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MINIREVIEWS

Challenges and recommendations when selecting empirical antibiotics in patients with cirrhosis

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Abstract

There is abundant evidence that bacterial infections are severe complications in patients with cirrhosis, being the most frequent trigger of acute-on-chronic liver failure and causing death in one of every four patients during hospitalization. For these reasons, early diagnosis and effective treatment of infections are mandatory to improve patient outcomes. However, treating physicians are challenged in daily practice since diagnosing bacterial infections is not always straightforward. This situation might lead to delayed antibiotic initiation or prescription of ineffective regimens, which are associated with poor outcomes. On the other hand, prescribing broad-spectrum antibiotics to all patients suspected of bacterial infections might favor bacterial resistance development. This is a significant concern given the alarming number of infections caused by multidrug-resistant microorganisms worldwide. Therefore, it is paramount to know the local epidemiology to propose tailored guidelines for empirical antibiotic selection in patients with cirrhosis in whom bacterial infections are suspected or confirmed. In this article, we will revise current knowledge in this area and highlight the importance of surveillance programs.

Key Words: Bacterial infections; Cirrhosis; Multidrug resistance; Antibiotic prophylaxis; Antibiotic stewardship

Core Tip: Practitioners who participate in caring for patients with cirrhosis are challenged when using antibiotics rationally. On one side, bacterial infections are frequent, severe, and not always straightforward to diagnose; on the other, scant granular data is publicly available about the causal microorganisms and their susceptibility patterns. According to experts, empiric antibiotic treatments should cover 80% of the common pathogens in stable patients and 90% in critically ill patients with suspected infections. Therefore, it is necessary to know the microorganisms expected to be involved in the most frequent bacterial infections and their susceptibility patterns to develop evidence-based guidelines. This opens a window of opportunity for research because bacterial infections and multidrug resistance are global health issues expected to grow over the following decades.

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INTRODUCTION

Impact of bacterial infections in patients with cirrhosis

Bacterial infections are extremely frequent in patients with cirrhosis, present in about 25%-46% of those hospitalized for an acute decompensating event. In two third of cases, infections are diagnosed at admission, whereas the remaining patients develop nosocomial infections[1,2]. The commonest infections in patients with cirrhosis include spontaneous bacterial peritonitis (SBP), urinary tract infection, pneumonia, spontaneous bacteremia, and skin and soft tissue infections[3]. Although gram-negative enteric organisms were the primary pathogens involved, gram-positive infections are increasing in prevalence. This situation might be favored by antibiotic prophylaxis, medical procedures, and prior hospitalizations, among other risk factors[2,4].

Bacterial infections are currently recognized as a surrogate for the final stage of chronic liver disease [5,6]. Even though any type of decompensation in patients with cirrhosis is associated with worsening survival, not all decompensating events carry the same weight in patients' prognosis. The relevance of bacterial infections as a prognostic factor has been clearly stated in a meta-analysis that found that they increase mortality four-fold in this population, considering 30% of patients die within one month and another 30% die one year after these infections are diagnosed[7].

Factors associated with an increased risk of infection are poor liver function, variceal bleeding, low ascitic fluid protein levels, prior SBP, and hospitalization[8]. In addition, bacterial infections have also been defined in the large prospective cohort study CANONIC as the most frequent trigger of acute-on-chronic liver failure (ACLF), negatively impacting patients' prognosis irrespective of the resolution of the infection[5]. In fact, infections as precipitant or complications arise in 50% of patients with ACLF and 70% of patients with three or more organ failures[9].

Challenges in timely diagnosis and treatment of bacterial infections

Early diagnosis of bacterial infections is crucial for the rapid initiation of antibiotic treatment[8]. However, this poses a challenge since they are often oligo-symptomatic. For example, only one-half of patients with cirrhosis and bacterial infections develop fever, and most do not present leukocytosis or systemic inflammatory response criteria[10]. This is why high clinical suspicion is critical; in fact, the European Association for the Study of the Liver (EASL) position paper on bacterial infections recommends that all patients with cirrhosis admitted to the hospital should be considered infected until proven otherwise[8]. Furthermore, it should also be considered in patients with cirrhosis that deteriorate their clinical status while admitted to the hospital[10].

