

Appropriate Empiric Antimicrobial Therapy of Nosocomial Pneumonia: The Role of the Carbapenems

Marin H Kollef MD

Nosocomial pneumonia is the leading cause of death in patients with hospital-acquired infections. The development of nosocomial pneumonia prolongs hospitalization, which may cause additional days in the intensive care unit, thereby increasing overall health care costs. Empiric treatment of nosocomial pneumonia with therapies that are subsequently shown to be inappropriate therapy (defined as antimicrobial therapy that does not cover the infecting pathogens) has a detrimental effect on patient survival and can increase morbidity, length of hospital stay, and mortality. Delayed therapy can also have similar consequences. Therefore, it is necessary to begin treatment with the most appropriate regimen as soon as possible. This review considers the early use of appropriate, broad-spectrum empiric antimicrobial therapy for treating patients with nosocomial pneumonia and describes where and when the carbapenems are particularly useful. The carbapenems are active against both Gram-positive and Gram-negative pathogens, including anaerobes; resistance to carbapenems remains rare. Key words: nosocomial pneumonia, antibiotics, carbapenems. [Respir Care 2004;49(12):1530–1541. © 2004 Daedalus Enterprises]

Introduction

Nosocomial pneumonia is the second most common hospital-acquired infection, after urinary tract infections¹ (Fig. 1), and accounts for between 27% and 47% of infections within the intensive care unit (ICU).^{1,2} It is the leading cause of death among patients with hospital-acquired infections,³ with reported mortality rates of 30–70%.^{4–8} The development of nosocomial pneumonia prolongs hospitalization, which may include additional days in the ICU, thereby increasing overall health care costs.^{9–11}

General approaches to the treatment of nosocomial pneumonia are currently based on guidelines published by the American Thoracic Society (ATS), last issued in 1996.¹² These guidelines classify nosocomial pneumonia into 3

levels of severity (mild-moderate with no risk factors, mild-moderate with risk factors, and severe pneumonia), and treatment choices are recommended for each level.

However, treatment choices that are inappropriate (subsequently found not to cover the infecting pathogens) have a detrimental effect on patient survival and can lead to increased morbidity and length of hospital stay.^{13–17} By contrast, early aggressive therapy with appropriate broad-spectrum regimens that optimize empiric therapy against the likely pathogens is associated with lower mortality rates and shorter hospital stay.^{15–18}

Therefore, a fresh approach to the effective treatment of nosocomial pneumonia is to use initial empiric broad-spectrum antibacterial treatment followed by precision therapy based on susceptibility results.¹⁹ This treatment strategy, which was first described in the 1960s for the treatment of febrile neutropenia, aims to get the initial use of the correct antimicrobial agent at the most appropriate dose to optimize the likelihood of clinical and bacteriological success and minimize drug-related toxicities. A further aim is to improve patient outcome with aggressive initial management while preventing emergence of antibacterial resistance that might arise from unnecessary or prolonged use of antibacterial agents.

This review focuses on how this approach can be used in the treatment of nosocomial pneumonia and, in partic-

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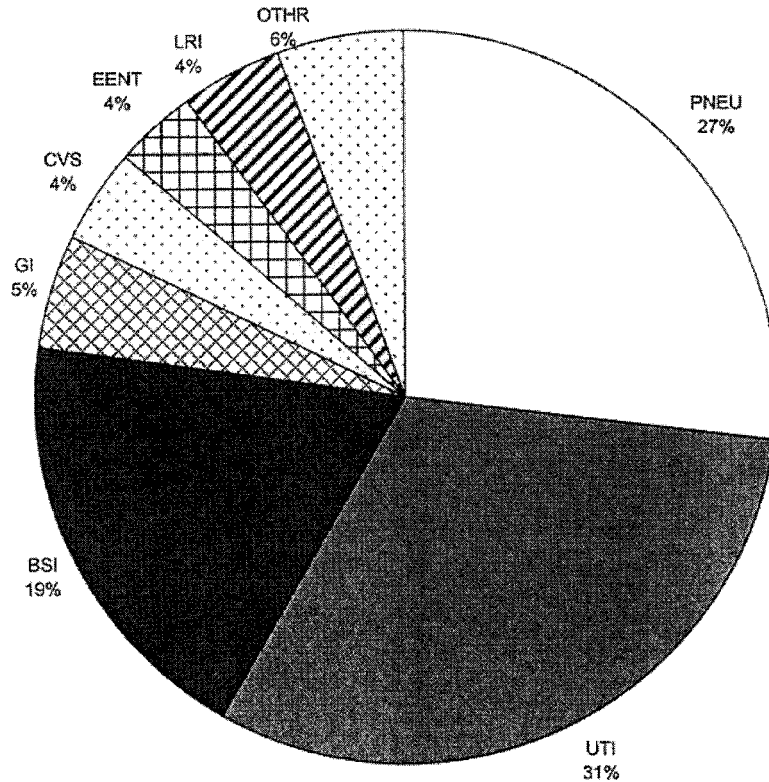


Fig. 1. Distribution of nosocomial infections among adult patients in medical intensive care units, from 1992 to 1997. PNEU, pneumonia; UTI, urinary tract infections; BSI, primary bloodstream infections; GI, gastrointestinal infections; CVS, cardiovascular system; EENT, eye, ear, nose, and throat infections; LRI, lower respiratory tract infections (other than pneumonia); OTHR, other. (From Reference 1, with permission.)

ular, on the role of the carbapenems. It is not the purpose of this review to imply that other antibiotic treatment options are not applicable in many treatment situations, but they are fully covered elsewhere (eg, in treatment guidelines). However, as a result of the increasing pressure to prescribe the carbapenems when Gram-negative infections are suspected (because of concern about creating drug-resistant bacteria), it is important to consider their role within treatment strategies for the management of pneumonia. The purpose of this review is to define situations in which carbapenems form a part of an appropriate treatment strategy. It is not my purpose to endorse the use of carbapenems in every patient being treated for nosocomial pneumonia.

