Journal of Antimicrobial Chemotherapy (2006) **58**, 916–929
doi:10.1093/jac/dkl354
Advance Access publication 22 September 2006

JAC

Two decades of imipenem therapy

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Imipenem, the first carbapenem discovered, was developed more than two decades ago in response to an unmet need for a highly potent, broad-spectrum antimicrobial agent with a strong safety profile. It has since been used to treat more than 26 million patients. In an era where antibiotic use has driven antibiotic resistance, choosing appropriate initial therapy for serious infection is critical. Appropriate antibiotic regimens must cover all likely pathogens, be administered promptly at the correct dosage and dosing interval, be well tolerated and prevent the emergence of resistance. While imipenem was initially reserved for use in intractable, serious infections, the benefits of early aggressive therapy are now known, making imipenem a core agent in de-escalation therapy due to proven efficacy and safety for indications such as nosocomial pneumonia, intra-abdominal infection, sepsis and febrile neutropenia. De-escalation therapy with an agent such as imipenem minimizes resistance development by initiating aggressive initial treatment and then tailoring therapy based on patient response and culture results, switching to a less expensive, narrower spectrum antibiotic regimen or shortening the duration of therapy. Imipenem has maintained sustained clinical efficacy, tolerability and *in vitro* activity against important bacterial pathogens for two decades. We review the factors that continue to make imipenem as appropriate an agent for de-escalation therapy now as it was 20 years ago.

Keywords: antibiotics, appropriate therapy, carbapenems, de-escalation, infections, pneumonia

Introduction

β-Lactams were among the first antimicrobial agents available for the therapy of infectious diseases. Over time, however, problems such as resistance development and selection of resistant organisms have become apparent. The medical need for compounds with broad-spectrum activity, rapid bactericidal action, limited resistance-promoting properties and good tolerability has been met with carbapenem compounds. Imipenem was the first carbapenem antibiotic selected for development more than two decades ago because it was a highly potent, broad-spectrum antimicrobial agent with a good safety profile.[1,2] Since that time more than 26 million patients have been treated with imipenem (data on file, Merck & Co., Inc.), and imipenem continues to play an important role in the empirical and as well as the targeted treatment of severe and difficult to treat infections. This review will summarize important features of imipenem, discuss the accumulated treatment experience that has been established over 20 years of therapy with imipenem, and discuss its place in targeted and de-escalation therapy.

Chemical properties

Imipenem (*N*-formimidoyl-thienamycin) is an amidine derivative of thienamycin that is 5–10 times more stable than the mother compound (Figure 1). Deliberate substitution of a methyl moiety in place of a sulphur was introduced to increase bactericidal activity and β-lactamase stability in the hydroxyethyl side chain. Imipenem is rapidly degraded by kidney dehydropeptidase-1, thus it was combined with cilastatin, an inhibitor of this enzyme. Cilastatin not only prevents the degradation of imipenem but also protects the kidneys against potential toxic effects exerted by higher doses of imipenem. Imipenem and cilastatin are combined in a 1:1 ratio. Because cilastatin has no antibacterial activity of its own, only the amount of imipenem is given for dosing purposes.

Mechanism of action

Like all other β-lactams, imipenem inhibits bacterial cell wall synthesis by binding to and inactivating relevant transpeptidases, known as penicillin binding proteins (PBPs). In *Escherichia coli*,

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imipenem inhibits the transpeptidase activities of PBPs-1A, -1B and -2, and the D-alanine carboxypeptidase activities of PBP-4 and PBP-5. It also causes strong inhibition of the transglycosylase activity of PBP-1A while it inhibits the transpeptidase activity of PBP-3 only weakly, which is consistent with the finding that it has low binding affinity to PBP-3 and does not inhibit septum formation by the cells.[3] This is in contrast to all other β-lactams, including other carbapenems that preferentially bind to PBP-1 and PBP-3. Consequently, imipenem induces sphere formation with subsequent cell rupture but not the filamentous growth of bacteria observed for other β-lactams. Therefore, imipenem therapy reduces the amount of lipopolysaccharide liberated during bacteriolysis.[4] This effect was shown to be clinically relevant in a study with patients suffering from Gram-negative urosepsis.[5] When compared with ceftazidime treatment, patients who received imipenem showed a faster defervescence, lower endotoxin levels and a tendency for faster normalization of cytokine levels.

The mode of action of imipenem allows for activity against Gram-positive and Gram-negative bacteria, cocci and bacilli, aerobes and anaerobes. Imipenem may have activity against *Mycobacteria* spp., but *Mycoplasma*, *Chlamydia*, *Legionella*, *Stenotrophomonas*, *Burkholderia*, *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus* (MRSA) are not within its antimicrobial spectrum.

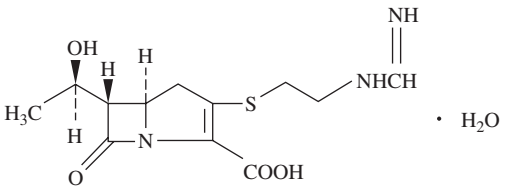

Figure 1. Imipenem (*N*-formimidoyl-thienamycin).

Mechanisms of resistance

Porins and efflux pumps

In order to reach their targets, carbapenems normally cross through protein channels in the outer membranes of Gram-negative bacteria called porins.[6] Porin OprD deficiencies can precipitate resistance to carbapenems. The OprD mutation, in conjunction with AmpC production, is responsible for imipenem resistance in *Pseudomonas aeruginosa*.[6,7] Porin defects in *Klebsiella* are also associated with carbapenem resistance.[8,9] A recent study found ertapenem selected for OprD mutants of *P. aeruginosa*, albeit rarely.[10]

Efflux pumps are proteins that remove certain molecules from the bacterial cell (Figure 2). They play an integral role in the intrinsic and acquired resistance of *P. aeruginosa* to antibiotics.[11,12] Imipenem is not a substrate of such efflux pumps, although meropenem is.[12–14] The most prevalent efflux system, MexAB-OprM, has been found to cause resistance to meropenem, but not imipenem, *in vitro*.[6,12–15] Overexpression of this system may emerge during antibiotic therapy and may result in treatment failure.[13,16] The MexAB-OprM system induces parallel-resistance to other antimicrobials such as fluoroquinolones, penicillins, cephalosporins, macrolides and sulphonamides.[6,13,14,17] This means that up-regulated efflux can quickly render fluoroquinolones and the majority of β-lactams ineffective against *Pseudomonas*, leaving the activity of imipenem and aminoglycosides unaffected.

Extended-spectrum β-lactamases

The most prevalent resistance mechanism against β-lactams is the production of β-lactamases. While many β-lactamases are not capable of hydrolysing cephalosporins, the so called extended-spectrum β-lactamases (ESBLs) have this ability with varying

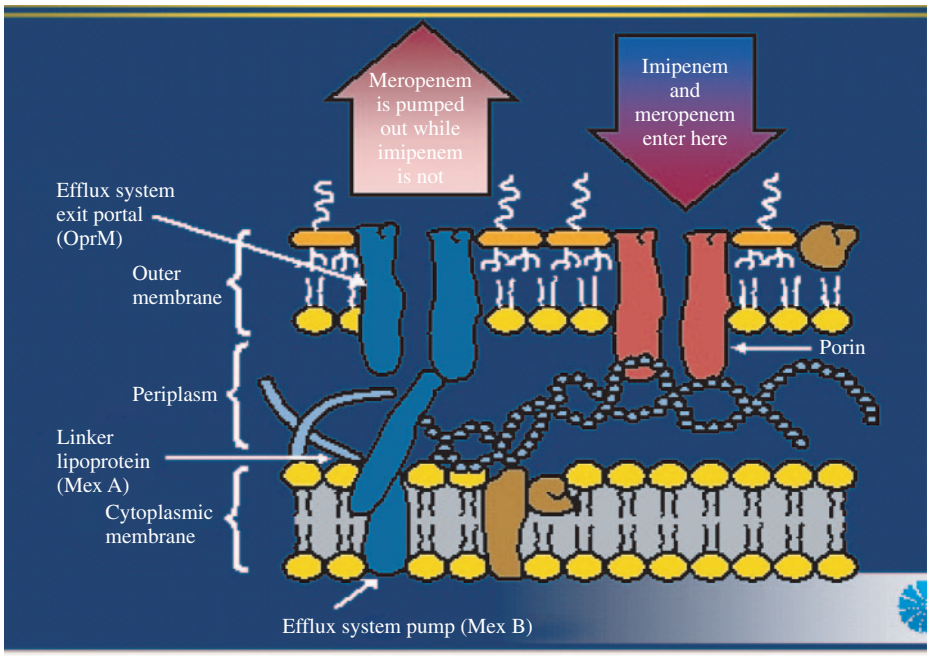

Figure 2. Mechanisms of resistance in *Pseudomonas*. Up-regulation of efflux pumps affects fluoroquinolones, penicillins, cephalosporins and meropenem, but does not affect imipenem.[6] Reproduced with permission from the University of Chicago Press.

specificity for individual cephalosporins.[18] Commonly found in *Klebsiella pneumoniae*, *E. coli* and other Enterobacteriaceae, ESBLs are plasmid-mediated and thus easily transferable. Some of the *in vitro* resistance to piperacillin/tazobactam among enteric pathogens may also be explained by the production of ESBL.[19] Carbapenems are not affected by ESBLs and are the agents of choice in these cases.[18,20–22] Chromosomally encoded type-1 β-lactamases such as AmpC are produced by *Enterobacter cloacae*, for example. Cephalosporins may be hydrolysed by AmpC while carbapenems retain activity.[23–25] Piperacillin/tazobactam appears to have limited *in vitro* activity against *Enterobacter* AmpC β-lactamases.[26]

Carbapenemases

Among the β-lactamases, metalloenzymes are distinguished by having a zinc ion required for enzymic activity.[27] Sometimes referred to as carbapenemases, they are able to hydrolyse many β-lactam antibiotics including carbapenems. Two types, IMP and VIM, have been identified, with IMP primarily isolated from the important pathogenic anaerobe *Bacteroides fragilis*[28–31] and VIM from isolates of *Pseudomonas* and Enterobacteriaceae.[32,33] The *cfiA* gene appears to be responsible for metallo-β-lactamase production in imipenem-resistant strains, and its presence is a better marker than metalloenzyme activity, which may not be expressed when the gene is silent.[30,34,35] Data do not point to plasmid-mediated transfer or spontaneous mutations causing resistance acquisition, although parallel-resistance arising from use of other classes of antibiotics such as quinolones may be an issue.[30,36,37] Although few clinically relevant *Bacteroides* have been reported that either produce metalloenzymes or contain the *cfiA* gene, this is clearly an area of research activity affecting all β-lactam antibiotics.[29,34] Target modifications such as those caused by and encoded for by the *mecA* gene in MRSA confer resistance to all β-lactams including the carbapenems.[38,39] Otherwise imipenem remains active against staphylococci.

