Meropenem
An Updated Review of its Use in the Management of Intra-Abdominal Infections

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Meropenem is a carbapenem antibacterial agent with a broad spectrum of activity which encompasses Gram-negative, Gram-positive and anaerobic bacteria. Like other carbapenems, meropenem is stable against chromosomal and extended-spectrum β-lactamasases.

In patients with moderate to severe intra-abdominal infections, empirical monotherapy with meropenem achieved clinical response rates ranging from 91 to 100% in 7 randomised comparative trials. Efficacy rates were similar to those of imipenem/cilastatin (94 to 97%), clindamycin plus tobramycin (93%) and, overall, to cefotaxime plus metronidazole (75 to 100%), although there were differences between trials versus this combination regimen. According to limited data, meropenem also achieved clinical response rates of over 80% in patients with severe intra-abdominal infections.

Meropenem is well tolerated, the most common adverse events being diarrhoea, rash, nausea/vomiting and inflammation at the injection site which are reported in <2.5% of patients each. Meropenem also has an improved CNS tolerability profile compared with imipenem/cilastatin.

Conclusions: Extensive comparative clinical data demonstrate that meropenem can be used effectively as empirical monotherapy in moderate to severe intra-abdominal infections. It also shows potential in the most severe forms of infection, although experience in this infection type remains limited. Compared with standard combination regimens, meropenem offers the benefits of ease of administration without the need for monitoring. It also offers improved CNS tolerability compared with imipenem/cilastatin with the option of a higher
maximum dosage, which may be a particular advantage in patients with severe intra-abdominal infections.

**Antibacterial Activity**

Meropenem has consistently strong activity against Enterobacteriaceae; over 98% of European and North American isolates in a large *in vitro* study were susceptible to the drug. Imipenem showed 4- to 32-fold less activity against the same pathogens. According to the same survey, 91% of *Pseudomonas aeruginosa* are susceptible to meropenem [minimum concentration required to inhibit 90% of isolates (MIC<sub>90</sub>) 4 mg/L] and meropenem exhibited good activity against *Acinetobacter baumannii* (MIC<sub>90</sub> values of 1 or 2 mg/L), although infrequent isolates with decreased susceptibility or resistance to the carbapenems have been documented worldwide.

Meropenem has good activity (MIC<sub>90</sub> ≤ 1 mg/L) against Gram-positive bacteria relevant to intra-abdominal infections including viridans streptococci, methicillin-susceptible *Staphylococcus epidermidis* and *S. aureus*. 71 and 79% of *Enterococcus faecalis* isolated from Europe and North America, respectively, were susceptible to meropenem. Imipenem had slightly more activity (up to 4-fold) than meropenem against Gram-positive bacteria.

*Stenotrophomonas maltophilia*, *E. faecium* and methicillin-resistant *S. aureus* are inherently resistant to the carbapenems.

Meropenem has good activity against anaerobes, including *Bacteroides fragilis*; over 98% of all species studied were susceptible to the drug. Imipenem seemed to have similar or slightly less (up to 4-fold) activity than meropenem against these bacteria.

Meropenem produces only minor alterations in the intestinal microflora of healthy volunteers; numbers of streptococci, enterobacteria, bacteroides, veillonella/acidaminococci and clostridia decreased and those of enterococci increased during a 7-day course of intravenous meropenem 1.5 g/day but all gut flora returned to normal within 2 weeks of completing treatment.

Meropenem, like other β-lactams, does exhibit an inoculum effect *in vitro*. However, MIC values reported at an inoculum of ~10<sup>7</sup> colony forming units (cfu)/spot did not exceed 4 mg/L for any organism including Enterobacteriaceae expressing chromosomal or plasmid-mediated β-lactamases.

Meropenem has a postantibiotic effect against both Gram-negative and Gram-positive bacteria.

**Pharmacokinetic Profile**

Meropenem has linear pharmacokinetics over the dose range 0.25 to 2 g. Mean peak plasma concentrations (C<sub>max</sub>) of meropenem following a single intravenous 1 g dose ranged from 54.8 to 61.6 mg/L in healthy volunteers.

Meropenem is distributed in the extracellular (interstitial) fluid. Typically, meropenem concentrations achieved in the abdominal tissues are in the range of 2 to 4 mg/L, although concentrations in the bile are higher and range from 7 to 15 mg/L. In patients with intra-abdominal infections, the volume of distribution (Vd) tends to be up to approximately 2-fold higher compared with values observed in healthy volunteers.

Meropenem is cleared predominantly in the kidney by both glomerular filtration and tubular secretion. Excretion is rapid and over 95% of an administered dose is excreted within 8 hours. Biliary excretion of meropenem is therefore limited; 2.1% of a drug dose is recovered in the faeces.

Meropenem has a single open-ring metabolite formed by hydrolysis which is
pharmacologically inactive. The elimination half-life \( (t_{1/2}) \) of meropenem is approximately 1 hour.

In patients with renal impairment, the clearance of meropenem is decreased and \( t_{1/2} \) prolonged. Dosage adjustment is therefore required based on creatinine clearance \( (C_{Lcr}) \). Meropenem is cleared by haemodialysis and continuous venovenous haemofiltration, and dosage adjustment may be required in these patients. The pharmacokinetics of meropenem are, however, unaltered in patients with hepatic impairment.

**Therapeutic Efficacy**

In intra-abdominal infections of moderate severity, meropenem 1.5 g/day achieved a satisfactory clinical response in 92 and 98% of patients compared with rates of 94 and 96% with imipenem/cilastatin 1.5 or 2 g/day in 2 multicentre, randomised trials.

In patients with moderate to severe infections, meropenem 3 g/day achieved clinical response rates ranging from 91 to 100% in 7 randomised trials. Efficacy rates were similar to those of imipenem/cilastatin (94 to 97%) and clindamycin plus tobramycin (93%). Compared with cefotaxime plus metronidazole in 3 trials, the regimens were similar in one trial (satisfactory clinical response in 93 vs 92%) but significantly different in the remaining 2 trials (95 with meropenem vs 75% with the combination regimen in one trial and 91 vs 100% in the other). Slight differences in bacteriological outcome were observed between regimens on a per pathogen basis, but statistical analyses were not performed.

The efficacy of meropenem appeared to be unaffected by the site of intra-abdominal infection according to a retrospective analysis of 4 clinical trials; meropenem consistently achieved a satisfactory response in over 89% of patients which was similar to that of comparator regimens.

In 2 comparative trials which recruited patients with severe infections, clinical response rates were 82 and 96% with meropenem 3 g/day versus 81 and 77% with imipenem/cilastatin 3 g/day in those patients with severe intra-abdominal infections (>50 patients per study).

In patients with intra-abdominal infections who failed therapy (4 to 16%), the most common persistent organisms following failure of meropenem therapy included *Escherichia coli*, other Enterobacteriaceae, enterococci, *Streptococcus* spp. and *P. aeruginosa*. Superinfections developed in similar numbers of patients receiving meropenem and comparator regimens.

**Pharmacoeconomic Considerations**

In the 2 cost analyses that compared delivery methods of meropenem, bolus administration was associated with delivery cost savings of approximately 30% in an Australian study and 45% in a UK study compared with an infusion of the drug.

**Tolerability**

A recent overview of clinical trial data involving 9514 patients found that the overall incidence of adverse events, drug-related adverse events, adverse events leading to withdrawal and mortality were similar between meropenem, imipenem/cilastatin and combination regimens. Drug-related events most frequently associated with meropenem are diarrhoea (2.3%), rash (1.4%), nausea/vomiting (1.4%) and local inflammation at the injection site (1.1%). A concern with imipenem/cilastatin is that the incidence of gastrointestinal events is linked to the rate of administration and dosage of the drug, although these events can be managed by slowing the rate of infusion of the drug. Meropenem can, however, be administered without regard to the rate of infusion or dose.
A tolerability concern with β-lactam agents is their potential to cause CNS toxicity and seizures. With regard to the CNS, meropenem appears to be well tolerated, whereas imipenem/cilastatin is associated with a risk of seizures, particularly in those with predisposing factors such as renal dysfunction, underlying CNS pathology or advanced age. In an overview of 46 clinical trials, which excluded patients with meningitis and a history of CNS disorders, the incidence of meropenem-related seizures was 0.08% of treatment exposures compared with 0.28% with imipenem/cilastatin, 0.05% with cephalosporin-based regimens and 0% with clindamycin plus an aminoglycoside.

Laboratory events most commonly associated with meropenem included thrombocytosis (1.6%) and increases in ALT (4.3%), AST (3.4%) and alkaline phosphatase (1.5%).

Dosage and Administration

Meropenem is indicated as monotherapy for the treatment of intra-abdominal infections. According to the manufacturer’s recommendations, meropenem should be administered at a dosage of 1.5 to 3 g/day in 3 divided doses depending on the type and severity of infection, the susceptibility of the pathogen(s) and the condition of the patient. This dosage range may, however, differ from that recommended on a national level. Meropenem can be administered as an intravenous bolus injection or infusion.

Dosage adjustment is required in patients with renal impairment (CL\text{CR} \leq 3 \text{ L/h}) but not in the elderly (CL\text{CR} >3 \text{ L/h}) or in patients with impaired hepatic function.

