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FOCUS EDITORIAL

Focus on antimicrobial use in the era of increasing antimicrobial resistance in ICU

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Antibiotic stewardship in the spectrum of resistance bacteria fight

Antimicrobial resistance in microorganisms increased inexorably driven by antimicrobial exposure in healthcare, agriculture, and the environment. Onward transmission is affected by standards of infection control, sanitation, access to clean water, access to quality-assured antimicrobials and diagnostic tests, travel, and migration [1, 2]. The intensive care unit (ICU) represents the best bacterial resistance amplifier. Indeed, the most critically ill patients with invasive procedures are treated with broad-spectrum antimicrobials in an environment with a huge number of healthcare workers and an extremely high risk of transmission from patient to patient.

Strategies to reduce curative antibiotic therapy to the bare essential are therefore needed and should include an immediate diagnostic process before starting early probabilistic antimicrobial therapy in case of severe sepsis or septic shock. The strategies proposed by a French multidisciplinary panel of experts using GRADE methods are detailed in this journal (67 recommendations) [3]. The key messages are that all antibiotic usage promotes antibiotic resistance. Adequate high dose is essential to cure patients but treatment should spare carbapenems in community-acquired infections. Combination therapy is suggested for patients with septic shock and neutropenia or in patients at high risk of multidrug-resistant bacterias. Antibiotics should be reassessed after 48–72 h and de-escalated. Duration of therapy should be reduced. In contrast, in the absence of severe sepsis, waiting for objective data to diagnose infection before treatment with antimicrobial drugs for suspected ICU-acquired infections does not worsen mortality and might be associated with better outcomes and use of antimicrobial drugs and should be discussed on daily rounds [4].

Among Gram-negative bacteria, *Acinetobacter baumannii* is particularly equipped to spread in ICUs and to become multiresistant. It became the first agent responsible for nosocomial infection in ICUs in many countries. Infection control strategies including hand hygiene, environmental cleaning, active screening, and contact precautions should therefore be added to antimicrobial stewardship programs. A task force organized by the infection section of the European Society of Intensive Care Medicine (ESICM) detailed strategies to control *A. baumannii* spread and adequate treatment regimens that should be used in case of *A. baumannii* infections [5].

In order to reduce cross transmission of bacteria, hand hygiene might not be sufficient because of imperfect compliance. An alternative approach may focus on limiting the reservoir of potential pathogens on the skin and in the mouth and gut of the patients. Whereas 2 % alcoholic chlorhexidine became the first-choice antiseptic for catheter infection prevention [6], the use of chlorhexidine as a topical agent for decolonization of a patient's mouth and skin is still debated. The recent review by Noto and Wheeler [7] suggests that cutaneous decolonization with chlorhexidine results in less Gram-positive multidrug-resistant acquisition (methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE)). The impact on bacteremia and nosocomial infections is largely driven by a decrease of coagulase-negative bacteremia, and available studies do not demonstrate any effect on Gram-negative infections. The benefit of chlorhexidine-based oropharyngeal decolonization is small and also requires further confirmation. Chlorhexidine use was also associated with the rise of infections due to organisms with reduced susceptibility and with rare occurrence of allergic or toxic reactions.

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Therefore, Noto and Wheeler concluded that the chlorhexidine-based decolonization should not be used widely. It should therefore remain in the armamentarium of strategies to prevent the spread of multidrug-resistant (MDR) microorganisms in case of epidemic.