The class A carbapenemases (e.g. KPC-1, KPC-2, KPC-3) have also proven to be clinically important. In a study in 10 hospitals in Brooklyn, NY, all 96 *Klebsiella* with KPC carbapenemases were carbapenem-resistant, with only a few of them retaining susceptibility to cephalosporins or fluoroquinolones.[40] Up to this time, strains producing KPC have primarily been reported in facilities in the United States.[41–43]

Resistance and infection control

It has been argued that the broad use of carbapenems results in rapid resistance development particularly in *P. aeruginosa* and *Acinetobacter* spp. and thus should be avoided.[44,45] However, these reports often have limitations such as lack of appropriate usage data (i.e. DDD per patient days), neglect of dosing issues, and lack of distinction between resistance development under therapy and spread of a resistant clone. Resistance due to clonal epidemiology is a public health issue that is best addressed by infection control measures. For example, an *in vitro* 1999 survey of 1599 clinical isolates of *A. baumannii* from 15 hospitals in Brooklyn, NY, USA found that more than 50% of these isolates were resistant to the carbapenems imipenem and meropenem.[46] A single strain, *Acinetobacter* Type 1, accounted for 62% of all resistant isolates, and this strain was found in all 15 hospitals. Four strains accounted for 97% of all *Acinetobacter* isolates. It was concluded that the rate of carbapenem resistance correlated with the use of cephalosporins and aztreonam, suggesting the potential for parallel-resistance. The fact that a single clone accounted for the majority of a total of 419 unique patient isolates points to the rampant spread of that clone among the hospitals in the study and the need for infection control rather than antibiotic restriction.

An outbreak of KPC class A carbapenemase-positive *Klebsiella* was reported in Brooklyn, NY.[40] All 96 isolates were carbapenem-resistant, and most were resistant to cephalosporins and fluoroquinolones. A citywide surveillance study reported rapid spread of this type of carbapenem resistance and parallel-resistance with other antibiotics, pointing to an immediate need for enhanced infection control measures.[47]

Finally, it has been argued that imipenem selects *Stenotrophomonas maltophilia*.[48] Other studies and our own experience do not support this notion.[49,50]

Susceptibility surveys

The potential for resistance has become as important a therapeutic consideration as efficacy or tolerability. It is a local problem with global implications. While resistance patterns must be determined at an institutional level to devise effective treatment strategies,[51] there is a consistent trend towards increasing resistance and novel mechanisms of resistance. Worldwide surveys are helpful in assessing general aspects of resistance development and in anticipating future medical needs. Generally speaking, phenotypic tests that determine MIC values are being used for this purpose. In order to compare different studies and the impact of methodology it is necessary to see the original MIC distributions, because wild-type strains of individual species should cluster at specific MIC values regardless of the source of the isolate. Furthermore, breakpoints are set differently in various parts of the world, so that the same MIC could result in different S-I-R classifications. As an example of these differences Table 1 shows the current breakpoints for carbapenems as put forward by the CLSI and the EUCAST. Moreover, breakpoints may change over time as more information becomes available. It may then be difficult to judge trends in resistance development. Thus susceptibility data should be given, e.g. as shown in Figure 3 (a and b).

A number of worldwide studies have analysed the phenotypic susceptibility of imipenem and other antimicrobial agents over time. Of note is the SENTRY survey,[52] the Nosocomial Prevalence and Resistance Survey (NPRS, Merck & Co., Inc.; Table 2) and the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) study (Table 3 and Figure 4).[53]

The SENTRY surveillance programme found ESBL-producing *K. pneumoniae* to be a major problem in Latin America (45.4% resistant), the Western Pacific (24.6%) and Europe (22.6%), with the vast majority of these isolates resistant to ceftazidime, ceftriaxone and aztreonam, as is characteristic of most ESBLs.[54] Worldwide, 99–100% of these *Klebsiella* isolates were susceptible to imipenem, although susceptibility to other broad-spectrum agents was highly variable. For example, *K. pneumoniae* were susceptible to cefepime in Canada (94.4%) and the US (87.6%), but much less so in Europe (63.6%) and Latin America (49.6%). The situation is much the same with *Acinetobacter* and *Pseudomonas.* While 88.6–95.5% of *Acinetobacter* isolates from North America and Latin America were susceptible to imipenem,

Table 1. Breakpoints for carbapenems as published by CLSI and EUCAST in 2005

Antibacterial agent			General breakpoints			Species-specific breakpoints										
			MIC (mg/L)													
Group	compound	abbreviation	susceptible (S)	intermediate (I)	resistant (R)	Enterobacteriaceae	*Pseudomonas*	*Acinetobacter*	*Staphylococcus*	*Enterococcus*	*Streptococcus* A, B, C, G	*S. pneumoniae*	*H. influenzae* (*H. flu only for CLSI*) *M. catarrhalis*	*N. gonorrhoeae*	*N. meningitidis*	Anaerobes
CLSI	imipenem	IMP				4/16	4/16	4/16	4/16	none	none	0.12/1	4/4	none	none	4/16
CLSI	meropenem	MER				4/16	4/16	4/16	4/16	none	0.5/0.5	0.25/1	0.5/0.5	none	0.25/0.25	4/16
CLSI	ertapenem	ETP				2/8	none	none	2/8	none	1/1	1/4	0.5/0.5	none	none	4/16
EUCAST	imipenem	IMP	≤2	>2–≤8	>8	2/8	4/8	2/8		4/8	IE	2/2	2/2	IE	–	2/8
EUCAST	meropenem	MER	≤2	>2–≤8	>8	2/8	2/8	2/8		–	IE	2/2	2/2	IE	0.25/0.25	2/8
EUCAST	ertapenem		≤0.5	>0.5–≤1	>1	0.5/1	–	–		–	IE	0.5/0.5	0.5/0.5	IE	–	0.5/1

CLSI, Clinical and Laboratory Standards Institute (formerly NCCLS); EUCAST, European Committee on Antibiotic Susceptibility Testing; IE, insufficient evidence.

only 67–70% in North America and fewer than 30% in Latin America were susceptible to piperacillin/tazobactam, ceftazidime and ciprofloxacin.[55] Between 1997 and 1999, susceptibility of *P. aeruginosa* to imipenem went from 90% to 86.2% in the Asia-Pacific region, from 83% to 92% in Canada, from 77% to 74.3% in Latin America, from 88% to 80.9% in the US and from 89.3% to 71.6% in Europe.[55]

NPRS has supported more than 500 susceptibility studies in ~50 countries. Similar to worldwide SENTRY,[52] NPRS data show increasing worldwide cephalosporin resistance among *Enterobacter*, *Klebsiella* and *E. coli*, and sustained susceptibility to imipenem has been observed (Table 2).

MYSTIC data reported that 99.6% of all Enterobacteriaceae isolated between 1997 and 2003 from 130 centres in Europe, North America and Latin America remained susceptible to imipenem, compared with 85–86% that remained susceptible to ceftazidime or piperacillin/tazobactam (Figure 4).[56] These susceptibility patterns have been noted worldwide (Table 3).[57]

Dosing, pharmacokinetics and pharmacodynamics

Dosing

Imipenem dosing is well established in adults, children, patients with impaired renal function and geriatric patients. It should be noted that the often used 4× 500 mg and 3× 1 g dosing result in approximately the same time above the MIC ($t > \text{MIC}$).[58] Patients with creatinine clearance of ≤70 mL/min/1.73 m^2 and/or body weight <70 kg require dosage reductions. For paediatric patients ≥3 months of age, the recommended dose for non-CNS infections is 15–25 mg/kg/dose every 6 h.

Pharmacokinetics and pharmacodynamics

The pharmacokinetics and pharmacodynamics of imipenem are well established and will be reviewed only briefly. Intravenous infusion of imipenem over 20 min results in peak plasma levels of imipenem ranging from 14 to 24 mg/L (250 mg dose), 21 to 58 mg/L (500 mg dose) and 41 to 83 mg/L (1000 mg dose). At these doses, plasma levels of imipenem decline to <1 mg/L after 4–6 h. The plasma half-life is ~1 h. The median concentration of imipenem 1 h after dosing is 5.6 mg/kg in lung tissue, 11.1 mg/kg in endometrial tissue, 22 mg/L in pleural fluid, 2.6 mg/L in cerebrospinal fluid (2 h post-dose) and 16.4 mg/L in interstitial fluid.

Co-administration with probenecid extends the half-life and increases the serum concentration. Approximately 10–20% of imipenem binds to human serum proteins. 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 in patients. Imipenem is distributed extensively in tissues and fluids.[59,60]

Carbapenem efficacy depends on the dosing interval duration during which free drug concentration exceeds the MIC. $t > \text{MIC}$ is the best pharmacodynamic predictor of carbapenem efficacy, with optimal cell kill achieved when 40% of the dosing interval has drug concentrations higher than the MIC.[58,61] A recent study compared the pharmacokinetic profiles of imipenem (1 g, intravenous, 30 min infusion) and meropenem (1 g, intravenous, 30 min infusion) in 20 patients who were critically ill with