1. Overview of Intra-Abdominal Infections

Intra-abdominal infections encompass a wide spectrum of conditions.[1] Most arise from the movement of micro-organisms from the gastrointestinal tract to sterile areas within the abdomen.[2] This can be caused by damage to the intestinal wall as a result of spontaneous perforation (appendicitis, perforated ulcer or diverticulitis), trauma or surgical intervention.

Fundamental principles for the management of intra-abdominal infections include general supportive measures, prompt surgical intervention and effective antibacterial therapy.[3] However, both host- and disease-specific factors can affect outcome. These factors include severity of illness, underlying disease including immune status, the type and timing of intervention and infection site.[4,5] For example, biliary tract infections and appendicitis are associated with mortality rates of 0 to 8%, whereas much higher rates of mortality are observed with infections involving the small intestine and large bowel (20 to 25% and 20 to 50%, respectively) and those occurring after intra-abdominal surgery (40 to 60%).[4] Infections that result after initial surgery or antibacterial therapy are particularly difficult to treat because they can involve drug-resistant pathogens, e.g. Gram-negative facultative bacilli, staphylococci and Pseudomonas aeruginosa.[6,7] These are quite distinct from most intra-abdominal infections which involve pathogens acquired from endogenous flora.

The aim of antimicrobial therapy is to prevent recurrent infections, reduce surgical wound complications and control bacteraemia. Once an infection is suspected, treatment is invariably empirical because the identity of the infecting pathogen(s) may not be known for 2 to 4 days after initiation of therapy.[8] The basic premise is that empirical therapy should cover Escherichia coli, other Enterobacteriaceae and Bacteroides fragilis;[6] the use of empirical regimens with broader coverage, e.g. other anaerobes, P. aeruginosa[3] and enterococci, is more controversial.
Traditionally, empirical regimens for intra-abdominal infections have consisted of combinations of 2 or 3 antibacterials in order to achieve sufficient coverage, generally clindamycin or metronidazole combined with either a cephalosporin or an aminoglycoside.[9] However, the advent of single agents with a broad antibacterial spectrum, such as the carbapenems and extended-spectrum cephalosporins, has allowed effective monotherapy against intra-abdominal infections.

This review focuses on meropenem, a parenteral carbapenem antibacterial agent, and its use in patients with intra-abdominal infections. It updates the review of meropenem previously published in Drugs[10] which considered its use in a range of infection types. The specific use of meropenem in patients with febrile neutropenia has been reviewed in Disease Management & Health Outcomes,[11] and more recently, its use in serious bacterial infections has also been reviewed in Drugs.[12]

2. Antibacterial Activity

2.1 Overview of In Vitro Activity

The activity profile of meropenem has been well established in both early in vitro studies and, more recently, in large surveillance studies. With the exception of one clinical trial which reported susceptibility data for isolated pathogens,[13] there is no large in vitro study which looks at the activity of meropenem against isolates taken exclusively from patients with intra-abdominal infections.

In the absence of data concerning this patient group, the 1997 study of Pfaller and Jones,[14] which tested the activity of meropenem against over 30,000 clinical isolates from Europe and North America, will form the basis of this overview. A summary of data from this study concerning pathogens relevant for intra-abdominal infections is provided in table I.

The results of several other large in vitro studies (over 4000 to 18,000 isolates per study) investigating the activity of meropenem are also available;[15-18] however, since their results are in close agreement with those of Pfaller and Jones, they will not be discussed in detail in this overview. In addition, the MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) surveillance study is an ongoing assessment of the activity of meropenem against isolates collected from hospital sources. The most recent results, presented only as an abstract, suggest that the activity of meropenem has remained unaltered during the first 3 years of the study (1997 to 1999).[19]

2.1.1 Gram-Negative Bacteria

Enterobacteriaceae

Meropenem has consistently strong activity against Enterobacteriaceae. Over 98% of strains tested by Pfaller and Jones[14] in Europe and North America were susceptible to meropenem. The minimum concentrations required to inhibit the growth of 90% of strains (MIC$_{90}$) ranged from <0.06 to 0.5 mg/L (table I). Imipenem demonstrated 4- to 32-fold less activity against the same pathogens (table I).[14]

Meropenem retained activity against ceftazidime-resistant (MIC $>$16 mg/L) Enterobacteriaceae: MIC$_{90}$ values ranged from 0.06 to 2 mg/L.[14,20] Consistent with this, meropenem was active at a concentration of 0.25 mg/L against all but 3 of 433 Klebsiella spp. known to produce extended-spectrum β-lactamases; the remaining 3 isolates were inhibited at concentrations of 2 to 4 mg/L.[21]

Non-Enteric Bacteria

In both Europe and North America, 91% of P. aeruginosa were susceptible to meropenem (MIC$_{90}$ 4 mg/L; table I). By comparison, imipenem inhibited 79.6 or 86.2% of strains, depending on the geographic location, with an MIC$_{90}$ of 16 mg/L.[14,20] Meropenem also compared well with ceftazidime (which inhibited 79 and 87% of strains) and ciprofloxacin (81 and 82%), and showed similar activity to piperacillin/tazobactam (92 and 95%) in this study.[14]

Meropenem exhibited good activity against Acinetobacter baumannii inhibiting ≥99% of strains with an MIC$_{90}$ of 1 or 2 mg/L (table I). Although the activity of the carbapenems generally remains strong against these difficult-to-treat
pathogens, infrequent outbreaks of isolates with decreased susceptibility or resistance to these agents have been documented worldwide.[15,17,22-24] Stenotrophomonas maltophilia are inherently resistant to the carbapenems (section 2.2.1). [14]

2.1.2 Gram-Positive Bacteria

Meropenem had good activity against viridans streptococci with respective MIC₉₀ values of 0.25, 0.12 and 1 mg/L against Streptococcus sanguis (n = 31), S. milleri (n = 22) and S. mitis (n = 12).[25]

In a Canadian study, the MIC₉₀ of meropenem was 2 mg/L against viridans group streptococci (n = 153).[26]

71 and 79% of Enterococcus faecalis isolated from Europe and North America, respectively, were susceptible to meropenem (table I); these rates were lower than those reported for imipenem (97 and 98%), piperacillin (91 and 99%) and piperacillin/tazobactam (98 and 95%).[14] 82% of E. durans and E. avium (n = 120) were susceptible to meropenem in a German study.[18]

![Table I. Overview of the in vitro activity of meropenem and imipenem against pathogens commonly implicated in intra-abdominal infections[14]](https://example.com/table-1)

<table>
<thead>
<tr>
<th>Species</th>
<th>Europe</th>
<th>North America</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>meropenem</td>
<td>imipenem</td>
</tr>
<tr>
<td></td>
<td>S (%)</td>
<td>MIC₉₀ (mg/L)</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>116 no. of isolates</td>
<td>100</td>
</tr>
<tr>
<td>Citrobacter freundii</td>
<td>445 no. of isolates</td>
<td>99.8</td>
</tr>
<tr>
<td>C. koseri</td>
<td>85 no. of isolates</td>
<td>100</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>167 no. of isolates</td>
<td>100</td>
</tr>
<tr>
<td>E. cloacae</td>
<td>683 no. of isolates</td>
<td>100</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>2228 no. of isolates</td>
<td>100</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td>354 no. of isolates</td>
<td>100</td>
</tr>
<tr>
<td>K. pneumoniae</td>
<td>860 no. of isolates</td>
<td>100</td>
</tr>
<tr>
<td>Morganella morganii</td>
<td>372 no. of isolates</td>
<td>100</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>997 no. of isolates</td>
<td>100</td>
</tr>
<tr>
<td>P. vulgaris</td>
<td>266 no. of isolates</td>
<td>100</td>
</tr>
<tr>
<td>Providencia retgeri</td>
<td>118 no. of isolates</td>
<td>100</td>
</tr>
<tr>
<td>P. stuartii</td>
<td>192 no. of isolates</td>
<td>100</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>2184 no. of isolates</td>
<td>91.0</td>
</tr>
<tr>
<td>Serratia marcescens</td>
<td>394 no. of isolates</td>
<td>99.7</td>
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<table>
<thead>
<tr>
<th>Species</th>
<th>Europe</th>
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<tbody>
<tr>
<td></td>
<td>meropenem</td>
<td>imipenem</td>
</tr>
<tr>
<td></td>
<td>S (%)</td>
<td>MIC₉₀ (mg/L)</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>901 no. of isolates</td>
<td>70.8</td>
</tr>
<tr>
<td>E. faecium</td>
<td>175 no. of isolates</td>
<td>23.4</td>
</tr>
<tr>
<td>Staphylococcus aureus (MS)</td>
<td>1478 no. of isolates</td>
<td>99.1</td>
</tr>
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</table>

<table>
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<tr>
<th>Anaerobes</th>
<th>Europe</th>
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<tbody>
<tr>
<td></td>
<td>meropenem</td>
<td>imipenem</td>
</tr>
<tr>
<td></td>
<td>S (%)</td>
<td>MIC₉₀ (mg/L)</td>
</tr>
<tr>
<td>Bacteroides fragilis</td>
<td>1130 no. of isolates</td>
<td>98.2</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>230 no. of isolates</td>
<td>100</td>
</tr>
<tr>
<td>C. difficile</td>
<td>106 no. of isolates</td>
<td>100</td>
</tr>
<tr>
<td>Peptostreptococcus anaerobius</td>
<td>102 no. of isolates</td>
<td>100</td>
</tr>
<tr>
<td>Prevotella bivia</td>
<td>158 no. of isolates</td>
<td>100</td>
</tr>
<tr>
<td>F. melaninogenica</td>
<td>44 no. of isolates</td>
<td>100</td>
</tr>
</tbody>
</table>

*Percentage of organisms considered to be susceptible (S) to meropenem or imipenem at the breakpoint set by the National Committee for Clinical Laboratory Standards (≤4 mg/L, for all organisms listed).