A rapid evaluation, including physical examination, ascitic and/or hydrothorax evaluation, and a chest X-ray, might rule in or out some of the most frequent infections in patients with cirrhosis, such as SBP, spontaneous bacterial empyema, pneumonia, and skin and soft tissue infections. However, urinary tract infection and spontaneous bacteriemia, representing more than 40% of the infections[3], are not easy to approach because their diagnosis is mainly based on cultures, which are usually available 24 to 48 h after the initial evaluation. In practice, the difficulty of ruling out these two infections might lead to unnecessary empiric antibiotic prescriptions.

Several biomarkers have been assessed to aid in promptly diagnosing bacterial infections. C-reactive protein, ferritin, or leukocyte count lack specificity for bacterial infections[11]. Furthermore, they can be influenced by immune dysfunction and hypersplenism, presenting lower values than expected[10,11]. Procalcitonin has been proposed as a more specific marker for bacterial infection. Nearly all tissues produce this biomarker in response to endotoxin or mediators released during bacterial infections, such as interleukin (IL)-1β, tumor necrosis factor-alpha, and IL-6. It has been proposed that it highly

correlates with the severity of bacterial infections and may help distinguish bacterial from viral infections or non-infectious inflammatory syndromes[8,11]. In a meta-analysis of more than 1000 patients with infections and cirrhosis, procalcitonin and C-reactive protein had acceptable accuracy for diagnosing bacterial infection among patients with cirrhosis compared with patients with normal liver function; however, their suggested applications differ. Procalcitonin was suggested as a rule-in tool [positive likelihood ratio = 7.38, 95% confidence interval (CI): 4.70-11.58], whereas C-reactive protein was suggested as a rule-out tool (negative likelihood ratio = 0.23, 95%CI: 0.13-0.41)[12]. Ultra-sensitive procalcitonin has been suggested more recently as a valuable tool for bacterial infection diagnosis, with a sensitivity of 97% and a negative predictive value of 98%, considering a cutoff value of 0.098 ng/mL [13]. Despite these promising data, these tools have yet to be integrated into everyday clinical practice.

Due to all these limitations, other auxiliary tools have been proposed and validated in this population to diagnose sepsis. One of these is the Sepsis-3 score, which defines sepsis as a Sequential/Sepsis-related Organ Failure Assessment (SOFA) score of at least two points at intensive care unit (ICU) admission or an increase in the SOFA score during ICU hospitalization and suspected infection[14,15]. This updated clinical score aims to achieve greater consistency for future trials and ease earlier diagnosis and management of patients with sepsis or at its risk[15]. Similarly, the qSOFA score considers a surrogate of poor prognosis the presence of at least two of the following: Respiratory rate of 22 breaths per minute or greater, altered mental status, or systolic blood pressure of 100 mmHg or lower[16]. This simplified score had a greater predictive validity for in-hospital mortality than SOFA and systemic inflammatory response syndrome when used outside of an ICU setting[17]. However, these scores must be broadly validated to be used as the standard of care.

When a bacterial infection is suspected in patients with cirrhosis, the immediate initiation of antibiotics is crucial in improving the prognosis. Similarly, to the scores mentioned above, the recommendation derives from studies and guidelines considering the general population. In the Surviving Sepsis Campaign 2021, the initiation of antimicrobials is considered an emergency in patients with sepsis or septic shock. In this latter group, for each hour of delay upon administration of antimicrobials, there is a 4%-13% increase in the odds of in-hospital mortality[14]. Similar findings have been reported in patients with cirrhosis and septic shock, where each hour of delay in using appropriate antimicrobials was associated with higher mortality[18,19].

