CHEST

Going Viral

Importance of Viral Pathogens in Nonventilated Hospital-Acquired Pneumonia

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Over the past decade, substantial resources have been focused on ventilator-associated pneumonia (VAP).[1,2] Research designed to enhance our appreciation of its pathophysiology has led to a multitude of preventive options.[1,2] Furthermore, the morbidity penalty associated with VAP underscores the importance of efforts to eliminate VAP as an ICU-related complication.[3] Most important, studies highlighting the importance of initially appropriate antimicrobial therapy have shown means through which we can reduce mortality related to VAP.[4,5]

VAP, however, is just 1 type of nosocomial pneumonia (NP). Hospitalized patients who are not ventilated are also at risk for pneumonia, and the pool of such subjects outside the ICU is substantial. Whether correctly or not, most guidelines for NP presume that hospital-acquired pneumonia affecting the nonventilated patient (NVHAP) shares many of the attributes and characteristics of VAP.[1] Given the potential extent of the problem, it is critical to begin to understand the epidemiology, microbiology, and outcomes specific to hospital-acquired pneumonia that arises in the spontaneously breathing patient.

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In this issue of *CHEST*, Micek and colleagues[6] help fill this void in patients who develop NVHAP. In a retrospective, single-center study, they report several important observations. First, NVHAP clearly results in attributable mortality. This finding is key, given that the mortality penalty associated with VAP is rather small. In other words, most patients die with VAP, not of it. In contrast, NVHAP appears to contribute substantially to the risk of death.[6] All the limitations inherent in a small, retrospective, single-center study notwithstanding, the relationship between NHVAP and excess mortality is concerning. Similarly, excess hospital length of stay resulting from a case of NHVAP appears longer than the added length of stay related to VAP.[6] These are compelling arguments for expanding quality and safety efforts related to NP beyond the ICU, because a narrow focus on VAP only neglects a companion disease that may lead to even more avoidable deaths and costs than one that already requires public reporting. With the findings from Micek et al[6] in hand, we need to demand more research into the early identification of those suffering from NVHAP and potential preventive measures.

Second, Micek et al[6] report striking results regarding the microbiology of NVHAP. Guidelines urge physicians in the United States to treat patients with suspected NVHAP with some combination of broad-spectrum antimicrobials. The major concerns are for such antibiotic-resistant organisms as *Pseudomonas aeruginosa*, extended spectrum beta-lactamase producing Enterobacteriaceae, and methicillin-resistant *Staphylococcus aureus*. Although the authors demonstrate that such pathogens can certainly be recovered in NHVAP, infections were equally likely to be viral as bacterial.[6]

In community-acquired pneumonia, the importance of viruses was recently confirmed by Jain and coworkers in a large multicenter surveillance study in which viruses were isolated twice as frequently as bacteria.[7] The importance of viral pathogens in NP, however, is a relatively recent discovery. Though recognized as important causes of NP among the immunocompromised, few

patients in the report by Micek et al[6] fell into this category through high-dose chemotherapy, a stem cell transplant, or a solid organ transplant. Admittedly, as a retrospective study relying on usual clinical practices, the current report by Micek et al[6] reflects a search for potential viral pathogens only when clinically suspected, rather than according to a systematic protocol for viral diagnostic tests. This suggests that the reported prevalence of viral infections represents an underestimate rather than an overestimate. Thus, one has to wonder how many of those patients classified as culture negative might have actually had an infection caused by a virus.

Several reports have implicated virus as an important cause of other forms of NP. Hong et al[8] documented viruses as causative in VAP in 22.5% of cases, whereas Choi and colleagues[9] estimated that nearly one-third of cases of health-care–associated pneumonia were related to viral infection. Taken as whole, these studies from various forms of NP suggest that we must search for viral pathogens in hospitalized patients with new-onset pneumonia rather than presume that viruses are only an issue in subjects with community-acquired pneumonia.

