



## Carbapenems: A Short Review about their Current Status

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**ABSTRACT:** In this review, we summarize the current “state of the art” of carbapenem antibiotics and their role in our antimicrobial armamentarium. Among the beta-lactams currently available, carbapenems are unique because they are relatively resistant to hydrolysis by most beta-lactamases. Herein, we described the cost effectiveness, safety, and advantages of carbapenems as compared to other antibiotics. We also highlight important features of the carbapenems that are presently in clinical use: imipenem-cilastatin, meropenem, ertapenem, doripenem, panipenem-betamipron, and biapenem. In closing, we emphasize some major challenges related to oral formulation of carbapenems and different strategies to overcome these challenges.

**KEYWORDS:** Antibiotics, carbapenems, oral antibiotics

### INTRODUCTION

Until the end of the 20<sup>th</sup> century, infectious diseases were the main causes of premature death and disability. It was only towards the mid-20<sup>th</sup> century when the toll of infectious diseases started to reduce from the introduction of safe, effective, affordable vaccines and the increasing availability of antibiotics.[1] However, communicable(infectious), material, and nutritional diseases combined still represent 28% of the disease burden globally in 2017.[2] Infectious disease causes local or systemic symptoms that can develop in multiple organ systems. Examples of such symptoms include cellulitis, Fever, Sepsis, and shock. These symptoms typically resolve with successful treatment of the underlying infection[3]Antibiotics can either kill or stop the reproduction of the bacteria causing the infection, allowing the host’s natural immune system to rid itself of the infection. However, there is an increasing emergence of antibiotic-resistant bacteria worldwide. Resulting in a crisis where bacterial infections are once again a threat. [4] Oral drug delivery holds many benefits over other dosage forms. It is the preferred route of administration due to a variety of factors. It is easy to use and painless[5] with high patient compliance and preference. It is cost-effective, has the least sterility issues and its application holds no safety risk. However, it holds certain limitations with regard to its application and formulation. The capacity to swallow is required and oral forms can be inappropriate in emergencies as they usually have slow onsets of action. Additional requirements for oral formulation also require the therapeutic agent to be chemically stable, enzymatically stable, and resistant to the environment of the gut with proper dissolution, permeability, and solubility characteristics.[6, 7] In a clinical setting Intravenous (IV) administration of antibiotics is preferred for serious infections. However, switch therapy (short IV therapy of 2-3 days followed by oral treatment for the remainder) has become feasible with the development of antibiotics with sufficient bioavailability.[8] When applicable, switching to oral antibiotics can reduce hospital stay; reduce nursing costs, save time and additional costs for the preparation, dispensing, application, and administration of IV routes in addition to decreasing morbidity and mortality associated with IV line infections.[8, 9]

### CARBAPENEMS FOR THE TREATMENT OF INFECTION

Carbapenems have a broad spectrum of activity against most bacterial strains of many species, are regarded as safe, are generally well-tolerated, and are often the last line of defense against resistant organisms. Imipenem and meropenem are mainly used to treat severe infections. Their efficacy is dose-dependent with higher doses often necessary for enough coverage of multi-resistant pathogens during empirical treatment.[10] However, carbapenems are orally inactive and are currently administered exclusively by injection. Barriers to oral absorption include poor lipophilicity to cross intestinal epithelium, the presence of an efflux pump on the surface of enterocytes, and poor stability in low pH as observed in gastric conditions.[11]

### What are carbapenems?

Carbapenems are Broad-spectrum beta-lactam antibiotic stable against most beta-lactamases and active against many gram-negative, gram-positive, and anaerobic bacteria. Their mechanism of action involves entering gram-negative bacteria through outer membrane proteins known as porins and acylating the penicillin-binding proteins, which are involved in bacterial cell wall synthesis. [12]



**How cost-effective are carbapenems**

A recent systematic review on the clinical cost-effectiveness of carbapenem sparing beta-lactams also showed that Meropenem remains more cost-effective in the hospital setting compared to carbapenem sparing beta-lactam options Ceftolozane-tazobactam, Ceftazidime-avibactam, and Temocillin for UTI(urinary tract infection) and IAI(intra-abdominal infection) caused by ESBL bacteria. [13]

