


Original Article

Microbiology, empiric therapy and its impact on the outcomes of nonventilated hospital-acquired, ventilated hospital-acquired, and ventilator-associated bacterial pneumonia in the United States, 2014–2019

Marya D. Zilberberg MD, MPH¹ , Brian H. Nathanson PhD², Laura A. Puzniak PhD, MPH³ and Andrew F. Shorr MD, MPH, MBA⁴

¹EviMed Research Group, Goshen, Massachusetts, ²OptiStatim, Longmeadow, Massachusetts, ³Merck & Company, Kenilworth, New Jersey and ⁴Washington Hospital Center, Washington, DC

Abstract

Objective: To explore whether microbiology profiles and the impact of inappropriate empiric treatment differ in the setting of hospital-acquired bacterial pneumonia that requires subsequent mechanical ventilation (vHABP) versus one that does not (nvHABP) versus ventilator-associated bacterial pneumonia (VABP).

Design: Multicenter retrospective cohort study within Premier Research database, 2014–2019.

Methods: We identified cases based on a previously published *International Classification of Disease, Ninth Revision/Tenth Revision Clinical Modification* (ICD-9/ICD-10-CM) algorithm, and we compared the 3 groups with respect to the bacterial pathogens isolated from their blood, sputum, or lower airway samples, and their respective rates of exposure to inappropriate empiric treatment. Using regression modeling we computed the effect of inappropriate empiric treatment on outcomes.

Results: Among 17,819 patients who met enrollment criteria, 26.5% had nvHABP, 25.6% vHABP, and 47.9% VABP. *S. aureus* (majority methicillin-susceptible) was the most frequently isolated organism, followed *P. aeruginosa*, *K. pneumoniae*, and *E. coli* with variations across the conditions. Rates of carbapenem resistance were highest in VABP (9.1%) and to third-generation cephalosporins in vHABP (14.9%). Patients with nvHABP were most likely to receive inappropriate empiric treatment (8.5%). Although inappropriate empiric treatment was associated with an increase in adjusted postinfection-onset hospital length of stay (2.3 days) and cost (\$12,142), its greatest magnitude was in the nvHABP group (4.9 days, \$13,147).

Conclusions: Substantial microbiologic differences exist among populations who suffer nvHABP, vHABP, and VABP, and inappropriate empiric treatment significantly worsens utilization outcomes. Given the moderate rates of carbapenem resistance and third-generation cephalosporin resistance, all patients require empiric coverage for a range of bacteria, including those targeting extended-spectrum β -lactamase and carbapenem resistance where appropriate.

(Received 12 July 2021; accepted 21 September 2021)

Author for correspondence: Marya Zilberberg, MD, MPH, EviMed Research Group, PO Box 303, Goshen, MA 01032. E-mail: evimedgroup@gmail.com. Or Andrew Shorr, MD, MPH, MBA, 110 Irving St NW, Washington, DC 20010. E-mail: Andrew.Shorr@gmail.com

PREVIOUS PRESENTATION. Portions of these data were presented at the ECCMID 2021 annual conference on July 9–12, 2021, in Vienna, Austria. Descriptive epidemiology and outcomes without detailed microbiology and treatment are included in “Descriptive epidemiology and outcomes of nonventilated hospital-acquired, ventilated hospital-acquired, and ventilator-associated bacterial pneumonia in the US, 2012–2019,” by MD Zilberberg, BH Nathanson, LA Puzniak, and AF Shorr in *Critical Care Medicine* 2022;50:460–468.

Cite this article: Zilberberg MD, *et al.* (2022). Microbiology, empiric therapy and its impact on the outcomes of nonventilated hospital-acquired, ventilated hospital-acquired, and ventilator-associated bacterial pneumonia in the United States, 2014–2019. *Infection Control & Hospital Epidemiology*, 43: 277–283, <https://doi.org/10.1017/ice.2021.464>

Nosocomial pneumonia, a continuing challenge in hospitals, is associated with substantial morbidity, mortality, and cost.¹ The delivery of timely, appropriate antibiotic therapy represents the most critical and modifiable factor that drives these outcomes.^{2–9} The ever-shifting landscape of antimicrobial resistance, however, complicates decision making regarding empiric treatment in severe infections. In nosocomial pneumonia, which includes hospital-acquired (HAP) and ventilator-associated (VAP) pneumonias, clinicians face a wide variety of potential pathogens and unpredictable resistance patterns, pitting the clinical mandate not to undertreat a potentially fatal infection against the public health reality that unnecessarily broad antibiotic administration promotes more resistance.

One tool available to clinicians to help them balance these competing risks is evidence-based clinical practice guidelines that provide recommendations in the context of current microbiological trends. However, clinical practice guideline updates lag behind the evolution of these trends. Additionally, because they generally represent an international or a national consensus, clinical practice guidelines are unable to consider regional differences in the distributions of specific microorganisms. For all these reasons, it is vital for clinicians to have access to more contemporary epidemiology to facilitate risk stratification to optimize prescription of antimicrobial regimens.

