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Acinetobacter baumannii resistant to everything: what should we do?

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Although the prevalence of species of the genus *Acinetobacter* other than *Acinetobacter baumannii* has seemingly increased as a cause of nosocomial infections in different geographical areas [1], the latter species continues to be the most prevalent in hospital settings. Several characteristics of this microorganism should be highlighted: (i) the intrinsic resistance associated with the interplay between decreased outer membrane permeability and constitutive expression of some efflux pumps; (ii) the acquisition of genetic elements such as resistance islands, which may carry up to 45 resistance genes or insertion sequence elements—these latter elements can be inserted upstream from some chromosomal genes and can contribute to the expression of these genes, such as bla_{ADC} or $bla_{OXA\text{-}51}$, encoding a chromosomal cephalosporinase and a carbapenemase, respectively, and in addition, mutations in genes related to the overexpression of efflux pumps (AdeABC and AdeIJK) can generate multiresistance, as these efflux pumps normally have different substrates; and (iii) the ability to survive in the environment, most likely associated with biofilm production, which can contribute to the acquisition of either mutations or genetic elements [2,3]. All the above-mentioned features lead to the development of multidrug-resistant, extended-drug-resistant and pan-drug-resistant *A. baumannii* strains. Therefore, not many alternatives are available to treat the infections caused by pan-resistant *A. baumannii* strains. The drugs currently available, which show a lower percentage of resistant clinical isolates, are colistin and tigecycline. Colistin has been used in several studies to treat infections caused by multidrug-resistant *A. baumannii*, with suboptimal results. To improve its efficacy, recent pharmacokinetic/pharmacodynamic data have led to the suggestion that the colistin dosage should be optimized with an initial loading dose, to enable therapeutic concentrations to be reached more rapidly [4]. Tigecycline has shown good *in vitro* activity against *A. baumannii*; however, few data, none of them definitive, have been reported from non-comparative studies concerning its efficacy in *A. baumannii* infections. Moreover, rapid appearance of resistance has occurred during the treatment, most likely associated with the overexpression of AdeABC and/or other efflux pumps. Among the possible combination therapies for the treatment of multidrug-resistant *A. baumannii* infections, rifampin plus colistin has been evaluated in ventilator-associated pneumonia and bacteraemia. Once more, the results have been discordant, and it may be stressed that a high dose of rifampin must be used; moreover, to avoid the appearance of rifampin resistance during the treatment, it is necessary to ensure, in the case of empirical therapy, that the drug combined with rifampin is active against the *A. baumannii* strains causing infections in a particular setting.

The problematic situation generated by *A. baumannii* has not been reflected in the development of new antibacterial agents against this microorganism. The last drugs developed, such as doripenem, ceftobiprole and ceftalorine, do not show activity against *A. baumannii* resistant to carbapenems or cephalosporins.

Taking into consideration all the above, it is evident that we desperately need new approaches, including new antibacterial agents, to control *A. baumannii* infections. The new drugs could be aimed at: (i) essential proteins or processes for the bacteria that have not been used so far; and (ii) processes such as antibiotic resistance and bacterial virulence. Targeting antibiotic resistance is an attractive approach, because it would help to reduce antibiotic resistance itself, and it would allow the recovery of antibiotics to which bacteria have already become resistant. In this sense, the development of efflux pumps or β-lactamase inhibitors should be noted. Studies on drugs targeting the mechanisms that allow bacteria to produce infections are also underway [5]. Antimicrobial peptides have attracted increasing interest as potential new antimicrobial agents. Some of these antimicrobial agents show good *in vitro* activity, even against colistin-resistant *A. baumannii.* Modifications to the basic structure of these peptides can be performed to improve their pharmacokinetic/pharmacodynamic features. Additionally, non-antimicrobial approaches need to be addressed. Recently, in a murine model of disseminated sepsis, active and passive immunization with an inactivated whole cell vaccine was

effective in preventing infection by *A. baumannii* [6]. Finally, it must be stressed that there is an urgent need to reinforce research on the epidemiology of resistance, surveillance, and the proven measures to control hospital infections.

Transparency Declaration

The authors declare that they have no conflict of interest.

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