

# Hospital-Acquired Pneumonia\*

## Risk Factors, Microbiology, and Treatment

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Pneumonia complicates hospitalization in 0.5 to 2.0% of patients and is associated with considerable morbidity and mortality. Risk factors for hospital-acquired pneumonia (HAP) include mechanical ventilation for > 48 h, residence in an ICU, duration of ICU or hospital stay, severity of underlying illness, and presence of comorbidities. *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Enterobacter* are the most common causes of HAP. Nearly half of HAP cases are polymicrobial. In patients receiving mechanical ventilation, *P aeruginosa*, *Acinetobacter*, methicillin-resistant *S aureus*, and other antibiotic-resistant bacteria assume increasing importance. Optimal therapy for HAP should take into account severity of illness, demographics, specific pathogens involved, and risk factors for antimicrobial resistance. When *P aeruginosa* is implicated, monotherapy, even with broad-spectrum antibiotics, is associated with rapid evolution of resistance and a high rate of clinical failures. For pseudomonal HAP, we advise combination therapy with an antipseudomonal  $\beta$ -lactam plus an aminoglycoside or a fluoroquinolone (eg, ciprofloxacin). (CHEST 2001; 119:373S-384S)

**Key words:** antibiotics; combination therapy; determinants of therapy; nosocomial infections; risk factors

**Abbreviations:** APACHE = acute physiology and chronic health evaluation; EGNB = enteric Gram-negative bacilli; HAP = hospital-acquired pneumonia; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; MV = mechanical ventilation; OR = odds ratio; VAP = ventilator-associated pneumonia

Hospital-acquired pneumonia (HAP) accounts for 15% of all nosocomial infections<sup>1</sup> and affects 0.5 to 2.0% of hospitalized patients.<sup>2,3</sup> The mortality rate for HAP exceeds 30%, although attributable mortality is lower.<sup>4-9</sup> Prompt use of appropriate antibiotics is essential to optimize the outcome of HAP.<sup>10-12</sup>

Antimicrobial strategies that encompass the most likely causative organisms while preventing emergence of resistance and controlling costs are needed.<sup>13,14</sup> Unfortunately, antimicrobial resistance has escalated dramatically within the past decade<sup>15-18</sup> and has created obstacles to effective antibiotic choices. These trends are most problematic in ICUs.<sup>17-24</sup> Appropriate choice of antibiotics requires an awareness of the relevant pathogens, antimicrobial resistance patterns, and the host and demographic factors that may lead to infections and/or evolution of antibiotic resistance.

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### MICROBIOLOGY OF HAP

The etiologic agents responsible for HAP have been elucidated in numerous studies.<sup>1,7,9,25-32</sup> Gram-negative bacteria, including *Pseudomonas aeruginosa*, *Enterobacter*, *Acinetobacter*, and enteric Gram-negative rods, are implicated in 55 to 85% of HAP cases; Gram-positive cocci (particularly *Staphylococcus aureus*) account for 20 to 30%; and 40 to 60% of cases are polymicrobial.<sup>1,7,9,25-29</sup> Acuity and severity of illness, duration of hospitalization, and prior antibiotic exposure are major determinants of likely pathogens.<sup>9,28,30</sup> In critically ill patients requiring prolonged mechanical ventilation (MV) in ICUs, *P aeruginosa* and *Acinetobacter* (eg, *Acinetobacter calcoaceticus* and *Acinetobacter baumannii*),<sup>30</sup> which are resistant to many antibiotics, account for 30 to 50% of HAP; these pathogens are uncommon in non-ICU settings.<sup>5,20,27,30-32</sup>

Over the past 2 decades, antimicrobial resistance has escalated dramatically in the United States and worldwide. The National Nosocomial Infections Surveillance System, which incorporates data from community, university, and municipal hospitals, elucidated the major pathogens responsible for HAP in the United States since the 1970s.<sup>25,29,33,34</sup> During this time, some pathogens have emerged as

important opportunistic pathogens in ICUs (Acinetobacter, methicillin-resistant *S aureus* [MRSA], Enterobacter), whereas the prevalence of other pathogens (*Klebsiella pneumoniae* and *P aeruginosa*) has remained stable or declined. *S aureus* was implicated in 13% of HAP from 1981 to 1986, 16% from 1986 to 1989, and 19% from 1990 to 1996.<sup>25,33,34</sup> During these intervals, Enterobacter was implicated in 7%, 11%, and 11% of cases of HAP, respectively. The prevalence of *K pneumoniae* during these time periods was 12%, 7%, and 8%, respectively. The prevalence of *P aeruginosa* remained constant, causing 17% of HAP during each of these time periods. The increasing prevalence of Enterobacter reflects selection pressure from heavy use of third-generation cephalosporins (particularly ceftazidime), which facilitates evolution of chromosomal inducible  $\beta$ -lactamases.<sup>35,36</sup> *S aureus* has also increased in frequency as a cause of nosocomial infections, bacteremias, and pneumonias.<sup>25,29,37</sup> An analysis of 112 medical ICUs from 97 National Nosocomial Infections Surveillance System hospitals from 1992 to 1997 cited *S aureus* as a cause of 20% of HAPs and 13% of bacteremias.<sup>29</sup> Liberal use of intravascular catheters and nasal carriage of *S aureus* are major risk factors for pneumonia caused by this pathogen.<sup>37-40</sup> Currently, > 30% of nosocomial isolates of *S aureus* in the United States are resistant to methicillin.<sup>1,22</sup>

Awareness of the relevant pathogens is critical to the successful design of empiric and pathogen-directed antibiotic therapies for HAP. Understanding the salient risk factors for HAP and for development of antimicrobial resistance may facilitate the development of strategies to decrease mortality and morbidity due to HAP. This will, in turn, decrease the overall cost and burden on the health-care system.