The term “carbapenems” is taken here to include the broad-spectrum agents meropenem and imipenem/cilastatin. Ertapenem is not suitable for the treatment of nosocomial pneumonia because of its lack of anti-pseudomonal activity. This is not intended to be a systematic review of the carbapenem literature: excellent reviews of that subject have already been published.^{20–26} Instead, this article reviews major trials of the carbapenems for treating nosocomial pneumonia.

Overview of Nosocomial Pneumonia

Nosocomial pneumonia is usually defined as hospital-acquired pneumonia that occurs at least 48 hours after admission to hospital but excludes any infection that was incubating at the time of admission.²⁷ The term also describes ventilator-associated pneumonia (VAP) that occurs more than 48 hours after initiation of mechanical ventilation.²⁸ Increased risk of hospital-acquired pneumonia is particularly associated with prior hospitalization or residency in a long-term care facility or nursing home, and with prior antimicrobial use^{11,27,29} (Table 1). Key risk factors for VAP include chronic lung disease, prolonged duration of mechanical ventilation, supine position, and previous antibiotic therapy.^{30,31}

Microbial Etiology of Pneumonia

Awareness of the main organisms that can cause nosocomial pneumonia is one of the keys to successful treatment. However, the causative pathogens often differ, depending on whether pneumonia is early- or late-onset, which can in turn impact the choice of treatment.

THE ROLE OF CARBAPENEMS IN TREATING NOSOCOMIAL PNEUMONIA

Table 1. Risk Factors for Developing Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia

Hospital-Acquired Pneumonia	Ventilator-Associated Pneumonia
<u>Patient-Related Risk Factors</u>	
Advanced age (> 60 years) Comorbid disease (eg, chronic lung disease) Previous antibiotic therapy Cardiothoracic or abdominal surgery APACHE II > 16 Smoking Prior hospitalization or residency of long-term care facility or nursing home Reflux	Supine position Comorbid disease (eg, chronic lung disease) Previous antibiotic therapy Stress ulcer prophylaxis with gastric pH-altering agents
<u>Device-Related Risk Factors</u>	
Tracheotomy Nasogastric tubes Short duration of nasotracheal or orotracheal intubation Long duration of nasotracheal or orotracheal intubation	Tracheotomy Nasogastric tubes Prolonged duration of mechanical ventilation Reintubation
<small>APACHE = Acute Physiology and Chronic Health Evaluation (Adapted from References 11, 27, and 29.)</small>	

Table 2. Common Pathogens Responsible for Early- and Late-Onset Nosocomial Pneumonia

Pathogen	Onset of Pneumonia*	Frequency (%)
<i>Streptococcus pneumoniae</i>	Early	10–20
<i>Haemophilus influenzae</i>	Early	5–15
Anaerobic bacteria	Early	10–30
<i>Staphylococcus aureus</i>	Early/Late	20–30
Gram-negative bacilli	Late	30–60
<i>Pseudomonas aeruginosa</i>		17
<i>Klebsiella pneumoniae</i>		7
<i>Acinetobacter</i> spp.		3
<i>Escherichia coli</i>		6
<i>Enterobacter</i> spp.		10
<i>Legionella pneumophila</i>	Late	0–15

*Early = onset within ≤ 4 days of hospitalization. Late = onset ≥ 5 days after hospitalization.
(Adapted from References 27 and 29.)

late-onset pneumonia include *S. aureus* and *Legionella pneumophila*^{29,31} (see Table 2). The presence of risk factors (eg, recent abdominal surgery, diabetes mellitus, head trauma) can influence the microbial etiology, as will local patterns of pathogen prevalence and antibacterial susceptibility.

The potential involvement of multiple-drug-resistant bacteria in late-onset nosocomial pneumonia is more likely to lead to inappropriate treatment with traditional antibiotic regimens.^{15,16} Additionally, enteric Gram-negative bacteria are becoming increasingly resistant to the β -lactam antibiotics because of the production of extended-spectrum β -lactamases and/or overproduction of AmpC β -lactamases. These enzymes hydrolyze cephalosporins, penicillins, and aztreonam (antibiotics containing an oxyimino group) but are inactive against carbapenems and cephamycins.³³

Current Treatment of Nosocomial Pneumonia

There are various published guidelines and recommendations for the treatment of nosocomial pneumonia.^{12,34} The ATS recommendations are the most extensive, and those from other geographical locations (Canada, Australia, Sweden, France, and Hong Kong) are similar in approach.³⁴ The ATS guidelines divide nosocomial pneumonia into 3 levels of severity (mild-moderate with no risk factors, mild-moderate with risk factors, and severe pneumonia), which are treated empirically with specific antibiotics¹² (Fig. 2).

