

ORIGINAL ARTICLE

Microbiology of Ventilator-Associated Pneumonia Compared With That of Hospital-Acquired Pneumonia

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OBJECTIVE. Nosocomial pneumonia is the leading cause of mortality attributed to nosocomial infection. Appropriate empirical therapy has been associated with improved survival, but data are limited regarding the etiologic agents of hospital-acquired pneumonia in non-ventilated patients (HAP). This evaluation assessed whether the currently recommended empirical therapy is appropriate for both ventilator-associated pneumonia (VAP) and HAP by evaluating the infecting flora.

DESIGN. Prospectively collected hospitalwide surveillance data was obtained by infection control professionals using standard Centers for Disease Control and Prevention definitions.

SETTING. A tertiary care academic hospital.

PATIENTS. All patients admitted from 2000 through 2003.

RESULTS. A total of 588 episodes of pneumonia were reported in 556 patients: 327 episodes of VAP in 309 patients, and 261 episodes of HAP in 247 patients. The infecting flora in ventilated patients included gram-positive cocci (32.0% [oxacillin-susceptible *Staphylococcus aureus* {OSSA}, 9.25%; oxacillin-resistant *Staphylococcus aureus* {ORSA}, 17.75%]), gram-negative bacilli (59.0% (*Pseudomonas aeruginosa*, 17.50%; *Stenotrophomonas maltophilia*, 6.75%; *Acinetobacter* species, 7.75%)), and miscellaneous pathogens (9.0%). The infecting flora in nonventilated patients included gram-positive cocci (42.59% [OSSA, 13.33%; ORSA, 20.37%]), gram-negative bacilli (39.63% [*P. aeruginosa*, 9.26%; *S. maltophilia*, 1.11%; *Acinetobacter* species, 3.33%]), and miscellaneous pathogens (17.78%).

CONCLUSIONS. Our data demonstrated that patients with HAP, compared with those with VAP, had a similar frequency of infection with ORSA but less commonly had infections due to *P. aeruginosa*, *Acinetobacter* species, and *S. maltophilia*. However, the overall frequency of infection with these pathogens was sufficiently high to warrant the use of empirical therapy likely to be active against them. Our data supports using the currently recommended empirical therapy for both HAP and VAP.

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It has been estimated that each year nearly 2 million patients in the United States acquire infections in the hospital, resulting in about 90,000 deaths.¹ Nosocomial pneumonia has been reported to be the second most common healthcare-associated infection in US intensive care units (ICUs),² but in a prevalence study of European ICUs pneumonia was the most prevalent nosocomial infection.³ Early administration of appropriate empirical therapy for nosocomial pneumonia has been demonstrated to significantly improve survival.⁴⁻⁷ For this reason, the most recent guideline by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) on the treatment of nosocomial pneumonia recommends empirical therapy.⁸ The choice of antimicrobial agents is made on the basis of the most likely

infecting flora and is modified according to time since admission (ie, 0-4 days or 5 days or more), prior receipt of antibiotics, and the presence of certain risk factors (eg, residence in an extended care facility or receipt of dialysis within the past 90 days for a patient receiving long-term dialysis). The current guideline distinguishes ventilator-associated pneumonia (VAP) from hospital-acquired pneumonia in nonventilated patients (HAP) and recommends similar therapy for both diagnoses. While the infecting flora associated with VAP has been well described,⁹ only limited data are available regarding the infecting flora associated with HAP.^{10,11} To validate the use of the same empirical therapy for VAP and HAP, as modified by the presence of specified risk factors, we analyzed our prospectively obtained data regarding the infecting flora

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associated with healthcare-associated pneumonia at a university hospital, stratified by receipt of mechanical ventilation (ie, VAP vs HAP).