#### EARLY-ONSET AND LATE-ONSET PNEUMONIA: INFLUENCE OF DURATION OF HOSPITALIZATION ON ETIOLOGIC AGENT

Early-onset HAP (occurring in the first 4 days of hospitalization) is often caused by community-acquired pathogens such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, or methicillin-susceptible *S aureus* (MSSA). In this context, pathogens with strong intrinsic or acquired antimicrobial resistances are rarely causative. In contrast, HAP developing  $\geq 5$  days after hospitalization ("late onset") is often caused by aerobic Gram-negative bacilli (eg, *P aeruginosa*, Enterobacteriaceae, or Acinetobacter) or MRSA.<sup>27,30,32</sup> Late-onset pneumonia is due to *P aeruginosa*, Acinetobacter, or MRSA in 30 to 71% of cases.<sup>26,27,30,41,42</sup>

*P aeruginosa* and drug-resistant pathogens are uncommon in the absence of previous antibiotic therapy or other risk factors. In two studies of ventilator-associated pneumonia (VAP), *P aeruginosa* was never implicated in 35 cases of early-onset VAP but was the causative agent in 6 of 29 cases (28%)<sup>41</sup> and 6 of 21 (29%) cases of late-onset VAP.<sup>27</sup> One study<sup>41</sup> of 24 patients with early-onset VAP implicated *S pneumoniae*, *H influenzae*, or *S aureus* in 54% of VAP cases. Only 17% had Gram-negative infections. In a separate study,<sup>27</sup> *S pneumoniae* and *H influenzae* were implicated in 25% of early-onset VAP cases but were never found in late-onset VAP. French investigators<sup>30</sup> evaluated 135 consecutive episodes of VAP and found that VAP occurring > 6 days after MV was caused by *P aeruginosa*, *A baumannii*, *Stenotrophomonas maltophilia*, or MRSA in 93 of 101 episodes (92%). In striking contrast, only 6 of 34 cases (18%) of VAP occurring within the first 6 days were caused by these four pathogens. All patients with these resistant organisms had received prior antibiotics. In a separate study, *P aeruginosa*, Acinetobacter, or *Xanthomonas maltophilia* were implicated in 20 of 87 cases (23%) of VAP occurring > 5 days after MV.<sup>42</sup> Mortality with these "high-risk" pathogens was 65%. In contrast, the mortality rate for other pathogens was 31%. Other studies<sup>6,8,9,28</sup> have confirmed higher mortality rates when these pathogens are implicated.

#### Influence of Prior Antibiotics on the Causative Pathogen

Prior antibiotic use, particularly the use of broad-spectrum antibiotics, is a critical risk factor for colonization or infection with *P aeruginosa*, Acinetobacter, MRSA, and other antibiotic-resistant bacteria. A sentinel study<sup>9</sup> of VAP in a French ICU noted that prior antimicrobial therapy markedly increased the rate of VAP caused by *P aeruginosa* or Acinetobacter. These two pathogens accounted for 65% of VAP cases among patients who had previously received antibiotics, compared with only 19% of VAP cases among antibiotic-naive patients.<sup>9</sup> In a subsequent study<sup>8</sup> of 48 patients with VAP, these investigators confirmed a higher mortality rate when VAP was caused by *P aeruginosa* or Acinetobacter (71% mortality), as compared with other pathogens (41% mortality). Spanish investigators<sup>28</sup> substantiated the impact of prior antibiotic use on pathogens responsible for VAP; in their study of 129 consecutive ICU patients with VAP, *P aeruginosa* was the causative agent in 40% of patients who had previously received antibiotics (within the preceding 10 days) but in only 5% of those who had not received antibiotics. Community-acquired pathogens (eg, Gram-positive cocci

or *H influenzae*) were responsible for only 19% of VAP cases among patients who had received prior antibiotics but for 77% of VAP in antibiotic-naïve patients. Consistent with earlier reports,<sup>8,9</sup> mortality was substantially higher when *P aeruginosa* was the causative agent.<sup>28</sup> Attributable mortality was only 4% among the antibiotic-naïve cohort vs 28% among patients who had previously received antibiotics.<sup>28</sup> No patient with VAP due to Gram-positive cocci or *H influenzae* died. This heightened mortality associated with prior antibiotic use reflects selection for more virulent, inherently antibiotic-resistant organisms. Additional risk factors associated with mortality in that study were advanced age, use of corticosteroids, presence of shock, late-onset VAP, and concomitant COPD. Others<sup>42</sup> have confirmed that late-onset VAP is often due to potentially antibiotic-resistant pathogens, which independently influence mortality.