Unfortunately, much of the timelier microbiology data in HAP/VAP relies on single-center or small multicenter evaluations. This necessarily puts into question the results' generalizability. Therefore, to balance the need to provide both a broader and more contemporary picture of the current microbiology of nosocomial pneumonia, we developed an algorithm to identify bacterial nosocomial pneumonia (ie, HAPB/VABP) in an administrative database enriched with microbiology results.¹⁰ We applied this algorithm to explore the microbiology of HAPB/VABP, the empiric treatment of these infections, as well as the impact of inappropriate empiric therapy on hospital outcomes. Because emerging literature suggests that ventilated HAPB (vHAPB) is distinct from nonventilated (nvHAPB), we further stratified our analyses by this factor.^{11,12}

Methods

Study design and patient population

We conducted a multicenter, retrospective, cohort study of hospitalized patients with culture-positive nvHAPB, vHAPB, or VABP to explore their microbiology, empiric treatment patterns, and impact of receiving inappropriate empiric treatment on hospital outcomes. The case identification approach relied on a slight modification of a previously published algorithm.¹⁰ The details of the study methods can be found in Zilberberg *et al*,¹⁴ an analysis conducted in the same cohort.¹⁴ Briefly, patients were included (1) if they were adults (aged >18 years) whose pneumonia diagnosis appeared in a secondary position, (2) if they had an index respiratory and/or blood culture obtained on hospital day 3 or later for HAPB, or (3) if they were on mechanical ventilation day 3 or later for VABP, and (4) if they were treated with an antibiotic on the day of the index culture and for the next >3 consecutive days. We excluded patients who fit the definition for either a complicated urinary tract infection or a complicated intra-abdominal infection to reduce misclassification.^{15,16} Because this study used existing fully deidentified data, it was exempt from ethics review under US 45 CFR 46.101(b)4.¹³

Data source

We obtained data from the Premier Research database, an electronic laboratory, pharmacy and billing data repository, for 2012 through the third quarter of 2019. The database has been described in detail previously.^{10,14-19} During the study period, ~200 US institutions submitted microbiology data. The details regarding this cohort are provided in the study by Zilberberg *et al*.¹⁴

Pneumonia classification

Pneumonia was defined as HAPB if, at the time of the index culture, the patient was not on mechanical ventilation and was defined as VABP if, at the time the index culture, the patient had been on mechanical ventilation for ≥ 3 days. HAPB was further subdivided into vHAPB and nvHAPB. Specifically, vHAPB designation was

given for patients who needed mechanical ventilation <5 days following the onset of index HAPB episode and nvHAPB if mechanical ventilation was not required.

Microbiology and empiric treatment

We examined both gram-positive and gram-negative pathogens that cause bacterial nosocomial pneumonia. Namely, the gram-negative organisms of interest included *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, *Haemophilus* spp, *Moraxella catarrhalis*, and Enterobacterales. The gram-positive pathogens of interest included *Staphylococcus aureus* (both methicillin-susceptible [MSSA] and MRSA), *Streptococcus pneumoniae*, and other *Streptococcus* spp.

Organisms were classified as S (susceptible), I (intermediate) or R (resistant), and I and R were grouped together as resistant. Carbapenem resistance was present when a gram-negative organism had an I or R in the susceptibility category to 1 of the 4 carbapenems: imipenem, meropenem, ertapenem, or doripenem. *P. aeruginosa* and *A. baumannii* were considered carbapenem resistant if they had an I or R in the susceptibility category to antipseudomonal carbapenems: imipenem, meropenem, or doripenem. All *S. maltophilia* isolates were assumed to be carbapenem resistant. The organism was carbapenem susceptible if it was susceptible to either a carbapenem or to a third-generation cephalosporin. Third-generation cephalosporin resistance (a phenotypic surrogate for extended-spectrum β -lactamase-containing organisms, ESBL) was defined as nonsusceptibility among Enterobacterales to any of the agents in that class. Resistance was identified to the following noncarbapenem antipseudomonal β -lactams: cefepime, ceftazidime, ceftazidime/avibactam, ceftolozane/tazobactam, and piperacillin/tazobactam.

Antimicrobial coverage was considered appropriate if a drug administered within 2 days of the index culture being obtained covered the recovered organism. All other treatment was defined as inappropriate empiric treatment. All microbiology results were based on the local testing done by participating hospitals using Clinical and Laboratory Standards Institute (CLSI) break points to determine susceptibilities.

Outcome variables

The primary outcome of interest was hospital mortality. Secondary outcomes included postinfection-onset duration of mechanical ventilation; postinfection intensive care unit (ICU) length of stay (LOS); hospital LOS (total and postinfection onset); hospital costs; and 30-day readmission rates among survivors.

