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EDITORIAL

Multiresistant bacterial infections in liver cirrhosis: Clinical impact and new empirical antibiotic treatment policies

Juan Acevedo

Juan Acevedo, Department of Gastroenterology and Hepatology, Queen Alexandra Hospital, PO6 3LY Portsmouth, United Kingdom

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Correspondence to: Juan Acevedo, MD, PhD, Department of Gastroenterology and Hepatology, Queen Alexandra Hospital, Southwick Hill Road, PO6 3LY Portsmouth, United Kingdom. juan.acevedo@porthosp.nhs.uk
Telephone: +44-23-92286000-1210
Fax: +44-23-92286822
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Abstract

Recently, important changes have been reported regarding the epidemiology of bacterial infections in liver cirrhosis. There is an emergence of multiresistant bacteria in many European countries and also worldwide, including the United States and South Korea. The classic empirical antibiotic treatment (third-generation cephalosporins, *e.g.*, ceftriaxone, cefotaxime or amoxicillin-clavulanic acid) is still effective in infections acquired in the community, but its failure rate in hospital acquired infections and in some health-care associated infections is high enough to ban its use in these settings. The current editorial focuses on the different epidemiology of bacterial infections in cirrhosis across countries and on its therapeutic implications.

Key words: Bacterial infections; Multiresistant bacteria; Antibiotic; Liver cirrhosis

Core tip: There is a growing prevalence of multiresistant bacteria in nosocomial and in health-care associated settings worldwide. Nowadays, it is necessary that all liver units assess the presence of antibiotic resistance in their population. The classical empirical antibiotic therapy, third generation cephalosporins, can no longer be employed in areas with high prevalence of multiresistant bacterial infections. The current editorial focuses on the different patterns of resistance across countries and on its therapeutic implications.

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INTRODUCTION

Liver cirrhosis carries a big burden for health care worldwide. In Europe around 29 million people have a chronic liver disease, and mortality rate is 170000/year. Bacterial infection represents one of the main causes of decompensation. Patients with cirrhosis have alterations in the immune system and therefore they are more susceptible to develop bacterial infection, sepsis, and death[1-5]. Infection is present at admission or develops during hospitalization in around 25%-30%

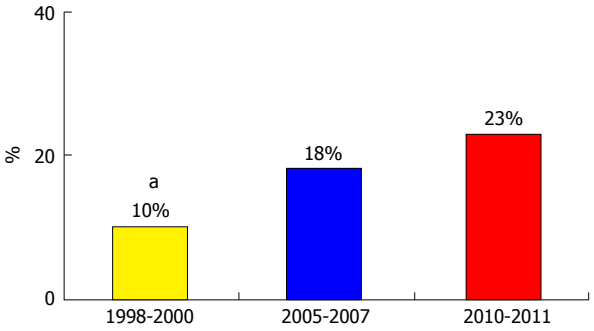

Figure 1 Increasing prevalence of multiresistant bacterial infections in a single center in Spain. Prevalence of multiresistant bacteria has doubled in the last decade (original work of the author). [a]*P* < 0.05 *vs* other periods.

of patients[5-7]. The most frequent infections in cirrhosis are spontaneous bacterial peritonitis (SBP), urinary tract infections (UTI), pneumonia, cellulitis and spontaneous bacteremia[1-3]. Bacterial infections are not only more frequent but also more severe in cirrhosis. Infection increases the probability of death 4 fold reaching 38% at 1 mo[8]. Infection can accentuate the preexisting circulatory dysfunction present in advanced cirrhosis leading to the development of hepatorenal syndrome and can also induce an excessive pro-inflammatory response that could contribute to develop multiple organ failure (acute-on-chronic liver failure) and septic shock[9]. Thus, prompt diagnosis and appropriate treatment of infection is crucial in the management of patients with cirrhosis[10,11].

GRADUAL EPIDEMIOLOGICAL CHANGES

The most common origin of infection is the community-acquired (CA) setting. The definition of healthcare associated (HCA) infection is infection which occurs previous to admission or during the first two days of hospitalization in patients in contact with the hospital setting during the last 3 mo[7].

Classically, gram-negative bacilli (GNB) accounted for the vast majority of infections (80%), but this preponderance of GNB changed at the start of the new millennium and the prevalence of gram-positive cocci (GPC) increased, accounting for almost half of the infections (47%). When infections were classified according to the origin of infection, GNB were still the most frequent bacteria causing CA infections (60%), while GPC were more prevalent in nosocomial infections (60%). This fact was explained by the increasing degree of instrumentalization of the cirrhotic patient (*i.e.*, variceal ligation, transjugular intrahepatic portosystemic shunt, and arterial chemoembolization or percutaneous ablation of hepatocellular carcinoma), and by the fact that cirrhotic patients with a critical illness are admitted into intensive care units which implies the insertion of central lines and other invasive procedures[6,7].

