Program Overview

Rising rates of nosocomially acquired multidrug-resistant (MDR) Gram-negative pathogens have drastically narrowed the spectrum of available therapeutic options. Resistance to antimicrobials is a mounting health concern, both in the United States and worldwide. Infections caused by resistant Gram-negative pathogens, such as Pseudomonas aeruginosa and Acinetobacter baumannii, result in higher morbidity, mortality, prolonged hospitalization, and increased costs compared with sensitive strains. Carbapenems possess high potency against a broad spectrum of organisms and are regarded as the agents of choice for serious infections with extended-spectrum β-lactamase–producing organisms. However, increased prevalence of pan-resistant P. aeruginosa and A. baumannii strains worldwide has limited the utility even of the carbapenems. To reduce the likelihood of emergence of resistance, clinical practice guidelines have been developed to direct antimicrobial treatment of nosocomial infections. Initial empiric therapy should offer broad-spectrum coverage of Gram-negative pathogens, and therapy should be tailored and de-escalated after positive culture results are obtained. Although the polymyxins have been reintroduced, particularly as a last-line treatment of MDR Gram-negative pathogens, heteroresistance to these agents has already been documented, highlighting the need for more appropriate use of antimicrobials to minimize suboptimal outcomes.

Doripenem, a novel, broad-spectrum carbapenem, offers impressive in vitro activity and clinical efficacy against P. aeruginosa and A. baumannii (including many MDR strains). Doripenem is well tolerated and its effects on the central nervous system are negligible. This special report profiles the properties of the carbapenem class, emphasizes key principles of clinical practice guidelines for antimicrobial treatment selection and use, and reviews doripenem, the pending addition to the carbapenem class.

Learning Objectives

After reviewing this supplement, participants should be able to:

1. Discuss the impact of resistant Gram-negative organisms on outcomes and management strategies in critically ill patients with pneumonia and intra-abdominal infections.
2. Choose appropriate guideline-based treatments for infections caused by resistant Gram-negative pathogens in critically ill patients.
3. Review features of available carbapenem agents.
4. Evaluate the utility of new agents to combat infections resulting from P. aeruginosa and A. baumannii.
5. Weigh the benefits and risks of each carbapenem-based treatment in managing infections in the intensive care unit.

Target Audience

This activity has been developed for critical care physicians and surgical critical care physicians.

Accreditation

University of Kentucky College of Medicine

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the University of Kentucky College of Medicine and Rxperience. The University of Kentucky College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The University of Kentucky College of Medicine designates this educational activity for a maximum of 1.5 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

The University of Kentucky College of Medicine presents this activity for educational purposes only. Participants are expected to utilize their own expertise and judgment while engaged in the practice of medicine. The content of the presentation is provided solely by presenters who have been selected for presentations because of recognized expertise in their field.
**Introduction to Carbapenem Agents**

Gram-negative pathogens belonging to the *Pseudomonas* and *Acinetobacter* species are prevalent and important causes of nosocomial infections among critically ill patients. Acquired mechanisms of resistance that exhibit multiple, diverse actions have caused some strains of these pathogens to be much more difficult to treat.1,2 The continuing increase in antimicrobial resistance across US hospitals remains a major concern for patients, clinicians, and public health officials.3

Outbreaks of nosocomial infection caused by Gram-negative pathogens are not isolated, regional occurrences but rather worldwide events and have most recently reached proportions of a global health issue.4 Based on in vitro and clinical data, carbapenems have been and continue to be the agents of choice for serious infections with extended-spectrum β-lactamase (ESBL)–producing organisms.5 However, resistance to β-lactam antimicrobials, including carbapenems, is increasing among strains of *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, leaving clinicians with a dearth of viable therapeutic options to treat nosocomially acquired Gram-negative infections. Interestingly, the polymyxins have been resurrected as last-resort treatments for patients infected with multidrug-resistant (MDR) pathogens.1 However, increased use of polymyxins will likely lead to emergence of resistance, thus underscoring the immediate need for recognition of the key risk factors for MDR acquisition; more responsible antimicrobial treatment selection and use; adherence to clinical practice guidelines for initial empiric therapy and de-escalation; and greater awareness and appreciation of the use of novel antimicrobials for critically ill patients with nosocomial infections.6–8

**Overview of the Carbapenems**

β-lactam antimicrobials comprise more than 50% of all antimicrobial therapies, and their efficacy and tolerability make them the most commonly prescribed antibiotic agents. The carbapenems represent one of the many antimicrobial groups in this category.9 Carbapenems demonstrate excellent in vitro activity because of their efficient penetration into bacteria, stability to hydrolysis by nearly all clinically important serine β-lactamases, and high affinity for essential penicillin-binding proteins (PBPs) of Gram-negative bacteria. These agents possess a broad spectrum of antimicrobial activity, exceeding that of most other antimicrobial classes. Agents in the carbapenem class include doripenem, ertapenem, faropenem, imipenem, meropenem, and panipenem/betamipron.10 The molecular structures of doripenem, ertapenem, imipenem, and meropenem are depicted in Figure 1.

