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Another clinical unmet need in liver patients: Multidrug resistant bacteria in decompensated cirrhosis

To the Editors:

We read with interest the article by Fernández *et al.* regarding the epidemiology, risk factors and impact of bacterial infections in cirrhotic patients in Europe.[1] While most of the previous studies came from single centers, this study addresses an emerging and threatening health issue in series of patients from different geographic areas. The prevalence of multidrug-resistant (MDR) bacteria in culture-positive infections was 29.2% and was significantly higher in Northern and Western Europe than Southern Europe. In a recent published study by Piano *et al.*,[2] the estimated global prevalence of MDR bacteria was 34% in patients with a positive culture, with a reported prevalence of 29% in Europe, despite relevant variability among European countries. Nevertheless, this issue may be underestimated.

Taking this into account, we retrospectively analyzed all bacterial infections with confirmed microbiological isolation in patients with decompensated liver cirrhosis that were admitted, between January 2009 and May 2016, to a non-transplant tertiary reference center from Porto, the largest city of northern Portugal. Three hundred and eight infections with positive cultures were identified, corresponding to 218 admissions, in a total of 161 patients. The median age of the patients was 63 years (interquartile range 55–71) and 67% of them were men. Alcohol-related liver disease (72%) and hepatitis C virus infection (10%) were the major causes of cirrhosis. The median model for end-stage liver disease score on admission was 20 (interquartile range 12–25). Among the infections evaluated, 87% were nosocomial and 13% community-acquired. Urinary tract infection (57%), bacteremia (12%) and spontaneous bacterial peritonitis (SBP; 8%) were the most common types of infection in patients with microbiological isolation. In 27% of patients, there were at least 2 concomitant bacterial infections. Gram-negative bacteria and gram-positive bacteria each accounted for 50% of positive cultures. MDR bacteria were isolated in 51% of cases (n = 158), the most common being extended spectrum β-lactamase producing *Enterobacteriaceae* (n = 39), *Enterococcus Faecium* (n = 34), *Enterococcus Faecalis* (n = 16), *Pseudomonas Aeruginosa* (n = 6) and *Methicillin-resistant Staphylococcus aureus* (n = 4). Overall, 19 cases of extensively drug-resistant (XDR) bacteria (6.2%) were isolated and there was 1 reported case of pandrug-resistant (PDR) bacteria. This was a patient admitted with SBP, and a positive culture for *Enterobacter cloacae* resistant to all available antimicrobial agents. The patient was under large-spectrum antibiotic therapy with ertapenem, but died 4 days after admission.

We aimed to identify risk factors for MDR infection (Table 1). In our cohort, in contrast to the study by Fernández *et al.*, the multivariate analysis showed that prophylaxis for SBP was associated with MDR bacterial infection. Other factors independently associated with MDR bacterial infections replicated those previously described, including hospitalization in an intensive/intermediate care unit in the previous month and

Table 1. Predictors of development of MDR infection.

	Unadjusted OR (95% CI)	*p* value	Covariate-adjusted OR (95% CI)	*p* value
Age	0.98 (0.96–0.99)	0.018	0.99 (0.97–1.01)	0.248
Immunosuppressants	2.84 (1.36–5.92)	0.005	1.84 (0.79–4.28)	0.159
Antibiotic prophylaxis for SBP	3.01 (1.69–5.36)	<0.001	2.25 (1.14–4.47)	**0.020**
Ascites on admission	1.79 (1.11–2.90)	0.018	1.27 (0.73–2.32)	0.398
MELD score on admission	1.03 (1.01–1.06)	0.016	1.01 (0.98–1.04)	0.508
Hospitalization in the previous 3 months	2.73 (1.70–4.39)	<0.001	1.58 (0.89–2.79)	0.118
Hospitalization in an intermediate/intensive care unit in the previous month	3.19 (1.78–5.74)	<0.001	2.50 (1.31–4.77)	**0.005**
Antibiotic therapy in the previous 6 months	3.50 (2.18–5.61)	<0.001	1.88 (1.06–3.32)	**0.030**

MDR, multidrug resistant; MELD, model for end-stage liver disease; OR, odds ratio; SBP, spontaneous bacterial peritonitis. Predictors of MDR infection were determined by binary logistic regression (SPSS® v.24.0 data)

antibiotic therapy in the previous 6 months. The occurrence of MDR bacterial infection was associated with a longer duration of hospitalization (21 ± 17 *vs.* 16 ± 12 days; $p = 0.008$), although with no significant association with mortality (in-hospital or 1 month after discharge) in the multivariate analysis.

Although previous epidemiological studies pointed to a lower prevalence of bacterial infections in hospitalized cirrhotic patients, our data shows an alarming frequency of MDR bacteria in patients admitted with decompensated cirrhosis. Interestingly, in our cohort, SBP prophylaxis with quinolones (25% of our patients) was associated with the emergence of MDR bacteria. Around 70% of our patients had alcohol-related liver disease, which is higher than other studies performed in Europe. Despite contradictory evidence, there is previous literature showing that alcohol-related liver disease and alcohol consumption, particularly alcoholic hepatitis, are associated with increased rates of infection and antibiotic resistance, which could partly explain our high rate of MDR infections.[3] Additionally, the emergence and identification of 1 case of PDR-bacteria is alarming and can have serious clinical consequences.

In conclusion, these recent studies highlight that the spread of MDR and XDR bacterial infections in patients with cirrhosis is a worrisome unmet clinical need. Thus, while new antibiotic strategies are awaited and global health initiatives are implemented, urgent efforts should be directed by national societies and locally to set up infection control measures and antibiotic stewardships to limit the spread of MDR bacteria in patients with cirrhosis.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.06.010.

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Reply to: "Another clinical unmet need in liver patients: Multidrug-resistant bacteria in decompensated cirrhosis"

To the Editor:

We thank Dr. Rui Morais for their interest in our recent publication that highlighted that antibiotic resistance constitutes a prevalent and alarming healthcare problem in patients with decompensated cirrhosis in Europe.[1] In just 7 years, the global prevalence of multidrug-resistant (MDR) bacterial infections increased from 29% to 38% in patients admitted to the hospital with acute decompensation. This Letter to the Editor reports retrospective data from a single center in Porto, Portugal, and shows that more than half of the culture positive infections (51%) were caused by MDR bacteria, mainly ESBL-producing *Enterobacteriaceae* and vancomycin-susceptible enterococci. The main reason behind the higher prevalence of MDR bacterial infections in the Portuguese series is that nosocomial infections were overrepresented in this cohort (87% of all infections), a factor that increases the risk of developing an MDR infection by almost 3-fold.[1] Moreover, our study showed a high heterogeneity in the prevalence and type of MDR bacteria among centers, even in the same geographical region or city. Authors also investigated independent risk factors for MDR infection in their series and found that long-term antibiotic prophylaxis increased the risk of infection by these difficult to treat strains by 2.25 (1.14–4.47, $p = 0.02$). This finding contrasts with our results but is in line with previously reported data.[2] The low number of patients on long-term quinolone prophylaxis in our study (n = 7) probably explains this discrepancy.