



## Rectal colonization by resistant bacteria is associated with infection by the colonizing strain and high mortality in decompensated cirrhosis

To the Editor:

We read with interest the research article by Prado *et al.*<sup>1</sup> about bacterial infections in cirrhosis. The authors reported that infections caused by multidrug-resistant organisms (MDROs) occurring in critically ill patients with cirrhosis were mainly due to the colonizing strain. We would like to report our experience in a different group of patients with cirrhosis without infection or another acute event.

Ninety-one consecutive patients with decompensated cirrhosis who were admitted for a scheduled paracentesis of ascites ( $n = 79$ ) or endoscopic surveillance of esophageal varices ( $n = 12$ ) during the 2018-2019 period were enrolled (75.3% males, median age 63 [IQR 54-72], MELD 22 [15.5-29]). Identification and resistance testing of bacterial pathogens collected from rectal swabs were performed at baseline using the culture technique described by Pouriki *et al.*<sup>2</sup> and the patients were prospectively evaluated for 6 months for the development of infection or death. At baseline, patients were thoroughly examined for common infections, including spontaneous bacterial peritonitis (SBP) or spontaneous bacteremia (SB) using conventional criteria.<sup>3,4</sup> Only patients with no evidence of infection were considered eligible. The patients were discharged soon after paracentesis of ascites or variceal ligation.

The etiology of liver disease was viral hepatitis in 31.6%, alcohol in 39.5% and miscellaneous in 28.9%. Bacteria were classified as multidrug-resistant (MDR), extensively drug-resistant (XDR) or pandrug-resistant (PDR) according to the international classification system.<sup>5</sup>

Twenty-eight (30.8%) patients were colonized by MDRO bacteria at baseline, either as a mixture of MDR/XDR organisms or as a single MDRO (MDR or XDR) population. No PDR organism was identified. More specifically, twenty-four patients were colonized by a single MDRO population: vancomycin-resistant (VRE) *E. faecium* ( $n = 8$ ), carbapenem-resistant (KPC) *K. pneumoniae* ( $n = 7$ ), extended-spectrum beta lactamase (ESBL) *Enterobacteriales* ( $n = 4$ ), *P. aeruginosa* ( $n = 3$ ), VIM-type metallo- $\beta$ -lactamase-producing *P. putida*, ( $n = 1$ ), *A. baumannii* ( $n = 1$ ). In those who were colonized by mixed populations, KPC *K. pneumoniae*/VRE *E. faecium* ( $n = 3$ ) and ESBL *E. coli*/*E. faecium* VRE ( $n = 1$ ) were isolated.

No statistically significant differences in clinical, demographic or laboratory data were observed between patients who were colonized by MDROs and those who were not. However, fecal XDR carriers had higher MELD ( $p = 0.042$ ), MELD-Na ( $p = 0.019$ ) and longer hospitalization over the past 6 months ( $p = 0.012$ )

compared to those who were not colonized by an XDR (both MDR and non-MDRO).

Eighteen patients had at least 3 sequential rectal samples during a period of 58 (35.5-106) days. Seven were initially colonized by MDROs. During follow-up, 3 out of 7 were decolonized from MDROs and one was decolonized from the old and recolonized by a new different MDRO strain. Three out of 11 non-MDROs were subsequently colonized by an MDRO pathogen. A hospitalization preceded new rectal MDRO colonization.

Seven patients with MDRO colonization developed culture-positive infections (SBP in 3, SB in 2, and urinary tract infections in 2) during the follow-up period. In 3 of them an identical XDR to the colonizing one was identified. More specifically, KPC *K. pneumoniae* in 1 SBP and VRE *E. faecium* in 2 SB cases were isolated. All infections caused by the same pathogen as the colonizing one emerged within 2 weeks following the recovery of rectal material. Thirteen patients without MDRO colonization at baseline developed culture-positive infections but only one was caused by an MDRO, 3 months after obtaining the rectal swab. The cumulative hazard of culture-positive infections was not statistically different between patients with and without MDRO (log rank  $p = 0.506$ ) (Fig. 1A).

The 6-month cumulative probability of survival was lower in patients colonized by an XDR compared to those who were not (log rank  $p = 0.004$ ) (Fig. 1B). The predicted probability of survival was lower in patients colonized by an XDR vs. those who were not, even when adjusting for age, sex and MELD score (dichotomized as  $>15$  and  $\leq 15$ ) (hazard ratio 2.072; 95% CI 1.080-3.975;  $p = 0.028$ , respectively) (Fig. 1B).

