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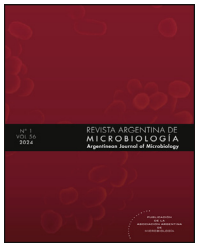

EDITORIAL

Carbapenemen-resistant Enterobacterales: An issue of global concern

Enterobacterias resistentes a los carbapenemes: una problemática de interés global

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Carbapenem-resistant Gram–negative bacilli, especially those belonging to the family Enterobacterales, are reported worldwide as critical pathogens of great concern due to the limited therapeutic options available. Indeed, carbapenem-resistant Enterobacterales (CRE) have been named as urgent or serious threats by the CDC.[1] Carbapenem resistance in this group of bacteria is mediated by carbapenemase production; these enzymes can be classified into classes A, B, or D, according to Ambler.[4] Class A carbapenem-hydrolyzing enzymes include *Klebsiella pneumoniae* carbapenemase (KPC), which, for more than 15 years, has been known for its global dissemination associated to the epidemic and successful clone ST258; nowadays there are over 100 allelic variants reported, being endemic in several countries. The other most prevalent carbapenemase is the class B, New Delhi metallobetalactamase (NDM), which was first reported in 2008 in India, then disseminated worldwide in transferable elements, being *K. pneumoniae* its usual host at present. The dissemination of NDM producers in hospital settings occurred in Argentina during/after the SARS-Covid pandemic, changing the epidemiology of the circulating carbapenemases in our area. To a lesser extent, we can mention class D carbapenemases, OXA-48 and its variants, which are highly prevalent in certain areas. It is worth mentioning that clinical isolates carrying CRE do not only show resistance to most β-lactamic agents, but also to the majority of non β-lactamic ones such as aminoglycosides, fluoroquinolones, sulfonamides, tetracyclines, being colistin, fosfomicyn and tigecycline and their combinations, sometimes the last resort alternatives.[5] It is known that many of these isolates are extensively-drug resistant or even pandrug-resistant, as the resistance rates to the previously mentioned antimicrobial agents in the last years are nearly 50% for tigecyline and fosfomycin, 90% for amikacin and around 40% for colistin in carbapenemase-producing *K. pneumoniae* (data from isolates from Hospital de Clinicas Jose de San Martin, Buenos Aires)

It is clear that such a concerning scenario must be tackled from both the microbiological and the medical point of view; on the one hand, it is essential that the mechanisms underlying the resistant phenotype are detected rapidly and accurately to install the most appropriate combination therapy, and on the other hand, the knowledge of the epidemiology in the area and in the particular hospital is vital to establish the most suitable empiric treatment.

In the last years, new β- lactam/ β-lactamase inhibitor combinations were developed and introduced to the hospital setting. However, they possess several limitations related to their ability to inhibit certain enzymes, PK/PD features and site of infection, among others. Ceftazidime-avibactam (CZA), meropenem-vaborbactam (MVB) and imipenem-relebactam (IRE) have been approved to be used in complicated urinary tract and intraabdominal infections and hospital-acquired pneumonia. The three combinations men-

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tioned are active against KPC enzymes whereas they lack activity against MBLs, being this last feature a strong disadvantage due to the high circulation of the NDM enzyme. With regard to class D carbapenemases, only CZA is able to hydrolyze it. Another antimicrobial agent introduced in the last years, yet not available in Argentina, is cefiderocol, a combination of a siderophore and a cephalosporin core which shows stability against hydrolysis by β- lactamases like CTX-M, KPC, NDM, OXA-48-like, among others.[3]

As it was previously mentioned, the treatment alternatives for MBL-producing Enterobacterales are limited, as CZA, MVB and IRE are inactive against MBLs. Aztreonam (AZT) is labile to serine carbapenemases, AmpC and extended-spectrum β-lactamase enzymes (ESBL), and it is stable to MBL carbapenemases, but most MBL-producing Enterobacterales isolates also express a cephalosporinase or other carbapenemase (KPC or OXA-48-like enzymes) that confer resistance to AZT. The fact that isolates carrying NDM and ESBL are disseminated worldwide and circulate at a high rate in our area, has created the need to develop new strategies such as the synergistic activity between CZA and AZT, which has proved to be successful in many reports and, to a lesser extent, the combination of clavulanic acid and AZT, which showed weaker inhibition compared to avibactam but could represent a more economical alternative for certain clinical uses.[2]

In summary, it is undeniable that the rise in antimicrobial resistance represents a global concern together with the lack of new antimicrobial agents with activity against all the disseminated mechanisms of resistance in Enterobacterales. At this point, it is important to note that developing countries usually do not have the same access to new drugs due to economic reasons. Therefore, combination therapy has become the standard treatment method for nosocomial infections in most medical centers. The fact that the epidemiology of the circulating CRE in each institution may be different, and that antimicrobial resistance is a dynamic process, urges an accurate and joint effort between the microbiology laboratory and the medical services to prevent, detect, report and treat these pathogens that usually cause infections with high mortality rates. It is worth highlighting that infection control policies should also be implemented in all centers to detect carriers and prevent the current and future dissemination of microorganisms.

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