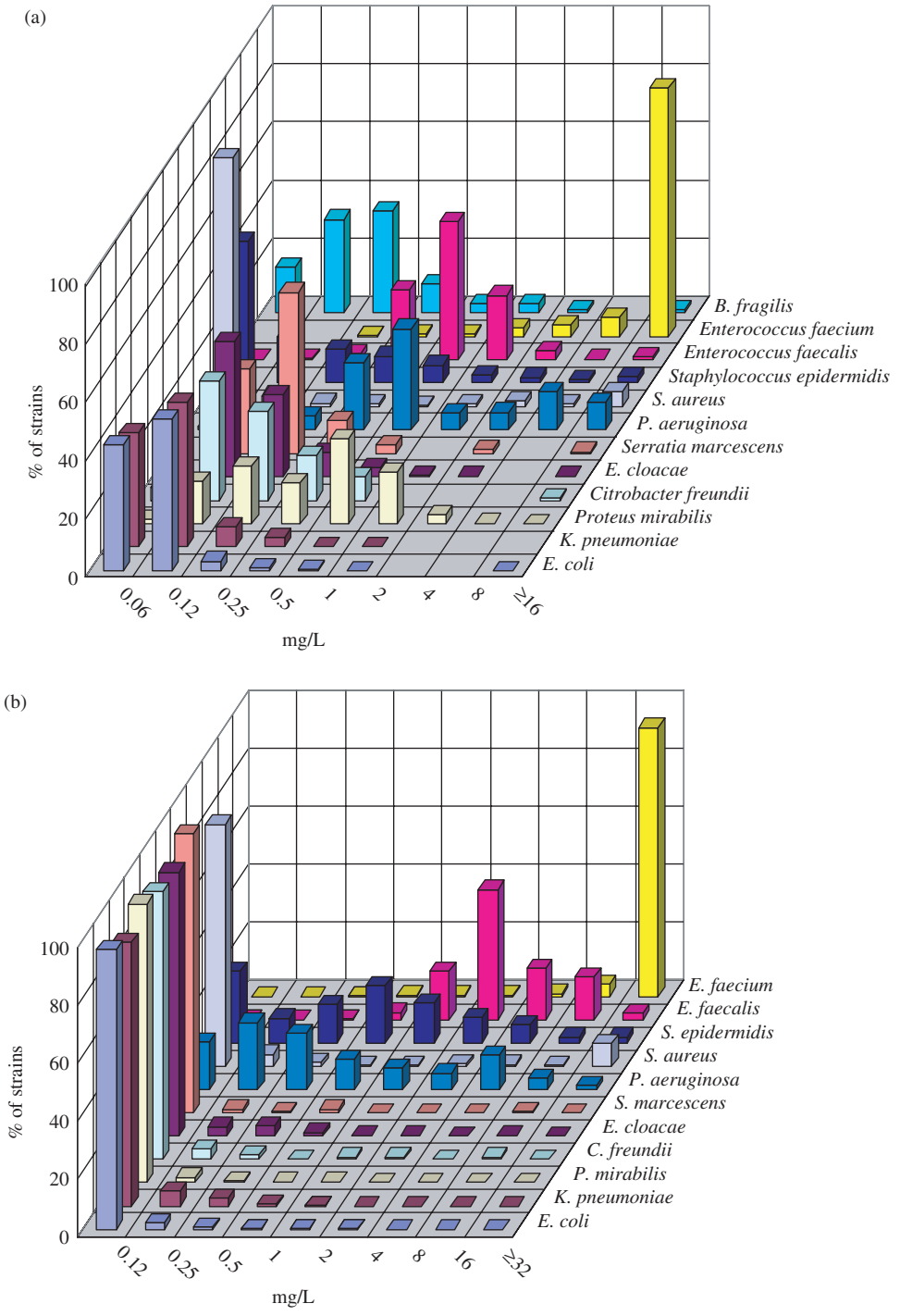

Figure 3. (a) MIC distributions of imipenem against various species. Strains used were clinical isolates obtained at the Institute for Medical Microbiology of the University of Leipzig in 2004. Copy strains were eliminated. The number of strains for individual species varies between $n = 2033$ (*S. aureus*) and $n = 103$ (*B. fragilis*). (b) MIC distributions of meropenem against various species. Strains used were the same clinical isolates as in (a); the tested concentrations were one dilution step higher.

sepsis.[62] Peak serum concentration (C_{max}) was significantly higher with imipenem than meropenem (90.1 ± 50.9 versus 46.6 ± 14.6 mg/L, $P < 0.01$) as was the area under the curve (216.5 ± 86.3 versus 99.5 ± 23.9 mg·h/L, $P < 0.01$). The mean volume of distribution and mean total plasma clearance were significantly higher with meropenem than imipenem (25 ± 4.1 versus 17.4 ± 4.5 L, $P < 0.01$ and 191 ± 52.2 versus 116.4 ± 42.3 mL/min, $P < 0.01$). The study estimated that imipenem would maintain $t >$ MIC for ~8 h after a single infusion, whereas meropenem would only maintain $t >$ MIC over this 8 h period for pathogens with an MIC ≤2 mg/L. The authors concluded that the two carbapenems were not dose equivalent in patients with sepsis,

Table 2. Worldwide Nosocomial Prevalence and Resistance Survey (NPRS) percentage susceptibility data[a] indicate that imipenem has remained consistently active against the most difficult to treat pathogens responsible for nosocomial infection (data on file, Merck & Co., Inc.)

	Percentage susceptibility to imipenem				
Country	*E. coli*	*P. aeruginosa*	*Klebsiella* spp.	*Enterobacter* spp.	*Acinetobacter* spp.
Argentina[b]	100 (n = 152)	65 (n = 194)	99 (n = 171)	99 (n = 104)	74 (n = 248)
Mexico[c]	96 (n = 92)	47 (n = 119)	97 (n = 46)	73 (n = 59)	71 (n = 41)
Peru[d]	92 (n = 77)	70 (n = 56)	82 (n = 39)	85 (n = 54)	48 (n = 27)
Cyprus[e]	98 (n = 175)	92 (n = 63)	97 (n = 105)	100 (n = 22)	93 (n = 15)
Germany[b]	100 (n = 147)	68 (n = 74)	100 (n = 90)	99 (n = 73)	100 (n = 24)
Sweden[d]	100 (n = 200)	81 (n = 91)	100 (n = 104)	99 (n = 69)	100 (n = 10)
Turkey[f]	99 (n = 109)	62 (n = 107)	100 (n = 94)	95 (n = 42)	66 (n = 104)
China[f]	100 (n = 399)	63 (n = 403)	99 (n = 389)	96 (n = 178)	94 (n = 339)
Russia[g]	100 (n = 308)	80 (n = 497)	100 (n = 313)	100 (n = 123)	95 (n = 106)
Korea[b]	100 (n = 75)	70 (n = 177)	98 (n = 137)	93 (n = 47)	91 (n = 143)
Philippines[d]	92 (n = 13)	75 (n = 22)	100 (n = 27)	80 (n = 71)	80 (n = 5)
Malaysia[f]	100 (n = 40)	78 (n = 110)	100 (n = 163)	100 (n = 40)	40 (n = 161)
Saudi Arabia[b]	98 (n = 93)	88 (n = 41)	93 (n = 47)	100 (n = 22)	100 (n = 14)
South Africa[b]	100 (n = 59)	65 (n = 88)	100 (n = 54)	99 (n = 76)	77 (n = 101)

[a]Each site evaluated 100 sequential isolates submitted during the care of ICU patients over a time span of 3 months. Studies were conducted using the Etest procedure. Results were reported for 'initial isolates', the first encountered sample of a given species from a specific patient. Results for repeated isolations were excluded to minimize bias. The breakpoints used were the 'fully susceptible' criteria of the NCCLS (M100-S9, 1999). In the specific case of imipenem, this breakpoint was 4 mg/L. In the case of *E. coli* and *Klebsiella* spp. the recommended criteria for ESBL were applied to ceftazidime and ceftriaxone. A ceftazidime/clavulanate Etest reagent was supplied for use in verification.
[b]2001.
[c]2002–2004.
[d]2002.
[e]2000.
[f]2003.
[g]1999.

with more research needed to clarify whether the more favourable pharmacokinetic profile of imipenem balances any greater *in vitro* potency of meropenem against Gram-negative pathogens.

A recent study simulated target attainment rates of imipenem and meropenem using the same dose of each drug (250, 500 and 1000 mg every 6 h and every 8 h) and 30 min infusions.[63] Imipenem achieved the pharmacodynamic goal more often than meropenem (58.3–99.2% for imipenem versus 46.9–99% for meropenem), although no statistically significant differences were noted. Studies have used 3 h infusions to optimize meropenem efficacy by increasing the t > MIC, while keeping the drug at room temperature for <4 h because drug potency decreases after this point.[64,65] A study examining a 3 h infusion of imipenem and meropenem at a variety of doses found no significant differences in ability to achieve the pharmacodynamic goal between imipenem and meropenem.[66]

Although these models suggest that imipenem and meropenem should have equal efficacy in a 3 h infusion, they may explain the higher dosing necessary for meropenem. If a 3 h infusion is necessary for meropenem to achieve the same efficacy as is possible with imipenem in a 1 h infusion, this would need to be taken into consideration. In other words, in order to be effective, it may be necessary to provide a higher dose of meropenem, or a longer infusion time. This was outlined in a literature review that suggested that administering meropenem 500 mg every 8 h infused over 30 min would have a much lower probability of attaining 40% t > MIC against *P. aeruginosa* (72.5%) than would 500 mg every 8 h infused over 3 h (87.9%) or 1000 mg every 8 h infused over 30 min (93.4%).[67] The pharmacokinetics of meropenem may need to be optimized to achieve the critical t > MIC.[61,67]

Indications and clinical studies

Imipenem is active against a broad spectrum of pathogens, making it particularly useful in the treatment of serious polymicrobial and mixed aerobic/anaerobic infections, as well as for initial empirical treatment. Guideline documents developed worldwide for serious infection recommend imipenem as effective initial targeted or empirical therapy in ventilator-associated pneumonia (VAP) hospital- and healthcare-acquired pneumonia (HAP and HCAP), intra-abdominal infection and febrile neutropenia. Imipenem is indicated for hospitalized patients with intra-abdominal, lower respiratory tract, gynaecological and genitourinary tract and skin and soft tissue infections, as well as for those with sepsis or endocarditis.[68,69] Extensive study has shown imipenem to be effective in these disease areas as well as in nosocomial and ventilator-associated pneumonia, febrile neutropenia and for the empirical treatment of serious infection.[70–84] Imipenem is also considered to be appropriate empirical therapy for serious infection when there is a high likelihood of infection with resistant organisms or multiple organisms that might otherwise require multidrug regimens.[85] In addition, using imipenem in preference to other antibiotics during the 5 day period after onset of bacteraemia due to an

ESBL-producing organism was independently associated with lower mortality in one study.[86] Imipenem has become a standard comparator in clinical studies for several indications.[76,87,88]

Efficacy in special situations

Mycobacterium spp.

There are multiple reports of imipenem efficacy against *Mycobacterium* spp. Three patients with *M. tuberculosis* infections recalcitrant to most standard antituberculosis agents had their infections cleared with imipenem and amikacin, with no recurrence in 12 months of follow-up.[89] However, an MIC of >100 mg/L for imipenem against *M. tuberculosis* strain H37Rv was described.[90]

A review of non-tuberculous mycobacteria listed imipenem as a parenteral drug of choice in the treatment of infections due to *Mycobacterium fortuitum*, *Mycobacterium chelonae*, *Mycobacterium smegmatis*, *M. chelonae*-like organism, *Mycobacterium peregrinum*, and sorbitol-positive and -negative biovariants of *M. fortuitum*.[91] Case reports have been published on the use of imipenem in the treatment of various infections due to *M. chelonae*, *M. fortuitum* and *Mycobacterium abscessus*.[92–98] While imipenem-containing regimens were successful in some of these cases, several involving *M. chelonae* showed little or no improvement during treatment that included imipenem. This may be due to variations in the *in vitro* activity of imipenem against different *Mycobacteria* isolates. One study reported that imipenem had good activity against three *M. fortuitum* biovariants but only slight activity against two *M. chelonae* subspecies.[99] A mouse model of disseminated *Mycobacterium avium* complex infections reported that ciprofloxacin in combination with amikacin and imipenem reduced both bacteraemia and mortality.[100]

Table 3. Imipenem has shown sustained susceptibility worldwide against *P. aeruginosa* and *Acinetobacter* spp. according to the MYSTIC programme[56,156]

Organism/ antimicrobial agent	Percentage susceptibility 1997–2000			Percentage susceptibility 2003—worldwide
	Europe	Americas	MEA	
Pseudomonas aeruginosa				
imipenem	68.5	76.4	58.1	84.6
ceftazidime	69.5	79.3	75.8	83.7
ciprofloxacin	74.6	67.5	19.8	68.7
piperacillin/tazobactam	82.1	85.9	88.7	90.3
meropenem	78.9	77.9	90.3	88.3
Acinetobacter spp.				
imipenem	80.6	64.6	62.7	91.9
ceftazidime	51.1	38.6	21.6	64
ciprofloxacin	46.8	45.8	16.7	58.6
piperacillin/tazobactam	42.4	41	54.9	61.3
meropenem	71.2	79.5	54.9	87.4

MEA, Middle East and Africa.
Breakpoints: imipenem and meropenem, 4 mg/L; piperacillin/tazobactam, 16 mg/L for *Acinetobacter* and 64 mg/L *Pseudomonas*; ciprofloxacin, 1 mg/L; ceftazidime, 8 mg/L.

