Update on the Efficacy and Tolerability of Meropenem in the Treatment of Serious Bacterial Infections

John F. Mohr III
University of Texas Health Science Center, Houston

Meropenem is a carbapenem antibiotic approved by the US Food and Drug Administration for the treatment of complicated skin and skin-structure infections, complicated intra-abdominal infections, and pediatric bacterial meningitis (in patients ≥3 months of age). In clinical trials, it also has shown efficacy as initial empirical therapy for the treatment of nosocomial pneumonia. Unlike other β-lactam antibiotics, including third-generation cephalosporins, carbapenems have shown activity against extended-spectrum β-lactamase–producing and AmpC chromosomal β-lactamase–producing bacteria. Compared with imipenem, meropenem is more active against gram-negative pathogens and somewhat less active against gram-positive pathogens, and it does not require coadministration of a renal dehydropeptidase inhibitor. In most comparative trials, clinical and bacteriological response rates with imipenem and meropenem were similar. Compared with clindamycin/tobramycin, meropenem is associated with a reduced length of hospital stay and a shorter duration of therapy among patients with complicated intra-abdominal infections. Meropenem is well tolerated by children and adults and has an acceptable safety profile. Alternative meropenem dosing strategies for the optimization of outcomes are under investigation.

Antibiotic resistance is increasing among multiple bacterial pathogens and is of particular concern for critically ill patients [1–3]. For example, bacterial production of extended-spectrum β-lactamase (ESBL) enzymes and AmpC chromosomal β-lactamase enzymes has conferred resistance to several commonly used β-lactam antibiotic agents, including third-generation cephalosporins that previously were effective as first- and second-line therapy for serious bacterial infections [3].

Carbapenems, a class of broad-spectrum antibiotics that includes imipenem, meropenem, ertapenem, and, most recently, doripenem, possess stability against hydrolysis by ESBL and AmpC chromosomal β-lactamase enzymes [1, 2, 4] and therefore are useful for the treatment of infections caused by bacteria that produce these enzymes. Ertapenem has shown less in vitro activity, compared with meropenem and imipenem, against nonfermentative, gram-negative bacilli such as Pseudomonas and Acinetobacter species, which limits the utility of ertapenem for the treatment of community-acquired infections [5]. Meropenem and imipenem have shown in vitro activity against aerobic gram-negative bacilli, aerobic gram-positive cocci, and some anaerobes; compared with imipenem, meropenem is somewhat more active against gram-negative pathogens and somewhat less active against most gram-positive pathogens [2, 3, 6–8]. In vivo, the susceptibility of imipenem to hydrolysis by renal dehydropeptidase requires its coadministration with the renal dehydropeptidase inhibitor cilastatin, to avoid subsequent nephrotoxicity. In contrast, this coadministration is not necessary with meropenem, ertapenem, or doripenem, because these agents are not hydrolyzed by renal dehydropeptidase [3, 4, 6, 9, 10].
Meropenem is active against organisms that cause serious infections in adults and children. It has demonstrated efficacy in the treatment of bacterial meningitis in children; skin, soft-tissue, bone, and joint infections; serious gastrointestinal infections; septicemia; febrile neutropenia; nosocomial pneumonia; cystic fibrosis–associated respiratory infections; and serious urinary tract infections [2, 3, 9, 11]. Currently, meropenem is approved by the US Food and Drug Administration (FDA) for the treatment of complicated skin and skin-structure infections in adults and children, serious intra-abdominal infections in adults and children, and bacterial meningitis in children aged ≥3 months [12].

Because of its activity against pathogens resistant to other agents, the overuse of meropenem should be avoided, to reduce the potential for the emergence of meropenem-resistant bacteria. For example, the use of meropenem as initial empirical therapy can be implemented after consideration of local surveillance data and patient characteristics, and, once susceptibility test results become available, therapy should be de-escalated [1, 5]. The use of meropenem for routine treatment of otitis media, acute exacerbations of chronic bronchitis, or surgical prophylaxis or for first-line treatment of community-acquired infections (including community-acquired pneumonia [CAP]), gynecological infections, and urological infections should be discouraged [2, 5].

**Efficacy**

**Complicated skin and skin-structure infections.** Skin and skin-structure infections are considered to be complicated when deep structures (e.g., fascia or muscle) are involved, when surgical intervention is necessary, and when significant comorbidities, such as diabetes mellitus, are present [13]. The most common pathogens associated with complicated skin and skin-structure infections in hospitalized patients in the United States and Canada, as determined by the SENTRY Antimicrobial Surveillance Program in 1997 and 2000, are *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Pseudomonas aeruginosa*, and *Enterococcus* species [13].

