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EDITORIAL

In 2035, will all bacteria be multidrug-resistant? No

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The spread of multidrug-resistant (MDR) bacteria has reached a threatening level. Extended-spectrum beta-lactamase-producing enterobacteriaceae (ESBLE) are now endemic in many hospitals worldwide as well as in the community, while resistance rates continue to rise steadily in *Acinetobacter baumannii* and *Pseudomonas aeruginosa* [1]. Even more alarming is the dissemination of carbapenemase-producing enterobacteriaceae (CPE), causing therapeutic and organizational problems in hospitals facing outbreaks or endemicity. This context could elicit serious concerns for the coming two decades; nevertheless, effective measures exist to stop the amplification of the problem and several axes of prevention remain to be fully exploited, leaving room for realistic hopes, at least for many parts of the world.

Conceptually, there are three mechanisms of increasing and two for decreasing the prevalence of carriage with MDR bacteria in healthcare settings, including in the intensive care unit (ICU). First, there is a certain fraction of patients colonized when admitted; second, MDR bacteria are selected within a patient as a result of selective pressure of antibiotics; and third, MDR bacteria are transferred between patients, either through healthcare workers or contaminated inanimate surfaces. The prevalence can decrease by discharging colonized patients (and admitting non-colonized patients) or by eradicating carriage of MDR bacteria. For the current debate, we will ignore the last two options and focus on the possibilities to reduce importation, selection, and transmission of MDR bacteria (Table 1).

The strongest arguments for our position are that, even in 2035, a conceivable proportion of ICU patients will be admitted directly from the community (or after little healthcare exposure) and that MDR bacteria will still not be widely prevalent outside the hospital setting. Thus far, there is reason to believe that MDR bacteria do not spread easily in healthy populations with low antibiotic selective pressure. For instance, a large abundance of livestock-associated methicillin-resistant *Staphylococcus aureus* (MRSA) in the agricultural industry has not created a clinically relevant prevalence of MRSA carriage in open populations [2]. Furthermore, in many countries—including in Europe—the prevalence of colonization with ESBLE among healthy subjects is around 5–10 %, and appears not to increase [3]. It is highly unlikely that, in such countries, CPE will be more successful in similar conditions. A prerequisite for maintaining this situation is that antibiotic use in primary care is either maintained at current levels or reduced by using regional or nationwide antibiotic restriction campaigns [4]. Eliminating unnecessary or inappropriate prescriptions in ambulatory patients is now strongly advocated in most action plans targeting bacterial resistance [5]; as a result, a large proportion of ICU patients will still be admitted without carrying MDR bacteria.

As antimicrobial consumption represents a major driver of bacterial resistance in the healthcare setting [4], avoiding antibiotic overuse—or misuse—stands as the most urgent action to control the dissemination of MDR pathogens. In this regard, infection prevention policies appear essential to contain the level of selection pressure in hospitalized patients [6]. Furthermore, antimicrobial stewardship programs (ASPs) may improve the quality of antibiotic prescription practices through a bundle of measures, including institutional restrictions for the use

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Table 1 Ten pivotal measures to avoid a situation of pan-drug resistance in the intensive care unit in 2035

Actions	Area of implementation	Objective
Containment of antimicrobial use in primary care	Community	Reduce importation of MDR bacteria (patients admitted from the community) by lowering antibiotic selection pressure outside the healthcare setting
Strict control of antibiotic consumption in veterinary medicine and agricultural/aquacultural industries	Community	
Prevention of environmental contamination with MDR bacteria	Community	
Universal compliance to hygiene guidelines	Hospital wards and ICU	Reduce importation (patients transferred from wards) and prevent cross-transmission of MDR bacteria
Screening for carriage of MDR bacteria and implementation of isolation precautions in identified carriers	Hospital wards and ICU	
Enhanced strategies for the diagnosis of bacterial infection to avoid unnecessary antibiotic prescriptions	Hospital wards and ICU	Preserve currently available broad-spectrum antibiotics and prevent the emergence of resistance by lowering antibiotic selection pressure in hospitalized patients (antibiotic stewardship initiatives)
Development of accurate tools to narrow the spectrum of empirical therapy	Hospital wards and ICU	
Systematic reassessment of empirical therapy and de-escalation whenever possible	Hospital wards and ICU	
Shortening of antimicrobial therapy (e.g., PCT-driven algorithm) whenever possible	Hospital wards and ICU	
Large-scale programs to promote and speed up the development of novel antimicrobial agents	Global	Offer new options to treat MDR bacteria

