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**Antibiotic treatment in cirrhotic patients**

Fiore F *et al.* Antibiotic treatment in cirrhosis

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**Abstract**

In this editorial, we comment on the article by Liakina V: “Antibiotic resistance in patients with liver cirrhosis: Prevalence and current approach to tackle” (*World J Clin Cases* 2023, 11: 7530-7542). In this excellent review, Liakina presents current data on bacterial complications in patients with cirrhosis. Bacterial infections are the most common complication in patients with liver cirrhosis. We focus specifically on spontaneous bacterial peritonitis (SBP) which is the most representative infectious complication. Liakina V suggested starting empirically, in all patients with suspected SBP, third-generation cephalosporins when the number of polymorphonuclear leukocytes (PMNs) in ascites is greater than 250/mm3. This statement creates some doubts in our clinical practice so we discuss on the unsolved pitfalls of diagnosis and treatment that are often encountered in patients with ascitic fluid infections, especially on bacterascites that is defined as ascitic bacterial growth with PMNs below 250/mm3. The severity of liver disease and overall prognosis are highly comparable for patients with bacterascites and SBP in some recent well-conducted studies. Furthermore, we present a brief analysis of the prevalence of antibiotic-resistant isolates with an introduction of currently approved antibiotic drug options to treat ascitic fluid infections avoiding antibiotic resistance. In light of the most recent epidemiological data, third-generation cephalosporins should not be considered as an empirical antibiotic treatment of choice for ascitic fluid infections.

**Key Words:** Spontaneous bacterial peritonitis; Bacterascites; Multidrug resistance; Cirrhosis; End-stage liver disease

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**Core Tip:** In this editorial, we comment on the article by Liakina: “Antibiotic resistance in patients with liver cirrhosis: Prevalence and current approach to tackle” (*World J Clin Cases* 2023, in press). Our focus is on the unresolved pitfalls in diagnosing and treating cirrhotic patients with an examination of the frequency of antibiotic-resistant isolates, a brief outline of resistance mechanisms in the most common causative agents, and a list of antibiotic drug options that are currently approved.

**INTRODUCTION**

In this editorial we comment on the review article by Liakina[1] published in the recent issue of the *World Journal of Clinical Cases*. Liakina[1] provided a summary of the present state regarding the impact of antibiotic resistance, examining the prevalence and pathways of both intrinsic and acquired bacterial resistance of most frequent infections in patients with liver cirrhosis. Recent recommendations regarding both prophylaxis and treatment of these infections were also examined.

Severe bacterial infections are the most common complication in patients with liver cirrhosis. We focus specifically on spontaneous bacterial peritonitis (SPB) which is the most representative infectious complication, though bloodstream infections, pneumonia, urinary tract infections, and skin and soft tissue/musculoskeletal (SST/MSK) infections are also frequent among cirrhotic patients. Infection is a frequent precipitant of acute-on-chronic liver failure (ACLF), a syndrome in cirrhotic patients with high short-term mortality. In a retrospective cohort study of 22589 ACLF patients, SBP was associated with a 1.79-fold increased odds of 90-d mortality *vs* no infection [95% confidence interval (95%CI): 1.58-2.02, *P* < 0.001], whereas SST/MSK infections had a lower relative odds of mortality (odds ratio = 0.48, 95%CI: 0.42-0.53, *P* < 0.001)[2].

Several factors such as bacterial overgrowth, modification of luminal factors, altered intestinal permeability, and immune dysfunction, are thought to be involved in the pathogenesis of these infectious complications. Moreover, healthcare exposure and ecological pressure on bacteria due to recurrent (treatment and prophylaxis) antimicrobial use are risk factors for the occurrence of infections due to multidrug-resistant (MDR) organisms (MDROs). In addition, antibiotic resistance is known to be a predictor of a poor outcome in severe infections, and it is associated with a high risk of inappropriate antibiotic treatment.

**The thorny issue of SPONTANEOUS ascitic fluid INFECTION**

SBP is difficult to manage due to its high mortality for the clinician[3]. In this excellent review, Liakina stated to start empirically, in all patients with suspected SBP, third-generation cephalosporins (3GCs) when the number of polymorphonuclear leukocytes (PMNs) in ascites is > 250/mm3. This statement creates some doubts in our clinical practice because the treatment is subject to neutrophil counts in ascitic fluid. Therefore, if we have a septic ascitic cirrhotic patient with abdominal pain/discomfort, we will not begin treatment of SBP if the neutrophil count in ascitic fluid does not exceed 250/mm3?

Bacterascites (BA) is defined as ascitic bacterial growth with PMNs below 250/mm3. The severity of liver disease and overall prognosis are highly comparable for patients with BA and SBP; approximately four-fifths of BA patients are symptomatic[4].