MIC₉₀ = minimum drug concentration required to inhibit the growth of 90% of isolates; MS = methicillin-sensitive.
Meropenem showed good activity against methicillin-susceptible *Staphylococcus epidermidis* (MIC$_{90}$ 0.5 mg/L; n = 31) [27] and *S. aureus* (MIC$_{90}$ 0.25 mg/L; table I). Imipenem had slightly more activity (up to 4-fold) than meropenem against these bacteria (table I).

As for other β-lactam agents, the carbapenems are inactive against *E. faecium* and methicillin-resistant *S. aureus* (MRSA). [14]

### 2.1.3 Anaerobes

Meropenem has good activity against anaerobes; over 98% of all studied species were susceptible to meropenem (table I). MIC$_{90}$ values for all anaerobes ranged from <0.06 mg/L for *Clostridium perfringens* to 2 mg/L for *C. difficile*. [14] Imipenem seemed to have similar or slightly less (up to 4-fold) activity than meropenem against these bacteria (table I). [14] A point of interest with regard to the treatment of intra-abdominal abscesses is that the *in vitro* activity of meropenem against *B. fragilis* group was virtually unaffected by alterations in pH (fig. 1). [28]

In 2 longitudinal studies, the susceptibility of *B. fragilis* to the carbapenems was unchanged [29] or even slightly improved [30] over 7- or 8-year study periods. In 2 other studies, which specifically looked at unusual anaerobes, meropenem inhibited 90% of all strains at concentrations of ≤2 mg/L, with the exception of *Actinomyces* spp. (n = 11; 4 mg/L) and *Lactobacillus* spp. (n = 15; 8 mg/L). [31,32]

### 2.2 Overview of Resistance Issues

For pathogens involved in intra-abdominal infections, the most likely resistance problem to be encountered is β-lactamase production. Other resistance mechanisms, because of the pathogens involved, are likely to be unusual and therefore will be discussed briefly for the purposes of completeness only.

#### 2.2.1 β-Lactamase Hydrolysis

The carbapenems are distinguished by their excellent stability against a wide range of serine-based β-lactamases. [33] These enzymes include chromosomally mediated β-lactamases and extended-spectrum variants of TEM and SHV. [34] Although stability against these common enzymes is not complete, the rate of hydrolysis is slow and only becomes significant when coupled with reduced outer membrane permeability (section 2.2.2). [33]

Some β-lactamases or carbapenemases, however, can effectively hydrolyse carbapenems (for reviews see Rasmussen & Bush [33] and Livermore [34]). These include: chromosomal enzymes which are ubiquitous in some unusual pathogens [e.g. *S. maltophilia*, *Aeromonas* spp., *Flavobacterium* (now *Chryseobacterium*) spp.]; chromosomal enzymes found rarely in other...
species (e.g. CcrA in a small subgroup of \textit{B. fragilis}; IMP-1 in \textit{P. aeruginosa} and \textit{Enterobacteriaceae}); and plasmid-mediated carbapenemases.\cite{22,33,34}

Imipenem is hydrolysed faster than meropenem by serine-based carbapenemases resulting in higher MIC values for relevant organisms.\cite{22,33} Both imipenem and meropenem induce chromosomal β-lactamases, although they do not appear to select stably derepressed mutants.\cite{35}

\subsection*{2.2.2 Impermeability Mechanisms}
Impermeability mechanisms constitute the major mechanism of resistance to the carbapenems and are most commonly found in \textit{P. aeruginosa}.\cite{36} Among \textit{Enterobacteriaceae}, isolated strains with outer membrane protein deficiencies have also been reported.\cite{36}

\subsection*{2.2.3 Alterations in Penicillin-Binding Proteins}
Modification of target penicillin-binding proteins (PBP) appears to be the least important of the 3 possible mechanisms of resistance for the carbapenems. Although unusual in Gram-negative bacteria, this mechanism of resistance has been implicated in \textit{A. baumannii}.\cite{36}

\subsection*{2.2.4 Selection of Resistance}
In general, meropenem seems to have a low potential for selecting resistant strains \textit{in vitro}, although the pattern of selection differs from that of imipenem. In one study, meropenem selected stably resistant mutants of \textit{Enterobacter cloacae} (uncharacterised), but only at concentrations of $\geq 32 \times$ MIC. Imipenem did not select resistant strains under the same conditions.\cite{37} In another study, meropenem selected porin-deficient mutants from 2 strains of \textit{K. pneumoniae} known to produce extended-spectrum β-lactamases. MIC values increased from 0.03 mg/L to 0.5 and 2 mg/L in the 2 strains. Imipenem also selected mutant strains (MIC values increased from 0.12 mg/L to 0.25 and 0.5 mg/L), although they were not porin deficient.\cite{38}

\subsection*{2.3 Other Effects}
\subsubsection*{2.3.1 Effects on Intestinal Flora}
Meropenem produces only minor alterations in the intestinal microflora of healthy volunteers, which is consistent with the fact that only about 2% of the drug is excreted in the faeces (section 3.1.2). Numbers of streptococci, enterobacteria, bacteroïdes, veillonella/acidaminococci and clostridia decreased and those of enterococci increased during a 7-day course of intravenous meropenem 0.5g every 8 hours in 10 healthy volunteers. All other intestinal flora were unaffected, although data were not supplied for fungi. \textit{C. difficile} was not isolated and colonisation with meropenem-resistant strains was not observed in any volunteer. All gut flora returned to normal within 2 weeks of completing treatment.\cite{39} There are currently no data concerning the 1g dose of meropenem or its effects in patients with intra-abdominal infections.

\subsubsection*{2.3.2 Inoculum Effect}
Bacteria are present throughout the gastrointestinal tract, although their distribution and numbers vary according to the precise anatomical site. Bacterial numbers range from $< 10^3$/ml in the stomach to as high as $10^{10}$ to $10^{12}$/ml in the colon\cite{1,40} and may also reach $10^9$/ml of pus in abscesses.\cite{41} β-lactams are affected to different degrees by the size of the bacterial inoculum, usually because of β-lactamase production.\cite{41} Given the high bacterial numbers in the gastrointestinal tract, this is an effect that may have clinical relevance in the treatment of intra-abdominal infections.

Meropenem, like other β-lactams, does exhibit an inoculum effect. However, the MIC values reported at a heavy inoculum [≈ $10^7$ colony forming units (cfu)/spot] remained generally low and ranged from 0.25 to 0.5 mg/L for \textit{B. fragilis},\cite{42} 0.03 to 2 mg/L for \textit{Enterobacteriaceae}, \textit{P. aeruginosa} and \textit{S. aureus},\cite{27} 0.03 to 1 mg/L for \textit{Enterobacteriaceae} expressing characterised chromosomal or plasmid-mediated broad- or extended-spectrum β-lactamases\cite{43,44} and 2 to 4 mg/L for \textit{P. aeruginosa} expressing a plasmid-mediated β-lactamase.\cite{44} A greater inoculum effect was observed with meropenem in strains expressing chromosomal...
β-lactamases (4- to 32-fold increase in MIC at 10⁷ cfu/ml) than in those expressing plasmid-mediated β-lactamases (0- to 4-fold change). [44]

2.3.3 Postantibiotic Effect

Carbapenems have a postantibiotic effect (PAE), defined as continued suppression of bacterial growth after short exposure to an antibiotic, against both Gram-negative and Gram-positive bacteria.[45] The size of the effect is, however, dependent on the assessment method used. If assessed using viable counts, PAEs were consistently ≤1.5 hours at meropenem concentrations of up to 75 mg/L against *P. aeruginosa, E. coli, K. oxytoca, K. pneumoniae* and *E. cloacae.*[45-48] However, if assessed using bioluminescence, PAEs ranged from 3.9 to 5.2 hours for *P. aeruginosa, E. coli, K. pneumoniae* and *E. cloacae* and 2.3 hours for *Serratia marcescens.*[47]

### 3. Pharmacokinetic Profile

The pharmacokinetic profile of meropenem is well established and described (for reviews see Mouton & van den Anker[52] and Drusano & Hutchinson[53]). A summary of the pharmacokinetics of meropenem in patients with intra-abdominal infections is provided in table II; for comparison, single dose data from healthy volunteers are also included in the table.