The first carbapenem that was developed, imipenem, is active against a broad spectrum of pathogens. Imipenem is coadministered with cilastatin—an inhibitor of human renal dehydropeptidase I—because imipenem is hydrolyzed by this enzyme.10 Imipenem is indicated for hospitalized patients with intra-abdominal infections (IAIs), lower respiratory tract infections, gynecologic and genitourinary tract infections, skin and soft tissue infections (SSTIs), sepsis, and endocarditis. Imipenem is considered an appropriate empirical treatment when there is a high likelihood of infection with resistant pathogens or multiple organisms, including aerobes and anaerobes. The plasma half-life of imipenem is approximately 1 hour, and it is 10% to 20% protein bound. The most common adverse effects of imipenem include phlebitis, thrombophlebitis, nausea, diarrhea, and vomiting. This agent is not indicated for central nervous system (CNS) infections because of its proconvulsive activity.11

Meropenem is a carbapenem that has activity against Gram-negative, Gram-positive, and anaerobic microorganisms. As is imipenem, meropenem is highly resistant to hydrolysis by most of the serine-based β-lactamases produced by Gram-negative bacteria. Meropenem is effective for the treatment of serious infections, including those acquired in the hospital or intensive care unit (ICU). Meropenem penetrates rapidly and widely into a range of body fluids and tissues, including cerebrospinal fluid, and its half-life is approximately 1 hour. The most common side effects associated with meropenem include diarrhea, rash, nausea, vomiting, and injection-site inflammation. Meropenem is well tolerated by the CNS in doses of 2 g every 8 hours, even in patients with bacterial meningitis.13

Ertapenem is a carbapenem that shares the activity of imipenem and meropenem against most species; however, it lacks significant activity against nonfermenters (ie, Gram-negative rods, including *Pseudomonas* and *Acinetobacter*) and thus has a limited role in nosocomial infection. Ertapenem has a long plasma half-life (~4 hours) that allows for once-daily dosing. Findings from clinical trials demonstrate equivalence with comparators for treatment of moderate to severe IAIs, pelvic infections, SSTIs, mild to moderate intra-abdominal sepsis, community-acquired pneumonia (CAP), and complicated urinary
tract infections (UTIs). Side effects include diarrhea, nausea, headache, and infusion-site reaction. Lastly, the risk of seizure is small, although definite.12

**Clinical Practice Guidelines for Selection of Antimicrobial Therapy**

**HAP Guidelines**

The American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) offer joint guidelines (2005) on the management of adults with hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and healthcare-associated pneumonia (HCAP). These guidelines recommend prompt, empiric, and broad-spectrum therapy for patients with HAP who are at risk for MDR pathogens. Broad-spectrum empiric antimicrobial therapy should be accompanied by a de-escalation commitment based on serial clinical and microbiologic data. In addition, there is minimal support for combination therapy in managing infection with *P. aeruginosa*, and carbapenems should be used at optimal doses to prevent emergence of resistance in *Acinetobacter*. Figure 2 summarizes the initial treatment strategies based on clinical responses of a patient with suspected HAP, VAP, or HCAP.

**FIGURE 1. MOLEcular STRUCTURE OF SELECT CARBApenEMS**

Adapted from references 11-14.

**FIGURE 2. INITIAL MANAGEMENT BASED ON CLINICAL RESPONSE OF THE PATIENT WITH SUSPECTED HAP**

HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; LRT, lower respiratory tract; VAP, ventilator-associated pneumonia; WBC, white blood cell count

Adapted from reference 15.
patient with suspected HAP, VAP, or HCAP. Figure 3 provides a treatment algorithm to guide clinicians in the initiation of antimicrobial therapy.

Antimicrobial selection should be based on risk factors for MDR pathogens, such as antimicrobial therapy within the past 90 days, time of current hospitalization, frequency of resistance in the hospital or community, risk factors for HCAP (eg, residence in nursing home, home infusion therapy), and immunosuppressive disease or therapy. Table 1 provides guidance on the recommended initial empiric antimicrobial for HAP or VAP patients without known risk factors for MDR pathogens (early onset and any disease severity).15 It is important to note that other antibiotics are also indicated for treatment of HAP, in addition to those stated in the guidelines. Table 2 summarizes the recommended, initial, broad-spectrum combination therapies for late-onset disease, risk factors, or MDR pathogens.15

Other key principles discussed in the ATS/IDSA guidelines for management of HAP, VAP, and HCAP include the following:

- Early, appropriate, broad-spectrum antimicrobial therapy should be initiated with adequate dosing to optimize antimicrobial therapy.
- An empiric therapy regimen should include agents from antibiotic classes different from those the patient has recently received.
- Combination therapy for a specific pathogen should be used judiciously for treatment of HAP.

### TABLE 1. INITIAL EMPIRIC THERAPY IN PATIENTS WITHOUT RISK FACTORS FOR MDR PATHOGENS

<table>
<thead>
<tr>
<th>Potential Pathogens</th>
<th>Recommended Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em>&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Ceftriaxone or Levofloxacin, moxifloxacin, or ciprofloxacin</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td></td>
</tr>
<tr>
<td>Methicillin-sensitive <em>Staphylococcus aureus</em></td>
<td></td>
</tr>
<tr>
<td>Antibiotic-sensitive enteric Gram-negative bacilli <em>Escherichia coli</em></td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter species</em></td>
<td></td>
</tr>
<tr>
<td><em>Proteus species</em></td>
<td></td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td></td>
</tr>
</tbody>
</table>

<sup>*</sup>The frequency of penicillin-resistant *S. pneumoniae* and MDR *S. pneumoniae* is increasing. Levofloxacin or moxifloxacin is preferred to ciprofloxacin, and the role of other new quinolones, such as gatifloxacin, has not been established.

