In an inhospitable ICU, not even antibiotic cycling or mixing are the solutions

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According to the World Health Organization antibiotic resistance is a clinical and public health priority (1). It is considered that antibiotic resistance is the cause of approximately 700,000 deaths annually worldwide (2). In fact, it has been discussed that, in an unaltered scenario in the absence of coordinated international series of actions aimed at efficient local antibiotic control measures, this number would rise to 10 million deaths per year in 2050 (2,3). The critical situation is a real challenge in intensive care units (ICUs), where pressures for selection and the emergence of resistance and risks of transmission of resistant pathogens are highest and where the patients are in especially fragile situations. The prevalence of antibiotic resistance in ICUs has been associated with a series of factors which, depending on their susceptibility to modification, offer potential targets for interventions that seek to mitigate antibiotic-resistant pathogens.

Among these interventions, different antibiotic-use strategies have been proposed to minimize the development and/or transmission of antibiotic-resistant microorganisms, including cycling, mixing and combined therapies. The cycling strategy was developed to increase the specific pressure exerted by an antibacterial agent during a cycling period and maximize the heterogeneity in the pressure between different cycles. The logic behind cycling is that the acquired resistance will be the lost (or diminished) in the different cycles because of both the inability of these mechanisms to confer resistance to the antibacterial agent used in the new cycle and the fitness cost which may be induced. Meanwhile, the mixing strategy maximizes the heterogeneity of the antibiotic pressure in a continuous model. Therefore, the logic of this strategy is to minimize the pressure exerted by a specific antimicrobial agent and to impair the dissemination of selected resistant microorganisms among patients because of the diversity of treatments.

A third strategy is the use of combined therapies. This strategy tries to hinder the selection of resistant microorganisms, which would need to develop or acquire two independent mechanisms of resistance, and increase the fitness costs of the development of such resistance (4).

The study performed by van Duijn and colleagues (5) was designed after a systematic literature review which highlights the need for more evidences for recommended an adequate antibiotic use strategy in ICUs. In the above mentioned systematic review done in 2006 were identified only 9 studies performed between 1984 and 2006 which address the effects of cycling and mixing strategies in the reduction of antibiotic resistant microorganisms in ICUs. A posterior literature review in 2012 added 8 new references (5).

Thereby, in their study van Duijn and colleagues (5) aimed to answer which treatment intervention was most effective in the reduction of antibiotic resistant Gram-negative in ICUs. They did not observe any differences between the use of cycling and mixing strategies, and concluded that their results support that the application of cycling and mixing in a real model is unlikely to achieve large effects on antibiotic resistance. The authors proposed the reduction of antibiotic consumption and the development of more efficient diagnostic tools as the probable more effective policies.

While measures to control the increasing levels of antibiotic-resistant microorganisms which will contribute to minimizing the selective pressure exerted by the antibacterial agents are essential (6), the conclusion of van Duijn and colleagues about mixing and cycling strategies is discouraging (5).

Different factors may affect the final effectiveness of these strategies, including the molecular mechanisms and genetic structure of resistance which are spreading in the community. Seems difficult, if not impossible, to reduce the prevalence of resistance in ICUs below that present at community levels. Furthermore, the type of microorganisms is related to final actions effectiveness. Thus, different interventions have not result in a reduction in the prevalence of *Enterobacteriaceae*, mostly carrying extended spectrum β-lactamases (ESBL) and vancomycin-resistant enterococci (6).

Additionally, the presence of colonizing microorganisms carrying a mechanism of antibiotic resistance able to affect two or more of the scheduled antimicrobial agents may impair the effectiveness of the strategies selected, requiring a change in therapeutic approach. Thus, several carbapenemases are able to hydrolyze carbapenems, 3rd and 4th generation cephalosporin and are also poorly inhibited by some early β-lactam inhibitors (7,8). In this sense, it has been described that the introduction of a completely unrelated antibacterial agent in the mixing or cycling strategies would contribute to the control of carbapenem-resistant microorganisms, especially *Pseudomonas aeruginosa* (9). Thus, it has been suggested that fluoroquinolone use in *P. aeruginosa* non-colonized patients diminishes the new acquisition of *P. aeruginosa*, even in settings with high levels of quinolones resistance (9). Similarly, the presence of mechanisms of resistance to unrelated antimicrobial agents in the same genetic structure may also result in their spreading through different microorganisms, thereby leading to a scenario similar to that mentioned above.

