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EDITORIAL

Bacterial resistance unrelated to antibiotic use: The perfect excuse?

La resistencia bacteriana no está relacionada con el consumo de antibióticos: ¿la excusa perfecta?

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Guidelines, recommendations and stewardship programmes[1–3] propose limiting antimicrobial exposure in humans as the core intervention to combat bacterial resistance. Specifically, it is expected that the risk of development of bacterial resistance to antibiotics will be reduced by shortening therapy and prophylaxis, as well as avoiding indications like colonization or non-bacterial infections. The underlying concept of these proposals is that direct contact of antimicrobials with the patient's flora provides a survival benefit to intrinsically resistant microorganisms by eliminating those that are susceptible and/or directly induces mechanisms of resistance. A multitude of more or less radical experiences limiting antimicrobial drug exposure[4] (see also references 1–11 and 25–34 in Álvarez-Lerma[5]) support that this strategy is associated with reduction, whereas increases are followed by worsening rates of resistance.[6] In discrepancy with these experiences and the accepted dogma, however, Álvarez-Lerma et al. report in this issue of *Medicina Intensiva* that consumption of several antipseudomonal antibiotics and their respective resistance in *Pseudomonas aeruginosa* are statistically unrelated.[5] The authors review ten years of the 3-monthly, April to June, Spanish National Nosocomial ICU-acquired Infection Surveillance Study (ENVIN-HELICS).[7] A data base of 187.100 critically ill patients, 11.652 (6.2%) of whom developed device-associated infection, 2.095 (13.6%) caused by *P. aeruginosa*, provides susceptibility data and consumption in days of antipseudomonal drug treatment over the 10-year study period. The author's analyses show that significant reductions in consumption of aminoglycosides, ceftazidime, cefepime, quinolones and carbapenems parallel significant increases in resistance of *P. aeruginosa* isolates to piperacillin-tazobactam, imipenem, meropenem, ceftazidime and cefepime.

Potential causes of this lack of association, as the authors correctly point out in their discussion, are that some bacterial reservoirs remain unaffected by reductions in antibiotic administration in the intensive care unit. A high percentage of patients being admitted to a given unit who have been or are currently on broad-spectrum antibiotics and carry or are infected with resistant bacteria may influence the efficacy of the combat against antimicrobial resistance of that unit, more so, if these are not detected at admission and barrier precautions are not implemented immediately. Secondly, the control of inanimate reservoirs of resistant bacteria is a formidable challenge in some units located in old buildings with contaminated tap water, sinks, and taps.

Other factors worth mentioning, that may contribute to a lack of association of antibiotic consumption and resistance rates, but are difficult to evaluate in retrospective analyses, are prescription behaviour of non-antipseudomonal antibiotics, both for therapy and prophylaxis, as well as for infections other than those captured in ENVIN-HELICS. Tracheobronchitis, for example, is currently a frequent and important indication for antibiotic administration in intu-

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bated patients,[8] with 61% caused by multidrug resistant bacteria and *P. aeruginosa* being the most frequent cause.

The ratio of resistant to susceptible *Pseudomonas* strains may have shifted from the years 2006 to 2016 in Spanish ICUs by reductions of susceptible strains in the denominator. This effect, admittedly, remains to be confirmed, and would require assessment of the protective or risk-increasing effects of the individual components of the Spanish National infection prevention and resistance bundles,[2,9–11] which were implemented in early 2009, as well as the synergistic combination of individual measures when applied in bundles. Of note is, that the above mentioned recommendations include direct antimicrobial interventions like the use of chlorhexidine for skin infection,[2,9] administration of topical antibiotics for selective decontamination of the digestive tract intubated patients[10] and a short course of intravenous antibiotics for the prevention of primary endogenous pneumonia. In fact, Álvarez-Lerma et al. show that *Pseudomonas* isolates slightly decrease from 217 to 199 over the study period, while the patient sample increases from 12,000 to 24,000 over the study period. In other words, prevention bundles may have reduced ICU-acquired infection rates, with a greater impact on infections caused by the more susceptible flora.

Finally, antibiotic diversity or heterogeneity has been associated with reductions in bacterial resistance, meaning that overuse of certain classes of drugs with the same mechanism of action, the opposite circumstance to diversity, should be avoided. Ideally, a similar percentage of exposure to the different antibiotic classes, i.e. 20% of patients, if 5 different groups are used, should be receiving beta-lactams, quinolones, tetracyclines, beta-lactam with beta-lactam inhibitor (BL-BLI), including the novel BL-BLI, and fosfomycin, in a given ICU. This concept is antagonistic to antibiotic cycling,[12] has been shown to be associated with lower resistance rates when compared to cycling[13] and has been proposed to reverse resistance in *P. aeruginosa* in a situation of homogeneity due to overuse of carbapenems.[6,14] Table 2 in Álvarez-Lerma et al.'s manuscript, in fact, shows marked homogeneity or lack of diversity, with noticeable preponderance of beta-lactam antibiotic use, ranging from 53 to 83% treatment days over the 10-year study period, with carbapenems being the choice in 1 of 3 patients. Achieving diversity is challenging, because randomized clinical trials-based decision algorithms are needed to support each antibiotic drug choice, but requires future studies to avoid the current overuse of carbapenems, i.e. as a carbapenem-sparing strategy.

In summary, Álvarez-Lerma's study results strongly suggest that other infection control and antibiotic policy factors influence resistances rates and should be considered when generating strategic plans to combat bacterial resistance. Rather than providing a waiver for the continued effort of reducing antibiotic exposure, they should be interpreted as an indication of the need to expand our efforts and incorporate additional measures to increase efficacy in tackling the problem of bacterial resistance.

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