Challenges in the selection of antibiotic prophylaxis or empiric treatment in the multidrug-resistant era

It has been stated in a consensus conference regarding infections in patients with cirrhosis that randomized clinical trials on antibiotic prophylaxis are affected by several methodological pitfalls: The majority of them were under-powered, considered short follow-up periods, had methodological flaws, and were conducted more than two decades ago, in a completely different epidemiological context than the one faced today[20]. Current recommendations are based on the results of these studies, which were performed in an epidemiological setting where microorganisms responsible for infections were rarely multidrug-resistant and when gram-negative bacilli predominated over gram-positive cocci. This has changed radically in the last 20 years, with an increasing prevalence of multidrug-resistant microorganisms (MDRO), especially in patients with decompensated cirrhosis prone to hospitalizations, prolonged antibiotic prophylaxis, and invasive procedures[21]. In fact, in a recent worldwide prospective multicenter study performed by Piano *et al*[3], the global prevalence of MDRO reached 34%. These findings differed significantly by country, with a prevalence higher than 70% in India, between 20%-30% in Argentina, Canada, and several western European countries, and lower than 20% in the United States and Russia. The consequences are not trivial: Infections caused by MDRO were associated with a lower efficacy of empirical antibiotic treatment, a longer duration of antibiotic therapy, a lower rate of resolution of the infection, and a higher incidence of septic shock than those with non-MDRO infections. Most importantly, mortality was significantly higher in patients with MDRO infections[3].

Rectal colonization by MDRO may guide empirical antibiotic therapy. A recently published study showed that MDRO rectal colonization is prevalent in critically ill patients with cirrhosis (up to 47% at admission) and is associated with an increased risk of infections caused by the MDRO colonizing strains [22]. Furthermore, colonization by MDRO has also been associated with higher mortality in the liver transplant waiting list[23] and higher mortality in patients with cirrhosis and hepatocellular carcinoma [24]. All in all, the frequency of rectal colonization surveillance and its interpretation when selecting empirical therapy is yet to be defined[25].

According to experts, empiric antibiotic treatment should effectively cover approximately 80% of expected bacteria in non-critically ill patients and 90% in critically ill patients[26]. However, in the scenario mentioned above in which infections by gram-positive bacteria and multidrug organisms are increasing, prior recommendations may need to be revised. Thus, the current challenge is whether we can still safely choose antibiotic prophylaxis and treatment based on the current practice guidelines or whether these general recommendations should be regularly updated and tailored according to local epidemiological information.

Antibiotic prophylaxis in patients with cirrhosis

Antibiotic prophylaxis should be prescribed in specific clinical situations where there is a high risk for bacterial infections and when the benefit of their use outweighs the risk for adverse events and the development of antibiotic resistance[10].

Antibiotic prophylaxis in patients with acute gastrointestinal bleeding: There is broad consensus regarding prescribing antibiotic prophylaxis in acute gastrointestinal bleeding in patients with cirrhosis. This is mainly based on their high rate of bacterial infections without antibiotic use (up to 50% during the first days of hospitalization) and on the efficacy of prophylaxis in preventing infections, re-bleeding, and death[27]. Furthermore, the proposed duration of treatment is of only seven days. Thus, the risk of inducing multidrug resistance is lower than in more extended prophylaxis strategies. Regarding the choice of antimicrobial agent, a meta-analysis reports several antibiotics regimens that have a beneficial effect, with cephalosporins, quinolones, and quinolones plus beta-lactams having a more substantial protective effect than other antibiotics. Notably, no significant difference between quinolones and cephalosporins was observed[28]. However, due to the emergence of quinolone-resistant organisms, most international guidelines recommend ceftriaxone as the antibiotic of choice[27,29-31]. In countries such as the United States, where norfloxacin has been discontinued, ceftriaxone is the only recommended option[32]. The EASL 2013 position paper suggests oral norfloxacin twice daily in patients with preserved liver function as the regimen of choice, endorsing ceftriaxone in patients with decompensated cirrhosis (those with at least two of the following findings: Ascites, severe malnutrition, encephalopathy, or jaundice). Additionally, oral nitrofurantoin or ertapenem is recommended in patients with infections caused by extended-spectrum b-lactamase-producing *Enterobacteriaceae* in the last three to six months[8]. However, in a more recent publication, this scientific society endorses the use of ceftriaxone 1 g/24 h for up to seven days not only in patients with advanced cirrhosis but also in those on quinolone prophylaxis and hospital settings with a high prevalence of quinolone-resistant bacterial infections, recommending oral quinolones only for the remaining patients. They stress these recommendations should be evaluated and cross-checked from the perspective of local resistance patterns[33].