Empiric treatment

Previous studies have shown conflicting evidence regarding the impact of inappropriate, initial antibiotic therapy in septic patients, but in the case of patients with severe sepsis or septic shock, survival depends on early initiation of effective antimicrobial treatment [8]. The choice of empiric appropriate therapy, meaning appropriate and early therapy at pharmacokinetic/pharmacodynamic (PK/PD)-optimized doses and dose intervals, is currently complex. MDR microorganisms are increasing, and inappropriate empirical treatment has been described as an independent predictor of 14-day mortality (OR, 1.48; 95 % CI, 1.01–2.18) for infections caused by *Klebsiella pneumoniae* (Kp)-producing carbapenemase (KPC) [9]. Moreover, in critically ill patients physiological alterations may severely modify antibiotic exposure. A post hoc analysis of the DALI study, simulating an empirical setting, found that target attainment during therapy with beta-lactam (BL) antibiotics was overall inadequate. Besides, use of intermittent bolus (IB) infusion resulted in a 3- to 4-fold increase in the likelihood of not reaching the desired PK/PD targets [10]. Nevertheless, the most recent relevant multicenter prospective clinical studies regarding PK/PD targets for BL antibiotics in critically ill patients have reached contradictory conclusions. The BLISS study observed that in patients with severe sepsis (without renal replacement), continuous infusion (CI) administration was associated with higher clinical cure rates (56 versus 34 %, $p = 0.011$) and better PK/PD target attainment compared to IB dosing for BL antibiotics [11]. In contrast, the BLING II study did not observe difference in clinical cure (52.4 versus 49.5 %, $p = 0.56$) between BL antibiotic administration by CI and IB [12]. These differences between the results may be explained by epidemiological settings, since in the second trial, the prevalence of MDR pathogens was very low and the probability of not reaching the PK/PD target using conventional dosing was very small. Furthermore, patients with acute renal failure, for whom continuous infusion could not improve PK, were included in BLING II and excluded in BLISS.

In addition, individual or local nosocomial risk factors, including colonization status with MDR bacteria, should support empirical treatment decisions [8].

Adequate dosing

The DALI study, a prospective, multinational pharmacokinetic point-prevalence study, was a breakthrough in our knowledge on antibiotic dosing in ICU patients [13]. Significant rates of insufficient β-lactam exposure were observed, with approximately 20 % of patients failing to attain the most conservative drug exposure targets (50 % $fT_{>MIC}$, where $fT_{>MIC}$ is the percentage of a 24-h time period that the unbound drug concentration exceeds the minimum inhibitory concentration, MIC) during empirical treatment, whereas more than 40 % failed to achieve a higher target (100 % $fT_{>MIC}$). Intermittent infusion of β-lactams and patients with augmented renal clearance were associated with lower drug exposures [10]. In line with these results was a randomized study by de Waele et al. in ICU patients with normal renal function, reporting very low baseline PK/PD target attainment both for those receiving piperacillin/tazobactam and meropenem. Among those randomized to daily therapeutic drug monitoring (TDM) and adaptation of doses, a higher proportion of patients attained both the 100 % $fT_{>MIC}$ and 100 % $fT_{>4MIC}$ target [14]. Apart from disease severity, increasing rates of PD target attainment were associated with better clinical outcomes [13]. Continuous infusion of β-lactams was associated with better clinical outcomes in a recent randomized controlled trial [12]. In light of these data, current empiric dosing recommendations of β-lactam antibiotics for ICU patients seem inadequate and need to be reconsidered [10].

Close monitoring of amikacin concentrations seems mandatory in ICU patients; despite a loading dose of 25 mg/kg of total body weight, the PD target was not attained in 33 % of patients. Positive 24-h fluid balance was predictive of target non-attainment, whereas low BMI tended to be associated with amikacin underdosing [15].

Usage of tigecycline was explored in a prospective observational study from 26 French ICUs; 65 % of patients received a combination with other antibiotics mostly targeted against Gram-negative infections and 94 % received the standard dose. Success rates of 65 % for patients alive at the end of treatment were comparable to clinical studies of severe infections, tending to decrease with illness severity, immunosuppression, bacteremia, and obesity [16]. Given that most patients received combination therapy, the study did not add much to the ongoing discussion of whether the current recommended scheme of 50 mg BID is adequate or not. However, the task force on management and prevention of *A. baumannii* infections in the ICU organized by the infection section of ESICM recommended a loading dose of 200 mg of tigecycline followed by 100 mg BID for the treatment of pneumonia and primary bacteremia [5].

Linezolid's plasma and pulmonary concentrations have been questioned in critically ill and obese patients. A randomized controlled study by De Pascale et al. comparing intermittent vs continuous infusion in moderately obese patients with VAP demonstrated suboptimal plasma concentrations with intermittent infusion. Continuous infusion overcame this issue, except for extreme MIC values above 4 mg/L and was associated with higher alveolar penetration and epithelial lining fluid (ELF) concentrations above 4 mg/L [17].