Transplant patients

Enterobacteriaceae, including *E. coli, Klebsiella* spp. and *Enterobacter* spp., are common causes of intra-abdominal, respiratory tract and bloodstream infections in transplant patients. These organisms are in many parts of the world commonly cephalosporin-resistant, due to ESBLs and inducible group 1 cephalosporinases. Because of this, third-generation cephalosporins should generally be avoided for treatment of serious infections in transplant recipients.[101]

Nocardia infections, although infrequent among heart, lung or heart–lung transplant recipients, are of concern. In a retrospective review of 540 transplant patients, 10 were found to have *Nocardia* infection; all isolates were susceptible to imipenem, trimethoprim/sulfamethoxazole and amikacin.[102] A single-centre study found that 3 of 233 heart-transplant recipients had *Nocardia* infections.[103] The authors suggested that a β-lactam/β-lactamase inhibitor with ciprofloxacin or amikacin followed by a short course of trimethoprim/sulfamethoxazole could be effective. A retrospective survey of nocardiosis in 9 hospitals in Italy found 30 patients with documented nocardiosis from 1982 and 1992.[104] Most strains tested were susceptible to imipenem and amikacin. In a rare case of post-cardiac transplantation mediastinal infection due to *Nocardia*, surgical debridement, dressing, sugaring and imipenem with ciprofloxacin were used for 4 weeks followed by oral ciprofloxacin for 1 year. Treatment was successful and well tolerated.[105] In addition, multiple case reports have described successful treatment of HIV-infected patients with concurrent pulmonary or cerebral *Nocardia* infection.[106–111]

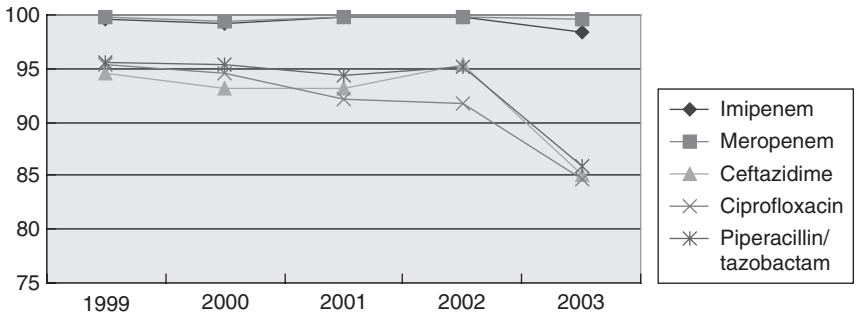

Figure 4. Imipenem showed sustained susceptibility against important Enterobacteriaceae across North America in the MYSTIC programme.[56,156] Four comparator antibiotics included in the MYSTIC study are shown.

Febrile neutropenia

The treatment of infectious complications in cancer patients has evolved as a consequence of the developments in the chemotherapy of cancer patients. An early non-comparative study of imipenem in 71 cancer patients with 79 febrile episodes reported a response rate of 67%.[112] A prospective, open label, randomized, multicentre study comparing cefepime and imipenem/cilastatin in patients with haematological malignancies and febrile neutropenia ($n = 180$) reported monotherapy success rates of 40% and 51% in the cefepime and imipenem groups, respectively (P = NS). The 4 week overall mortality rate was 5%.[87] Another study comparing imipenem and cefepime in the treatment of patients with cancer and febrile neutropenia found a 68% response rate to the imipenem regimen, compared with a 75% response rate to the cefepime regimen ($P = 0.2$).[77] Imipenem and ceftazidime plus tobramycin were found to have similar efficacy in cancer patients with febrile neutropenia, with successful outcomes in 78% (35 of 45) of the imipenem group patients and 71% (29 of 41) of the ceftazidime group patients.[113] In a prospective, randomized study, imipenem and sulbactam/cefoperazone plus amikacin were compared for empirical therapy of febrile neutropenia in 30 evaluable episodes in cancer patients. The clinical response rate was 60% ($P > 0.05$) for both regimens.[114] A prospective study of 83 febrile neutropenic cancer patients randomized patients to imipenem or piperacillin plus amikacin. The overall response rate for clinically or microbiologically documented infections was 90% with imipenem versus 76% with the piperacillin regimen (P = NS).[115] Sixty-six patients undergoing bone marrow transplant were randomized to receive netilmicin plus either imipenem or ceftazidime as empirical antimicrobial therapy for febrile neutropenia.[116] Positive clinical response was observed in 80% of receiving the imipenem regimen and 73% of those receiving the ceftazidime regimen.

Paediatric patients

The use of imipenem is well established in children with non-CNS infections who were from 3 months to 16 years of age, as indicated below. The dose of imipenem used in most studies was 100 mg/kg/day for patients $\leq$3 years of age or 60 mg/kg/day for those >3 years of age, divided in four equal doses. A multicentre, open, non-comparative trial involving 178 infants and children with bacterial infections evaluated the efficacy of imipenem.[117] A favourable clinical response was achieved in 98 of 100 patients. Adverse reactions, generally mild and reversible, included diarrhoea/vomiting (5.1%), irritation of intravenous infusion site (3.3%) and rash (2.2%). Changes in laboratory test values reported most frequently were thrombocytosis (8.9%), elevations in aspartate aminotransferase (7.9%) and alanine aminotransferase (5.6%) and eosinophilia (8.4%). Infections were caused by a broad spectrum of pathogens including *Haemophilus influenzae*, *S. aureus*, *P. aeruginosa* and anaerobes.

In another study, children ($n = 144$, 22 days to 15 years old) hospitalized for non-CNS bacterial infections received imipenem (100 mg/kg/day for patients $\leq$3 years of age; 60 mg/kg for those >3 years of age) for 9.4 days (range 3–28 days).[118] Diagnoses in the 74 evaluable children included bronchopneumonia with or without empyema (20%), peritonitis complicating appendicitis (16%), skin/soft tissue abscesses (14%), septicaemia (11%) and miscellaneous other infections (39%). Among evaluable patients, 95% were clinically cured or improved. One child, a marasmic child with *Pseudomonas* pneumonitis, died during therapy; 12% of children had non-serious adverse experiences possibly related to imipenem.

A multicentre study evaluated imipenem in severe infections in children with granulocytopenia and haematological diseases and cancers.[119] Children who had received prior antibiotics had an efficacy rate of 79.2%, while those who had not received previous treatment had an efficacy rate of 80.6%. Three children experienced nausea, vomiting and/or diarrhoea; two children had abnormal liver function test parameters that recovered after cessation of the drug treatment.

Twenty-five children (5 months to 11.3 years) with acute osteomyelitis ($n = 7$), suppurative arthritis ($n = 11$) or both ($n = 7$) were treated with imipenem.[120] Bacterial pathogens identified included *S. aureus*, *H. influenzae*, *P. aeruginosa*, *Streptococcus pneumoniae*, group A *Streptococcus*, *Kingella kingae* and *Citrobacter amalonaticus*. All isolates were susceptible to imipenem *in vitro*. All but one child with *P. aeruginosa* osteomyelitis responded favourably to imipenem. The median duration to resolution of symptoms was 6 days. Adverse reactions included maculopapular rash ($n = 1$), diarrhoea ($n = 1$) and mild transient elevation of alanine aminotransferase levels ($n = 3$).

Safety and tolerability

The good safety profile of imipenem is well established after 29 years of research and 20 years of clinical experience in 26 million patients from more than 100 countries. Adverse effects seldom require discontinuation and serious side effects are rare. The most common drug-related adverse events reported in at least 1% of patients in clinical trials included phlebitis/thrombophlebitis (3.1%), nausea (2.0%), diarrhoea (1.8%) and vomiting (1.5%).

Seizures

Imipenem is not indicated for CNS infections because of its proconvulsive activity.[121–124] Dosage monitoring systems have resulted in decreased seizure incidence in patients treated with imipenem, making it important to examine the current, real-life incidence of seizure with carbapenems. A meta-analysis of 37 papers published between 1984 and 1999 reporting the use of imipenem was done to ascertain the true incidence of seizures when variables known to increase the risk or seizure are factored in.[125] Among 5761 adult patients treated with imipenem 81 seizures were reported, corresponding to a 1.4% incidence of seizures. Yearly data from US product labelling indicate that the seizure rate for imipenem has consistently been 0.4%, compared with 0.5–0.7% for meropenem. No seizures were reported in two comparative studies of imipenem and meropenem ($n = 200$ and $n = 232$, respectively).[74,126] Recognition of the factors that predispose patients to seizure, such as kidney dysfunction, prior history of seizure, metabolic derangement, anoxia, and phenytoin discontinuation, and use of appropriate carbapenem doses have substantially reduced concerns about seizure risk with carbapenems.[127]

Overdose

The main dosage concern with imipenem is correct dosage adjustment in patients with renal impairment. The risk of producing a seizure is highly associated with improper dose adjustment

in relation to kidney function.[128] If appropriate care is taken, seizures occur in <1% of patients treated. It is possible that concomitant administration of drugs with neurotoxic profiles, such as theophylline given in overdose, may increase the risk of seizures.[128] In patients with normal kidney function, the maximum total daily dosage should not exceed 50 mg/kg/day or 4.0 g/day, whichever is lower.

Drug interactions

In general, ganciclovir and imipenem should not be used concomitantly because seizures have been reported in patients who received these drugs together. Concomitant administration of imipenem and probenecid results in only minimal increases in plasma levels of imipenem and plasma half-life, thus it is not recommended that imipenem and probenecid be co-administered. Imipenem should not be mixed into solution with other antibiotics, although it may be administered concomitantly with other antibiotics, such as aminoglycosides.