#### 3.1 Overview of Pharmacokinetics

**3.1.1 Absorption and Distribution**

As for other β-lactam agents, meropenem has linear pharmacokinetics over the dose range 0.25 to 2g.[53] Mean peak plasma concentrations (C<sub>max</sub>) of meropenem following a single 1g dose ranged from 54.8 to 61.6 mg/L in healthy volunteers (table II). However, in adult patients with intra-abdominal infections, both C<sub>max</sub> and area under the plasma concentration-time curve (AUC) were slightly lower compared with healthy volunteers (table II). Steady-state trough concentrations are approximately 0.25 mg/L with a dosage regimen of meropenem 1g administered 8-hourly in healthy volunteers.[53]

Meropenem is distributed in the extracellular (interstitial) fluid. In patients with intra-abdominal infections, the volume of distribution (Vd) tended to be up to approximately 2-fold higher compared with values observed in healthy volunteers (table II). Increases in Vd have been described with other antibacterial agents in surgical patients, including those with intra-abdominal sepsis.[54,55] Body-fluid shifts, possibly attributable to altered micro-

### Table II. Steady-state pharmacokinetics of intravenous meropenem in patients with intra-abdominal infections. Pharmacokinetic parameters were assessed after surgery. For comparison, single dose pharmacokinetic data of meropenem in healthy volunteers are also included[12,49]

<table>
<thead>
<tr>
<th>Patient group (no. patients/volunteers)</th>
<th>Meropenem (g)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</th>
<th>AUC (mg·L·h)</th>
<th>Vd (L)</th>
<th>CL (L/h)</th>
<th>CL&lt;sub&gt;R&lt;/sub&gt; (L/h)</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
</tr>
</thead>
</table>
| Healthy volunteers
  Adults[12] (n = 6-30/study) 1           | 54.8-61.6     | 66.9-77.5              | 12.5-23      | 11.3-16.8 | 7.9-11.9 | 1-1.4           |
  Adults[12] (n = 4-8/study) 0.5          | 21.1-35.6     | 28-39.6                | 11.7-26.1    | 11.2-19.8 | 7.6-15.1 | 0.8-1.54        |
  Elderly[49] (n = 8) 0.5                  | 37            | 58.4                   | 13.2<sup>a</sup> | 8.3<sup>b</sup> | 5.9<sup>b</sup> | 1.3             |
| Patients with intra-abdominal infections
  Adults[50] (n = 12) 1 q8h                | 47.6          | 57.5                   | 26.7         | 18.9    | 8.2      | 1.0             |
  Adults/elderly[51] (n = 8) 1 q8h        | NR            | 100                    | 20.7         | 11.4    | NR       | 1.3             |

<sup>a</sup> The age range of the volunteer group was 67-80 (mean 73) years.
<sup>b</sup> Unit given per 1.73m<sup>2</sup> of body surface area.
<sup>c</sup> Patients had moderate/severe surgical infections [peritonitis (n = 5), cellulitis (n = 2) or cholangitis (n = 1)]. The age range of the patient group was 23-79 (mean 60) years.

AUC = area under plasma concentration-time curve; CL = total body clearance; CL<sub>R</sub> = renal clearance; C<sub>max</sub> = peak plasma concentration; NR = not reported; q8h = every 8 hours; t<sub>1/2</sub> = elimination half-life; Vd = volume of distribution.
vascular permeability during sepsis or postoperative fluid sequestration, may explain these differences.\(^{[54,55]}\)

Meropenem concentrations in abdominal tissues and plasma following administration of a single 1g dose are shown in figure 2. Typically, meropenem concentrations in these tissues were in the range of 2 to 4 mg/L or 10 to 20% of \(C_{\text{max}}\), and were detectable in the colonic tissue for the whole dosing interval (fig. 2).\(^{[56]}\)

In normal and chronically inflamed pancreatic tissue, mean meropenem concentrations were 1.59 (range 0.24 to 3.16) mg/kg and 1.25 (range 0.33 to 2.31) mg/kg for 2.5 to 5.5 hours after pancreatic resection and administration of a 1g dose (n = 10).\(^{[59]}\) Meropenem concentrations in the bile were higher than those in abdominal tissues and ranged from 7 to 15 mg/L up to 3.5 hours after administration of a 1g dose.\(^{[56,60]}\) Meropenem was also distributed into the bile of patients with an obstructed biliary tree (mean 8.1 mg/L; n = 13), although these concentrations were significantly lower than those achieved in patients without biliary obstruction (14.8 mg/L; n = 11; \(p < 0.05\)).\(^{[60]}\) Plasma protein binding of meropenem is low (<20%).\(^{[53,56]}\)

### 3.1.2 Metabolism and Elimination

Meropenem is cleared predominantly in the kidney by both glomerular filtration and tubular secretion.\(^{[52]}\) Excretion is rapid and over 80% of an administered dose is excreted within 3 hours increasing to 95% within 8 hours.\(^{[61]}\) Over a 12-hour period, 71% of the parent drug was recovered from the urine and 19% as the metabolite.\(^{[61]}\) Biliary excretion of meropenem is therefore limited; 2.1% of a drug dose is recovered in the faeces.\(^{[61]}\)

Meropenem has a single open-ring metabolite (ICI 213689) which is pharmacologically inactive.\(^{[53]}\) It is formed by hydrolysis either by renal dehydropeptidase-I (DHP-I) or spontaneous chemical breakdown.\(^{[61]}\) The elimination half-life \((t_{1/2})\) of meropenem is approximately 1 hour (table II).

### 3.2 Special Patient Groups

#### 3.2.1 Elderly

In elderly patients, the clearance of meropenem is decreased and \(t_{1/2}\) prolonged secondary to the age-related decline in renal function. Following a single 0.5g dose of meropenem, the total body clearance of meropenem was 8.3 L/h \(\cdot\) 1.73m\(^2\) in 8 healthy elderly volunteers versus 12.2 L/h \(\cdot\) 1.73m\(^2\) in 8 younger volunteers. The respective values for \(t_{1/2}\) were 1.3 and 0.8 hours (table II).\(^{[49]}\) Dosage adjustment is therefore required in elderly patients with a creatinine clearance (CL\(_{\text{CR}}\)) of \(\leq 3\) L/h (section 7). The pharmacokinetics of meropenem appear to be otherwise unaltered in older patients with intra-abdominal infection (table II).\(^{[51]}\)

#### 3.2.2 Renal and Hepatic Impairment

In keeping with the renal elimination of meropenem, the clearance (total body and renal) of the drug decreases and \(t_{1/2}\) increases as CL\(_{\text{CR}}\) declines.\(^{[12]}\) For this reason, dosage reductions are recommended in patients with a CL\(_{\text{CR}}\) of \(\leq 51\) ml/min \((\leq 3\) L/h; section 7).

Since meropenem is effectively cleared by haemodialysis, administration of a unit dose is

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**Fig. 2.** Distribution of meropenem in abdominal tissues. Abdominal tissue samples were taken from patients undergoing elective intra-abdominal surgery (n = 66),\(^{[56]}\) peritoneal exudate samples from patients undergoing elective laparotomy (n = 26)\(^{[56,57]}\) and plasma samples from healthy volunteers (n = 6).\(^{[58]}\) All patients and volunteers received a single 1g dose of meropenem administered as a 30-minute intravenous infusion.
recommended following haemodialysis in order to restore plasma drug concentrations (section 7). In patients undergoing continuous veno-venous haemofiltration, an estimated 45 to 47% of a dose of meropenem is removed giving rise to the suggestion that a dosage of at least 1g once daily should be given to this patient group.\(^\text{[12]}\)

The pharmacokinetics of meropenem are, however, unaltered in patients with chronic stable alcoholic cirrhosis compared with controls\(^\text{[62]}\) and therefore no dosage adjustment is required in this patient group (section 7).

### 4. Therapeutic Efficacy

The efficacy of empirical monotherapy with meropenem in hospitalised patients with intra-abdominal infections has been assessed in several comparative clinical trials. Patients with infections of varying severities were included in these trials; for ease of understanding, they have been divided into moderate, moderate to severe and severe categories. All studies were multicentre and randomised, and 1 trial was double-blind.\(^\text{[63]}\) Although most clinical studies recruited patients with intra-abdominal infections only, 3 trials also included patients with other infection types.\(^\text{[64-66]}\)

Patients with moderate infections were defined as those who generally had an Acute Physiology and Chronic Health Evaluation (APACHE) II score of ≤10 and mainly comprised patients with appendicitis (table III). Patients with moderate to severe infections were those with more difficult-to-treat infections, including lower bowel traumatic perforations and infections arising from previous surgery (tables IV and V). These infections were usually community acquired (77 to 96%).\(^\text{[63,64,69]}\) Patients with severe infections were generally in intensive care and had difficult-to-treat infections which were often nosocomial or hospital acquired (table VI). Mortality rates in trials of patients with moderate to severe infection varied from 1 to 10%;\(^\text{[13,63,68,72,73]}\) higher rates (16 to 28%) were reported in trials that recruited patients with more severe infections.\(^\text{[64-66]}\)

Meropenem was administered intravenously generally at a dosage of 1g every 8 hours in patients with moderate to severe infections for a duration of 5 to 10 days. A lower dosage of 0.5g every 8 hours was used in 2 trials of patients with moderate infections.\(^\text{[13,68]}\) Most patients underwent surgery in conjunction with antibacterial therapy.

Primary end-points included clinical and bacteriological response. A satisfactory clinical re-

Table III. Comparative efficacy of meropenem (MEM) in the empirical treatment of patients with moderate intra-abdominal infections: summary of multicentre randomised trials. Patients generally had appendicitis and an APACHE II score of ≤10 (80-91% of pts). Drugs were administered intravenously every 8 hours for a period of between 5 to 10 days.