In mild-moderate pneumonia with no risk factors (as described in the ATS guidelines), the core organisms are

Early-onset nosocomial pneumonia (ie, that develops after > 2 d but < 4 d of hospitalization) is usually caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or methicillin-susceptible *Staphylococcus aureus*^{29,31} (Table 2). In recent years the incidence of nosocomial pneumonia caused by methicillin-resistant *S. aureus* has increased in many countries.³²

In contrast, late-onset nosocomial pneumonia (ie, that develops after hospital day 5) is caused most frequently by hospital-acquired, often multiple-drug-resistant, Gram-negative bacilli (eg, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*),^{29,31} although methicillin-resistant *S. aureus* still needs to be considered. Additional causes of

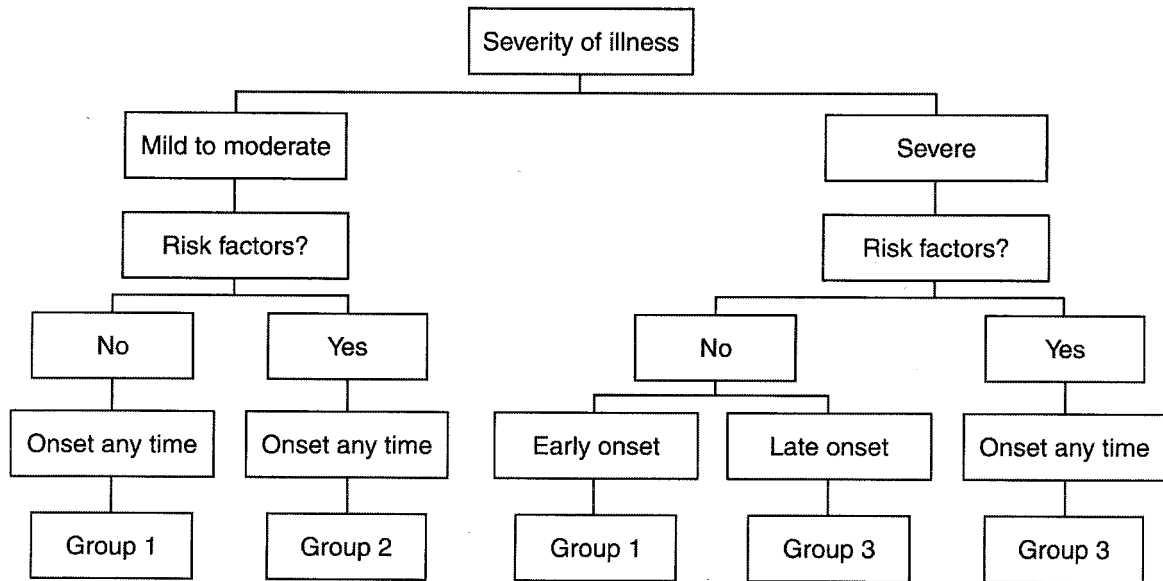


Fig. 2. American Thoracic Society algorithm for classifying patients with nosocomial pneumonia. (Groups 1, 2, and 3 are defined in Table 3). (From Reference 12, with permission.)

Table 3. Treatment Guidelines, Based on American Thoracic Society Guidelines¹²

ATS Classification	Organisms	Antibiotics
Group 1	Enteric Gram-negative bacteria <i>Escherichia coli</i> <i>Klebsiella</i> spp. <i>Proteus</i> spp. <i>Serratia marcescens</i> <i>Haemophilus influenzae</i> Methicillin-sensitive <i>Staphylococcus aureus</i> <i>Streptococcus pneumoniae</i>	Third-generation nonpseudomonal cephalosporins (cefotaxime, ceftioxone), if <i>Enterobacter</i> is suspected; use in combination with another agent OR β -lactam/ β -lactamase inhibitor combination (ampicillin/sulbactam, ticarcillin/clavulanate, piperacillin/tazobactam) If allergic to penicillin: use a fluoroquinolone (ciprofloxacin) or clindamycin plus aztreonam
Group 2	Group 1 organisms plus: Anaerobes <i>Staphylococcus aureus</i> <i>Legionella</i> <i>Pseudomonas aeruginosa</i>	Group 1 antibiotics plus: Clindamycin or β -lactam/ β -lactamase inhibitor combination Vancomycin (until methicillin-resistant <i>S. aureus</i> excluded) Erythromycin with or without rifampin Treat as severe hospital-acquired pneumonia
Group 3	Group 1 organisms plus: <i>Acinetobacter</i> spp. <i>Pseudomonas aeruginosa</i> <i>Staphylococcus aureus</i> (consider methicillin-resistant)	Group 1 antibiotics plus: Aminoglycoside or ciprofloxacin plus one of the following: Anti-pseudomonal penicillin (piperacillin, ticarcillin) Anti-pseudomonal β -lactam/ β -lactamase inhibitor combination (piperacillin/tazobactam, ticarcillin/clavulanate) Aztreonam Imipenem (or meropenem*) with or without vancomycin

ATS = American Thoracic Society
*Released since guidelines were published

most frequently encountered regardless of whether the pneumonia occurred early or late (Table 3). Monotherapy is appropriate, with agents such as a second-generation cephalosporin (eg, cefuroxime), a nonpseudomonal third-

generation cephalosporin (eg, ceftriaxome) or a β -lactam/ β -lactamase inhibitor (eg, ampicillin/sulbactam, piperacillin/tazobactam). A fourth-generation cephalosporin such as cefepime could also be used.