METHODS

This study was conducted at the University of North Carolina (UNC) Hospitals. During the period analyzed, 2000 through 2003, infection control surveillance was conducted by 5 infection control professionals supervised by 2 full-time faculty. Comprehensive hospitalwide surveillance (ie, of all patients and hospital locations) was performed using criteria developed by the Centers for Disease Control and Prevention (CDC),¹² with the exception that the diagnosis of pneumonia required demonstration of an infiltrate on a chest radiograph. This modified definition is similar to the most recent definition used by hospitals participating in the National Nosocomial Infections Surveillance (NNIS) System.¹³ Hospital-acquired pneumonia (HAP) was defined as pneumonia that developed 48 hours or more after admission that was not incubating at the time of admission. Ventilator-associated pneumonia (VAP) was defined as pneumonia that developed more than 48 hours after endotracheal intubation. Our definitions for HAP and VAP were consistent with those used for these diagnoses by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA).⁸ Our database did not include patients with a diagnosis of community-acquired pneumonia (CAP) or healthcare-associated pneumonia (HCAP). Cases were entered into a computerized database after having been reviewed by a nurse supervisor and a physician who specialized in infectious diseases and critical care medicine. Specimens were considered adequate for processing by the UNC Microbiology Laboratory if they were of 1 of the following 3 types: (1) bronchoscopically obtained specimens (cultures of bronchoalveolar lavage fluid samples were performed quantitatively, and isolates reported if results showed 10^4 or more colony forming units (cfu) per mL; cultures of bronchial brush samples were performed semi-quantitatively); (2) expectorated sputum in which the number of polymorphonuclear cells exceeded the number of epithelial cells and organisms (other than just yeast) seen during oil immersion examination; and (3) tracheal aspirates in which there were 25 epithelial cells or fewer per low-power field and organisms (other than yeast) seen during oil immersion examination. Pathogens isolated from the respiratory tract were identified using standard techniques.

Data available from this prospectively maintained database included the patient's name, age, sex, unit number, and admission date; the date of onset of infection; the site of infection; indwelling devices present (ie, endotracheal tube and/or central venous catheters), and the infecting pathogen(s). The antimicrobial susceptibilities of the infecting flora were recorded on patient case forms but not entered into the computerized database, with the exception of oxacillin resistance

in *Staphylococcus aureus* and vancomycin resistance in *Enterococcus* species. *P* values were calculated using the 2-tailed Fisher exact test.

RESULTS

Epidemiology

During the period of this study, 2000 through 2003, our hospital had 158,519 patients admitted. Overall, 5,000 (3.15%) of these patients developed a total of 5,997 healthcare-associated infections (3.78 infections per 100 patients admitted). The number of nosocomial pneumonia cases by year was as follows: in 2000, there were 141 infections; in 2001, there were 145 infections; in 2002, there were 133 infections; and in 2003, there were 169 infections. A total of 588 lower respiratory tract infections were reported in 556 patients (Table 1). Thus, the overall incidence of nosocomial pneumonia was 0.37%.

Approximately 85% of the VAP cases occurred in patients from the surgical service. Although HAP occurred most commonly in patients from the surgical service (56%), patients from the medical service accounted for approximately one-third of all cases. More than 90% of the VAP cases occurred in patients housed in ICUs, whereas approximately 67% of the HAP cases occurred in patients not housed in ICUs.

For patients with VAP, the time from admission to the onset of infection was as follows: mean, 22.4 days; median, 12.0 days; and mode, 4 days. For patients with HAP, the time from admission to infection was as follows: mean, 25.0 days; median, 11.5 days; and mode, 4 days. Overall, 14.4% of the VAP cases and 20.9% of the HAP cases occurred within the first 4 days of hospitalization.

Microbiology

A pathogen was isolated from 92.4% of patients with VAP but from only 76.6% of patients with HAP. Overall, 400 path-

TABLE 1. Epidemiology of Ventilator-Associated Pneumonia (VAP) and Hospital-Acquired Pneumonia in Nonventilated Patients (HAP)

Variable	VAP	HAP
No. of patients	309	247
No. of infections	327	261
No. of infections per patient	1.06	1.06
Service		
Medical	35 (10.7)	83 (31.8)
Surgical	277 (84.7)	145 (55.6)
Pediatric	9 (2.8)	6 (2.3)
Other	6 (1.8)	27 (10.3)
Location		
ICU	296 (90.5)	85 (32.6)
Non-ICU ward	31 (9.5)	176 (67.4)

NOTE. Data are no. (%) of patients, unless otherwise indicated. ICU, intensive care unit.

ogens were isolated from 327 cases of VAP, and 270 pathogens were isolated from 261 cases of HAP (Table 2).