<table>
<thead>
<tr>
<th>Study</th>
<th>Most common diagnoses (% of pts)</th>
<th>No. of enrolled pts</th>
<th>Drug and dosage (g/day)</th>
<th>Percentage of pts with satisfactory response* (no. of evaluable pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basoli et al.(^\text{[67]})</td>
<td>Appendicitis (36%), cholecystitis (13%), diverticulitis (12%)</td>
<td>148 MEM 3 139</td>
<td>IPM/C 1.5</td>
<td>95 (100) 98 (100)</td>
</tr>
<tr>
<td>Brismar et al.(^\text{[13]})</td>
<td>Appendicitis (65%) which was usually perforated</td>
<td>132 MEM 1.5 117</td>
<td>IPM/C 1.5</td>
<td>98 (99) 96 (101)</td>
</tr>
<tr>
<td>Zanetti et al.(^\text{[68]})</td>
<td>Diverticulitis (42%), appendicitis (30%), colitis (14%), duodenal/gastric ulcer (13%)</td>
<td>82 MEM 1.5 79</td>
<td>IPM/C 2®</td>
<td>92 (71) 94 (64)</td>
</tr>
</tbody>
</table>

* Clinical response was satisfactory if symptoms were either cured or improved. Bacteriological response was satisfactory if there was proven or presumptive (satisfactory clinical response but no specimen obtained for culture) eradication of primary pathogens.

a Percentage of isolated pathogens eradicated.

b Administered every 6 hours.

c APACHE = Acute Physiology and Chronic Health Evaluation; IPM/C = imipenem/cilastatin; pts = patients.
response was defined as either complete resolution or improvement of symptoms at the end of treatment; a satisfactory bacteriological response was defined as proven or presumptive eradication of causative pathogen(s). Although overall clinical and bacteriological outcomes were generally reported, microbiological data, specifically in treatment failures, were limited in some investigations. Most studies included a 2- to 4-week follow-up period to assess rates of relapse and failure but few studies actually reported these results.

The efficacy of meropenem monotherapy has also been evaluated in 2 clinical trials enrolling children; however, the proportion of children with intra-abdominal infections in these studies was small (<8%), and consequently, these data along

### Table IV. Comparative efficacy of meropenem (MEM) in the empirical treatment of patients with moderate to severe intra-abdominal infections: summary of multicentre randomised trials, 1 of which was double-blind. All drugs were administered intravenously every 8 hours for a period of between 5 to 10 days

<table>
<thead>
<tr>
<th>Study</th>
<th>Infection severity and site (% of pts)</th>
<th>No. of enrolled pts</th>
<th>Drug and dosage (g/day)</th>
<th>Percentage of pts with satisfactory responsea (no. of evaluable pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>clinical bacteriological</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MEM 3</td>
<td>96b (82) 84b (82)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IPM/C 3</td>
<td>94b (88) 81b (88)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MEM 3</td>
<td>100b (28) 90b (NR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IPM/C 3</td>
<td>97 (31) 100b (NR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MEM 3</td>
<td>98 (43) 96 (27)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IPM/C 3</td>
<td>95 (41) 96 (27)</td>
</tr>
<tr>
<td></td>
<td>Moderate (60%) to severe (25%) infection, mainly appendicitis (34%), small/large bowel (21%) caused by previous surgery (18%), cholangitis (15%)</td>
<td>116</td>
<td>MEM 3</td>
<td>91* (70) 90 (48)</td>
</tr>
<tr>
<td></td>
<td>Moderate to severe infection, mainly appendicitis (42%), gastric or duodenal ulcer perforation (26%) or cholecystitis (15%)</td>
<td>30</td>
<td>MEM 3</td>
<td>95* (43) 94 (33)</td>
</tr>
<tr>
<td></td>
<td>Peritonitis (76%)</td>
<td>43</td>
<td>MEM 3</td>
<td>93* (68) 92 (NR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IPM/C 3</td>
<td>97 (42) 92 (32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MEM 3</td>
<td>93* (68) 92 (32)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>IPM/C 3</td>
<td>97 (42) 92 (32)</td>
</tr>
<tr>
<td></td>
<td>Moderate to severe (26%) infections, mainly appendicitis (34%), stomach (17%), small bowel (16%), colon/rectum (14%)</td>
<td>77</td>
<td>MEM 3</td>
<td>91** (70) 90 (48)</td>
</tr>
<tr>
<td></td>
<td>Perforated appendix (37%), colon (33%), epigastric (30%)</td>
<td>48</td>
<td>MEM 3</td>
<td>95 (43) 94 (33)</td>
</tr>
<tr>
<td></td>
<td>Serious bacterial infections including intra-abdominal infections (76%)</td>
<td>81</td>
<td>CTX 6 + MTR 1.5</td>
<td>75 (40) 81 (32)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MEM 3</td>
<td>93 (68) 92 (NR)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CTX 6 + MTR 1.5</td>
<td>75 (40) 81 (32)</td>
</tr>
<tr>
<td></td>
<td>Complicated appendicitis (73%), large/small bowel perforation (13%), abscess (4%)</td>
<td>215</td>
<td>MEM 3</td>
<td>967 (97) 967 (97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CM 2.7 + TM 15 mg/kg</td>
<td>93 (94) 93 (94)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MEM 3</td>
<td>96 (97) 96 (97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IPM/C 3</td>
<td>94 (94) 93 (94)</td>
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<td></td>
<td></td>
<td></td>
<td>MEM 3</td>
<td>96 (97) 96 (97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IPM/C 3</td>
<td>94 (94) 93 (94)</td>
</tr>
</tbody>
</table>

- **a** Clinical response was satisfactory if symptoms were either cured or improved. Bacteriological response was satisfactory if there was proven or presumptive (satisfactory clinical response but no specimen obtained for culture) eradication of primary pathogens. All responses were assessed at the end of treatment.
- **b** At follow-up 2 to 4 weeks after the end of treatment, 90 and 88% of pts receiving MEM and IPM/C, respectively, had a satisfactory clinical response and 84 and 79% of pts had a satisfactory bacteriological response.
- **c** At follow-up ≥1 month after the end of treatment, 97 and 94% of pts receiving MEM and IPM/C, respectively, had a satisfactory clinical response.
- **d** Percentage of isolated pathogens eradicated.
- **e** Three treatment failures occurred because of surgical misadventure.
- **f** At follow-up 8 weeks after the end of treatment, 96 and 93% of pts receiving MEM and CTX + MTR, respectively, had a satisfactory clinical response.
- **g** At follow-up 4 to 14 days after the end of treatment, 98 and 93% of pts receiving MEM and CM + TM, respectively, had a satisfactory clinical response and 100% of pts in both the MEM and CM + TM groups had a satisfactory bacteriological response.

NR = not reported; pts = patients; * p < 0.008 vs comparator.
with those from noncomparative studies will not be discussed further. Currently there are no available data on the use of meropenem in patients with chronic ambulatory peritoneal dialysis-associated peritonitis.

4.1 Moderate Infections

A satisfactory clinical response was obtained in 92 and 98% of patients with intra-abdominal infections of moderate severity treated with meropenem 1.5 g/day compared with rates of 94 and 96% with imipenem/cilastatin 1.5 or 2 g/day in 2 multicentre, randomised trials (table III). Similar results (95 vs 98%) were obtained in an Italian-based study in which patients received a 3 g/day dosage of meropenem but a reduced 1.5 g/day dosage of imipenem/cilastatin.

Bacteriological response rates (95 to 98% for both drugs) were similar to the rates of clinical response in 2 trials, although slightly lower rates were documented in the remaining trial which gave results on a per pathogen basis (87% with meropenem vs 93% with imipenem/cilastatin).

4.2 Moderate to Severe Infections

4.2.1 Comparisons with Imipenem/Cilastatin

Clinical Response

In patients with moderate to severe infections, clinical response rates were similar in patients who received either meropenem or imipenem/cilastatin (both 1g every 8 hours) in 3 multicentre, randomised trials (table IV). In these trials, patients receiving meropenem had response rates ranging from 96 to 100%; corresponding response rates in imipenem/cilastatin recipients ranged from 94 to 97%.

At follow-up (generally 2 to 4 weeks after the end of treatment), clinical responses in evaluable patients were similar to those obtained at the end of treatment.

Bacteriological Response

In patients receiving meropenem, satisfactory bacteriological eradication rates ranged from 84 to 96%; those in patients receiving imipenem/cilastatin ranged from 81 to 100% (table IV).

On a per pathogen basis, meropenem and imipenem/cilastatin were similar in the eradication of Gram-negative pathogens at a dosage of 3 g/day (87 to 95% vs 93 to 100%) in 3 multicentre trials.
which provided details (table V). Variable eradication rates were obtained for meropenem (range 80 to 100%) and imipenem/cilastatin (range 90 to 100%) against Gram-positive pathogens. Although meropenem and imipenem/cilastatin produced similar high eradication rates against anaerobic bacteria, the number of isolates was small in 2 of 3 studies (table V). No statistical comparisons were available for these data.

### 4.2.2 Comparisons with Cefotaxime plus Metronidazole

#### Clinical Response

Three clinical trials which compared meropenem with a cefalosporin-based regimen consisting of cefotaxime (1 or 2 g every 8 hours) plus metronidazole (0.5 g every 8 hours) reported contrasting results (table IV). Patients receiving meropenem (1 g every 8 hours), however, achieved high rates (91 to 95%) of satisfactory clinical response in all trials.