Carbapenems as appropriate therapy

With the introduction of new carbapenems with different spectra of activity, it has become necessary to differentiate among the available agents so that the most appropriate agent can be selected. The place of carbapenems in appropriate therapy has been addressed in several recent publications. A carbapenem classification scheme was proposed to delineate the optimal use of these agents (Table 4).[69] Ertapenem, a Group 1 carbapenem, is best suited for use in infections where non-fermenting Gram-negative bacilli such as *Pseudomonas* and *Acinetobacter* are not usually involved. Imipenem and meropenem, classified as Group 2, are considered to be among the most reliable agents for nosocomial infections. Brink *et al.*[129] agreed that Group 2 agents are appropriate empirical treatment for patients with severe or nosocomial infection when used in accordance with local surveillance data. Nevertheless, it is still difficult to give clear recommendations for the selection of a single carbapenem compound in a particular situation. Whenever imipenem and meropenem were tested against each other in clinical studies, significant differences were not observed. This does not come as a surprise since clinical trials are usually designed to show non-inferiority rather than superiority of a compound. This is a clear limitation of the evidence base that is generated with such studies. Ertapenem was not tested against imipenem or meropenem in clinical trials. However, despite the fact that ertapenem has no significant activity against enterococci and only 5% of the drug is unbound in the serum, it has shown non-inferiority to the established broad-spectrum therapy with piperacillin/tazobactam in patients with intra-abdominal infections.[130] *In vitro* advantages of one compound in terms of MIC values may be contrasted by less favourable pharmacokinetic properties. Because of differences in local epidemiologic situations, all recent guidelines point to this fact and the necessity to adjust treatment recommendations accordingly. Finally, pharmaco-economic considerations may vary with country, healthcare system, re-embursement forms, contracts and medical practice.

Imipenem has an important role in the treatment of HAP and VAP.[131–134] These infections are burdened with treatment failure, often in the range of 30–40%, and these are clearly related to an increased mortality.[135,136] If adequate therapy is used, treatment failure decreases.[135–138] Ibrahim *et al.*[139] demonstrated a decrease in inadequate initial therapy when initiating a strategy that included imipenem plus vancomycin and a quinolone or β-lactam. Recent American Thoracic Society (ATS) guidelines recommend among other compounds ertapenem for early onset HAP or VAP in patients with no known risk factors for multidrug-resistant pathogens.[140] Conversely, imipenem and meropenem are among those that in combination with an antipseudomonal fluoroquinolone or an aminoglycoside are recommended for patients with late onset disease or risk factors for multidrug-resistant pathogens. Moreover, the addition of linezolid or vancomycin is recommended if there is a likelihood for MRSA.

Imipenem is regarded as an agent of choice in the treatment of severe nosocomial infections.[69,129,141–143] The patients most likely to benefit from imipenem would include those who are suspected of being infected with *P. aeruginosa*, an ESBL-producing *E. coli* or *Klebsiella*, *Acinetobacter* or any multidrug-resistant pathogen, and those with polymicrobic or mixed aerobic/anaerobic infections. The utility of this recommendation was illustrated by data suggesting that when a carbapenem was administered during the first 5 days in patients with ESBL-producing *K. pneumoniae* bacteraemia, the mortality rate was 5% compared with a mortality rate of 43% when any other antibiotic

Table 4. Classification scheme for carbapenems (adapted from Shah and Isaacs 2003)[69]

Group	Characteristics	Carbapenems	Indications
Group 1	broad-spectrum, limited activity versus non-fermenting Gram-negative bacilli; suitable for community-acquired infection	ertapenem	complicated IAI complicated SSI acute PI CAP complicated UTI
Group 2	broad-spectrum, activity versus non-fermenting Gram-negative bacilli; suitable for nosocomial infection	imipenem	IAI LRTI gynaecological infections septicaemia[a] genitourinary tract infections bone and joint infections skin and soft tissue infections endocarditis[a]
		meropenem	IAI bacterial meningitis
Group 3	activity against MRSA	none available	none

IAI, intra-abdominal infection; SSI, skin and skin structure infection; PI, pelvic infection; CAP, community-acquired infection; UTI, urinary tract infection.
[a]Not indicated for therapy with the intramuscular formulation.

was used ($P = 0.01$).[86] Similarly, a bowel colonization study suggested that piperacillin/tazobactam may not retain activity against AmpC producers in some cases.[144,145]

Mono versus combination therapy

There are three reasons given for combining antimicrobial agents: (i) to broaden the spectrum of activity; (ii) to achieve synergistic effects; and (iii) to prevent resistance development. In the case of carbapenem therapy these reasons might not be convincing since these agents have an inherent broad spectrum of activity, synergy even *in vitro* has only inconsistently been demonstrated and prevention of resistance development has not been well documented. Hence, a number of studies have addressed the question of whether imipenem can be used as monotherapy in severe nosocomial infections. The results were conflicting.[146,147] However, two meta-analyses clearly showed that there was no advantage for combination therapy employing aminoglycosides, not even in *Pseudomonas* infections.[125,147] However, combination therapy was associated with a significantly higher rate of nephrotoxicity.

De-escalation therapy

For decades escalation therapy was advocated in the treatment of infectious disease. Antibiotic therapy was initiated with a basic agent and only if this approach failed after 72 h, more potent compounds were used. Rising resistance rates and better understanding of the inflammatory process prompted some experts to advocate initial therapy with broad-spectrum, highly active compounds at least in severe infections. This concept was initially referred to as 'intervention therapy'. Although not the only suitable agents for this concept, carbapenems always played an essential role in this approach. The concerns about engendering resistance through overuse of potent antibiotics were met by expanding the concept to the 'de-escalation therapy', whereby the initial therapy was tailored once microbiological culture results and susceptibility tests were available. The two-stage approach of using aggressive initial therapy followed by de-escalation allows serious infection to be treated immediately and effectively while avoiding antibiotic overuse, potential resistance and excessive cost. Meanwhile this concept has been proven by a number of studies that showed that the appropriate initial therapy is a crucial factor in outcome of the patient.[148–150]

Cost is a practical consideration in selecting treatment. Imipenem is a cost-effective treatment for serious infection,[151–154] particularly if de-escalation to an oral regimen is possible.[152] A formulary feasibility study found that imipenem and piperacillin/tazobactam were both effective and suitable for intra-abdominal infection, pneumonia, febrile neutropenia, and skin and soft tissue infection, but that imipenem should be retained due to the prevalence of multidrug-resistant Gram-negative pathogens.[75] A more recent study of febrile neutropenic patients reported that overall treatment costs were 189.55 euros less with imipenem than piperacillin/tazobactam ($P < 0.001$).[155] Imipenem monotherapy has been recommended in polymicrobial infections where combination therapy would be more costly, although imipenem combination therapy was recommended if *Pseudomonas* was present.[85] This sustained susceptibility, efficacy, tolerability and cost-effectiveness are the hallmarks of appropriate initial therapy.

Conclusions

Imipenem, the first in the carbapenem class, has pioneered broad-spectrum antibiotic usage. It has been used in 26 million patients over 20 years and still demonstrates potent antibiotic activity against life-threatening pathogens, including those that are multidrug resistant. Imipenem is still used as the benchmark for comparison with other agents and remains an antibiotic of choice for the treatment of serious infection. Early aggressive therapy with a broad-spectrum agent is essential to reduce mortality and minimize resistance. Imipenem has remained a key asset in the setting of appropriate antibiotic therapy for 20 years due to its efficacy, tolerability and sustained pathogen susceptibilities. The option to de-escalate allows physicians to achieve the goal of treating critically ill patients aggressively while maintaining the option to narrow treatment as needed to avoid resistance.

Acknowledgements

We thank Wendy Horn, PhD, for the help in preparing this manuscript, which was funded by Merck & Co., Inc.

Transparency declarations

A.C.R., E.J.C.G. and A.T. have received reimbursements for attending congresses, fees for speaking, consultancy fees, and funds for research other than directly for this work from various pharmaceutical companies (including Merck & Co., Inc.).

References

1. Birnbaum J, Kahan FM, Kropp H *et al*. Carbapenems, a new class of β-lactam antibiotics. Discovery and development of imipenem/cilastatin. *Am J Med* 1985; **787**: 3–21.

2. Kropp H, Gerckens L, Sundelof JG *et al*. Antibacterial activity of imipenem: the first thienamycin antibiotic. *Rev Infect Dis* 1985; **7** Suppl 3: S389–410.

3. Hashizume T, Ishino F, Nakagawa J *et al*. Studies on the mechanism of action of imipenem (*N*-formimidoylthienamycin) *in vitro*: binding to the penicillin-binding proteins (PBPs) in *Escherichia coli* and *Pseudomonas aeruginosa*, and inhibition of enzyme activities due to the PBPs in *E. coli*. *J Antibiot* 1984; **37**: 394–400.

4. Jackson JJ, Kropp H. β-Lactam antibiotic-induced release of free endotoxin: *in vitro* comparison of penicillin-binding protein (PBP) 2-specific imipenem and PBP 3-specific ceftazidime. *J Infect Dis* 1992; **165**: 1033–41.

5. Prins JM, van Agtmael MA, Kuijper ED *et al*. Antibiotic-induced endotoxin release in patients with gram-negative urosepsis: a double-blind study comparing imipenem and ceftazidime. *J Infect Dis* 1995; **172**: 886–91.

6. Livermore D. Multiple mechanisms of anitmicrobial resistance in *Pseudomonas aeruginosa*: our worst nightmare? *Clin Infect Dis* 2002; **34**: 634.

7. Livermore D. Of *Pseudomonas*, porins, pumps and carbapenems. *J Antimicrob Chemother* 2001; **47**: 247–50.

8. Jacoby G, Mills DM, Chow N. Role of β-lactamases and porins in resistance to ertapenem and other β-lactams in *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2004; **48**: 3203–6.

9. Martinez-Martinez L, Pascual A, Hernandez-Alle S *et al*. Roles of β-lactamases and porins in activities of carbapenems and cephalosporins against *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 1999; **43**: 1669–73.

10. Livermore D, Mushtaz S, Warner M. Selectivity of ertapenem for *Pseudomonas aeruginosa* mutants cross-resistant to other carbapenems. *J Antibiotic Chemother* 2005; **55**: 306–11.

11. Harris A, Torres-Vera C, Veokatarman L *et al*. Epidemiology and clinical outcomes of patients with multiresistant *Pseudomonas aeruginosa*. *Clin Infect Dis* 1999; **28**: 1128–33.

12. Masuda N, Sakagawa E, Ohya *et al*. Substrate specificities of MexAB-OprM, MexCD-OprJ, and MexXY-OprM efflux pumps in *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2000; **44**: 3322–7.

