriate antibiotic treatment.

In this review, we will focus on the importance of changes in bacterial ecology these last years and we will also study the emergence of antibiotics resistance in order to better adapt the therapeutic management of cirrhotic patients.

What evolution in infectious agents has been noticed in the recent years?

Site of infections

Due to dysbiosis and increased bacterial translocation leading to chronic stimulation of the innate immune system via Toll Like receptor 4 (TLR4) recognition of lipopolysaccharide (LPS) and to the alteration of innate and adaptive immunity, cirrhotic patients are prone to develop spontaneous and secondary bacterial infections (Fig. 1) [1,2,17—20]. In terms of frequency, the most common ones are spontaneous bacterial peritonitis (SBP), urinary tract infections, pulmonary infections, bacteremia and skin infections. SBP is a the most frequent one in cases of cirrhosis, representing 30% of bacterial infections in hospitalized patients as shown in the recent study of Piano et al. [10]. After a first episode of SBP, the chances of survival within one year have been estimated to 40% [21]. The second type of infection frequently observed is urinary tract infections which are two times more frequent in cases of cirrhosis than in the general population and related to *Escherichia Coli* infection in the majority of cases [22]. Pulmonary infections take the third place and their high incidence in this population of patients can be partly explained by the occurrence of hepatic encephalopathy and gastrointestinal bleeding, two frequent complications which can lead to a orotracheal intubation but also to a predisposition of *Streptococcus pneumoniae* and *Haemophilius influenza* infections in case of chronic alcohol intake [23,24]. Then, Bacteremia is ten times more common in patients with cirrhosis in comparison with the general population and is, in the majority of cases, related to health-care associated infections. Interestingly, in about three quarters of cases, no primary infectious disease was identified [25,26]. Skin infections are also frequent in case of cirrhosis and favoured by hepatic encephalopathy, the presence of edema of the lower limbs, malnutrition, and peripheral or central venous catheters. An early diagnosis must be done as skin infections can lead to necrotizing fasciitis associated with high mortality rate (up to 76% in some studies) [27,28]. In recent studies which were published, SBP, urinary tract infection, and pneumonia remained the most frequent sites of infection observed in patients with cirrhosis [10,29—35].

Modification in bacterial ecology

During the last decades, it was established that infections were mainly community-based and secondary associated to Gram-negative bacteria in approximately 70% of cases [36,37]. However, the bacterial ecology has changed in recent years due to an increased rate of Gram-positive Cocci infections and also nosocomial and health-care associated infections, now accounting for almost 40% of all bacterial infections (Tables 1 and 2) [6,29—35]. This evolution of the bacterial profile can be explained by an improvement of the patients' care (endoscopic band ligation, porto-systemic intrahepatic transjugular shunt, transjugular hepatic biopsy, percutaneous treatment and chemo embolization for hepatocellular carcinoma...), and the fact that patients suffering from cirrhosis at an advanced stage are more likely to be admitted to intensive care unit (ICU), a condition associated with invasive devices [6,10,35]. Piano et al. recently published the results of a worldwide study considering 1302 patients with bacterial infections (43% from Europe, 32% from Asia and 25% from America). Among the 959 isolated bacteria, 57% were Gram negative bacteria, 38% Gram positive bacteria and 4% of the cultures were positive