Statistical analyses

We report descriptive statistics to compare nvHAPB, vHAPB, and VABP groups across their infection characteristics, microbiology, and empirical treatment regimens. Continuous variables are reported as means with standard deviations and as medians with interquartile ranges (IQR). Differences between mean values were tested using a 1-way ANOVA test and between medians using the Kruskal-Wallis test. Categorical data are summarized as proportions, and the χ^2 test used to examine intergroup differences unless a cell count was <5, wherein the Fisher exact test was used.

To examine the impact of inappropriate empiric treatment compared to appropriate treatment on hospital outcomes, we employed multivariable logistic regression for modeling the binary outcomes of mortality and 30-day readmission endpoints and

generalized linear regression models for the continuous outcomes. All models derived robust standard errors based on clustering at the hospital level. The model included the following variables: demographic characteristics; comorbidity burden; acute illness severity as measured by the need for ICU admission, dialysis, and vasopressor use; whether the admission was due to medical or surgical diagnosis; diagnosis of acute trauma or neurologic insult; duration of hospital stay from admission to index date, a variety of common treatments provided to patients in the ICU (eg, nutritional support, inotropes), and hospital structural characteristics (census region, size, teaching status, urbanicity).¹⁴ Interaction effects between empiric treatment status (ie, appropriate or inappropriate) and pneumonia type were explored in each model and as subanalyses, and separate regression models were rerun for each outcome in each of the 3 patient groups. $P < .05$ was considered statistically significant. Notably, however, because of the large sample size, statistical significance may not indicate clinical significance.

Results

Among 17,819 patients who met enrollment criteria, 26.5% had an nvHABP, 25.6% had a vHABP, and 47.9% had a VABP. VABP accounted for the highest proportion of pneumonias in the northeastern United States (54.0%) and the lowest in the West census region (44.3%) (Table 1).

Mean time to infection was shortest in the VABP and longest in the nvHABP groups (Table 1). Although most infections were monomicrobial, a substantial proportion harbored 2 or more offending organisms, with VABP having the highest prevalence (17.8%). Having 3 or more organisms was rare. More than three-quarters of all isolates came from a respiratory source, with the remainder from blood and a small minority from both (Table 1). Among 521 patients with both respiratory and blood isolates, 384 (73.7%) were concordant. Bacteremia was most common in the setting of nvHABP (24.4%) and least in VABP (5.4%), and 46.2% of all blood cultures grew *S. aureus*.

The single most common organism across all 3 pneumonia groups was *S. aureus*, occurring in nearly 40% of each pneumonia type (Fig. 1). MSSA was slightly more prevalent than MRSA in each group. MRSA was most common and MSSA was least common in VABP, and the reverse was true in nvHABP. *P. aeruginosa*, the next most prevalent pathogen, was present in 16.8% of VABP patients and 19.2% of vHABP patients, with 18.5% of the nvHABP group harboring *P. aeruginosa*. *E. coli* and *K. pneumoniae* accounted for 12%–13% of all infections, except for a lower prevalence of *E. coli* in VABP patients (8.7%) (Fig. 1). *A. baumannii*, though rare across all pneumonia types, was more than twice as likely in the setting of VABP (3.2%) as in nvHABP (1.5%) or vHABP (1.5%). Similarly, *S. marcescens* and *E. aerogenes* were both substantially more frequent in VABP than in either nvHABP or vHABP. Among the gram-negative organisms, the rates of carbapenem resistance ranged from 6.8% in vHABP to 9.1% in VABP. Across all pneumonia types, 4 organisms accounted for 80% of all carbapenem-resistant pathogens: *S. maltophilia*, *A. baumannii*, *P. aeruginosa*, and *P. mirabilis*. Third-generation cephalosporin resistance was more prevalent than carbapenem resistance, present among Enterobacteriales in 14.4% in nvHABP, 14.9% in vHABP, and 12.6% in VABP (Table 1).

During the index admissions and prior to the onset of their pneumonia, >70% of each group had received antibiotics. Within the 90 days prior to the index admission date, the

Table 1. Infection Characteristics

Characteristic	nvHABP (N=4,728)		vHABP (N=4,561)		VABP (N=8,530)		P Value
	No.	%	No.	%	No.	%	
Census region	1,134	23.98	1,135	24.88	2,136	25.04	<.001
Midwest	757	16.01	757	16.60	1,777	20.83	
Northeast	2,311	48.88	2,200	48.24	3,894	45.65	
South	526	11.13	382	8.38	723	8.48	
West	526	11.13	382	8.38	723	8.48	
Polymicrobial							
>2 organisms	555	11.74	694	15.22	1,516	17.77	<.001
>3 organisms	60	1.27	69	1.51	159	1.86	.028
Culture source							
Blood	1,155	24.43	625	13.70	464	5.44	<.001
Sputum	2,883	60.98	2,297	50.36	4,187	49.09	<.001
Respiratory	774	16.37	1,897	41.59	4,173	48.92	<.001
Antimicrobial resistance							
Carbapenem resistant	213	7.60	186	6.84	493	9.10	.001
Third-generation cephalosporin resistant	272	14.43	284	14.90	493	12.86	.066
Noncarbapenem anti-pseudomonal β -lactam-resistant ^c	691	14.62	730	16.01	1,406	16.48	.018