In patients with mild-moderate hospital-acquired pneumonia with risk factors, the antibacterial choice is different. For example, if anaerobic organisms are suspected, clindamycin or a β -lactam/ β -lactamase inhibitor is added, whereas if methicillin-resistant *S. aureus* is suspected, vancomycin or linezolid should be added.

Patients with severe hospital-acquired pneumonia fall into 2 categories: those who do not have any risk factors and develop pneumonia early in their hospitalization (< 5 d) and those with severe hospital-acquired pneumonia who have risk factors for highly resistant Gram-negative pathogens and/or develop pneumonia later during their hospitalization (> 5 d). The former group is treated in a similar way to patients with mild-moderate pneumonia without risk factors. The latter group requires combination therapy directed at the core organisms and also Gram-negative bacilli (eg, aminoglycoside or ciprofloxacin and an anti-pseudomonal β -lactam agent, ceftazidime or cefoperazone, imipenem or meropenem, or aztreonem).

The ATS guidelines have not been updated since their development in 1995, and several new antimicrobial agents are now available that were not available when the guidelines were drafted (eg, cefepime, linezolid, and meropenem). In addition, knowledge about pneumonia treatment has improved. New combined ATS/Infectious Diseases Society of America guidelines are due to be published soon.

Effect of Resistance on Antibiotic Selection

As resistance continues to increase, some of the antimicrobial agents traditionally used in the treatment of nosocomial pneumonia are becoming less active, at least in terms of in vitro testing. For example, increasing resistance to ciprofloxacin in Gram-negative bacteria has been reported,^{35,36} and the appearance of ciprofloxacin-resistant strains has been associated with therapeutic failure, especially where *P. aeruginosa* is involved.³⁷ In addition, resistance to cephalosporins has also increased in recent years as a result of extended-spectrum β -lactamases, which confer resistance to many commonly used antibacterial agents.^{38,39}

Pipercillin/tazobactam has shown good activity against isolates of *Pseudomonas* spp. but only limited activity against the AmpC mediated β -lactamases found in *Enterobacter* spp. and *Citrobacter* spp.⁴⁰ By contrast, resistance to the carbapenems remains rare, despite nearly 20 years of therapeutic use.⁴¹⁻⁴⁴

Consequences of Inappropriate Therapy

Inappropriate antibiotic treatment occurs when a patient is administered an antimicrobial agent to which the causative microorganism is subsequently found to be resistant,

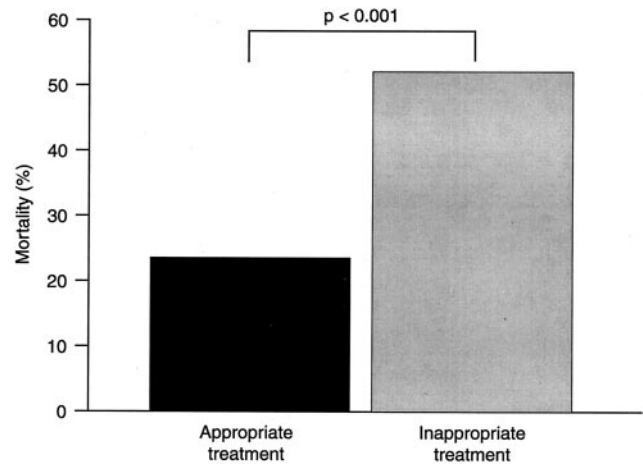


Fig. 3. Effect of appropriate and inappropriate therapy on mortality. (From Reference 15, with permission.)

or that lacks activity against the infecting organism. Clinical evidence shows that inappropriate initial empiric therapy is associated with increased mortality and increased costs to the health care system, through extended periods of mechanical ventilation, increased length of hospital stay, or a need for alternative drugs or therapeutic interventions.¹⁴⁻¹⁸

Increased Mortality

Patients with nosocomial pneumonia have greater mortality rates than those without it.⁴⁻⁸ A number of studies provide evidence that mortality increases still further when patients are treated inappropriately.^{15,17,18} In one study the hospital mortality rate from all causes was statistically greater for infected patients receiving inappropriate antimicrobial therapy than for infected patients receiving adequate treatment (52.1% vs 23.5%, $p < 0.001$, Fig. 3).¹⁵ Confounding factors can complicate the situation and make it difficult to prove a direct cause. However, a multiple logistic regression analysis controlling for potential confounding factors demonstrated that the risk of hospital mortality was more than 4 times greater among infected patients receiving inappropriate antimicrobial treatment than among patients who did not possess that risk factor (adjusted odds ratio 4.26).¹⁵ Another study, which evaluated the appropriateness of antimicrobial therapy in patients with VAP, also reported a significant difference in mortality rates with appropriate and inappropriate therapy (16.2% vs 24.7%, respectively, $p < 0.039$).¹⁸ Recent studies have confirmed those observations.⁴⁵⁻⁴⁷

Increased Costs

The unit cost of any antimicrobial agent used to treat infected patients is small compared with the overall ex-

penses incurred through hospitalization. Inappropriate antimicrobial therapy therefore has major cost implications, particularly if it increases the length of hospitalization/ICU stay. Evidence for that assertion comes from a study by Ibrahim et al,¹⁴ who showed that, compared with patients who received inappropriate antimicrobial therapy, those on appropriate therapy had significantly shorter duration of mechanical ventilation (7 d vs 11 d, respectively, $p < 0.001$) and shorter ICU stay (9 d vs 13.5 d, respectively, $p < 0.001$).

