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What's new in antimicrobial use and resistance in critically ill patients?

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Infection is a major factor impacting the clinical outcome among patients requiring intensive care unit (ICU) support. The causes of infection in the ICU are multifactorial, and the consequences depend on the source involved, the associated organisms, the underlying morbidity, and the timeliness and appropriateness of the treatment or interventions received. The causative organisms for infections have evolved over the years. The recent French EPISS study showed an incidence of 13.5 % in episodes of septic shock among ICU patients [1]. Strikingly, around 50 % of the microbial isolates were Gram-negative bacteria, displaying a reversal of the pattern seen in previous studies in which Gram-positive bacteria predominated. Approximately two-thirds of patients presented community-acquired infections, and more than half had respiratory tract infections as the primary site of infection for the origin of the septic shock [1]. In the same study the authors reported a significant reduction in mortality by approximately 17 % between 2000 and 2011. The data suggests that infection management has improved over the last decade, and undoubtedly, the publication of international clinical practice guidelines for management contributed to this trend [2]. In the EUROBACT study the most frequently isolated pathogens from bloodstream infections were Gram-negatives: *Acinetobacter* spp., *Klebsiella* spp., and *Pseudomonas* spp. [3]. All three pathogens reflected the phenomenon of growing resistance summarized by the acronym 'ESCAPE', containing the initials of the most frequent multidrug-resistant (MDR) microorganisms (*Enterococcus faecium*, *Staphylococcus aureus*, *Clostridium difficile*, *Acinetobacter baumannii*, and *Enterobacteriaceae*). The phenomenon of MDR organisms is ubiquitous, as three-quarters of European countries have reported at least one extensively drug-resistant (XDR) organisms in ICU patients [4].

Regarding the spread of bacterial resistances within the 30 European countries, the recent EARS-Net data are of some concern [4]. The majority of *Escherichia coli* and *Klebsiella pneumoniae* isolates reported by EARS-Net in 2012 were resistant to at least one of the antimicrobials tested, and many had combined resistance to third-generation cephalosporins, fluoroquinolones, and aminoglycosides. This is consistent with the continuously increasing trends of antimicrobial resistance and the high percentage of extended spectrum beta-lactamase (ESBL)-positive isolates. Moreover, beta-lactamases such IMP, VIM, *K. pneumoniae* carbapenemases (KPC), and OXA, which are frequently seen in Gram-negative isolates, are capable of conferring resistance to carbapenems and lead to the insurgence of infections caused by MDR pathogens susceptible only to colistin [4]. Carbapenem resistance

and resistance to multiple antimicrobial groups are also common in *Pseudomonas aeruginosa* and *Acinetobacter* spp. isolates. A present and most worrisome problem is the emergence of colistin resistance in KPC, which involved in some countries up to 20 % of the isolates [5]. The spread of colistin resistance can be related to the extensive use of this drug in empiric and targeted treatment and also due to the ecological effect of topical use in selective decontamination protocols in ICUs [6]. Subtherapeutic concentrations of colistin may favor resistance development; therefore, it was suggested that a higher loading dose of six or nine million units should be given in critically ill patients in order to obtain faster bacterial eradication [7]. Regarding methicillin-resistant *S. aureus* (MRSA), the European population-weighted mean rates decreased significantly over the last 4 years. Despite this, MRSA remains a public health priority showing a European population-weighted mean of 17.8 % [5]. During recent years, an increase in vancomycin and teicoplanin MIC values towards MRSA have been observed worldwide and the circulation of strains with higher MICs have become more common, especially in ICU [8]. Isolates with vancomycin MICs greater than 1 μg/ml have been associated with higher rates of vancomycin treatment failure, prolonged duration of bacteremia, and poor clinical outcomes including mortality. In a recent study Murray et al. [9] demonstrated that early use of daptomycin was associated with significantly less clinical failure, 30-day mortality, and persistent bacteremia compared to dose-adjusted vancomycin in the setting of MRSA bacteremia with high vancomycin MICs. Recent studies demonstrate marked variability in the pharmacokinetics of daptomycin in acutely ill patients despite use of current recommended doses (6 mg/kg/day). Falcone et al. observed high daptomycin clearance among a subset of critically ill patients and significantly lower drug exposures with the use of standard doses. Their simulations suggest that higher doses (8–10 mg/kg/day) are likely necessary at the onset of therapy of MRSA bacteremia in critically ill patients [10].