Note. nvHABP, nonventilated HABP; vHABP, ventilated HABP; VABP, ventilator-associated bacterial pneumonia.

^aDenominator consists of patients with gram-negative pathogens only.

^bDenominator consists of patients with Enterobacteriales only.

^cIncludes cefepime, ceftazidime, ceftazidime/avibactam, ceftolozane/tazobactam, and piperacillin/tazobactam.

prevalence of antimicrobial treatment had ranged from 8.9% in VABP to 16.0% in nvHABP (Table 2). Vancomycin and antipseudomonal penicillins with β -lactamase inhibitor were the most common empiric regimens across all 3 pneumonia types. Inappropriate empiric treatment was administered in 8.5% of nvHABP, 5.6% of vHABP, and 7.2% of VABP patients.

Table 3 shows the impact of inappropriate empiric treatment on the adjusted outcomes. Although inappropriate empiric treatment was not associated with a significant increase in hospital mortality or the risk of a 30-day readmission among survivors, there were substantial increases in the LOS across the continuum of care, ranging from 1.1 (95% confidence interval [CI], 0.4–1.8) extra days in the ICU to 4.8 (95% CI, 2.5–7.1) additional days in the hospital. Inappropriate empiric treatment was also associated with the attributable cost of \$12,142 (95% CI, \$3,272–\$21,013). Whether the pathogen was gram-positive or gram-negative did not alter this relationship significantly (data not shown). The association of inappropriate empiric treatment with several components of resource use varied by pneumonia type (Table 4). Total hospital LOS (8.7 days; 95% CI 3.3, 14.1), postinfection onset LOS (4.9 days; 95% CI, 3.0–6.9), and costs (\$13,147; 95% CI, \$3,009–\$23,284) were much greater in the nvHABP group than in the other 2 pneumonia categories. Among the remaining outcomes examined, the impact of inappropriate empiric treatment was of similar magnitude across the groups.

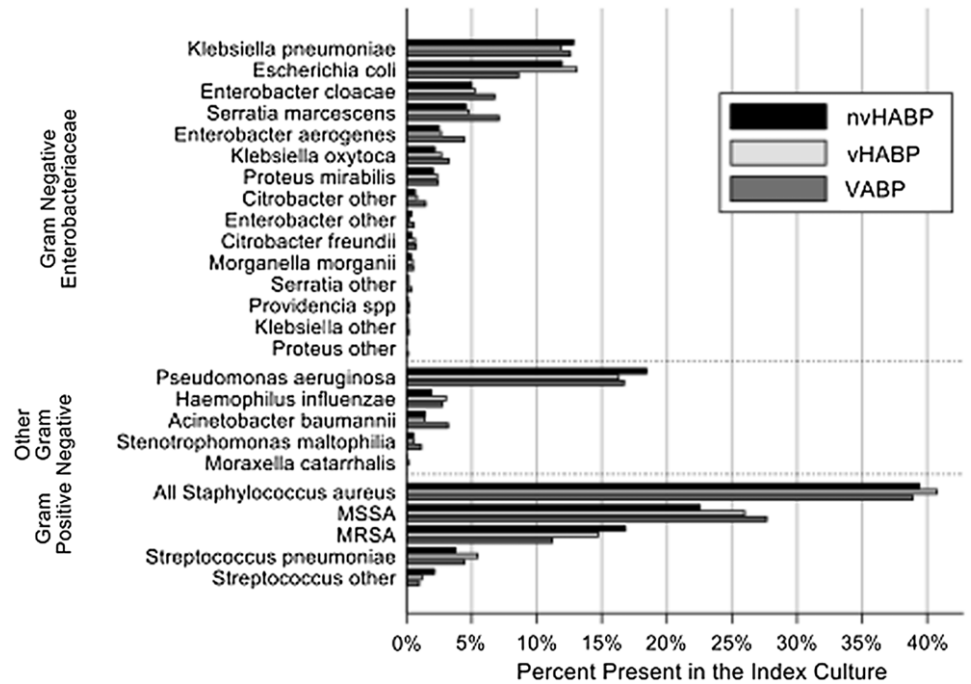


Fig. 1. Distribution of pathogens. Note. SA, *S. aureus*; MRSA, methicillin-resistant SA; MSSA, methicillin-susceptible SA.