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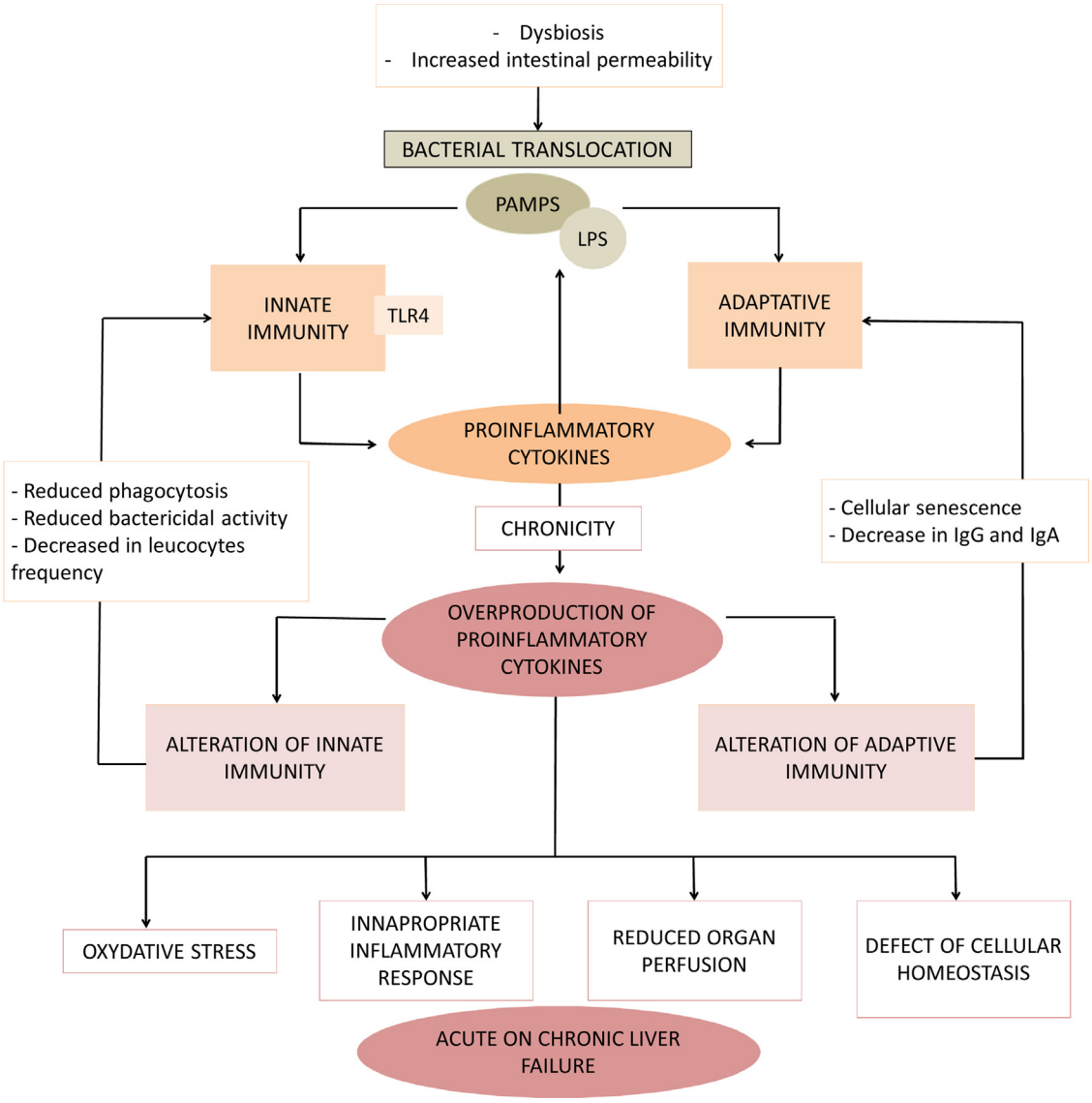

Figure 1 Mechanisms involved in infections in patients with cirrhosis leading to Acute on Chronic liver Failure. Intestinal bacterial overgrowth, dysbiosis and increased intestinal permeability lead to chronic stimulation of immune system of patients with cirrhosis. In response to chronic microbial challenge, several abnormalities in the innate and adaptive components will appear leading to a state of acquired immunodeficiency. Thus, bacterial infections may cause an exaggerated systemic inflammation that can be responsible for tissue damage and organ failure in patients with cirrhosis leading to Acute on chronic liver failure. LPS: lipopolysaccharide; PAMPS: Pathogen-associated molecular pattern; TLR4: Toll Like receptor 4.

Table 1 Definitions of community acquired, healthcare associated and nosocomial infections.

Community acquired infections	Infection diagnosed before of within the first 2 days after admission in patients without any contact with a hospital facility within the last 3 months
Healthcare associated infections	Infection diagnosed before of within the first 2 days after admission in patients which were in contact with a hospital facility within the last 3 months
Nosocomial infections	Infection diagnosed after 2 days of hospitalization

for fungi [10]. In this series, more Gram-positive bacteria were diagnosed in America (37%) and in Europe (43%) compared to Asia (28%), confirming the previous results from France, England and Italy in favour of an increase of the prevalence of Gram positive bacteria in Europe in recent years [31—34,38]. In Asia, Gram-negative bacteria remained largely the most frequent ones (70—82%) (Table 1) [29,33—35].