MDR, multidrug-resistant

Adapted from reference 15.

### TABLE 2. INITIAL EMPIRIC THERAPY FOR LATE-ONSET DISEASE, RISK FACTORS, OR MDR PATHOGENS

<table>
<thead>
<tr>
<th>Potential Pathogens</th>
<th>Initial, Broad-Spectrum, Combination Antibiotic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pseudomonas aeruginosa</em>&lt;sup&gt;ESBL&lt;/sup&gt;, <em>Klebsiella pneumoniae</em>&lt;sup&gt;ESBL&lt;/sup&gt;</td>
<td>Antipseudomonal cephalosporin or Antipseudomonal carbapenem or β-lactam/β-lactamase inhibitor plus Antipseudomonal fluoroquinolone* or Aminoglycoside</td>
</tr>
<tr>
<td><em>Acinetobacter species</em>&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Methicillin-resistant <em>Staphylococcus aureus</em></td>
<td></td>
</tr>
<tr>
<td><em>Legionella pneumophila</em>&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>*</sup>If an ESBL strain such as *K. pneumoniae* or an *Acinetobacter* species is suspected, a carbapenem is a reliable choice. If *L. pneumophila* is suspected, the combination antibiotic regimen should include a macrolide (eg, azithromycin), or a fluoroquinolone (eg, ciprofloxacin or levofloxacin) should be used rather than an aminoglycoside.

<sup>*</sup>If MRSA risk factors are present or there is a high incidence locally. ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant

Adapted from reference 15.
De-escalation of antibiotics should be considered based on culture results and clinical response. A shorter duration of antibiotic therapy (ie, 7 to 8 days) is recommended in patients with uncomplicated HAP, VAP, or HCAP who have received appropriate initial therapy and demonstrated a good clinical response, with no evidence of infection with nonfermenting Gram-negative bacilli.15

**IAI/Complicated IAI (cIAI) Guidelines**

Both the IDSA (2003) and the Surgical Infection Society (SIS; 2002) have issued guidelines on the management of IAIs. A cIAI extends beyond the hollow viscus of origin into the periitoneal space and is associated with either abscess formation or with peritonitis. Antimicrobial therapy should be initiated as soon as a cIAI is suspected. In some instances, a multidrug regimen (eg, an aminoglycoside plus fluoroquinolone or carbapenem plus vancomycin) is recommended. Only carbapenems and broad-spectrum penicillins (combined with a β-lactamase inhibitor) are recommended for monotherapy treatment of cIAIs,9,16 because only these agents have a spectrum that effectively covers both aerobes and anaerobes.17 Tables 3 and 4 compare IDSA and SIS recommendations with regard to severity and risk status of patients with cIAIs, respectively.9,16

**Therapy With Carbapenem Agents**

Clinicians who treat documented resistant Gram-negative infections must consider the role of monotherapy (eg, carbapenems or colistin) and the possibility of combination therapy, as well as factors related to empiric treatment and de-escalation. The therapies of choice for treatment of infections with ESBL-producing organisms include fluoroquinolones (for UTIs), carbapenems (bacteremia, HAP, and IAI), and meropenem (meningitis).15

Multiple studies highlight the efficacy of carbapenems as monotherapy for the treatment of ESBL-producing Klebsiella

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**TABLE 3. IDSA- AND SIS-RECOMMENDED ANTIMICROBIAL REGIMENS: MILD TO MODERATE/LOWER RISK**

<table>
<thead>
<tr>
<th>IDSA</th>
<th>SIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild to Moderate Infections</strong></td>
<td><strong>Lower-Risk Patients</strong></td>
</tr>
<tr>
<td><strong>Single-Agent Regimen</strong></td>
<td></td>
</tr>
<tr>
<td>• Ampicillin/sulbactam*</td>
<td>• Cefotetan</td>
</tr>
<tr>
<td>• Ticarcillin/clavulanic acid</td>
<td>• Cefoxitin</td>
</tr>
<tr>
<td>• Ertapenem</td>
<td>• Ertapenem</td>
</tr>
<tr>
<td></td>
<td>• Meropenem</td>
</tr>
<tr>
<td><strong>Combination Regimen</strong></td>
<td><strong>Combination Regimen</strong></td>
</tr>
<tr>
<td>• Cefazolin or cefuroxime + metronidazole</td>
<td>• Ciprofloxacin + metronidazole</td>
</tr>
<tr>
<td>• Fluoroquinolone-based therapy + metronidazole†</td>
<td>• Aminoglycoside + anti-anaerobe</td>
</tr>
<tr>
<td></td>
<td>• Aztreonam + clindamycin</td>
</tr>
<tr>
<td></td>
<td>• Cefuroxime + metronidazole</td>
</tr>
<tr>
<td></td>
<td>• Third-/fourth-generation cephalosporin + anti-anaerobe</td>
</tr>
</tbody>
</table>

*Because increasing resistance of *E. coli* to ampicillin and to ampicillin/sulbactam has been reported, local susceptibility profiles should be reviewed before use.
†Fluoroquinolones=ciprofloxacin, levofloxacin, moxifloxacin, or gatifloxacin. Because increasing resistance of *Bacteroides fragilis* group isolates to available quinolones has been reported, these agents should be used in combination with metronidazole.