Among patients with VAP, gram-positive cocci were isolated from 32.0% of infections, gram-negative bacilli from 59.0%, and the remainder of isolates were miscellaneous pathogens. The most common gram-positive pathogen isolated was *Staphylococcus aureus*. Approximately two-thirds of *S. aureus* isolates were oxacillin resistant. Approximately two-thirds of the gram-negative isolates were non-Enterobacteriaceae bacilli, principally *Pseudomonas aeruginosa*, *Acinetobacter* species, *Stenotrophomonas maltophilia*, and *Haemophilus* species.

Among patients with HAP, gram-positive cocci were isolated from 42.59% of infections, gram-negative bacilli from 39.63%, and the remainder of isolates were miscellaneous pathogens. The most common gram-positive pathogen isolated was *S. aureus*. Sixty percent of *S. aureus* isolates were oxacillin resistant. Slightly less than half of the gram-negative pathogens isolated were non-Enterobacteriaceae bacilli, principally *P. aeruginosa*, *Acinetobacter* species, *Haemophilus* species, and *Moraxella catarrhalis*.

Compared with pneumonia in ventilated patients, pneumonia in nonventilated patients was more likely to be caused by gram-positive cocci ($P < .01$), especially *Streptococcus pneu-*

TABLE 2. Relative Frequency of Isolation of Selected Pathogens from Patients With Ventilator-Associated Pneumonia (VAP) and Nonventilated Patients With Hospital-Acquired Pneumonia (HAP)

Pathogen, by class	No. (%) of isolates		P
	Patients with VAP ^a	Patients with HAP ^b	
Gram-positive cocci	128 (32.00)	115 (42.59)	.0054
<i>Staphylococcus aureus</i>			
All	108 (27.00)	91 (33.70)	.070
Oxacillin-susceptible	37 (9.25)	36 (13.33)	.102
Oxacillin-resistant	71 (17.75)	55 (20.37)	.421
<i>Streptococcus pneumoniae</i>	8 (2.00)	15 (5.56)	.017
Coagulase-negative staphylococci	6 (1.50)	3 (1.11)	.745
<i>Enterococcus</i> species	4 (1.00)	4 (1.48)	.720
Other	2 (0.50)	2 (0.74)	1
Gram-negative bacilli	236 (59.00)	107 (39.63)	<.001
Enterobacteriaceae	59 (14.75)	44 (16.30)	.587
<i>Escherichia coli</i>	15 (3.75)	8 (2.96)	.669
<i>Klebsiella pneumoniae</i>	8 (2.00)	13 (4.81)	.045
<i>Klebsiella</i> species	0 (0.00)	2 (0.74)	.163
<i>Enterobacter</i> species	9 (2.25)	8 (2.96)	.621
<i>Citrobacter</i> species	3 (0.75)	2 (0.74)	1
<i>Serratia marcescens</i>	10 (2.50)	5 (1.85)	.791
<i>Proteus</i> species	2 (0.50)	1 (0.37)	1
Other	12 (3.00)	5 (1.85)	.456
Non-Enterobacteriaceae bacilli	160 (40.75)	53 (19.63)	<0.001
<i>Pseudomonas aeruginosa</i>	70 (17.50)	25 (9.26)	0.003
<i>Acinetobacter</i> species	31 (7.75)	9 (3.33)	0.020
<i>Stenotrophomonas maltophilia</i>	27 (6.75)	3 (1.11)	<0.001
<i>Hemophilus influenzae</i>	18 (4.50)	6 (2.22)	0.141
<i>Hemophilus</i> species	3 (0.75)	2 (0.74)	1
<i>Moraxella catarrhalis</i>	6 (1.50)	7 (2.59)	0.394
Other	8 (2.00)	1 (0.37)	0.092
Other gram-negative bacilli	14 (3.50)	10 (3.70)	1
Miscellaneous bacteria	5 (1.25)	3 (1.11)	1
Oropharyngeal flora	15 (3.75)	20 (7.41)	0.050
Viruses	0 (0.00)	5 (1.85)	0.010
Fungi	16 (4.00)	20 (7.41)	0.079
Total, all pathogens	400 (100)	270 (100)	

^a Excludes patients for whom sputum culture was not performed ($N = 15$) or whose sputum sample did not yield a pathogen on culture ($N = 10$).