Inappropriate therapy can lead to the emergence of antibiotic resistance, not only by selecting for the more resistant isolates but also by eradicating the patient's indigenous flora, which might otherwise compete with the infecting pathogen.^{48,49} Beyond the direct additional costs of treating patients with resistant organisms, the emergence of resistant pathogens in a hospital might necessitate the introduction of additional intensive infection-control measures, which in turn will increase costs.^{13,50}

Appropriate Empiric Antibacterial Therapy

Aggressive broad-spectrum initial therapy is an approach to antibacterial use that intends to provide appropriate initial antibacterial treatment that will cover most likely bacterial pathogens while limiting the emergence of resistance by restricting treatment duration.¹⁹ This is achieved by narrowing the antibacterial regimen once the pathogens and their susceptibility profiles have been determined, and by using the shortest clinically acceptable course of therapy.¹⁹ This approach can be applied to all nosocomial infections, but is especially relevant to nosocomial pneumonia.

Initial Appropriate Therapy

To counter increasing resistance concerns, clinicians should be confident that their first choice of antimicrobial therapy is active against key pathogens that might cause nosocomial pneumonia. As the range of possible organisms is large, a broad-spectrum regimen is appropriate.^{49,51,52} The factors that should be considered when selecting treatment are:⁵³

- Knowledge of frequent pathogens and their local patterns of susceptibility
- Factors that increase the likelihood of increasing resistance, including specific risk factors (eg, prior antimicrobial use) and time since admission to hospital
- Duration of mechanical ventilation before the patient developed pneumonia
- Presence of underlying disease
- Cause of admission

The types of pathogens associated with nosocomial infections in ICUs, along with their antibiotic susceptibility

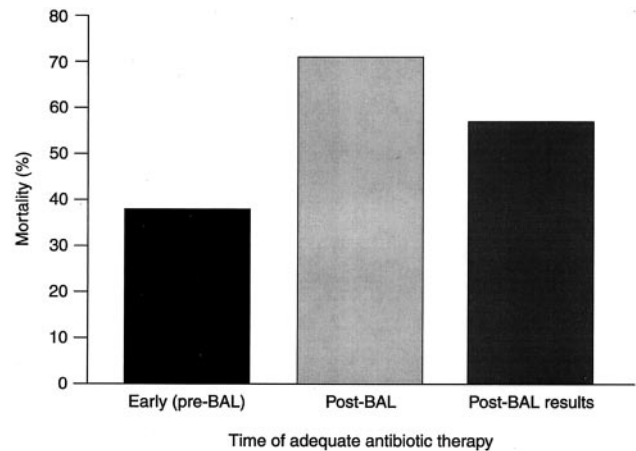


Fig. 4. Importance of early treatment on outcome. Antibiotic therapy was evaluated at 3 different time points: before bronchoalveolar lavage (BAL), immediately after BAL, and after evaluating the therapy choices that were guided by the antimicrobial sensitivity data. (From Reference 17, with permission.)

profiles, differ between ICUs, hospitals, cities, and countries.⁵⁴ Therefore, the choice of initial antimicrobial therapy must be modified to take into account local patterns of resistance.

Timing of Empiric Therapy

Antimicrobial treatment should be initiated as soon as infection is suspected, since a delay in starting treatment will reduce the effectiveness of therapy and increase the risk of mortality.^{17,55} In a recent multivariate analysis of VAP, Iregui et al⁵⁵ showed that delaying appropriate antimicrobial therapy for 24 hours significantly increased the risk of death (7.7-fold higher than nondelayed therapy). Similar results were reported by Luna et al¹⁷ when appropriate therapy was delayed in patients with VAP until bronchoscopy was performed or until bronchoscopy results were known. Mortality was higher than if treatment had been given at the time of first establishing a clinical diagnosis of VAP (Fig. 4), suggesting that the information from the bronchoscopy became available too late to influence survival.

Tailoring Therapy

Following initial appropriate antibacterial therapy, laboratory data on the identification and susceptibility profile of the causative pathogen allow therapy to be tailored to less potent, narrow-spectrum agents in line with susceptibility results. This reduces unnecessary use of potent antibiotics, thereby potentially helping to limit the development of resistance to these agents, which is one of the concerns of using broad-spectrum agents.

