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CARBAPENEM RESISTANCE

General Medicine

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ABSTRACT

In present time, Carbapenem resistance is an emerging problem throughout the World and is an important threat to public health as well as treatment challenge to clinicians.

KEYWORDS

Carbapenem Cre Beta Lactamases Polymyxin

INTRODUCTION

Carbapenems play a critically important role in our antibiotic armamentarium. Of the many hundreds of different β-lactams, carbapenems possess the broadest spectrum of activity and greatest potency against majority of Gram-negative and Gram-positive bacteria. As a result, they are often used as "last-line agents" or "antibiotics of last resort" when patients with infections become gravely ill or are suspected of harboring resistant bacteria (1, 2, 3). Unfortunately, the recent emergence of multidrug-resistant (MDR) pathogens seriously threatens this class of lifesaving drugs (4).

Similar to penicillins and cephalosporins, carbapenems are members of the beta lactam class of antibiotics, which kill bacteria by binding to penicillin-binding proteins (PBP). Carbapenem-resistant gram-negative bacteria, namely, carbapenem-resistant Enterobacteriaceae (CRE), *Acinetobacter baumannii* (CRAB) and *Pseudomonas aeruginosa* (CRPsA), pose a significant threat to public health. These bacteria uses certain mechanism like production of β-lactamases, efflux pumps, and mutations that alter the expression and/or function of porins and PBPs which are responsible for the resistance to carbapenems (5). Recently, there has been a plethora of research information on carbapenem resistance; however, there are few comprehensive review papers. This article therefore seeks to provide an in-depth review of carbapenem resistance providing up-to-date information on the subject.

RISK FACTORS FOR CARBAPENEM RESISTANCE

There are a number of factors that predispose persons to infections by CRE and other multi-drug resistant (MDR) Gram-negatives including ESBL producers. Exposure to these resistant organisms can cause serious infections in patients with the following reported risk factors: immune-suppression, advanced age, admission to intensive care unit (ICU), mechanical ventilation, previous exposure to antimicrobials, organ or stem-cell transplantation and prolonged hospital stay.

The main risk factors for Carbapenem-resistant Enterobacteriaceae (CRE) acquisition or infection were exposure to healthcare, including admission to the ICU, medical devices, invasive procedures, and antibiotics (6).

Risk factors associated with carbapenem-resistant *K. pneumoniae* (CRKP) infection include recent organ or stem-cell transplantation, receipt of mechanical ventilation, and longer hospital stay (7). Patients with hematologic malignancies usually undergo more frequent exposure to healthcare, longer duration of antibiotic therapy, more invasive procedures and have pre-existing immunosuppression. All of these factors can increase the risk for infections (8, 9).

With respect to antimicrobial agents, the risk of CRE acquisition appears to be much higher in the developing world particularly in sub-Saharan Africa where there is a predominance of irrational use of such drugs (10, 11).

CARBAPENEM RESISTANCE MECHANISMS

There are two mechanisms with which bacterias develop resistance to carbapenems.

One is intrinsic resistance, in which a large numbers of bacteria, both commensals and pathogens, naturally tend to be resistant to certain classes of antimicrobial agents. This insensitivity is termed intrinsic resistance (12).

The other is acquired resistance. Bacteria have acquired multiple mechanisms of resistance including enzymatic inactivation, target site mutation and efflux pumps.

Gram-positive bacteria become resistant to carbapenems and other beta-lactams through mutation-derived changes of their PBPs, while Gram-negatives commonly recruit other mechanisms to overcome the effect of carbapenem antibiotics. One of which is tripartite efflux pump, the overexpression of efflux pumps that expel carbapenems, mostly meropenem, may lead to carbapenem resistance associated with multidrug resistance (MDR). The other mechanism is production of beta-lactamases that are able to inactivate carbapenems together with other beta-lactam antibiotics and therefore called carbapen em ases(13).

Genetic determinants of CR have been classified into: Ambler class A beta lactamases which include; KPC, GES/IBC, SME, NMC-A, IMI and SFC (14-17), Ambler class B beta lactamases which are termed as Metallo beta Lactamases consisting of NDM, VIM, IMP, SPM, GIM, SIM, KHM, AIM, DIM, SMB, TMB and FIM (15). IMP, VIM and NDM plasmid mediated Metallo beta lactamases are of worldwide occurrence possibly because the genes that code for them are located on mobile genetic elements and carbapenem hydrolyzing class D beta lactamases (CHDLs) encompass various group of oxacillinases (OXA) with hydrolytic activity of amino and carboxy penicillins (18)

TREATMENT OPTIONS:

By far, polymyxins are the antibiotic class for which most CR GNB present *in vitro* susceptibility, and polymyxin-only-susceptible (POS) isolates account for a significant proportion of CR GNB with XDR profile (17,19-24). The most frequently used adjuvant therapies for CR GNB infections are: tigecycline, fosfomycin, aminoglycosides and rifampicin.