Meropenem is effective for the treatment of most complicated skin and skin-structure infections caused by *P. aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Bacteroides fragilis*, *Peptostreptococcus* species, *Streptococcus pyogenes*, *Streptococcus agalactiae*, viridans group streptococci, vancomycin-susceptible *Enterococcus faecalis*, and β-lactamase–producing and non-β-lactamase–producing methicillin-susceptible isolates of *S. aureus* [12]. For patients with normal renal function, the approved dosage of meropenem for the treatment of complicated skin and skin-structure infections is 500 mg every 8 h for adults and 10 mg/kg every 8 h (to a maximum of 500 mg) for pediatric patients, infused over 15–30 min (or administered by bolus injection over 3–5 min) [12].

In a pivotal trial of the use of meropenem in the treatment of complicated skin and skin-structure infections, its efficacy was shown to be similar to that of imipenem/cilastatin [14]. This large, double-blind, multicenter, international trial included patients (>13 years of age; N = 1076) with complicated cellulitis, complex and perirectal abscesses, surgical site and traumatic wound infections, infected diabetes-related and ischemic ulcers, and other bacterial skin infections who required hospitalization, surgery, and parenteral antibiotics. Within 72 h before patient enrollment, specimens for culture and susceptibility testing were obtained from each patient, to ensure that the causative pathogens were susceptible to the study drugs; only those patients harboring susceptible pathogens were enrolled. Patients were allocated randomly to treatment with meropenem or with imipenem/cilastatin, each administered as a 20–30-min, 500-mg intravenous infusion every 8 h for a minimum of 3 days (during which hospitalization was required) and a maximum of 14 days. After 3 days, patients could be switched to oral antibiotic therapy if the infection had improved and they were able to tolerate oral antibiotic therapy.

The primary end point was clinical outcome at posttreatment follow-up (target time to follow-up was 7–14 days, and the limit was 28 days) in the clinically evaluable population and in the modified intent-to-treat population (eligible patients who received at least 1 dose of the study drug). In these populations, cure rates with meropenem were 86.2% and 73.1%, respectively, and cure rates with imipenem/cilastatin were 82.9% and 74.9%, respectively; thus, meropenem was established as statistically noninferior to imipenem/cilastatin. The meropenem and imipenem/cilastatin treatment groups also were similar with regard to clinical response at the end-of-treatment assessment (93.5% and 92.3%, respectively, of the clinically evaluable population and 91.0% and 91.1%, respectively, of the eligible patients who received at least 1 dose of study drug); mean duration of therapy (5.8 and 6.0 days, respectively); proportion of patients who were switched to oral antibiotic therapy (48% and 51%, respectively); and requirement for surgical intervention (27% and 25%, respectively) [14].

A post hoc subgroup analysis of these data found that both agents were equally effective for patients with and those without diabetes mellitus. The cure rates for patients with and those without diabetes mellitus in the clinically evaluable population were 85.6% and 86.6%, respectively, with meropenem and 72.4% and 89.9%, respectively, with imipenem/cilastatin [15].

A summary of these and other selected trials that compared the efficacy of meropenem with that of imipenem/cilastatin in patients with complicated skin and skin-structure infections is presented in table 1. The results of all these trials support the conclusion that the efficacy of meropenem is similar to that of imipenem/cilastatin for the treatment of complicated skin and skin-structure infections. In addition, empirical therapy with
<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient population(s)</th>
<th>Patient characteristics</th>
<th>Treatment regimen</th>
<th>Main outcomes, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lam et al. 1991 [16]:</td>
<td>44 CE</td>
<td>≥19 years of age; hospitalized with infections involving the extremities, trunk, or perineum</td>
<td>Meropenem: 500 mg iv, q8h</td>
<td>Cure rate (at end of treatment): 100; Comparator: 100</td>
</tr>
<tr>
<td>Nichols et al. 1995 [17]:</td>
<td>243 CE</td>
<td>≥18 years of age; hospitalized with abscess, cellulitis, infected ulcer, or other skin or soft-tissue infection</td>
<td>Imipenem: 500 mg iv, q6h</td>
<td>Clinical response rate: 98; bacteriological response rate: 94</td>
</tr>
<tr>
<td>Fabian et al. 2005 [14]:</td>
<td>1076 enrolled: 692 MITT and 548 CE</td>
<td>≥13 years of age; hospitalized with complicated cellulitis, complex or perirectal abscess, surgical site or traumatic wound infection, infected diabetes-related or ischemic ulcers, or other bacterial skin infection</td>
<td>Imipenem/cilastatin: 500 mg iv, q8h</td>
<td>Cure rate (at follow-up): MITT population, 73.1; CE population, 86.2; Comparator: Cure rate (at follow-up): MITT population, 74.9; CE population, 82.9</td>
</tr>
<tr>
<td>Embil et al. 2006 [15]:</td>
<td>202 CE with DM; 346 CE without DM</td>
<td>Same as [14]</td>
<td>Same as [14]</td>
<td>Cure rate (at follow-up): patients with DM, 85.6; patients without DM, 86.6; Comparator: Cure rate (at follow-up): patients with DM, 72.4; patients without DM, 89.0</td>
</tr>
</tbody>
</table>

