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Review Article

An overview of carbapenem, its resistance and therapeutic options for infections caused by carbapenem resistant bacteria

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ABSTRACT

Carbapenems are beta-lactam drugs that have broadest spectrum of activity. They are commonly used as the drugs of last resort to treat complicated bacterial infections. They bind to penicillin binding proteins (PBPs) and inhibit cell wall synthesis in bacteria. Important members that are in clinical use include doripenem, ertapenem, imipenem, and meropenem. Unlike other members, imipenem is hydrolyzed significantly by renal dehydropeptidase; therefore, it is administered together with an inhibitor of renal dehydropeptidase, cilastatin. Carbapenems are usually administered intravenously due to their low oral bioavailability. Most common side effects of these drugs include nausea, vomiting, diarrhea, skin rashes, and reactions at the infusion sites. Increasing resistance to these antibiotics is being reported throughout the world and is posing a threat to public health. Primary mechanisms of carbapenem resistance include expulsion of drug and inactivation of the drug by production of carbapenemases which may not only hydrolyze carbapenem, but also cephalosporin, penicillin, and aztreonam. Resistance especially among Gram negative bacteria is of much concern since there are only limited therapeutic options available for infections caused by carbapenem resistant Gram-negative bacterial pathogens. Commonly used drugs to treat such infections include polymyxins, fosfomycin and tigecycline.

Keywords: Carbapenems, Drugs of last resort, Resistance, Therapeutic options

INTRODUCTION

Carbapenems are the important drugs in our antibiotic armamentarium. Of the various beta-lactams, carbapenems exhibit the broadest spectrum of activity and greatest potency against Gram-positive and Gram-negative bacteria.¹ They are often regarded as “last-line agents” or “antibiotics of last resort” in treatment of serious infections.² However, emergence of carbapenem resistant pathogens such as carbapenem resistant *Enterobacteriaceae* (CRE), *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in infections such as hospital acquired infections has not only seriously threatened this class of lifesaving drugs but also have posed a significant threat to public health.^{1,3} These

resistant pathogens are difficult to treat and are associated with high mortality.³

The purpose of this article is to review the important pharmacological characteristics of carbapenem and its resistance as well as to find out the options available for treatment of infections caused by carbapenem resistant bacterial pathogens.

A literature search was done using Medline database, Google database and online journals. The search was limited to publications in the English language. The search terms ‘carbapenem’, ‘pharmacology of carbapenem’, ‘carbapenem resistance’ and ‘therapeutic/treatment options for infections caused by

carbapenem resistant pathogens' were used. Additional information was obtained from standard book and the websites of agencies such as Centers for Disease Control and Prevention (CDC), World Health Organization (WHO) and European centre for disease prevention and control.

STRUCTURE OF CARBAPENEM

Structurally, carbapenems are similar to the penicillins (penams), but the sulfur atom in position 1 of the structure of penicillin has been replaced with a carbon atom.¹ Thus, their bicyclic core consists of a beta-lactam ring fused to a pyrroline ring (Figure 1). Combination of these two rings confers exceptional stability against most beta-lactamases (enzymes that inactivate beta-lactams) including ampicillin and carbenicillin (Amp C) and the extended spectrum beta-lactamases (ESBLs).⁴

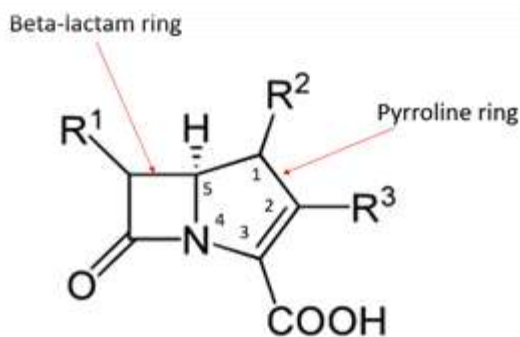


Figure 1: Structure of carbapenem.

MECHANISM OF ACTION

Carbapenems bind to penicillin binding proteins (PBPs) which are enzymes (i.e., transpeptidases, transglycosylases, and carboxypeptidases) that catalyze the formation of peptidoglycan in the cell wall of bacteria.¹ They permanently acylate the PBPs, inhibit the cell wall synthesis and kill the bacterial cells.¹

MEMBERS APPROVED FOR USE IN UNITED STATES

Of its various members, doripenem, ertapenem, imipenem, and meropenem are approved for use in the United States.⁵

SPECTRUM OF ACTIVITY AND RESPONSE TO DEHYDROPEPTIDASE⁵

Imipenem is the first member of carbapenem available for the treatment of complex bacterial infections. It has a wide spectrum with good activity against many Gram-negative rods, including *P. aeruginosa*, Gram positive organisms, and anaerobes. It is resistant to most beta-lactamases but not carbapenemases or metallo beta-

lactamases. Common bacteria resistant to this drug include *Enterococcus faecium*, methicillin-resistant strains of Staphylococci, *Clostridium difficile*, *Burkholderia cepacia*, and *Stenotrophomonas maltophilia*. This drug is inactivated by dehydropeptidases in renal tubules, resulting in low urinary concentrations. Consequently, it is administered together with an inhibitor of renal dehydropeptidase, cilastatin, for clinical use.