Prior antibiotic use is the most common risk factor for colonization and infection with MRSA. In a retrospective study<sup>43</sup> from Japan, 31 of 32 patients (97%) with HAP due to MRSA had received prior antibiotics. Rello and colleagues<sup>44</sup> reviewed 49 patients with VAP due to *S aureus*. All 11 with MRSA had received prior antibiotics during that hospitalization. In contrast, only 8 of 38 patients (21%) with MSSA had received prior antibiotics. Other risk factors for pneumonia due to MRSA include use of corticosteroids, prolonged (> 6 days) MV, and COPD (Table 1). Cranioencephalic trauma was more common (58%) among patients with HAP due to MSSA than among those with MRSA (18%). A recent study<sup>37</sup> of 86 cases of bacteremic pneumonia due to *S aureus* cited higher rates of prior antibiotic use (38%) among 32 patients with MRSA than among 54 cases of MSSA (7%). Mortality rates are higher in patients with pneumonia caused by MRSA than in those with pneumonia caused by methicillin-susceptible strains.<sup>37,44,45</sup> This heightened mortality likely reflects more serious comorbidities rather than differences in the virulence of the organisms.<sup>46</sup> French investigators<sup>30</sup> evaluated 135 consecutive episodes of VAP in an ICU to identify risk factors for *P aeruginosa*, *Acinetobacter*, MRSA, and *S malto-*

*philia*. Independent risk factors for these pathogens included prior antibiotic use (odds ratio [OR], 13.5), MV lasting > 6 days (OR, 6.0), and prior use of broad-spectrum antibiotics (OR, 4.1). Of 39 patients with VAP caused by *P aeruginosa*, 37 patients (90%) had previously received antibiotics and 35 (90%) had received MV for > 6 days.

#### MV AS A RISK FACTOR FOR HAP

The critical risk factors for developing HAP are summarized in Table 2. Prolonged (> 48 h) MV is the most important factor associated with HAP, with pneumonia developing in 9 to 40% of patients who require > 48 h of MV.<sup>4,7-9,26,27,47-49</sup> However, HAP may occur within 48 h of intubation.<sup>50</sup> Risk factors for VAP within the first 48 h following intubation as determined by univariate analysis include large-volume aspiration, sedation, decreased level of consciousness, Glasgow coma scale rating < 9, emergency procedure, cardiopulmonary resuscitation, and respiratory/cardiac arrest as cause of intubation.<sup>50</sup> By multivariate analysis, cardiopulmonary resuscitation (OR, 5.1) and continuous sedation (OR, 4.4) remained as risk factors for HAP, while prior antibiotic use was protective (OR, 0.29).

In a prospective study,<sup>27</sup> HAP developed in 27 of 223 patients (12.1%) receiving MV but in only 1 of 135 patients (0.7%) not receiving MV. In this study,<sup>27</sup> independent risk factors for VAP were low serum albumin level on hospital admission ( $\leq 2.2$  g/dL), high maximum positive end-expiratory pressure ( $\geq 7.5$  cm H<sub>2</sub>O), absence of antibiotic therapy, upper-respiratory-tract colonization by Gram-negative bacilli, smoking, and duration of MV. In a multicenter prospective study<sup>49</sup> of 16 ICUs in Canada, VAP developed in 177 of 1,014 patients (17.5%) requiring MV for > 48 h. The daily risk for VAP was highest (3.3%) among patients who were in the ICU for 5 days and decreased to 1.3% for patients who were in the ICU for 15 days.<sup>49</sup> Decreasing the risk of pneumonia from MV may be difficult, since the greatest risk lies in the intubation itself. Increasing use of noninvasive ventilatory methods<sup>51,52</sup> in lieu of conventional MV may ultimately lead to fewer cases of VAP, but this has yet to be confirmed.

Table 1—Attributes Associated With *S aureus* Pneumonia\*

Attributes	MSSA (n = 38)	MRSA (n = 11)
Prior antibiotic use	21	100
Attributable mortality	3	55
Bacteremia	11	36
Septic shock	8	27

\*Data, expressed as %, from Rello et al.<sup>44</sup>

Table 2—Risk Factors for the Development of HAP

MV > 48 h
Prior antibiotic use and resistance in the ICU
Duration of ICU or hospital stay
Severity of underlying illness, APACHE
ARDS, other health problems

## ROLE OF OROPHARYNGEAL, TRACHEAL, AND GASTRIC COLONIZATION

Several studies<sup>27,53-56</sup> indicate that the dominant mechanism responsible for HAP is colonization of the upper respiratory tract (*ie*, oropharynx and trachea) with pathogenic bacteria, followed by subclinical microaspiration, while colonization of the GI tract plays a minor role. Oropharyngeal or tracheal colonization with *P aeruginosa* or enteric Gram-negative bacilli (EGNB) is common in ICU patients, increases with length of hospitalization and severity of illness, and is an important risk factor for HAP.<sup>53-55</sup> In a prospective study<sup>27</sup> of VAP, the causative organism was recovered from tracheal secretions in 29 of 31 patients (93.5%) before the onset of pneumonia. Other sites were colonized less frequently, including the oropharynx (42%), the nares (42%), and the stomach (36%). Gastric colonization preceded tracheal colonization in only four cases.

In one prospective study,<sup>56</sup> surveillance cultures of oropharynx, trachea, and stomach were performed in 141 ICU patients requiring MV for > 48 h. VAP due to EGNB or *P aeruginosa* developed in 26 patients (18%). Prior colonization with the same species was documented in the oropharynx in 85% and in the trachea in 96% of patients with VAP. Gastric colonization was not a risk factor for VAP. Talon and colleagues<sup>54</sup> prospectively assessed rates of colonization with *P aeruginosa* among 190 patients requiring MV in a surgical ICU. During the ICU stay, *P aeruginosa* grew from tracheal aspirates of 44 patients (23%), 13 of whom developed pneumonia. Consistent with other studies,<sup>27,56</sup> the lower respiratory tract (not the GI tract) was the first site of colonization, and the contribution of environmental sources was small. Risk factors for tracheal or bronchial colonization with *P aeruginosa* included length of hospitalization of > 10 days, prior use of third-generation cephalosporins, surgical emergencies, and alcoholism. Multivariate analysis revealed two risk factors for pseudomonal pneumonia: treatment with metronidazole (OR, 16) and COPD (OR, 37.9).