**NOTE.** CE, clinically evaluable; DM, diabetes mellitus; iv, intravenously; MITT, modified intent-to-treat (patients who received at least 1 dose of study drug); q6h, every 6 h; q8h, every 8 h.
meropenem versus imipenem/cilastatin (both administered as 1 g every 8 h) has been assessed in randomized, open-label trials with patients with a variety of serious infections, including complicated skin and skin-structure infections [18, 19]. However, even though both treatments showed activity in a subpopulation of patients with complicated skin and skin-structure infections, too few patients were included in the trial for comparisons to be made between groups [18, 19]. This issue also was the case in randomized, open-label trials that compared meropenem (500 mg every 8 h) to ceftazidime (2 g every 8 h) plus amikacin (15 mg/kg/day in 2 or 3 divided doses) in adults [20] and meropenem (20 mg/kg 3 times daily) to ceftazidime (10–30 mg/kg 3 times daily) in children aged 1 month to 15 years [21].

Since the completion of clinical trials of the use of meropenem in the treatment of complicated skin and skin-structure infections, the epidemiology of these types of infection has shifted dramatically. Community-associated methicillin-resistant S. aureus (MRSA), an organism against which meropenem has not shown in vitro activity, has emerged as a common pathogen [22, 23]. Therefore, when MRSA infection is suspected on the basis of local epidemiology and risk factors, the use of an antibiotic agent with activity against MRSA may be warranted in combination with meropenem.

**Complicated intra-abdominal infections.** Guidelines endorsed by the Infectious Diseases Society of America (IDSA), the Surgical Infection Society, the American Society for Microbiology, and the Society of Infectious Disease Pharmacists recommend that empirical therapy for community-acquired complicated intra-abdominal infections should be effective against enteric gram-negative aerobic and facultative bacilli and against β-lactam-susceptible gram-positive cocci. For distal small bowel and colon-derived infections, as well as proximal small bowel perforations in the presence of obstruction, therapy should encompass treatment of infection by obligate anaerobic bacilli [24]. For nosocomial infections, local pathogen prevalence and resistance patterns must be considered [24]. The broad-spectrum coverage of the carbapenems makes them well suited to empirical therapy for the treatment of serious intra-abdominal infections in many settings, although they are not active against MRSA or most Enterococcus faecium [25].

Meropenem is indicated for the treatment of complicated intra-abdominal infections caused by E. coli, Klebsiella pneumoniae, P. aeruginosa, B. fragilis, Bacteroides thetaiotaomicron, and Peptostreptococcus species [12], at a dosage of 1 g every 8 h for adults and 20 mg/kg every 8 h (to a maximum of 1 g) for children, infused over 15–30 min (or administered by bolus injection over 3–5 min) for patients with normal renal function [12].

Selected trials of the use of meropenem in patients with complicated intra-abdominal infections are summarized in table 2. Comparisons of meropenem with clindamycin/tobramycin demonstrated similar clinical cure rates and microbiological eradication rates with both treatments. A randomized, double-blind, multicenter trial enrolled patients (≥18 years of age) with intra-abdominal infections (complicated appendicitis, gynecological infection, hepatobiliary infection, pancreatic infection, intra-abdominal abscess, and perforation of stomach or bowel) that required surgery and parenteral antibiotic therapy [30]. Patients were treated with meropenem (1 g every 8 h) or clindamycin (900 mg every 8 h) plus tobramycin (5 mg/kg/day in 3 divided doses) for ≥5 days. In the population of clinically evaluable patients (n = 191), 89 (92%) of 97 patients were cured with meropenem, and 81 (86%) of 94 patients were cured with clindamycin plus tobramycin. Bacteriological response rates also were similar between the groups. However, in a subpopulation of patients with advanced appendicitis (n = 129) in this trial, treatment with meropenem was superior to treatment with clindamycin plus tobramycin for end points such as the mean number of postoperative days with a fever (>38°C (3.1 vs. 4.4; P = .003), mean total days of hospital stay (8.0 vs. 9.4; P = .01), and mean number of days of antibiotic therapy (6.1 vs. 7.3; P < .001) [31].

As shown in table 2, most of the large clinical trials that compared meropenem with other therapies among patients with complicated intra-abdominal infections have found similar cure and microbiological response rates between groups. Although in 1 trial a significantly higher clinical cure rate at the end of treatment was obtained with the combination of cefotaxime plus metronidazole, compared with meropenem (100% vs. 91%, respectively; P = .008), the investigators attributed this difference to surgical complications, rather than to drug failure, and the clinical cure rate at follow-up did not differ significantly between the cefotaxime plus metronidazole and meropenem groups [28]. The same regimens—namely, meropenem (1 g every 8 h) and cefotaxime (2 g every 8 h) plus metronidazole (0.5 g every 8 h)—were compared in a smaller trial with patients with serious intra-abdominal infections [32]. The results showed that 41 (95.3%) of 43 patients were cured with meropenem, whereas 30 (75%) of 40 patients were cured with cefotaxime plus metronidazole (P = .008).

