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New developments in carbapenems

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ABSTRACT

Antibiotic resistance among Gram-negative pathogens in hospitals is a growing threat to patients and is driving the increased use of carbapenems. Carbapenems are potent members of the β-lactam family of antibiotics, with a history of safety and efficacy for serious infections that exceeds 20 years. Original and review articles were identified from a Medline search (1979–2008). Reference citations from identified publications, abstracts from the Interscience Conferences on Antimicrobial Agents and Chemotherapy and package inserts were also used. Carbapenems are effective in treating severe infections at diverse sites, with relatively low resistance rates and a favourable safety profile. Carbapenems are the β-lactams of choice for the treatment of infections caused by multidrug-resistant organisms. Optimized dosing of carbapenems should limit the emergence of resistance and prolong the utility of these agents. The newly approved doripenem should prove to be a valuable addition to the currently available carbapenems: imipenem, meropenem and ertapenem.

Keywords Carbapenems, β-lactams, multidrug resistance, review

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INTRODUCTION

β-Lactams comprise more than half of all antibiotics.

They are among the most widely prescribed antimicrobial agents in both community and hospital settings, because they have a long history of efficacy and safety [1]. The use of β-lactams for more than 60 years has, however, resulted in a dramatic increase in the rates of resistance that now threatens the utility of the majority of this large drug family. Enzymes have appeared with potent hydrolytic activity against penicillins, cephalosporins, cephamycins, β-lactam–β-lactamase inhibitor combinations, and even carbapenems [2,3]. Several bacterial species have acquired these enzymes, thus becoming multidrug-resistant, and leaving clinicians with few therapeutic options [4]. Within the β-lactam family, carbapenems have historically been the drugs of choice for the treatment of severe infections caused by multidrug-resistant organisms [5].

Antimicrobial resistance continues to evolve, and presents serious challenges concerning the therapy of both nosocomial and community-acquired infections; 50–60% of the more than two million nosocomial infections in the USA each year are caused by antimicrobial-resistant bacteria [6]. Although carbapenems retain nearly universal activity against *Enterobacteriaceae*, rates of resistance to carbapenems are increasing in *Pseudomonas* and *Acinetobacter* spp. [7].

On the other hand, reports of *Enterobacteriaceae* harbouring enzymes such as metallo-β-lactamases and carbapenemases are increasingly being recognized [8–12]. Such bacteria can develop resistance to all β-lactam antibiotics, including carbapenems.

Resistance to antimicrobial agents is mediated by many factors, including β-lactamases, porin loss, efflux pumps, and target modifications.

β-Lactamases are enzymes that hydrolyze β-lactam agents. They are ubiquitous in Gram-negative bacilli, and are the major cause of

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resistance to β-lactams in Gram-negative bacteria. The genes of these enzymes can be either chromosome- or plasmid-borne. The latter pose a significant threat in the context of controlling bacterial resistance, because plasmid-borne β-lactamase genes are readily transferable among bacteria, allowing an effective and rapid spread of resistance. The β-lactamases with the greatest impact in the nosocomial setting are mainly extended-spectrum β-lactamases (ESBLs), AmpC-type β-lactamases and carbapenemases.

Carbapenemases (metallo-β-lactamases and active-site serine carbapenemases) are fairly uncommon, although they are a source of considerable concern, due to a spectrum of activity that encompasses almost all known β-lactams, from penicillins to the carbapenems, and they are generally not susceptible to current class A β-lactamase inhibitors [6]. The most clinically important bacteria harbouring carbapenemases are *Pseudomonas* and *Acinetobacter*, although sporadic reports of carbapenemase-mediated resistance to carbapenems in *Enterobacteriaceae* have appeared [3,13–16]. Historically, carbapenems have retained stability to almost all clinically relevant β-lactamases, but some class B β-lactamases (IMP, VIM, SPM, GIMs), along with some rare class A (SPE, NMC-A, IMI-1, KPC) and class D enzymes (OXAs), are able to hydrolyze these antibiotics (Kattan JN, Guzman AM, Correa A *et al*. Evidence for widespread dissemination of OXA-23-like carbapenemases in *Acinetobacter baumannii* in Colombia. Programs and Abstracts of the American Society for Microbiology's 46th Annual International Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Francisco, 2006, Abstract C2-598) [3,17,18]. Although class B enzymes are generally chromosome-encoded, plasmid-carbapenems have been reported in *Bacteroides fragilis* [19], *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and members of the *Enterobacteriaceae* family [1,20–22].