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Table 2 Summary of the recent study focusing on bacterial infections in patients with cirrhosis.

	Study	Characteristics of the study	Gram-negative bacteria	Gram-positive bacteria
Asia	Park et al. *J Korean Med sci* 2015 (Korea) [32]	65 positive cultures (2010–2012)[a] Case control study MDR prevalence: 87% Community-acquired 87% Hospital-acquired 13%	63% in total (41/65) 14% ESBL-P (9/65) 32% Quinolone-R (21/65)	35% in total (23/65) 20% MRSA (13/65) 0% VRE (0/65)
	Jain et al. *J Clin Exp Hepatol* 2017 (Inde) [33]	240 positive cultures (2014–2015) MDR prevalence: 69% Community-acquired 4% Health-care associated 41% Hospital-acquired 55%	82.5% in total (198/240) 48% ESBL-P (116/240) 19% CRE (46/240)	17.5% in total (42/240) 2% MRSA (4/240) 0% VRE (0/240)
	Zhao et al. *Expert Rev Gastroenterol Hepatol* 2018 (China) [34]	635 positive cultures (2011–2017) MDR prevalence: 44% Community-acquired 30% Health-care associated 21.5% Hospital-acquired 48.5%	70% in total (444/635) 11% ESBL-P (67/635) 14% CRE (91/635)	30% in total (191/635) 2% MRSA (14/635) 8.5% VSE (54/635) 0.2% VRE (1/635)
America	Tandon et al. *Clin Gastroenterol Hepatol* 2012 (U.S.A.) [14]	70 positive cultures (2009–2010) MDR prevalence: 47% Hospital-acquired 30%	54% in total (38/70)[b] 10% ESBL-P (7/70)	44% in total (31/70) 4% MRSA (3/70) 17% VRE (12/70)
Europe	Fernández et al. *Hepatology* 2012 (Espagne) [6]	First cohort 2005–2007 271 positive cultures in total MDR prevalence: 18% Community-acquired 32% Health-care associated 32% Hospital-acquired 36% Second cohort 2010–2011 110 positive cultures in total MDR prevalence: 28% Community-acquired 30% Health-care associated 25% Hospital-acquired 45%	First cohort 2005–2007 54% in total 16% ESBL-P (44/271) Second cohort 2010–2011 ? in total 11% ESBL-P (12/110)	First cohort 2005–2007 44% in total 5% MRSA (14/271) Second cohort 2010–2011 ? in total 5% MRSA (6/110)
	Nahon et al. *Gut* 2017 (France) [29]	98 positive cultures (2006–2012) MDR prevalence? Community-acquired 84% Hospital-acquired 16%	57% in total (56/98) 20% Quinolone-R (20/98) 4% ESBL-P (4/98)	44% in total (43/98) 7% MRSA (7/98) 1% VRE (1/98)
	Dionigi et al. *Am J gastroenterol* 2017 (England) [30]	239 positive cultures (2007–2008) MDR prevalence 23% Hospital-acquired 40%	42% in total (100/239) 8% ESBL-P (20/239)	58% in total (139/239) 9% MRSA (22/239)
	Salerno et al. *Liver Int* 2017 (Italy) [31]	313 positive cultures (2007–2009) MDR prevalence 27% Community-acquired 55% Hospital-acquired 45%	53% in total (167/313) 23% Quinolone-R (73/313) 21% ESBL-P (67/313) 4.5% CRE (14/313)	43% in total (136/313) 9% MRSA (29/313) 0.01% VRE (1/313)
	Fernández et al. *J Hepatol* 2018 (Europe) [35]	First cohort 2011 264 positive cultures in total MDR prevalence: 28% Community-acquired 30% Health-care associated 17.5% Hospital-acquired 52.5% Second cohort 2017–2018 MDR prevalence: 38%	First cohort 2011 ? in total 11% ESBL-P (30/264) 2% CRE (6/264)	First cohort 2011 ? in total 4.5% MRSA (12/264) 6% VSE (15/264) 1% VRE (3/264)

CRE: carbapenem-resistant enterobacteriaceae; ESBL-P: Extended spectrum beta-lactamase-producer; MRSA: methicillin-resistant staphylococcus aureus; VRE: vancomycin-resistant; VSE: vancomycin-susceptible. Percentages were calculated by number of germ out of total positive cultures

[a] 1 candida isolated in the bacterial cultures.