A recent prospective study<sup>26</sup> of 48 head-injured patients requiring MV found a strong relationship between upper-airway colonization and subsequent colonization of the tracheobronchial tree. During ICU stay, colonization with *P aeruginosa* or EGNB increased significantly at all sites (*ie*, upper airway, lower airway, stomach).<sup>26</sup> Previous use of antibiotics increased the risk of colonization with EGNB or *P aeruginosa* (OR, 6.1) but protected against colonization with *S pneumoniae*, *H influenzae*, or *S aureus* (OR, 0.20).<sup>26</sup> Factors associated with late-onset VAP included the following: tracheobronchial colonization with EGNB or *P aeruginosa* (OR, 5.4), duration

of MV (OR, 7.7), and prolonged antibiotic treatment (OR, 11.1).<sup>26</sup> By multivariate analysis, only the use of antibiotics for > 24 h within the preceding 15 days was a risk factor for late-onset pneumonia (OR, 9.2).

Although these various studies suggest that gastric colonization is not a dominant factor, it is undoubtedly involved in some cases of VAP. Direct microaspiration of gastric contents to lower airways, particularly in the supine position, may cause VAP in some patients.<sup>32,57</sup> Strategies that alkalize the GI tract may promote colonization and infection.<sup>57-59</sup> The use of antacids or histamine H<sub>2</sub>-receptor antagonists appears to increase the risk of HAP when compared with sucralfate,<sup>57-60</sup> but the clinical importance of this finding is disputed.<sup>59-62</sup>

## OTHER POTENTIAL CAUSES OF HAP

Although uncommon, inhalation of contaminated aerosols from environmental sources such as nebulizers or ventilator tubing has been implicated in epidemics of infections due to diverse pathogens.<sup>32,54,57</sup> Inadequate hand washing by medical personnel may facilitate the spread of resistant bacteria.<sup>32,53</sup> Nosocomial sinusitis may also cause VAP. In three studies<sup>63-65</sup> of patients requiring MV, the incidence of VAP ranged from 29 to 67% among patients with sinusitis, compared with 5 to 43% in patients without sinusitis. The same microorganism was isolated from lung and sinuses in 38 to 56% of patients.<sup>63-65</sup> Sinusitis may be less common in orotracheally vs nasotracheally intubated patients.<sup>65</sup> Aggressive search for and treatment of sinusitis may reduce the incidence of VAP. Hematogenous spread from extrapulmonary sites of infection (*eg*, wounds, soft tissue, or the urinary tract) is a well-documented but less common cause of HAP.<sup>59</sup>

## ARDS

VAP complicates ARDS in 34 to 60% of patients, typically > 7 days after initiation of MV.<sup>7,66,67</sup> Clinical and radiographic criteria cannot distinguish VAP from progression of the fibroproliferative phase of ARDS.<sup>67</sup> Chastre and colleagues<sup>7</sup> evaluated 243 consecutive patients who required MV for > 48 h. VAP developed in 31 of 56 patients (55%) with ARDS but in only 53 of 187 (28%) patients without ARDS. The actuarial risk of VAP in patients with ARDS was 14% at 10 days and 58% by day 20. Another study<sup>66</sup> prospectively examined 30 patients with severe ARDS; 24 episodes of VAP developed in 18 patients (60%) at a mean of 9.8 days after the onset of ARDS. Ante-

cedent colonization of the lower respiratory tract was detected in 18 episodes in 14 patients, 16 of which developed into VAP within 2 to 6 days. Thus, colonization preceded VAP in 16 of 24 cases (67%). Recurrent infections were caused by the same infecting organism.

Pathogens that cause VAP-complicating ARDS are often highly resistant, reflecting selection pressure from prior antibiotic use.<sup>7</sup> *P aeruginosa* is implicated in 20 to 43% of cases, MRSA in 15 to 28%, and *Acinetobacter* in 6 to 25%.<sup>7,66,67</sup> Mortality rates of VAP in patients with ARDS are high (> 50%).<sup>7,66,67</sup>

#### ROLE OF PROPHYLACTIC ANTIBIOTICS

The use of prophylactic antibiotics to prevent HAP is controversial. Some studies<sup>27,50</sup> have documented a protective effect of antibiotics (*ie*, reduced risk of HAP) among high-risk ICU patients. In one randomized controlled trial,<sup>68</sup> two 1.5-g doses of cefuroxime given 12 h apart reduced the incidence of VAP and shortened ICU stay in a cohort of 100 ICU patients with closed head injuries or stroke who required MV for > 3 days. VAP developed in 12 of 50 patients (24%) receiving cefuroxime compared with 25 of 50 patients (50%) in the control group not receiving prophylactic antibiotics. Brief prophylaxis with a single antibiotic may have a role for focused indications (*eg*, head-injured patients in ICUs), but liberal and prolonged use of prophylactic antibiotics may contribute to acquisition of *P aeruginosa*, *Acinetobacter*, and other potentially resistant pathogens.<sup>26,28,30,54,69</sup> Aggressive multiagent prophylactic regimens aimed at reducing the incidence of HAP and regimens employing nonabsorbable antibiotics, an oral adhesive antimicrobial paste, and parenteral agents to reduce GI tract colonization and infection with EGNB failed to influence mortality or length of hospital stay.<sup>69</sup> Such regimens are expensive and logistically difficult and may actually increase antimicrobial resistance. Additional studies are required to determine whether prophylactic antibiotic therapy can reduce morbidity, mortality, or costs in selected groups of patients. Additional nonantibiotic preventive strategies to prevent HAP are promising and are reviewed elsewhere.<sup>32,59</sup>