These β-lactamases have emerged as significant threats to treatment with all β-lactams by becoming epidemic and endemic in the Far East [23], Europe [10] and South America [22,24]. For perspective, it is worth noting that despite the occurrence of carbapenemases, the most common means by which bacteria become carbapenem-resistant in most of the world is via loss of permeability, or through loss of porins, increased efflux of the drug, by increased efflux pump, and target modifications activity [25].

In porin loss, the loss of a membrane protein channel decreases the rate of entry of antibiotics into the periplasm, thus raising the MIC. If combined with β-lactamase production, porin loss may confer resistance to one or many antibiotics simultaneously. An example of this mechanism is the loss of a specific porin known as OprD in *P. aeruginosa* along with simultaneous production of AmpC, which confers resistance to carbapenems, particularly imipenem [26]. Many Gram-negative bacteria are able to expel antibiotics after entry by utilizing energy-dependent efflux mechanisms. The best studied and described efflux mechanisms are those of *P. aeruginosa*, in which four multidrug efflux pumps have been well characterized (MexAB–OprM, MexCD–OprJ, MexEF–OprN and MexXY–OprM) [27–29]; each has a preferential set of antimicrobial substrates, including meropenem and ertapenem, which are pumped out of the cell by OprM.

Resistance in *Pseudomonas* and *Acinetobacter* is more likely to affect carbapenems because of low membrane permeability and simultaneous expression of multiple resistance mechanisms. With Gram-negative organisms having a plethora of resistance mechanisms at their disposal, carbapenems emerge as the last line of defence in many cases [30,31]. The development of new drugs and the more rational use of currently available antibiotics should help to limit the problem of multidrug-resistant pathogens and prevent the loss of carbapenems as antibiotics of last resort in clinical practice.

Carbapenems occupy a unique position in the β-lactam family of antibacterials. As a class, carbapenems are innately stable to most β-lactamases of Ambler classes A, C and D. Their broad spectrum of activity and their stability in the presence of this wide range of β-lactamases make them important therapeutic options for treating serious infections involving resistant *Enterobacteriaceae* (including ESBL-producing and AmpC-overproducing isolates), anaerobes, *P. aeruginosa*, and *Acinetobacter* spp. [1]. Carbapenems are recommended for the empirical treatment of a variety of severe infections, e.g. nosocomial pneumonia, complicated intra-abdominal infection, septicaemia, complicated skin and skin structure infection, complicated urinary tract

infection, meningitis, and acute exacerbations of cystic fibrosis [32–36].

The first carbapenems discovered were olivanic acids produced by *Streptomyces olivaceus*. This was followed by the discovery of thienamycin in 1976 [37]. The latter was found in the course of a soil-screening programme to identify inhibitors of peptidoglycan synthesis [37,38]. It was produced by a previously unknown *Streptomyces* spp. that received the name *Streptomyces cattleya*, as the pigment in its aerial mycelium resembled the colour of the cattleya orchid [20]. These compounds were chemically unstable, so they were not used clinically.

Years later, a more stable thienamycin derivative, *N*-formimidoyl thienamycin (known as imipenem), was synthesized and approved for use in 1984 [39]. This compound was therapeutically useful, as it was more stable in the solid state and in concentrated solution. However, an additional instability to a mammalian hydrolase from the renal brush border, dehydropeptidase-I (DHP-I), led to the decrease of imipenem levels in urine and the production of a potentially nephrotoxic metabolite [40,41]. The development of an additional compound, cilastatin, to be co-administered in a 1 : 1 ratio with imipenem, prevented hydrolysis by DHP-I and reduced nephrotoxicity [40]. Meropenem was the first carbapenem with a 1-β-methyl group and 2-thiopyrrolidinyl moiety, which renders this antibiotic stable to DHP-I. Other carbapenems, for parenteral administration, were discovered later, and include biapenem, panipenem, ertapenem, lenapenem, E-1010, S-4661 and BMS-181139. Carbapenems that are orally administered include sanfetrinem, DZ-2640, CS-834 and GV-129606 [20].

A recently proposed classification system for carbapenems divides them into two groups [42]. Group 1 carbapenems, e.g. ertapenem, are defined as broad-spectrum agents that have limited activity against non-fermentative Gram-negative bacilli and are most suited for use in community-acquired infections, whereas group 2 carbapenems, e.g. imipenem, meropenem and doripenem, are broad-spectrum agents that are active against non-fermentative Gram-negative bacilli and are particularly useful in treating nosocomial infections. A third group of carbapenems has also been suggested. This category includes agents with activity against methicillin-resistant *Staphylococcus aureus*, such as PZ-601, a carbapenem under development (Lolans K, Quinn JP. PZ-601 susceptibility against Gram-negative pathogens with known resistance mechanisms. Programs and Abstracts of the American Society for Microbiology's 47th Annual International Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, 2007). Table 1 lists each group of carbapenems and the pathogens typically covered by each.

