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Review Article

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Prevalence and antibiotics susceptibility patterns of carbapenem resistant *Enterobacteriaceae*

Abstract

Enterobacteriaceae is a family of Gram negative rods. However it natural habitat in the intestinal tract of humans and animals, but it has been implicated in many human diseases. The emergence of antimicrobial resistance among *Enterobacteriaceae* isolates has been increasingly reported worldwide and has become a major threat to the provision of healthcare. Carbapenems is beta-lactam antibiotics which is considered as a last line of therapy for multidrug resistant. The occurrence of carbapenem resistance among *Enterobacteriaceae* is a major health challenge which reduce the antibiotics choices that use to treat the infections which cause by these bacteria. This review was focused to increase our understanding about carbapenem resistance; and to display the size and extent of this problem base on up to day published works. The prevalence of carbapenem resistance *Enterobacteriaceae* (CRE) is slightly different among different countries, and their resistance rate for commonly uses antibiotics has been significantly detected. The use of combined antibiotics seem to be is only up to day known therapeutic choice. The major worrisome, treatment of the infections causes by these multidrugs resistant organisms is extremely difficult which may results in high mortality rates and healthcare costs. We need to focus on continues searching for other highly effective and low cost alternatives therapies.

Keywords: antimicrobials resistant, carbapenemase producing Enterobacteriaceae, carbapenem resistant Enterobacteriaceae, clinical isolates, prevalence

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Introduction

Enterobacteriaceae is a family of Gram negative rods, facultative anaerobes, ferment a wide range of carbohydrates, possess a complex antigenic structure, and produce a variety of toxins and other virulence factors.[1,2] Natural habitat in the intestinal tract of humans and animals.[2] It is more than 40 genera and 150 species. Only few genera were consider as true pathogens (*Escherichia, Salmonella, Shigella,* and *Yerssina*), and few are opportunistic pathogens (*Klebsiella, Citrobacter, Enterobacter, Proteus, Provodencia, Morganella*, *Serritia,* and Edwardsella).[2,3] Different members of *Enterobacteriaceae* has been known as a causatives of different intra-intestinal (as diarrhea) and extra-intestinal diseases includes wound infections, pneumonia, septicemia, bacteremia, and meningitis.[2]

The emergence of antimicrobial resistance among *Enterobacteriaceae* has been increasingly reported worldwide and has become a major threat to the provision of healthcare.[1] The resistance of carbapenems are increased dramatically worldwide and recently among members of *Enterobacteriaceae* family.[4]

Carbapenems is beta-lactam antibiotics (includes imepenem, meropenem , ertapenem and doripenem) which is considered as a last line of therapy for multidrug resistant (MDR).[5,6] Carbapenem resistance has been detected and considered as a one of major health problem worldwide and limit the choice of selected antibiotics therapies to treat bacterial infections.[7] Carbapenem resistance may result either from production of carbapenemase that breakdown carbapenem or production of beta-lactamase (ESBLs or Ampc) together with porin loss. Carbapenemase producing *enterobacteriaceae* (CPE) produce carbapenemase which is a main mechanism of carbapenem resistance.[8] Carbapenemase was classified molecularly to three classes (A, B, and D).[4,8] *K. pneumoniae* carbapenemase (KPC) which belong to molecular class A , OXA48 (class D), and New Delhi metallo beta-latamase (class B) are the most common carbapenemases produce by *Enterobacteriaceae* family.[4,8] These enzymes (K. pneumoniae carbapenemase, OXA48, and New Delhi metallo beta-latamase) confer resistance to virtually all beta-lactam agents, including penicillins, cephalosporins, monobactams, and carbapenems.[4] Detection of carbapenem resistance can be perform phenotypically or genotypically using molecular techniques.[9,10] This review was focused to increase our understanding about carbapenem resistance; and to display the size and extent of this problem base on up to day published works.

Prevalence of CRE

Understanding the prevalence of CRE is necessary to provide information on the temporal, and geographic occurrence of carbapenem resistance; and the size of this problem in order to facilitate its prevention and control. Base on previously published researches, the prevalence's of CRE among clinical samples were slightly different among different regions in the world.