In a retrospective analysis of 114 patients with BA and 88 patients with SBP, Oey *et al*[4] found that the mortality rate in the BA cohort (30-d: 36%; 6-mo: 62%; 1-year mortality: 66%) was not statistically different from that of the SBP cohort (30-d: 13%-49%; 6-mo: 52%-59%; 1-year mortality: 49%-70%). In another Chinese retrospective study, Ning *et al*[5] enrolled a total of 600 patients: 192 with BA and 408 with SBP. The 30-d mortality was 13.5% in the BA cohort and 25.7% in the SBP cohort. In a comparative study from Taiwan, Chu *et al*[6] found that in-hospital mortality was 54.5% for SBP and 50% for symptomatic BA.

High mortality rates have also been reported by European studies; Piroth *et al*[7], in a retrospective analysis of 57 patients with SBP and 140 with BA, found high in-hospital mortality (37% in SBP and 18.5% in BA cohort). Lutz *et al*[8], in a prospective observational cohort study enrolling 28 patients with BA and 43 with SBP, found 1-year mortality of 61% in the BA cohort and 47% in the SBP cohort.

King *et al*[9] evaluated retrospectively 176 cases of SBP and 213 cases of BA from 2008 to 2018. The authors found that the SBP patients had significantly higher Model for End-Stage Liver Disease (MELD) scores, peripheral blood white cell counts, and rates of *Enterobacteriaceae* and MDR. Patients with SBP had a lower survival rate at 30 d and 3 mo compared to BA, but no significant difference remained at 6 mo and beyond. The predicted mortality calculated by the MELD score alone was significantly lower than the mortality across all MELD groups for both SBP and BA; BA had a greater negative impact on patient survival than what was predicted by the MELD score[9]. The mortality rates are certainly not unequivocal in cirrhotic patients, and mortality does not depend on infection alone but *in primis* on liver and kidney function and the timeliness of medical treatment. That said, following the literature mentioned above, mortality is high in all BA patients.

**MDROs CAUSING ASCITIC FLUID INFECTION**

Nonsusceptibility to at least one antibiotic in at least three antimicrobial categories is the definition of MDR bacteria[10]. MDR has emerged as one of the principal public health problems; bacteria that are no longer susceptible to common antibiotics are causing an increasing range of infections[11]. MDR bacterial infections are a principal health problem even in decompensated cirrhotic patients with ACLF: MDR prevalence increased from 29% to 38% in culture-positive infections from 2011 to 2017/2018 in Europe[12].

Geographical areas have a significant difference in the prevalence of MDR bacteria; the prevalence of MDR across Europe is highly variable (ranging from 57% in Israel to 17% in Russia). Remarkably, MDR bacterial infections are very common in Indian centres (73% of isolates), whereas their prevalence is quite low in North American centres (16% in the United States and 24% in Canada); the global prevalence of MDR is 34% (95% confidence interval 31%–37%), with Asia seeming to have the highest prevalence[13].

The SBP mortality rates have remained the same in recent years despite advances in medical knowledge[14], which may be a result of the increase in MDR. The emergence of MDR has made ineffective cephalosporins which have been the cornerstone of SBP empirical antibiotic treatment for many years. A French retrospective analysis of 57 patients with SBP and 140 with BA found a 37% mortality for SBP *vs* an 18.5% mortality for BA; interestingly, no significant association was found for the empirical antimicrobial treatment given to the two groups, with a single antibiotic antimicrobial coverage of less than 60% of isolates[7]. The risk of 3GC resistance in nosocomial SBP is not significantly higher than that in community-acquired SBP, according to studies that enrolled patients in the last decade[15]. In a recent retrospective study conducted at two large academic tertiary care centres in Los Angeles, California from January 2015 to January 2021, 267 patients with SBP were enrolled, and the bacterial culture test of ascitic fluid was positive in 88 patients. MDR status was seen in 36 (41%) of the 88 positive cultures[16]. In a recent retrospective Chinese study analyzing data from January 2015 to December 2020 of 377 patients with SBP and 794 with BA, MDR bacteria comprised 49.7% of Gram-positive and 48.8% of Gram-negative bacteria (GNB). Interestingly, there is no statistical difference for MDR in the two groups: MDR bacteria comprised 44.7% in BA and 49.3% in SBP[17].

Although the prevalence of MDR certainly varies from centre to centre, the latest data show an increase in MDR up to almost 50% of pathogens isolated from ascitic fluid culture.