Colonization by an MDRO was demonstrated to be a risk factor for mortality in patients with cirrhosis, both in a previous investigation from our Center<sup>2</sup> and a German study over a 2-year follow-up period.<sup>6</sup> Moreover, Prado *et al.* showed that MDRO carriers had worse hospital survival in the Barcelona cohort.<sup>1</sup>

In conclusion, a high prevalence of colonization with MDROs, especially XDRs, was observed in this cohort of patients with decompensated cirrhosis without acute events at baseline. Endogenous infections which developed soon after the study of rectal colonization were attributed to the isolated colonizing bacteria. Rectal colonization with resistant strains has an unfavorable effect on survival. Fecal colonization is a dynamic process which could alter over time. Consequently, local epidemiological periodic surveillance for colonizing bacteria is mandatory in order to implement infection-control practices and guide empirical antibiotic treatment.

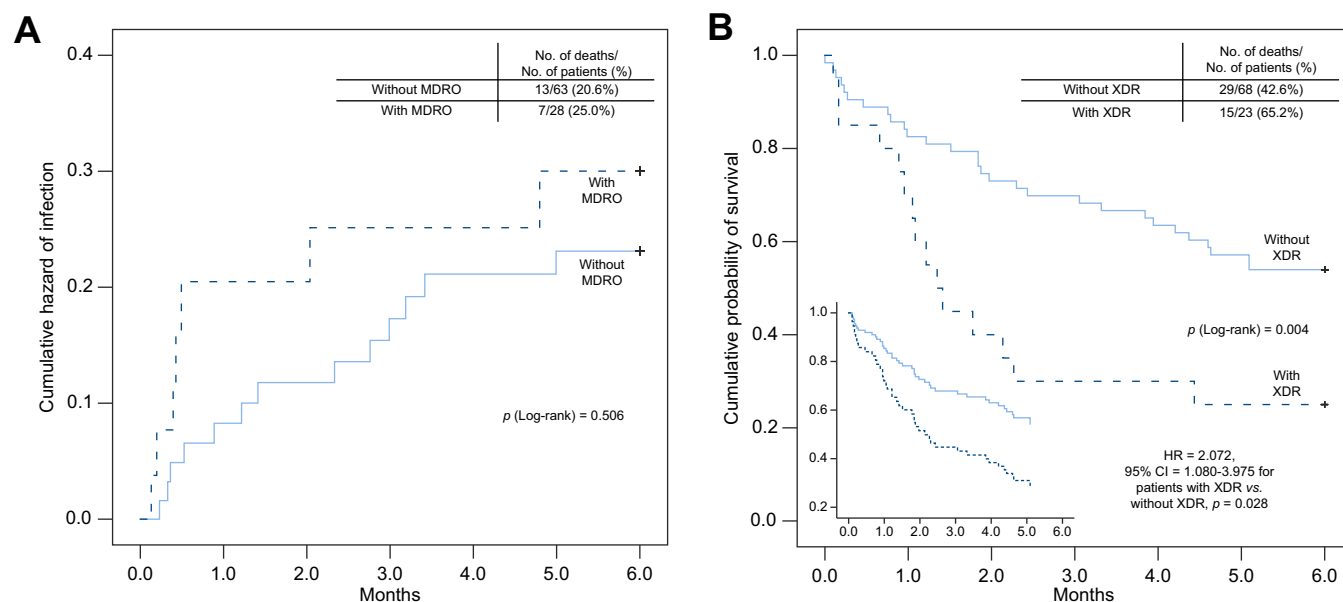
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**Fig. 1. Kaplan-Meier curves.** The differences were assessed by log-rank test. (A) There was no difference in cumulative hazard of culture-positive infections between patients with and without rectal colonization by MDROs (MDR/XDR) ( $p = 0.506$ ) (B) Observed non-adjusted 6-month probability of survival of cases was lower in patients colonized by an XDR vs. those who were not ( $p = 0.004$ ). The inset showed that the predicted 6-month probability of survival was lower in patients with XDR colonization compared to those without when adjusted for age, sex and MELD score (Cox proportional-hazards model). MDRO, multidrug-resistant organism; MELD, model for end-stage liver disease; XDR, extensively drug resistant organism.

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### Conflict of interest

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

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### Authors' contributions

Sophia Pouriki, acquisition of data; Theodoros Alexopoulos, Larisa Vasilieva and Alexandra Alexopoulou, analysis and interpretation of data; Sophia Pouriki and Alexandra Alexopoulou, drafting of the manuscript; Alexandra Alexopoulou and Georgia Vrioni, study concept and design and critical revision of the manuscript for important intellectual content; Theodoros Alexopoulos and Larisa Vasilieva statistical analysis; Georgia Vrioni, material support

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### Supplementary data

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