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PRACTICE

THERAPEUTICS

Carbapenem antibiotics for serious infections

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Philip Routledge, professor of clinical pharmacology, Cardiff University. To suggest a topic for this series, please email us at practice@bmj.com

An 81 year old woman with a long term, indwelling urinary catheter is admitted with fever and hypotension thought to be due to septicaemia secondary to urinary tract infection. She is treated empirically with intravenous cefotaxime and gentamicin, but her condition deteriorates over 24 hours, with increasing hypotension and continuing fever. For broader spectrum coverage, her empirical antibiotic treatment is changed to intravenous meropenem. The next day, urine and blood cultures grow an *Escherichia coli* producing an extended spectrum β lactamase (ESBL), conferring resistance to cefotaxime and gentamicin but not to meropenem. The meropenem is continued for seven days, with clinical and bacteriological resolution of the patient's infection.

What are carbapenems?

Carbapenems are β lactam antibiotics, as are penicillins and cephalosporins, but differ from these other classes in their exact chemical structure. Carbapenem use has increased as a result of the rising resistance to cephalosporin antibiotics in Enterobacteriaceae (*Escherichia coli*, *Klebsiella*, *Enterobacter*, and related genera). This cephalosporin resistance is largely due to the spread of extended spectrum β lactamases (ESBLs), which hydrolyse cephalosporins.[1] ESBL producers are associated with poor clinical outcomes in severe infections: a meta-analysis found that bacteraemias caused by bacteria with these enzymes had 1.85-fold increased mortality (95% confidence interval 1.39 to 2.47, P<0.001), reflecting extended delays before effective therapy was initiated.[2] ESBLs now occur in 10–12% of *E coli* from bacteraemias in the UK[3] and in 50–80% of those in India and China, with many ESBL producing strains also resistant to quinolones and aminoglycosides.[4]

Carbapenems are the sole β lactam antibiotics with proven efficacy in severe infections due to ESBL producing bacteria: most Enterobacteriaceae strains with ESBLs in the UK are resistant to the β lactamase inhibitor combinations of amoxicillin-clavulanate and piperacillin-tazobactam—not because the ESBLs evade inhibition but because ESBL producers often also have secondary, inhibitor resistant "OXA" β lactamases. Fifth generation cephalosporins (such as ceftaroline) are no more stable than earlier analogues to ESBLs and so are not an alternative to carbapenems in this context.

Four carbapenems are available in the UK (table 1⇓). However, ESBL proliferation and the consequent increase in carbapenem use in turn selects for carbapenem resistance, and, although slow to emerge in Enterobacteriaceae, this is now accumulating via the spread of carbapenem-destroying β lactamases ("carbapenemases").[6] Bacteria with these enzymes often are exceptionally resistant,[7] leaving few treatment options.

The growing need to use carbapenems, increasing carbapenem resistance, and a lack of good reserve agents beyond carbapenems means that a delicate balance must be struck between providing optimal therapy to patients who may die if they do not receive a carbapenem and avoiding profligate carbapenem use with its consequences for future patients.

How well do carbapenems work?

Target bacteria

Carbapenems have a penicillin-like mechanism, inhibiting cell wall synthesis. They are active against most pathogens, but some resistance is emerging.

Enterobacteriaceae—Risk factors for ESBLs should guide carbapenem use, along with laboratory testing of susceptibility, particularly for seriously ill patients. The rising prevalence of

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carbapenemases means that universal susceptibility can no longer be assumed: acquired carbapenemases of types KPC, OXA-48, VIM, and NDM occur in <1% of UK Enterobacteriaceae (that is, they are 10-fold less prevalent than ESBLs), but NDM carbapenemase is seen in 2–8% of Enterobacteriaceae in India,[8] and KPC or VIM carbapenemases occur in about 40% of *Klebsiella pneumoniae* from bacteraemias in Greece.[9] Despite their overall rarity in the UK, local clusters of carbapenemase producers, mostly *K pneumoniae* with VIM or KPC enzymes, are emerging, while strains with NDM enzyme are repeatedly imported from the Indian subcontinent.[10]

Pseudomonas aeruginosa—Imipenem, meropenem, and doripenem are inherently active against *P aeruginosa*, but resistance can arise via bacterial mutations affecting uptake or (except imipenem) efflux. Such mutants are sometimes selected during treatment, particularly with imipenem.[11] Ertapenem is not active against *P aeruginosa.*

Acinetobacter spp—Imipenem, meropenem, and doripenem were active, but resistance is now widespread because of hospital to hospital spread of clones with OXA carbapenemases.[12] Ertapenem is not active.