Meropenem and imipenem/cilastatin have achieved comparable clinical cure and bacteriological response rates in several large comparative clinical trials with patients with complicated intra-abdominal infections (table 2); similar findings have been reported in smaller trials [33] and for subpopulations of patients with complicated intra-abdominal infections in randomized trials that included patients with a variety of serious bacterial infections [18, 19, 21]. The results of 1 such trial with patients in an intensive care unit (ICU) who had lower respiratory tract infections (patients undergoing mechanical ventilation), intra-abdominal infections, or sepsis appeared to show...
Table 2. Efficacy of meropenem in selected trials with patients with complicated intra-abdominal infections.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient population</th>
<th>Patient characteristics</th>
<th>Treatment regimen</th>
<th>Main outcomes, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brismar et al. 1995</td>
<td>189 CE</td>
<td>&gt;18 years of age; signs and symptoms of intra-abdominal infection requiring operation</td>
<td>500 mg iv, q8h</td>
<td>Cure rate (at end of treatment): 98; bacteriological response rate (at end of treatment): 95</td>
</tr>
<tr>
<td>Geroulanos 1995</td>
<td>170 CE</td>
<td>&gt;18 years of age; hospitalized with evidence of a systemic inflammatory response and signs of abdominal infection</td>
<td>1 g iv, q8h</td>
<td>Cure rate (at end of treatment/at follow-up): 96/90; bacteriological response rate (at end of treatment/at follow-up): 84/84</td>
</tr>
<tr>
<td>Huizinga et al. 1995</td>
<td>148 CE</td>
<td>&gt;18 years of age; signs and symptoms of intra-abdominal infection requiring operation</td>
<td>1 g iv, q8h</td>
<td>Cure rate (at end of treatment/at follow-up): 90/93; bacteriological response rate (at end of treatment/at follow-up): 81/79</td>
</tr>
<tr>
<td>Basoli et al. 1997</td>
<td>201 CE</td>
<td>&gt;18 years of age; hospitalized with serious, complicated intra-abdominal infections of mild to moderate severity</td>
<td>3 g iv, q8h</td>
<td>Cure rate (at follow-up): 95; bacteriological response rate (at follow-up): 96</td>
</tr>
<tr>
<td>Wilson 1997</td>
<td>191 CE</td>
<td>&gt;18 years of age; hospitalized with evidence of abdominal infection requiring surgery and parenteral antibiotic therapy</td>
<td>1 g iv, q8h</td>
<td>Cure rate (at end of treatment): 92; bacteriological response rate (at end of treatment): 96</td>
</tr>
</tbody>
</table>

NOTE. CE, clinically evaluable; iv, intravenously; q8h, every 8 h.
a higher clinical cure rate with meropenem (1 g every 8 h) than with imipenem/cilastatin (1 g every 8 h) (95.5% vs. 76.7%, respectively) in a subpopulation of patients with complicated intra-abdominal infections; however, the groups were not large enough to enable statistical comparison [34].

**Pediatric bacterial meningitis.** Meropenem penetrates well into most body fluids and tissues, including CSF [12], and its CSF penetration through inflamed meninges is higher than that through uninflamed meninges [12]. Meropenem is indicated for the treatment of bacterial meningitis caused by *Streptococcus pneumoniae*, β-lactamase–producing and non–β-lactamase–producing isolates of *Haemophilus influenzae*, and *Neisseria meningitidis* in children aged ≥3 months [12]. The approved dosage for pediatric patients with normal renal function is 40 mg/kg every 8 h (maximum of 2 g), infused over 15–30 min (or administered by bolus injection over 3–5 min) [12].

On the basis of pharmacokinetic data for meropenem and cefotaxime reported in the published literature and MIC data for *S. pneumoniae*, *H. influenzae*, and *N. meningitidis* isolated from pediatric patients with bacterial meningitis in clinical trials, a Monte Carlo simulation was performed for 5000 patients with bacterial meningitis at 10 years of age, to determine the probability of each drug attaining bactericidal activity in CSF (i.e., the cumulative fraction of response [CFR]) after the administration of meropenem (40 mg/kg every 8 h) or cefotaxime (75 mg/kg every 6 h). Bactericidal exposure, defined as the percentage of time that free-drug concentrations were higher than the MIC (% > MIC), was 40% for meropenem and 50% for cefotaxime [35]. For each regimen, the CFR against *S. pneumoniae*, *H. influenzae*, and *N. meningitidis* was determined. For meropenem, these values were 94.7%, 94.3%, and 96.1%, respectively, which were significantly higher than the corresponding values for cefotaxime (84.3%, 84.8%, and 91.6%, respectively; P < .001 for each pathogen), suggesting that in this application meropenem may perform better than cefotaxime at these doses [35]. Although this type of analysis is useful for identifying regimens that are most likely to succeed, without involving large numbers of pediatric patients in numerous clinical trials, the findings for the identified regimens should be confirmed in clinical trials.