[b] 1 urinary tract infection caused by mixed gram-positive and gram-negative organism.

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Increase of multidrug resistant and extensively drug-resistant organisms

Due to antibiotic overuse and failure measures to prevent the spread of MDR and XDR organisms, resistance to antibiotics is currently a major global public health problem in the general population but also in patients with cirrhosis who cumulate several risk factors for MDR and XDR bacteria such as recurrent hospitalizations, invasive procedures and repeated exposures to antibiotics. MDR bacteria are specific bacteria resistant to three or more of the main antibiotic families. Among them, the most frequent ones are extended-spectrum beta-lactamase producing (ESBL-P) bacteria (mostly affecting *Escherichia coli* and *Klebsiella pneumoniae* which have become resistant to third-generation cephalosporins), carbapenem-resistant enterobacteriaceae (CRE), Methicillin-resistant Staphylococcus aureus (MRSA), and vancomycin-resistant enterococci (VRE) (38). In cases of cirrhosis, antibiotic prophylaxis is recommended in several situations. Third-generation cephalosporins has been validated as an antibiotic prophylaxis for intestinal bleeding but also as an empirical antibiotic therapy for most infections in cirrhotic patients, thus exposing to the emergence of resistant clones. In fact, recent studies showed that beta-lactam antibiotics were not effective in a significant part of infections in cirrhosis, especially in health-care associated and hospital-acquired infections [10—16,36,39—41].

Worldwide, Piano et al. showed that MDR bacteria were more frequent in Asia (51%) compared to Europe (29%) and America (27%). In this series, bacterial infections were mostly community acquired (56% in Asia, 48% in America and 43% in Europe) and the highest rate of nosocomial infection was observed in Europe (20% in Asia, 22% in America and 32% in Europe). ESBL Enterobacteriaceae were the most common ones in all geographical areas (17% in America, 14% in Asia and 9% in Europe) and CRE predominated in Asia (11% in Asia, 1% in America and 4% in Europe) [10]. These data confirmed previous Asian studies showing a high rate of MDR organisms (up to 69% in the Indian study or Jain et al.) with a predominance of ESBL Enterobacteriaceae and CRE except in Korea where MRSA were more frequent (Table 1) [32—34]. This high rate of MDR bacteria could be explained partly by over-the-counter access to antibiotics frequently observed in India [42]. Interestingly, the prevalence of MDR organism changed quickly in Europe in the last few years. First, Fernandez et al. showed an increase in the prevalence of MDR bacteria in cirrhotic patients from 18% in 2005—2007 to 28% in 2010—2011 [6]. The same trend was observed in England and Italy with MDR bacteria rate of 23% and 27% respectively in the 2007—2009 period. Then, in the Canonic series conducted in 2011, MDR bacteria accounted for 29% of culture-positive episode with higher rates of MDR diagnosis in Northern and Eastern Europe. While in the recent series dating from 2017-2018, MDR strains accounted for 38% of culture-positive samples and were more frequently isolated in Eastern and Southern Europe and associated with an increase rate of CRE. We should also point out that the bacterial ecology and the type of resistance varied according to the centers of care within the same country [35]. In the French Resist study performed in 2016, the rate of MDR was 10% [39]. Few data are available regarding the American continent, MDR organism prevalence in the study of Tandon et al. was 47% with a predominance of VRE and ESBL-P (2009—2010) [14].

Regarding the different studies available, in Asian countries (particularly India), the use of systemic antibiotics for the treatment of a bacterial infection for at least 5 days in the previous 3 months, invasive procedures in the previous month, and the exposure to health care (health-care associated and hospital-acquired infections), the site of infections (urinary tract infection, pneumonia, skin and soft tissue infection) and ICU stay were associated to MDR bacteria occurrence in multivariate analysis [10,36]. MDR organisms had a higher incidence of treatment failure, which led to more frequent septic shocks, and were responsible for a higher hospital mortality rate [10—16,32,35,39—41]. The cumulative incidence of mortality within 28 days in patients showing MDR infections varied between 29% to 35% according to the studies, which is significantly higher compared to infected patients without MDR organisms [10,35].