When assessing the effectiveness of current antibiotic prophylaxis strategies, a recent large multicenter study of patients with cirrhosis and variceal bleeding found that almost 20% of patients developed a bacterial infection despite using the recommendations mentioned above[34]. On the other hand, the need for routine antibiotic prophylaxis has been questioned in less severely ill patients (Child-Pugh A) due to their lower risk of infections and death[35].

Despite an acceptable consensus regarding the use of ceftriaxone as the prophylaxis of choice, this should be adapted considering the growing worldwide prevalence of MDRO, the severity of the underlying liver disease, and/or the setting of the bleeding episode (community-onset *vs* nosocomial). For example, antibiotic prophylaxis should not be the same in a patient admitted for variceal bleeding as in a patient who bleeds while in the ICU receiving antibiotics for a prior bacterial infection.

Long-term primary and secondary prophylaxis of SBP: Primary prophylaxis is proposed for patients with ascites and severe impairment of liver function, without a prior episode of SBP. The criteria used differs slightly according to different guidelines. The EASL guidelines recommend primary prophylaxis should be started on patients with low protein concentration in ascites (< 1.5 g/L), liver failure (Child-Turcotte-Pugh score > 9 and bilirubin > 3 mg/dL), and either renal dysfunction or hyponatremia[33]. In contrast, the American Association for the Study of Liver Diseases (AASLD) 2021 practice guidelines suggest primary prophylaxis could be considered in patients with the same threshold of ascitic protein accompanied by liver failure (Child-Turcotte-Pugh score > 9 and bilirubin > 3 mg/dL), renal dysfunction or hyponatremia[31]. In the latter guideline, primary prophylaxis is left to each physician's discretion since available studies are considered of variable quality and thus insufficient to support a consensus guidance recommendation. The impact of primary prophylaxis on overall survival, and not only on SBP occurrence, is a topic of ongoing research. Recently, the effect of long-term (six months) primary prophylaxis with norfloxacin has been evaluated in a randomized controlled trial that included 291 Child C patients. The risk of death at six months was significantly lower in patients with ascites fluid protein concentrations < 1.5 g/L, whereas it had no effect in patients with higher ascites protein count. Interestingly, norfloxacin significantly decreased any gram-negative bacterial infection without increasing infections caused by Clostridium difficile or MDROs[36]. Further data regarding the efficacy and safety of primary prophylaxis of SBP is expected from the ASEPTIC trial, which aims to evaluate the impact of cotrimoxazole treatment *vs* placebo during 18 mo of therapy in overall survival SBP incidence, and antimicrobial resistance, among other objectives[37].

Secondary prophylaxis (*i.e.*, in patients with at least one prior episode of SBP) rationale is based on the high risk of SBP recurrence, and the significant impact antibiotic prophylaxis has on reducing its incidence. In a trial performed more than 30 years ago, secondary prophylaxis with norfloxacin significantly reduced the probability of SBP recurrence compared to placebo (20% *vs* 68%, respectively)[38]. However, the current benefit of secondary prophylaxis with norfloxacin has recently been challenged due to the growing prevalence of quinolone-resistant bacteria and heterogeneous results in observational studies[39,40]. Several alternative strategies have been proposed to norfloxacin, using

other antimicrobials such as ciprofloxacin, rifaximin, ceftriaxone, or cotrimoxazole with different frequencies of administration (daily, five days a week, weekly). Interestingly, in a recently published meta-analysis, only daily rifaximin significantly reduced SBP recurrence compared to other antibiotics or placebo[41]. However, due to methodological concerns affecting available trials, rifaximin is not considered the standard of care for prophylaxis of SBP[42]. This poses a challenge for the treating physician when facing a patients who are under rifaximin treatment for hepatic encephalopathy that need to start prophylaxis for SBP: The aforementioned EASL guidelines state that no recommendation can be provided to guide the choice of antimicrobial among patients already on rifaximin[33]: Choosing either antibiotic or both becomes a personalized choice.

Rational selection of empiric antibiotics: Easier said than done

In daily practice, various forces drive the decision to start empiric antibiotic treatment. Given the high incidence and severe impact of bacterial infections in patients with cirrhosis, it is likely that antibiotics are overused in this population. In fact, a recent sub-analysis of the ATTIRE clinical trial suggested that half of the antibiotics prescribed to hospitalized patients with decompensated cirrhosis might not be necessary[43].