Stenotrophomonas maltophilia—This species is resistant to all carbapenems because of endogenous carbapenemase production.

Gram positive pathogens—Carbapenems are active against most Gram positive bacteria, except MRSA and ampicillin resistant (most) *Enterococcus faecium*; resistance is due to insensitive targets not carbapenemases.

Anaerobic bacteria—Carbapenems are active against clinically important anaerobic bacteria and, unlike cephalosporins, do not need combination with metronidazole in intra-abdominal infections.

Individual carbapenems

The properties, doses, and indications of individual carbapenems are listed in table 1⇓.

Imipenem-cilastatin and meropenem—These carbapenems have a similar spectrum of activity, with meropenem having slightly superior in vitro activity against *P aeruginosa* and Enterobacteriaceae, whereas imipenem is slightly more active against enterococci, *Acinetobacter*, and some staphylococci. Use of imipenem-cilastatin has declined, and meropenem is now the most prescribed analogue in the UK. Both have similar indications (table 1⇓). A meta-analysis of 27 randomised controlled trials directly comparing imipenem-cilastatin with meropenem found meropenem to be narrowly superior in both clinical and bacteriological outcomes.[13] The clinical response rates (complete remission or improvement in signs and symptoms of sepsis) for meropenem and imipenem were 91.4% (1660/1817 patients) and 87.2% (1731/1985) (z=3.18, P=0.001), whereas bacteriological response rates (eradication or presumed eradication of all pathogens) were 85.1% (963/1131) and 82.8% (929/1122) (z=2.67, P=0.008) respectively. There was no significant difference in mortality in the nine trials reporting data (7.4% for meropenem, 9.7% for imipenem, z=0.11, P=0.91). There was no evidence of heterogeneity or publication bias, and analyses were robust to changes in inclusion and exclusion criteria and use of a random effects model. Meropenem is favoured in infections of the central nervous system because of its lower proconvulsive activity, and was found to be more effective and safer than imipenem-cilastatin in the treatment of brain abscesses.[14]

Doripenem—This recently launched analogue has similar activity to meropenem. It is twice as active in vitro against *P aeruginosa*,[15] but whether this translates into clinical efficacy is debatable. Phase III clinical trials found doripenem was slightly less likely than imipenem to select for resistance in *P aeruginosa* pneumonia,[11] but a recent phase IV trial comparing doripenem with imipenem-cilastatin in ventilator associated pneumonia was stopped because of excess deaths in the doripenem arm (21.5% at 28 days *v* 14.8%; www.medscape.com/viewarticle/756530). Direct clinical comparison with meropenem is lacking.

Ertapenem—This analogue has a narrower spectrum and is not active against *Pseudomonas* spp or *Acinetobacter* spp. It has once daily dosing, and some authors consider it suitable for hospital-wide deployment as a "general purpose" antibiotic and for outpatient parenteral antibiotic therapy (OPAT). There is observational evidence that its general purpose use may not adversely affect the resistance ecology, and it was associated with less use of imipenem and meropenem and with less resistance to these drugs among *P aeruginosa*.[16 17] In our view, however, such wide deployment should be approached with caution because of the growing spread of carbapenemases. In most countries outside the EU, ertapenem is licensed for complicated urinary tract infections, and it is widely used off-label for these in the UK when ESBL producers are present or suspected.

Empirical and prophylactic use

Rising resistance to the cephalosporins and quinolones conventionally used to treat Gram negative sepsis is leading to growing empirical use of carbapenems in this setting. It is argued that such use should be followed by "de-escalation" to a narrower spectrum antibiotic once susceptibility results become available.[18] This approach seeks to reduce the excess mortality associated with ineffective empirical treatment of infections from ESBL producing Enterobacteriaceae[2] and to minimise unnecessary carbapenem use. However, enforcement can be difficult (i) when the patient is responding well and the physician is reluctant to abandon the carbapenem, or (ii) when no pathogen is isolated, leaving uncertainty about whether the carbapenem is warranted. A cohort study in California found that de-escalation was undertaken in only half the patients where it was possible.[19] However, it might be possible to facilitate de-escalation by means of microbiology or infectious disease review 48 hours after starting treatment.

Prophylactic use of carbapenems to reduce infection in severe necrotising pancreatitis has developed, but a large multicentre, randomised, double blind, placebo controlled study failed to support this use of meropenem.[20]

How safe are carbapenems?