**TABLE 4. IDSA- AND SIS-RECOMMENDED ANTIMICROBIAL REGIMENS: HIGH SEVERITY/HIGHER RISK**

<table>
<thead>
<tr>
<th>IDSA</th>
<th>SIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-Severity Infections</strong></td>
<td><strong>Higher-Risk Patients</strong></td>
</tr>
<tr>
<td><strong>Single-Agent Regimen</strong></td>
<td></td>
</tr>
<tr>
<td>• Piperacillin/tazobactam</td>
<td>• Piperacillin/tazobactam</td>
</tr>
<tr>
<td>• Imipenem/cilastatin</td>
<td>• Imipenem/cilastatin</td>
</tr>
<tr>
<td>• Meropenem</td>
<td>• Meropenem</td>
</tr>
<tr>
<td><strong>Combination Regimen</strong></td>
<td><strong>Combination Regimen</strong></td>
</tr>
<tr>
<td>• Third/fourth-generation cephalosporin + metronidazole</td>
<td>• Ciprofloxacin + metronidazole</td>
</tr>
<tr>
<td>• Aztreonam + metronidazole</td>
<td>• Aminoglycoside + anti-anaerobe</td>
</tr>
<tr>
<td>• Ciprofloxacin + metronidazole</td>
<td>• Aztreonam + clindamycin</td>
</tr>
<tr>
<td></td>
<td>• Third-/fourth-generation cephalosporin + anti-anaerobe</td>
</tr>
</tbody>
</table>

IDSA, Infectious Diseases Society of America; SIS, Surgical Infection Society
Adapted from references 9 and 16.
*pneumoniae* and *Escherichia coli* infections. In a prospective, observational study of patients with *K. pneumoniae* bacteremia (455 episodes in 440 patients; 85 episodes caused by ESBL-producing organisms), use of a carbapenem, mainly imipenem, was associated with lower 14-day mortality compared with other antimicrobials (OR, 0.173; 95% CI, 0.039-0.755; *P* = 0.012).

Du and colleagues demonstrated lower mortality with imipenem than with cephalosporins for the treatment of ESBL-producing *E. coli* or *K. pneumoniae* bloodstream infection. ESBLs were produced by 27% of isolates. Patients treated with imipenem were more likely to survive, whereas those receiving cephalosporin treatment tended to have poorer outcomes (1/19 vs 14/40; *P* = 0.023). In addition, compared with monotherapy, combination therapy neither resulted in treatment success nor improved patient outcome.

In a multicenter, open-label, randomized, parallel-group trial, the Belgian Multicenter Study Group compared the efficacy and tolerability of meropenem and imipenem/cilastatin (both 1 g/8 h intravenously) as empirical monotherapy in 212 ICU patients (n=107 meropenem; n=105 imipenem/cilastatin) with serious bacterial infections, including lower respiratory tract infection in ventilated patients, IAI, and sepsis. Predominant pathogens included *E. coli*, *Enterobacter* species, and *P. aeruginosa*. Both treatments demonstrated similar satisfactory clinical and bacteriologic response rates, as illustrated in Figure 4.

There has been renewed interest in the use of polymyxins as alternative treatments for critically ill patients infected with strains of *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae* that are resistant to almost all available antimicrobials. Polymyxins are a group of polypeptide cationic antimicrobials that include colistin (polymyxin E) and polymyxin B. Both of these agents were discovered in the 1940s and were widely used parenterally for approximately 20 years. They fell out of use after reports of neurologic and renal adverse effects. Currently, these medications are viewed as last-resort agents in patients infected with MDR pathogens.

A retrospective case series study by Michalopoulos and colleagues examined the efficacy and safety of colistin in 43 critically ill patients with ICU-acquired infection (primarily VAP and bacteremia) characterized by MDR *P. aeruginosa* and/or *A. baumannii*. Clinical cure of infection was achieved in 69.8% of patients (30/43); 25.6% (11/43) did not respond to treatment, and all of these patients died. Deterioration of renal function occurred in 18.6% (8/43) of patients.

In a retrospective chart review of 37 ICU patients with MDR *A. baumannii*, clinical cure was observed in 22 of 29 (76%) of patients treated with polymyxin B. Crude mortality was 27% (9/33), with 3 deaths attributed to polymyxin B treatment failure. Nephrotoxicity was observed in 21% and neurotoxicity in 6% of patients treated with polymyxin B. Generalizability of findings may be limited by the relatively young age of patients in this study, as well as by the large number of trauma patients with few comorbidities.