CARBAPENEM ACTIVITIES

β-Lactam antibiotics share a common structure, the four-membered lactam ring. Carbapenems differ from other β-lactam antibiotics in that they possess a carbon instead of a sulphone in the four-position of the thyazolidinic moiety of the β-lactam ring [20]. They have a broad spectrum of antimicrobial activity that exceeds that of most other classes of antimicrobials [43]. Carbapenems are rapidly bactericidal agents because they bind with high affinity to most high molecular weight penicillin-binding proteins of Gram-negative and Gram-positive bacteria [44]. Carbapenems (except ertapenem) are active against clinically significant

Table 1. Carbapenem groups and spectrum of activity for each compound

Carbapenem group	Group 1 Ertapenem	Group 2 Imipenem Meropenem Doripenem	Group 3 PZ-601
Gram-negative aerobes			
Acinetobacter	Resistant	Susceptible	Resistant
Burkholderia cepacia	Resistant	Variable	Resistant
Enterobacteriaceae	Susceptible	Susceptible	Susceptible
Haemophilus	Susceptible	Susceptible	Susceptible
Moraxella	Susceptible	Susceptible	Susceptible
Neisseria	Susceptible	Susceptible	Susceptible
Pseudomonas aeruginosa	Resistant	Susceptible	Resistant
Stenotrophomonas maltophilia	Resistant	Resistant	Resistant
Gram-positive aerobes			
Enterococcus faecalis	Resistant	Variable	Variable
Enterococcus faecium (ampicillin-resistant)	Resistant	Resistant	Resistant
Listeria	Resistant	Susceptible	Not reported
Staphylococcus aureus (methicillin-susceptible)	Susceptible	Susceptible	Susceptible
S. aureus (methicillin-resistant)	Resistant	Resistant	Susceptible
Streptococcus pneumoniae (penicillin-susceptible)	Susceptible	Susceptible	Susceptible
Streptococcus pneumoniae (penicillin-resistant)	Susceptible	Susceptible	Susceptible
Streptococcus pyogenes	Susceptible	Susceptible	Susceptible
Viridans group streptococci	Susceptible	Susceptible	Susceptible
Anaerobes			
Bacteroides	Susceptible	Susceptible	Susceptible
Clostridium difficile	Susceptible	Susceptible	Not reported
Eubacterium	Susceptible	Susceptible	Not reported
Fusobacterium	Susceptible	Susceptible	Not reported
Peptostreptococcus	Susceptible	Susceptible	Not reported
Propionibacterium	Not reported	Susceptible	Not reported

Gram-negative non-fermenters such as *P. aeruginosa*, *Burkholderia cepacia* and *Acinetobacter* spp. [45,46]. They also retain activity against streptococci, methicillin-sensitive staphylococci, *Neisseria* and *Haemophilus* [39]. Unlike most other broad-spectrum antibiotics, carbapenems are active against most Gram-positive and Gram-negative anaerobes, including subspecies of *B. fragilis*, *Bacteroides thetaiotaomicron*, *Prevotella bivia*, *Fusobacterium nucleatum*, *Fusobacterium mortiferum*, *Peptostreptococcus asaccharolyticus* and *Clostridium perfringens* [36,39]. Carbapenem-resistant bacteria include: ampicillin-resistant *Enterococcus faecium*, methicillin-resistant staphylococci, *Stenotrophomonas maltophilia* and some isolates of *Clostridium difficile* [47,48].

The enhanced activity of carbapenems is due to several factors: (i) they are smaller molecules than cephalosporins and are zwitterions (i.e. they have both positive and negative charges in solution), both of which properties facilitate rapid penetration across the Gram-negative outer membrane [39]; (ii) they have high affinity for essential penicillin-binding proteins (PBP-2, PBP-4, PBP-3 and PBP-1b) from a broad range of bacteria [20]; and (iii) they are resistant to a broad range of β-lactamases from Gram-positive and Gram-negative bacteria. Table 2 lists the current CLSI and EUCAST breakpoints for carbapenems [49,50].