13. Ziha-Zarifi I, Llanes C, Kohler T *et al*. *In vivo* emergence of multidrug-resistant mutants of *Pseudomonas aeruginosa* overexpressing the active efflux system MexA-MexB-OprM. *Antimicrob Agents Chemother* 1999; **43**: 287–91.

14. Kohler T, Michea-Hamzehpour M, Epp SF *et al*. Carbapenem activities against *Pseudomonas aeruginosa*: respective contributions of OprD and efflux systems. *Antimicrob Agents Chemother* 1999; **43**: 424–27.

15. Guinea J, Cercenado E, Garcia-Garrote F *et al*. Prevalence of efflux pumps among clinical isolates of multiple antibiotic resistant *Pseudomonas aeruginosa*. In: *Abstracts of the Fortieth Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, CA, 2000*. Abstract 1034, p. 87. American Society for Microbiology, Washington, DC, USA.

16. Brink A, van den Ende J, Botha M. Antibiotic failure in clinical strains of *Pseudomonas aeruginosa* overexpressing active efflux systems. In: *Tenth International Congress on Infectious Diseases, Singapore, 2002*. Abstract 60.010, p. 136. Excerpta Medica Medical Communications BV, Amsterdam, Netherlands.

17. Poole K. Multidrug efflux pumps and antimicrobial resistance in *Pseudomonas aeruginosa* and related organisms. *J Mol Microbiol Biotechnol* 2001; **3**: 255–64.

18. Paterson D. Recommendation for treatment of severe infections caused by Enterobacteriaceae producing extended-spectrum β-lactamases (ESBLs). *Clin Microbiol Infect* 2000; **6**: 460–3.

19. Livermore DM, Carter MW, Bagel S *et al*. *In vitro* activities of ertapenem (MK-0826) against recent clinical bacteria collected in Europe and Australia. *Anitmicrob Agents Chemother* 2001; **45**: 1860–7.

20. Paterson D. 'Collateral damage' from cephalosporin or quinolone antibiotic therapy. *Clin Infect Dis* 2004; **38** Suppl 4: S341–5.

21. Paterson D, Ko W-C, Von Gottberg A *et al*. Antibiotic therapy for *Klebsiella pneumoniae* bacteremia: implications of production of extended-spectrum β-lactamases. *Clin Infect Dis* 2004; **39**: 31–7.

22. Gold H, Moellering RC Jr. Antimicrobial-drug resistance. *N Engl J Med* 1996; **335**: 1445–53.

23. Paterson DL, Ko W-C, Von Gottberg A *et al*. Outcome of cephalosporin treatment for serious infections due to apparently susceptible organisms producing extended-spectrum β-lactamases: implications for the clinical microbiology laboratory. *J Clin Microbiol* 2001; **39**: 2206–12.

24. Sanders C, Sanders WE Jr. Type 1 β-lactamases of gram-negative bacteria: interactions with β-lactam antibiotics. *J Infect Dis* 1986; **5**: 792–800.

25. Sanders C, Sanders WE Jr. Inducible β-lactamases: clinical and epidemiologic implications for use of newer cephalosporins. *Rev Infect Dis* 1988; **10**: 830–8.

26. Johnson D, Biedenbach DJ, Jones RN. Potency and antimicrobial spectrum update for piperacillin/tazobactam (2000): emphasis on its activity against resistant organism populations and generally untested species causing community-acquired respiratory tract infection. *Diag Microbiol Infect Dis* 2002; **43**: 49–60.

27. Moloughney J, Thomas J, Toney J. Novel IMP-1 metallo-β-lactamase inhibitors can reverse meropenem resistance in *Escherichia coli* expressing IMP-1. *FEMS Microbiol Lett* 2005; **243**: 65–71.

28. Soki J, Fodor E, Hecht DW *et al*. Molecular characterization of imipenem-resistant, *cfiA*-positive *Bacteroides fragilis* isolates from the USA, Hungary and Kuwait. *J Med Microbiol* 2004; **53**: 413–19.

29. Soki J, Urban E, Szoke I *et al*. Prevalence of the carbapenemase gene (*cfiA*) among clinical and normal flora. *J Med Microbiol* 2000; **49**: 427–30.

30. Yamazoe K, Kato N, Kato H *et al*. Distribution of the *cfiA* gene among *Bacteroides fragilis* strains in Japan and relatedness of *cfiA* to imipenem resistance. *Antimicrob Agents Chemother* 1999; **43**: 2808–10.

31. Bandoh K, Ueno K, Watanabe K *et al*. Susceptibility patterns and resistance to imipenem in the *Bacteroides fragilis* group species in Japan: a four-year study. *Clin Infect Dis* 1993; **16** Suppl 4: 382–6.

32. Lartigue M, Poirel L, Nordmann P. First detection of a carbapenem-hydrolyzing metalloenzyme in an Enterobacteriaceae isolate in France. *Antimicrob Agents Chemother* 2004; **48**: 4929–30.

33. Poirel L, Naas T, Nicolas D *et al*. Characterization of VIM-2, a carbapenem-hydrolyzing metallo-β-lactamase and its plasmid- and integron-borne gene from a *Pseudomonas aeruginosa* clinical isolate in France. *Antimicrob Agents Chemother* 2000; **44**: 891–7.

34. Edwards R, Hawkyard CV, Garvey MT *et al*. Prevalence and degree of expression of the carbapenemase gene (*cfiA*) among clinical isolates of *Bacteroides fragilis* in Nottingham, UK. *J Antimicrob Chemother* 1999; **43**: 273–6.

35. Nagy E, Soki J, Urban E *et al*. Occurrence of metronidazole and imipenem resistance among *Bacteroides fragilis* group clinical isolates in Hungary. *Acta Biol Hung* 2001; **52**: 271–80.

36. Hovde L, Rotschafer S, Ibrahim K *et al*. Mutation prevention concentration of ceftriaxone, meropenem, imipenem, and ertapenem against three strains of *Streptococcus pneumoniae*. *Diagn Microbiol Infect Dis* 2003; **45**: 265–7.

37. Trouillet JL, Vuagnat A, Combes A *et al*. *Pseudomonas aeruginosa* ventilator-associated pneumonia: comparison of episodes due to piperacillin-resistant versus piperacillin-susceptible organisms. *Clin Infect Dis* 2002; **34**: 1047–54.

38. Ang J, Ezike E, Asmar BI. Antibacterial resistance. *Indian J Pediatr* 2004; **71**: 229–39.

39. Bodi M, Ardanuy C, Rello J. Impact of Gram-positive resistance on outcome of nosocomial pneumonia. *Crit Care Med* 2001; **29** Suppl: N82–6.

40. Bratu S, Tolaney P, Karumudi U *et al*. Carbapenemase-producing *Klebsiella pneumoniae* in Brooklyn, NY: molecular epidemiology and *in vitro* activity of polymixin B and other agents. *J Antimicrob Chemother* 2005; **56**: 128–32.

41. Smith Moland E, Hanson ND, Herrera VL *et al*. Plasmid-mediated, carbapenem-hydrolysing β-lactamase, KPC-2, in *Klebsiella pneumoniae* isolates. *J Antimicrob Chemother* 2003; **51**: 711–14.

42. Yigit H, Queenan AM, Anderson GJ *et al*. Novel carbapenem-hydrolyzing β-lactamase, KPC-1, from a carbapenem-resistant strain of *Klebsiella pneumoniae*. *Antimicrob Agents Chemother* 2001; **45**: 1151–61.

43. Woodford N, Tierno PM Jr, Young K *et al*. Outbreak of *Klebsiella pneumoniae* producing a new carbapenem-hydrolyzing class A β-lactamase, KPC-3, in a New York medical center. *Antimicrob Agents Chemother* 2004; **48**: 4793–99.

44. Jaccard C, Troillet N, Harbarth S *et al*. Prospective randomized comparison of imipenem-cilastatin and piperacillin-tazobactam in nosocomial pneumonia or peritonitis. *Antimicrob Agents Chemother* 1998; **42**: 2966–72.

45. Lepper PM, Grusa E, Reichl H *et al*. Consumption of imipenem correlates with β-lactam resistance in *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother* 2002; **46**: 2920–5.

46. Landman D, Quale JM, Mayorga D *et al*. Citywide clonal outbreak of multiresistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in Brooklyn, NY. *Arch Intern Med* 2002; **162**: 1515–20.

47. Bratu S, Landman D, Haag R *et al*. Rapid spread of carbapenem-resistant *Klebsiella pneumoniae* in New York city: a new threat to our antibiotic armamentarium. *Arch Intern Med* 2005; **165**: 1430–5.

48. Sanyal SC, Mokaddas EM. The increase in carbapenem use and emergence of *Stenotrophomonas maltophilia* as an important nosocomial pathogen. *J Chemother* 1999; **11**: 28–33.

49. Carmeli Y, Samore MH. Comparison of treatment with imipenem vs. ceftazidime as a predisposing factor for nosocomial acquisition of *Stenotrophomonas maltophilia*: a historical cohort study. *Clin Infect Dis* 1997; **24**: 1131–4.

50. Schaumann R, Stein K, Eckhardt C *et al*. Infections caused by *Stenotrophomonas maltophilia*—a prospective study. *Infection* 2001; **29**: 205–8.

51. Rello J, Sa-Borges M, Correa H *et al*. Variations in etiology of ventilator-associated pneumonia across four treatment sites: implications for antimicrobial prescribing practices. *Am J Respir Crit Care Med* 1999; **160**: 608–13.

52. Bell J, Turnidge J. SENTRY Antimicrobial Surveillance Program Asia-Pacific region and South Africa. *Commun Dis Intell* 2003; **27** Suppl: S61–6.

53. Unal S, Masterton R, Goossens H. Bacteraemia in Europe-antimicrobial susceptibility data from the MYSTIC surveillance programme. *Int J Antimicrob Agents* 2004; **23**: 155–63.

54. Winokur P, Canton R, Casellas JM *et al*. Variations in the prevalence of strains expressing an extended-spectrum β-lactamase phenotype and characterization of isolates from Europe, the Americas, and the Western Pacific region. *Clin Infect Dis* 2001; **32**: S94–103.

55. Gales A, Jones RN, Forward KR *et al*. Emerging importance of multidrug-resistant *Acinetobacter* species and *Stenotrophomonas maltophilia* as pathogens in seriously ill patients: geographic patterns, epidemiological features, and trends in the SENTRY antimicrobial surveillance program (1997–1999). *Clin Infect Dis* 2001; **32** Suppl 2: S104–13.

56. Turner P. Susceptibility of meropenem and comparators tested against 30,634 Enterobacteriaceae isolated in the MYSTIC Programme (1997–2003). *Diagn Microbiol Infect Dis* 2004; **50**: 291–3.