**How safe are carbapenems?**

The Australian Medicines Handbook (AMH) lists more common side effects (>1%) of carbapenems include nausea, vomiting, and headache. Less common (<1%) side effects of carbapenem include Clostridium difficile-associated disease, cutaneous adverse reactions, eosinophilia, and systemic symptoms and seizures. With rare side effects (<0.1%) being anaphylaxis.[14] Liang, Emily H et al. reported an incidence of; 0 anaphylaxis, 0.002% serious cutaneous adverse reactions, 0.022% Drug eruption with Eosinophilia and systemic symptoms, 0.11% Nephropathy, and 10.1% Clostridium difficile associated disease out of 21 716 individuals with 40 162 total courses of carbapenems.[15] Michele Bartoletti et al reported a 3% incidence of Clostridium difficile associated disease in 168 patients treated with a meropenem-based regimen.[16] Therefore the risk of Clostridium difficile-associated disease may be higher than reported in the AMH. But this is debatable as many patients would likely have been treated with other antibiotics before receiving carbapenems. [17]

The risk of Seizure is thought to be related to Beta Lactams binding to 7-aminobutyric acid (GABA) receptors. Seizure risk is reported to range from 3-33% for imipenem-cilastatin and less than 1% for meropenem, doripenem, and ertapenem.[18] However, the risk of seizure is highly associated with inadequate dose adjustment in renal dysfunction. If adequate precaution is taken, the rate of seizure is <1%. [19]

Cross-sensitivity with penicillins is also an issue. The first prospective study of cross-reactivity reported a sensitivity of 47.4% between imipenem and penicillin allergy. Hence cross-reactivity was initially reported as 50%. However, this study was limited by small sample size, the use of a non-standardized imipenem skin test, and the fact that imipenem was not administered. When studies that verified penicillin allergy by acceptable standards and tested for carbapenem allergy with full therapeutic dose to carbapenem skin test-negative patients are examined, the cross-reactivity between skin tests appears to be around 1%. [20]

**How effective are carbapenems compared to other antibiotics?**

Carbapenems boast the broadest spectrum and potency against gram-negative bacteria among beta-lactam antibiotics. They are stable against hydrolysis by most B-lactamases and remain the gold standard treatment in critically ill patients for ESBL producing Enterobacteriaceae besides E.coli. [21] Alternatives to carbapenems include cefepime, aminoglycosides, fosfomycin, temocillin, piperacillin-tazobactam, ceftazidime-avibactam, and ceftolozane-tazobactam. [13, 21] Treatment success rate for meropenem is reported at 85% while temocillin, piperacillin-tazobactam, ceftazidime-avibactam, and ceftolozane-tazobactam was reported at 93%, 88%, 88%, and 94% respectively. It was noted, however, that carbapenems remain the most cost-effective treatment.[13] Cefepime has been noted to be inferior to meropenem and other alternatives due to high mortality. Fosfomycin is effective for the treatment of both ESBL-producing *K.pneumoniae* and *E.coli* with its susceptibility ranging from 15% to 100% and 81% to 100% respectively. However, accurate dosing is difficult when fosfomycin’s volume of distribution increases in critically ill patients. Aminoglycosides can be given in combination for ESBL infections but monotherapy is not recommended [21].

**Table 1:** Physiochemical properties of carbapenems

Drug	Molecular weight	Log P-value	Hydrogen bond donor	Hydrogen bond acceptor	Rotatable bond count	Mass
Imipenem[22]	299.35g/mol	-0.7	3	6	6	299.09g/mol
Meropenem[23]	383.5g/mol	-2.4	3	7	5	383.15g/mol
Ertapenem[24]	475.5g/mol	-1.5	5	9	7	475.14g/mol
Tebipenem pivoxil[25]	497.6g/mol	2.3	1	9	10	497.17g/mol
Biapenem[26]	350.4g/mol	1.4	1	6	3	350.10g/mol
Panipenem[27]	339.4g/mol	0	3	6	5	339.13g/mol
Doripenem[28]	420.5g/mol	-3.4	5	10	7	420.11g/mol



## Physiological barriers to carbapenem drug delivery

Possible physiological barriers to oral carbapenem drug delivery include diffusion across the intestinal epithelium, the presence of an efflux system, and the low gastric pH and in an aqueous solution. Most carbapenems have poor membrane permeability due to their hydrophilic properties. It was also noted that the secretion of meropenem was 5 times greater than absorption in rat ileal segments in the presence of active transport. Secretion was noted to be energy-dependent and may be facilitated by a similar pathway as other beta-lactam antibiotics such as cefazolin, cefoperazone, and cefloridine. However, more research will be required to confirm this theory. At body temperatures (37 °C) Meropenem was stable in pH 6.8 with only 10% degraded after 6 hours but was highly unstable in pH 1.2 with 80% degraded by 30 mins with less than 5% remaining after 1 hour. However, it was noted that meropenem was stable towards gastric enzymes. [11]