Duration of Therapy

The duration of antibacterial treatment should be limited to the shortest effective course of therapy, to reduce the risk of creating resistance. The success of shorter durations of antimicrobial therapy has been reported by some investigators. In a prospective, randomized, double-blind trial, Chastre et al reported that short-course (8 d) antimicrobial therapy was associated with the same clinical efficacy as long-course (15 d) therapy in microbiologically confirmed VAP.⁵⁶ Between patients treated for 8 days and those treated for 15 days there were no significant differences in mortality rate (18.8% vs 17.2%, respectively) or infection-recurrence rate (28.9% vs 26.0%, respectively). However, the authors cautioned that prolonged treatment may be beneficial in the subset of patients with infections caused by nonfermenting Gram-negative bacteria (*P. aeruginosa* and *A. baumannii*).

Dennesen et al evaluated the resolution of the signs and symptoms in 27 patients with VAP.⁵⁷ Patients received appropriate antimicrobial therapy, and clinical variables (highest temperature, leukocyte count, semi-quantitative cultures of endotracheal aspirates, and the ratio of P_{aO_2} to fraction of inspired oxygen [F_{IO_2}]) were assessed until day 14. Within the first 6 d after the start of antimicrobial therapy, there were significant improvements in all the clinical variables. Newly acquired colonization with predominantly resistant pathogens occurred mainly in the second week of therapy. The authors concluded that 7 d of therapy for VAP would be sufficient and could prevent recolonization with resistant pathogens.

Antibiotic Cycling

Antibiotic cycling (the scheduled rotation of antibiotics) is based on the hypothesis that withdrawal of an antibiotic from use for a defined period of time will limit antibiotic pressure as a stimulus for antibiotic resistance. Gerding et al used cycle times of 12–51 mo over 10 years, to control the use of aminoglycosides.⁵⁸ They found that there was significantly reduced resistance to gentamicin and tobramycin following the introduction of amikacin. When gentamicin was rapidly reintroduced following a period of amikacin, there was an associated rapid increase in gentamicin resistance. However, there was no significant change in aminoglycoside resistance when gentamicin was reintroduced gradually. In another study, Kollef et al examined the influence of a scheduled antimicrobial change on the incidence of nosocomial infections among patients undergoing cardiac surgery, using a 6-month “before” period during which ceftazidime (cephalosporin) was employed, and a 6-month “after” period during which ciprofloxacin (fluoroquinolone) was employed. They reported a significantly lower incidence of VAP in the “after” period

than in the “before” period, which they believed to be primarily due to the significant reduction in the incidence of VAP attributed to resistant Gram-negative bacteria. In addition, a lower incidence of Gram-negative bacteremia due to resistant pathogens was also observed in the “after” period.⁵⁹ Although antibiotic cycling may be of substantial clinical benefit, it is only one of a number of strategies that can offer clinicians effective treatment options while also reducing the emergence of antimicrobial resistance. In addition, there are differing opinions on its effectiveness, and further research is required to evaluate the role of antibiotic cycling.

Protocols and Guidelines

Protocols and guidelines have been used successfully to avoid unnecessary antibacterial administration and/or to shorten therapy.^{60,61} Singh et al used a scoring system to identify patients with suspected VAP so that unnecessary antimicrobial therapy could be minimized.⁶¹ Patients with a clinical pulmonary infection score of ≤ 6 (implying low likelihood of pneumonia) were randomized to receive either standard therapy (10–21 d) or therapy with re-evaluation at 3 days. If the patient’s clinical pulmonary infection score remained ≤ 6 at 3 days, therapy was withdrawn, but if the score was > 6 , therapy was continued. Antibiotics were continued in only 28% of patients whose score was ≤ 6 , compared with 90% of the patients in the standard therapy group ($p = 0.0001$). Despite a shorter duration and lower cost of antimicrobial therapy, mortality and length of stay were not higher among the patients who received the shorter course.⁶¹

In another study, Ibrahim et al implemented clinical guidelines based on local antimicrobial susceptibility patterns for the treatment of VAP.⁶⁰ The guideline recommended a 7-day course of appropriate antimicrobial therapy for patients with VAP. Use of antibiotic treatment beyond 7 days was encouraged only for patients with persistent signs and symptoms consistent with active infection (eg, fever $> 38.3^\circ\text{C}$, circulating leukocyte count $> 10,000/\mu\text{L}$, lack of improvement on the chest radiograph, continued purulent sputum). Application of those guidelines successfully shortened the duration of antibiotic treatment (8.6 d vs 14.8 d, $p < 0.001$) and increased the proportion of patients receiving initial appropriate antibiotic treatment (94% vs 48%, $p < 0.001$).⁶⁰

Evidence for the Use of Carbapenems in the Empiric Treatment of Pneumonia

The carbapenems (meropenem and imipenem/cilastatin) possess a broad-spectrum of antibacterial activity that makes them suitable for empiric treatment of nosocomial pneumonia in certain situations.