57. Turner P. MYSTIC (Meropenem Yearly Susceptibility Test Information Collection): a global overview. *J Antimicrob Chemother* 2000; **46**: 9–23.

58. Mouton JW, Touw DJ, Horrevorts AM *et al*. Comparative pharmacokinetics of the carbapenems: clinical implications. *Clin Pharmacokinet* 2000; **39**: 185–201.

59. Balfour J, Bryson H, Brogden R. Imipenem/cilastatin. An update of its antibacterial activity, pharmacokinetics and therapeutic efficacy in the treatment of serious infections. *Drugs* 1996; **51**: 99–136.

60. Lavan G, Nord C. Adverse effects of monobactams and carbapenems. *Drug Safety* 1995; **12**: 305–13.

61. Drusano G. Prevention of resistance: a goal for dose selection for antimicrobial agents. *Clin Infect Dis* 2003; **36** Suppl 1: S42–50.

62. Novelli A, Adembri C, Livi P *et al*. Pharmacokinetic evaluation of meropenem and imipenem in critically ill patients with sepsis. *Clin Pharmacokinet* 2005; **44**: 539–49.

63. Lee LS, Bertino JS Jr. Comparison of imipenem/cilastatin and meropenem attainment of pharmacodynamic target goals at various dosage regimens using a short infusion time (30-minutes). *Clin Pharmacol Therapeut* 2004; **75**: P14.

64. Kuti JL, Dandekar PK, Nightingale CH *et al*. Use of Monte Carlo simulation to design an optimized pharmacodynamic dosing strategy for meropenem. *J Clin Pharmacol* 2003; **43**: 1116–23.

65. Dandekar PK, Maglio D, Sutherland CA *et al*. Pharmacokinetics of meropenem 0.5 and 2 g every 8 hours as a 3-hour infusion. *Phamacotherapy* 2003; **23**: 988–91.

66. Lee LS, Bertino JS Jr. Use of a prolonged infusion time (3-hours) in attaining pharmacodynamic target goals of imipenem-cilastatin and meropenem at various dosing regimens. *Clin Pharmacol Therapeut* 2004; **75**: P15.

67. Mattoes H, Kuti JL, Drusano GL *et al*. Optimizing antimicrobial pharmacodynamics: dosage strategies for meropenem. *Clin Ther* 2004; **26**: 1187–98.

68. Neu HC. Clinical perspectives on imipenem. *J Antimicrob Chemother* 1983; **12** Suppl D: 149–53.

69. Shah P, Isaacs RD. Ertapenem, the first of a new group of carbapenems. *J Antimicrob Chemother* 2003; **52**: 538–42.

70. Jaccard C, Troillet N, Harbarth S *et al*. Prospective randomized comparison of imipenem-cilastatin and piperacillin-tazobactam in nosocomial pneumonia or peritonitis. *Antimicrob Agents Chemother* 1998; **42**: 2966–72.

71. Torres A, Bauer TT, Leon-Gil C *et al*. Treatment of severe nosocomial pneumonia: a prospective randomised comparison of intravenous ciprofloxacin with imipenem/cilastatin. *Thorax* 2000; **55**: 1033–9.

72. Eron L. Imipenem/cilastatin therapy of bactermia. *Am J Med* 1985; **78** Suppl 6A: 95–9.

73. Zanetti G, Bally F, Greub G *et al*. Cefepime versus imipenem-cilastatin for treatment of nosocomial pneumonia in intensive care unit patients: a multicenter, evaluator-blind, prospective, randomized study. *Anitmicrob Agents Chemother* 2003; **47**: 3442–7.

74. Basoli A, Zarba EZ, Mazzocchi P *et al*. Imipenem/cilastatin (1.5 g daily) versus meropenem (3.0 g daily) in patients with intra-abdominal infections: results of a prospective, randomized, multicentre trial. *Scand J Infect Dis* 1997; **29**: 503–8.

75. Marra F, Reynolds R, Stiver G *et al*. Piperacillin/tazobactam versus imipenem: a double-blind, randomized formulary feasibility study at a major teaching hospital. *Diagn Microbiol Infect Dis* 1998; **31**: 355–68.

76. West M, Boulanger BR, Fogarty C *et al*. Levofloxacin compared with imipenem/cilastatin followed by ciprofloxacin in adult patients with nosocomial pneumonia: a multicenter, prospective, randomized, open-label study. *Clin Ther* 2003; **2592**: 485–506.

77. Raad,II, Escalante C, Hachem RY *et al*. Treatment of febrile neutropenic patients with cancer who require hospitalization: a prospective randomized study comparing imipenem and cefepime. *Cancer* 2003; **98**: 1039–47.

78. Cherif H, Bjorkholm M, Engervall P *et al*. A prospective, randomized study comparing cefepime and imipenem-cilastatin in the empirical treatment of febrile neutropenia in patients treated for haematological malignancies. *Scand J Inf Dis* 2004; **36**: 593–600.

79. Verwaest C. Meropenem versus imipenem/cilastatin as empirical monotherapy for serious bacterial infections in the intensive care unit. *Clin Microbiol Infect* 2000; **6**: 294–302.

80. Garau J, Blanquer J, Cobu L *et al*. Prospective, randomised, multicentre study of meropenem versus imipenem/cilastatin as empiric monotherapy in severe nosocomial infections. *Eur J Clin Microbiol Infect Dis* 1997; **16**: 789–96.

81. Berkeley AS, Freedman K, Hirsch J *et al*. Imipenem/cilastatin in the treatment of obstetric and gynecologic infections. *Am J Med* 1985; **78**: 71–6.

82. Cox C, Corrado ML. Safety and efficacy of imipenem/cilastatin in treatment of obstetric and gynecological infections. *Am J Med* 1985; **78**: 84–91.

83. Fink M, Snydman DR, Niederman MS *et al*. Treatment of severe pneumonia in hospitalized patients: results of a multicenter, randomized, double-blind trial comparing intravenous ciprofloxacin with imipenem-cilastatin. The Severe Pneumonia Study Group. *Antimicrob Agents Chemother* 1994; **38**: 547–57.

84. Hartenauer U, Kljucar S, Bender HJ. Meropenem versus imipenem/cilastatin for the treatment of serious bacterial infections at ICU. *Antiinfective Drugs Chemother* 1997; **15**: 65–70.

85. Chambers H. Other β-lactam antibotics. In: Mandell G, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*. New York: Churchill Livingstone, 2000; 291–9.

86. Paterson D, Ko W-C, Von Gottberg A *et al*. International prospective study of *Klebsiella pneumoniae* bacteremia: implications of extended-spectrum β-lactamase production in nosocomial infections. *Ann Intern Med* 2004; **140**: 26–32.

87. Cherif H, Bjorkholm M, Engervall P *et al*. A prospective, randomized study comparing cefepime and imipenem-cilastatin in the empirical treatment of febrile neutropenia in patients treated for haematological malignancies. *Scand J Infect Dis* 2004; **36**: 593–600.

88. Erasmo AA, Crisostomo AC, Yan LN *et al*. Randomized comparison of piperacilin/tazobactam versus imipenem/cilastitin in the treatment of patiens with intra-abdominal infection. *Asian J Surg* 2004; **27**: 227–35.

89. Chambers H, Turner J, Wagner C *et al*. Imipenem (IMI) + amikacin (AK) in combination chemotherapy of multiple-drug resistant (MDR) tuberculosis (TB). In: *Abstracts of the Thirty-sixth Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LO, 1996.* Abstract LM27, p. 285. American Society for Microbiology, Washington, DC, USA

90. Sanders C, Sanders WE. Sch 29482: comparative activity against Enterobacteriaceae multiply-resistant to β-lactam antibiotics and mycobacteria. *J Antimicrob Chemother* 1982; **9** Suppl C: 59–69.

91. Guay D. Nontuberculous mycobacterial infections. *Ann Pharmacother* 1996; **30**: 819–30.

92. Lie T, Hofer M. Tuberkulose nach Lebertransplantation [Tuberculosis after liver transplant]. *Dtsch Med Wochenschr* 1988; **113**: 731–4.

93. Widgerow A, Brink AJ, Koornhof HJ *et al*. Atypical *Mycobacterium* and breast surgery. *Ann Plast Surg* 1995; **35**: 204–7.

94. Moorthy R, Rao NA. Atypical mycobacterial wound infection after blepharoplasty. *Br J Ophthalmol* 1995; **79**: 93.

95. Tebas P, Sultan F, Wallace RJ *et al*. Rapid development of resistance to clarithromycin following monotherapy for disseminated *Mycobacterium chelonae* infection in a heart transplant patient. *Clin Infect Dis* 1995; **20**: 443–4.

96. Nylen O, Alestig K, Fasth A *et al*. Infections of the ear with nontuberculous mycobacteria in three children. *Pediatr Infect Dis J* 1994; **13**: 653–6.

97. Broadway D, Kerr-Muir MG, Eykyn SJ *et al*. *Mycobacterium chelonei* keratitis: a case report and review of previously reported cases. *Eye* 1994; **8**: 134–42.

98. Yew W, Chau CH, Lee J *et al*. Cholestatic hepatitis in a patient who received clarithromycin therapy for a *Mycobacterium chelonae* lung infection. *Clin Infect Dis* 1993; **18**: 1025–6.

99. Swenson J, Wallace RJ, Silcox VA *et al*. Antimicrobial susceptibility of five subgroups of *Mycobacterium fortuitum* and *Mycobacterium chelonae*. *Antimicrob Agents Chemother* 1985; **28**: 807–11.

100. Inderlied C, Kolonoski PT, Wu M *et al*. Amikacin, ciprofloxacin and imipenem treatment for disseminated *Mycobacterium avium* complex infection of beige mice. *Antimicrob Agents Chemother* 1989; **33**: 176–80.

101. Paterson D. Serious infections caused by enteric gram-negative bacilli–mechanisms of antibiotic resistance and implications for therapy of gram-negative sepsis in the transplanted patient. *Semin Respir Infect* 2002; **17**: 260–4.

102. Roberts S, Franklin JC, Mijch A *et al*. Nocardia infection in heart-lung transplant recipients at Alfred Hospital, Melbourne, Australia, 1989–1998. *Clin Infect Dis* 2000; **31**: 968–72.

103. Tripodi M, Adinolfi LE, Andreana A *et al*. Treatment of pulmonary nocardiosis in heart-transplant patients: importance of susceptibility studies. *Clin Transplant* 2001; **15**: 415–20.

104. Farina C, Boiron P, Goglio A *et al*. Human nocardiosis in northern Italy from 1982 to 1992. Northern Italy Collaborative Group on Nocardiosis. *Scand J Inf Dis* 1995; **27**: 23–7.

105. Thaler F, Gotainer B, Teodori G *et al*. Mediastinitis due to *Nocardia asteroides* after cardiac transplantation. *Intensive Care Med* 1992; **18**: 127–8.