Colistin was also evaluated by Reina and colleagues in a prospective cohort study of 185 patients infected with *A. baumannii* and *P. aeruginosa* after an ICU stay of more than 48 hours. Fifty-five patients were treated with colistin. Of 130 patients in the noncolistin group, 81% were treated with carbapenems. There were no differences between groups in the frequency of clinical cure on day 6 of treatment (15% vs 17%) or number alive at discharge (71% vs 74%). Overall, outcomes with colistin were the same as outcomes for carbapenems, and mean creatinine levels remained normal throughout treatment.

A recent review of 5 studies of treatment with I.V. colistin of VAP resulting from *P. aeruginosa* or *A. baumannii* reported clinical cure rates ranging from 25% to 62%, despite high severity of illness at baseline. De novo nephrotoxicity rates ranged from 8% to 36%, despite close attention to appropriate dosing and duration of treatment. Neurotoxicity was reported in only 1 patient across the 5 studies, and this was the only patient for whom colistin treatment was discontinued in these studies.

Now that colistin has re-emerged as acceptable therapy for MDR *A. baumannii* infections, its use has increased worldwide and heteroresistance has since been recorded. Recently, a team of investigators became the first to report heteroresistance to colistin in clinical isolates of *A. baumannii* obtained...
from an Australian hospital (14 from patients admitted to the ICU) that were apparently susceptible to colistin based on MICs. Population analysis profiles demonstrated that heteroresistance to colistin occurred in 15 of the 16 A. baumannii clinical isolates; most clinical isolates grew in the presence of 3 to 10 µg/mL of colistin. These findings send a clear message to clinicians: If colistin is used inappropriately, rapid development of resistance and treatment failures may eventually follow.7

Doripenem: Safety, Efficacy, and Comparative Data

Doripenem is a novel, broad-spectrum parenteral carbapenem. Doripenem’s molecular structure (see Figure 1 on page 3) confers β-lactamase stability and resistance to inactivation by renal dehydropeptidases. This new addition to the carbapenem class has demonstrated impressive in vitro activation by renal dehydropeptidases. This new addition to the treatment by all metallo-

In Vitro Activity

Comparative Data

Doripenem: Reducing/Preventing Emergence of Resistance

Use of doripenem may reduce emergence of resistant pathogens, as evidenced in a number of studies. Sakyo and colleagues examined the potency of doripenem, meropenem, and imipenem in preventing the emergence of carbapenem-resistant P. aeruginosa mutants. In total, 140 P. aeruginosa isolates were investigated for carbapenem resistance. The isolation frequency of each mutant was examined at concentrations of one half or one quarter MIC of each carbapenem for that mutant. Mutants were not selected on agar containing doripenem at more than 10–3 per cell per generation; however, mutants were selected on agar containing meropenem or imipenem at frequencies of approximately 10–3 to 10–2. These data indicate that of all the carbapenems, doripenem exhibited the lowest drug concentration and the narrowest range of drug concentration for selection of carbapenem-resistant mutants, and doripenem therefore had the greatest ability to prevent the emergence of mutants.27

β-lactams used in combination with aminoglycosides may provide synergistic activity against Gram-negative pathogens. In an in vitro study, doripenem was tested in combination with gentamicin to determine resistance selection during subinhibitory passaging using P. aeruginosa isolates with elevated MIC values (n=6). Doripenem MIC values increased 2- to 8-fold and higher in 4 isolates, whereas 2 strains maintained the baseline doripenem MIC. When doripenem plus gentamicin was tested, 3 strains maintained the original doripenem MIC values, 2 strains had a 2-fold increase, and only 1 strain showed a 4-fold increase in doripenem MIC values. Thus, the combination of doripenem plus an aminoglycoside may be an effective treatment of infections caused by P. aeruginosa with elevated carbapenem MIC values, with lower risk of selecting further resistance.28

Mushtaq and colleagues evaluated in vitro resistance selection potential of antimicrobial agents versus characterized isolates, mutants, and transconjugants of P. aeruginosa. Doripenem MICs were lower than meropenem for strains with elevated intrinsic resistance. Furthermore, mutant selection (single step) with doripenem occurred with fewer strains than with other agents. The final multiple of the MIC achieved was

<table>
<thead>
<tr>
<th>Carbapenem</th>
<th>Activity Against P. aeruginosa; MIC90, µg/mL</th>
<th>Against Acinetobacter species; MIC90, µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doripenem</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Meropenem</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>&gt;8</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Imipenem</td>
<td>&gt;8</td>
<td>2</td>
</tr>
</tbody>
</table>

Adapted from reference 25.

In an vitro study by Jones and colleagues, only doripenem (75.8% inhibited at ≤4 µg/mL), imipenem, and meropenem demonstrated activity against wild-type A. baumannii isolates. Doripenem and imipenem were the most potent agents (MIC90, 0.5 µg/mL) and inhibited strains at potentially achievable breakpoint concentrations. Moreover, doripenem was 2- and 4-fold more potent than meropenem and imipenem against P. aeruginosa, respectively.11

Doripenem: Reducing/Preventing Emergence of Resistance

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β-lactams used in combination with aminoglycosides may provide synergistic activity against Gram-negative pathogens. In an in vitro study, doripenem was tested in combination with gentamicin to determine resistance selection during subinhibitory passaging using P. aeruginosa isolates with elevated MIC values (n=6). Doripenem MIC values increased 2- to 8-fold and higher in 4 isolates, whereas 2 strains maintained the baseline doripenem MIC. When doripenem plus gentamicin was tested, 3 strains maintained the original doripenem MIC values, 2 strains had a 2-fold increase, and only 1 strain showed a 4-fold increase in doripenem MIC values. Thus, the combination of doripenem plus an aminoglycoside may be an effective treatment of infections caused by P. aeruginosa with elevated carbapenem MIC values, with lower risk of selecting further resistance.28