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Table 4. Clinical Efficacy of the Carbapenems

Antibiotics and Daily Dosage	n	Details of Infection	Patients With Satisfactory Response (%)		Study
			Clinical	Bacteriological	
Meropenem 3 g	69	Ventilator-associated pneumonia	83	75	Alvarez-Lerma et al ⁷²
Ceftazidime 6 g + amikacin 15 mg/kg every 12 h	71		66	53	
Meropenem 3 g	63	Nosocomial lower-respiratory-tract infections	89	89	Sieger et al ⁷⁶
Ceftazidime 6 g + tobramycin 3 mg/kg	58		72	67	
Imipenem/cilastatin 2 g	101	Nosocomial pneumonia	74	N/A	Zanetti et al ⁷³
Cefepime 6 g	108		70	N/A	
Imipenem/cilastatin 2–4 g*	78	Severe pneumonia requiring mechanical ventilation	79	50	Torres et al ³⁷
Ciprofloxacin 800–1200 mg/d*	74		71	49	
Imipenem/cilastatin 2 g*	79	Nosocomial pneumonia	71	N/A	Jaccard et al ⁷⁵
piperacillin-tazobactam 13.5 g*	75		83	N/A	
Imipenem/cilastatin 3g*	200	Severe pneumonia	56	59	Fink et al ⁷⁴
Ciprofloxacin 1200 mg*	202		69	69	
Imipenem/cilastatin 3g	87	Serious bacterial infection	77	83	Colardyn et al ⁷⁷
Meropenem 3g	90		76	77	
Imipenem/cilastatin 3g	40	Serious bacterial infection	85	88	Hartenauer et al ⁷⁸
Meropenem 3g	40		88	94	
Imipenem/cilastatin 3g	105	Serious bacterial infection	68	60	Verwaest et al ⁷⁹
Meropenem 3g	107		77	67	

*Doses adjusted according to renal creatinine clearance
NA = not provided

Microbiology

The broad-spectrum carbapenems (meropenem and imipenem) are active against both Gram-positive and Gram-negative pathogens, including anaerobes.^{62,63} In particular, they are active against β -lactamase producing organisms, including extended-spectrum β -lactamase-producers (eg, *Escherichia coli* and *Klebsiella* spp.^{40,64,65}) and AmpC β -lactamase producers such as *Citrobacter* spp. and *Enterobacter* spp.^{40,65} Meropenem and imipenem are also active against nonfermenting Gram-negative bacteria such as *P. aeruginosa* and *Acinetobacter* spp.^{65–67} Overall, meropenem has better in vitro activity against enteric Gram-negative bacteria than does imipenem. However, imipenem has greater in vitro activity against some Gram-positive bacteria, notably staphylococci. Despite the carbapenems' potent in vitro activity, it must be remembered that laboratory-based sensitivities do not always translate directly into improved clinical outcomes, since other confounding factors have to be considered.

Resistance to meropenem and imipenem/cilastatin is rare, despite their use over a substantial period.^{41–44,68} Both carbapenems are active against *P. aeruginosa*, though mero-

penem has demonstrated better in vitro activity against this generally difficult-to-treat pathogen, including activity against some imipenem-resistant strains.⁶⁶ It should be noted that neither imipenem/cilastatin nor meropenem is active against methicillin-resistant *S. aureus*, *Enterococcus faecium*, or *S. maltophilia*.^{26,69}

The most recently approved member of the carbapenems, ertapenem, is not indicated for the treatment of nosocomial pneumonia, because it lacks antipseudomonal activity,⁷⁰ and data are available only for its use in treating community-acquired pneumonia.⁷¹

Clinical Efficacy

Several studies have demonstrated the efficacy of the carbapenems in the treatment of nosocomial pneumonia.^{37,72–76} In those studies, clinical and bacteriological response rates were the primary end points (Table 4).

In a large, randomized study with patients with VAP, empiric monotherapy with meropenem was compared with a combination of ceftazidime and amikacin.⁷² When non-evaluable patients were excluded from the analysis, the satisfactory clinical response was significantly greater with

the meropenem (82%) than with the ceftazidime/amikacin (66%) patients ($p = 0.044$). In another randomized trial with patients with nosocomial lower-respiratory tract infections, meropenem was significantly more efficacious than ceftazidime and tobramycin.⁷⁶ Satisfactory clinical responses were significantly greater in the meropenem group than in the ceftazidime/tobramycin patients (89% vs 72%, respectively, $p = 0.04$). The corresponding bacteriological response rates were 89% and 67%, respectively, ($p = 0.006$), and in many cases meropenem eradicated 100% of pretreatment pathogens.⁷⁶

In 3 comparator studies containing large numbers of patients with pneumonia, clinical and bacteriological response rates were shown to be similar following treatment with meropenem and imipenem/cilastatin⁷⁷⁻⁷⁹ (see Table 4).

A randomized trial with patients with severe pneumonia compared ciprofloxacin with imipenem/cilastatin.⁷⁴ Clinical response rate was significantly higher in the ciprofloxacin-treated patients (69% vs 56%, $p = 0.021$). In a more recent study, with patients with severe nosocomial pneumonia, ciprofloxacin and imipenem/cilastatin were compared, and clinical success rates were similar for the ciprofloxacin-treated patients and the imipenem-treated patients (71% vs 79%, respectively), and bacteriological response rates were also similar (49% vs 50%).³⁷ However, increasing resistance to ciprofloxacin among Gram-negative bacteria such as *P. aeruginosa* has recently been reported,^{35,36} whereas resistance to imipenem/cilastatin has not.⁴³

In a randomized trial that compared imipenem/cilastatin with piperacillin-tazobactam, the clinical success rates were 71% and 83%, respectively.⁷⁵ Since patients treated with imipenem/cilastatin were often more bacteremic than those treated with piperacillin-tazobactam, which could have been a confounding factor, a stratified analysis was performed, and it confirmed that there were no differences between the treatment groups.⁷⁵ Another study demonstrated that imipenem/cilastatin was as effective as cefepime for monotherapy of nosocomial pneumonia (74% vs 70%, respectively).⁷³ In addition, the all-cause 30-day mortality rate was lower among the patients treated with imipenem/cilastatin than among those treated with cefepime (19% vs 26%, respectively).