SAFETY ADVANTAGES OF CARBAPENEMS

One reason why β-lactams are the most frequently prescribed class of antibiotics is their superior safety profile, as compared with other antibiotics [45]. Carbapenems are generally well tolerated. Allergic reactions to β-lactam compounds are the most common adverse events in treatment with carbapenems; these include rash, urticaria and immediate hypersensitivity. Major adverse effects such as diarrhoea, pseudomembranous colitis, coagulation abnormalities, nephrotoxicity and hepatotoxicity occur with frequencies similar to those of comparators [44].

DIFFERENCES AMONG INDIVIDUAL CARBAPENEMS

As the oldest of the carbapenems, imipenem is still used considerably, although it has

Table 2. Breakpoints for carbapenems as published by CLSI and EUCAST

		General breakpoints, MIC (mg/L)			Species-specific breakpoints									
Antibacterial agent	Group	Susceptible	Intermediate	Resistant	*Enterobacteriaceae*	*Pseudomonas*	*Acinetobacter*	*Staphylococcus*	*Enterococcus*	*Streptococcus* A, B, C, G[a]	*Streptococcus pneumoniae*	*Haemophilus influenzae*, *Moraxella catarrhalis*[a]	*Neisseria meningitidis*[a]	Anaerobes
IMP	CLSI	–	–	–	4/16	4/16	4/16	4/16	–	–	0.12/1	4/4	–	4/16
IMP	EUCAST	≤2	>2 to ≤8	>8	2/8	4/8	2/8	–	4/8	2/2	2/2	2/2	–	2/8
MER	CLSI	–	–	–	4/16	4/16	4/16	4/16	–	0.5/0.5	0.25/1	0.5/0.5	0.25/0.25	4/16
MER	EUCAST	≤2	>2 to ≤8	>8	2/8	2/8	2/8	–	–	2/2	2/2	2/2	0.25/0.25	2/8
ETP	CLSI	–	–	–	2/8	–	–	2/8	–	1/1	1/4	0.5/0.5	–	4/16
ETP	EUCAST	≤0.5	>0.5 to ≤1	>1	0.5/1	–	–	–	–	0.5/0.5	0.5/0.5	0.5/0.5	–	1/1[a]

IMP, imipenem; MER, meropenem; ETP, ertapenem; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antibiotic Susceptibility Testing.
[a]Strains with MIC values above the S/I breakpoint are rare or not yet reported.

several disadvantages as compared with newer carbapenems [39]. It is not approved by the US Food and Drug Administration (FDA) for meningitis, and should be avoided in the treatment of central nervous system infections because of its propensity to cause seizures in patients with elevated risk factors, e.g. renal failure or structural brain disease [44]. It is typically very active against *P. aeruginosa* and *Acinetobacter* spp. However, resistance to imipenem during therapy has been described since 1986 [52]. Downregulation of the carbapenem-specific OprD porin in *P. aeruginosa* can lead to this type of resistance [53–55]. Mutational loss of OprD is frequent during imipenem therapy, reaching 25% or more in strains causing difficult infections [56,57]. Loss of OprD does not confer reduced susceptibility to other β-lactams; however, it does affect all carbapenems. Similar to *P. aeruginosa*, *Enterobacter* spp. can also become resistant during therapy with imipenem, although this is much less common and appears to require a combination of porin loss and increased activity of a β-lactamase-like AmpC [55,58,59]. Imipenem is slightly more active against Gram-positive bacteria than are other carbapenems. Imipenem is excreted renally, with 70% of imipenem recovered in the urine within 10 h and no detectable urinary excretion after that time. Accumulation is not observed in plasma or urine, even with regimens administered as frequently as every 6 h. Imipenem is distributed extensively in tissues and fluids [60]. The recommended adult dose of imipenem for patients with normal renal function is 250 mg to 1 g intravenously every 6–8 h. The paediatric dose is 15–25 mg/kg every 6–8 h. Dose adjustment is required for patients with creatinine clearance of less than 50 mL/min or body weight of less than 70 kg [44]. Unfortunately, the low stability of imipenem (10% degradation at 25°C after 3.5 h) limits the possible duration of infusion of this carbapenem; it must therefore be dosed as 30–60-min infusions [51].

Panipenem (RS-533), introduced into clinical practice in Japan in 1993, was the second approved carbapenem. It is susceptible to hydrolysis by DHP-I and thus requires the co-administration of an inhibitor of this enzyme, betamipron [20]. This drug, which is not discussed further in this article, is approved in Japan, China and South Korea [44].