Meropenem was compared with cefotaxime in 2 randomized, prospective clinical trials with pediatric patients with bacterial meningitis. In a study of 190 patients aged 3 months to 14 years who were enrolled between April 1992 and July 1993 from South Africa, Argentina, France, and Israel and who were hospitalized with clinical signs and symptoms of bacterial meningitis, a meropenem dosage of 40 mg/kg every 8 h was compared with a cefotaxime dosage of 75–100 mg/kg every 8 h. The recommended treatment durations were 7 days for *N. meningitidis* infection, 10 days for *H. influenzae* and *S. pneumoniae* infections, and 14 days for gram-negative bacilli infections [36]. Although treatment with other antibiotics was not permitted, the administration of dexamethasone was allowed.

For the 139 patients with bacterial meningitis confirmed by CSF culture (75 in the meropenem group and 64 in the cefotaxime group), the mean duration of therapy was similar with both agents (9.9 and 9.7 days, respectively), and the median time for body temperature to fall below 38°C was 2 days with both agents [36]. Because 22 patients with bacterial meningitis proved by CSF culture (17 randomized to receive meropenem and 5 randomized to receive cefotaxime) had preexisting neurological abnormalities, results were stratified by the presence or absence of preexisting neurological abnormalities. Cure rates for treatment with meropenem were 47% and 79% for patients with and those without preexisting neurological abnormalities, respectively, and the corresponding values for cefotaxime were 60% and 83%. The respective cure rates with audiological sequelae for patients with and those without preexisting neurological abnormalities were 6% and 16% with meropenem and 20% and 12% with cefotaxime. The respective cure rates with neurological sequelae for patients with and those without preexisting neurological abnormalities were 35% and 3% with meropenem and 0% and 2% with cefotaxime, and the corresponding cure rates with audiological and neurological sequelae were 12% and 2% with meropenem and 20% and 0% with cefotaxime. In the meropenem group, no deaths occurred in either stratum while the patients were receiving therapy; in the cefotaxime group, 2 deaths occurred among the patients without preexisting neurological abnormalities. The rate of pathogen eradication was 100% with both treatments [36].

A second trial included 154 patients, aged 2 months to 12 years, who were hospitalized with clinical signs and symptoms of bacterial meningitis. Patients were enrolled from December 1992 through December 1996 from Costa Rica, the United States, and the Dominican Republic [37]. Patients were randomized to receive a meropenem dosage of 40 mg/kg every 8 h or a cefotaxime dosage of 45 mg/kg every 6 h. The recommended treatment durations were 7 days for *N. meningitidis* infection, 7–10 days for *H. influenzae* type b infection, and 10–14 days for *S. pneumoniae* infection. In addition, all subjects received an intravenous dosage of dexamethasone of 0.15 mg/kg every 6 h for the first 4 days of antibiotic treatment [37].

At the end of treatment or at 5–7 weeks of follow-up, no statistically significant differences in outcomes were seen in the meropenem group (n = 79 at the end of treatment; n = 76 at follow-up) versus the cefotaxime group (n = 75 at the end of treatment; n = 72 at follow-up). The rates of cure and survival with sequelae at the end of treatment were 46% and 52%, respectively, with meropenem and 56% and 40%, respectively, with cefotaxime. The rates of cure and survival with sequelae at 5–7 weeks of follow-up were 54% and 45%, respectively, with meropenem and 58% and 40%, respectively, with cefotaxime.
NOSOCOMIAL PNEUMONIA. Nosocomial pneumonia includes hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and health care–associated pneumonia (HCAP). Guidelines from the American Thoracic Society (ATS) and the IDSA define HAP as pneumonia that arises ≥2 days in an acute care hospital within 90 days of admission. They also define VAP as pneumonia that occurs more than 48–72 h after intubation, and HCAP as pneumonia that occurs more than 48 h after hospital admission and that was not incubating at the time of admission. VAP as pneumonia that occurs more than 48 h after hospital admission and that was not incubating at the time of admission, VAP as pneumonia that occurs more than 48 h after intubation, and HCAP as pneumonia in patients hospitalized for ≥2 days in an acute care hospital within 90 days of infection who had been nursing home or long-term-care facility residents; who had received intravenous antibiotic therapy, chemotherapy, or wound therapy within 30 days of infection; or who had attended a hospital or hemodialysis clinic. Nosocomial pneumonia is difficult to diagnose because the initial signs and symptoms are common in many disorders in hospitalized patients. For example, a chest radiograph showing pulmonary infiltrates may be attributable to congestive heart failure, preexisting interstitial lung disease, lung carcinomas, pulmonary embolism, pulmonary hemorrhage, systemic lupus erythematosus, or acute respiratory distress syndrome. For patients with suspected nosocomial pneumonia, initial empirical therapy with broad-spectrum antibiotics is recommended until culture results are obtained. A 10,000-subject Monte Carlo simulation was performed to assess the probability of achieving bactericidal exposure with various regimens of meropenem, imipenem/cilastatin, cefazedime, cepefime, piperacillin/tazobactam, and ciprofloxacin when used for empirical therapy for the treatment of nosocomial pneumonia. Prevalence data for common pathogens that cause nosocomial pneumonia were derived from the 2000 SENTRY Antimicrobial Surveillance Program, and susceptibility data for these pathogens were obtained from the 2003 Meropenem Yearly Susceptibility Test Information Collection Program database. Pharmacokinetic data for the previously mentioned antibiotics were obtained from the published results of studies with healthy volunteers. Bactericidal exposure was defined as 40%T > MIC for meropenem and imipenem/cilastatin and 50%T > MIC for ceftazidime, cepafime, and piperacillin/tazobactam; for ciprofloxacin, bactericidal exposure was defined as an area under the plasma concentration–time curve/MIC ratio of 125. Meropenem at 1 g every 8 h, imipenem/cilastatin at 1 g every 8 h, and imipenem/cilastatin at 500 mg every 6 h were among those regimens with at least a 90% probability of achieving their bactericidal target, whereas ceftazidime (1 g every 8 h) and ciprofloxacin (400 mg every 8–12 h) had a <68% probability. These dosing regimens are based on mathematical modeling and suggest successful treatment. Clinical research trials are necessary to confirm their effectiveness.