#### EMPIRIC TREATMENT OF HAP

Initial inadequate antimicrobial therapy for HAP is an independent risk factor for increased mortality.<sup>11,12</sup> Prompt use of appropriate antibiotics for HAP is critical to optimization of outcome. Because of the high mortality associated with HAP, initial

therapy (while awaiting results of cultures) must be empiric and cover a broad spectrum of possible pathogens. Demographics, host factors (*eg*, severity and acuity of illness, comorbidities), duration of hospitalization, prior antibiotic use, and antimicrobial resistance patterns within the hospital or ICU need to be taken into account when selecting antibiotics for empiric treatment. Rates of resistance are influenced by type and size of hospital, ICU or non-ICU setting, anatomic site of isolation, and patterns of prior antibiotic use within individual patients or institutions.<sup>17,70</sup> Empiric treatment for HAP occurring within the first 4 days of hospitalization in patients without severe comorbidities or exposure to antibiotics need not encompass *P aeruginosa* or potentially resistant pathogens. However, broader-spectrum coverage (to include these pathogens) is advised for HAP in critically ill ICU patients requiring prolonged MV or those who have received prior antibiotics. In this context, we combine an antipseudomonal  $\beta$ -lactam plus an aminoglycoside (if no contraindications to aminoglycoside use exist). Alternatively, a fluoroquinolone can be substituted for the aminoglycoside.

#### TREATMENT OF PSEUDOMONAL HAP

Because of the high mortality rates among patients with pseudomonal HAP, most investigators use two antibiotics with *in vitro* activity against *P aeruginosa*.<sup>6</sup> *P aeruginosa* is intrinsically resistant to most antibiotics. The most active agents (> 80% activity) are the carbapenems, piperacillin, cefepime, ceftazidime, ciprofloxacin, and aminoglycosides.<sup>17,71,72</sup> The optimal agent(s) for pseudomonal HAP is not clear, as randomized therapeutic trials have not been done (to my knowledge). Data have been extrapolated from subsets of patients with pseudomonal pneumonia enrolled in HAP studies<sup>5,73,74</sup> or from retrospective reviews.<sup>75</sup> Efficacy of antibiotic therapy is clouded by small sample sizes and heterogeneous patient populations. Several studies<sup>5,75,76</sup> have shown that monotherapy for pseudomonal HAP is associated with a high rate of clinical failures, relapses, mortality, and development of resistance in 30 to 50% of patients. A multicenter trial<sup>5</sup> randomized 405 patients with severe pneumonia (78% were nosocomial; 79% required MV) to monotherapy with either imipenem/cilastatin, 1 g q8h, or ciprofloxacin, 500 mg q8h. Clinical responses occurred in 59% with imipenem/cilastatin and in 69% with ciprofloxacin. However, when *P aeruginosa* was isolated, only 41% responded to imipenem/cilastatin and 33% responded to ciprofloxacin. Resistance developed in 53% of patients treated with imipenem/cilastatin and in 33% of patients treated with ciprofloxacin.

Other studies<sup>74,77,78</sup> using cephalosporin-based regimens have noted high failure rates when *Pseudomonas* was responsible for HAP. One study<sup>77</sup> randomized ICU patients with pneumonia to treatment with ceftazidime or cefpirome (with or without a second agent). Of 49 patients with pseudomonal HAP, 18 patients (37%) died. Other randomized trials of HAP using ceftazidime plus an aminoglycoside cited clinical responses in only 33% of patients<sup>74</sup> to 50% of patients<sup>78</sup> when *P aeruginosa* was the causative agent.

Theoretically, combining antimicrobial agents that act at different sites in a bacterial cell may limit resistance. However, the advantage of adding a second agent has not been proven in clinical trials. A retrospective review<sup>75</sup> of 38 consecutive ICU patients with VAP due to *P aeruginosa* found no survival benefit with combination antibiotic therapy. Overall mortality was 69% (attributable mortality was at least 38%). Nine of the 10 patients whose deaths were attributed to *P aeruginosa* had received combination therapy with a  $\beta$ -lactam and an aminoglycoside. Mortality was lower in patients receiving ciprofloxacin as part of the regimen. The impact of antibiotic choice could not be ascertained, since other factors (*ie*, multiorgan failure, septic shock, and APACHE [acute physiology and chronic health evaluation] III scores) were independently associated with mortality.<sup>75</sup> Rello and colleagues<sup>6</sup> prospectively studied 30 patients with pseudomonal VAP. All four patients receiving inappropriate therapy died. The remaining 26 patients received combination therapy with amikacin plus either piperacillin, ciprofloxacin, or imipenem/cilastatin. In this group, overall mortality was 42%, although attributable mortality was only 14%. Again, the influence of antibiotic regimen on mortality in this study<sup>6</sup> was not clear, since independent risk factors for mortality included severe sepsis, severe comorbidities, multiple organ failure, residence in ICUs, and increasing APACHE II scores. Recurrent infection in patients with *P aeruginosa* HAP is common and usually reflects relapse due to persistent infection rather than a new infection.<sup>79</sup> Persistent or relapsing disease may occur despite use of a combination of agents to which *P aeruginosa* is susceptible in *in vitro* testing.<sup>6,75,79</sup>

