Progress in Hepatology-rectal Colonization by Resistant Bacteria Increases the Risk of Infection by the Colonizing Strain in Critically Ill Patients with Cirrhosis

Antimicrobial resistance has emerged as a global threat, and multidrug resistance organisms (MDROs) form one of the foremost challenges in the setting of decompensated cirrhosis. In this study, the authors examine two separate cohorts (Barcelona and Frankfurt cohorts) from two critical care units, one with prospective data and another with a retrospective analysis.[1] The study's primary objective was to ascertain the prevalence of rectal colonization by MDROs in critically ill patients, understand their epidemiological characteristics, and assess their prognostic impact. Rectal colonization was determined with cultures from rectal swabs at admission (within 48 h) and then weekly till discharge or death. The Barcelona cohort included patients both with (n = 174) and without liver disease (n = 312), while the Frankfurt cohort was composed of only patients with cirrhosis (n = 421).

From the Barcelona cohort, the first key finding was the presence of significantly higher epidemiological risk factors (recent hospitalization, including ICU admission, antibiotic prophylaxis, and recent history of MDRO isolation). In this cohort, the prevalence of MDRO rectal colonization was significantly higher in patients with cirrhosis at admission. Interestingly, during the ICU stay, rates of rectal colonization were similar between those with cirrhosis and those without liver disease. Extended-spectrum beta-lactamase (ESBL) *Enterobacterales* were the most common isolated organisms, with MDR-*Escherichia coli* and *Klebsiella pneumonia* being more prevalent in patients with cirrhosis. The key factors that were associated with MDRO colonization in cirrhosis were antibiotic prophylaxis, overall disease severity, mechanical ventilation, and need for renal replacement therapy. Overall proven bacterial infections, infections with resistant organisms, and cumulative incident MDRO infections were more common in MDRO colonizers. The highlight of the cohort was a significantly higher rate of infection caused by corresponding resistant colonizers in patients with cirrhosis than those without as well as MDRO colonization as an independent predictor of infection by the corresponding resistant strain in cirrhotic (HR: 7.41; 95% CI: 2.58–21.30) and non-cirrhotic groups (HR: 5.65; 95% CI: 2.36–13.54). Lastly, colonization with MDROs was associated with increased mortality in patients with cirrhosis.

The Frankfurt cohort only comprised patients with cirrhosis. Almost half (47%) of the cohort had MDRO colonization at admission, with vancomycin-resistant enterococci (VRE) being the commonest colonizer instead of ESBLs, as seen in the Barcelona cohort. In tune with the observations of the Barcelona cohort, infections due to resistant strains were more common in MDRO colonizers, with almost 90% of cases having the same MDR bacteria isolated in rectal swabs. However, the in-hospital mortality in this cohort was similar among MDRO colonizers and non-colonizers, although the development of incident VRE infection predicted worse survival.

The intuitive concept of association of rectal carriage of MDROs and subsequent development of proven MDRO infections with a focus on Carbapenem-resistant *Enterobacteriaceae* and *Pseudomonas* infections has previously been demonstrated in intensive care as well as liver transplantation setting.[2–4] However, the fundamental merits of this study lie in incorporating two large cohorts of patients with cirrhosis and meticulous follow-up for incident infections. MDRO infections in cirrhosis pose one of the most crucial challenges in clinical practice, and identifying the appropriate subset at risk for these infections for early directed therapy has remained a vexing predicament. Analysis of the study draws home two crucial points: a definitive risk of rectal colonization for incident infections and variance in the bacteriological profiles in different settings, which again re-enforces the need for individualized antimicrobial policy decisions rather than umbrella guidelines. The results of this study will generate evidence for future policymaking. However, certain key facts still need to be treated with caution. One of the cohorts has a relatively broad timespan of enrolment (2010–2018), which may influence the overall temporal trends of microbiological profiles. Additionally, although the cohorts included patients with cirrhosis primarily, some heterogeneity remained due to the incorporation of patients with acute liver failure and post-liver transplant patients who may behave differently. Lastly, as the choice and decision of empirical antibiotics in acute and chronic liver failure remain an elusive frontier, future studies focusing on Acute on Chronic Liver Failure (ACLF), a population with intrinsically high mortality, should stem out in the background of this crucial work.[5]

Abbreviations: ACLF: acute on chronic liver failure; ESBL: extended-spectrum beta-lactamase; MDROs: multidrug resistance organisms; VRE: vancomycin-resistant enterococci

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CONFLICT OF INTEREST

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Updated Efficacy and Safety Data from IMbrave150: Atezolizumab Plus Bevacizumab vs. Sorafenib for Unresectable Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common primary liver tumor and remains a significant cause of cancer-related death globally. The incidence of HCC has been on the rise along with a proportionate rising trend in mortality.[1] However, since the landmark sorafenib in advanced hepatocellular carcinoma (SHARP) trial of the efficacy of sorafenib in advanced HCC, there was little progress made in the armamentarium against advanced HCC for almost a decade. The advent of combination immunotherapy opened up a whole new paradigm in the management of HCC. The preliminary results of the IMbrave150 trial, which used a combination of the anti-programmed death-ligand 1 molecule atezolizumab with anti-vascular endothelial growth factor agent bevacizumab (A+B) marked an epoch in the timeline of HCC management. The results of the trial ultimately catapulted the position of the combination as a first-line therapy in the management of advanced HCC.[2,3] At the time of publishing of the initial results of the IMbrave150 after a median 8.6 months of follow-up, the median overall survival (OS) which was one of the co-primary endpoints was not reached in A+B arm while it was 13.2 months with sorafenib, providing a significant reduction in the hazard for death [HR 0.58 (95% CI 0.42–0.79; $P < 0.001$)]. The current study provided an updated post hoc analysis of the follow-up data from the IMbrave 150 trial.

Overall, in the trial, 501 patients were randomized to receive A+B (n = 336) or sorafenib (n = 165). At the time of analysis, 200 were discontinued in the A+ B arm (death = 179, rest lost to follow-up or withdrawal of consent) while 122 were discontinued in the sorafenib arm (death = 99, rest lost to follow-up or withdrawal of consent). The key results of the updated analysis show a median OS of 19.2 months (95% CI 17.0–23.7) in the

Abbreviations: HCC: Hepatocellular carcinoma; OS: overall survival

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