Although meropenem is not currently approved by the FDA for the treatment of nosocomial pneumonia, it has demonstrated efficacy for this indication in numerous clinical trials, and it is one of the antibiotics recommended in the ATS/IDSA guidelines as initial empirical therapy (1 g every 8 h) for the treatment of HAP, VAP, and HCAP in patients with late-onset disease or with risk factors for being infected with multidrug-resistant pathogens. In a prospective, open-label, nonrandomized clinical trial, administration of this meropenem regimen for at least 72 h to 111 clinically evaluable patients ≥13 years of age with HAP (60 of whom were patients with VAP) achieved clinical response (cure or improvement) rates of 74% at the end of treatment and 64% after 7–14 days of follow-up. Microbiological response rates were 79% at the end of treatment and 74% at follow-up. In the subgroup of patients with VAP, the clinical response rates at the end of treatment and at follow-up were 68% and 63%, respectively. The corresponding microbiological response rates were 75% and 72%. No formal comparisons were made between patients with and those without VAP. A smaller prospective, open-label, noncomparative clinical trial investigated the efficacy of the same meropenem regimen in 25 patients ≥18 years of age with VAP (76% of the population) or aspiration nosocomial pneumonia (24% of the population) in a hospital with a high prevalence of antimicrobial-resistant bacteria. The clinical response rate was 76% at the end of treatment and 48% at follow-up. In infants with nosocomial pneumonia caused by multidrug-resistant Acinetobacter baumannii or K. pneumoniae (n = 32), meropenem at 20 mg/kg every 8 h (every 12 h for the first week of life in preterm infants) achieved clinical and bacteriological response rates at the end of treatment of 87.5% in a prospective, noncomparative clinical trial. In prospective, open-label, randomized, comparative trials, monotherapy with meropenem (1 g every 8 h) was superior to combination therapy with ceftazidime (2 g) plus tobramycin (1 mg/kg every 8 h) in patients with HAP and to combination therapy with ceftazidime (2 g every 8 h) plus amikacin (15 mg/kg/day) in patients with VAP. The comparison with ceftazidime/tobramycin involved 121 clinically evaluable patients ≥18 years of age (with the exception of 1 patient in the ceftazidime/tobramycin group who was 17 years of age) and the clinical response rate at the end of treatment was
significantly higher with meropenem than with ceftazidime/tobramycin (89% vs. 72%, respectively; $P = .04$); this result was also true for the bacteriological response rate (89% vs. 67%, respectively; $P = .006$). For the subpopulation of patients who were undergoing mechanical ventilation (73% of patients in the meropenem group and 67% of patients in the ceftazidime/tobramycin group), the clinical response rate at the end of treatment was 87% with meropenem and 72% with ceftazidime/tobramycin, and the bacteriological response rates were 91% and 69%, respectively [45]. The comparison with ceftazidime/amikacin involved 116 clinically evaluable patients >18 years of age. The clinical response rate at the end of treatment was significantly higher with meropenem than with ceftazidime/amikacin (82.5% vs. 66.1%, respectively; $P = .044$); this result also was true for the bacteriological response rate (74.5% vs. 53.3%, respectively; $P = .030$) [46].