#### COMBINATION OF AMINOGLYCOSIDE AND $\beta$ -LACTAM ANTIBIOTICS

Aminoglycosides are not adequate as monotherapy for treating HAP, but the combination of an aminoglycoside plus a  $\beta$ -lactam may extend the spectrum of activity, achieve synergy, and (theoretically) reduce the emergence of resistance. Despite extensive

clinical use, the adjunctive benefit of aminoglycosides in treating HAP is controversial. Aminoglycosides penetrate poorly into bronchopulmonary secretions and the lung, are inactivated under conditions of low pH, and have serious potential toxicities (particularly nephrotoxicity).<sup>80</sup> Optimization of aminoglycoside dosing and pharmacodynamics may be critical to successful treatment of severe HAP caused by Gram-negative bacteria. In one series<sup>81</sup> of 78 patients with HAP, clinical response to therapy was more rapid when target ratios of maximal concentration of aminoglycoside in serum to the minimal inhibitory concentration were achieved.

Data supporting incremental benefit of aminoglycosides for the treatment of HAP are sparse. One nonrandomized prospective study<sup>82</sup> of 200 patients with *P aeruginosa* bacteremias cited lower mortality rates with combination therapy than with monotherapy (Table 3). The most common antibiotic combinations used were piperacillin/tobramycin (25%) and ticarcillin/tobramycin (24%). Among the subset of patients with pseudomonal pneumonia, the incremental benefit of combination therapy was striking (Table 3). A controlled, multicenter, randomized European trial<sup>83</sup> of 129 patients with cancer, granulocytopenia, and Gram-negative bacteremia supported an adjunctive role for an aminoglycoside. In that study, patients were randomized to one of three treatment arms (Table 4). Clinical response rates were highest with ceftazidime plus long-course (9 days) amikacin treatment. The benefit of the aminoglycoside was more pronounced when *P aeruginosa* was implicated. Among patients with pseudomonal bacteremias, only 5 of 13 patients (38%) responded to ceftazidime/short-course amikacin treatment, whereas 8 of 9 patients (89%) responded to ceftazidime/long-course amikacin treatment.

In contrast, two retrospective studies<sup>84,85</sup> of bacteremias due to *P aeruginosa* cited similar mortality rates with monotherapy or combination therapy. However, few patients had pneumonia, so these data are not readily applicable to pseudomonal HAP.

**Table 3—Survival in Subsets of Patients With *P aeruginosa* Bacteremia: Combination Antibiotic Therapy Compared With Monotherapy\***

Patient Subset	Mortality Rates		p Value
	Combination Therapy	Monotherapy	
Pneumonia	7/20 (35)	7/8 (88)	0.033
Critically ill	18/37 (49)	11/12 (92)	0.016
Noncritically ill	20/106 (19)	9/31 (29)	NS
Malignancy	21/66 (32)	9/19 (47)	NS
All	38/143 (27)	20/43 (47)	0.023

\*Data, presented as No./total (%), from Hilf et al,<sup>82</sup> with permission from Excerpta Medica, Inc. NS = not significant.

**Table 4—Clinical Success Rates With Combination Therapy in Gram-Negative Bacteremia\***

Therapy	Success Rates	
	All GNB	<i>P aeruginosa</i>
Azlocillin plus amikacin (9 d)	16/40 (40)	6/12 (50)
Ceftazidime plus amikacin (3 d)	20/42 (48)	5/13 (38)
Ceftazidime plus amikacin (9 d)	38/47 (81)	8/9 (89)

\*Data, presented as No./total (%), adapted from EORTC International Antimicrobial Therapy Cooperative Group,<sup>63</sup> with permission. GNB = Gram-negative bacteria.

Monotherapy may be adequate therapy for HAP due to Enterobacteriaceae and susceptible organisms but is suboptimal for infections due to *P aeruginosa* or Acinetobacter.<sup>5,19,20</sup> In a randomized trial of 405 patients with severe pneumonia, monotherapy with ciprofloxacin (400 mg q8h) or imipenem (1 g q8h) was equivalent in overall clinical response rates (69% and 59%, respectively). Response rates against Enterobacteriaceae were higher (93% with ciprofloxacin; 65% with imipenem) than against *P aeruginosa* (only 33% and 41%, respectively).<sup>5</sup> Furthermore, *P aeruginosa* isolates acquired resistance during therapy in 33% of patients treated with ciprofloxacin and in 53% of patients receiving imipenem/cilastatin.

#### CARBAPENEMS

The carbapenems (eg, imipenem/cilastatin, meropenem) have broad-spectrum activity and resist degradation by  $\beta$ -lactamases capable of hydrolyzing penicillins or cephalosporins.<sup>16</sup> Despite excellent *in vitro* antimicrobial activity, response rates in pseudomonal HAP with imipenem/cilastatin monotherapy are suboptimal (40 to 80%); resistance, which may not be prevented by the addition of an aminoglycoside,<sup>86</sup> develops in up to 53% of patients treated with imipenem/cilastatin.<sup>5,73</sup> Liberal use of imipenem may result in highly resistant strains of *P aeruginosa*,<sup>72</sup> Acinetobacter,<sup>87</sup> and *Burkholderia cepacia*.<sup>88-90</sup> The risk for emergence of resistance among *P aeruginosa* is higher with imipenem/cilastatin than with other antibiotic classes.<sup>91</sup> In a recent study<sup>91</sup> of 271 patients with infections caused by *P aeruginosa*, resistance developed in 10.2% of patients receiving antibiotic therapy. Hazards ratios for the emergence of resistance to individual antibiotics were as follows: ceftazidime, 0.8; piperacillin, 5.2; ciprofloxacin, 5.2; and imipenem, 44. Given the propensity for evolution of resistance, we reserve imipenem/cilastatin for treatment of infections in which resistance to other  $\beta$ -lactam antibiotics is proven or suspected.

