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ANNALS OF MEDICINE & SURGERY

OPEN

Carbapenem-resistance worldwide: a call for action – correspondence

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Dear Editor,

Antibiotic resistance is one of the major global health concerns that poses a threat on both individual and societal levels. As a result of the emerging novel bacterial pathogen and resistance to several antibiotic classes, many antibiotics have been futile in coping with these infections. In the United States, it is estimated that 23 000 people with antibiotic-resistant infections die due to the limited treatment options and severe symptoms caused by drug-resistant organisms[1].

It is interesting to note that carbapenems, a class of antibiotics including doripenem, ertapenem, meropenem, and imipenem, have a significant impact in treating multidrug resistance and hospital-acquired extended-spectrum β-lactamase infections. However, the usage of carbapenem antibiotics around the world is risky due to the evolution of resistance to them[2].

Enzyme synthesis, efflux pumps, and porin mutations are the three main methods by which *Enterobacteriaceae* acquire carbapenem resistance. The primary mode of resistance among them is enzyme synthesis[3]. The enzymes responsible for hydrolyzing carbapenems in resistant bacteria are called carbapenemases, which are β-lactamases that can hydrolyze carbapenems, penicillin, cephalosporins, and monobactam. Four primary classes of carbapenemases have been classified based on amino acid homology (classes A, B, C, and D)[4]. β-lactamases which are found in molecular classes A, C, and D, contain serine at their active sites, whereas molecular class B β-lactamases are metalloenzymes with an active site containing zinc[4]. Metallo-β-lactamases (MBL), Klebsiella pneumonia carbapenemase (KPC), and oxacillinase (OXA-48)-like are the three primary categories of enzymes that cause the majority of carbapenem resistance[3]. More details are shown in Figure 1.

Nevertheless, a significant health issue is an alarming rise in resistance to these final resource agents. The primary risk factors for the emergence of resistance are the abuse of antibiotics, genetic mobile elements, worldwide travel, and poor infection control techniques. Saudi Arabia, like other Gulf nations, is under pressure from the emergence of multiple resistant pathogens like carbapenem-resistant *Enterobacteriaceae* (CRE). Traveling both inside and outside of the Gulf region poses a significant risk for the spread of resistant *Enterobacteriaceae* strains[5]. *Enterobacteriaceae* multiple resistant variants, which typically produce extended-spectrum β-lactamases and carbapenemases like KPC and New Delhi MBL-1 (NDM-1), are resistant to cephalosporins and have recently spread across the globe. However, there are only a few medications, including polymyxins, tigecycline, fosfomycin, and aminoglycosides, either alone or in combination with other antibiotics, that can be used to treat CRE infections. Compared to monotherapy, combination therapy had a better clinical outcome[5].

In the United States, Colombia, Argentina, Greece, and Italy, KPC-producing *Enterobacteriaceae* are widespread. However, in Pakistan, India, and Sri Lanka, the MBL NDM-1 is the major carbapenemase-producing resistance, and OXA-48-like enzyme producers are widespread in North Africa, the Middle East, Turkey, and Malta[3]. Figure 2 demonstrates the demographical distribution of carbapenem-resistance ambler classes endemicity. Because all three groups of enzymes are plasmid-mediated, the horizontal transmission will likely be simpler, and that carbapenem resistance will spread more quickly throughout the world[3].

Due to the few available alternatives for treatment and inadequate early therapy, CRE infections are associated with poor results. Additionally, evidence suggested that CRE infections have worse outcomes than those caused by sensitive *Enterobacterales*[6]. Moreover, a CRE infection is linked to lengthier hospital stays and higher medical expenses[6].

There is little information about the molecular epidemiology of CRE in the Middle East and Gulf countries in particular. Based on the available research, OXA-48 and NDM are the two most common carbapenemase strains in Saudi Arabia. The extensive geographic range of the Arab region and the ongoing influx of both native and foreign pilgrims are possible influences on the dissemination of CRE strains. There is still a lack of clarity regarding the precise molecular epidemiology and consequences of CRE[6].

Self-medication is one of the factors that is acknowledged on a global scale as being the most prevalent and obvious contributor to bacteria that are resistant to antibiotics. Self-medication is the phrase used to describe taking medications on one's own will or at the suggestion of someone who is not a licensed medical expert. Advertisements on television, radio, and print media, as well as recommendations from family and

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Annals of Medicine & Surgery (2023) 85:564–566