^b Excludes patients for whom sputum culture was not performed ($N = 35$) or whose sputum sample did not yield a pathogen on culture ($N = 26$).

moniae ($P < .05$). Pneumonia in nonventilated patients was less likely to be caused by non-Enterobacteriaceae bacilli ($P < .001$), including *P. aeruginosa* ($P = .003$), *Acinetobacter* species ($P < .05$), and *S. maltophilia* ($P < .001$). The percentage of infections due to Enterobacteriaceae was similar in both groups ($P = .60$).

When patients with VAP and patients with HAP were stratified by the location where they received care (ICU vs non-ICU ward), there were no dramatic differences apparent with regard to etiologic agents (Table 3). Patients with VAP had a significantly lower rate of infection with *Escherichia coli* while residing in the ICU, whereas patients with HAP had a significantly lower rate of infection with oxacillin-resistant *S. aureus* while residing in the ICU.

Microbiology As a Function of Time of Infection

In patients with VAP, the pathogens statistically associated with early onset of infection (ie, 0-4 days after endotracheal intubation) included oxacillin-susceptible *S. aureus*, *S. pneumoniae*, and *Hemophilus* species (Table 4). Pathogens occurring more frequently after 5 or more days of hospitalization included *Acinetobacter* species and *S. maltophilia*. Enteric gram-negative pathogens were not statistically associated with either early or late onset of infection.

In patients with HAP, the pathogens statistically associated with early onset of infection (ie, 0-4 days after hospitalization)

included only *S. pneumoniae*, although oxacillin-susceptible *S. aureus* infections tended to occur early (Table 5). Pathogens occurring more frequently after 5 or more days of hospitalization included oxacillin-resistant *S. aureus* and *P. aeruginosa*. Enteric gram-negative pathogens were not statistically associated with either early or late onset of infection.

DISCUSSION

Nosocomial pneumonia is an important cause of morbidity and mortality for hospitalized patients. The epidemiology, diagnosis, treatment, prevention, and outcome of nosocomial pneumonia have been the subject of several recent reviews.^{9,14-17} In the United States, pneumonia accounts for approximately 15% of all healthcare-associated infections and 25% of nosocomial infections in ICUs. The primary risk factor for the development of nosocomial pneumonia is receipt of mechanical ventilation. The microbiology of VAP has been well described. Chastre and Fagon⁹ recently summarized the etiology of VAP as determined by bronchoscopic techniques in 24 studies. On this analysis, the etiologic agents of VAP included gram-positive cocci (34% of isolates [*S. aureus*, 20%]), Enterobacteriaceae (14%), *P. aeruginosa* (24%), *Acinetobacter* species (8%), *S. maltophilia* (2%), *Haemophilus* species (10%), and miscellaneous pathogens (8%). Only limited data are available regarding the epidemiology of HAP,

TABLE 3. Relative Frequency of Isolation of Selected Pathogens From Patients With Ventilator-Associated Pneumonia (VAP) and Nonventilated Patients With Hospital-Acquired Pneumonia (HAP), as a Function of Hospital Location of Care