The stability and modifying rate of gut or respiratory tract microbiota, among others even in the presence of exogenous antibiotic pressure should also be considered, especially in patients with lengthy hospital stay and healthcare personnel. During patient management or even by air dissemination, this later group may act as involuntary microorganism-spreading agents. Furthermore, common personal devices, such as cell phones may act as a reservoir of highly resistant microorganisms (10,11). Therefore, the implementation of measures such as hand hygiene and the use of masks, as well as limited access to personal devices (e.g., cell phones) in ICUs and the need to raise awareness about the need to remove gloves before handling any personal object may be a complementary firewall to limit the spread of resistant microorganism. While in specific populations such as international travelers different studies have provided an overall vision of the relative ease by which antibiotic-resistant determinants are added to the gut microbiota and the rates of loss after travel return (12), to our knowledge, data about ICUs patients and healthcare personnel are mostly limited to phenotypic characterization or to specific antibiotic resistance genes. A related finding is the unexpected long-term survival and dissemination of relevant pathogens in the air such as carbapenem-resistant *Acinetobacter baumannii* (13) which may lead to nosocomial infections several weeks the introduction of the microorganism to the ICU.

In their study, van Duijn and colleagues (5) conclude that the most effective action to minimize the impact of antibiotic resistance in ICUs is better antibiotic management leading to diminished antibiotic consumption and a subsequent reduction in the pressure exerted on microorganisms. The authors conclude that to achieve this goal better diagnostic tools which facilitate the identification of patients requiring antibiotic treatments are needed, thereby avoid prolonged unnecessary use of antibiotics. Although the antibiotics selected in this study were structurally related, and therefore the presence of mechanisms of resistance able to affect two or more of the selected antimicrobial agents cannot be ruled out, we consider that the authors are right; the effectiveness of some of the above mentioned measures, as well as those tested by the authors, may have a modest impact on the current scenario of high levels of antibiotic consumption. In this sense, could a reduction in the access of antibiotic-resistant microorganisms to ICUs be one of the first and most effective actions to be taken?

Usually, hospitals, the community, farms, food or environment tend to be considered as independent compartments, and ICUs as special and unrelated settings. However, this is not correct. Why do we consider ICUs as isolated environments? While it is true that ICUs are environments with special characteristics which favour the acquisition and spread of resistance, it should also be taken into account that ICUs, and in fact all hospital settings, are interconnected with surrounding environments, such as the community. Although ICUs are independent and closed units, in which a series of barriers and protocols limits the introduction and exit of antibiotic resistant microorganisms, the mechanisms of antibiotic resistance which spread within the community, or which are present in other hospital areas, are those which are continuously introduced into ICUs both by new patients, healthcare personnel, external devices, food, water or air. Therefore, it has been described that different forces interactions underlie the development and spreading of antibiotic-resistance in ICUs (14): (I) the development of antibiotic resistance during antibiotic treatment within ICU; (II) the selection of a pre-existent antibiotic-resistant bacterial population, either pathogenic or not, previously introduced in the ICU from an external source (community or other hospital area). It is of note that the introduced mechanisms of resistance might be transferred to other ICUs resident microorganisms which therefore become antibiotic-resistant; (III) spreading of antibiotic-resistant microorganisms between patients.

Furthermore, in a recent study done in a ICU of Jakarta (Indonesia) carbapenem-nonsusceptible *Acinetobacter baumannii-calcoaceticus* complex were detected in patients samples but also in samples from healthcare personnel (15) showing that healthcare personnel may also be a door for the entrance/exit of antibiotic resistance microorganisms in ICUs. The setting of the ICUs is, in fact, the tip of the iceberg, being a magic mirror which reflects an amplified and worrisome image of the situation.

In summary, van Duijn and colleagues (5) did not observe any differences between mixing and cycling strategies and mortality rates were equivalent between these strategies and the baseline study. In this scenario actions to reduce antibiotic pressure in ICUs are necessary, including better diagnostic tools resulting in more rational antibiotic use. Furthermore, despite their strong specificities focused to control and minimize external pressures, ICUs are a part of a whole; therefore, the reduction of antibiotic consumption in the community, livestock or pets would be a positive force to reduce the arrival of antibiotic-resistant microorganisms to this setting.

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