Received 11 January 2023; Accepted 26 January 2023

Published online 9 March 2023

http://dx.doi.org/10.1097/MS9.0000000000000262

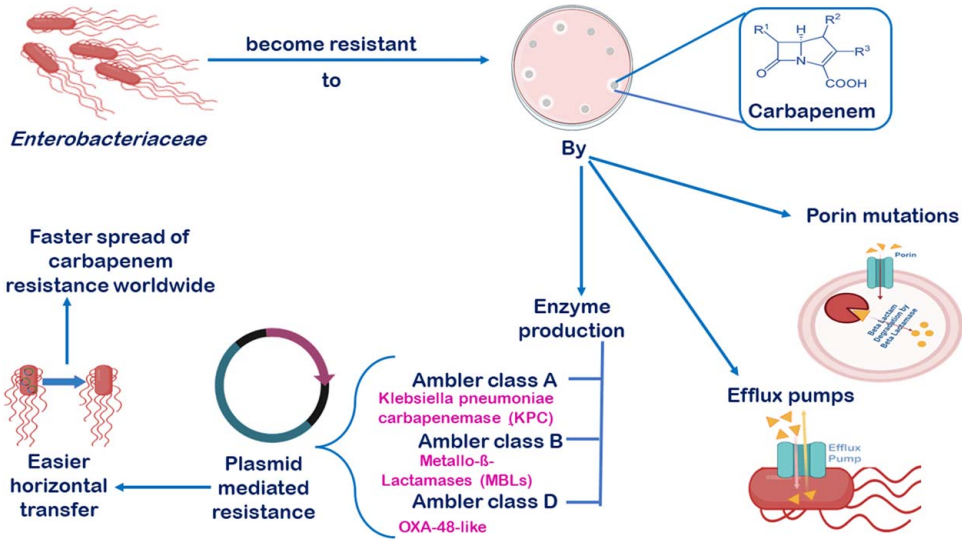

Figure 1. The figure shows the classification of carbapenem resistance.

friends, are the most prevalent and important factors that lead people to begin using medications without seeking professional assistance[1].

To fight drug-resistant infections and lower the mortality rate related to drug resistance, it is urgently necessary to identify novel antibiotics. This need can be met by promoting global collaborative research projects and raising public awareness of self-medication and the negative effects of antibiotic misuse[1]. The scientific and medical communities must work together to slow the development of resistance. Also, new therapeutic guidelines for the treatment of CRE infections are urgently needed. This includes the creation of novel medications as well as the repurposing of currently existing antibiotics like fosfomycin, aminoglycosides, and colistin[3].

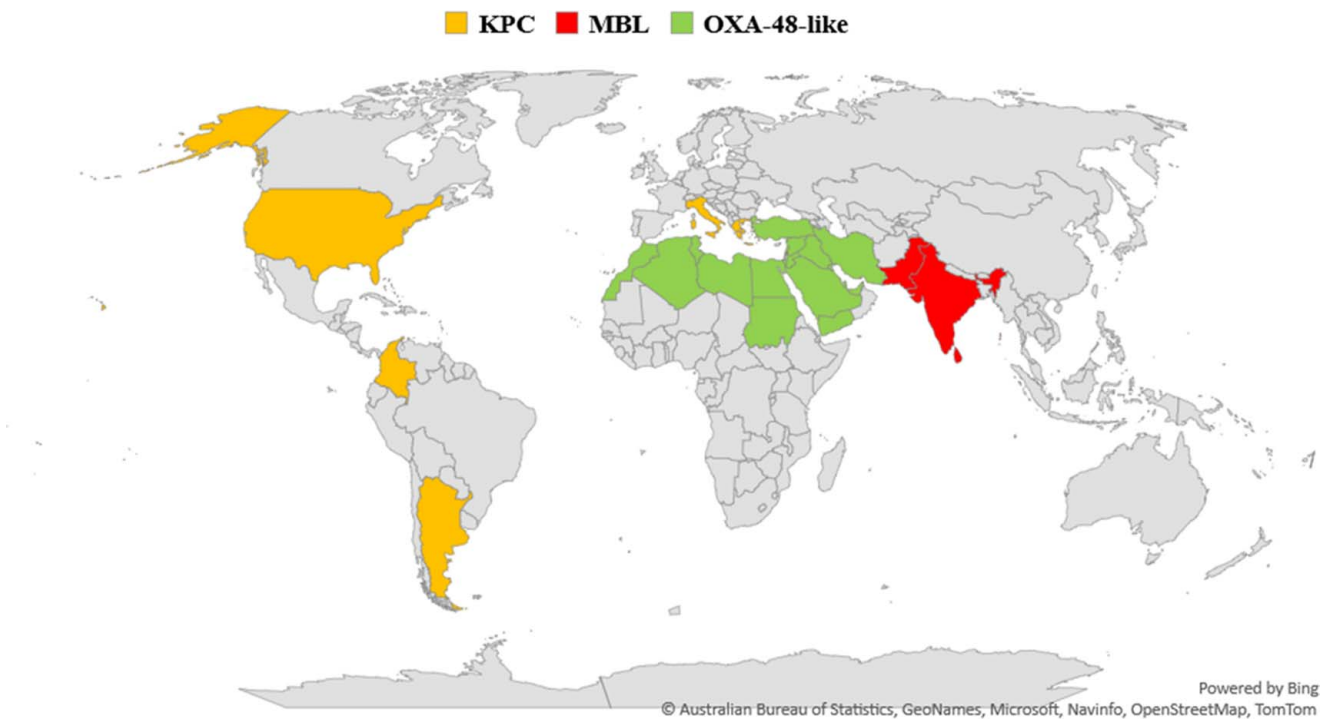

Figure 2. Demonstrates the demographical distribution of carbapenem resistance ambler classes endemicity. KPC, Klebsiella pneumonia carbapenemase; MBL, metallo-β-lactamases; OXA-48, oxacillinase-48.

Ethical approval

Not applicable.

Patient consent

Not applicable.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution

A.B.M.: the conception and design of the study; A.B.M., N.H., O. B.M.: made the first draft; H.H., A.K., and A.B.M.: updated the manuscript; K.A. and A.K.: reviewed the final draft and edited the final manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Conflicts of interest disclosure

The authors declare no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: NA.
2. Unique identifying number or registration ID: NA.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): NA.

Guarantor

All authors.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Acknowledgments

Not applicable.

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