Pathogen, by class	No. (%) of isolates			
	Patients with VAP ^a		Patients with HAP ^b	
	ICU	Non-ICU	ICU	Non-ICU
Gram-positive cocci				
<i>Staphylococcus aureus</i>				
Oxacillin-susceptible	35 (9.59)	2 (5.71)	13 (12.87)	23 (13.61)
Oxacillin-resistant	69 (18.90)	2 (5.71)	13 (12.87)	42 (24.85) ^c
<i>Streptococcus pneumoniae</i>	7 (1.92)	1 (2.86)	7 (6.93)	8 (4.73)
Gram-negative bacilli				
<i>Enterobacter</i> species				
<i>Escherichia coli</i>	9 (2.47)	0 (0.00)	2 (1.98)	6 (3.55)
<i>Escherichia coli</i>	10 (2.74)	5 (14.29) ^c	3 (2.97)	5 (2.96)
<i>Klebsiella pneumoniae</i>	6 (1.64)	2 (5.71)	5 (4.95)	8 (4.73)
<i>Serratia marcescens</i>	8 (2.19)	2 (5.71)	3 (2.97)	2 (1.18)
<i>Acinetobacter</i> species	29 (7.95)	2 (5.71)	4 (3.96)	5 (2.96)
<i>Stenotrophomonas maltophilia</i>	25 (6.85)	2 (5.71)	2 (1.98)	1 (0.59)
<i>Pseudomonas aeruginosa</i>	60 (16.44)	10 (28.57)	11 (10.89)	14 (8.28)
<i>Moraxella catarrhalis</i>	6 (1.64)	0 (0.00)	2 (1.98)	5 (2.96)
<i>Hemophilus</i> species	18 (4.93)	0 (0.00)	4 (3.96)	2 (1.18)
Total, all pathogens	365	35	101	169

NOTE. ICU, housed in the intensive care unit; non-ICU, housed in a ward other than the ICU.

^a Excludes patients for whom sputum culture was not performed ($N = 15$) or whose sputum sample did not yield a pathogen on culture ($N = 10$).

^b Excludes patients for whom sputum culture was not performed ($N = 35$) or whose sputum sample did not yield a pathogen on culture ($N = 26$).

^c $P \leq .05$, by 2-tailed Fisher exact test.

TABLE 4. Frequency of Isolation of Selected Pathogens from Patients With Ventilator-Associated Pneumonia (VAP), as a Function of Duration of Hospitalization

Pathogen, by class	No. (%) of isolates		P
	Patients with early-onset VAP	Patients with late-onset VAP	
Gram-positive cocci			
<i>Staphylococcus aureus</i>			
Oxacillin-susceptible	12 (18.75)	24 (7.19)	.006
Oxacillin-resistant	8 (12.50)	63 (18.86)	.149
<i>Streptococcus pneumoniae</i>	4 (6.25)	4 (1.20)	.026
Gram-negative bacilli			
<i>Enterobacter</i> species	1 (1.56)	8 (2.40)	.561
<i>Escherichia coli</i>	2 (3.13)	13 (3.89)	.556
<i>Klebsiella pneumoniae</i>	1 (1.56)	7 (2.10)	.623
<i>Serratia marcescens</i>	2 (3.13)	8 (2.40)	.497
<i>Acinetobacter</i> species	0 (0.00)	31 (9.28)	.003
<i>Stenotrophomonas maltophilia</i>	1 (1.56)	26 (7.78)	.049
<i>Pseudomonas aeruginosa</i>	8 (12.50)	61 (18.26)	.176
<i>Moraxella catarrhalis</i>	2 (3.13)	4 (1.20)	.176
<i>Hemophilus</i> species	12 (18.75)	10 (2.99)	<.001
Total, all pathogens	64	334	

NOTE. Time of onset of infection was not available for 2 infections, each involving 1 pathogen. P values determined by 2-tailed Fisher exact test. Early-onset VAP, onset 0-4 days after endotracheal intubation; late-onset VAP onset >4 days after endotracheal intubation.

including the causative pathogens.^{10,11} Because current treatment guidelines recommend the same empirical antibiotic therapy for VAP and HAP, we reviewed our prospectively obtained data on nosocomial pneumonia to determine whether the pathogens isolated from patients with VAP and those isolated from patients with HAP were similar.

