



Emerging Resistance to Carbapenems: A Potential Threat to The Management of Infectious Disease

KEYWORDS

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ABSTRACT Carbapenems are well known for their broadest spectrum of clinical activity and utmost potency among the different β -lactam antibiotics. Unfortunately, the recent emergence of multidrug-resistant pathogens seriously threatens this class of lifesaving drugs. Recently, alarm has been raised over the spread of drug resistance to carbapenem antibiotics among these coliforms, commonly due to production of various β -lactamase. Carbapenem resistant strains are increasingly being detected in every corner of the world. The spread carbapenem resistant strains seem to be a potential nightmare situation. This is a new threat for the humanity. Carbapenem resistance genes are moving across the globe. The carbapenem resistant bacteria appear suddenly and spread rapidly before the public health care systems and laboratories can detect it. Currently we have few options left among new antibiotics to combat against the carbapenem resistant bacterial strains, none of them are safe.

Antimicrobial resistance (AMR) is unresponsiveness of a microorganism to an antimicrobial agent to which it was previously sensitive. Resistant organisms (they include bacteria, fungi, viruses and some parasites) are able to withstand attack by antimicrobial medicines, such as antibiotics, antifungals, antivirals, and antimalarials, so that standard treatments become ineffective and infection persist increasing risk of spread to others. The development of resistance is a natural and ancient phenomenon that occurs when microorganisms are exposed to antimicrobial drugs, and resistant traits can be exchanged between certain types of bacteria (WHO, 2013). The development of antibiotic resistance started right from beginning of use of antibiotics. Alexander Fleming, who discovered the first antibiotic, warned about the possibility of antibiotic resistance. The phenomenon of antibiotic resistance was detected just after the discovery of antibiotic (McKenna, 2013). The irrational use of antimicrobial medicines accelerates this natural phenomenon. Poor infection control practices encourage the spread of resistant strains (WHO, 2013).

Rising level of antimicrobial resistance is major crisis of this era, and emerging resistance to carbapenems is not less than a nightmare. Carbapenems is an important element of our antibiotic resources. Among the various β -lactams currently available, carbapenems has a unique status as it has broader spectrum and are relatively resistant to hydrolysis by most β -lactamases. In addition carbapenems diffuse easily in bacteria and hence it is more efficient. Carbapenems are resistant to beta-lactamase as it circumvent β -lactamase enzyme by binding it with high affinity and acylating the enzyme, rendering it inactive (Drawz & Bonomo, 2010). Among different β -lactams, carbapenems possess the broadest spectrum of activity and great potency. Carbapenems are active against both some gram-positive, good number of Gram-negative bacteria, and anaerobes. But they are not active against intracellular bacteria, such as the Chlamydiae. Carbapenems are unique in its class of β -lactams capable of inhibiting L,d-transpeptidases (Mainardi et al., 2008). As a result, they are considered as "last-line agents" or "antibiotics of last resort" to deal with serious infections and multi drug resistant strains (Angela et al., 2011).

Thienamycin is the parent compound of all carbapenem. A carbapenem has common structure having the 4:5 fused ring lactam of penicillins with a double bond between C-2 and C-3 but with the substitution of carbon for sulfur at C-1. The hydroxyethyl side chain of thienamycin is a radical departure from the structure of conventional penicillins and cephalo-

sporins, all of which have an acylamino substituent on the β -lactam ring. This hydroxyethyl side chain is a key attribute of carbapenems and is important for activity. Although thienamycin is a natural product and its purification process is not efficient. With the course of time, the semisynthetic product like Imipenem, Meropenem, Ertapenem, Doripenem,, Panipenem, Biapenem gained more importance (Krisztina et al., 2011).

Mechanisms of resistance to carbapenems occurs through production of β -lactamases, efflux pumps, and mutations that alter the expression or function of porins and PBPs. Combinations of these mechanisms can result in high levels of resistance to carbapenems in certain bacterial species, especially in *Klebsilla pneumoniae*, *P. aeruginosa*, and *A. baumannii* (Mena et al., 2006; Krisztina et al., 2011). Carbapenem resistance in Gram-positive cocci occurs as a result of substitutions in amino acid sequences of PBPs or production of a new carbapenem-resistant PBP (Koga, et al 2009). While among Gram-negative bacteria carbapenem resistance is due to expression of β -lactamases and efflux pumps, as well as porin loss and alterations in PBP (Pearson, Van Delden & Iglewski, 1999).