Consider de-escalation

De-escalation of antimicrobial therapy is a strategy to reduce the spectrum of antimicrobials and aims to prevent the emergence of bacterial resistance [18]. The quality of the studies analyzing the effect of de-escalation is weak. There is no uniform definition of de-escalation that includes the decrease of the number of antimicrobials, the shortening of the duration of antibiotic therapy, and the switch of the pivotal antibiotic to a narrower agent. Available studies suggested an association between de-escalation and a better outcome.

Garnacho-Montero et al. designed a prospective observational cohort of 712 patients with severe sepsis. De-escalation was defined as a discontinuation of an antimicrobial agent or change of antibiotic to one with the narrowest spectrum [19]. They found that de-escalation was only applied in 35 % of the cases and was associated with a significantly lower risk of death even after adjustment based on risk factors of death. In contrast, in an open randomized non-inferiority trial, Leone et al. [20] failed to demonstrate the non-inferiority of narrowing the spectrum of the pivotal antimicrobial on the duration of ICU stay. The intervention also increased the rates of superinfection and was paradoxically associated with more days on antibiotic. This paradoxical effect of de-escalation is partly due to an unexpected disequilibrium between both groups in terms of source of infection and initial use of carbapenems and fluoroquinolones. The decrease of antibiotic pressure to reduce antibiotic resistance is therefore challenging and may need optimization of the pharmacokinetics of the antimicrobials given [10] and a better understanding of the impact of antimicrobials on the human, mainly gut, microbiota.

The applicability of de-escalation in MDR infections has not been extensively explored and should be considered individually. In this setting de-escalation implies mostly reducing the antibiotic treatment duration on the basis of the patient's clinical response and the underlying infection. To help in shortening the duration of antibiotic therapy the most promising parameter appears to be plasma levels of procalcitonin [21]. In addition, development of rapid diagnostic tools and antimicrobial susceptibility testing are needed.

Table 1 summarizes the principal components of ICU strategies for stewardship and antimicrobial use.

Table 1 Principal components of ICU strategies for stewardship and antimicrobial use in the era of increasing antimicrobial resistance

Leadership commitment
Implementing antibiotic stewardship programs
Implementing infection control practices
Improve communication between laboratory and clinical staff
Implement local resistance data for developing local antibiotic guidelines
Multidisciplinary approach
A multidisciplinary team including infectious diseases specialists, microbiologists, pharmacists, ICU physicians, and nurses should be in charge of developing a specific ICU antibiotic stewardship program
Daily rounds for case discussions
Implementation of modern antimicrobial use approach
Aggressive good quality microbiological sampling (blood cultures; distal airway sampling; urine culture; systematic sampling of wound, drain discharge, and any collection suspected of being infected) before starting new antimicrobials
Selection of empirical antimicrobials according to the clinical conditions, the presence of risk factors for resistant microorganisms, and the local epidemiology
Achievement of adequate pharmacokinetic/pharmacodynamic parameters of the antimicrobial agents used (extended/continuous infusion, TDM)
Systematic de-escalation
Systematic reduction of the duration of antimicrobial treatment according to the clinical evolution and the kinetics of biomarkers such as procalcitonin
Monitoring and feedback
Monitoring antibiotic prescribing and resistance patterns
Regular reporting of information on antibiotic use and resistance to doctors, nurses, and relevant staff

Abbreviations
BL: Beta-lactam; CI: Continuous infusion; ELF: Epithelial lining fluid; IB: Intermittent bolus; Kp: *Klebsiella pneumoniae*; KPC: Carbapenemase-producing *Klebsiella pneumoniae*; MIC: Minimum inhibitory concentration; MDR: Multidrug resistant; MRSA: Methicillin-resistant *Staphylococcus aureus*; PK/PD: Pharmacokinetic/pharmacodynamics; TDM: Therapeutic drug monitoring; VRE: Vancomycin-resistant enterococci.

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