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Infection with multi-resistant agents in the ICU: how to escape?

Infecção por patógenos multi-resistentes na UTI: como escapar?

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Infections caused by potentially drug-resistant pathogens steadily increase in intensive care units (ICUs) and are a major cause of overall prevalence in hospitals. Resistance is likely because ICU patients often have complex illnesses and use many antibiotics.[1,2] Indeed, more than 70% of critically ill patients will be given an antimicrobial drug during their ICU stay.[1] In addition, infections are highly involved in ICU morbidity and mortality; the prevalence of infections caused by germs that require progressively more complex therapy has grown in recent years.[1-3] Additionally, although multidrug-resistant germs are a worldwide problem, their mechanisms of resistance and sensitivity patterns vary widely across different regions, making any generalization difficult.[4]

In recent years, the surge of drug resistance has become a challenge for hospital systems.[2] The exposure to antimicrobials and resultant inappropriate use are the primary factors related to the development of resistance. The main pathogens associated with nosocomial infection, together representing higher therapeutic-limiting resistance risks, were grouped in an acronym known as ESKAPE (Chart 1).[2] Although the mechanisms of resistance are not the same, all ESKAPE pathogens share a growing prevalence due to the selective pressure from policies (or their absence) for antimicrobial use, particularly in ICUs. In addition, the development of new drugs able to broaden our therapeutic armamentarium is very limited, as no drugs are currently under development for most of the ESKAPE germs, especially for the gram-negative pathogens.[5]

Chart 1- ESKAPE pathogens

E	*Enterococcus faecium* (VRE)
S	*Staphylococcus aureus* (MRSA)
K	*Klebsiella* and *Escherichia coli* producing ESBL
A	*Acinetobacter baumannii*
P	*Pseudomonas aeruginosa*
E	*Enterobacteriaceae*

Source: Translated from: Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al. Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis. 2009;48(1):1-12.

VRE - vancomycin-resistant *Enterococci*; MRSA – methicilin-resistant *Staphylococcus aureus*; ESBL – Extended Spectrum Beta-Lactamases.

Therefore, the improvement of clinical outcomes and minimization of the risk of emergence of bacterial resistance will fundamentally come from

strategies for the appropriate use of currently available drugs. The biggest challenge is to design policies for the rational use of antibiotics. Policies must not only consider the indications for antibiotics use but also their optimal use, maximizing clinical effectiveness and reducing the drug's exposure and ecologic impact.[6] Strategies for avoiding homogeneous prescriptions against the ESKAPE pathogens have been apparently effective against emerging resistance, especially in patients with gram-negative mechanical ventilation-associated pneumonia (VAP).[2]

Although often considered to be antagonistic concepts, the clinical effectiveness of antibiotic therapy and the minimization of surge of resistance risks could be considered complementary instead. The classic approach for minimizing the risks of resistance maintained that fewer antibiotic drugs should be selected in a minimum-use policy (i.e., minimum dose, spectrum, treatment time, and therapeutic options). Adjustments were only to be made based on the available microbiological data. However, this strategy often resulted in delayed initiation of the appropriate therapy. Unfortunately, the clinical results were unsatisfactory, mainly in critically ill patients, whose rates of inappropriate therapy reached 30-50% in different case series using this approach, with evident clinical outcome impacts.[7-9] A so-called modern approach has proposed the permanent use of broad spectrum antimicrobials, based on monotone protocols, sometimes with exaggerated duration, minimizing the value of microbiological information in a typical policy like "a winning team should not be changed". This approach has led to the improved use of empirical therapy, but also increased antimicrobial use and the surge of resistance; however, this strategy also failed to provide the predicted improvement in clinical outcomes.[10,11] The artificiality of this antagonism between policies aimed at improving the clinical outcomes and those aimed at overall outcomes is therefore evident; improving overall outcomes will come from a policy encompassing both views.