Carbapenemases belongs to specific β -lactamases family. Expression of this enzyme seems to be the most common cause of carbapenem resistance. Some important classes of carbapenemases are class A carbapenemases (e.g., KPC and GES enzymes), class B metallo- β -lactamases (e.g., VIM, IMP, and NDM β -lactamases), and class D carbapenemases have recently reported. Although, class C β -lactamases, such as CMY-10 and PDC β -lactamases are not much affective, but it can lead to carbapenem resistance, particularly when it is expressed in combination with other resistance mechanisms (Krisztina., et al 2011; Elizabeth et al., 2012). It is frightening that bacterial strain producing ESBL and carbapenemase are also being found in the food animals, various food animal species and food products (Lee, 2013). A carbapenem-resistant isolate of *Escherichia coli*, which lacked OmpF and OmpC porins, carried a marR mutation and expressed a functional yedS, a normally nontranslated gene. MarR and YedS render these strains resistant to carbapenems. The production of YedS was regulated by the small RNA MicF in a MarA-dependent way (Stuart et al., 2013).

The bacterial strain producing the New Delhi metallo-beta-lactamase (NDM-1) was first detected in India. It had frightened the developed nation also. These isolates carrying NMD-1 commonly belongs *Escherichia coli*, *Klebsiella pneu-*

moniae, and *Enterobacter cloacae*. This strain seems to be prevalent in India (Center for Disease Control and Prevention, 2010).

Patients infected with carbapenem-resistant strains need more intensive care and aggressive multiple antibiotic therapy. It is found that the crude and attributable mortality rates associated with carbapenem-resistant strains are high as compared to non carbapenem-resistant strains (Borer et al., 2009; Ben-David et al., 2011). These carbapenem resistant strains are threat to critical care management of infectious disease (Karen, 2010). Carbapenemase producing bugs respond only to colistin, tigecycline, and fosfomycin, none of which is an 'ideal' antibiotic. These antibiotics are not effective for every patient and have serious adverse effects. It seems very unlikely in terms of availability of new antibiotics (Livermore, 2012; McKenna, 2013).

The carbapenem resistance was detected almost 15 years ago, but it was not public-health problem at that time. Now it has become public health concern as the carbapenem resistant bugs are not confined to the walls of hospital. The Indian superbug NMD-1 is detected even in sewage and municipal water supply system. It seems that they were undetected in radar and exploded suddenly before they were detected. The important reason of sudden spread of carbapenem resistance was that, they were difficult to detect. The rapid dissemination of carbapenem resistant strains occurred by transmission from person to person rather than arising independently in each location. Beside this, the carriers of this deadly bugs is also detected which seems to play important role in transmission (McKenna, 2013).

It is not too late to implement the intervention to prevent the spread carbapenem resistant bacteria. Multi-dimensional approaches are required to combat these carbapenem resistant bacteria. There is need to strictly implement hygienic practices like hand-washing, use of gloves, barrier nursing, isolation of patient having infection with carbapenem resistant strains, stop irrational use of carbapenem, prompt and aggressive treatment of infection caused by carbapenem resistant strains, promotion of selection of antibiotic based on culture and sensitivity analysis. There is urgent need for formulation of antibiotic guidelines and standard infection control practices.

These versatile and potent antimicrobial agents had served the humanity for more than three decades. Unfortunately, pathogens are developing resistance to this class of antimicrobial agents. Emergence of carbapenem resistance has seriously threatens health care sector as this lifesaving drugs will no more be effective as it was previously. We are on the edge to lose this novel class of antimicrobial agent. This is the time to awake and make conscious efforts in order to keep these potent antibiotics effective. If the current trend is allowed to continue as such, we will soon find carbapenems only in literature not in clinical practice.

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