EDITORIAL

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De-escalation as a potential way of reducing antibiotic use and antimicrobial resistance in ICU

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Nowadays all the lights are red. Antibiotic resistant strains are more and more prevalent [1] and the availability of new antibiotic agents is becoming exceptional.

More than two-thirds of cases of ICU-acquired bacteremia are caused by multidrug-resistant or extensively drug-resistant bacteria [2]. Although the prevalence of methicillin-resistant *Staphylococcus aureus* is decreasing, the increasing rates of glycopeptide-resistant enterococci, extended-spectrum β-lactamase-producing *Enterobacteriaceae*, and Gram-negative bacteria resistant to carbapenems are worrisome.

The spread of bacterial resistance is mediated by three important factors. First, the bacteria itself may acquire resistance by mutation and, more frequently, by plasmid-mediated gene exchange between species in particular within the digestive microbiota. Second, the antibiotic selection pressure promotes the growth of resistant bugs by killing the susceptible ones. Third, cross-transmission of resistant bacteria may facilitate spread from one patient to another.

ICUs are the epicenters of antibiotic resistance because (1) more than 80 % of the patients may receive antibiotic treatment on a given day [3]; (2) the illness severity of the patients and the use of invasive procedures increase the likelihood of successful acquisition and persistent colonization with new strains; (3) the unstable hemodynamic conditions predispose to establishing suboptimal concentrations of antibiotics at the infection site; (4) the high healthcare workload favors the risk of cross-transmission of resistant strains.

To interrupt cross-transmission appropriate hand hygiene, skin cleansing, and contact precautions are key preventive measures. The immediate effect of appropriate antibiotic therapy on emergence and dissemination of antibiotic resistance is more complex and difficult to measure [4, 5]. Indeed, associations between antibiotic exposure and resistance at an individual, unit, hospital, regional, or national level have been frequently demonstrated [6]. However, the total effect of antibiotic pressure is due to a direct effect on the individual who receives the antibiotic agent, but also to the indirect impact on the transmissibility of resistant and susceptible strains within an entity such as an ICU [5].

Many studies demonstrated the link between antibiotic use and antibiotic resistance, both at a unit [5, 7–10] and at an individual level on the infecting flora [5, 11, 12] and on the gut microbiota [13]. However, the intensity of the effect is very difficult to evaluate because of the numerous uncontrolled factors and methodological issues, such as absence of regular screening of the patient's gut flora [4, 5].

First, on an individual basis, antibiotic therapy clearly increases the risk of antibiotic resistant bacteria selection at the infection site [5, 11, 12]. In healthy subjects and in patients with community-acquired infections, antibiotic agents have a marked effect on intestinal microbiota diversity. The cessation of antimicrobial administration is associated with an incomplete and slow return to the pretreatment state [14]. In ICUs, the impact of antibiotic use on the gut microbiota has been demonstrated. As an example, treatment with imipenem is associated with a more than twofold increase in the imipenem-resistant Gram-negative bacteria. The effect is significant even after a 1-day course of imipenem [13].

The effect on the individual (mainly gut) microbiota varies according to the patients' characteristics and clinical situations, between molecules, drug concentrations, and duration of antibiotic administration [15]. For instance, prolonged perioperative antibiotic prophylaxis was associated with an increased risk of selection of glycopeptide-resistant enterococci and cephalosporin-resistant enterobacteria [16]. Overall, the impact of a decrease in antimicrobial use is certain, but the effect varies according to patients' characteristics, clinical conditions, molecules, route of administration, and dosage.

Antibiotics need to be given early to infected people, properly using aggressive initial dosing and stopping early when possible. The main rules for antibiotic treatment are listed in Table 1. One of the possible ways to decrease antibiotic use, and subsequently to constrain antibiotic resistance, is to apply streamlined (or de-escalated) therapy whenever possible.

In a recent article in *Intensive Care Medicine*, Leone et al. [17] reported a randomized controlled trial (RCT) evaluating the impact of antibiotic treatment de-escalation. It had no significant impact of length of ICU stay and even increased the number of antimicrobial days as well as the risk of superinfection. The impact of de-escalation on individual gut microbiota was not evaluated.

The study is important because it is the first eagerly awaited RCT conducted on this specific topic. Only one previously published controlled clinical trial has been performed, demonstrating that narrow-spectrum antibiotic therapy in neonates decreased the likelihood of resistance [18].

However, the study results should be cautiously analyzed and mitigated. First, patients enrolled were not consecutive as reflected by the relatively low number of patients enrolled per year and per ICU. The appropriateness of the initial antimicrobial dosing was not reported and not followed. Second, there was a large variability in the main judgment criteria that seriously impacts the power of the study. Indeed, the standard deviation of the duration of ICU stay from inclusion to discharge was more than 12 days in both groups. With a 2-day non-inferiority margin, more than 500 patients per arm would have been necessary to allow a definite conclusion to be drawn. Third, the population enrolled was seriously unbalanced, especially for age, SAPS II, the delay between admission and inclusion, the delay between sepsis and inclusion, and the lungs as the source of infection. Note that the authors acknowledged that lung as the source of infection was significantly associated with the length of ICU stay. Fourth, the duration of combination therapy was longer in the continuation group as compared to the de-escalation group; this difference occurs after enrollment and may have been influenced by the open-label nature of the study. Finally, in the subgroup analysis that includes only lung infections, the durations of ICU stay were similar in the de-escalation group (14 vs. 15 in median, $P = 0.53$). However the number of superinfections was still higher in the de-escalation group (39 vs. 22 %, $P = 0.2$).

Given the absence of difference in mortality between groups, the repeated results of observational studies showing de-escalation and reduced treatment duration as proper ways to reduce antibiotic use, and the serious flaws of this RCT, de-escalation should remain recommended and be carefully evaluated in further studies.

Table 1 Rules for initial antimicrobial treatment of infections in ICU to avoid antimicrobial resistance

Diagnostic	Perform immediate diagnostic test before starting new antimicrobials
Choosing antibiotics	Available guidelines
	Gram stain examination and molecular techniques may help with initial choice of molecules
	Previous knowledge about individual, unit, or hospital colonizing flora
	Combination therapy in Gram-negative infection may help to increase the spectrum (but is not recommended to decrease resistance)
	An antimicrobial stewardship team may help to define local procedures and provide individual advice
Conducting antimicrobial therapy	Use appropriate high initial antibiotic dosing
	Control the infection source (drainage, surgery) as quickly as possible
	In patients with documented infection de-escalate to the molecule with the narrowest spectrum and similar efficacy
Stopping rules	Discontinue antibiotics in patients with negative culture and no evidence of clinical infections
	Stop the antimicrobial therapy early in case of rapid improvement. A rapid decrease of the procalcitonin level may help

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