Safety and Tolerability

The carbapenems are generally well-tolerated antimicrobial agents, and similar incidences of adverse events have been reported among patients treated with meropenem and those treated with imipenem/cilastatin or cephalosporin-based treatment.⁷⁶⁻⁸⁰ Nausea and vomiting have been reported during rapid administration or higher-dose administration of imipenem/cilastatin, whereas nausea and vomiting appear to be less of a problem with mero-

penem.^{81,82} Meropenem has a good central nervous system tolerability profile.⁸¹ Imipenem/cilastatin appears more likely to be associated with seizures in patients with some degree of renal impairment, which is not an uncommon situation in ICU patients.⁸³ Careful dose adjustment based on age, weight, and renal function data given in the imipenem/cilastatin prescribing information⁸⁴ is likely to reduce the occurrence of seizures. For meropenem, dose adjustment only needs to be based on renal function. Imipenem/cilastatin or meropenem should be administered with caution to patients who are allergic to penicillin, since hypersensitivity reactions have been reported in some (11%) patients with penicillin allergy following carbapenem treatment.⁸⁵

In conclusion, meropenem and imipenem/cilastatin are active against the majority of pathogens that cause nosocomial pneumonia. Both of these carbapenems have been shown to be effective clinically and they are generally well tolerated.

When and Where to Use the Carbapenems in Nosocomial Pneumonia

The carbapenems are particularly appropriate for late-onset nosocomial pneumonia and when multiple-drug-resistant bacteria, including extended-spectrum β -lactamase-producers and AmpC β -lactamases, are suspected. In addition, they are also appropriate for patients who have been recently hospitalized, have resided in a nursing home, or who have recently received antibiotic treatment, all of whom have a higher risk of infection with multiple-drug-resistant pathogens⁸⁶ (Table 5). Early empiric therapy with appropriate agents is important in this type of infection, since the associated mortality rate is high.

The carbapenems also have a role as second-line therapy in cases where previous therapy has failed, because carbapenems have a broad spectrum of antimicrobial activity and sustained activity against Gram-negative organisms that are resistant to other antimicrobial classes, such as the cephalosporins, aminoglycosides, and fluoroquinolones.

When methicillin-resistant *S. aureus* is the suspected pathogen, vancomycin or linezolid should be used, because none of the currently approved carbapenems have useful activity against *S. aureus*.⁸⁶

Conclusions

The treatment of nosocomial pneumonia is based on guidelines and recommendations, in particular the ATS guidelines. Even though those guidelines are useful, several new antimicrobials are available that were not available when the guidelines were drafted, and clinicians need to consider factors such as treatment duration and amend-

THE ROLE OF CARBAPENEMS IN TREATING NOSOCOMIAL PNEUMONIA

Table 5. Appropriate Empirical Treatment With the Carbapenems

Scenario	General Comments
Late-onset or severe pneumonia - likely causative agents such as <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter</i> spp., extended-spectrum β -lactamases-producers (eg <i>Klebsiella</i> spp.), AmpC beta-lactamase-producers (eg <i>Serratia</i> spp., <i>Citrobacter</i> spp.).	Empirical antibiotic selection should be based on local epidemiologic data. Initial antibiotic coverage should include all potential pathogens. Carbapenems are first-line candidates when margin for therapeutic error is small (eg severely ill patient, high index of suspicion for multiple-drug-resistant strain).
In cases where previous therapy has failed.	Patients referred from other units will have had previous antibiotics. Use carbapenems as second-line treatment rather than as drugs of last resort. If pathogen known to be carbapenem-susceptible, use carbapenems as definitive therapy. The carbapenems have a broad-spectrum of activity and they retain activity against Gram-negative organisms resistant to other antimicrobial classes.

ing antibiotic management as soon as culture results are available. In addition, the changing patterns of antimicrobial resistance and the lack of development of new antimicrobials necessitates a review of current treatment strategies.

Tailoring of antibacterial therapy is an approach to antibacterial use that attempts to provide appropriate initial treatment while limiting the emergence of resistance. Initial empiric therapy should include a broad-spectrum agent that has good activity against potentially resistant strains such as *P. aeruginosa* and extended-spectrum β -lactamase-producing *K. pneumoniae*. Once the causative pathogens and their susceptibility profiles have been determined, the antibacterial regimen can be narrowed and the shortest clinically acceptable course of therapy is used.

Of the antimicrobial classes currently available, the carbapenems (meropenem and imipenem/cilastatin) have the broadest spectrum of activity, sustained susceptibility data, and present a reliable option for empiric therapy. Carbapenems are appropriate for use in certain situations, including late-onset nosocomial pneumonia and when multiple-drug-resistant Gram-negative bacteria are suspected. The carbapenems are active against both Gram-positive and Gram-negative pathogens, including anaerobes, and resistance to carbapenems is rare. In addition, they have good tolerability profiles.

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