The presence of MDR organisms in the community has emerged over the past decades as a critical problem. A recent study found a high prevalence of MDR bacteria among patients with pneumonia who were admitted to ICU (7.6 % in Spain and 3.3 % in the UK) and, particularly, those who received mechanical ventilation. These findings raise the question whether all critically ill patients with severe pneumonia admitted to ICU should receive a broad-spectrum antibiotic treatment against MDR bacteria regardless of the presence of risk factors [11].

A variety of studies including infected and septic patients show that inappropriate antimicrobial therapy is a consistent predictor of poor outcomes [12]. From a clinical perspective this means that the antimicrobial therapy must almost always be empiric in order to obtain a timely initiation. The choice of antibiotics and the timing of their administration cannot wait for isolation and identification of the causative organism and determination of the organism's sensitivity to various antibiotics. These principles lead to the observation that combination antimicrobial therapy may be the preferred option for empirical therapy [2]. A recent Spanish study demonstrated that a pre-emptive approach with meropenem and linezolid for 3 days was effective in reducing the incidence and delaying the onset of ventilator-associated pneumonia (VAP) in very high risk patients admitted to ICU [13]. However, in the same study, the authors reported the selection of linezolid-resistant staphylococci after the study period. The ecological consequences have to be carefully evaluated when this strategy is used [13].

While it is now well recognized that early appropriate antimicrobial therapy reduces infection-related morbidity and mortality in the critically ill patients, the importance of pharmacodynamic (PD) dosing to optimize drug exposure continues to evolve. At the dawn of this new millennium, the emergence of beta-lactam resistance in *Enterobacteriaceae* and *P. aeruginosa* coupled with the lack of new agents under development prompted a reassessment of conventional dosing techniques. Since it is well recognized that beta-lactam efficacy is driven by the time the drug concentration exceeds the MIC ($T > MIC$) of the target pathogen, many of these strategies focused on altering infusion times.

In the clinical setting, beta-lactam optimization strategies often include the use of a prolonged infusion (i.e., same dose administered over 3–4 h) for each dosing interval or as a continuous infusion where the total daily dose is given at a constant rate over 24 h. Each of these strategies has been reported to enhance the efficacy when compared to conventional regimens [14, 15].

It is important to recognize that, when given in the same total daily dose, both the prolonged and continuous infusion regimens will produce the same $T > MIC$ and each of these dosing regimens will provide substantially more exposure than the same dose given as an intermittent (i.e., 0.5 h) infusion. Therefore, the preferential strategy choice should be based on the stability of the molecule and on the intravenous access in the context of polytherapeutics. Additionally, it is important to acknowledge that the clinical benefit of these infusion-related optimization strategies will only be observed in situations where conventional regimens do not achieve adequate $T > MIC$, e.g., towards pathogens displaying elevated MIC and/or augmented renal function.

Hence, in the setting of a population of overwhelming susceptible pathogens the benefits of the prolonged administration strategies have been questioned [16]. As with any therapeutic intervention, the impact of PD optimization on outcomes will depend on the patients selected (i.e., suspected pathogen, susceptibility, renal function, etc.) as well as a systematic implementation of

infection management techniques. In the context of antimicrobial stewardship, a pathway for the management of VAP has been implemented. The strategy consists of improved diagnostic methods, PD optimized regimens for aminoglycosides and vancomycin, both continuous and prolonged infusion regimens in addition to providing guidance on de-escalation strategies, and duration of therapy. While this infection-based strategy reduced related morbidity, mortality, length of stay, superinfections, cost of care and improved efficacy towards high MIC pathogens, it is recognized that without a consistent implementation across the care continuum these benefits would have not been achieved [17].

In the context of antibiotic stewardship, a recent meta-analysis shows that procalcitonin-guided antibiotic therapy algorithms could help in reducing the duration of antimicrobial administration without having a negative impact on survival in critically ill patients [18].

While bacterial causes of infections have increased with the general incidence trend, invasive fungal infections represent a growing cause of sepsis in critically ill patients associated with substantial morbidity and mortality. While *Candida* and *Aspergillus* species remain the most frequent causes of fungal infections in the ICU, the spectrum of opportunistic fungi (*Pneumocystis jirovecii*, *Cryptococcus*, *Zygomycetes*, *Scedosporium*, and *Penicillium marneffei*) causing invasive infections is expanding in acutely ill immunocompromised hosts. Invasive aspergillosis has been recognized recently as an increasingly common problem in patients without classical risk factors, such as patients with chronic obstructive pulmonary diseases treated with corticosteroids. Recently, a

Table 1 Novelties in antimicrobial resistance and antibiotics use in critically ill patients