Table 1 summarizes the currently available antimicrobial agents and their recommended doses for treatment of CRE infections.

Table 1:

Antimicrobial agents	Recommended dose for CRE infections[a]	Comments
Meropenem	2 g every 8 h by prolonged infusion for isolates with MICs of 2–8 mg/L	May not be effective for isolates with MIC > 8 mg/L
Ertapenem	Consider 2 g every 24 h	Used in double-carbapenem therapy
Colistin	Loading dose of 9 MU, followed by 9 MU/day in 2–3 divided doses	
Polymyxin B	Loading dose of 2–2.5 mg/kg, followed by 5 mg/kg/day in 2 divided doses	
Tigecycline	Loading dose of 100 mg, followed by 50 mg every 12 h	Consider loading dose of 200 mg, followed by 100 mg every 12 h for severe infections
Eravacycline	1 mg/kg every 12 h	Approved by FDA in August 2018 for the treatment of cIAI. Activity against carbapenem-resistant *Enterobacteriaceae* has been

		demonstrated *in vitro*. Clinical data in CRE infections are still lacking
Gentamicin Tobramycin	5–7 mg/kg/day	Used in combination therapy. Consider a higher dose of 10–15 mg/kg/day for severe infections without other options. Risk of toxicity may increase. TDM is recommended
Amikacin	15–20 mg/kg/day	Used in combination therapy. Consider a higher dose of 25–30 mg/kg/day for severe infections without other options. Risk of toxicity may increase. TDM is recommended
Plazomicin	15 mg/kg/day	Approved by FDA in June 2018 for the treatment of cUTI including pyelonephritis. Activity against ESBL- and carbapenemase-producing *Enterobacteriaceae* has been demonstrated *in vitro*. Clinical data in CRE infections are still lacking
Fosfomycin	4 g every 6 h to 8 g every 8 h	Used in combination therapy
Aztreonam	1–2 g every 8 h	MBL producers are susceptible if not ESBL or AmpC producers
Ceftazidime	1–2 g every 8 h	OXA-48 producers are susceptible if not ESBL or AmpC producers
Ceftazidime/avibactam	2.5 g (2 g/0.5 g) every 8 h	KPC and OXA-48 producers are frequently susceptible
Meropenem/vaborbactam	2 g (1 g/1 g) every 8 h	KPC producers are frequently susceptible

cAI, complicated intraabdominal infection; cUTI, complicated urinary tract infection; ESBL, extended-spectrum β-lactamase; KPC, Klebsiella pneumoniae carbapenemase; MBL, metallo-β-lactamase; MIC, minimum inhibitory concentration; OXA, oxacillinase; TDM, therapeutic drug monitoring.
Adapted from Rodríguez-Baño et al. (2018).
[a]*For patients with normal renal function.*

In the past few years, antibiotic combinations against CR GNB have been proposed as the best practice in the management of infections by these organisms.

COMBINATION WITH POLYMYXIN:

One meta-analysis compared colistin monotherapy with combination treatments in multiresistant *A. baumannii* infections. Although microbiological eradication was significantly higher in the combination group, this benefit was not reflected in mortality, length of stay in intensive care, or nephrotoxicity. The greatest limiting factor was the wide heterogeneity of the antibiotic combinations used (25). A meta-analysis that included other gram-negative bacteria concluded that polymyxin monotherapy was inferior to a combination of polymyxin with carbapenem and to combinations with tigecycline, aminoglycosides, or fosfomycin (26).

COMBINATION WITH TIGECYCLINE:

A meta-analysis on the efficacy of tigecycline revealed a benefit of combination treatment and a tendency towards superiority of high-dose treatment (200 mg at first, followed by 100 mg every 12 h) over the standard dosage (100 mg at first, followed by 50 mg every 12 h) (27).

DOUBLE CARBAPENEM THERAPY:

The findings of non-controlled case series suggest that combinations of two carbapenems (ertapenem plus prolonged infusion of meropenem or doripenem) can be successful in the treatment of CRKP infections, with clinical cure rates of 39 to 77.8% (28,29).

CONCLUSION:

In the recent past, carbapenems were potent against all multiple drug resistant (MDR) Gram negative bacteria and in combination with their negligible toxicity to the host, carbapenems became the preferred last resort antibiotics for the treatment of MDR Gram negative bacterial infections. But nowadays, there is emerging carbapenem resistance, which is a major threat to public health.

The main risk factors for Carbapenem-resistant infections were found to be: exposure to healthcare, including admission to the ICU, medical devices, invasive procedures, and prolonged use of antibiotics.

Carbapenem resistance is due to several mechanisms namely: through mutation-derived changes of their PBPs, tripartite efflux pump, production of beta-lactamases.

The most frequently used adjuvant therapies for CR GNB infections are carbapenems, tigecycline, fosfomycin, aminoglycosides, rifam p icin and several combinations like with polymyxin, tigecycline, double carbapenem

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