The discovery that stability to human renal DHP-I can be achieved by introducing a 1-β-methyl substituent at C-1 led to the synthesis and introduction of meropenem (SM7338) in 1995 [39,61,62]. Meropenem is primarily excreted by the kidneys, with *c.* 50–75% of the dose being excreted unchanged in the urine and a further 25% being excreted as a microbiologically inactive open β-lactam metabolite [63]. Meropenem has a spectrum of activity similar to that of imipenem (including *P. aeruginosa* and *Acinetobacter* spp.) and is slightly more active against Gram-negative aerobic bacteria. This agent is a substrate for the multidrug efflux system MexAB–OprM, present in *P. aeruginosa* [54,64]. Overexpression of this efflux system raises the MIC of meropenem and other substrate antibiotics, but not of imipenem. Downregulation of the porin OprD also raises the MIC of meropenem, but usually not to the degree of outright resistance, as defined by conventional breakpoints [56]. Rather, the combination of a β-lactamase and downregulation of outer membrane proteins, like OprD, and an efflux system, such as MexAB–OprM, are needed for outright resistance to meropenem to occur.

Meropenem is approved by the US FDA for the treatment of bacterial meningitis in children aged 3 months and older, and is efficacious in adults [44]. The recommended adult dose of meropenem for patients with normal renal function is 500–1000 mg intravenously every 8 h, although daily doses of 6 g seem to be safe [65]. The paediatric dose is 20–40 mg/kg every 6–8 h. Dose adjustment is required for patients with creatinine clearance of less than 50 mL/min [44]. Some investigators have dosed meropenem as a 3-h infusion in an attempt to improve efficacy against resistant pathogens [21,39,66].

Ertapenem (MK-0826) is a 1-β-methyl carbapenem developed in 2001 [67] to be more resistant than imipenem to DPH-I inactivation, and therefore, does not require the addition of a DPH-I inhibitor such as cilastatin or betamipron [20]. Elimination follows non-linear kinetics, partly owing to the concentration dependence of protein binding. Approximately 80% of excretion is via the kidneys, with half as the native compound and half as the open-ring derivative; a further 10% is eliminated via the faeces [68]. Ertapenem possesses a longer apparent elimination half-life than imipenem and meropenem. This longer

half-life allows for a convenient, once-daily administration schedule [69]. Ertapenem is an important option for the empirical treatment of complicated community-acquired bacterial infections, where a mixed flora of anaerobes and aerobes is likely, e.g. community-acquired pneumonia, complicated skin and skin structure infection, complicated urinary tract infection, or community-acquired complicated intra-abdominal infection, in both children and adults [69]. Ertapenem is now an option for the treatment of some nosocomial infections, but it lacks antimicrobial activity against non-fermenting Gram-negatives such as *P. aeruginosa* and *Acinetobacter* spp., and thus cannot be used when they are suspected pathogens [21]. A recent study demonstrated the greater efficacy of ertapenem in comparison with cefotetan for elective colorectal procedures, making this drug a potential option for prophylaxis of surgical site infection following abdominal surgery [70]. Despite its being generally effective against infections caused by ESBL-producing pathogens, ertapenem has decreased *in vitro* activity as compared with other carbapenems against some bacteria that produce ESBLs [71]. The most common form of ertapenem resistance in *Enterobacteriaceae* is the combination of AmpC production and porin loss. This type of resistance has been reported during therapy in an ESBL-producing *Klebsiella pneumoniae* strain [72]. Similar to imipenem and meropenem, ertapenem has anti-anaerobic activity and is thus especially useful in a single daily dose regimen for polymicrobial infections [44]. Although it penetrates into cerebrospinal fluid, ertapenem is not approved for the treatment of bacterial meningitis.

One concern that has limited the use of ertapenem is the fear that its use will select for imipenem, meropenem or doripenem resistance in *P. aeruginosa*. This appears unlikely, on the basis of *in vitro* studies [73]. Furthermore, a comprehensive study of gut-colonized patients with intra-abdominal infections treated with one of two comparators, ceftriaxone–metronidazole or piperacillin–tazobactam, not only showed no increase in imipenem-resistant *P. aeruginosa* in ertapenem-treated patients, but also showed less emergence of resistance in enterics in these patients than in those treated with either comparator [74,75].

The recommended adult dose of ertapenem for patients with normal renal function is 1000 mg, intravenously or intramuscularly, once daily, and 500 mg once daily for patients with creatinine clearance of less than 30 mL/min or on dialysis [44]. Paediatric dosing is 15 mg/kg every 12 h for patients between the ages of 3 months and 12 years.