Mushtaq and colleagues evaluated in vitro resistance selection potential of antimicrobial agents versus characterized isolates, mutants, and transconjugants of P. aeruginosa. Doripenem MICs were lower than meropenem for strains with elevated intrinsic resistance. Furthermore, mutant selection (single step) with doripenem occurred with fewer strains than with other agents. The final multiple of the MIC achieved was
lower for doripenem than for other agents and never exceeded 4 times the starting MIC. Other carbapenems selected mutants from among more test strains.29

**Doripenem Clinical Efficacy**

At the 2006 Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) meeting, Malafaia and colleagues presented findings from a large, randomized, double-dummy, multicenter Phase III trial comparing the efficacy and safety of doripenem (500 mg I.V. infusion every 8 hours over 60 minutes) versus meropenem (1 g I.V. bolus every 8 hours over 3-5 minutes) for treatment of adult patients (n=486) with cIAIs.30 Patients could be switched to oral amoxicillin-clavulanate after 9 or more doses of doripenem or meropenem. Table 6 summarizes patient characteristics of the microbiologically evaluable population at test-of-cure (TOC) analysis. The total duration of study therapy was 5 to 14 days. The primary end point was clinical response at the TOC visit 21 to 60 days post-therapy. Figure 5 illustrates the clinical cure rate for both agents at the TOC visit for the microbiologically evaluable population. Doripenem was noninferior to meropenem for the treatment of cIAI. Also illustrated in Figure 5 are the clinical cures for the microbiologic modified intent-to-treat population. In this study, doripenem was effective against major causative organisms (E. coli, K. pneumoniae, P. aeruginosa, S. intermedii, Bacteroides caccum, B. thetaetao micron, B. fragilis, and B. uniformis) and was generally well tolerated. Nausea occurred in 3.7% and 2.6% in the doripenem and meropenem groups, respectively, and diarrhea occurred in 2.5% and 3.0% in each group, respectively.

**Optimizing Treatment With Carbapenems**

For β-lactams, the best predictor of bacterial killing is the time during which drug concentration exceeds the MIC of the organism. Lodise and colleagues evaluated an extended-infusion dosing scheme for piperacillin-tazobactam therapy, using a Monte Carlo simulation, to improve clinical outcomes in critically ill patients with P. aeruginosa infections. Among patients with APACHE-II scores of 17 or greater, the 14-day mortality rate was significantly lower among patients who received extended-infusion therapy (4 hours) than among patients who received intermittent-infusion therapy (30 minutes), and the median duration of hospital stay was significantly shorter.31 Likewise, extending infusion time may confer advantages in treatment with carbapenems. In healthy volunteers, a 2-hour infusion of imipenem resulted in serum concentrations exceeding organism MIC for extended time periods, compared with a half-hour infusion.32 The advantages of prolonged infusion with meropenem were demonstrated in an in vitro hollow-fiber infection model by Tam and colleagues. In this study, selective amplification of resistant subpopulations of P. aeruginosa was reduced with extended meropenem infusion.33

Adverse CNS effects, particularly the lower seizure threshold, of β-lactam antimicrobials are well known, although the data on seizure activity are somewhat inconclusive. In the literature, imipenem has been associated with a 3% incidence of seizures. The mechanism of seizure action of imipenem is multifactorial and believed to be related to the agent’s ability to reduce inhibition of epileptic discharges by blocking γ-aminobutyric acid (GABA)-A receptor, to its action on α-amino-3-hydroxy-5-methyl-isoxazolepropionate (AMPA) and N-methyl-D-aspartate (NDMA) receptor complexes, or possibly to its penicillin-like activity.34

Wong and colleagues evaluated the efficacy and safety of combination imipenem/cilastatin in 21 young children with bacterial meningitis. The study was terminated when 7 patients (33%) developed seizure activity after antibiotic therapy was given, leading investigators to conclude that the utility of imipenem/cilastatin for bacterial meningitis in children may be limited by a possible increased incidence of drug-related seizure activity.35

Observations from 1,754 patients treated with imipenem/cilastatin in Phase III dose-ranging studies in the United States demonstrated that 52 patients (3%) had seizures, of which 16 (0.9%) were considered to be associated with imipenem. Of the 1,754 patients, 946 (54%) were treated with 2 g of imipenem/cilastin per day for serious infections. The majority of seizure types were generalized tonic-clonic (n=37), with the rest divided between focal seizures and myoclonus. Imipenem dosages in excess of manufacturer recommendations were associated with increased risk of seizures.36 A possible clinical concern is that physicians may use suboptimal doses in an effort to avoid possible seizures with imipenem, thereby complicating overall treatment outcomes.