Recently, XDR bacteria, referring to bacteria resistant to at least one antibiotic in all classes except 2. In the study of Piano et al., the rate of XDR was 16% in Asia, 4% in America and 5% in Europe. Various criteria such as living in India, presenting urinary tract infection and pneumonia as well as exposure to health care (health-care associated and hospital-acquired infections) were independently associated with XDR infections occurrence [10].

Highlighting fungal infections

Although most of the available studies are retrospective and only refer to *Candida albicans*, fungal infections appear to be more common in patients with cirrhosis than in the general population. Indeed, in the multi-center study of Galbois et al., including 31,251 patients in ICU for septic shock, the fungal infections were more frequent in cirrhotic than non-cirrhotic patients (9.9% vs. 6.3%, $P < 0.05$) [43]. Unfortunately, due to a lack of clinical signs, the diagnosis remain difficult and is most of the time delayed and responsible for a high mortality rate. Until recently, the most common isolated species was *Candida albicans*. However, with changing epidemiology depending on geographic allocation, *non-Candida albicans* has emerged as the predominant species in many countries such as *Candida glabatra* especially in Europe and in the USA and *Candida tropicalis* in Asia. In cases of cirrhosis, although an increase prevalence of *non-Candida albicans* has been observed, *Candida albicans* remains the most frequent one [44—52].

In the majority of cases, candidemia will be observed and special diagnosis techniques are available. Alexpoulou et al. studied 185 cirrhotic patients with positive blood culture, 4.3% of patients had both bacterial and fungal infection and 6% isolated fungal infection (*Candida albicans* 58%). Their occurrence was unrelated to the severity of the cirrhosis, but they occurred more frequently in patients with impaired renal function. Moreover, in 42.2% of cases, candidemia occurred in patients with chronic alcohol intake [44]. To date, the diagnosis of candidemia is largely based

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on blood culture, although it can be nonspecific and takes at least 48—72 hours due to the slow multiplication rate of Candida. Even if the blood culture remains the gold standard, non-invasive tests can be used such as (1,3)-b-D-glucan (BDG) (se 71%, Sp 81%), Galactomann (se 71%, Sp 89%) and PCR (se 75%, Sp 88%). In addition, other scoring systems to assess patients at high risk of invasive candidemia such as Candida score and Candida colonization index are available. Four parameters are included in the Candida score (multifocal colonization: 1 point; surgery: 1 point; parenteral nutrition: 1 point; and severe sepsis: 2 points) and a score > 3 is associated with a high probability of developing candidemia. The Candida colonization index, which is a ratio of division of a number of different body sites colonized by the same strains by the total number of body sites investigated, can also be used to predict the risks of developing invasive candidemia. Nevertheless, the applicability of these scoring systems in patients with cirrhosis has not been validated [51,52].

Even if candidemia remains the most common type of fungal infection, positive fungal culture can also be noticed in ascites. Spontaneous fungal peritonitis (SFP) refers to positive fungal cultures associated with polymorphic nuclear (PMN) cell counts of $\geq$ 250 cells/mm^3 in the ascitic fluid without intraabdominal sources of infection while fungal ascites is defined by positive fungal cultures with low PMN cell counts. SFP are often nosocomial infections, caused by *Candida albicans* and associated with concomitant SBP and higher mortality [45]. Fungal cultures are not systematically performed but SFP must be discussed in cases of persistent high PMN cell counts after 48 hours of empirical antibiotic treatment. Furthermore, gastrointestinal bleeding (increased intestinal permeability), prolonged antibiotic exposure (fungi overgrowth in intestinal flora), chronic alcohol intake, ICU hospitalizations, impaired renal function, refractory ascites and central devices were associated with SFP [45—50].