That said, the next step after confirmation or suspicion of sepsis is to start an empiric antibiotic treatment, which will be selected taking into account the site of the infection (SBP, urinary tract infection, *etc.*), the type of infection (community-acquired, health-care-associated, or nosocomial), and the pattern of resistance according to the local epidemiology. However, it is also important to consider the degree of liver failure, renal function, and potential allergies, among other variables. Another critical factor that has to be taken into account is the severity of the infection, which might be explored by evaluating the presence and number of organ failures or by calculating scores like CLIF-C AD, CLIF-C ACLF, and quick SOFA, among others[33], as was previously discussed.

Several models to predict the risk of infection by multidrug-resistance organisms were published to refine the selection of the empirical antibiotic treatment. Unfortunately, none were developed or validated in patients with cirrhosis, and their performance was moderate[44,45]. The most desirable tool to guide the selection of antibiotics would be real-time techniques that inform on the involved microorganisms and their antibiotic susceptibility pattern. Gram stain preparation is the only widely available and straightforward approach, but it provides limited information. However, in the future, other rapid molecular tests still under development or validation could give this information in minutes or hours and might help select empirical treatments in patients with cirrhosis[46].

Guidelines for antibiotic selection and protocols for rapid evaluation of patients with suspicion of sepsis are very helpful[47]. However, the need for knowledge about the expected local microorganisms and their susceptibility patterns are some of the barriers to developing these guidelines. Therefore, the World Health Assembly proposed a plan for antimicrobial resistance in 2015, which enhances surveillance of antimicrobial susceptibility patterns to generate evidence-based empiric antibiotic recommendations. Surveillance can be performed at different levels, from single institutions to states or countries. But ideally, each institution should count on sufficient granular data to generate its recommendations which would guide the treating physician to select the shortest treatment duration with the lowest-spectrum antibiotic, which will cover 80%-90% of the anticipated microorganisms using an adequate dose and route of administration[3,48].

It is known that keeping an active surveillance program that performs periodic reports and recommendations requires a multidisciplinary expert team, is time-consuming, and is costly[49]. Therefore, scientific societies or governmental organizations should implement and lead these programs and report their results at different levels. For example, Argentina and Uruguay launched a surveillance program for bacterial infections in patients with cirrhosis in October 2018, which hepatologists, infectious diseases, and epidemiologists lead and aims to serve as a platform to perform evidence-based recommendations regarding empirical antibiotic selection in this population[50].

The most recently published recommendations for empiric antibiotic treatment in patients with cirrhosis can be found in the AASLD and EASL guidelines for managing patients with decompensated cirrhosis (Table 1)[31,33]. These recommendations should be adopted with caution after revisiting the epidemiological particularities that a given center or region might have and discussing them with infectious disease specialists and microbiologists.

For example, for the case of empirical treatment of SBP, guidelines suggest using a third-generation cephalosporin or piperacillin-tazobactam. However, it should be noted that there are essential differences among third-generation cephalosporins. Ceftazidime, ceftriaxone, and cefepime are mainly used to treat community-acquired SBP, but their spectrum varies. Generally speaking, cefepime and ceftriaxone cover most gram-negative and gram-positive bacteria, which are expected to cause community-acquired SBP. However, ceftazidime does not cover gram-positive bacteria, like *Streptococcus spp*, which are known to be highly prevalent in some regions in patients with community-acquired infections, like SBP and spontaneous bacteremia[39,51]. Similarly, these guidelines recommend using fluoroquinolones (ciprofloxacin or levofloxacin) in patients with community-acquired urinary tract infection, which might offer inadequate coverage in regions where the prevalence of resistance of community uropathogens to fluoroquinolones is known or expected to be high.