A medical chart review of 75 patients receiving imipenem in a municipal hospital during a 6-month interval was conducted by Koppel and colleagues. Findings from this study demonstrated that imipenem use is safe and is not associated with

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**TABLE 6. PATIENT CHARACTERISTICS OF THE ME AT TOC ANALYSIS**

<table>
<thead>
<tr>
<th>Primary Site of Infection</th>
<th>I.V. Doripenem; n=162 (%)</th>
<th>I.V. Meropenem; n=153 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complicated localized appendicitis</td>
<td>57 (35.2)</td>
<td>42 (27.5)</td>
</tr>
<tr>
<td>Other sites of IAI</td>
<td>105 (64.8)</td>
<td>111 (72.5)</td>
</tr>
</tbody>
</table>

**Infection Process (%)**

<table>
<thead>
<tr>
<th>Infection</th>
<th>I.V. Doripenem; n=162 (%)</th>
<th>I.V. Meropenem; n=153 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized peritonitis</td>
<td>76 (46.9)</td>
<td>81 (52.9)</td>
</tr>
<tr>
<td>Localized infection</td>
<td>46 (28.4)</td>
<td>30 (19.6)</td>
</tr>
<tr>
<td>Single abscess</td>
<td>33 (20.4)</td>
<td>36 (23.5)</td>
</tr>
<tr>
<td>Multiple abscess</td>
<td>5 (3.1)</td>
<td>4 (2.6)</td>
</tr>
<tr>
<td>Postoperative infection</td>
<td>10 (6.2)</td>
<td>12 (7.8)</td>
</tr>
</tbody>
</table>

IAI, intra-abdominal infection; ME, microbiologically evaluable; TOC, test of cure

Adapted from reference 30.
increased risk of seizure. Of the 75 charts reviewed, only 4 patients had seizures during imipenem treatment and 8 patients had seizures before or after imipenem use. Although the incidence of seizure was greater among critically ill patients, it did not differ with use of imipenem. Determining the proper dose of imipenem at initiation of therapy and avoiding dosing at more than 2 g per day appears to mitigate the risk for seizures related to imipenem.34

In an animal model study, doripenem showed no convulsive activity when administered via I.V. or intracerebroventricular route. Furthermore, this agent did not potentiate seizures in the pentyleneetetrazol (PTZ)-induced convulsive model, had a low affinity for GABA receptors compared with other β-lactams, did not induce seizure discharges when used concomitantly with valproic acid in the PTZ- or bicuculine-induced seizure model, and caused no changes in electroencephalogram (EEG) or behavior in any animal studied. These findings suggest that doripenem neurotoxicity may be negligible in clinical use settings. Conversely, imipenem produced seizure discharges on EEG and/or convulsive activity in rats, mice, and dogs; and meropenem caused shaking behavior in rats and spikes or seizure discharges in dogs.37

**FIGURE 5. DORIPENEM EFFICACY NONINFERIOR TO MEROPENEM FOR TREATMENT OF CIAI**

<table>
<thead>
<tr>
<th>Clinical Cure (%)</th>
<th>Microbiologically Evaluable</th>
<th>Microbiological Modified ITT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doripenem</td>
<td>83.3% 83.0%</td>
<td>74.5% 75.7%</td>
</tr>
<tr>
<td>Meropenem</td>
<td>135/162 127/153</td>
<td>149/200 140/185</td>
</tr>
</tbody>
</table>

95% CI, -8.6 –+9.2 95% CI, -10.3 –+8.0

**Summary**

The carbapenem class of antimicrobials is characterized by excellent in vitro activity and broad-spectrum antimicrobial activity. These agents are considered to be the therapy of choice for infection with ESBL-producing pathogens. Doripenem represents a novel, broad-spectrum carbapenem with impressive nonclinical activity and documented success in clinical trials. The unique characteristics of doripenem, including greater activity against Gram-negative MDR pathogens and a favorable toxicology profile, offer clinicians a practical treatment to combat these pathogens in critically ill patients. Use of polymyxins has resurfaced for those patients infected with *A. baumannii, P. aeruginosa*, or other isolates that are resistant to virtually all available antimicrobial agents. However, heteroresistance to colistin has recently been documented; thus, overuse or misuse of these agents can rapidly lead to development of resistance and negative outcomes. Adherence to clinical practice guidelines for the treatment of nosocomially acquired Gram-negative pathogens ensures appropriate antimicrobial selection and judicious use of available agents for MDR pathogens, and can reduce emergence of resistance.

**References**


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**Post-test**

Choose the single-letter response that best answers the question or completes the sentence.

1. **β-lactam antimicrobials, the most commonly prescribed antimicrobial agents because of their efficacy and tolerability, comprise _____.
   a. 10% to 25% of all antimicrobial therapies
   b. <15% of all antimicrobial therapies
   c. >50% of all antimicrobial therapies
   d. >80% of all antimicrobial therapies

2. Which of the following statements does not explain why carbapenems demonstrate excellent in vitro activity?
   a. Carbapenems efficiently penetrate bacteria.
   b. Carbapenems offer narrow-spectrum antimicrobial activity.
   c. Carbapenems have a high affinity for essential PBPs of Gram-negative bacteria.
   d. Carbapenems offer stability to hydrolysis by nearly all clinically important serine β-lactamases.

