BJHBS

The challenge of carbapenem resistance

Silvia T. Castro,[1] José Augusto A. Pereira,[2] Eduardo A. R. de Castro[1]

The global resistance of microorganisms to antimicrobials is one of the most important public health challenges in recent decades. This problem has gained even more relevance in the case of Gram-negative microorganisms, resulting in a shortage of medicines for the treatment of infections caused by these multi-resistant bacterial agents.

Charting the evolution of this resistance among microorganisms in the hospital environment is essential for: the projection of resistance in the coming decades; the rational use of antimicrobials; and the adoption of measures to minimize the impact of the resistance in this scenario.

The most modern antimicrobial agents, which act on multi-resistant bacteria, are expensive, which limits their availability and makes their use even more difficult, especially in the public health networks of developing countries. Moreover, new drugs for treatment of multidrug-resistant infections are often unavailable due to their high cost.

In recent years, the Pedro Ernesto University Hospital (HUPE) achieved recognition in the health care sector of the State of Rio de Janeiro because of its quaternary care and by offering a range of specialties that serve patients who require lengthy hospital stays and often need invasive devices, which favor colonization/infection by hospital microorganism that are generally resistant to three or more classes of antimicrobials. Therefore, it is necessary to use these anti-infectious agents, which act on multi-resistant bacteria, to treat infections developed during hospitalization. Furthermore, the hospital also treats patients transferred from other institutions, who may bring multi-resistant microorganisms with them, which makes antimicrobial therapy more complex and challenging.

1. Serviço de Controle de Infecção Hospitalar, Hospital Universitário Pedro Ernesto, Universidade do Estado do Rio de Janeiro (UERJ). Rio de Janeiro, RJ, Brazil.

2. Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro (UERJ). Rio de Janeiro, RJ, Brazil.

*Correspondence address:
E-mail: stheescastro@gmail.com
ORCID: https://orcid.org/0000-0003-2985-749X

BJHBS, Rio de Janeiro, 2023;22(2):130-132
DOI: 10.12957/bjhbs.2023.80042
Received on 24/10/2023.

Resistance to antimicrobials in Gram-negative microorganisms that colonize or infect patients occurs mainly through the production of enzymes encoded by genes that can be located on plasmids and can be transferred to other microorganisms.

Extended-spectrum beta-lactamases (ESBL) were found in the 1980s to cause resistance in third and fourth generation cephalosporins.[1] This fact led to a more frequent use of carbapenems, which are stable to these enzymes. At the end of the 1990s,[2] resistance to carbapenems was detected due to the production of enzyme encodes by the bla_{KPC} gene. Other genes, such as bla_{IMP}, bla_{VIH}, and bla_{NDM} were detected at a later date, between 2001 and 2005.

The article "Prevalence of carbapenem-resistant *Enterobacteriaceae* in and out-of-hospital environments", by Olivella and colleagues,[3] in which 30 patients hospitalized at HUPE-

UERJ were evaluated, identified 13 (43.3%) carbapenem-resistant strains. One third patients from the community were analyzed, in 13 (29%) of which, carbapenem-resistant strains were identified. According to Nordmann,[4] "it is possible that, and of great concern for carbapenem resistance, a process similar to that for ESBL-producing strains decades ago will occur, causing endemic infections in the community".

Given this scenario, we sought to evaluate the occurrence of these resistances in Gram-negative microorganisms collected from HUPE patients during two periods: from 2005 to 2006 and 2022.[5]

During the first period, the presence of beta-lactam resistance genes was investigated in 44 microorganisms isolated from various clinical materials, and Polymerase Chain Reaction (PCR) tests and phenotypic tests were conducted for sensitivity to antimicrobials, including carbapenems. PCR is capable of detecting *bla*$_{SHV}$, *bla*$_{TEM}$, and *bla*$_{CTXM}$ genes. The phenotypic tests carried out did not detect resistance to carbapenems in these strains. During this period, 28 strains of *Klebsiella pneumoniae* were identified and, in these microorganisms, *bla*$_{CTXM}$ were detected in 12 patients (42.8%). At the same time, 6 *Escherichia coli* strains were detected, in which 3 (50%) occurrences of *bla*$_{CTXM}$ were found. No resistance genes were detected in the 10 other microorganisms isolated during this period. In phenotypic tests, no carbapenem resistance was detected.