As with other β lactam antibiotics, the most important adverse event is drug hypersensitivity (allergic reactions), particularly type 1 (IgE mediated) reactions manifesting as immediate anaphylaxis, angio-oedema, and urticaria The frequency of hypersensitivity to carbapenems in the general population is estimated to be less than 3%.[21]

The risk of cross reactivity between penicillin and carbapenem antibiotics was initially reported as high as 50%, perhaps because of the broad definition used for an allergic reaction (rash, wheezing, etc) rather than specific skin testing. In a recent systematic review of four prospective studies, patients allergic to penicillin were identified by skin testing and were then skin tested with a carbapenem.[22] The reported incidence of cross reactivity between penicillins and carbapenems was about 1%, prompting the authors to suggest reconsidering the current

avoidance of carbapenems in patients allergic to penicillin. This position is supported by a case series of 110 penicillin allergic patients, 51 with a history of anaphylaxis with penicillin, who were treated for one to four weeks with meropenem without a single episode of allergy.[23] The clinical benefits of using a carbapenem, one of the most potent broad spectrum antibiotics, should be balanced against the small risk of allergy, even in patients severely allergic to penicillin. The box outlines the precautions to take when prescribing carbapenems.

Other important adverse effects are dose related seizures, possibly from binding to γ-aminobutyric acid receptors.[25] Imipenem-cilastatin is generally accepted to have a higher seizure rate than later carbapenems, but comparisons are complicated by different drug regimens and patient mixes, with some clinicians avoiding high risk patients.[25] Thus, a seizure rate of 1.5% was reported in a large early study of imipenem that included many patients with neurological disorders. The overall seizure rate for meropenem (about 0.8%) seems to be lower, and it is the only carbapenem indicated for meningitis.[25] Ertapenem has a reported overall seizure rate of 0.5%,[25] and doripenem seems to lack proconvulsive activity.[26]

Cephalosporins and quinolones are strongly associated with *Clostridium difficile* infection. Carbapenems have been implicated too,[27] but analysis is complicated because many patients receiving these drugs have already received multiple other antibiotics. Prescribing for high risk patients (such as those with previous antibiotic use or elderly patients) should involve a careful weighing of potential benefit against risk.

Commonly encountered adverse effects with imipenem, meropenem, and ertapenem are nausea and vomiting (1.4–4.7%), diarrhoea (1.4–5.6%), thrombophlebitis (1.0–1.3%), and rash (1.1–1.4%).[5]

In an industry sponsored meta-analysis of all adverse events reported in 18 randomised controlled trials directly comparing imipenem-cilastatin and meropenem, meropenem had a slightly lower rate (25.4% (338/1332) *v* 29.3% (380/1297), z=2.40, P=0.02).[13]

What are the precautions?

The box summarises the precautions that prescribers should consider when treating patients with carbapenems.

How cost effective are carbapenems?

Cost effectiveness of antibiotics varies with rates of resistance in the target pathogens, which in turn vary with time and place. The high acquisition costs of carbapenems relative to other antibiotics may be mitigated if they prevent treatment failures with antibiotics to which the bacteria prove resistant. An industry sponsored, cost utility analysis of treatment of severe pneumonia in UK critical care units with either piperacillin-tazobactam or meropenem showed that their costs of treatment were £19 978 and £19 026 respectively, with quality adjusted life years (QALYs) gained of 4.768 and 4.654 respectively.[28] Meropenem costs have fallen recently with the introduction of non-proprietary product.

How are carbapenems taken and monitored?

All carbapenems except tebipenem (an oral drug approved only in Japan) are administered parenterally. Standard regimens are included in table 1⇓. Some hospitals have changed the 1 g three times daily regimen of meropenem to 0.5 g four times daily, decreasing use and acquisition cost by a third. A qualitative systematic review concluded that both regimens were pharmacodynamically equivalent,[29] but that there was little clinical evidence to support the off-label regimen; moreover, the relative instability of stored meropenem poses a substantial risk.[30]

To gain best efficacy despite a modest dose (0.5 g three times daily), doripenem can be given as a prolonged (four hour) infusion; three hour infusions have also been used off-label for meropenem, but are best avoided for imipenem, which is less stable in solution. Liver and renal function should be monitored while carbapenems are administered (box). Recommendations for dose modification in renal failure and renal replacement treatment differ for all four carbapenems, so consult the relevant data sheets for details.

How do carbapenems compare with other antibiotics?

Carbapenems have the broadest spectrum of all antibiotics and are the antibiotics with the best evidence for efficacy for infections due to ESBL producers. The alternative treatments for ESBL producers, which are also the only remaining antibiotics against many carbapenemase producers, all have important drawbacks (table 2⇓).