Other comparative trials of patients with serious bacterial infections have included patients with nosocomial pneumonia; however, in many cases, statistical comparisons between the meropenem and comparator groups were not done for subpopulations. When the meropenem and ceftazidime/amikacin regimens previously described were compared in a population of hospitalized patients with serious bacterial infections, the subpopulation with hospital-acquired lower respiratory tract infections (>90% of which consisted of patients with HAP) had a clinical response rate at the end of treatment of 81% with meropenem and 72% with ceftazidime/amikacin, which appears to be consistent with the results reported above but does not achieve statistical significance. Bacteriological response rates were 71% and 76%, respectively [20]. Several trials that have compared meropenem with imipenem/cilastatin have reported similar clinical and bacteriological response rates with both treatments in subpopulations of patients with nosocomial pneumonia or other lower respiratory tract infections [18, 34, 47]. In 1 study, clinical response was achieved with meropenem in 33 (89%) of 37 patients, compared with 32 (76%) of 42 patients with imipenem/cilastatin, in a subpopulation of patients with lower respiratory tract infections; however, the difference between groups was not analyzed for statistical significance [19]. Treatment with meropenem (1 g every 8 h) or a combination of cefuroxime (1.5 g every 8 h) and gentamicin (4 mg/kg/day in 2 or 3 divided doses) with or without metronidazole (0.5 g every 6 h) achieved a clinical response in 17 (85%) of 20 and 16 (76%) of 21 elderly patients with pneumonia, respectively; this difference was not significant [48].

**Alternative dosing strategies.** Alternative meropenem dosing strategies have been investigated to determine their effects on pharmacodynamic efficacy and economic end points. A retrospective analysis of patient medical records found no difference in rates of clinical success between patients who received meropenem dosages of 500 mg every 6 h ($n = 45$) or 1 g every 8 h ($n = 40$); however, a significant savings in drug acquisition cost was associated with the meropenem dosage of 500 mg every 6 h [49]. A pharmacokinetic study with 15 critically ill patients demonstrated that intermittent administration of 2 g of meropenem every 8 h for 2 days and continuous infusion of 3 g of meropenem per day (after a loading dose of 2 g) for 2 days achieved 100% $T > MIC$ for bacterial strains commonly found in patients in ICUs [50]. Although clinical efficacy was not assessed in that study, the results raised the possibility that a continuous dosing regimen could achieve a similar response with a lower amount of the drug.

The results of a small retrospective cohort analysis of patients with VAP caused by gram-negative bacilli who had received meropenem as initial empirical therapy support its administration by continuous infusion [51]. All patients also received a tobramycin dosage of 7 mg/kg/day as a 60-min infusion. Among patients ($n = 42$) who received a continuous infusion (over 360 min) of 1 g of meropenem every 6 h, the clinical cure rate was significantly higher, compared with patients ($n = 47$) who received a 30-min infusion of 1 g of meropenem every 6 h (90.5% vs. 59.6%, respectively; $P < .001$). When infections caused by *P. aeruginosa* were analyzed, the corresponding cure rates were 84.6% versus 40% ($P = .02$); the corresponding cure rates for infections caused by pathogens with MICs ≥0.5 μg/mL were 81% versus 29.4% ($P = .003$).

An analysis that used a population-based pharmacokinetic model of meropenem therapy (7900 simulated concentration-time profiles for each regimen) based on clinical trial data from patients with intra-abdominal infections, CAP, and VAP, along with MIC data, showed that changing the duration of infusion from 0.5 to 3 h increased the likelihood of achieving the bactericidal target (40% $T > MIC$) from 64% to 90% [52]. A small pharmacokinetic study of 9 patients with VAP found that, for pathogens of intermediate resistance, a 3-h infusion of 1 or 2 g of meropenem every 8 h provided a higher $T > MIC$ than did bolus injection of 1 g of meropenem every 8 h [53]. Additional investigations of alternative meropenem dosing strategies to maximize response, minimize drug dose, and reduce costs are ongoing.

**SAFETY AND TOLERABILITY**

**Overall tolerability.** Meropenem was well tolerated in the clinical trials summarized in this article, with adverse-event profiles similar to those of its comparators when used in a variety of patient populations. Although imipenem has been associated with neurotoxicity at high doses and gastrointestinal toxicity at rapid infusion rates, the risks of these adverse events with meropenem are much lower [54]. A newly published review of the safety of meropenem, based on data from 55 studies with >6000 hospitalized patients with serious bacterial infections, reported that the most common adverse events possibly
or probably related to the administration of meropenem were diarrhea, rash, and nausea/vomiting, although the overall frequency of each of these adverse events was <3% [55]. A comparison of common drug-related adverse events with meropenem and cephalosporin-based regimens, imipenem/cilastatin regimens, and clindamycin/aminoglycoside-based regimens showed that, with the exceptions of lower rates of nausea/vomiting with cephalosporin-based regimens, higher rates of nausea/vomiting and lower rates of diarrhea with imipenem/cilastatin, and higher rates of diarrhea and lower rates of injection-site reactions with clindamycin/aminoglycoside-based regimens, the adverse-event incidence profiles were similar with all treatments (table 3) [55].