Between 2000 and 2003, there were 588 lower respiratory tract infections reported in 556 patients cared for in our hospital. Our data revealed that the bacterial etiology of VAP and HAP differed quantitatively, but were qualitatively similar. Patients with VAP, compared with those with HAP, were more likely to be from the surgical service and to be cared for in an ICU. The etiologic agents of VAP at our hospital were similar to those reported by Chastre and Fagon⁹ in their review of the literature. While the overall frequency of infection with gram-positive cocci was virtually identical, our patients had a higher frequency of infections with *S. aureus*. The frequency of infection with enteric bacilli, approximately 15%, was similar. The frequency of infection with gram-negative pathogens that are more likely to exhibit resistance to multiple antibiotics (ie, *P. aeruginosa*, *Acinetobacter* species, and *S. maltophilia*)¹⁸ was also similar, although we had fewer patients infected with *P. aeruginosa* and more patients infected with *S. maltophilia*. Compared with patients with VAP, our patients with HAP had a higher frequency of infection with gram-positive cocci and a lower frequency of infection with nonenteric gram-negative bacilli. However, more than 13%

of patients with HAP had pneumonia due to *P. aeruginosa*, *Acinetobacter* species, or *S. maltophilia*. Recently, Kollef and colleagues¹¹ noted that *Pseudomonas* species or *Acinetobacter* species were associated with more than 20% of cases of HAP. From a clinical perspective, this frequency is clinically high enough to warrant the use of antibiotics with activity against these pathogens when choosing an empirical regiment for the treatment of nosocomial pneumonia. Hence, the recommendations of the current ATS/IDSA guideline⁸ are appropriate for the treatment of patients with either VAP or HAP. The guideline also recommends similar therapy for patients with risk factors for infection with more-resistant pathogens (eg, methicillin-resistant *Staphylococcus aureus* [MRSA] and *P. aeruginosa*), such as admission from an extended care facility, recent hospital admission, or recent antibiotic therapy (such cases of pneumonia are now termed healthcare-associated pneumonia). However, patients with healthcare-associated pneumonia are not ascertained using Centers for Disease Control and Prevention nosocomial pneumonia criteria and therefore were not included in our database.

The pathogens associated with HAP have been reported to differ depending on the time of onset of infection.¹⁹⁻²⁴ Early-onset pneumonia has been associated with higher frequencies of infection with *S. pneumoniae*, *H. influenzae*, and oxacillin-susceptible *S. aureus*. In contrast, late-onset pneumonia has been associated with higher frequencies of infection with oxacillin-resistant *S. aureus*, *P. aeruginosa*, *Acinetobacter* species,

TABLE 5. Frequency of Isolation of Selected Pathogens From Non-ventilated Patients With Hospital-Acquired Pneumonia (HAP), as a Function of Duration of Hospitalization

Pathogen	No. (%) of isolates		P
	Patients with early-onset HAP	Patients with late-onset HAP	
Gram-positive cocci			
<i>Staphylococcus aureus</i>			
Oxacillin-susceptible	13 (19.40)	22 (11.00)	.063
Oxacillin-resistant	8 (11.94)	47 (23.50)	.028
<i>Streptococcus pneumoniae</i>	8 (11.94)	7 (3.50)	.015
Gram-negative bacilli			
<i>Enterobacter</i> species	2 (2.99)	6 (3.00)	.639
<i>Escherichia coli</i>	1 (1.49)	7 (3.50)	.361
<i>Klebsiella</i> species	3 (4.48)	12 (6.00)	.454
<i>Serratia marcescens</i>	2 (2.99)	3 (1.50)	.369
<i>Acinetobacter</i> species	2 (2.99)	7 (3.50)	.598
<i>Stenotrophomonas maltophilia</i>	1 (1.49)	2 (1.00)	.581
<i>Pseudomonas aeruginosa</i>	2 (2.99)	23 (11.50)	.026
<i>Moraxella catarrhalis</i>	3 (4.48)	4 (2.00)	.244
<i>Hemophilus</i> species	4 (5.97)	4 (2.00)	.122
Total, all pathogens	67	200	