One study found that a significantly higher proportion of patients receiving meropenem achieved a satisfactory clinical response compared with those receiving the cefalosporin-based regimen (95 vs 75%; p = 0.008) [table IV]. However, in another study in patients with local or diffuse peritonitis, those receiving the cephalosporin-based regimen had a significantly better response rate compared with those receiving meropenem (100 vs 91%; p = 0.008). This apparent difference in clinical response may have been attributable to a slight imbalance between treatment groups: a higher proportion of patients in the meropenem group had APACHE II scores between 11 and 20 (19 vs 12% of patients receiving cefotaxime plus metronidazole), and were more likely to have nasogastric tubes (74 vs 59%), indwelling catheters (68 vs 55%) or, more significantly, infections attributable to previous intra-abdominal surgery (9 vs 1 patient). In the third trial, meropenem 3 g/day produced a similar rate of clinical response compared with low dose cefotaxime (1 g every 8 hours) plus metronidazole (0.5 g every 8 hours) in patients with a range of serious bacterial infections (table IV); 76% of patients in this study had intra-abdominal infections. Bacteriological Response

Bacteriological eradication rates with meropenem were consistently similar to those achieved with cefotaxime plus metronidazole in 2 trials reporting these data (table IV).
When analysed by pathogen in 2 studies (table V), meropenem showed similar eradication rates to the cephalosporin-based regimen against Gram-negative and anaerobic pathogens in 1 study. In another study, meropenem was marginally more effective than cephalosporin-based treatment against Gram-negative pathogens (94 vs 81%), although a statistical analysis was not provided.

In both studies, the cephalosporin-based regimen tended to be slightly more effective against Gram-positive pathogens with eradication rates of 100 vs 89 and 93%; there were only 13 Gram-positive isolates in 1 study and statistical data were not provided in either study (table V).

4.2.3 Comparison with Clindamycin plus Tobramycin

Clinical Response

Preliminary data from the trial of Wilson have been previously reported by Bern et al. and Condon et al., but these papers will not be discussed further. According to Wilson, meropenem (1 g every 8 hours) when compared with clindamycin (0.9 g every 8 hours) plus tobramycin (15 mg/kg/day) produced similar clinical response rates in a multicentre, randomised, double-blind study (table IV); rates were 96% after meropenem and 93% after clindamycin plus tobramycin. The rate of satisfactory clinical response was maintained at follow-up performed 4 to 14 days later.

Bacteriological Response

Bacteriological response rates were 96 and 93%, respectively, after meropenem and clindamycin plus tobramycin (table IV). These rates improved to 100% in both treatment groups at follow-up 4 to 14 days later, and were maintained through to day 42 in the aminoglycoside-based group versus 94% of patients in the meropenem group.

Meropenem demonstrated marginally higher rates of eradication compared with clindamycin and tobramycin against Gram-negative (99 vs 90%), Gram-positive (99 vs 90%) and anaerobic organisms (97 vs 87%) [table V]; however, no statistical analyses were reported.

4.3 Severe Infections

Meropenem and imipenem/cilastatin demonstrated similar clinical efficacy in 2 comparative trials which recruited patients with serious infections and included over 50 patients each with severe intra-abdominal infections (table VI). Administered at dosages of 3 g/day, clinical response rates were 82 and 96% with meropenem versus 81 and 77% with imipenem/cilastatin in patients with intra-abdominal infections in the 2 trials. Relapses were observed during the follow-up period in 1 meropenem and 3 imipenem/cilastatin recipient(s) with intra-abdominal infections in one trial which provided details. In those for whom empirical treatment was unsuccessful, a total of 11 of 14 patients had infections from previous surgery, confirming that this is a difficult-to-treat patient group.

Bacteriological response rates were also similar with meropenem and imipenem/cilastatin (68 and 78% vs 70 and 70%); although details of bacteriological outcome according to causative pathogen and of superinfections were provided in both trials, they were not detailed on a per infection basis and so will not be discussed further.

Good results were also obtained with meropenem in 3 other randomised studies which recruited patients with serious infections including a very small proportion of patients with intra-abdominal infections. Ten of 13 patients receiving meropenem 3 g/day versus 5 of 7 patients treated with imipenem/cilastatin 3 g/day achieved a satisfactory clinical response in 1 trial as did 3 of 3 versus 3 of 5 patients in another. In the last trial, which recruited patients aged ≥ 65 years, 4 of 7 recipients of meropenem 3 g/day and 2 of 3 recipients of cefuroxime 4.5 g/day plus gentamicin 4 mg/kg achieved a satisfactory outcome.

4.4 Efficacy According to Infection Site

Clinical trials investigating the efficacy of antibacterial regimens in the treatment of intra-abdominal
infections invariably recruit a mixed group of patients with infections at different anatomical sites. Not all infections have a similar outcome; infections involving the lower gastrointestinal tract tend to have a poorer outcome than some other infection types, including appendicitis (section 1).[1,85]

In a retrospective analysis of 4 clinical trials,[85] meropenem consistently achieved a satisfactory response rate in over 89% of patients regardless of the anatomical site of intra-abdominal infection (n = 217; fig. 3). Comparator regimens generally performed equally well (n = 212), although statistical analysis was inappropriate because the data were combined from different clinical trials. Notably all regimens, with the possible exception of imipenem/cilastatin, performed best in patients with complicated appendicitis (fig. 3).[85]

The efficacy of meropenem was also retained in both diffuse and localised peritonitis (fig. 4) and in patients with concurrent septicaemia. In 3 clinical trials that provided data on the outcome of patients with septicaemia, meropenem 3 g/day achieved a satisfactory response in 3 of 3 patients in 2 trials[69,72] and 35 of 38 patients in another.[64]

4.5 Persistent Pathogens and Superinfections

Superinfections and bacteriological failures were documented in a number of studies.[113,69,72,73,80,81] In those which reported bacteriological results, bacteriological failure was reported in 4 to 16% of patients (table IV) and the most common persistent organisms following meropenem therapy included E. coli, other Enterobacteriaceae, enterococci, Streptococcus spp. and P. aeruginosa.[63,64,67,73,80,81] The resistance phenotypes of persistent pathogens were not characterised in any study.

This picture is consistent with an overview of 6 clinical trials[86] which reported eradication rates achieved with meropenem in patients with intra-abdominal infections on a per pathogen basis. Eradication rates exceeded 90% for E. coli (n = 185), K. pneumoniae (n = 26), B. fragilis (n = 67) and S. epidermidis (n = 14). Other pathogens were eradicated at a rate of 78% for E. faecalis (n = 18), 80% for E. cloacae (n = 10) and 89% for P. aeruginosa (n = 28).

Superinfections in meropenem recipients were reported in 3 studies: these occurred in 2 of 48 patients,[72] 5 of 82 patients,[69] and 9 of 94
patients. Similar rates were observed with comparator regimens: 3 of 52 with cefotaxime plus metronidazole, and 12 of 88 and 5 of 81 patients with imipenem/cilastatin. Superinfecting pathogens, which were reported in 2 studies, were E. faecalis and coagulase-negative staphylococci in 1 study, and E. coli (2 isolates), K. oxytoca (1), E. aerogenes (1), E. faecalis (3), Enterococcus spp. (1), S. milleri (3), Peptostreptococcus spp. (1), C. innocuum (1), B. fragilis (3), other Bacteroides spp. (5), Fusobacterium prausnitzii (1) and Candida spp. (1) in the other. Resistant superinfecting organisms reported in 1 study were enterococci, S. milleri and coagulase-negative staphylococci; 10 strains were resistant to meropenem compared with 9 to imipenem/cilastatin.

5. Pharmacoeconomic Considerations

This section provides a brief overview of the published pharmacoeconomic data on meropenem that are relevant to its use in the treatment of intra-abdominal infections. The cost analyses available for meropenem pertain to direct drug-related costs only; a summary of these is provided in table VII (for review see Holliday & Benfield). A single cost-effectiveness study in patients with intra-abdominal infections has also recently been published.

Unlike imipenem/cilastatin, meropenem can be administered by bolus injection or infusion (section 7). In 2 clinical trials in patients with intra-abdominal infections which provided appropriate data, meropenem was administered by bolus injection in just over half (≤60%) of the patient group.

In the 2 cost analyses that compared delivery methods of meropenem, bolus administration was associated with delivery cost savings of approximately 30% in an Australian study (table VII) and 45% in a UK study compared with an infusion of the drug. Savings were related to the use of fewer consumables and slightly lower labour costs in one study. Any differences in total direct costs between the various meropenem and imipenem/cilastatin regimens was predominantly a reflection of these differences in delivery costs (table VII).