Topic	Intervention	Area of future investigations
Predominance of Gram-negative pathogens in sepsis	Adequate empiric therapy	Prospective surveillance studies
Increasing antimicrobial resistance in Gram-negatives [ESBL, carbapenemases (KPC, OXA, IMP, VIM)]	Limit use of cephalosporins, fluoroquinolones, and carbapenems Heterogeneous/mixed use of different classes of antibiotics Discouragement of prioritization/cycling program Antimicrobial stewardship program	Evaluate impact of stewardship program
Colistin resistance in *Enterobacteriaceae*	Limit empiric use of colistin Limit topical use of colistin Use loading dose of colistin in treatment (6/9 unit millions)	Prospective randomized trial with empirical colistin in critically ill patients Pharmacokinetics data on tissue distribution of colistin
Higher MIC for vancomycin in *S. aureus*	Adequate blood level of vancomycin (>15 mg/ml) Early daptomcyin Daptomycin (8–10 mg/kg/day)	Further guidance as to which patients will benefit most from early high-dose daptomycin
MRSA	Infection control	
Role of MDR in community-acquired infections	Broad-spectrum antibiotic therapy Use of multiplex real-time PCR to rapidly detect resistance gene	Prospective studies to evaluate impact of these new diagnostic technologies
Early appropriate antimicrobial therapy	Combination therapy	Prospective studies comparing combination with single therapy for Gram-negative infections
Adequate antimicrobial therapy: PK/PD	Adequate dosage Therapeutic drug monitoring (TDM)	
De-escalation	PCT-guided therapy	Impact of de-escalation on bacterial resistances
Beta-lactam optimization	Prolonged infusion (3–4 h) Continuous infusion	Prospective studies
Invasive aspergillosis in non-neutropenic patients	Clinical algorithm to discriminate colonization from putative invasive pulmonary aspergillosis	Prospective studies with the new clinical algorithm
High mortality for *Candida* infections	Early empiric therapy within 12 h Adequate source control	Evaluate prospectively early therapy on mortality
Early diagnosis of fungal infections	Mannan Galactomannan 1,3-Beta-D-glucan Risk stratification with scores (*Candida* score)	Impact on clinical practice (availability, costs)
Echinocandins use in pre-emptive, empiric, and target therapy of *Candida* infections	ESCMID guidelines in candidemia International consensus on intra-abdominal candidiasis	Impact on morbidity and mortality

clinical algorithm has been proposed to discriminate colonization with *Aspergillus* from putative invasive pulmonary aspergillosis [19].

Early diagnosis is crucial to initiate antifungal therapy promptly. Non-culture-based methods aimed at the detection of components of the fungal cell walls (mannan, galactomannan, and, most recently, 1,3-beta-D-glucan) have yielded promising results For diagnosing intra-abdominal candidiasis in surgical ICU patients, serial measurements of 1,3-beta-D-glucan were better than the *Candida* score or colonization indexes [20, 21]. Very recently, a promising biosensing platform combining PCR technology and nanoparticle-based hybridization was found to be both rapid (less than 3 h) and accurate in detecting as low as one CFU per milliliter in blood spiked with *Candida* species [22].

There is limited new information regarding prophylaxis, pre-emptive, and targeted therapy of invasive candidiasis. The results of one important clinical trial have been published so far only in abstract form. The MSG-01 study showed that caspofungin prophylaxis was associated with a trend in reduction of probable and proven candidasis, without impact on mortality [23]. A patient-level quantitative review of seven clinical trials of candidemia and invasive candidiasis indicated that the use of echinocandin was associated with statistically significant reduced mortality [24].

Last year, the European Society for Clinical Microbiology and Infectious Diseases published treatment guidelines for the management of invasive candidiasis [25] and recently a multinational consensus proposed a new pathway for the management of intra-abdominal candidiasis [26]. In both cases echinocandins were the preferred recommended drugs for critically ill patients. In particular several epidemiological data over recent decades have shown that non-candidemic invasive candidiasis, mostly peritonitis, is a frequent and life-threatening complication in surgical critically ill patients. Patients who test positive for fungal infection during the course of intra-abdominal infections are a source of confusion to many physicians, leading to a reductive assimilation of the peritonitis cases with those of other forms of invasive candidiasis and candidemia, and this approach may unfortunately be responsible for a large overuse of antifungals. The recent consensus even in the light of moderate or low quality of evidence elaborated specific statements addressing the management of intra-abdominal candidiasis. However the experts reckoned the urgency of dedicated studies in this clinical setting for the validation of the proposed statements [26].

Table 1 summarizes all the novelties in antimicrobial resistance and antibiotics use in critically ill patients.

Conflicts of interest The authors declare no conflict of interests.

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