Discussion

Across groups of patients with nvHABP, vHABP, and VABP, the general prevalence of various pathogens was mostly similar, with the exception of several organisms. Namely, *E. coli* was less prevalent, whereas *S. marcescens*, *E. aerogenes*, and *A. baumannii* were more common in VABP than in the other 2 pneumonia types. Similarly, MRSA, while common in all forms of nosocomial pneumonia, was less prevalent in VABP than in nvHABP. The case was reversed for MSSA. The prevalences of carbapenem resistance and third-generation cephalosporin resistance were quite high, and carbapenem resistance was most common in the setting of VABP in patients with positive cultures. We observed that inappropriate empiric treatment in was infrequent during this period. Although it does not appear to be significantly associated with increased hospital mortality and 30-day readmission, it independently adds substantially to postinfection-onset duration of mechanical ventilation, ICU and hospital LOS, and overall costs. Interestingly, the impact of inappropriate empiric treatment appears to vary by pneumonia type, being most resource intensive in patients with nvHABP, where it adds 4.9 days to the postinfection-onset LOS and >\$13,000 to the total hospital bill.

To our knowledge, ours is the first study in approximately a decade to elucidate the microbiology in bacterial nosocomial pneumonia, particularly in the context of stratifying epidemiology as a function of the pneumonia types and the subtypes of HABP (ventilated vs nonventilated). Esperatti et al¹¹ studied the similarities and differences between VABP and what they termed nonventilated ICU-acquired pneumonia (NV-ICUAP). In this single-center cohort from Spain, the investigators enrolled 315 patients who met their criteria for VABP and NV-ICUAP. Among the 151 (47.9%) patients who had an organism isolated, the pathogen distribution was largely similar to our findings. That is, *P. aeruginosa*, MRSA, and MSSA were most common organisms, and their relative prevalence across pneumonia types was similar to our findings. In their study, as in ours, MSSA was more often associated with VABP and MRSA was more often

associated with NV-ICUAP. The prevalence of *P. aeruginosa*, though higher in VABP than in NV-ICUAP in the Spanish study and lower in ours, was not substantively different across the pneumonia types. Overall, the enteric gram-negative pathogen distribution we observed was similar to that reported by Esperatti et al.¹¹

Our data comport with other US-based estimates. For example, an analysis from the National Healthcare Safety Network (NHSN) in the years 2011–2012 revealed a similar distribution of common organisms in VAP.²⁰ In this study, *S. aureus* was most common, followed by *P. aeruginosa* and *K. pneumoniae*, a pattern also reported by Quartin et al²¹ in a multinational study with the data collected from 2004 to 2010.^{20,21} Moreover, the latter investigators reported a similar pathogen distribution to ours in HABP, although the prevalence of MRSA far exceeded that of MSSA.²¹ The high prevalence of these organisms along with their likelihoods of carrying carbapenem resistance and ESBL, respectively, suggest that broad empiric coverage continues to be a necessity in HABP and VABP.

One other US-based study delved into the contemporary microbiology of nosocomial pneumonia with the specific focus on carbapenem resistance.²² Using the Premier database between the years 2010 and 2015, the investigators derived a cohort of patients with HAP or VAP and a positive respiratory culture for a gram-negative organism. Of the 6,483 respiratory cultures included in the analysis, 70% were in the setting of HAP and the remainder in VAP; the corresponding carbapenem resistance rates were 9.9% and 27.6%, respectively. Although they diverged from these rates somewhat, our estimates are likely to be more accurate for a number of reasons. First, by applying a case-finding algorithm that maximized specificity (eg, excluding other infection types), we were less likely to misclassify patients. Second, we did not limit the culture source to respiratory, but included positive blood cultures as well. This is an important distinction for 2 reasons. First, respiratory cultures tend to overrepresent colonization with resistant organisms when compared to blood cultures.¹⁹ Second, because the vast majority of cultures in the study by