Of interest also are the delivery costs for ceftazidime 2g plus metronidazole 0.5g given 3 times daily by infusion which were approximately £110 compared with £90 for meropenem 1g given 3 times daily (delivery method not stated; data estimated from a graph). The duration of hospitalisation, a major healthcare cost, also has implications for the overall costs of treatment. In 3 clinical trials in patients with intra-abdominal infections that presented these
data, 2 reported similar mean durations of hospitalisation with meropenem versus cefotaxime plus metronidazole (11.5 vs 11.7 days)\textsuperscript{[64]} and imipenem/cilastatin (17 vs 16.9 days).\textsuperscript{[68]} but the remaining study reported a significantly shorter hospital stay with meropenem than with clindamycin plus tobramycin (8 vs 9.4 days; \(p = 0.01\)).\textsuperscript{[80]}

A retrospective cost-effective analysis, which compared meropenem and imipenem/cilastatin based on the data from the trial by Basoli et al.\textsuperscript{[67]} (table III), is available.\textsuperscript{[91]} The analysis, however, was based on a study which used nonequivalent dosages of the 2 agents (imipenem/cilastatin 1.5 g/day vs meropenem 3 g/day), a factor which is likely to have had a considerable effect on the cost outcome as direct costs only were considered in the analysis. From the perspective of the Italian National Health Service, it was estimated that treatment with imipenem/cilastatin 1.5 g/day cost L3.6 million/patient versus L4.5 million for meropenem administered at the higher dosage of 3 g/day. The results were similar from the perspective of a private health insurer also.

### 6. Tolerability

The tolerability of meropenem has been evaluated in a number of safety analyses conducted in patients with a wide range of infections, including intra-abdominal infections.\textsuperscript{[93-95]} This review focuses on an overview of tolerability data obtained from clinical trials of meropenem compared with other therapeutic regimens in 9514 patients.\textsuperscript{[93]} Data from 46 trials (45 comparative and 1 non-comparative) were evaluated in this overview.

### Table VII. Direct drug-related costs of meropenem (MEM) and imipenem/cilastatin (IPM/C): summary of 3 cost analyses

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country (year)</th>
<th>Dosage regimen</th>
<th>Method of delivery</th>
<th>Costs(^a)</th>
<th>delivery (b)</th>
<th>total (per day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marquina et al.\textsuperscript{[87]}</td>
<td>Spain (NA)</td>
<td>MEM 0.5 tid</td>
<td>Infusion</td>
<td>Pta2.52 Pta0.12</td>
<td>Pta7.91</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MEM 1 tid</td>
<td>Infusion</td>
<td>Pta4.37 Pta0.12</td>
<td>Pta13.46</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPM/C 0.5 qid</td>
<td>Infusion</td>
<td>Pta2.07 Pta0.10</td>
<td>Pta9.41</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPM/C 1 tid/qid</td>
<td>Infusion</td>
<td>Pta4.13 Pta0.16</td>
<td>Pta15.86</td>
<td></td>
</tr>
<tr>
<td>Plumridge\textsuperscript{[88]}</td>
<td>Australia (1997)</td>
<td>MEM 0.5 tid</td>
<td>Bolus</td>
<td>A$26.67 A$6.26</td>
<td>A$98.79</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MEM 1 tid</td>
<td>Bolus</td>
<td>A$53.34 A$6.86</td>
<td>A$180.60</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MEM 0.5 tid</td>
<td>Infusion</td>
<td>A$26.67 A$9.24</td>
<td>A$107.73</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MEM 1 tid</td>
<td>Infusion</td>
<td>A$53.34 A$9.99</td>
<td>A$189.99</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPM/C 0.5 tid</td>
<td>Infusion</td>
<td>A$24.81 A$11.23</td>
<td>A$108.12</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPM/C 1 tid</td>
<td>Infusion</td>
<td>A$49.62 A$14.52</td>
<td>A$192.42</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPM/C 0.5 qid</td>
<td>Infusion</td>
<td>A$24.81 A$11.23</td>
<td>A$144.16</td>
<td></td>
</tr>
<tr>
<td>Smyth et al.\textsuperscript{[89]}</td>
<td>UK (1996)</td>
<td>MEM 0.5 tid</td>
<td>Bolus</td>
<td>£15.00 NA</td>
<td>£52.86(^c)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MEM 1 tid</td>
<td>Bolus</td>
<td>£30.00 NA</td>
<td>£97.14(^c)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MEM 0.5 tid</td>
<td>Infusion</td>
<td>£15.00 NA</td>
<td>£58.57(^c)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MEM 1 tid</td>
<td>Infusion</td>
<td>£30.00 NA</td>
<td>£103.57(^c)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPM/C 0.5 tid</td>
<td>Infusion</td>
<td>£15.00 NA</td>
<td>£60.71(^c)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPM/C 1 tid</td>
<td>Infusion</td>
<td>£30.00 NA</td>
<td>£107.14(^c)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPM/C 0.5 qid</td>
<td>Infusion</td>
<td>£15.00 NA</td>
<td>£77.14(^c)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IPM/C 1 qid</td>
<td>Infusion</td>
<td>£30.00 NA</td>
<td>£141.43(^c)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Conversion factors as of 20 June 2000: $US1.00 = A$0.38 = £0.66 = Pta172.39.

\(^b\) Included the costs associated with labour (preparation, administration and observation),\textsuperscript{[87]} labour and consumables (needles, syringes, diluent, ethanol swab, minibag of sterile solution, minibag label and saline flushes for intravenous lines)\textsuperscript{[88]} and costs of labour (preparation, administration), consumables (gloves, needles, diluent, syringes, etc) and waste disposal.\textsuperscript{[89]}

\(^c\) Data estimated from a graph.

NA = not available; Pta = peseta; qid = 4 times daily; tid = 3 times daily.
which compared meropenem (5026 treatment exposures) with imipenem/cilastatin (1801 treatment exposures), cephalosporin-based regimens (2423 treatment exposures) and clindamycin plus aminoglycoside regimens (527 treatment exposures). No statistical comparisons were made between meropenem and the comparator regimens. The most common types of infections included lower respiratory tract (2196 treatment exposures), intra-abdominal (2131 treatment exposures) and urinary tract infections (1192 treatment exposures); children were also included in this review (926 treatment exposures).

Data from clinical trials in patients with intra-abdominal infections (section 4) are also included where they expand on the information provided by the overview.

6.1 Overview of Tolerability Profile

The overall incidences of adverse events, drug-related adverse events (definitely, probably or possibly related to the drug), adverse events leading to withdrawal and mortality were similar between meropenem and its comparators (fig. 5). These results are generally supported by those from trials involving patients with intra-abdominal infections which showed a similar incidence of clinical adverse events with meropenem and comparator regimens. [13,63,64,67,71-73,80]

Drug-related events most frequently associated with meropenem were diarrhoea (2.3%), rash (1.4%), nausea/vomiting (1.4%) and local inflammation at the injection site (1.1%; fig. 6). Other events (headache, pruritus, abdominal pain, and sepsis) were reported at an incidence of <0.4%. There was no indication that the incidence of diarrhoea, rash or nausea/vomiting with meropenem was dose related. [93]

6.2 Gastrointestinal Events

Gastrointestinal events, a characteristic adverse effect of most antibacterial agents, are likely to be particularly relevant to patients who have recently undergone intra-abdominal surgery. A concern with imipenem/cilastatin is that the incidence of nausea and vomiting is linked to the rate of administration and dosage of the drug. [96-98] With meropenem, however, the incidence of nausea and vomiting is not dose related (n = 3504) [93] and the agent can be administered without regard to the rate of infusion (section 7).
Gastrointestinal events associated with imipenem/cilastatin can be managed, to some degree, by decreasing the rate of infusion of the drug. This option was pursued in some of the trials involving patients with intra-abdominal infections (imipenem/cilastatin was infused over 30- to 60-minutes); consequently, the reported incidence of gastrointestinal events in these trials was generally low (3 reports of nausea and vomiting with imipenem/cilastatin [68,69] vs 2 reports with meropenem [69]).

In trials of patients with intra-abdominal infections that reported relevant details, one case of C. difficile-related colitis was reported with meropenem 3 g/day and one case also with the comparator regimen (cefotaxime plus metronidazole). In 2 other trials which tested stool specimens in patients who developed diarrhoea, no sample was found to be positive for C. difficile toxin.

6.3 Seizure Potential

A tolerability concern with β-lactam agents is their potential to cause CNS toxicity and seizures. With regard to the CNS, meropenem appears to be well tolerated and is therefore indicated in those with meningitis. Imipenem/cilastatin, on the other hand, is associated with a risk of seizures, particularly in those with predisposing factors such as renal dysfunction, underlying CNS pathology or advanced age, and is not recommended at dosages in excess of 4 g/day because of associated neurotoxicity.

In an overview of 46 clinical trials, which excluded patients with meningitis and a history of...
CNS disorders, the incidence of meropenem-related seizures was 0.08% of treatment exposures.[93] In comparison, the incidence of seizures with imipenem/cilastatin was 0.28% and 0.05% with cephalosporin-based therapies. No seizures associated with clindamycin plus aminoglycoside were reported. The 4 patients who developed seizures with meropenem were elderly and 2 had renal impairment (CLCR 2.5 and 3.1 L/h).[93]

In clinical trials in patients with intra-abdominal infections which compared meropenem with imipenem/cilastatin,[13,65,67-71] cefotaxime plus metronidazole[64,72,73] or clindamycin plus tobramycin,[63,80,81] there were no reports of seizures with meropenem. Convulsions were reported in 2 patients treated with imipenem/cilastatin[13,66] and there was also 1 report of a patient with convulsions after cefotaxime plus metronidazole.[72] Most studies excluded those with a history of CNS disorders or seizures.[63-66,68,69,71-73,81]

6.4 Laboratory Events

The incidence of laboratory adverse events was similar between meropenem and imipenem/cilastatin recipients. However, cephalosporin-based regimens tended to produce a lower incidence and clindamycin plus aminoglycoside a slightly higher incidence of events; no statistical analysis of the results was provided.[93] Laboratory events most commonly associated (≥1% of treatment exposures) with meropenem included thrombocytosis (1.6%) and increases in ALT (4.3%), AST (3.4%) and alkaline phosphatase (1.5%).[93]

These findings were consistent with those observed in clinical trials,[13,63,68,70,72,73,81] although a higher incidence of increases in ALT and AST were observed with meropenem in 1 study.[63]

6.5 Elderly Patients

Elderly patients (>65 years of age) experienced more adverse events compared with younger patients after receiving meropenem (45 vs 39%) according to an overview of clinical trial data.[95] However, the frequency of drug-related events and drug-related withdrawals was similar between groups.[95] Similar trends were seen in the imipenem/cilastatin and cephalosporin comparator groups.[95]

Most clinical trials in patients with intra-abdominal infections comparing meropenem with imipenem/cilastatin,[13,67-69,71] cefotaxime plus metronidazole[64,72,73] or clindamycin plus tobramycin[63,81] included a proportion of elderly patients in their study population. Except for 2 elderly patients receiving meropenem 3 g/day who died of complications caused by underlying disease subsequent to septic shock, no other studies specifically reported adverse events in the elderly associated with meropenem.