Doripenem and meropenem are similar to imipenem but are more effective Gram-negative aerobes and slightly less effective against Gram positive bacteria. These drugs are not significantly hydrolyzed by renal dehydropeptidase and do not require an inhibitor.

Ertapenem has lesser activity than the other carbapenems against *P. aeruginosa* and *Acinetobacter* species. It is not hydrolyzed by renal dehydropeptidase.

PHARMACOKINETICS

All clinically useful carbapenems have low oral bioavailability and are poorly absorbed through gastrointestinal tract.¹ Therefore, they must be administered intravenously but imipenem-cilastatin and ertapenem can also be delivered intramuscularly.⁶ They penetrate body tissues and fluids well, including the cerebrospinal fluid.⁵

All carbapenems similar to other beta-lactams are eliminated predominately by renal excretion and the dose must be adjusted in patients with renal insufficiency.⁵ Carbapenems exhibit unique pharmacological properties and are typically used to treat complicated bacterial infections.⁵

ADVERSE EFFECTS

Nausea, vomiting, diarrhea, skin rashes, and reactions at the infusion sites are the most common adverse effects of carbapenems which tend to be more common with imipenem.⁵ In patients with renal failure, excessive levels of imipenem may lead to seizures. Meropenem, doripenem, and ertapenem are much less likely to cause seizures than imipenem.⁵

Nephrotoxicity, neurotoxicity, and immunomodulation have also been reported with the use of carbapenems, and thus patient's underlying conditions and predisposing factors should be considered when administering any carbapenem.¹ In addition, the use of carbapenems has also been found to alter the intestinal microflora and select for carbapenem resistant isolates.¹

RESISTANCE

Literatures have shown that resistance to carbapenems is increasing throughout the world.⁷⁻⁹ The resistance is considered as one of major health problems worldwide

and limits the choice of selected antibiotic therapies to treat bacterial infections.

Mechanism of resistance

Bacteria exhibit two types of resistance to carbapenems: intrinsic and acquired.⁴ Bacteria such as *Stenotrophomonas maltophilia* which possesses endogenous metallo-beta-lactamase (MBL) L1 are intrinsically resistant.¹⁰ However, this type of resistance is not common among clinically important bacteria and for most of them carbapenem resistance is acquired by mutational events or gene acquisition via horizontal gene transfer.⁴ The primary mechanisms of carbapenem resistance mediated by gene acquisition include expulsion of drug and inactivation of the drug by production of carbapenemases. The important mechanisms are outlined below:

Mutation

Mutation of penicillin binding proteins alters the target and carbapenem is unable to bind to them whereas mutation in outer membrane porin proteins (through which drugs enter into bacterial cell) of gram-negative bacteria prevents carbapenems reaching their PBPs by diminishing the permeability of their outer membrane.⁴

Expulsion of drugs

Expulsion of carbapenems out of the periplasmic space commonly occurs through a tripartite efflux pump systems composed of a protein transporter of the cytoplasmic membrane, a periplasmic connective protein and an outer membrane porin.⁴ The overexpression of efflux pumps is commonly associated with multidrug resistance (MDR), since quinolones, penicillins, cephalosporins and aminoglycosides are common efflux pump substrates.⁴

Inactivation by enzymes

Carbapenemases produced by bacteria can hydrolyze carbapenems and render the drug ineffective. They are considered the most potent beta-lactamases.^{4,11} In general, they also hydrolyze other beta-lactam drugs such as cephalosporins, penicillin, and aztreonam. They belong to different Ambler classes (Table 1).¹¹

In terms of carbapenem hydrolysis and geographical spread, the most effective carbapenemases are KPC, VIM, IMP, NDM and OXA-48 types.⁴

Carbapenemases coding genes are commonly located on mobile genetic elements and have the potential to be widespread all over the world.¹¹ They were originally described in gram-positive bacteria such as *Bacillus cereus* and *Bacillus licheniformis*.¹¹ However, they are now reported commonly on Gram-negative bacteria such

as members of *Enterobacteriaceae*, *P. aeruginosa* and *Acinetobacter species*.¹¹

Distinct mechanisms of resistance have been observed in Gram-positive cocci and Gram-negative rods.¹ In Gram-positive cocci, carbapenem resistance is typically the result of alteration of PBP, whereas production of carbapenemases, expression efflux pumps, mutation in porin and alterations in PBP are associated with the resistance in Gram-negative rods with the first one being the primary mechanism.^{1,11}

Table 1: Types of carbapenemases.