Table 2. Antimicrobial Treatments and Outcomes

Treatment	nvHABP (N=4,728)		vHABP (N=4,561)		VABP (N=8,530)		P Value
	No.	%	No.	%	No.	%	
Prior antimicrobials							
Antibiotics during index hospitalization prior to pneumonia onset	3,578	75.68	3,243	71.10	6,785	79.54	<.001
Antibiotics during 90 d prior to index admission	758	16.03	717	15.72	758	8.89	<.001
Empiric treatment							
Antipseudomonal penicillins with β -lactamase inhibitor	2,038	43.10	2,284	50.08	3,826	44.85	<.001
Extended spectrum cephalosporins	1,588	33.59	1,503	32.95	3,174	37.21	<.001
Antipseudomonal fluoroquinolones	1,204	25.47	987	21.64	1,664	19.51	<.001
Antipseudomonal carbapenems	685	14.49	882	19.34	1,397	16.38	<.001
Aminoglycosides	211	4.46	293	6.42	591	6.93	<.001
Penicillins with β-lactamase inhibitors							
Tetracyclines	154	3.26	108	2.37	138	1.62	<.001
Folate pathway inhibitors	98	2.07	82	1.80	132	1.55	.084
Polymyxins	19	0.40	27	0.59	52	0.61	.273
Antipseudomonal cephalosporins	1,028	21.74	1,027	22.52	2,290	26.85	<.001
Aztreonam	190	4.02	204	4.47	276	3.24	.001
Fosfomycin	1	0.04	1	0.02	5	0.06	.637
Tigecycline	50	1.06	63	1.38	96	1.13	.299
3rd generation cephalosporin	771	16.31	705	15.46	1,304	15.29	.287
Vancomycin	2,792	59.05	3,225	70.71	5,488	64.34	<.001
Linezolid	277	5.86	329	7.21	470	5.51	<.001
Empiric treatment appropriateness							
Appropriate empiric treatment	3,856	81.56	3,929	86.14	7,178	84.15	<.001
Inappropriate empiric treatment	403	8.52	254	5.57	615	7.21	
Indeterminate	469	9.92	378	8.29	737	8.64	

Note. nvHABP, nonventilated hospital-acquired bacterial pneumonia; vHABP, ventilated hospital-acquired bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia.

Cai et al²² were from patients with HAP, they were unlikely to have originated from the lower airway, thus setting up an even greater bias for identifying colonization rather than infection. The overrepresentation of HAP by a factor of more than 2:1 in their study also suggests a high degree of misclassification. Specifically, in other studies the distribution is either more balanced or, as in ours, essentially reversed.^{11,21}

The prevalence of bacteremia in our study also parallels that observed by Quartin et al.²¹ More importantly, it is consistent with the literature contained within the recent clinical practice

Table 3. Adjusted Contribution of Inappropriate Empiric Treatment to Outcomes

Outcome	Point estimate	95% CI	P Value
Mortality, OR	1.11	(0.96–1.27)	.151
30-day readmission, OR	1.16	(0.97–1.39)	.109
Total hospital LOS, additional days	4.8	(2.5–7.1)	<.001
Postinfection-onset hospital LOS, additional days	2.3	(1.2–3.4)	<.001
Postinfection-onset ICU LOS, additional days	1.1	(0.4–1.8)	.001
Postinfection-onset MV duration, additional days ^a	0.6	(–0.1 to 1.3)	.079
Hospital costs, additional \$	12,142	(3,272–21,013)	<.001

Note. OR, odds ratio; CI, confidence interval; LOS, length of stay; ICU, intensive care unit; MV, mechanical ventilation.

^aVentilated hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia only.

guidelines.²³ Notably, the proportion of all *S. aureus* isolates that were MRSA was lower in our study than in the previous analyses.^{20,21} Such an encouraging pattern mirrors that reported in the setting of hospital-onset bloodstream infections in the United States. Namely, evidence from both NHSN and CDC-funded Emerging Infections Program (EPI) suggests a decrease in MRSA over time.^{24–26}

Another potentially encouraging finding in the current study was the rate of inappropriate empiric treatment, which was lower than we had reported in a prior contemporary cohort of patients with HABP/VABP.¹⁰ However, this small reduction may have been due to differences in the patients and organism mix. Nonetheless, compared to reports from 20 years ago when the issue and impact of inappropriate empiric treatment in nosocomial pneumonia initially received attention, it appears that rates of inappropriate empiric treatment have fallen substantially, which is encouraging. This reduction in the rate of inappropriate empiric treatment potentially explains our failure to detect its impact on mortality. The rate of inappropriate empiric treatment may have been sufficiently low enough to no longer alter mortality measurably but large enough to continue an adverse impact on morbidity and cost. It is also possible that we undercounted cases of inappropriate empiric treatment, given that we required patients have antimicrobial treatment on the day of the index culture as an inclusion criterion, thus leaving out those who failed to receive timely treatment.

Our study had several limitations. To reduce the risk for selection bias, we defined the enrollment criteria prospectively. To mitigate misclassification, we used a previously published, though not clinically validated, algorithm. We also excluded other potential sources of infection, and included microbiology specimens from specific sources, pharmacy data, and dates of cultures and treatments. If present, however, such misclassification would drive the differences between groups toward null. The data did not allow us to differentiate between infection and colonization. If a large proportion of what we identified as culture-positive nosocomial pneumonia simply represent colonization, then our analyses underestimate the potential adverse impact of inappropriate empiric treatment on nosocomial pneumonia outcomes. Despite

Table 4. Differential Impact of Inappropriate Empiric Treatment by Pneumonia Type