More advanced knowledge is required to provide a scenario that allows us to realize a new paradigm. The knowledge of specific aspects of critically ill patients of the resistance-inducing mechanisms and antimicrobial pharmacology allows us to glimpse changes to this scenario. This new understanding provides recommendations that could impact clinical outcomes and the surge of resistance. We advanced from a concept of appropriate antibiotic therapy to one of optimized antibiotic therapy, which includes pharmacokinetic and pharmacodynamic (PK/PD) aspects and fundamental host features. As a result, we can provide some recommendations for the rational use of antimicrobials in critically ill patients.

Steps for rational use of antimicrobials in the ICU:

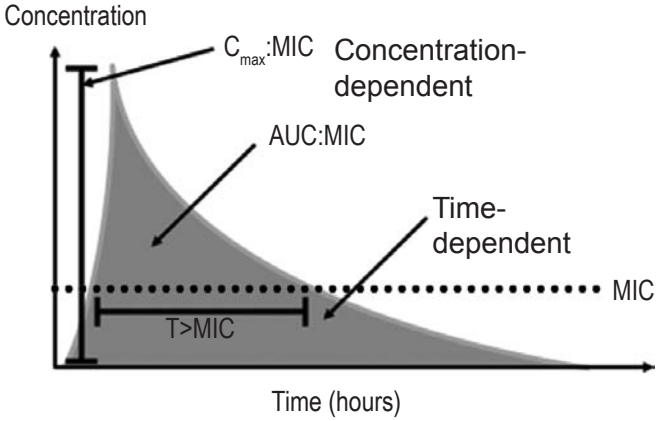
First step: Fast, appropriate and optimized initiation

Several studies have shown the negative impact of inappropriate empirical therapy on clinical outcomes.[7-9] In addition, delayed antibiotic therapy initiation is also associated with poorer outcomes.[12] Fundamentally, the drug choice should be based on the patient's clinical condition and potential resistant pathogen risk factors to determine the more or less broad antibiotic coverage and on the local microbiologic flora for nosocomial or healthcare-associated infections.[13] However, little consideration has been given to how the selected antimicrobial is used in specific medical conditions, specifically the dose, the administration regimen and the impact on the clinical outcome or induction of resistance. Changes related to the pathophysiology of sepsis, such as hyperdynamic hemodynamics, increased vascular permeability, increased volume of distribution, changes to the renal vascularization and the eventually increased renal clearance during the first 48 hours of sepsis are known to result in insufficient serum concentrations when some antibiotics are used in their usual dosages.[13-15] These often underestimated aspects may have two relevant impacts: first, low concentrations will lead to limited tissue penetration,[16] low concentration at the infection site,[15] little trustworthy bactericidal activity estimated from minimal inhibitory concentrations of the isolated germs and, consequently, unsatisfactory or sub-optimal clinical outcomes. Second, the exposure of the pathogens to sublethal antimicrobial doses predispose to surge of resistance.[17] Therefore, when PK/PD information of the selected antimicrobial drug are considered, maximizing of clinical outcomes and minimizing the risk of resistance are no longer antagonistic, but part of the same therapeutic approach.

Second step: Optimized prescription

Most of the literature suggests that antimicrobial doses are not designed or based on studies that included critically ill patients. Therefore, the risk of inappropriately low doses is high because of the changed volume of distribution, mainly during the initial phase (first 48-72 hours) of sepsis. Therefore,

not only doses but also dosage regimens should provide maximal bactericidal effects, quickly reducing the bacterial load and therefore reducing the time of exposure to the antimicrobial drug and potential surge of bacterial resistance risks. For this reason, the PK/PD information of antimicrobial drugs should be considered (Figure 1). For example, in aminoglycosides, the ideal maximal doses should be combined into one single daily dose with the goal of reaching maximal peak concentrations and therefore maximizing the pharmacodynamic endpoint: maximal concentration/minimal inhibitory concentration (C_{max}/MIC). However, the rationale is different for beta-lactams; these drugs' bactericidal activity relates to the time during which the pathogen is exposed to concentrations at the infection site above the minimal inhibitory concentration (T>MIC), where prolonged or continuous infusion strategies are preferred. Clinical trials using this approach in critically ill patients have shown improved clinical outcomes and a more beneficial impact in more severely ill patients.[18-20] Additionally, dose adjustments to prevent toxicity often limit the antibiotic effectiveness. For example, in patients under continued hemodialysis or hemofiltration with high-performance devices, as is currently common in ICUs, dose adjustments for renal function are probably not necessary, as these devices provide drug clearances that sometimes are even above normal. Reduced serum concentrations were found in clinical trials that assessed these patients.[21] Additionally, aspects related to protein binding should be taken into prescribing considerations. Chart 2 shows some dosage alternatives based on the above discussion.