Furthermore, the need for long term antibiotic prophylaxis, usually with norfloxacin, also carries the risk of emerging of quinolone-resistant and cotrimoxazole-resistant bacteria. Around 50% of GNB were resistant to these antibiotics in a big study performed in 2000[7].

Multiresistant (MR) bacteria are resistant to 3 or more of the principal antibiotic families, including β-lactams[12]. The most common are extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-*E*), *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-susceptible *Enterococcus* (VSE) and vancomycin-resistant *Enterococcus* (VRE).

In 2000, only 1.2% of bacteria were resistant to third generation cephalosporins (TGC). Unfortunately, many recent studies from different countries show a growth in the prevalence of MR bacterial infections in cirrhosis. Fernández *et al*[7] reported a steady growth in the prevalence of MR bacterial infections, this prevalence rose from 10% to 23% during the period 1998-2011 in a single Spanish center[7] (Figure 1). MR bacteria were extremely frequent in the nosocomial setting, causing 35%-39% of infections, but the prevalence was very low in the CA setting, 0%-4%; and prevalence of MR bacteria in the HCA setting was intermediate, between 14% and 20%[7] (Figure 2).

DIVERSITY OF MR BACTERIA TYPES ACROSS COUNTRIES

Epidemiology of multiresistance differs among different countries and even among hospitals located in the same area. ESBL-*E* are predominant in Southern Europe and Asia[7,13-25], meanwhile MRSA and VRE are prevalent in the United States[26]. Carbapenemase-producing *K. pneumoniae* is a current problem described in some hospitals in Italy[27]. Table 1 shows the prevalence of different MR bacterial infections across countries in the cirrhotic population. The marked epidemiological differences observed among countries and centers suggest that local epidemiology should be evaluated regularly and that empiric antibiotic treatment of nosocomial infections in cirrhosis should be adjusted in accordance with the specific local pattern of multiresistance.

FAILURE OF TGC TREATMENT IN NOSOCOMIAL INFECTIONS AND CLINICAL OUTCOME

Early and appropriate antibiotic therapy is fundamental in the management of infections in patients with cirrhosis. Since the late 1980's, TGC have been recommended as empirical antibiotic therapy of the main infections in cirrhotic population because they cover a wide variety of bacteria and they are safe[28-31].

Nevertheless, recent studies demonstrate that β-lactams are not effective in an important part of infections in cirrhosis, especially in nosocomial infections[7]. TGC have scarce efficacy in nosocomial infections (40%). This

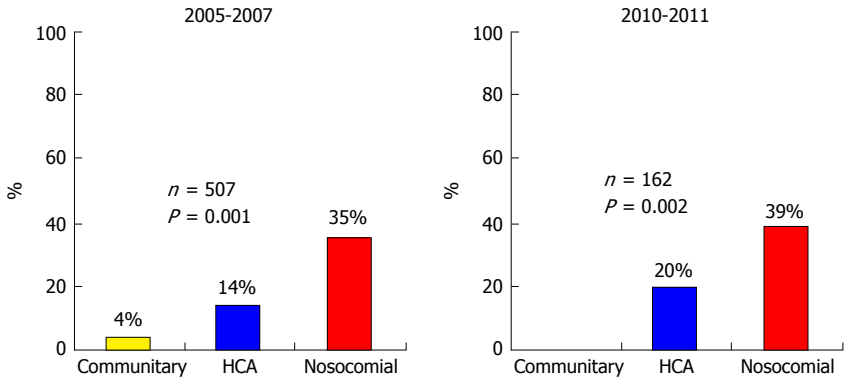

Figure 2 Prevalence of multiresistant bacterial infections according to the site of acquisition. Multiresistant bacteria are present predominantly in the nosocomial and healthcare associated (HCA) infections. *P* value in both graphics refers to χ^2 linear-by-linear association statistic (original work of the author).

