Infections in the ICU—the big problem!

Emergence and spread of MDR pathogens have become a major leading cause of death worldwide and a major problem in ICU patients (1). ESKAPE pathogens (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Escherichia coli/Enterobacter cloacae) reflect the strongest challenge today (2). The increasing prevalence of MDR bacteria is associated with increased 3rd generation cephalosporins-resistant K. pneumoniae and cephalosporins-resistant E. coli which lead to more frequent use of carbapenems and to the emergence of XDR and/or PDR Enterobacteriaceae (3). The emergence of carbapenemase producing K. pneumoniae [carbapenemase-producing Enterobacterales (CPE)] is of particular concern in Italy and Greece, the prevalence of vancomycin-resistant Enterococcus (VRE) has also increased, ceftazidime-resistant P. aeruginosa remains stable while a decrease of methicillin-resistant Staphylococcus aureus (MRSA) was observed (4). These differences vary according to the bacterial species and geographical region. The unsafety of intensivists against a probable infection lead to a massive consumption of antibiotics (up 50% of ICU patients under empirical antibiotic therapy have no confirmed infection) while de-escalation and shortened treatment duration are considered insufficiently in those with documented infection, promoting substantial ecological side effects and dissemination of MDR pathogens.

The optimization of antibiotic therapy in the ICU is extremely important supporting the need of better identification of at risk patients for MDR infections, more accurate diagnostic tools, individualization of single-drug or combination empirical regimen and early and adequate dosing to ensure the attainment of pharmacokinetics/pharmacodynamics targets (3). The evidence-based administration and antibiotic stewardship programs (ASP), the performance of infection control programs, the PK/PD-based dosing, the development of new antibiotics and application of vaccination program reflect important strategies to fight the difficult infections (3). Therapeutic drug monitoring (TDM), present a method with which may be minimized the risk of antimicrobial toxicity and maximized the drug efficacy through PK optimization (especially for aminoglycosides and glycopeptides). The routine TDM in optimizing beta-lactam dosing remains controversial because of the lack of a standardized protocol to measure beta-lactam concentrations, the unclear optimal timing and number of samples to describe the time course of drug concentrations, the association between non-adequate beta-lactam concentrations and therapeutic failure is based only on retrospective studies, the unclear role of adequate beta-lactam levels in the emergence of resistant strains and the unclear optimal duration of beta-lactam levels exceeding the MIC or the unclear optimal PK target in case of empirical therapy (5,6).

The arsenal of antibiotics against MDR/XDR bacteria is awaiting promising molecules. There are five recent new regimens, namely ceftolozane/tazobactam, ceftazidime/avibactam, imipenem/relebactam, meropenem/vaborbactam and plazomicin while two molecules in late stage of development are quite promising in the treatment of XDR pathogens, because they retain activity in the presence of metallo-enzymes; cefiderocol and cefepime-zidebactam (7). Nebulisation of antibiotics, is an unstandardized rescue therapy in mechanically ventilated (MV) patients lacking however protocolisation and experience (8). Alternative to antibiotics strategies, include new delivery methods (nebulization, encapsulation of antibiotics), vaccines—monoclonal antibodies (MA), development and modulation of patients’ immune response and modulators of bacterial cell wall (9). Finally, bacteriophages, bacteriocins and anti-quorum sensing molecules with species specific targets that bypass current mechanisms of resistance represent the dawn in antimicrobial therapy for XDRs (9).

Candida spp are the major causes of fungal infections in non-immunocompromized ICU patients while invasive aspergillosis is encountered mainly in ICU patients with chronic obstructive pulmonary disease, liver cirrhosis and diabetes (10). Invasive candidiasis is associated with specific risk factors. Microbiological cultures are the main diagnostic methods for invasive fungal infections but new molecular tests contribute to the faster diagnosis. The available antifungals have different spectrum of activity while the knowledge of the mechanism of action, efficacy and adverse effects is crucial in managing ICU patients.

In conclusion, the fight against infections in the ICU, especially against MDR/XDRs, include the in-depth understanding of their pathogenicity, resistance mechanisms and interactions with the host, the evidence-based administration of antibiotics (early, adequately, appropriately) and non-antibiotic approaches.
Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/jeccm.2019.10.08

View this article at: http://dx.doi.org/10.21037/jeccm.2019.10.08