Table 1 Empiric antibiotic recommendations in patients with cirrhosis, according to source, severity and type of infection

Infection	AASLD	EASL
Spontaneous infections (peritonitis, bacteremia[1], empyema)	Community acquired: Third-generation cephalosporins	Community acquired: Third-generation cephalosporins or piperacillin/tazobactam Healthcare-associated: Area dependent: Like nosocomial infections if high prevalence of MDRO or sepsis
	Nosocomial: Piperacillin/tazobactam and daptomycin (if known VRE in past or evidence of GI colonization) or meropenem if known to harbor MDR gram-negative organisms	Nosocomial: Carbapenems alone or carbapenems and daptomycin, vancomycin or linezolid if high prevalence of MDR gram-positive bacteria or sepsis
Pyelonephritis/urinary tract infection	Uncomplicated pyelonephritis: Fluoroquinolones (ciprofloxacin or levofloxacin). Severe pyelonephritis: Third-generation cephalosporins (*e.g.*, ceftriaxone). If recent antibiotic exposure: Piperacilin/tazobactam or carbapenem	Community acquired: Uncomplicated: Ciprofloxacin or cotrimoxazole. If sepsis: Third-generation cephalosporins or piperacillin/tazobactam. Healthcare-associated: Area dependent: Like nosocomial infections if high prevalence of MDROs or if sepsis. Nosocomial: Uncomplicated: Fosfomycin or nitrofurantoin. If sepsis: Meropenem and teicoplanin or vancomycin
Pneumonia	Community acquired: (1) Non-severe: B-lactam and macrolide or respiratory fluoroquinolones; and (2) Severe: B-lactam and macrolide or B-lactam and fluoroquinolones. Vancomycin can be added if patient has prior respiratory isolation of MRSA. Hospital acquired (not ventilator associated): (1) Non-severe (not septic, not intubated): One of the following: Piperacillin/tazobactam or cefepime or levofloxacin. Vancomycin can be added if MRSA was isolated in the last 90 d or if antibiotics were used in the last 90 d; and (2) Severe (presence of sepsis or requiring intubation). One of the following: Piperacilin tazobactam or cefepime or meropenem and levofloxacin. Vancomycin can be added if MRSA was isolated in the last 90 d or if antibiotics were used in the last 90 d. Pseudomonas coverage: If there is prior respiratory isolation of pseudomonas of recent use of parenteral antibiotics or hospitalization	Community acquired: Piperacillin/tazobactam or ceftriaxone and macrolide or levofloxacin or moxifloxacin. Healthcare-associated: Area dependent: Like nosocomial infections if high prevalence of MDROs or if sepsis. Nosocomial: Ceftazidime or meropenem and levofloxacin ± glycopeptides or linezolid
Cellulitis	Moderate (with systemic signs of infection): Penicillin or ceftriaxone or cefazolin or clindamycin. Severe (failed antibiotics, presence of sepsis): Vancomycin and piperacillin/tazobactam	Community acquired: Piperacillin/tazobactam or third-generation cephalosporins and oxacillin. Healthcare-associated: Area dependent: Like nosocomial infections if high prevalence of MDROs or if sepsis. Nosocomial: Third-generation cephalosporin or meropenem and oxacillin or glycopeptides or daptomycin or linezolid

[1]European Association for the Study of the Liver refers only to spontaneous bacterial peritonitis and spontaneous bacterial empyema.
AASLD: American Association for the Study of the Liver; EASL: European Association for the Study of the Liver; GI: Gastrointestinal; MDR: Multidrug-resistant; MDROs: Multidrug-resistant microorganisms; MRSA: Methicillin-resistant *Staphylococcus aureus*; VRE: Vancomycin-resistant enterococcus.

Final thoughts

There is an evident conflict between ensuring adequate antibiotic prophylaxis or empiric treatment and rationalizing broad-spectrum antibiotics in patients with cirrhosis. After reviewing the literature in search of information that may be useful to guide the rational use of antibiotics in this population, several shortcomings emerge. There is insufficient granular data on the susceptibility patterns of the microorganisms involved in bacterial infections. This should stimulate research and publications of descriptive studies that serve as a platform for developing evidence-based guidelines. Many centers worldwide likely have valuable information that needs to be published. Part of the complexity of this type of research is that the microorganisms involved and their susceptibility patterns change over time. Therefore, it is necessary to have sustained surveillance programs and not just short-term studies.

CONCLUSION

Since the World Health Organization anticipates that drug resistance will have a catastrophic impact on health systems and the global economy by 2050, all healthcare professionals that participate at different levels in the care of patients with cirrhosis should advocate for the rational use of antibiotics.

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