## Currently available carbapenems formulations

Besides tebipenem, all carbapenems are orally inactive and administered by injection. Imipenem is administered as a 20 to 60 min intravenous infusion. After reconstitution, 10% of imipenem degrades after 3.5 hours and 30% at 24 hours at room temperature. This limits its use as an extended (3-4 hours) infusion. Imipenem is also given with Cilastatin, a dehydropeptidase 1 (DHP-1) inhibitor, as it is rapidly inactivated by renal DHP-1. [29, 30] Meropenem is administered as a 15 to 30 min intravenous infusion. After reconstitution, 10% of meropenem degrades after 5.25 hours and 22% degrades after 24 hours at room temperature. However, degradation can be prevented by maintaining the reconstituted solution at 4 degrees Celsius. This limits its use as an extended infusion. Ertapenem is administered as a 30 min intravenous infusion. After reconstitution, it is stable for about 6 hours at room temperature. Ertapenem displays high protein binding and half-life allowing for once-daily dosing. [30] Doripenem is administered as a 1 hour intravenous infusion. After reconstitution, it is stable for about 12 hours at room temperature. However, it carries a higher mortality risk and a lower treatment success as compared to imipenem-cilastatin. [30-32]

## TRENDS IN ORAL DELIVERY OF CARBAPENEMS

### Prodrug

Prodrugs are inactive conjugates that go through chemical transformation in-vivo to release active medication. By adding a cleavable moiety, the prodrug strategy can and have been employed to overcome poor Pharmacokinetic properties of compounds without affecting their activity or binding at their target sites. Depending on the active compound, the cleavable moiety is usually added to increase hydrophilicity or lipophilicity. [33] There are currently no oral carbapenems approved for use in adults. Tebipenem pivoxil is the only oral pro-drug carbapenem and is only available in Japan for pediatric otitis media, sinusitis, and pneumonia in children. An adult formulation currently in development for complicated urinary tract infection. Hydrophilic properties of many beta-lactams result in poor membrane permeability and hence, oral bioavailability. The chemical introduction of a lipophilic group, tebipenem's pivoxil ester at the 3-position, improves oral bioavailability by improving its lipophilicity. However, tebipenem pivoxil has had higher intestinal absorption compared to other similar prodrugs (80% vs <50%). [34, 35] It is suggested that carrier-mediated transport is also involved in the oral absorption of tebipenem pivoxil. Simple diffusion could not account for tebipenem's absorption, as it exists mainly as a cation at its main site of absorption, the small intestine. Additionally, its absorption was energy-dependent, decreased in the absence of ATP, and decreased temperature. It was noted that OATP1A2 and OATP2B1 transporters were involved in the influx transport of Tebipenem Pivoxil prodrug and not Tebipenem. With OATP2B1 more likely to contribute more to the absorption of Tebipenem Pivoxil. [35] Additionally, tebipenem is more stable to DHP-1 compared to meropenem and does not need to be administered with cilastatin as compared to imipenem. Sulopenem is another carbapenem prodrug currently in development but it is still currently in phase 2 clinical studies. [34]

### Nanoparticle-based

Nanoparticle-based drug formulations have the benefit of increasing bioavailability, providing controlled release, shielding medicines from unwanted enzymatic degradation [36], decreasing toxicity, decreasing side effects, improving biodistribution, and extending a drug's lifecycle as nanoparticles allow properties such as solubility, drug release profiles, diffusible, bioavailability and immunogenicity to be modified. [37] It has been noted that nanoparticles can be used to overcome delivery challenges such as degradation from the gastric environment and poor membrane permeability. Nanoparticles can be used for the development of new drug delivery systems for existing drugs. [36, 38] With the choice of nanoparticle depending on the physicochemical properties of the drug. [37] Examples of nanoparticle delivery systems used for in-vivo treatment include; Liposomal-based systems, chitosan,



alginate, Xanthan gum, cellulose, polymeric micelles, Dendrimers, inorganic nanoparticles, metallic nanoparticles, nanocrystals, quantum dots, protein, and polysaccharide nanoparticles. (Table 2) The use of nanoparticles as delivery mediums has been explored for carbapenems. However, the focus of the studies was to use nanoparticles to overcome carbapenem resistance. [39, 40]

## CONCLUSION

Despite increasing carbapenem resistance and the availability of alternative antibiotics, carbapenems remain an important broad-spectrum antibiotic for the treatment of serious infection. Currently approved formulations hold limitations such as a lack of oral bioavailability, the need for DHP-1 inhibitors, and poor stability once reconstituted as IV preparations. Prodrug approaches to carbapenem are an effective approach as shown by the success of Tebipenem Pivoxil. However, Tebipenem Pivoxil has yet to be approved for use in adults and is currently only approved in Japan. There is a lack of research for the use of nanoparticle delivery for oral delivery of carbapenems. Research in this field will allow the carbapenems currently available to overcome the limitations of their physicochemical properties.

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