Doripenem (S-4661) is a parenteral 1-β-methyl carbapenem that has completed phase 3 trials for nosocomial pneumonia (including ventilator-associated pneumonia), complicated intra-abdominal infection, and complicated urinary tract infection. Doripenem is licensed for adults for the treatment of complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis, in the USA.

It is undergoing regulatory review for the treatment of complicated urinary tract infections and intra-abdominal infections in Europe, and for the treatment of nosocomial pneumonia, including ventilator-associated pneumonia, in both the USA and Europe. A recent clinical trial comparing doripenem and imipenem for the treatment of ventilator-associated pneumonia showed less emergence of resistance among *P. aeruginosa* isolates in the doripenem arm, although the numbers were modest and the clinical outcomes were the same in both groups [76]. This carbapenem has stability against human DPH-I [77] and a wide spectrum of activity [78]. It combines the *in vitro* activity of imipenem against Gram-positive pathogens and of meropenem against Gram-negative pathogens [1,78]. Its renal elimination is similar to that of meropenem, with a mean urinary recovery, of doripenem, of 75% over 24 h [79]. Doripenem retains activity against ESBL- and AmpC-producing *Enterobacteriaceae* [80]. The MICs of doripenem are lower for *P. aeruginosa* than are those of other antipseudomonal agents, and it inhibits a great proportion of otherwise carbapenem-resistant *P. aeruginosa* at ≤4 mg/L [80–83].

When compared with several other antipseudomonal agents, including other carbapenems, doripenem was associated with the lowest rate of spontaneous resistance *in vitro* [84]. When it was combined with an aminoglycoside *in vitro*, doripenem resistance selection in *P. aeruginosa* was decreased even further [85]. Against a wide range of bacteria, doripenem can be safely combined with various antimicrobial agents (amikacin, co-trimoxazole, levofloxacin, daptomycin and linezolid) without risk of antagonism [86] (Mushtaq S,

Warner M, Ge Y, Kaniga K, Livermore DM. *In-vitro* interactions of doripenem with other antibacterial agents. Programs and Abstracts of the American Society for Microbiology's 45th Annual International Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Washington, DC, 2005). Unlike treatment with imipenem, treatment with doripenem is expected to carry a low risk of seizures [87]. Its enhanced stability in solution makes it suitable for extended infusions (3 h), thus potentially minimizing resistance development and improving efficacy [88] (Floren L, Wikler M, Kilfoil T, Ge Y. A phase I, double-blind, placebo-controlled study to determine the safety, tolerability, and pharmacokinetics (PK) of prolonged-infusion regimens of doripenem (DOR) in healthy subjects. Programs and Abstracts of the American Society for Microbiology's 46th Annual International Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Washington, DC, 2004, Abstract A16). Doripenem at doses of 500 mg every 8 h was shown to be non-inferior, in terms of safety and efficacy, to meropenem at doses of 1 g every 8 h in a phase 3 trial for complicated intra-abdominal infections (Malafaia O, Umeh O, Jang J. Doripenem versus meropenem for the treatment of complicated intra-abdominal infections. Programs and Abstracts of the American Society for Microbiology's 46th Annual International Conference on Antimicrobial Agents and Chemotherapy (ICAAC), San Francisco, CA, 2006, Poster E-0221). Likewise, the compound met non-inferiority criteria for efficacy as compared with piperacillin–tazobactam (Rea-Neto A, Niederman M, Prokocimer P, Lee M, Kaniga K, Friedland I. Efficacy and safety of intravenous doripenem vs piperacillin/tazobactam in nosocomial pneumonia. Programs and Abstracts of the American Society for Microbiology's 47th Annual International Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, 2007, Abstract L-731) for the treatment of hospital-acquired pneumonia and as compared with imipenem for the treatment of ventilator-associated pneumonia [76,89].

CONCLUSION

The progressive rise of broad resistance among non-fermenters, as well as an ever-increasing prevalence and diversity of β-lactamases in *Enterobacteriaceae*, is driving the increased use of carbapenems. Although the development of bacterial resistance to carbapenems largely parallels its use, the rate of emergence of resistance has been relatively low. Twenty-three years after the first release of a carbapenem into wide use, carbapenems remain invaluable, with low resistance rates and favourable safety profiles [32,33,35,36,90]. The newest member, doripenem, should prove to be a valuable addition to the carbapenem class.

TRANSPARENCY DECLARATION

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