Future treatments for infections due to carbapenemase producers will probably involve (*a*) new β lactamase inhibitors (such as avibactam) combined with cephalosporins and (*b*) novel classes of antibiotics. However, the former do not overcome all carbapenemases, and the latter are only just entering phase II trials with success uncertain.

For the foreseeable future, good stewardship of carbapenems is critical, along with strict infection control to prevent the spread of the resistant strains, particularly those with carbapenemases that are beginning to circulate in the UK.[10]

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Precautions when prescribing carbapenems

Use

The selection of a carbapenem should take into account the severity of the infection, the local prevalence of resistance to other suitable agents, and the risk of selecting for resistance in the infecting bacteria and commensal flora. Because ertapenem lacks activity against *Pseudomonas* spp and other non-fermentative Gram negative bacilli, do not use it if those are likely pathogens

Susceptibility testing allows targeted use of carbapenems, and the stepping down from empirical carbapenem use. Excessive use will potentially select for resistance and may increase the probability of *Clostridium difficile* infection

Contraindications and cautions

Hypersensitivity—Avoid carbapenems in patients with documented hypersensitivity to any carbapenem. Patients with a reported or documented type 1 penicillin hypersensitivity or a positive skin test to penicillin have about a 1% risk of cross reaction to carbapenems in skin tests. If a carbapenem is used, ensure appropriate treatment is available at the bedside when administering the first dose. Carbapenems should be used only for severe infections caused by multiresistant bacteria in patients at high risk of allergy as the possibility of a severe reaction, though small, is real

Central nervous system conditions—In patients with neurological conditions likely to precipitate seizures, carefully consider potential benefits against risks, especially with imipenem-cilastatin. Meropenem is recommended in meningitis if a carbapenem is required. Avoid carbapenems in patients with epilepsy if possible, and discontinue if seizures develop

C difficile infection—Avoid carbapenems in patients with a history of *C difficile* infection or at high risk of contracting it (such as those who are elderly, have repeated hospital admissions, or have previously used antibiotics) unless this risk is outweighed by the clinical benefit of a broad spectrum, highly active antibiotic

Hepatotoxicity—Monitor hepatic function during treatment: 1.5–4.3% of patients have abnormal results from liver function tests, and there is an associated rare risk of hepatic dysfunction, with cholestasis and cytolysis, particularly in patients with pre-existing liver disease

Moderate or severe renal impairment—Adjust doses in patients with moderate or severe renal impairment (creatine clearance ≤50 mL/min), as excretion of carbapenems is mainly renal. Details are given in the data sheet for each compound

Drug interactions

Warfarin—The Summary of Product Characteristics for carbapenems advises that the international normalised ratio (INR) of patients given carbapenems who are also taking warfarin may be elevated, but no specific cases of this phenomenon are reported in the literature

Valproic acid—Avoid coadministration of carbapenems as there are several reports that they may markedly reduce levels of valproic acid[24]

Tips for patients

- Carbapenems are powerful antibiotics that kill bacteria causing a range of diseases including pneumonia, urinary tract infections, serious skin infections, meningitis, and septicaemia (blood poisoning)
- They are given only for serious infections
- Carbapenems can only be given through an intravenous drip, which usually does not cause irritation at the injection site
- If you have a severe allergy to penicillin, you generally should not be given a carbapenem. However, many patients with a mild or moderate allergy can tolerate carbapenems. Your doctor will carefully assess whether any allergy risk outweighs the benefit you may gain from having a carbapenem
- Nausea, vomiting, and diarrhoea occur in some patients (1–5%) but normally are not severe. If your diarrhoea is profuse and frequent, inform your doctor as carbapenems occasionally precipitate infection with *Clostridium difficile*
- If you have epilepsy or other diseases of the brain you should tell your doctor
- If you are taking sodium valproate (an epilepsy medicine), tell your doctor as there is a small risk of convulsions with carbapenems