Approximately 16 years later, samples isolated from blood cultures of 90 patients, using a multiplex PCR (Biofire FilmArray BCID) capable of detecting the *bla*$_{CTXM}$, *bla*$_{IMP,}$ *bla*$_{VIM}$, *bla*$_{NDM}$, *bla*$_{KPC}$ and *bla*$_{OXA48}$ genes, identified 29 *K. pneumoniae* strains and 23 *E. coli* strains, in addition to 38 other Gram-negative microorganisms. The most frequent genes were *bla*$_{CTXM}$ (which was detected in 18 (48.65%) cases); *bla*$_{KPC}$, detected in 12 (32.43%) cases; *bla*$_{NDM}$ in 5 (13.51%); and *bla*$_{OXA48}$ in 2 (5.40%).

Therefore, high proportions of the *bla*$_{CTXM}$ genes were detected in both periods, although with greater frequency in 2022, despite the decrease in the prescription of third generation cephalosporins at HUPE-UERJ in recent years.

The presence of genes encoding resistance to carbapenems was observed in 2022, with a high frequency (51.34%) of Gram-negative strains resistant to antimicrobial beta-lactams, which is extremely worrying due to the potential for spread of this resistance.

The high frequency of *K. pneumoniae* in 2022 is worrying since this agent "is a notorious collector of multidrug resistance plasmids". The rapid global dissemination of KPC producing *K. pneumoniae* implies multiple forms of transmission.[6]

The fact that the *bla*$_{CTXM}$ genes did not decrease during the most recent period and that they are often associated with carbapenem resistance genes shows a difference from the case of oxacillin-resistant *Staphylococcus aureus*, where the I, II, III genetic cassettes were replaced by IV, V, VI (CA-MARSA) ones.[7]

The transfer of antimicrobial resistance genes is a challenge, and the containment of resistance is more complicated in hospitals with old architecture, with wards that contain a large number of beds. These characteristics indirectly increase hospitalization costs and morbidity/mortality numbers and can cause a gradual increase in difficulties in controlling bacterial resistance for the health network in general.

The complexity of the phenomenon of microbial resistance to antimicrobials causes difficulties in addressing hospital infections, and the spread of resistance genes is likely to intensify in the coming years. A systemic approach, including investment in research and a reduction in the length of hospital stays, is necessary to reduce bacterial resistance, which is a serious global problem.

References

1. Livermore DM. Defining an extended-spectrum β-lactamase. Clin Microbiol Infect. 2008 Jan;14:3–10.
2. Weber DJ, Talbot TR. Mayhall's Hospital epidemiology and infection prevention. Philadelphia, PA: Wolters Kluwer; 2021; 20. Chapter 20.
3. Olivella JGB, Fonseca BO, Fonseca AS, et al. Prevalence of carbapenem-resistant Enterobacteriaceae in in- and out-of-hospital environments. BJHBS [Internet]. 2023 Jul. 17 [cited 2023 Oct. 10];22(1):15-22. Available from: https://bjhbs.hupe.uerj.br/bjhbs/article/view/55.
4. Nordmann P, Naas T, Poirel L. Global Spread of Carbapenemase-producing *Enterobacteriaceae*. Emerg Infect Dis. 2011 Oct;17(10):1791-8.
5. Santos FHBS, Gonçalves VD, Fonseca AS. Análise de genes de resistência a betalactâmicos em bactérias Gram negativas isoladas nos anos de 2005/2006 e 2022 no Hospital Universitário Pedro Ernesto. Apresentado no 61°-Congresso Científico do HUPE (pôster)
6. Tzouvelekis LS, Markogiannakis A, Psichogiou M, et al. Carbapenemases in *Klebsiella pneumoniae* and Other *Enterobacteriaceae*: An Evolving Crisis of Global Dimensions. Clin Microbiol Rev. 2012 Oct 1;25(4):682–707.
7. Correal JCD, Marques EA, Guilherme WL, et al. Infecções por Staphylococcus aureus: mudança do perfil epidemiológico no Hospital Universitário Pedro Ernesto. Rev HUPE. 2013;12(3):31-46.