106. Tulczynska J SJ, Sordillo EM *et al*. Pulmonary nocardiosis: a potential complication when adjunctive corticosteroid therapy is used to treat *Pneumocystis carinii* pneumonia in a patient with AIDS. *AIDS Patient Care* 1995; **9**: 104–5.

107. Ogg G, Lynn WA, Peters M *et al*. Cerebral nocardia abscess in a patient with AIDS: correlation of magnetic resonance and white cell scanning images with neuropathological findings. *J Infect* 1997; **35**: 311–3.

108. Granier H, Robinet G, Masure O *et al*. Nocardiosis and AIDS. A case report and review of the literature. *Med Mal Infect* 1992; **22**: 496–9.

109. Desfemmes T, Cadranel J, Delisle F *et al*. Pulmonary and cerebral nocardiosis in an HIV patient. *Rev Mal Respir* 1993; **10**: 262–4.

110. Tissot B, Carles B, Chraibi-Hasseini K *et al*. Pulmonary nocardiosis in an HIV-positive African. *Rev Med Interne* 1994; **15**: 116–9.

111. Debat-Zoguereh D, Bonnet E, Bensa P *et al*. Subcutaneous abscess led to diagnosis of pulmonary nocardiosis in a patient infected with human immunodeficiency virus. *Med Mal Infect* 1993; **23**: 577–80.

112. Bodey G, Alvarez ME, Jones PG *et al*. Imipenem-cilastatin as initial therapy for febrile cancer patients. *Antimicrob Agents Chemother* 1986; **30**: 211–4.

113. Miller J, Butler T, Beveridge RA *et al*. Efficacy and tolerability of imipenem-cilastatin versus ceftazidime plus tobramycin as empiric therapy of presumed bacterial infection in neutropenic cancer patients. *Clin Ther* 1993; **15**: 486–99.

114. Ozyilkan O, Yalcintas U, Baskan S. Imipenem-cilastatin versus sulbactam-cefoperazone plus amikacin in the initial treatment of febrile neutropenic cancer patients. *Korean J Intern Med* 1999; **14**: 15–9.

115. Vandercam B, Ezzeddine H, Agaliotis D *et al*. Imipenem/cilastatin versus piperacillin plus amikacin as empiric therapy in the treatment of febrile episodes in neutropenic patients with haematologic malignancies. *Acta Clin Beig* 1989; **44**: 99–109.

116. Laszlo D, Bacci S, Bosi A *et al*. Randomized trial comparing netilmicin plus imipenem-cilastatin versus netilmicin plus ceftazidime as empiric therapy for febrile neutropenic bone marrow transplant recipients. *J Chemother* 1997; **9**: 95–101.

117. Ahonkhai V, Cyhan GM, Wilson SE *et al*. Imipenem-cilastatin in pediatric patients: an overview of safety and efficacy in studies conducted in the United States. *Pediatr Infect Dis J* 1989; **8**: 740–4.

118. Nalin D, Hart CB, Shih WJ *et al*. Imipenem/cilastatin for pediatric infections in hospitalized patients. *Scand J Infect Dis Suppl* 1987; **52**: 56–64.

119. Takeda T, Hatae Y, Nakadate H *et al*. A multi-institutional study on the efficacy and toxicity of imipenem/cilastatin sodium in severe infections complicating hematological diseases and cancers in children. Study Group of Infectious Diseases in Pediatric Hematology/Oncology in Hokkaido. (Japanese). *Jpn J Antibiot* 1993; **46**: 388–96.

120. Freij B, Kusmiesz H, Shelton S *et al*. Imipenem and cilastatin in acute osteomyelitis and suppurative arthritis. Therapy in infants and children. *Am J Dis Child* 1987; **141**: 335–42.

121. Calandra GB, Wang C, Aziz M *et al*. The safty profile of imipenem/cilastatin: worldwide clinical experience based on 3470 patients. *J Antimib Chemother* 1986; **18** Suppl E: 193–202.

122. Pestotnik S, Classen DC, Evans RS *et al*. Prospective surveillance of imipenem/cilastatin use and associated seizures using a hospital information system. *Ann Pharmacother* 1993; **27**: 497–501.

123. Day IP, Goudie J, Nishiki K *et al*. Correlation between *in vitro* and *in vivo* models of proconvulsive activity with the carbapenem antibiotics, biapenem, imipenem/cilastatin, and meropenem. *Toxicol Lett* 1995; **76**: 239–43.

124. Norrby SR. Neurotoxicity of carbapenem antibacterials. *Drug Saf* 1996; **15**: 87–90.

125. Karam G. Seizure propensity with carbapenems. A clinical conundrum. In press.

126. Geroulanos S. Meropenem versus imipenem/cilastatin in intra-abdominal infections requiring surgery. *J Antimicrob Chemother* 1995; **36** Suppl A: 195–205.

127. Koppel B, Hauser WA, Politis C *et al*. Seizures in the critically ill: the role of imipenem. *Epilepsia* 2004; **42**: 1590–3.

128. Alvan G, Nord CE. Adverse effects of monobactams and carbapenems. *Drug Saf* 1995; **12**: 305–13.

129. Brink AJ, Feldman C, Grolman DC *et al*. Appropriate use of the carbapenems. *S Afr Med J* 2004; **94**: 857–61.

130. Solomkin JS, Yellin AE, Rotstein OD *et al*. Ertapenem versus piperacillin/tazobactam in the treatment of complicated intraabdominal

infections: results of a double-blind, randomized comparative phase III trial. *Ann Surg* 2003; **237**: 235–45.

131. Iregui M, Ward S, Sherman G *et al*. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. *Chest* 2002; **122**: 262–8.

132. Kollef M. Hospital-acquired pneumonia and de-escalation of antimicrobial treatment. *Crit Care Med* 2001; **29**: 1473–5.

133. Kollef M. Appropriate empiric antimicrobial therapy of nosocomial pneumonia: the role of the carbapenems. *Resp Care* 2004; **49**: 1530–41.

134. Kollef MH. Appropriate empirical antibacterial therapy for nosocomial infections. Getting it right the first time. *Drugs* 2003; **63**: 2157–68.

135. Kollef MH, Sherman G, Ward S *et al*. Inadequate antimicrobial treatment of infections. A risk factor for hospital mortality among critically ill patients. *Chest* 1999; **115**: 462–74.

136. Valles J, Rello J, Ochagavia A *et al*. Community-acquired bloodstream infection in critically ill adult patients. Impact of shock and inappropriate antibiotic therapy on survival. *Chest* 2003; **123**: 1615–24.

137. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A *et al*. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. *Crit Care Med* 2003; **31**: 2742–51.

138. Leone M, Bourgoin A, Cambon S *et al*. Empirical antimicrobial therapy of septic shock patients: adequacy and impact on the outcome. *Crit Care Med* 2003; **41**: 462–7.

139. Ibrahim E, Sherman G, Ward S *et al*. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest* 2000; **118**: 146–55.

140. ATS. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; **171**: 388–416.

141. Niederman M. Reexamining quinolone use in the intensive care unit: use them right or lose the fight against resistant bacteria. *Crit Care Med* 2005; **33**: 443–4.

142. Kollef M. Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. *Clin Infect Dis* 2000; **31** Suppl 4: S131–8.

143. Luna C, Famiglietti A, Absi R *et al*. Community-acquired pneumonia. Etiology, epidemiology, and outcome at a teaching hospital in Argentina. *Chest* 2000; **118**: 1344–54.

144. Dorso KL, Woods G, Friedland I *et al*. *In vitro* kill rates of ertapenem, ceftriaxone (CRO) and piperacillin/tazobactan (pip/taz) against intra-abdominal pathogens. *One hundred and second General Meeting of the American Society of Microbiology, Salt Lake City, UT, 2002*. Poster A-156. American Society for Microbiology, Washington, DC, USA.

145. Dinubile M, Friedland I, Chan CY *et al*. Bowel colonization with resistant gram-negative bacilli after antimicrobial therapy of intra-abdominal infections: observations from two randomized comparative clinical trials of ertapenem therapy. *Eur J Clin Microbiol Infect Dis* 2005; **24**: 443–9.

146. Rolston KVI, Berkey P, Bodey GP *et al*. A comparison of imipenem to ceftazidime with or without amikacin as empiric therapy in febrile neutropenic patients. *Arch Intern Med* 1992; **152**: 283–91.

147. Kojima A, Shinkai T, Soejima Y *et al*. A randomized prospective study of imipenem-cilastatin with or without amikacin as an empirical antibiotic treatment for febrile neutropenic patients. *Am J Clin Oncol* 1994; **17**: 400–4.

148. Höffken G, Niederman M. Nosocomial pneumonia. The importance of a de-escalating strategy for antibiotic treatment of pneumonia in the ICU. *Chest* 2002; **122**: 2183–96.

149. Rello J, Vidaur L, Sandiumenge A *et al*. De-escalation therapy in ventilator-associated pneumonia. *Crit Care Med* 2004; **32**: 2183–90.

150. Chastre J, Wolff M, Fagon JY *et al*. Comparison of 8 vs. 15 days of antibiotic therapy for ventilator-associated pneumonia in adults. *JAMA* 2003; **290**: 2588–98.

151. Dietrich ES, Patz E, Frank U *et al*. Cost-effectiveness of ceftazidime or imipenem/cilastatin versus ceftriaxone + aminoglycoside in the treatment of febrile episodes in neutropenic cancer patients in Germany. *Infection* 1999; **27**: 23–7.

152. Walters D, Solomkin J, Paladino J. Cost effectiveness of ciprofloxacin plus metronidazole versus imipenem-cilastatin in the treatment of intra-abdominal infections. *Pharmacoeconomics* 1999; **16**: 551–61.

153. Rodloff A, Kujath P, Lunstedt B *et al*. Comparative study of the cost-effectiveness of initial therapy with imipenem/cilastatin in secondary peritonitis. *Chirurg* 1998; **69**: 1093–1100.

154. Rodloff AC, Laubenthal HJ, Bastian A *et al*. Comparative study of the cost-/effectiveness relationship of initial therapy with imipenem/cilastatin in nosocomial pneumonia. *Anasthesiol Intensivmed Notfallmed Schmerzther* 1996; **31**: 172–80.

155. Sanz M, Bermúdez A, Montserrat R *et al*. Imipenem/cilastatin versus piperacillin/tazobactam plus amikacin for empirical therapy in febrile neutropenic patients: results of the COSTINE study. *Clin Infect Dis* 2005; **21**: 645–55.

156. Mutnick A, Rhomberg PR, Sader HS *et al*. Antimicrobial usage and resistance trend relationships from the MYSTIC programme in North America (1999–2001). *J Antimicrob Chemother* 2004; **53**: 290–6.