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Understanding why resistant bacteria are associated with higher mortality in ICU patients

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Incidence of infections related to multidrug-resistant bacteria

The incidence of infections related to multidrug-resistant (MDR) bacteria is high in the ICU. Based on the results of the large multinational EPIC II study, MDR bacteria represented 36 % of microorganisms identified in patients with confirmed infection [1]. The main risk factors for resistance are prior exposure to antibiotics, prolonged hospital and ICU length of stay (LOS), invasive devices, comorbidities and local epidemiology [2–4].

Multidrug-resistant bacteria as a risk factor for mortality

Multidrug resistance is a well-known risk factor for mortality in critically ill patients with severe infections. A recent meta-analysis supports the findings of previous studies showing that MDR presence is an important determinant of mortality due to nosocomial infections attributed to Gram-negative bacteria (GNB) [5]. In addition, Infections caused by MDR pathogens are associated with higher costs and prolonged LOS [6] in a self-perpetuating cycle, as LOS is a risk factor for MDR acquisition.

Determinants of increased mortality patients with infections due to MDR bacteria

The delayed administration of effective antimicrobial therapy is a key issue when addressing the prognosis of critically ill patients infected with MDR pathogens [4, 7]. Inappropriate initial antimicrobial therapy (IIAT) is a strong predictor of fatal outcome after adjustment on background conditions and sepsis severity. Infections due to MDR bacteria have repeatedly been shown to represent a major risk factor for IIAT (Fig. 1). In patients with bacteremia due to extended-spectrum beta-lactamase-producing Enterobacteriaceae, the likelihood of IIAT is five-fold higher than in those infected with strains susceptible to first-line beta-lactams [8]. In a recent multinational study including 740 patients with hospital-

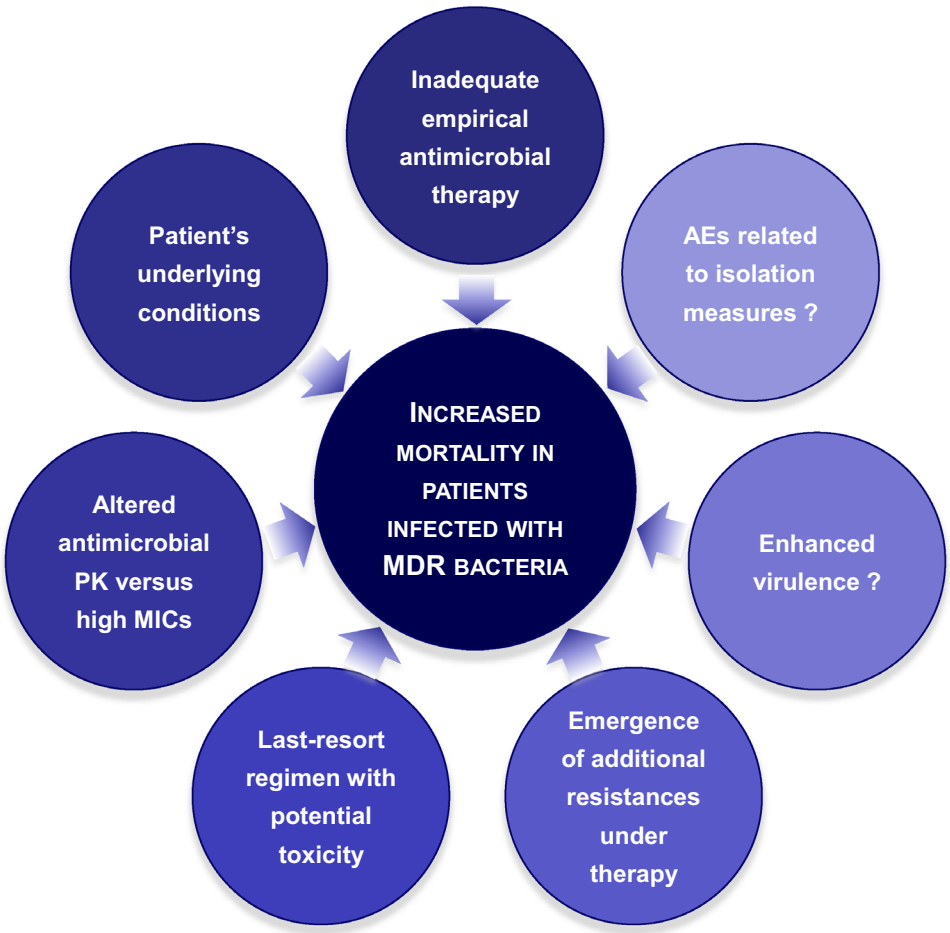

Fig. 1 Determinants of impaired outcome in critically ill patients infected with multidrug-resistant pathogens. *MDR* multidrug-resistant, *PK* pharmacokinetics, *MIC* minimal inhibitory concentration, *AE* adverse event