Africa

The emergence of CRE has been observed and reported in many studies includes Oduyebo OO et al.[11] (Nigeria), Legese MH et al.[12]

(Ethiopia), Okoche D et al.[13] (Uganda), Amer WH et al.[14] (Egypt), Camara A et al.[15] (Senegal), and Wartiti MA et al.[16] (Morocco) which reported the prevalence of CRE were 15.2%, 12.12%, 28.6%, 62.7%, 5.1%, and 2.8% respectively.[11–16]

Asia

In Asia, the prevalence of CRE among clinical samples was determined in many studies includes Rao A et al.[17] (India), Amjad A et al.[18] (Pakistan), Jamal WY et al.[19] (Kuwait), Li Y et al.[20] (China), Kandeel A et al.[21] (Saudi Arabia), Nair PK et al.[22] (India), Zaidah A et al.[23] (Malaysia), Jan R et al.[24] (South India) and Khare V et al.[25] (India) which reported the prevalence of CRE were 13.95%, 69%, 8%, 18.1%, 1.77% ,12.26%, 5.76%, 8% and 37.9% respectively.[17–25]

Europe, Australia, and America (North and South)

The occurrence of CRE has been investigated in many studies includes Huang T et al.[26] (Belgium), Baran I et al.[27] (Turkey), Mathersa J et al.[28] (USA), Pfaller MA et al.[29] (Latin America), Partina I et al.[30] (Russia), Pfaller MA et al.[31] (Australia and New Zealand) and Logan LK et al.[32] (USA) which reported the frequency of CRE were 3.46%, 2.8%, 5.7%, 6.6%, 11.6%, 0.1% and 0.08% respectively.[26–32] Also Sader HS et al.[33] study were found the occurrence of CRE in Poland, Italy, Greece and Romania were 17.3%, 7.5%, 7.4%, and 5.0% respectively.[33]

Antibiotics susceptibility patterns of CRE

All members of carbapenem resistance *Enterobacteriaceae* showed high resistant rate for all or most commonly uses penicillins, cephalosporins, monobactams, and quinolones as it reported by many studies.[34–40] The antibiotics which has a good activity on most CRE isolates were fosfomycin, tigecycline, polymyxin, amikacin, gentamycin and colistin.[33,41–47]

Many studies suggests the use of combined therapies to treat CRE. Falagas ME et al.[48] study suggests the use of combined antibiotics may offer a comparative advantage over monotherapy.[48] Nabarro LB et al.[49] Study conclude there is increasing evidence to support the use of combination therapy to treat infections that cause by CRE.[49] Fredborg M et al.[50] study conclude meropenem triple combinations with a polymyxin and rifampin exhibited highest synergistic activity against carbapenem producing *Enterobacteriaceae*.[50]

Discussion

Carbapenem is a one of antibiotics that offer broad spectrum activity and use as a last line therapy for multidrug resistant bacteria. The treatment of infections causes by drugs resistance bacteria is sometime impossible and may lead to unexpected or bad complications. Antimicrobial resistance increases the cost of health care, and possibility of complications. Without effective antimicrobials for prevention and treatment of CRE infections, medical procedures become very high risk. The major worrisome, treatment of the infections causes by these multidrug organisms is extremely difficult which may results in high mortality rates and healthcare costs.

In this review, we found carbapenem resistance has been emerged worldwide and is beginning to spread. This emergence might result from the absence of public health surveillance programs in most countries that hided this problem, so the public health surveillance programs must be establish in all countries to facilitate the discovery of problems as early as possible. Also new alternatives therapies need to be developed to encounter bacteria with this kind of resistance; and the hospitals need excellent infection treatment and control to prevent the morbidity and spread of CRE.

Also we found the prevalence of CRE in African countries are slightly low when compare with Asian countries; and in Australia and American countries is slightly low when compare with African countries. While the prevalence of CRE in European countries seem to be same in African. Also there is a marked reduction in the susceptibility of carbapenem resistance isolates to anther antibiotics. This differences in the prevalence of CRE and their susceptibility to antibiotics among the isolates of different world countries may arise from the different in geographical location and poor infection control in health care settings or the misuse and availability of non-prescribed therapies that describe by WHO as a accelerators of drugs resistant.

As we found the use of combined therapies up to day is only known appropriate and highly effective choice for treatment of CRE infections. But the use of combined therapies lead knock down the beneficial flora in the body and may associate with many serious diseases or unexpected complications. So the looking for anther alternatives therapies may be a one of the solutions for this problem.

Conclusion

The prevalence of CRE has been emerged worldwide. As we displayed there is a significant rate of carbapenem resistance among *Enterobacteriaceae*. Formulating an antimicrobial policy with its strict implementation and regular surveillance must be establish. Further studies need to focus on continues searching for a highly effective, low cost, and minimum side effect alternatives therapies.

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Competing interests

We declare that we have no competing interests.

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