Most of the time, the diagnosis is delayed and fungal infections are associated with treatment failure and high mortality rates [45—51]. Regarding the series, only half of the patients with positive fungal cultures received antifungal agents and non-treated patients died for most of them [44,47]. Among 169 episodes of candidemia and 72 SFP analyzed by Bassetti et al., the mortality rate within 30 days was 35.3% and was independently associated with candidemia (OR = 2.2, 95% CI: 1.2—4.5), septic shock (OR = 3.2, 95% CI: 1.7—6), and an absence of adequate antifungal treatment (OR = 0.4, 95% CI: 0.3—0.9) [51]. Moreover, for Alexpoulou et al., the fungal infections were associated with a 6-month higher mortality rate than non-fungal infection (89.5% versus 53%, P = 0.001) [44].

Thus, it is necessary to maintain a high level of caution regarding patients with cirrhosis, especially those with impaired renal function and/or receiving antimicrobial treatment with limited clinical response to ensure early adapted therapeutics. Besides, discussing prophylactic/preemptive antifungal treatment in specific risky situations (such as no improvement of patients in ICU after 48 hours of antibiotics, in case of dialysis, corticosteroids, central devices...) could be also helpful to reduce the mortality rate among the patients with cirrhosis.

How to manage infections in patients with cirrhosis today?

How to manage the growing prevalence of resistant bacterial infections?

The prescription of antibiotics must follow specific rules of good practice. When an infection is suspected, a maximum number of cultures must be performed in order to identify the causative bacteria with its in vitro sensitivity to antibiotics. In fact, the initial assessment is crucial and aims at determining the site of infections, to assess the potential risks of health-associated or hospital-acquired infections and the severity of the current infectious episode. Indeed, the distinction between community-acquired on the one hand, and healthcare-associated and hospital-acquired infections on the other hand, as well as local ecology, is crucial for the choice of the prescribed antibiotic therapy [1,2] (Table 3). An Empirical antibiotic treatment should be initiated as soon as possible after the diagnosis of a bacterial infection. Indeed, any delay in the administration of an effective antibiotic treatment has been associated with an increased risk of septic shock and a risk of death [52]. Nevertheless, this antibiotic treatment must be adapted to the site of infection and bacterial ecology as several studies have shown that the inefficacy of empirical treatment was the strongest predictor of short term mortality in cirrhotic patients with bacterial infections [10,35]. If the administration of third-generation cephalosporins is indicated, cefotaxime could be preferred instead of biliary excretion antibiotics such as ceftriaxone which promote the colonization of the microbiota by ESBL-P [53,54].

Once antibiotic therapy is started, it remains necessary to evaluate the impact of treatment within 48 hours. If the infection has not been confirmed, the antibiotic therapy should be stopped. If the cultures are positive, it is important to replace the antibiotic initially prescribed by an antibiotic also covering the germ but having a narrower spectrum in order to reduce the risk of resistance occurrence.

Finally, a second reassessment must be done within seven days to assess the evolution of the infection under treatment and determine the duration of it. In the majority of cases, a treatment of seven days is sufficient. It can even be reduced to five days in case of SBP without associated sepsis [1,2].

The use of nephrotoxic antibiotics in cirrhotic patients (aminoglycosides and glycopeptides) increases the risk of renal failure and therefore mortality, whatever the level of hepatic insufficiency might be. However, in cases of septic shocks, the benefit/risk ratio of the use of these antibiotics should not exclude them completely from the management of cirrhotic patients; their administration remains possible, but must be justified and monitored (peak and residual) [55].

What is the place for albumin in the treatment of bacterial infections?

Bacterial infections expose the patient to the occurrence of acute kidney injury (AKI) which is considered to be a major poor prognostic factor. This phenomenon is due to the

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Table 3 Empirical Antibiotic strategy for Nosocomial and Health care associated infections depending on the presence of multidrug resistant bacteria (adapted from references 1 and 2).