Ambler carbapenemase group	Enzyme family
Group A	Not metalloenzyme carbapenemase (NmCA)
	Serratia marcescens enzyme (SME)
	Imipenem-hydrolyzing beta-lactamase (IMI)
	<i>Klebsiella pneumoniae</i> carbapenemase (KPC)
Group B	Guiana extended spectrum (GES)
	Imipenemase (IMP)
	Verona-integron-encoded metallo-beta-lactamase (VIM)
Group C (emerging)	New Delhi metallo-beta-lactamase (NDM)
	AmpC type (ACT)
	<i>Cephamecinase</i> (CMY)
	<i>Acinetobacter</i> -derived cephalosporinase (ADC)

RISK GROUPS FOR CARBAPENEM RESISTANT BACTERIAL INFECTIONS

As outlined by CDC, the people whose care requires devices like ventilators (breathing machines), urinary (bladder) catheters, or intravenous (vein) catheters, patients who are taking long courses of certain antibiotics, and patients with weakened immune systems are at high risk for carbapenem resistant bacterial infections, particularly infections with CRE.¹²

EPIDEMIOLOGY OF CARBAPENEM RESISTANT BACTERIA

Rapid spread of carbapenem resistant bacteria worldwide is an important concern.¹³ However, exact global prevalence of all these bacteria remains unclear. Of these bacteria, carbapenem-resistant *P. aeruginosa* (CRPA), *A. baumannii* (CRAB) and *Enterobacteriaceae* (CRE) are the important pathogens causing hospital acquired infections (HAIs) and are prioritized by the WHO as

critical pathogens that require urgent drug research and the development.^{13,14}

A study done over 20 years (1997-2016) from the SENTRY anti-microbial surveillance program which included carbapenem resistance rates (n=52 022 isolates) globally (except Africa and the Middle-East) indicated that carbapenem resistance in *P. aeruginosa* was 17.4% (as per the susceptibility testing determined by CLSI guidelines).¹⁵ European centre for disease prevention and control in 2017 also reported high rates (25-60%) of carbapenem resistance in *P. aeruginosa* in Southern and Eastern Europe.¹⁶

Globally carbapenem resistance was detected in 40-70% of the isolates of *A. baumannii* responsible for ICU-acquired infections.¹⁷ In the United States, the resistance rates among *A. baumannii* in central line-associated blood stream infection and catheter-associated urinary tract infections were reported as 47% and 64%, respectively.^{18,19} In Europe, it was found to be 33.4% among the isolates causing blood stream infection.¹⁶

The global epidemiology of CRE is yet to be known.¹³ A prospective, multinational study on carbapenemase-producing *Enterobacteriaceae* (CPE) has reported infection prevalence of CPE to be 1.3 per 10 000 hospital admissions.²⁰ In the United States, a systemic review highlighted that that incidence of CRE was found to be 0.3-2.93 infections per 100 000 person-years.²¹ Over 10% of *K. pneumoniae*, a member of *Enterobacteriaceae*, that causes health care associated infections in US hospitals are currently found to be carbapenem resistant.²² The prevalence of CRE infections in the community remains unclear, but a review published in 2017 reported it in the range of 0.04 to 29.5%.²³

HUMAN-RELATED FACTORS CONTRIBUTING TO EMERGENCE AND SPREAD OF CARBAPENEM RESISTANCE

The major human related factors that contribute to emergence and spread of carbapenem resistance are reported as: (a) immoderate antibiotic prescription combined with the uncontrolled public access to antibiotics in many countries with poor sales regulations (b) the lack of infection control measures in healthcare facilities once carbapenem resistance has emerged and (c) the use of subtherapeutic doses of antibiotics for the promotion of animal growth in the agricultural sector.⁴

PREVENTION AND CONTROL OF INFECTIONS WITH CARBAPENEM RESISTANT PATHOGENS

WHO recommends the following measures for prevention and control of infections associated with carbapenem resistant pathogens, particularly CRE.³

Recommendation 1

Multimodal IPC strategies should be implemented to prevent and control CRE infection or colonization and that these should consist of at least the following: hand hygiene, surveillance, contact precautions, patient isolation (single room isolation or co-horting) and environmental cleaning.