MDR multidrug-resistant, *ICU* intensive care unit, *PCT* procalcitonin

of certain broad-spectrum agents that markedly foster resistance (notably carbapenems and fluoroquinolones) and scheduled feedback in an attempt to sustain behavioral changes on a long-term basis [5]. The first step is to more accurately define the diagnosis of bacterial infections, thus limiting unnecessary selection pressure in patients with systemic inflammatory response but no bacterial sepsis. Low plasma levels of procalcitonin (PCT) can rule out the need for antimicrobial prescription in ambulatory patients with respiratory tract infections [7], and whether PCT may be safely used to guide not starting antibiotics in septic critically ill patients deserves further investigations. Other novel diagnostic approaches based on rapid molecular assays also have potential to identify critically ill patients who actually require antibiotics [8]. Once the diagnosis of bacterial infection is deemed likely, a challenging dilemma is to ensure adequate empirical antimicrobial coverage with the narrowest spectrum of activity, a problem in patient populations with high colonization rates of MDR pathogens. Indeed, ESBLE carriage in otherwise uninfected critically ill patients has been associated with a three-fold increase in the empirical use of carbapenems during the ICU stay when compared to non-carriers [9]. Yet, documented absence of carriage might be used to withhold maximum broad-spectrum antibiotics in case of infection [10], and the development of rapid diagnostic tools—including phenotypic methods, mass spectrometry, or PCR-based assays—for earlier identification of pathogens and resistance patterns offers promising perspectives to target narrower-spectrum empirical therapy [6].

Reassessment of antibiotic therapy with predefined strategies for de-escalation forms another pivotal aspect of ASPs. De-escalation can be performed safely in critically ill patients [11], but only when relevant culture results are available. Therefore, de-escalation can only be meaningfully used to control antibiotic resistance if microbiological diagnostics are applied systematically. Next, ASP components targeting pharmacokinetic/pharmacodynamic parameters (e.g., high-dose regimens, extended β-lactam infusion, or therapeutic drug monitoring) could conceivably prevent the emergence of resistant mutants at the infection site by avoiding underdosing and sublethal concentrations [12]. Also, antibiotic courses can often be safely shortened [6], which is essential as even a couple of days of antibiotic administration increases the likelihood of colonization with resistant Gram-negative bacilli in ICU patients [1]. The reliability of PCT-driven algorithms to customize treatment duration in patients with rapid organ failure resolution is now well established, enabling ICU physicians to reduce antimicrobial exposure without deleterious outcomes [7, 13].

Although further studies remain necessary to appraise the ecological benefits of ASPs, evidence already exists that reducing the overall volume of broad-spectrum beta-lactams and fluoroquinolones consumption in a given hospital can significantly decrease local resistance rates in enterobacteriaceae and non-fermenting Gram-negative bacilli, including in the ICU [14].

Hygiene compliance and the implementation of isolation precautions for identified carriers are key measures to prevent cross-transmission of MDR bacteria

in hospitalized patients, especially in the ICU [6]. For instance, a nearly two-fold decrease in the incidence of MRSA infections was observed in a large network of French university-affiliated hospitals over a 15-year period following the launch of a multifaceted program comprising the promotion of alcohol-based hand rubbing, carriage surveillance, barrier precautions, training, and feedback [15]. In another study conducted in 13 European ICUs, improving hand hygiene in combination with daily chlorhexidine bathing was associated with reduced MRSA acquisition rates [16]. Nowadays, a vast majority of hospital staff members are confronted with multidrug resistance in their routine practice, and one could hope that this situation will further raise awareness about the problem, thereby easing the implementation and acceptation of constraining prevention campaigns in the years to come.

Finally, large-scaled initiatives are currently employed to facilitate more rapid development and clinical evaluation of new antimicrobial agents [17]. These efforts, plus the use of efficient ASPs [5], improved infection diagnostics [8], earlier targeted narrow-spectrum antibiotic use [6], better dosing strategies [12], shorter antibiotic duration [18, 19], adequate hygiene policies [6], and controlled antibiotic use outside the healthcare setting [4] further strengthen our position that effective treatments will remain available in 2035.

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