Type of infection	Community-acquired infections	Nosocomial infections Health care associated if high prevalence of MDR or if sepsis	To cover ESBL-P	To cover MRSA and VSE	To cover VRE
Spontaneous bacterial peritonitis	3rd generation cephalosporin Cefotaxime or Ceftriaxone	Beta-lactam/beta-lactamase inhibitor Piperacillin/tazobactam	Switch Beta-lactam/beta-lactamase inhibitor for carbapenems meropenem	Add Glycopeptides vancomycin intravenous teicoplanin	Switch glycopeptides for oxazolidinones linezolid Or daptomycin
Spontaneous bacteremia	3rd generation cephalosporin Cefotaxime or Ceftriaxone	Beta-lactam/beta-lactamase inhibitor Piperacillin/tazobactam	Switch Beta-lactam/beta-lactamase inhibitor for carbapenems meropenem	Add Glycopeptides vancomycin intravenous teicoplanin	Switch glycopeptides for oxazolidinones linezolid Or daptomycin
Urinary tract infection	Uncomplicated: Quinolone ciprofloxacine Or cotrimoxazole If sepsis 3rd generation cephalosporin Cefotaxime or Ceftriaxone	Uncomplicated: nitrofurantoin Or fosfomycin If sepsis Beta-lactam/beta-lactamase inhibitor piperacillin/tazobactam	Switch Beta-lactam/beta-lactamase inhibitor for carbapenems meropenem	Add Glycopeptides vancomycin intravenous teicoplanin	Switch glycopeptides for oxazolidinones linezolid
Pneumonia	Quinolone: ciprofloxacine or moxifloxacin Or 3rd generation cephalosporin + macrolide	3rd generation cephalosporin Ceftazidime	Switch 3rd generation cephalosporin for carbapenems and quinolone meropenoem + ciprofloxacin	Add Glycopeptides[a] vancomycin intravenous teicoplanin	Switch glycopeptides for oxazolidinones linezolid

CRE: carbapenem-resistant enterobacteriaceae; ESBL-P: extended spectrum beta-lactamase-producer; MRSA: methicillin-resistant staphylococcus aureus; VRE: vancomycin-resistant; VSE: vancomycin-susceptible

[a] In case of pneumonia, it is recommended to add glycopeptides in Ventilator-associated pneumonia, previous antibiotic therapy, nasal MRSA carriage.

increase of circulating vasoconstrictor substances secondary to a decrease in cardiac output and a reduction in peripheral vascular resistance caused by the prominent release of pro-inflammatory cytokines. In patients presenting high risks of AKI with SBP, a randomized controlled clinical trial showed that the administration of antibiotics in combination with albumin at day-1 and day-3 reduced the risk of developing AKI as well as the mortality rate compared to antibiotics alone [56]. It is to be spotted that this effect was not observed in patients with low risks of mortality (total bilirubin < 4 mg/dL and creatinine < 1 mg/dL) [57,58]. The beneficial action of albumin can be explained by its oncotic power, but also by its anti-oxidant and immunomodulatory properties.

Nevertheless, the administration of albumin in infections other than SBP was not associated with increased survival in 2 randomized studies but only to an improvement of the renal function [59,60]. Moreover, in the study of Thevenot et al., the albumin administration was responsible for two deaths due to acute pulmonary edema (8.3%) [60]. Consequently, the administration of albumin is recommended only in cases of SBP and the risk of cardiac complications should be considered when prescribing [1,2].

Prophylaxis of infections at the time of bacterial resistance, where do we stand?

According to EASL guidelines, prophylaxis for bacterial infections is recommended after a first episode of SBP, in patients at high risk of developing SBP and in patients with gastrointestinal bleeding [1,2] (Table 4). However, as previously mentioned, some studies showed an increased risk of developing ESBL-P and bacteria resistant to quinolones in case of long-term administration of quinolones [6,10,61]. In this context, rifaximin, which induces little change in the stool microbiome and does not increase the antibiotic resistance, could be a potential alternative to norfloxacin. In the meta-analysis of Goel et al., a subgroup analysis showed that rifaximin reduced the risk of SBP by 47% compared to no

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Table 4 Indication of antibiotic prophylaxis in patient with cirrhosis.

