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.

Finally, and in contrast with our study, the authors did not find a significant association between antibiotic resistance and mortality. However, the retrospective nature of the Portuguese study limits its capacity to adequately address this issue, very well demonstrated in large scale studies published recently.[1,3]

Our study and the data reported in the letter by Morais *et al.*, demand the urgent evaluation of new strategies aimed at preventing the spread of antibiotic resistance in the cirrhotic population, including epidemiological surveillance and antibiotic stewardship programs and rapid microbiological tests.

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

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Comparison of risk of hepatocellular carcinoma between tenofovir and entecavir: One direction or no direction

To the Editor:

We read with interest the study by Kim *et al.* that was recently published in the *Journal of Hepatology*.[1] The authors concluded that the risk of hepatocellular carcinoma (HCC) did not differ between patients treated with entecavir (ETV) and those treated with tenofovir disoproxil fumarate (TDF). This seems to contradict our earlier publication, which showed a lower risk of HCC with TDF than with ETV.[2] The contradicting results should be interpreted with caution, taking into account differences in the characteristics of the study population, study design, statistical power, and potential confounding.

The most prominent difference between the 2 studies is the number of patients with cirrhosis included in the analyses. Although the 2 studies applied a similar definition for cirrhosis (image diagnosis or platelet count, <150,000/μl), cirrhosis was more prevalent in our study population (58.8%) than in that of Kim *et al.* (31.4%). The number of patients included in the propensity score-matched analysis was greater in our study (510 *vs.* 380 pairs). Furthermore, the mean baseline hepatitis B virus (HBV) DNA levels were higher in our study (6.6 *vs.* 5.6 $\log_{10}$ IU/ml). Lastly, patients with decompensated cirrhosis were included in our study but excluded in the study of Kim *et al.* All these factors indicate that the patients in our study had a higher risk of developing HCC than those in the study by Kim *et al.* We are particularly curious why the authors excluded patients with decompensated cirrhosis in their analysis. It is already well known that hepatic decompensation is reversible in most patients by treatment with ETV or TDF.[3,4] Patients with decompensated cirrhosis have the highest risk of HCC, which may increase the statistical power of the analyses greatly. It is obvious that with insufficient statistical power, a significant difference in HCC incidence could not be identified between the 2 treatments.

Another important issue to be raised is the consideration of treatment modification during follow-up. In our study, treatment was modified in 11.7% of patients in the ETV group, mostly to TDF, during follow-up because of incomplete viral suppression (HBV DNA level, ≥100 IU/ml), virological breakthrough, or drug resistance. We censored the patients at 6 months after the treatment modification. However, Kim, *et al.* did not report the rate of treatment modification in their study, and it seems that the factor was not adjusted in their analyses. If TDF confers a lower risk of HCC than ETV, the patients in the ETV group with treatment modification from ETV to TDF during follow-up may have a reduced risk of HCC, consequently diluting the statistically significant difference in HCC risk between the 2 original groups.

We also have a concern about the propensity score-matched analysis in the study of Kim *et al.* They used only 9 variables for the matching, and well-known predictors of HCC, such as HBV DNA levels, alanine aminotransferase levels, and international normalized ratio, were not included in the matching for an unreported reason, despite the availability of data. As many variables are included in the matching process, the risk of confounding can be minimized, and we used 16 matching variables in our study.

The annual incidence of HCC in patients with chronic HBV infection ranges from 0.2% to 1% without cirrhosis and from 1% to 5% with cirrhosis. Comparative effectiveness research that compares these rare outcomes requires sufficient numbers of