Recommendation 2

Hand hygiene best practices according to the WHO guidelines on hand hygiene in health care should be implemented.

Recommendation 3

Surveillance of CRE infection (s) should be performed; and surveillance cultures for asymptomatic CRE colonization should also be performed, guided by local epidemiology and risk assessment. Populations to be considered for such surveillance include patients with previous CRE colonization, patient contacts of CRE colonized or infected patients and patients with a history of recent hospitalization in endemic CRE settings.

Recommendation 4

Contact precautions should be implemented when providing care for patients colonized or infected with CRE.

Recommendation 5

Patients colonized or infected with CRE should be physically separated from non-colonized or non-infected patients using (a) single room isolation or (b) by co-horting patients with the same resistant pathogen.

Recommendation 6

Compliance with environmental cleaning protocols of the immediate surrounding area (that is, the "patient zone") of patients colonized or infected with CRE should be ensured.

Recommendation 7

Surveillance cultures of the environment for CRE should be considered when epidemiologically indicated.

Recommendation 8

Monitoring, auditing of the implementation of multimodal strategies and feedback of results to health care workers and decision-makers is recommended.

TREATMENT OPTIONS FOR INFECTIONS CAUSED BY CARBAPENEM RESISTANT PATHOGENS

For treatment of infections caused by carbapenem resistant Gram-positive bacteria, there are some alternatives (such as glycopeptides, linezolid and daptomycin) to carbapenem. However, the therapeutic options are limited for infections caused by carbapenem resistant Gram-negative bacterial pathogens.⁴ Carbapenemase producing Gram-negative bacteria usually exhibit resistance to all or almost all beta-lactams and also commonly bear the genes encoding for resistance against fluoroquinolones and/or aminoglycosides.⁴ Therefore, for these bacteria, the important last resort choices that are currently available include older agents such as polymyxins and fosfomycin, which were rarely used in the past because of efficacy and/or toxicity concerns, and the newer tigecycline.⁴ These drugs, based on the antimicrobial susceptibility data, can be used as: monotherapy using one of the possibly still active *in vitro* agents (which may be colistin, tigecycline or fosfomycin); or combination therapy without a carbapenem; or combination therapy with two or more drugs including at least one carbapenem, preferably when the carbapenem's MIC is 4 mg/L.⁴ The last approach is considered as the most effective therapeutic strategy in terms of mortality.²⁴

Polymyxins

Polymyxins are regarded as the most active agents against carbapenem resistant Gram-negative bacteria.²⁵ They show their activity against most species in the family of *Enterobacteriaceae* (except for *Serratia marcescens* and *Proteus, Providencia, Morganella, and Hafnia* species), *P. aeruginosa*, *A. baumannii*, and some *S. maltophilia* strains.²⁶

Chemically, they are cationic polypeptides.²⁷ Polymyxin B and polymyxin E (colistin) are the two polymyxins available for clinical use.²⁷ Polymyxin B is administered as its active form (polymyxin B sulfate) whereas colistin is administered as an inactive pro-drug, CMS (also called colistimethate) which results in a prolonged period of low plasma concentrations of the active drug and theoretically might increase the risk of resistance development.^{26,28}

Polymyxins bind to negatively charged phosphate moieties in the lipid A fraction of lipopolysaccharide (LPS) present in the outer membrane of Gram-negative bacteria and causes the disruption of cell membranes that results in loss of intracellular products, thus achieving bactericidal activity.²⁷

Polymyxin B was introduced into the clinical practice in the United States in the mid-1950s, and colistin towards the end of that decade.²⁷ Due to toxicity (nephrotoxicity and neurotoxicity) concerns and availability of other antibacterials such as aminoglycosides and cephalosporins

that were safer than polymyxins, they took as secondary place in antibiotic armamentarium.²⁷ For decades, their use was confined to inhalation therapy in patients with cystic fibrosis, as a component of gastrointestinal tract decontamination regimens, and as topical antibiotic therapy.²⁷

Polymyxins, due to their broad spectrum of activity, were "rediscovered" in the late 1990s, initially to address the therapeutic challenge posed by carbapenem-resistant *A. baumannii* (CRAB) and *P. aeruginosa*.²⁷ Clinical studies have supported the effectiveness of polymyxins but reemphasized the concerns of nephrotoxicity and neurotoxicity associated with these drugs.²⁹ Nephrotoxicity has been observed more frequently with colistin than polymyxin B.³⁰ Though these drugs are useful, emergence of resistance has a negative impact on their continued utility for the treatment of CRE infections.²⁷ Resistance has been reported from various parts of the world.³¹⁻³³