Table 1 Prevalence of different multiresistant bacteria across countries

Type of multiresistant bacteria	Prevalence rate
ESBL	South Korea, 4%-29%[13,14,19,20,24]
	Italy, 8%-20%[17,21]
	Spain and United States, 6%-9%[7,15,26]
	France, Denmark and Germany, < 5%[22,23,25]
MRSA	Italy, 7%[17,21]
	United States, 5%[26]
	Spain, 3%-4%[7,15]
	France, 2%[23]
	Denmark, Germany, 0%[22,25]
Pseudomonas aeruginosa	Spain, South Korea, 2%-3%[7,13-15,19,20,24]
	Germany, 1%[22]
	Denmark, France, 0%[23,25]
VSE	Denmark, 12%[25]
	Germany, 10%[22]
	France, 5%[23]
	Spain, 1%-7%[7,15]
VRE	United States, 9%[26]
	Spain, France, Denmark, Germany, 0%[7,15,22,23,25]

ESBL: Extended-spectrum β-lactamase-producing *Enterobacteriaceae* (bacteria with chromosomal β-lactamases are also included); MRSA: Methicillin-resistant *Staphylococcus aureus*; VSE: Vancomycin-susceptible *Enterococcus*; VRE: Vancomycin-resistant *Enterococcus*.

fact is reproduced in the main types of infections as SBP, UTI and spontaneous bacteremia with efficacies of 26%, 29% and 18%, respectively. Efficacy of empirical antibiotic therapy is also lower in HCA infections compared to community-acquired infections (73% *vs* 83%), especially in pneumonia and UTI. Other groups from Italy, Germany and Turkey have also reported a reduced efficacy of TGC in SBP, with rates of failure from 18% to 41%[21,22,32].

MR bacterial infections have a poor outcome because they entail a higher incidence of treatment failure (70% *vs* 92%, $P < 0.0001$), they lead more frequently to septic shock (26% *vs* 10%; $P < 0.0001$), and cause a much higher hospital mortality rate (25% *vs* 12%; $P = 0.001$) than those infections produced by susceptible bacteria. The delay in the initiation of an appropriate antibiotic treatment is one of the main explanations for this fact[7].

RISK FACTORS FOR MR BACTERIAL INFECTIONS

Risk factors for MR bacteria constitute an important tool to identify the group of infected patients who would benefit from changing the empirical antibiotic therapy in order to cover MR bacteria. The main risk factors for the development of MR bacterial infections in the general population are current or recent hospitalization, healthcare contact (*i.e.*, hemodyalisis) and prior exposure to β-lactams or quinolones[33-37]. The same risk factors have been reported in cirrhosis. Hospital acquired and healthcare associated infections, long-term norfloxacin prophylaxis, recent infection by MR bacteria, recent use of β-lactams within the last 3 mo or systemic antibiotics in the past 30 d, upper gastrointestinal bleeding and diabetes mellitus[7,15,26].

CHANGING THE EMPIRICAL ANTIBIOTIC TREATMENT OF BACTERIAL INFECTIONS IN CIRRHOSIS

Taking into account the high failure rate of TGC in a large percentage of nosocomial infections and in a subgroup of healthcare associated infections due to the emergence of MR bacteria in these settings, it is clear that empirical antibiotic treatment in cirrhosis should be chosen in accordance with severity and type of infection, and also according to the origin of infection and to the existence of risk factors for MR bacterial infection[38-40]. The AASLD guideline was updated in 2012[41] and an EASL position statement came into light in 2013[42], both recommending substantial changes to empirical antibiotic treatment in the nosocomial setting.

Regular epidemiology assessment should be carried out in all centers and policies regarding empiric antibiotic treatment in cirrhosis should be updated and tailored according to the specific epidemiological pattern of

Table 2 Suggested empirical antibiotic therapy of bacterial infections in cirrhosis

Type of infection	Community-acquired infections	Nosocomial and HCA[1] infections	Local epidemiological pattern
SBP, SBE and SB	Third generation cephalosporin Or amoxicillin/clavulanic acid	Piperacilin/tazobactam Or carbapenem Plus glycopeptides (or linezolid)	Low prevalence of MR bacteria ESBL-*E* MRSA and VSE (when VRE)
Urinary tract infections	Third generation cephalosporin Or amoxicillin/clavulanic acid	Without sepsis: Nitrofurantoin or fosfomycin With sepsis: Piperacilin/tazobactam Or carbapenem Or plus glycopeptides (or linezolid)	VSE Low prevalence of MR bacteria ESBL-*E* MRSA and VSE (when VRE)
Pneumonia	Amoxicillin/clavulanic acid Or ceftriaxone + macrolide Or levofloxacin Or moxifloxacin	Piperacilin/tazobactam Meropenem or ceftazidime + ciprofloxacin Plus vancomycin (or linezolid)	Low prevalence of MR bacteria ESBL-E and *P. aeruginosa* MRSA and VSE (when VRE)
Skin and soft tissue infections	Amoxicillin/clavulanic acid Or third generation cephalosporin plus oxacillin	Meropenem or ceftazidime + oxacillin Plus glycopeptides (or linezolid or daptomycin)	ESBL-E and *P. aeruginosa* MRSA and VSE (when VRE)