7. Dosage and Administration

Meropenem is indicated as monotherapy for the treatment of intra-abdominal infections.[102,103] According to the manufacturer’s recommendations,[99] meropenem should be administered intravenously at a dosage of 1.5 to 3 g/day in 3 divided doses depending on the type and severity of infection, the susceptibility of the pathogen(s) and the condition of the patient.[99] However, at a national level, dosage recommendations may vary. For example, in the US a fixed dosage of 1 g every 8 hours is recommended for adult patients with intra-abdominal infections[104] and, in the UK,[102] a similar dosage is recommended for the treatment of peritonitis. Meropenem can be administered as an intravenous bolus injection over approximately 3 to 5 minutes or an intravenous infusion over approximately 15 to 30 minutes.[99,102,103]

Dosage recommendations for meropenem in special patient groups is presented in table VIII. Additionally, because meropenem is cleared by haemodialysis, a unit dose relative to the type and severity of infection should be administered after haemodialysis.[102,103] There are currently no dosage recommendations for patients undergoing peritoneal dialysis or haemofiltration; however, an estimated 45 to 47% of a dose of meropenem is removed in those undergoing continuous venovenous haemofiltration giving rise to the suggestion...
that the dosage in this patient group should be increased to at least 1g daily.[12]

8. Place of Meropenem in the Management of Patients with Intra-Abdominal Infections

Antibacterial therapy forms only part of any programme for the management of intra-abdominal infections. Early intervention, appropriate surgery and respiratory, haemodynamic and nutritional support are also key components. The exact contribution of any antibacterial regimen can therefore be difficult to isolate, but its function is to reduce the incidence of abscesses or peritonitis and wound complications.

A debate that is central to the effective management of intra-abdominal infections is that of breadth of coverage of the initial empirical regimen, but there is little consensus on this issue. Many question the need for a regimen which covers more than the common facultative and obligate anaerobes in the treatment of milder community-acquired infections.[1,5,6] This viewpoint is supported by the purpose-designed trial of Christou et al.[3] which demonstrated similar clinical outcomes with broad- (imipenem/cilastatin) and limited-spectrum (cefoxitin) agents in patients with moderate intra-abdominal infections. This has lead some to suggest that broad-spectrum regimens should be reserved for second-line therapy or for the treatment of more severe or difficult-to-treat infections.[105]

Another concern regarding the unnecessary use of broad-spectrum agents, as with any bacterial infection, is the possible development of unwanted bacterial resistance. However, it is interesting to note in the trial by Christou et al.[3] that resistance developed in significantly more cefoxitin than imipenem/cilastatin recipients (12 vs 1; p = 0.003) and also that treatment failure resulted in death in 2 cefoxitin recipients, suggesting that the broader spectrum agent did offer some added benefit to this patient group.

In the treatment of more severe or nosocomial infections, it is well recognised that broad antibacterial coverage is needed and indeed may be life-saving.[105] Nosocomial intra-abdominal infections are associated with high levels of morbidity and mortality.[7] Further, it has been demonstrated that the number of treatment failures increases as a function of infection severity (assessed by APACHE II score).[106]

It is against this background that the results achieved with meropenem in the treatment of intra-abdominal infections should be viewed. Meropenem is a broad-spectrum agent with an activity profile that encompasses Gram-negative, Gram-positive and anaerobic bacteria. As empirical monotherapy, meropenem achieved satisfactory clinical response rates in excess of 90% of patients with moderate to severe infections acquired predominantly in the community. The efficacy of meropenem was similar to that of other standard regimens in this patient group; bacteriological data did not reveal any differences between regimens.

Clearly a range of effective empirical options are available for the treatment of moderate to severe intra-abdominal infections and appropriate selection for an individual patient is important. Although there is little to distinguish between the standard combination regimens of cefotaxime plus metronidazole or clindamycin plus tobramycin and meropenem in terms of efficacy in this patient group, meropenem does offer some theoretical benefits. As a β-lactam agent, meropenem does not have the renal and auditory tolerability problems associated with aminoglycoside-containing

### Table VIII. Dosages recommendations for intravenous meropenem in special patient groups[99,102,104]

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Recommended dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly patients</td>
<td>1g q8h a</td>
</tr>
<tr>
<td>Patients with hepatic impairment</td>
<td>None</td>
</tr>
<tr>
<td>Patients with renal impairment</td>
<td></td>
</tr>
<tr>
<td>CLCR 1.56 to 3 L/h</td>
<td>1g q12h</td>
</tr>
<tr>
<td>CLCR 0.6 to 1.5 L/h</td>
<td>0.5g q12h</td>
</tr>
<tr>
<td>CLCR &lt;0.6 L/h</td>
<td>0.5g q24h</td>
</tr>
</tbody>
</table>

a No dosage adjustment is necessary in patients with a CLCR >3 L/h.

CLCR = creatinine clearance; qxh = every x hours; .
regimens nor does it require therapeutic drug monitoring or renal function tests. It also offers the convenience of a single agent with a relatively simple administration schedule compared to that of the combination regimens. Preliminary reports suggesting that delivery costs are 18% lower with meropenem compared with combination regimens are also worth investigating further from a cost perspective.

Meropenem and imipenem/cilastatin also showed similar efficacy in the treatment of patients with moderate to severe intra-abdominal infections. This is despite subtle differences between their in vitro activity profiles. For example, meropenem has greater activity against Gram-negative organisms, imipenem against Gram-positive organisms and meropenem is more stable against hydrolysis by serine-based β-lactamases. The similar clinical results are possibly a function of the numbers of patients involved in these trials or the fact that most infections were community acquired.

Meropenem and imipenem/cilastatin do, however, differ with regard to their tolerability profiles. The risk of seizures with meropenem is comparable to that of the cephalosporins. Imipenem/cilastatin, on the other hand, is associated with a risk of seizures, particularly in certain patient groups. For this reason, meropenem can be administered in patients with CNS disorders and up to a maximum dosage of 6 g/day versus 4 g/day for imipenem/cilastatin. Another point of difference, one that is potentially important in those who have recently undergone intra-abdominal surgery, is that of gastrointestinal events which with imipenem/cilastatin are linked to rate of administration and dosage. Although these can be managed by slowing the rate of infusion, this contrasts with meropenem which can be administered without regard for this factor.

In some trials in patients with infections of moderate severity, meropenem was administered successfully at a lower dosage of 1.5 g/day and achieved similar results to imipenem/cilastatin 1.5 or 2 g/day. These findings are in contrast to 2 other trials which reported treatment failure in 19 to 24% of patients with intra-abdominal infections following treatment with imipenem/cilastatin 1.5 g/day. Both study groups suggested that a higher dosage of imipenem/cilastatin may have yielded a better response rate. Further studies are therefore required to confirm that the 1.5 and 3 g/day dosages of carbapenems are interchangeable in patients with moderate infections.

At the other end of the severity spectrum, meropenem achieved a satisfactory clinical response in over 80% of patients with severe infections, most of whom were in intensive care and had nosocomial infections. Response rates appeared to be better than or similar to those with imipenem/cilastatin in the same trials, although small patient numbers did not permit a statistical comparison of the 2 agents. In one trial, most failures were observed in those who had infections secondary to previous surgery, a patient group that is particularly difficult to treat.

Bacteriological data were not available specifically for patients with severe intra-abdominal infections, although Colardyn et al. suggested that a higher off-label dosage of 6 g/day or combination treatment should be considered for difficult-to-treat pathogens such as P. aeruginosa. Further trials which specifically recruit patients with severe intra-abdominal infections or large trials, in which patients are stratified according to infection severity, are required to confirm the efficacy of meropenem in severe disease.

In conclusion, extensive comparative clinical data demonstrate that meropenem can be used effectively as empirical monotherapy in moderate to severe intra-abdominal infections. It also shows potential in the most severe forms of infection, although experience in this infection type remains limited. Compared with standard combination regimens, meropenem offers the benefits of ease of administration without the need for monitoring. It also offers improved CNS tolerability compared with imipenem/cilastatin with the option of a higher maximum dosage, which may be a particular advantage in patients with severe intra-abdominal infections.
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