Fosfomycin

Fosfomycin is a cell wall active agent discovered in 1969.²⁷ It penetrates bacterial cell wall through the transport systems and inhibits the first step in the synthesis of peptidoglycan by blocking the formation of N-acetylmuramic acid.²⁷ It is a bactericidal drug with a broad spectrum of activity that includes Gram-positive (e.g. *Enterococcus faecalis*) and Gram-negative bacteria (e.g. *Escherichia coli*).³⁴ Moreover, the drug has been found to be effective against approximately 80% of CRE, especially KPC-producing *K. pneumoniae*, even in strains that display decreased susceptibility to colistin and tigecycline.^{35,36}

The drug has a unique pharmacokinetic profile.²⁷ The drug is >50% bioavailable after oral administration, has a prolonged half-life, penetrates well into the tissues and is largely excreted unchanged into the urine, and achieves high penetration into the genitourinary system including the prostate.²⁷ It is commonly used for treatment of bloodstream infection, endocarditis, meningitis, endophthalmitis, pneumonia, diabetic foot infections, peritonitis, gastroenteritis etc. It is well tolerated, with nausea, vomiting and diarrhea, or skin rashes, occurring in up to 5% of patients.³⁷

Mechanism of action and safety profile of the drugs make it suitable for synergistic combination therapy, including regimens containing beta-lactams and aminoglycosides.²⁷ When the drug is used alone, rapid emergence of resistance has been reported.³⁸

Tigecycline

Tigecycline is a glycylcycline bacteriostatic antibiotic, related to tetracyclines.²⁷ It interferes with protein synthesis by binding to the 30S ribosomal subunit. The

drug received the first approval for clinical use from food and drug administration (FDA) in 2005.³⁹

Tigecycline was designed to overcome tetracycline resistance mechanisms (ribosome protection and active efflux).⁴⁰ It has broad spectrum of activity against both Gram positive and Gram negative pathogens, with notable exceptions of *P. aeruginosa*, *Proteus* species, and *Providencia species*.⁴¹ Among carbapenem-resistant Gram-negative pathogens, it shows its activity against the majority of CRE, *A. baumannii*, and *S. maltophilia* strains. Tigecycline is mostly used in combination regimens when treating carbapenem resistant Gram-negative infections.⁴⁰

Since tigecycline is poorly absorbed through gastrointestinal tract, it requires intravenous administration.⁴² Adverse effects of this drug are usually mild and include nausea and vomiting.⁴²

Tigecycline is primarily indicated for the treatment of complicated skin and soft tissue infections and complicated intra-abdominal infections when caused by CRE, among other MDR pathogens.⁴³ Tigecycline is generally not recommended for bacteremia because of its bacteriostatic activity and low steady-state concentrations in serum at current dosing recommendation.⁴⁰ However, it may still play an important role in the treatment of carbapenem-resistant *K. pneumoniae* bloodstream infection, especially as a part of combination regimens including colistin and carbapenems.²⁷

Although tigecycline achieves low concentration in the urine, some studies have recommended its use in high doses for the treatment of urinary tract infection (UTI).⁴⁴ In clinical practice, the use of tigecycline to treat CRE (especially KPC-producing *K. pneumoniae*) UTI is common, but may be associated with the development of resistance.²⁷

Emerging drugs

In the situation of evolving resistance against available antibiotics, world is currently in need of new antibiotics. A combination of avibactam and ceftazidime has been approved by FDA for treating complicated urinary tract and complicated intra-abdominal infections.⁴⁵ Avibactam is a novel beta-lactamase inhibitor whereas ceftazidime is a third-generation cephalosporin. The combination shows in vitro activity against some CRE isolates.⁴⁶ However, clinical data on its efficacy in severe infections caused by CRE are scarce.

Other novel antimicrobials which show in vitro activity against CRE are in different phases of clinical trials.⁴⁵ Those antimicrobials include other combinations of avibactam with beta-lactams (i.e., ceftaroline fosamil-avibactam and aztreonam-avibactam), the combinations of carbapenems with beta-lactamase inhibitors (i.e., meropenem-vaborbactam and imipenem/cilastatin-

relebactam), a new aminoglycoside (plazomicin) and a new tetracycline (eravacycline).

CONCLUSION

Carbapenems are very useful drugs and are often regarded as the antibiotics of last resort in treatment of serious infections. However, emergence of resistance against this drug has posed a therapeutic challenge. Only few options are available for treatment of infections caused by carbapenem resistant pathogens.

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