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Tables

Table 1| Carbapenems available in the UK

Spectrum of activity*	Dose†	Licensed indications (in European Union)
Imipenem		
Enterobacteriaceae *Pseudomonas* and *Acinetobacter*‡ Meticillin susceptible staphylococci *Enterococcus faecalis*‡ Streptococci Anaerobes, including *Bacteroides* spp	500 mg three times daily to 1 g four times daily§	Lower respiratory tract infections Intra-abdominal infections Genitourinary infections Gynaecological infections Septicaemia Bone and joint infections Skin and soft tissue infection
Meropenem		
Enterobacteriaceae‡ *Pseudomonas* and *Acinetobacter* Meticillin susceptible staphylococci *E faecalis*¶ Streptococci Anaerobes, including *Bacteroides* spp	500 mg to 2 g three times daily Use high dose for meningitis, cystic fibrosis, or against less susceptible pathogens	Community acquired and nosocomial pneumonia Bronchopulmonary infections in cystic fibrosis Complicated urinary tract infections Complicated intra-abdominal infections Intrapartum and postpartum infections Complicated skin and soft tissue infections Acute bacterial meningitis Neutropenic fevers suspected to be due to a bacterial infection.
Doripenem		
Enterobacteriaceae *Pseudomonas*‡ and *Acinetobacter* Meticillin susceptible staphylococci E faecalis Streptococci Anaerobes, including *Bacteroides* spp	500 mg three times daily can infused over 4 hours	Nosocomial pneumonia (including ventilator associated pneumonia)** Complicated intra-abdominal infections Complicated urinary tract infections
Ertapenem		
Enterobacteriaceae Meticillin susceptible staphylococci *E faecalis*¶ Streptococci Anaerobes, including *Bacteroides* spp	1 g once daily	Intra-abdominal infections Community acquired pneumonia Acute gynaecological infections Diabetic foot infections of the skin and soft tissue Prophylaxis of surgical site infection following elective colorectal surgery Licensed for complicated urinary tract infections outside the EU, widely used off-label for these within the EU

*Excludes strains with acquired resistance.

†All carbapenems are only available parenterally. Doses of all may be adjusted for renal impairment (see individual data sheets for guidance).

‡Most active carbapenem analogue against this bacterial group.

§The first commercial carbapenem, it is degraded by human dehydropeptidase (DHP-1) in the proximal renal tubules,[5] necessitating co-administration with the DHP-1 inhibitor cilastatin. Later carbapenems are less vulnerable to DHP-1 and don't require cilastatin.[5]

¶Marginal activity against this bacterial group.

**Recent failure in phase IV clinical trials in ventilator associated pneumonia described in text.

Table 2| Alternatives to carbapenems for treatment of infecting bacteria that produce extended spectrum β lactamases (ESBLs) and possible treatments for infections due to bacteria that produce carbapenemases

Evidence for potential use	Caveats
Polymyxins (such as colistin)	
Low minimum inhibitory concentration for most carbapenemase producers, including *Acinetobacter* and *Pseudomonas aeruginosa* Results from case series	Significant nephrotoxicity Poorer outcomes in pneumonia than in infection at other sites Lack activity against Proteeae and *Serratia* spp Polymyxin resistant *Klebsiella pneumoniae* with KPC carbapenemase circulating in Greece
Tigecycline	
Low minimum inhibitory concentration for many carbapenemase producers Results from case series	Marginal activity against *K pneumoniae* at EU breakpoints (drug concentrations defining border between susceptibility and resistance), not active against *P aeruginosa*, *Proteus* spp, and *Morganella* spp FDA and EMA warnings of excess mortality in clinical trials[31] Failed to show non-inferiority to imipenem in nosocomial pneumonia trials[29] Prone to induce nausea and vomiting
Fosfomycin	
Low minimum inhibitory concentration for many carbapenemase producing Enterobacteriaceae Results from case series	Not marketed in the UK; pharmacist must import Scanty data on efficacy of intravenous formulation in severe infection Risk of mutational resistance
Nitrofurantoin	
Active in vitro against many ESBL producing *Escherichia coli*	Suitable only for lower urinary infections Not reliably active against Enterobacteriaceae except *E coli* ; inactive against *P aeruginosa* and *Acinetobacter* spp Poorly tolerated by some patients
β Lactamase inhibitor combinations (such as piperacillin-tazobactam, amoxicillin-clavulanate)	
Active against some ESBL producers, depending on amount of enzyme and other coproduced β lactamases	Many ESBL producers resistant Nearly all carbapenemase producers resistant
Aminoglycosides, fluoroquinolones, co-trimoxazole	
None	Many ESBL producers resistant Nearly all carbapenemase producers resistant
Temocillin	
Stable to all ESBLs and AmpC type β lactamases, no activity against some carbapenemase producers; may be active against some strains with KPC carbapenemases	Only available parentally No activity against *Pseudomonas* or *Acinetobacter* spp
Fifth generation cephalosporins (such as ceftaroline)	
None	ESBL producers resistant Nearly all carbapenemase producers resistant

FDA=Food and Drug Administration. EMA=European Medicines Agency.