MIC – minimum inhibitory concentration; AUC – area under the curve.

Figure 1 - Concentration versus time curve, presenting antimicrobial pharmacodynamics.

Chart 2 – Optimized regimen suggestions for critically ill patients

Antibiotics	Doses
• Cefepime	2 g every 8 hours over a 3-hour infusion.
• Piperacillin + tazobactam	4.5 g every 8 hours over a 4-hour infusion.
• Meropenem	2 g every 8 hours over a 3-hour infusion.
• Amikacin	15-30 mg/kg as a single daily dose.

Third step: De-escalation and early withdrawal

Once microbiological analysis results are available, it is fundamental to reduce the spectrum to specifically cover the identified germ and reduce unnecessary exposure to broader spectrum antibiotics. Although often merely considered as a restrictive strategy that would only be relevant for minimizing the surge of resistance, clinical evidence suggests that de-escalation, when possible, is associated with better outcomes.[22] This result is clearer with some specific pathogens; for example, studies have shown poorer outcomes in patients with *Staphylococcus aureus* infections caused by methicillin-sensitive strains (MSSA) treated with vancomycin instead of the specific spectrum drug oxacillin.[23] The use of a standard treatment timecourse, e.g., 14 or 21 days, has also been shown to be inappropriate. A more rational approach includes the use of clinical endpoints, such as the resolution of fever or leukocytosis[24,25] or the use of biomarkers[26,27] that allow the evaluation of the clinical course of severely ill patients. Compared with the traditional approach, reducing the number of days on treatment results in similar mortality rates, lengths of hospital stay and lengths of ICU stay for both groups, potentially leading to a reduced time on antimicrobial therapy.[28] These strategies' impact on reducing exposure is expected to be assessed soon in prospective trials.

This issue includes guidelines for treating treatment of severe sepsis and septic shock where aspects related to the infective agent were analyzed with the best available evidence. These guidelines include up-to-date information emphasizing the optimization of prescribing antimicrobials with pharmacokinetics and pharmacodynamics considerations, possible de-escalation and complementary aspects aimed at improved clinical outcomes with reduced exposure and lower risks of developing bacterial resistance.[29,30]

Because of the increasing problem of microbial resistance, one should search for strategies that prioritize the rational use of resources. The most

Chart 3 – Main errors in antimicrobial use in critically ill patients

1.	Choosing the antibiotic based only on the *in vitro* sensitivity.
2.	Ignoring PK/PD features when prescribing the dose and dosage.
3.	Not considering serum albumin levels when prescribing highly protein-bound antibiotics.
4.	Overlooking patients with changed volume of distribution that could need dose adjustments.
5.	Underestimating the creatinine clearance when prescribing the antibiotic dose during the acute phase of sepsis.
6.	Overlooking the high effectiveness of new renal replacement methods and limiting the antibiotic doses.
7.	Using standard doses and regimens that may lead to sub-therapeutic doses in severely ill patients.
8.	Overlooking local patterns of resistance.
9	Failing to use clinical response endpoints for determining the duration of the therapy.
10.	Prolonging the antimicrobial therapy unnecessarily.

relevant aspects we frequently overlook in treating severe infection patients are summarized in Chart 3. Changing our practices to individualize management, avoid homogeneous selective pressure and employ the entire potential of our antimicrobial choices are useful strategies to escape the adverse consequences associated with the reality of emerging resistance.

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