3. In an animal model study, which agent(s) caused NO seizure discharges or shaking behavior in rats, mice, or dogs?
   a. Meropenem and doripenem
   b. Meropenem and imipenem
   c. Meropenem only
   d. Doripenem only

4. In the case of HAP, VAP, or HCAP, when MDR Gram-negative infection is suspected, guidelines recommend _____.
   a. Isolation of patients to prevent the spread of bacteria
   b. Monotherapy up front with an antimicrobial that targets specific bacteria
   c. Empiric therapy with doripenem, followed by imipenem
   d. Empiric therapy with an antibiotic and carbapenem with or without a β-lactamase inhibitor plus an anti-pseudomonal fluoroquinolone or an aminoglycoside
5. For adult patients with HAP, ATS and IDSA recommend ______.
   a. broad-spectrum therapy for patients at risk for MDR pathogens
   b. combination antimicrobial therapy
   c. aggressive monotherapy treatment that targets *P. aeruginosa*
   d. ceftriaxone/metronidazole for the treatment of mild to moderate infections

6. Which of the following statements is true based on the ATS/IDSA guidelines for the management of HAP?
   a. Antimicrobial de-escalation should be conducted based solely on the patient’s clinical response.
   b. An empiric therapy regimen should include agents from different antimicrobial classes than the patient has recently received.
   c. A shorter duration of therapy is pertinent in patients with complicated HAP who have received initially appropriate therapy and have experienced a good clinical response.
   d. Combination antimicrobial therapy is required in all patients with HAP.

7. Which of the following statements is true based on the IDSA and SIS guidelines for the management of cIAIs?
   a. Antimicrobial therapy should commence once cIAI is confirmed.
   b. Broad-spectrum penicillins are the only recommended monotherapy for cIAIs because their spectrum of activity effectively covers aerobes and anaerobes.
   c. Multidrug regimens are not indicated for the treatment of cIAIs.
   d. Only carbapenems and broad-spectrum penicillins are recommended monotherapy for the treatment of cIAIs since their spectrum of activities effectively cover aerobes and anaerobes.

8. Based on SIS guidelines, it is recommended that a patient at lower risk for cIAI be treated with ______.
   a. ciprofloxacin monotherapy
   b. aztreonam monotherapy
   c. meropenem monotherapy
   d. clindamycin monotherapy

9. In a prospective, observational study of patients with *K. pneumoniae* bacteremia, multivariate analysis and other predictors of mortality demonstrated that use of a carbapenem during the 5-day period after onset of bacteremia resulting from an ESBL-producing organism was independently associated with ______.
   a. neither treatment success nor improved patient outcome
   b. lower mortality
   c. a 30% mortality rate
   d. lower morbidity and mortality

10. The Belgian Multicenter Study Group compared the efficacy and tolerability of meropenem and imipenem/cilastatin as empirical monotherapy in 212 ICU patients with serious bacterial infections. Results demonstrated that ______.
    a. meropenem was significantly more clinically and bacteriologically efficacious than imipenem/cilastatin for the empirical monotherapy of serious bacterial infections in ICU patients
    b. the clinical response rate of meropenem surpassed the clinical response rate of imipenem-cilastatin
    c. meropenem was at least as clinically and bacteriologically efficacious as imipenem/cilastatin for the empirical monotherapy of serious bacterial infections in ICU patients
    d. imipenem/cilastatin was significantly more efficacious than meropenem when used as empirical monotherapy for serious bacterial infections in ICU patients

11. Based on a retrospective chart review of 37 ICU patients with MDR *A. baumannii* who received polymyxin B ______.
    a. neurotoxicity was more common than nephrotoxicity
    b. generalizability of findings may be limited by older age of patients
    c. crude mortality for these patients was 17%
    d. clinical cure rate for these patients was 76%

12. In an in vitro study by Jones and colleagues, which of the following demonstrated activity against wild-type *A. baumannii* isolates?
    a. Imipenem and meropenem
    b. Meropenem and doripenem
    c. Doripenem
    d. Doripenem, imipenem, and meropenem

13. Sakyo and colleagues examined the potency of 3 antimicrobials and their ability to prevent the emergence of carbapenem-resistant *P. aeruginosa* mutants. Based on their findings, these investigators determined that ______.
    a. doripenem and meropenem had equal ability to prevent the emergence of mutants
    b. doripenem had the greatest ability to prevent emergence of mutants
    c. imipenem had the greatest ability to prevent emergence of mutants
    d. meropenem had the greatest ability to prevent emergence of mutants

14. Clinically, the efficacy of doripenem for treatment of cIAIs is comparable with that of ______.
    a. meropenem
    b. ertapenem
    c. faropenem
    d. imipenem

15. In an animal model study evaluating the effects of doripenem on CNS activity, which of the following were evident?
    a. Doripenem, compared with other β-lactams, had a high affinity for GABA receptors.
    b. Doripenem potentiated seizures in the PTZ-induced convulsive model.
    c. Doripenem caused no changes in EEG or behavior in any animal studied.
    d. Doripenem demonstrated convulsive activity only in rats.
**Answer Sheet & Evaluation Form**

Emerging Modalities to Combat Resistant Gram-Negative Pathogens in Critically Ill Patients: Part 2: Focus on the Carbapenems

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Expiration Date: August 31, 2008

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