Additionally, the significance of viruses as a cause of NP has several clear clinical implications. Because antibiotics will not help those suffering from a viral infection, the search for (and potential identification of) a viral cause will facilitate antibiotic de-escalation and stewardship. In many situations, culture negative NVHAP patients receive a 7- to 10-day course of antibiotics. By limiting exposure to such agents because a virus has been identified, we can help prevent the emergence of further resistance as well as individual consequences of unnecessary antibiotic exposure, such as gut dysbiosis and *Clostridium difficile* infection.

Finally, as rapid diagnostic tools are being developed for pneumonia, the manufacturers of these tests need to ensure that they include means not only for identifying bacteria, but also for determining if a viral pathogen is present.

In summary, the results presented by Micek et al[6] not only provide important information about the outcomes related to NVHAP, they also point to potential ways for practicing clinicians to improve the care of their patients.

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CHEST

A Case-Control Study Assessing the Impact of Nonventilated Hospital-Acquired Pneumonia on Patient Outcomes

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BACKGROUND: Nonventilated hospital-acquired pneumonia (NVHAP) is a serious nosocomial infection that is increasingly attributed to antibiotic-resistant bacteria.

METHODS: This is a retrospective case-control study comparing patients with and those without NVHAP from January 1, 2014 to December 31, 2014 at Barnes-Jewish Hospital, a 1,300-bed urban academic medical center in St. Louis, Missouri.

RESULTS: One hundred seventy-four consecutive patients with NVHAP were enrolled. A random sample of 696 control patients matched by age, sex, race, and hospital admission date were selected from a total of 5,322 potential matched control subjects. NVHAP was pathogen-negative in 98 cases (56.3%). Respiratory viruses were identified in 42 patients (24.1%), gram-negative bacteria were seen in 25 patients (14.4%), and gram-positive bacteria were identified in 20 patients (11.5%). Individuals in whom NVHAP developed were more likely to die (15.5% vs 1.6%; $P < .01$), to require intensive care (56.3% vs 22.8%; $P < .01$) or mechanical ventilation (19.0% vs 3.9%; $P < 0.01$), and to have a longer hospital length of stay (15.9 days [range, 9.8-26.3 days] vs 4.4 days [range, 2.9-7.3 days]; $P < 0.01$). This case-control study identified a strong association between hospital mortality and NVHAP, with patients who acquired NVHAP having an 8.4 times greater odds of death (95% CI, 5.6-12.5).

CONCLUSIONS: The occurrence of NVHAP was associated with significant increases in mortality, the use of intensive care and mechanical ventilation, and hospital length of stay. We also found that respiratory viruses were an important cause of NVHAP. These findings suggest that efforts aimed at the successful prevention of NVHAP could improve patient outcomes and reduce health-care costs. CHEST 2016; 150(5):1008-1014

KEY WORDS: antibiotic resistance; outcomes; pneumonia

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ABBREVIATIONS: HAP = hospital-acquired pneumonia; MDR = multidrug-resistant; NVHAP = nonventilated hospital-acquired pneumonia; VAP = ventilator-associated pneumonia

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Hospital-acquired pneumonia (HAP) is a frequent and severe infection in hospitalized patients, with most reports focusing on HAP acquired in ICUs in the form of ventilator-associated pneumonia (VAP).[1-3] Increasingly, antibiotic-resistant pathogens including extended-spectrum beta-lactamase-producing and carbapenem-resistant Enterobacteriaceae, methicillin-resistant *Staphylococcus aureus*, and multidrug-resistant (MDR) nonfermenting gram-negative bacilli (*Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*) are associated with HAP.[4] Respiratory viruses have also recently been identified as potentially important causative pathogens for HAP.[5] Antibiotic-resistant bacteria as well as respiratory viruses pose an ongoing challenge to hospitals, both in patient treatment and in the prevention of transmission of these pathogens from patient to patient. Unfortunately, most clinical studies assessing the impact of HAP on patient outcomes[6-8] and guidelines for the prevention of HAP[1,9-11] are directed at VAP, with little attention focused on nonventilated HAP (NVHAP). This is likely the result of the greater severity of illness in patients in the ICU setting, as well as the ability to more precisely define the presence of true infection in ventilated patients with pneumonia using diagnostic techniques such as BAL with quantitative cultures.