Data evaluating meropenem for HAP are limited. In one multicenter trial,<sup>92</sup> patients with HAP were randomized to treatment with meropenem (1 g q8h) alone or ceftazidime (2 g q8h) plus tobramycin. Clinical responses were cited in 56 of 63 patients (89%) receiving meropenem and in 42 of 58 patients (72%) receiving ceftazidime/tobramycin. *P aeruginosa* was eradicated in 12 of 15 pathogens (80%) isolated from patients receiving meropenem. Additional studies are required to assess the role of meropenem for pseudomonal HAP.

A clinical advantage associated with the use of carbapenems is the lack of an inoculum effect. The inoculum effect is a laboratory phenomenon in which an increase in the minimum inhibitory concentration of a given antibiotic results from an increase in the number of organisms inoculated.<sup>93</sup> Imipenem and meropenem have been shown to be unaffected by such an effect at high inocula.<sup>94,95</sup>

#### CEPHALOSPORINS

Numerous studies (as reviewed by Lynch<sup>86</sup>) have cited high cure rates (> 80%) with third-generation cephalosporins alone for community-acquired pneumonia or HAP. However, monotherapy with a cephalosporin may not be adequate for severe HAP due to *P aeruginosa*, Acinetobacter, or isolates displaying high-grade resistance to  $\beta$ -lactam antibiotics. When *P aeruginosa* is a cause of HAP, failure rates with cephalosporins (alone or combined with aminoglycosides) are high (often > 50%).<sup>74,77,78</sup> Further, liberal use of third-generation cephalosporins is associated with emergence of resistance to  $\beta$ -lactamases among Enterobacter<sup>35</sup> and extended-spectrum  $\beta$ -lactamases among Enterobacteriaceae.<sup>36,97</sup> These resistance trends may be curtailed by switching from cephalosporins to  $\beta$ -lactam/ $\beta$ -lactamase inhibitors.<sup>36,97</sup>

Perhaps of greater use is the fourth-generation cephalosporin cefepime. Effective against Gram-positive and Gram-negative aerobic bacteria, cefepime not only has a broader spectrum of antimicrobial activity than the third-generation cephalosporins, it also has a reduced affinity for most  $\beta$ -lactamases.<sup>98,99</sup> Cefepime is thus less susceptible to hydrolysis and degradation by  $\beta$ -lactamases compared with other cephalosporins.<sup>98,99</sup>

#### COMBINATION THERAPY WITH $\beta$ -LACTAM AND FLUOROQUINOLONES

Strategies combining a  $\beta$ -lactam antibiotic with a fluoroquinolone with antipseudomonal activity (eg, ciprofloxacin, levofloxacin) are of interest, but clinical data employing such combinations are limited.

Ciprofloxacin is the most active fluoroquinolone *in vitro* against *P aeruginosa* (based on minimal inhibitory concentrations)<sup>100,101</sup>; however, the activity of levofloxacin may be adequate based on concentration-time curve and pharmacodynamics.<sup>102</sup> While extensive clinical experience has been gained with ciprofloxacin for HAP,<sup>5,103,104</sup> data evaluating levofloxacin for HAP are limited. Ciprofloxacin monotherapy may be adequate for Enterobacteriaceae and other selected pathogens, but it is not adequate for infections due to *P aeruginosa*. In a study of 47 ICU patients with Gram-negative HAP, 63% responded to ciprofloxacin (concomitant antibiotics were administered in 42%).<sup>104</sup> However, when *P aeruginosa* was isolated, the organism persisted in 10 of 13 patients and resistance developed in all 10 during therapy. Overzealous use of fluoroquinolones may lead to higher rates of resistance to fluoroquinolones<sup>105</sup> as well as cross-resistance to other antibiotic classes. The high rates of clinical failures and evolution of resistance observed with *P aeruginosa*<sup>5,104</sup> are not unique to ciprofloxacin but suggest that monotherapy, regardless of agent, is not adequate to treat this pathogen.

#### PIPERACILLIN/TAZOBACTAM

Piperacillin/tazobactam, a ureidopenicillin with excellent activity against *P aeruginosa*,<sup>30,71</sup> may be used for serious nosocomial infections (including HAP). For empiric therapy of HAP, this agent should be combined with an aminoglycoside or fluoroquinolone until *P aeruginosa* has been excluded as the causative agent. Three randomized trials<sup>73,74,78</sup> evaluated piperacillin/tazobactam (with or without an aminoglycoside) as therapy for HAP. One study<sup>74</sup> from 27 ICUs in France randomized 127 patients with VAP to treatment with amikacin plus either piperacillin/tazobactam, 4.5 g qid, or ceftazidime, 1 g qid. Clinical cure rates were 51% in the piperacillin/tazobactam cohort, compared with 36% of patients treated with ceftazidime/amikacin (not significant). Bacteriologic failures were more common in ceftazidime-treated patients (51%) compared with those treated with piperacillin/tazobactam (33%). However, 28-day mortality rates were similar (16% and 20%, respectively). When *P aeruginosa* was isolated, success rates were 40% or 39% with piperacillin/tazobactam or ceftazidime, respectively. Lower-respiratory-tract superinfections were more common with ceftazidime (21%) than with the piperacillin/tazobactam plus amikacin combination (9%).