In a study that reviewed the safety profile of meropenem, the incidence of seizures among 3911 patients who received meropenem was 0.38% (n = 15), whereas the incidence among 1154 patients who received imipenem/cilastatin was 0.43% (n = 5) [54]. A total of 6 of the 15 patients who had a seizure while receiving meropenem and 4 of the 5 patients who had a seizure while receiving imipenem/cilastatin had a preexisting CNS disorder [54]. Given that seizures with meropenem are extremely rare and that most occur in patients with underlying CNS disorders, causality is difficult to correlate.

Pediatric patients. Meropenem was well tolerated in both of the published trials with pediatric patients with bacterial meningitis described above, and no meropenem-associated seizures were reported in either of the trials [36, 37]. It is important to note that the use of meropenem to treat pediatric patients with renal impairment has not been studied extensively [12]. The kidney is the major route of elimination of meropenem, and dosage adjustment is required for adults with renal impairment [12].

A more-comprehensive assessment of meropenem safety in pediatric patients was done with data from 383 children with meningitis, 382 children with lower respiratory tract infections, 166 children with intra-abdominal infections, and 131 children with complicated skin and skin-structure infections [55]. The safety profile of meropenem in children was found to be similar to that of cephalosporins. The most common adverse events experienced with meropenem were diarrhea (4.5%) and rash (2.2%). Among children with meningitis who had received meropenem, no drug-related seizures were reported [55].

Laboratory abnormalities. The large safety analysis described above also identified a similar incidence of laboratory abnormalities with meropenem, cephalosporin-based regimens, and imipenem/cilastatin, whereas the incidence with a clindamycin/aminoglycoside-based regimen was somewhat higher [55]. The most common abnormalities identified were thrombocytosis (1.3%, 1.2%, 1.2%, and 4.6%, respectively), increased alanine transaminase level (3.7%, 2.6%, 2.4%, and 5.7%, respectively), and increased aspartate transaminase level (2.9%, 1.9%, 2.3%, and 4.6%, respectively). Additional adverse events, identified through the FDA’s postmarketing Adverse Event Reporting System and categorized as possibly, probably, or definitely related to drug treatment, were the following hematological or skin abnormalities: agranulocytosis, neutropenia, leukopenia, positive direct or indirect Coombs test result, hemolytic anemia, toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, and erythema multiforme [12].

**SUMMARY**

Serious bacterial infections require prompt, appropriate treatment, to minimize the risk of morbidity and mortality. To

<table>
<thead>
<tr>
<th>Table 3. Incidence of common drug-related adverse events with antibiotic regimens in clinical trials with patients with serious bacterial infections.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse event</strong></td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Injection-site reaction</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Pruritus</td>
</tr>
<tr>
<td>Other*</td>
</tr>
</tbody>
</table>

**NOTE.** Data are percentage of patients who experienced the adverse event. Adapted from Linden P. Safety profile of meropenem: an updated review of over 6000 patients treated with meropenem. Drug Saf 2007;30:662 [55], with permission from Wolters Kluwer.

*Includes constipation, oral candidiasis, glossitis, hypotension, and renal failure. |
achieve this goal, broad-spectrum antibiotics are recommended as initial empirical therapy, followed by streamlining to more-specific therapy after culture results are known, to minimize the development of antibiotic resistance. Unlike third-generation cephalosporins, the carbapenem antibiotics meropenem and imipenem are active against ESBL-producing and AmpC chromosomal β-lactamase-producing bacteria, and they should be used judiciously, to minimize the potential for the emergence of carbapenem-resistant bacteria. Meropenem is a well-established carbapenem that is more active than imipenem against gram-negative pathogens and somewhat less active than imipenem against gram-positive pathogens. Unlike imipenem, meropenem does not require coadministration of a renal dehydropeptidase inhibitor, such as cilastatin. Meropenem achieves high rates of clinical and bacteriological response among patients with complicated skin and skin-structure infections, complicated intra-abdominal infections, pediatric bacterial meningitis, and nosocomial pneumonia, and it is well tolerated. In most comparative trials, clinical and bacteriological response rates with meropenem and imipenem/cilastatin were similar. Research is focused on the optimization of meropenem dosing strategies on the basis of pharmacodynamic concepts, local rates of pathogen prevalence, and antibiotic resistance profiles.

Acknowledgments

I thank Stephanie M. Leinbach, who provided freelance medical writing support, and Judy E. Fallon from Scientific Connexions, who provided editing assistance, both funded by AstraZeneca.

Supplement sponsorship. This article was published as part of a supplement entitled “Update on the Appropriate Use of Meropenem for the Treatment of Serious Bacterial Infections,” sponsored by AstraZeneca LP. Potential conflicts of interest. J.F.M. has received research grants from AstraZeneca and Elan Pharmaceuticals; has been a member of the speakers’ bureau for Elan Pharmaceuticals, Wyeth, and AstraZeneca; and currently is an employee of Cubist Pharmaceuticals.

References

31. Berne TV, Yellin AE, Appleman MD, Heseltine PNR, Gill MA. Meropenem versus tobramycin with clindamycin in the antibiotic man-