acquired *Pseudomonas aeruginosa* pneumonia, the frequency of IIAT was 38 % in episodes due to an MDR isolate versus 19 % in those involving a non-MDR isolate. IIAT may be even more frequent in KPC carbapenemase-producing *Klebsiella pneumonia*, carbapenem-resistant *Acinetobacter baumannii*, or MDR *Stenotrophomonas maltophilia* infections [9]. Overall, convincing evidence exists to support the link between IIAT and increased mortality in ICU patients infected with MDR GNB [6]. Patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections are similarly exposed to high rates of IIAT, resulting in a twofold rise in the adjusted probability of death [10]. However, few studies have evaluated the impact of multidrug resistance on mortality in patients with adequate initial antibiotic treatment. In this subset of patients, and after careful adjustment for confounders, multidrug resistance probably has no significant effect on mortality [11].

Other potential explanations for the high mortality rate in patients with infections related to MDR bacteria include drug toxicity, altered pharmacokinetic of antibiotics, subsequent resistance and comorbidities. The limited number of therapeutic options may require the use of last-resort antimicrobial regimens with potential toxicity. For instance, prolonged high-dose colistin or aminoglycoside schemes for carbapenem-resistant GNB may promote the development of acute kidney injury, most notably in cases of pre-existing renal dysfunction, shock or concomitant use of other nephrotoxic drugs [12]. Further, the use of very high off-label doses of antimicrobials, such as carbapenms, cefepim, and tigecyclin, may also be associated with higher toxicity.

The pharmacokinetic properties of several antimicrobial classes are dramatically altered in patients with critical illnesses, which may lead to suboptimal dosing and impaired treatment response [9]. In fact, several pathophysiological aspects contribute to a risk for lower concentrations of antimicrobial agents, mainly within the first 24–48 h of treatment. Hyperdynamic state of shock, augmented renal clearance and vascular permeability, contributing to increasing distribution volume, are main factors associated with the lower concentration of antimicrobial in patients with severe sepsis and septic shock. This appears especially relevant for MDR pathogens with high minimal inhibitory concentrations of the prescribed drugs. Moreover, additional resistance may

occasionally emerge under therapy following chromosomal mutations and mutant selection (e.g., acquired drug impermeability due to porin deletion, or over-expression of efflux systems or intrinsic beta-lactamases), in particular for *P. aeruginosa* and other non-fermenting GNB [13].

Additive factors not related to the use of antimicrobial therapy should also be considered. The patient's underlying condition notably acts as a significant confounder for prognosis appraisal in this situation. Indeed, features such as advanced age, chronic diseases, prolonged ICU stay or the need for invasive life-sustaining therapies increase the risk of infections due to MDR pathogens but simultaneously exert an independent impact on the hazard of dying in the ICU [14]. Then, contact isolation policies are widely implemented in patients colonized or infected with MDR bacteria in an attempt to prevent cross-transmission and local outbreaks. These measures may lessen the frequency of healthcare workers' interventions and interfere with patient monitoring, leading to higher rates of medical errors and preventable adverse events during the ICU stay [15]. Therefore, and although it warrants further investigation, this facet of patient management could conceivably contribute to a poorer outcome. Lastly, there is a consensual concept that the "energetic cost" of multidrug resistance implies reduced virulence. However, plasmids bearing resistance genes in GNB may also encode virulence determinants or factors enhancing the fitness of the recipient strain. For *P. aeruginosa*, another counter-argument is the fact that MDR phenotypes are more commonly observed in strains with type III secretion systems producing ExoU, a pivotal virulence factor responsible for alveolar epithelial injury and pneumonia severity [16]. To date, the relationship between resistance and virulence remains of equivocal clinical significance and should probably be addressed using a strain-by-strain rather than a species-level approach.

Conclusions and future directions

Efforts should be made to increase the probability of providing appropriate initial antimicrobial treatment in patients with infections related to MDR bacteria, and to reduce subsequent emergence of resistance. Adequate antimicrobial dosing is a crucial issue in critically ill patients. Toxicity of antimicrobial treatment should also be carefully monitored. Moreover, preventive strategies aimed at reducing the spread of MDR bacteria in the ICU are essential to reduce the incidence of infections related to these bacteria.

Future studies should determine the accuracy of rapid diagnosis methods in increasing the rate of appropriate initial antimicrobial treatment and reducing unnecessary antimicrobial treatment. The impact of monoclonal antibodies against *S. aureus*, and *P. aeruginosa* on outcome is currently being investigated in patients colonized or infected by these bacteria. The results of these studies will provide interesting information on how to reduce the pathogenicity of MDR bacteria in critically ill patients.

Compliance with ethical standards

Conflicts of interest FB: MSD (advisory board), Pfizer (conference invitation), Novartis (speaker fees); TL: none; SN: Bayer (advisory board).

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