Outcome	nvHABP			vHABP			VABP		
	Point Estimate	95% CI	P Value	Point Estimate	95% CI	P Value	Point Estimate	95% CI	P Value
Total hospital LOS, additional days	8.7 d	(3.3–14.1)	<.001	2.3 d	(–1.1 to 5.7)	.187	1.8 d	(0.1–3.5)	.042
Postinfection-onset hospital LOS, additional days	4.9 d	(3.0–6.9)	<.001	0.6 d	(–1.3 to 2.5)	.559	1.5 d	(–0.2 to 3.2)	.075
Hospital costs, additional \$	\$13,147	(3,009–23,284)	<.001	\$4,658	(–2,424 to 11,750)	.198	\$6,161	(928–11,394)	.021

Note. nvHABP, nonventilated hospital-acquired bacterial pneumonia; vHABP, ventilated hospital-acquired bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia; CI, confidence interval; LOS, length of stay.

^avHABP and VABP only.

adjusting for a large number of confounders, the possibility of residual confounding remains. For example, our analysis focuses only on the period of empiric treatment. To examine potential confounding from the totality of the hospitalization would require more detailed longitudinal data than available in the current data set. Although generalizability of this large, multicenter geographically representative database is of minimal concern, our results capture only hospital-based events among patients who were culture-positive for common pathogens, and lack such data points as postdischarge death. As such, these findings may not generalize to nosocomial pneumonia with negative cultures. Despite these limitations, ours is the largest and most contemporary multicenter cohort study to examine the microbiology, treatment, and outcomes of nosocomial pneumonia in the United States.

In summary, we have demonstrated that there are substantial differences between populations who suffer from nvHABP, vHABP, and VABP. Although their microbiology varies, the general prevalence of such resistant organisms as MRSA appears to be lower currently than in the past. Despite having marginal impact on hospital mortality and the risk of readmission within 30 days, inappropriate empiric treatment remains an important modifiable risk factor that significantly worsens utilization outcomes, and this effect is most pronounced among patients with nvHABP. On the other hand, the rate of inappropriate empiric treatment may have also decreased, potentially highlighting the efficacy of adoption of clinical practice guidelines. Given the moderate rates of carbapenem resistance and third-generation cephalosporin resistance, our observations suggest that, depending on their clinical risk profile, patients require empiric antibiotic regimens that cover a range of bacteria, including those with a high likelihood of extended-spectrum β -lactamase and carbapenem resistance. This needs to be accompanied by meticulous attention to prompt de-escalation where appropriate to prevent further proliferation of antimicrobial resistance. Alternatively, if rapid diagnostics are proven to be both accurate and reliable, adopting an approach that utilized a rapid test that excluded the presence of resistance would allow one to start with narrower options. In the end, clinical trials and cost-effectiveness analyses will be required to delineate the tradeoffs and outcomes with these possible approaches.

Acknowledgments.

Financial support. This study was supported by a grant from Merck Sharp & Dohme, a subsidiary of Merck & Co, Kenilworth, New Jersey.

Conflicts of interest. M.D.Z. is employed by EviMed Research Group, and she has received research grant support from Merck Sharp & Dohme, a subsidiary

of Merck & Co. B.H.N. is employed by OptiStatim and has received support from EviMed Research Group. L.A.P. is an employee of and a stockholder in Merck Sharp & Dohme, a subsidiary of Merck & Co. A.F.S. is a consultant to and has received research grant support from Merck Sharp & Dohme, a subsidiary of Merck & Co. M.D.Z. and A.F.S. have received grant support and/or have served as consultants to Lungpacer, Melinta, Tetrphaser, Pfizer, Astellas, Shionogi, The Medicines Company, Spero, and Theravance.