A multicenter trial<sup>78</sup> in the United States randomized 300 patients with HAP to combination therapy

with tobramycin plus either piperacillin/tazobactam, 3.375 g q4h, or ceftazidime, 2 g q8h. The aminoglycoside therapy could be discontinued at the discretion of the investigator once a pathogen was known. Among evaluable patients, final clinical responses, overall microbiological response rates, and *P aeruginosa* eradication were higher with piperacillin/tazobactam than with ceftazidime (Table 5). Mortality was 7.7% in piperacillin/tazobactam-treated patients compared with 17% with ceftazidime ( $p = 0.03$ ).

Another trial<sup>73</sup> in Switzerland randomized patients with HAP to monotherapy with piperacillin/tazobactam, 4.5 g qid, or imipenem/cilastatin, 0.5 g qid. Among 154 evaluable patients, clinical success rates were similar with piperacillin/tazobactam and imipenem/cilastatin (Table 6). However, among 45 patients with pseudomonal HAP, a higher percentage of patients responded to treatment with piperacillin/tazobactam compared with imipenem/cilastatin (Table 6). Antimicrobial resistance developed in six patients treated with imipenem/cilastatin but in only one patient treated with piperacillin/tazobactam. Combined, the results from the studies cited above suggest that piperacillin/tazobactam is at least as effective (and possibly more effective) than ceftazidime or imipenem/cilastatin for HAP, particularly when *P aeruginosa* is isolated.

#### CONCLUSION

HAP is a serious problem in the ICU, leading to lengthened hospital stays, higher health-care costs, and increased rates of morbidity and mortality. The problem is perpetuated by the expanding number of opportunistic antibiotic-resistant pathogens that commonly cause HAP. Prolonged MV is a critical risk factor for HAP. In addition, prior use of antibiotics and inadequate antimicrobial therapy increases the risk of acquiring antimicrobial-resistant pathogens. *P aeruginosa* is one of the most difficult to treat of those pathogens responsible for HAP; it may

**Table 5—Piperacillin/Tazobactam Plus Tobramycin Compared With Ceftazidime Plus Tobramycin in Lower-Respiratory-Tract Infections\***

Response	Clinical Success With Tobramycin and		p Value
	Piperacillin/Tazobactam	Ceftazidime	
Clinical response (final)	74	50	0.006
Microbiological response	65	38	0.003
<i>P aeruginosa</i> eradication	67	30	0.199

\*Data, presented as %, from Joshi et al.<sup>78</sup>

**Table 6—Clinical Success of Piperacillin/Tazobactam Compared With Imipenem/Cilastatin in Nosocomial Pneumonia\***

Clinical Outcome	Piperacillin/ Tazobactam	Imipenem/ Cilastatin	p Value†
Success against all pathogens	62/75 (83)	56/79 (71)	NS
Success against <i>P aeruginosa</i>	19/21 (90)	12/24 (50)	0.004
Deaths (infection)	7/75 (9)	6/79 (8)	NS

\*Data, presented as No. of patients/total (%), adapted from Jaccard et al.<sup>73</sup> with permission. See Table 3 for abbreviation.

†Two-tailed Fisher's Exact Test.

contain both intrinsic and acquired forms of antibiotic resistance. Empiric treatment of late-onset HAP should include antipseudomonal agents until *P aeruginosa* is excluded as the causative agent.

## APPENDIX

*Dr. George Eliopoulos:* How good is piperacillin/tazobactam as an antistaphylococcal agent? I think this is an important question because as the prevalence of MRSA has increased and vancomycin use has increased, so has the emergence of vancomycin-resistant enterococci.

*Dr. David Bowton:* Piperacillin/tazobactam definitely has activity against MRSA. Aminopenicillins have higher affinity for altered penicillin-binding proteins, and if you can protect the agent itself from  $\beta$ -lactamases you have a higher probability of getting binding.

*Dr. Michael Miller:* Part of the reason may be because of prevention of induction of the protein, but there also may be binding sites to which the acyl-ampicillins bind and do so a little better than some of the other drugs.

*Dr. David Wu:* To respond to the concerns about *S aureus*, if you exclude the MRSA, the activity of piperacillin/tazobactam is very good for MSSA. In the recent publication by Joshi et al,<sup>78</sup> 11 of 16 patients (69%) with *S aureus* pneumonia achieved clinical resolution with piperacillin/tazobactam vs only 5 of 15 patients (33%) with ceftazidime. For pneumococci, clinical resolution occurred in 85% of patients receiving piperacillin/tazobactam vs 88% receiving ceftazidime. Finally, for *Haemophilus*, 22 of 22 patients achieved clinical resolution receiving piperacillin/tazobactam, vs 5 of 10 patients receiving ceftazidime. Thus, piperacillin/tazobactam was very active against all three organisms examined.

*Dr. Gary Noskin:* If you look at antibiotic-resistant *Pseudomonas*, the percentage increase is the highest of all the different organisms. About one fourth of them are resistant to quinolones. This trend can only worsen as combination therapy employing  $\beta$ -lactams and quinolones for empiric therapy in nosocomial pneumonia increases.

*Dr. Joseph Lynch:* I recommend combination therapy with an aminoglycoside, but I am struck, when I see patients in different hospitals, by how many are receiving combinations of something like piperacillin/tazobactam and a fluoroquinolone.

*Dr. Noskin:* This is probably because physicians are worried about the nephrotoxicity, and it is easier to use fluoroquinolone to remove that worry. However, people should be educated about the synergistic effect between aminoglycosides and  $\beta$ -lactams and about how the combination can potentially lower the development of resistance.

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