	Primary prophylaxis of SBP In patients with Low protein ascites (< 15 g/L)	Secondary prophylaxis of SBP	Primary prophylaxis in case of gastrointestinal bleeding
Indications	In patients with a Child-Pugh score ≥ 9 and serum bilirubin ≥ 3 mg/dL With Impaired renal function or Hyponatremia	After a first episode of SBP	Decompensated cirrhosis Previous quinolone prophylaxis Hospital settings with high prevalence of quinolone resistant bacterial infections
Treatment	Norfloxacin 400 mg/day	Norfloxacin 400 mg/day	Ceftriaxone 1 g/day
Duration	Until death Until liver transplantation Until improvement in liver function to a compensated status and resolution of ascites	Until death Until liver transplantation Until Resolution of ascites	Seven days

SBP: spontaneous bacterial peritonitis.

antibiotics for primary prophylaxis and by 74% compared to systemic antibiotics for secondary prophylaxis. Nevertheless, only 3 out of the 9-series studied were randomized so the results must be interpreted with caution [62]. Further randomized controlled studies are needed to evaluate this potential beneficial effect of rifaximin without increasing the risk of resistant bacterial infections.

What strategy to adopt in case of fungal infections?

An early administration of antifungal treatment, when indicated, has been associated with improved outcomes, especially in patients with severe infections [63,64]. Antifungal agents comprise 4 major categories: the polyenes (amphotericin B), the triazoles (fluconazole, itraconazole, voriconazole, and posaconazole), the echinocandins (caspofungin, anidulafungin, and micafungin), and flucytosine. Among them, Triazoles remain the most antifungal class prescribed. Nevertheless, some studies reported an increasing prevalence of azole resistant *non-albicans spp*. Echinocandins, a new antifungal class, are currently recommended as the first line treatment in critically ill patients. Compared to azoles, the echinocandins present reduced the liver and renal toxicity and are associated with minimal adverse effects. Both caspofungin and micafungin undergo minimal hepatic metabolism, but neither drug is a major substrate for cytochrome P450. The usual intravenous dosing regimens for invasive candidiasis are as follows: caspofungin: loading dose 70 mg, then 50 mg daily; anidulafungin: loading dose 200 mg, then 100 mg daily; and micafungin: 100 mg daily (no loading dose needed). No dose adjustement are recommended in case of moderate and severe liver disease except for Caspofungin (loading dose 70 mg, then 35 mg daily) [65—68]. De-escalation from echinocandins to fluconazole is advised in critically ill patients with cirrhosis and fungal infections when their condition is stable and sensitivity tests are available.

Regarding SFP, echinocandins are also recommended as first-line treatment for patients with cirrhosis and nosocomial SFP or critically ill patients with liver cirrhosis and community-acquired SFP [68].

Need for implementation of infection prevention and control measures

In addition to the proper use of antibiotics, it is necessary to develop prevention and control measures for MDR and XDR infections. Currently, there is no general consensus on the most effective strategy to prevent the spread of MDR and XDR infections. In fact, some barriers exist such as the number of different bacterial species involved, the difference in mechanisms of resistance and the transmission mechanisms. In a recent European study, contact precaution measures and spatial isolation of patients were applied in 96% and 71% of the centers respectively. However, a screening at admission was only performed in 22% of the centers. The Reasons for low compliance varied according to the countries and regions but the most frequent ones were the lack of appropriate education regarding prevention and control measures, financial restraints and structural reasons (lack of single rooms) [69].

Even if the implementation of specific measures may be difficult in some countries, mostly due to financial restraints, we have to face and prevent this spread of MDR and XDR worldwide and some strategies could be proposed:

- the development of clinical staff and dedicated educational programs to educate the whole hospital staff and to give advice regarding antibiotic prescription;
- the screening of patients at admission, especially the ones who live in areas of high MDR bacterias;
- using contact and barrier precaution measures when needed.

Conclusion

In patients with cirrhosis, bacterial infections represent a turning point in the course of the liver disease and are associated with high mortality. In recent years, changes in bacterial ecology, increasing bacterial resistance and highlighting fungal infections have made the management of infections in cases of cirrhosis more difficult. To contain the phenomenon of resistance, it is now crucial to take into account the emergence of resistance and individual/local

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ecology in order to propose the most suitable anti-infectious treatments possible. Moreover, a fungal infection must always be evoked in these high-risks patients, especially in the absence of clinical improvement under appropriate antibiotic treatment.

Disclosure of interest

The authors declare that they have no competing interest.

Authors' contributions

Drs. Allaire and Cadranel take responsibility for the integrity of data and the accuracy of data analysis.

Acknowledgment

Fanny Hadad.

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