References

- Magill SS, Edwards JR, Bamberg W *et al*. Multistate point-prevalence survey of healthcare-associated infections. *N Engl J Med* 2014;370:1198–1208.
- Freire AT, Melynk V, Kim MJ, *et al*. Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. *Diagn Microbiol Infect Dis* 2010;68:140–151
- Kollef MH, Chastre J, Clavel M, *et al*. A randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin or ventilator-associated pneumonia. *Crit Care* 2012;16:R218.
- Ramirez J, Dartois N, Gandjini H, Yan JL, Korth-Bradley J, McGovern PC. Randomized phase 2 trial to evaluate the clinical efficacy of two high-dosage tigecycline regimens versus imipenem-cilastatin for treatment of hospital-acquired pneumonia. *Antimicrob Agents Chemother* 2013;57:1756–1762.
- Réa-Neto A, Niederman M, Lobo SM, *et al*. Efficacy and safety of doripenem versus piperacillin/tazobactam in nosocomial pneumonia: a randomized, open-label, multicenter study. *Curr Med Res Opin* 2008;24:2113–2126.
- Chastre J, Wunderink R, Prokocimer P, Lee M, Kaniga K, Friedland I. Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: a multicenter, randomized study. *Crit Care Med* 2008;36:1089–1096.
- Rubinstein E, Lalani T, Corey GR, *et al*; ATTAIN Study Group. Telavancin versus vancomycin for hospital-acquired pneumonia due to gram-positive pathogens. *Clin Infect Dis* 2011;52:31–40.
- Wunderink RG, Niederman MS, Kollef MH, *et al*. Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. *Clin Infect Dis* 2012;54:621–629.
- Wunderink RG, Rello J, Cammarata SK, Croos-Dabrera RV, Kollef MH. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest* 2003;124:1789–1797.
- Zilberberg MD, Nathanson BH, Sulham K, Fan W, Shorr AF. A novel algorithm to analyze epidemiology and outcomes of carbapenem resistance among patients with hospital-acquired and ventilator-associated pneumonia: a retrospective cohort study. *Chest* 2019;155:1119–1130
- Esperatti M, Ferrer M, Theessen A, *et al*. Nosocomial pneumonia in the intensive care unit acquired by mechanically ventilated versus nonventilated patients. *Am J Respir Crit Care Med* 2010;182:1533–1539.
- Valleccoccia MS, Dominedo C, Cutuli SL, Martin-Loeches I, Torres A, De Pascale G. Is ventilated hospital-acquired pneumonia a worse entity than ventilator-associated pneumonia? *Eur Resp Rev* 2020;29:200023.

13. Office for Human Research Protections. Human Subject regulations decision charts. US Department of Health and Human Services website. <https://www.hhs.gov/ohrp/regulations-and-policy/decision-charts/index.html>. Accessed February 3, 2021.
14. Zilberberg MD, Nathanson BH, Puzniak LA, Shorr AF. Descriptive epidemiology and outcomes of nonventilated hospital-acquired, ventilated hospital-acquired, and ventilator-associated bacterial pneumonia in the US, 2012–2019. *Crit Care Med* 2022;50:460–468.
15. Zilberberg MD, Nathanson BH, Sulham K, Fan W, Shorr AF. Development and validation of a bedside instrument to predict carbapenem resistance among gram-negative pathogens in complicated urinary tract infections. *Infect Control Hosp Epidemiol* 2018;39:1112–1114.
16. Zilberberg MD, Ditch K, Lawrence K, Olesky M, Shorr MD. Carbapenem treatment and outcomes among patients with culture-positive complicated intra-abdominal infections in US hospitals: a retrospective cohort study. *Open Forum Infect Dis* 2019;6(12):ofz504.
17. Rothberg MB, Pekow PS, Priya A, *et al*. Using highly detailed administrative data to predict pneumonia mortality. *PLoS One* 2014;9(1):e87382.
18. Rothberg MB, Haessler S, Lagu T, *et al*. Outcomes of patients with healthcare-associated pneumonia: worse disease or sicker patients? *Infect Control Hosp Epidemiol* 2014;35 suppl 3:S107–S115.
19. Haessler S, Lindenauer PK, Zilberberg MD, *et al*. Blood cultures versus respiratory cultures: 2 different views of pneumonia. *Clin Infect Dis* 2020;71:1604–1612.
20. Weiner LM, Webb AK, Limbago B, *et al*. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014. *Infect Control Hosp Epidemiol* 2016;37:1211–1301.
21. Quartin AA, Scerpella EG, Puttagunta S, Kett DH. A comparison of microbiology and demographics among patients with healthcare-associated, hospital-acquired, and ventilator-associated pneumonia: a retrospective analysis of 1,184 patients from a large, international study. *BMC Infect Dis* 2013;13:561.
22. Cai B, Echols R, Corvino F, *et al*. Carbapenem-resistance [sic] pathogens in HAP/VAP patients in US hospitals between 2010 and 2015. *Eur Resp J* 2018;52 suppl 62:PA2636.
23. Kalil AC, Metersky ML, Klompas M, *et al*. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Disease Society of America and the American Thoracic Society. *Clin Infect Dis* 2016;63:e61–e111.
24. US Department of Health and Human Services. Data summary of HAIs in the US: assessing progress 2006–2016. Centers for Disease Control and Prevention website. <https://www.cdc.gov/hai/data/archive/data-summary-assessing-progress.html>. Published 2017. Accessed March 3, 2022.
25. US Department of Health and Human Services. 2016 National and state healthcare-associated infections progress report. Centers for Disease Control and Prevention website. <https://www.cdc.gov/hai/data/portal/progress-report.html>. Published 2017. Accessed March 3, 2022.
26. Kourtis AP, Hatfield K, Baggs J, *et al*. Vital Signs: epidemiology and recent trends in methicillin-resistant and in methicillin-susceptible *Staphylococcus aureus* Bloodstream infections—United States. *Morb Mortal Wkly Rep* 2019;68:214–219.