NOTE. Time of onset of infection was not available for 3 infections, each involving 1 pathogen. P values determined by Fisher exact test (2-tailed). Early-onset HAP, onset 0-4 days after hospitalization; late-onset HAP, onset >4 days of hospitalization.

and *S. maltophilia*. Comparisons among studies are limited by differing definitions of early-onset infection (ie, ranging from less than 4 days to less than 7 days) and of late-onset infection (ie, ranging from 4 days or more to 7 days or more), baseline time (ie, admission to hospital, admission to ICU, or initiation of mechanical ventilation), and initial exclusionary period for nosocomial pneumonia (ie, 48-72 hours). Our data, which were based on a 4-day cutoff between early- and late-onset pneumonia, as in the ATS/IDSA guideline,⁸ demonstrated that early-onset infections were more likely to be caused by *S. pneumoniae*, oxacillin-susceptible *S. aureus*, and *H. influenzae*, whereas late-onset infections were more likely to be caused by oxacillin-resistant *S. aureus*, *Acinetobacter* species, *S. maltophilia*, and *P. aeruginosa*. This pattern was found for both VAP and HAP. However, more than 26% of cases of early-onset VAP and more than 19% of early-onset cases of HAP were due to pathogens requiring treatment with broad-spectrum agents (ie, *P. aeruginosa*, *S. maltophilia*, or *Acinetobacter* species) or therapy active against oxacillin-resistant *S. aureus*. Thus, our data are similar to those of Ibrahim and colleagues,²² who reported that oxacillin-resistant *S. aureus* and *P. aeruginosa* can be important pathogens in early-onset pneumonia. Using a 7-day cutoff, Giantsou and colleagues²⁴ reported that similar proportions of early- and late-onset cases of VAP were caused by multiresistant pathogens, *P. aeruginosa*, and MRSA. The explanation for our findings, and those of others, is that factors other than time of onset (such as recent hospitalization and/or prior receipt of antibiotics) affect the frequency of infection with specific drug-resistant pathogens.^{18,25,26} For example, the duration of mechanical ventilation and prior antibiotic use has been shown to independently predict infection with resistant pathogens.¹⁸ Unfortunately, we could not further stratify our patients by factors such as receipt of prior antibiotic therapy because this information is not included in our database. Such stratification of patients eligible for narrow-spectrum antibiotic therapy (ie, those developing hospital-acquired pneumonia within 4 days of hospitalization who have received no prior antimicrobial therapy and have no risk factors for multidrug-resistant pathogens) is likely to result in only a small percentage of patients being eligible for such therapy.

The strengths of our study include the consistent and strict use of CDC criteria for ascertainment of nosocomial pneumonia, the prospective acquisition of the data, and the use of comprehensive hospitalwide surveillance. There are several limitations that affect our data. First, no data were available on the use of antibiotics prior to the onset of pneumonia. As previously noted, the prior use of antibiotics is a well-described and independent risk factor for pneumonia due to drug-resistant pathogens.¹⁸ Second, infecting flora was most often isolated from tracheal aspiration samples, for patients with VAP, and from expectorated sputum samples, for patients with HAP. Although sputum samples obtained by tracheal aspiration are known to be a less accurate reflection of the true infecting flora associated with VAP, the close match

between our etiologic data and those obtained in studies that have used bronchoscopic techniques argues that our data are appropriate for comparing the pathogens associated with VAP and HAP. Finally, our analysis was based on the time from admission to the onset of infection, similar to the method for calculating time intervals used in the ATS/IDSA guideline.⁸ We were unable to analyze our data for patients with VAP according to duration of mechanical ventilation.

In conclusion, our data demonstrated that patients with HAP, compared with those with VAP, less commonly had infections with nonenteric bacteria, including *P. aeruginosa*, *Acinetobacter* species, and *S. maltophilia*. However, the overall frequency of infection with these pathogens was sufficiently high to warrant the use of empirical therapy likely to be active against these pathogens in hospitalized, nonventilated patients with suspected pneumonia. In addition, similar to patients with VAP, patients with HAP can have the nature of their infecting flora influenced by duration of hospitalization.

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