[1]HCA infections with at least two of the following risk factors for MR bacteria: long-term norfloxacin prophylaxis, recent infection by MR bacteria in the last 6 mo, recent use of β-lactams in the last 3 mo. SBP: Spontaneous bacterial peritonitis; SBE: Spontaneous bacterial empyema; SB: Spontaneous bacteremia; HCA: Health-care associated; ESBL-*E*: Extended-spectrum β-lactamase producing *Enterobacteriaceae*; MRSA: Methicillin-resistant *Staphylococcus aureus*; VSE: Vancomycin-susceptible *Enterococcus*; VRE: Vancomycin resistant *Enterococcus*.

multiresistance in the area.

CURRENT EMPIRICAL ANTIBIOTIC TREATMENT OF COMMUNITY-ACQUIRED INFECTIONS

TGC are still effective in infections acquired in the community in cirrhosis with resolution rates of around 80%[7]. Quinolones should not be used in patients on norfloxacin prophylaxis or in zones with a high prevalence of quinolone-resistant bacteria[1,6]. For the empirical therapy of UTI we can employ trimethoprim-sulfamethoxazole, quinolones or β-lactams. β-lactams are the baseline treatment of pneumonia (in combination with levofloxacin, moxifloxacin or a macrolide) and cellulitis as well[38-42] (Table 2).

CURRENT EMPIRICAL TREATMENT OF NOSOCOMIAL INFECTIONS

Empirical antibiotic therapy should be selected in accordance with the local epidemiological pattern of multiresistance[38-42]. In zones with a high prevalence of ESBL-*E*, carbapenems should be employed as empirical treatment of spontaneous infections such as SBP, spontaneous bacteremia and spontaneous empyema. A glycopeptide (vancomycin or teicoplanin) should also be added to this empirical treatment in zones with a high prevalence of MRSA or VSE. In the United States and other countries with a high prevalence of VRE, glycopeptides should be substituted for linezolid or daptomycin[38-42]. However, in zones with a low rate of MR bacteria, piperacillin-tazobactam can be employed to treat spontaneous infections[38-42] (Table 2).

Nosocomial UTI without sepsis should be treated with oral nitrofurantoin or fosfomycin. UTI with sepsis should be treated with carbapenems plus glycopeptides to cover ESBL-*E* and VSE (Table 2)[38-42]. Again, in zones with a scarce prevalence of MR bacteria, piperacillin-tazobactam can be employed in UTI with sepsis (Table 2).

In zones with a high prevalence of MR bacteria, nosocomial cellulitis should be covered against MRSA and *Pseudomonas aeruginosa.* Thus, ceftazidime or carbapenem plus a glycopeptide can be employed. In areas with low rate of MR bacteria, cloxacillin or amoxicillin-clavulanic acid can be employed[38-42] (Table 2).

Empirical treatment of hospital acquired pneumonia should follow the local guidelines recommended for the general population.

CURRENT EMPIRICAL TREATMENT OF HEALTHCARE-ASSOCIATED INFECTIONS

TGC and amoxicillin-clavulanic acid are effective when employed in SBP (resolution rate: 71% compared to 78% in CA infections) or cellulitis (resolution rate: 81% *vs* 82% in CA infections). However, their efficacy is low in HCA pneumonia (33%) and UTI (59%)[7,38]. Therefore, empirical antibiotic therapy for HCA UTI and pneumonia and for patients with HCA spontaneous infections with two or more risk factors of infection caused by MR bacteria or those patients with severe sepsis or septic shock should follow the same scheme recommended in nosocomial infections (Table 2)[38,40].

In general, de-escalation to the most suitable antibiotic should be done soon after the report from microbiological tests (about 50% of cases) in order to

reduce the emergence of antibiotic resistance[38,40].

CONCLUSION

In conclusion, recent data demonstrate that TGC are not appropriate for the treatment of nosocomial infections in cirrhosis because of the high prevalence of MR bacteria in this setting. New antibiotic strategies for these infections should be adjusted in accordance with the local epidemiological pattern of multiresistance. In areas with high prevalence of ESBL-*E*, guidelines should include the use of carbapenems. In zones with high prevalence of MRSA and VSE glycopeptides are needed and in zones with high prevalence of VRE linezolid or daptomycin are needed as initial treatment of nosocomial infections in cirrhosis. Early de-escalation of antibiotics according to the microbiological results is also mandatory.

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