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

Footnote

References

1. Tackling drug-resistant infections globally: Final report and recommendations, Available online: http://amrreview.org; 2016 [accessed 15 September 2019].
2. Mulani MS, Kamble EE, Kumkar SN, et al. Emerging Strategies to Combat ESKAPE Pathogens in the Era of Antimicrobial Resistance: A Review. Front Microbiol 2019;10:539.
3. Li H, Zhang J, Liu Y, et al. Molecular characteristics of carbapenemase-producing Enterobacteriaceae in China from 2008 to 2011: predominance of KPC-2 enzyme. Diagn Microbiol Infect Dis 2014;78:63-5.
4. Annual surveillance reports on antimicrobial resistance. European Centre for Disease Prevention and Control. Available online: https://ecdc.europa.eu/en/antimicrobial-resistance/surveillanceand-disease-data/report; 2018 [accessed 15 September 2019]
5. Mouton JW, Muller AE, Canton R, et al. MIC-based dose adjustment: facts and fables. J Antimicrob Chemother 2018;73:564-8.
6. Huttner A, Harbarth S, Hope WW, et al. Therapeutic drug monitoring of the β-lactam antibiotics: what is the evidence and which patients should we be using it for? J Antimicrob Chemother 2015;70:3178-83.
7. Horcajada JP, Montero M, Oliver A, et al. Epidemiology and Treatment of Multidrug-Resistant and Extensively Drug-Resistant Pseudomonas aeruginosa Infections. Clin Microbiol Rev 2019. doi: 10.1128/CMR.00031-19.
8. Solé-Lleonart C, Roberts JA, Chastre J, et al. Global survey on nebulization of antimicrobial agents in mechanically ventilated patients: a call for international guidelines. Clin Microbiol Infect 2016;22:359-64.
9. Tümmler B. Emerging therapies against infections with Pseudomonas aeruginosa. F1000Res 2019. doi: 10.12688/f1000research.19509.1.
10. Ostrosky-Zeichner L, Al-Obaidi M. Invasive Fungal Infections in the Intensive Care Unit. Infect Dis Clin North Am 2017;31:475-87.

George Dimopoulos   Yuetian Yu   Zhongheng Zhang

George Dimopoulos, MD, PhD, FCCP, FECCM
Department of Critical Care Medicine, "ATTIKON" University Hospital,
National and Kapodistrian University of Athens, Athens, Greece.
(Email: gdimop@med.uoa.gr)
Yuetian Yu, MD
Department of Critical Care Medicine, Renji Hospital, School of Medicine,
Shanghai Jiao Tong University, Shanghai 200001, China.
(Email: fishyyt@sina.com)
Zhongheng Zhang, MD, MM
Department of Emergency Medicine, Sir Run-Run Shaw Hospital,
Zhejiang University School of Medicine, Hangzhou 310016, China.
(Email: zh_zhang1984@zju.edu.cn)

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