**ANTIBIOTIC TREATMENT TAILORED ON CIRRHOTIC PATIENTs**

For some decades, 3GCs were the cornerstone of the treatment for serious bacterial infections (including SPB) among cirrhotic patients. However, the emergence and spread of 3GC resistance in community and healthcare settings have significantly reduced the effectiveness of these agents because a high rate of inappropriate antibiotic treatment, and consequently a high risk of poor outcomes. More recently, an analysis of studies that enrolled patients in the last decade did not show a significantly higher relative risk of 3GC resistance in nosocomial SBP compared with community-acquired SBP. Therefore, in centres with high rates of 3GC resistance, these antibiotics should not be used initially even for community-acquired SBP management[15]. In this context, a de-escalation strategy (starting with broad-spectrum antibiotic therapy and then narrowing the antibiotic spectrum at the arrival of the cultural specimen) seems to be more appropriate than an escalation strategy (starting with a cephalosporin and then at the arrival of the cultural examination or therapeutic failure to switch to wider spectrum antibiotics). In a randomized open-label study, Merli *et al*[18] showed that the use of broad-spectrum antibiotic regimes for the management of healthcare infections [imipenem (IMI)/cilastatin (CIL) plus vancomycin (VAN) for SPB and other intra-abdominal infections, IMI/CIL for urinary tract infections, IMI/CIL plus VAN and azitromycin for pneumonia, and IMI/CIL or tigecycline (TGC) for soft tissue infections, respectively] was associated with a lower rate of in-hospital mortality compared to standard regimens [mainly based on 3GCs; 25% *vs* 6% (*P = 0.01*)]. Similarly, in a subsequent randomized and controlled trial, Piano *et al*[19] compared *ab initio* a 3GC [ceftazidime (CAZ)] or a carbapenem [meropenem (MER)] plus daptomycin: The combination of a carbapenem plus daptomycin was significantly more effective than a 3GC in the treatment of nosocomial SBP (86.7 *vs* 25%; *P* < 0.001). The spread of carbapenemase-producing *Enterobacterales* (CPE) poses a further and dangerous problem for the management of infectious complications among cirrhotic patients. For these infections, several antibiotic regimens including high-dose MER and/or high-dose TGC plus old antibiotics [colistin or aminoglycosides (mainly amikacin and gentamicin)] were utilized by Fiore *et al*[20]. However, newer antibiotics have been introduced with enhanced antimicrobial effectiveness in recent years. CAZ/avibactam (AVI) has activity against several GNB, including CAZ-resistant strains. It is active against GNB strains producing Ambler class A [extended-spectrum β-lactamase (EsβL) and *K. pneumoniae* carbapenemase (KPC)], class C (AmpC), and some class D (OXA-48) enzymes, whereas it is inactive against metallo-β-lactamases (MβL) and Acinetobacter OXA-type carbapenemases[21]. In an Italian cohort study, Feldman *et al*[22] observed that CAZ/AVI therapy (monotherapy or combination therapy) was associated with lower rates of treatment failure due to KPC infections independent of the severity of liver disease compared to regimens without CAZ/AVI (7% *vs* 38%; *P =* 0.032). Moreover, CAZ/AVI therapy improved in-hospital survival (log-rank test: *P =* 0.035) adjusted for Child class and monotherapy or combination therapy[22].

MER/vaborbactam (VAB) and IMI/CIL/relebactam (REL), two novel carbapenem-β-lactamase inhibitor combinations, have activity against GNB producing Ambler class A (EsβL and KPC) and class C β-lactamases (AmpC), but it is inactive against class B (MβL) and D (OXA) enzymes[21].

Both agents are approved for the treatment of complicated urinary tract infections, complicated intra-abdominal infections, and nosocomial pneumonia due to GNB with limited therapeutic options. However, to date, no clinical experiences have been reported. Hepatic impairment is not expected to have any clinically relevant impact on both MER/VAB and IMI/CIL/REL, as the drugs are primarily eliminated by renal excretion. Cefiderocol is a first-in-class siderophore cephalosporin antibiotic that has a broad spectrum of activity against MDR and extensively drug-resistant GNB including non-fermentative bacteria such as *P. aeruginosa* and *A. baumannii*. Cefiderocol is mainly renally eliminated and no dose adjustment is required in patients with hepatic impairment but hepatic enzyme increase was reported*.* Eravacycline (EVC) is a novel synthetic fluorocycline antibiotic with broad-spectrum activity. Overall, EVC shows *in vitro* activity that is equivalent to or 2- to 4-fold greater than TGC against *Enterobacterales* and Gram-positive bacteria. EVC has demonstrated activity against CPE and *A. baumannii*. It is currently approved for the treatment of complicated intra-abdominal infections. EVC has a hepatic metabolism but no dose adjustment is necessary in patients with hepatic impairment. Only in patients with severe hepatic impairment (Child-Pugh class C), exposure may be increased. Aztreonam (ATM)-AVI is an investigational treatment for infections caused by GNB with limited treatment options. ATM/AVI is a promising option against MβL-producing bacteria but it has also activity against GNB-producing Ambler class A (ESβL and KPC), class C (AmpC), and some class D enzymes (OXA-48 producers)[21]. Finally, in critically ill cirrhotic patients with multiple-site candidal colonization or with yeast strains isolated, an anti-fungal regimen should be considered (mainly echinocandins) because of a non-negligible risk of candidal infection[23,24].

**CONCLUSION**

In septic cirrhotic patients, the clinical signs must timely guide timely empirical antibiotic therapy rather than neutrophil counts in ascitic fluid: BA has a similar impact to SBP on patient survival beyond 30 d. Relevant differences in the prevalence of MDR bacteria are observed across the different centres with a prevalence of almost 50% in the most recent studies. In the last decade, there seems to be no significantly higher risk of third-generation cephalosporin resistance in nosocomial SBP compared to community-acquired SBP. Furthermore, the prevalence of MDR in BA or SBP seems to be similar.

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