Available studies suggest that NVHAP appears to have causative microorganisms and outcomes that are similar to those in VAP.[12-15] However, there is a lack of controlled studies focusing on NVHAP to quantitatively determine the impact of this nosocomial infection on patient outcomes. The availability of such data could influence hospitals and physicians to increase the efforts aimed at preventing NVHAP, as well as improve the treatment of this nosocomial infection. Therefore, we performed a case-control study to describe the causative pathogens associated with NVHAP and to determine the influence of NVHAP on patient outcomes.

Methods

Subjects and Study Design

This was a single-center retrospective case-control study of patients with NVHAP performed at Barnes-Jewish Hospital (a 1,300-bed urban academic medical center in St. Louis, Missouri) between January 1, 2014 and December 31, 2014. The study protocol was approved by the Washington University Institutional Review Board (IRB No. 201409001), and informed consent was waived. Adult patients ($\geq$ 19 years of age) admitted to the hospital for more than 48 h were eligible for participation. Patients were excluded if they were transferred from an outside hospital.

Definitions

We defined NVHAP cases in accordance with the American Thoracic Society's position statement on nosocomial pneumonia.[1] All patients with a respiratory culture specimen obtained during the study period were screened for study entry. NVHAP was defined as a new or progressive radiographic infiltrate developing more than 48 h after hospital admission plus at least two of the following clinical features: fever $>$ 38°C, leukocytosis ($>$ 10 $\times$ 10^9 cells/L), leukopenia ($\leq$ 4 $\times$ 10^9 cells/L), or purulent secretions. The Charlson comorbidity index was used as a summative score of underlying disease states.[16] The presence of a new or progressive radiographic infiltrate was based on the interpretation of the chest radiograph by board-certified radiologists blinded to the study. All patient charts identified as having new or progressive infiltrates were reviewed by one of the investigators (M. H. K.) to confirm the radiographic findings and by two other investigators (S. T. M., B. C.) to identify patients meeting the case definition for NVHAP. Pneumonia was classified as pathogen-negative if all respiratory culture results and applied molecular techniques failed to identify a pathogen. Pathogen-positive pneumonia was defined as growth of a pathogenic organism from sputum, tracheal aspirate, or bronchoscopic or blind BAL fluid when tracheal aspirates and bronchoscopic or blind BAL fluid were obtained in patients with NVHAP within 24 h after respiratory failure developed. Additionally, a positive urinary antigen test result for *Legionella* qualified as a positive culture result, as did positive qualitative nucleic acid multiplex test results for respiratory viruses, *Bordetella pertussis, Chlamydophila pneumoniae, and Mycoplasma pneumoniae* (FilmArray Respiratory Panel, BioFire Diagnostics).

Population Control Subjects

We selected control subjects by using a risk set sampling scheme. Four control subjects were selected for each case, matched on age, sex, race, and hospital admission date within 1 month of the case patient admission date. A random sample of matched control patients was selected for each case of NVHAP using a random number generator.

End Points

The main end point evaluated was hospital mortality. Secondary measures included ICU admission, mechanical ventilation, length of stay, and 30-day readmission after the index hospitalization.

Statistical Analysis

The primary data analysis compared patients with NVHAP to those without NVHAP. Categorical variables were compared using the χ^2 or Fisher exact test as appropriate. Continuous variables were compared using the Mann-Whitney *U* test. Data from the matched case-control study were analyzed using conditional fixed-effect logistic analysis. Model goodness of fit was assessed by the Hosmer-Lemeshow test. All tests were two-tailed, and *P* values $<$ .05 were considered significant. All statistical analyses were performed using IBM SPSS Statistics, version 22.0 (SPSS).

Results

A total of 174 cases of NVHAP were identified, and 696 control subjects were selected (Fig 1). Among the 174 patients with NVHAP, 148 (85.1%) had blood culture samples obtained (8 of 148 being positive) and 174 (100%) had at least one respiratory tract culture specimen obtained (sputum, 45.4%; tracheal aspirate, 23.6%; BAL fluid, 31.0%) (40 of 174 being positive). Nucleic acid multiplex tests were performed on respiratory samples from 92 patients (52.9%), with NVHAP (42 of 92 being positive). There were 98 pathogen-negative (56.3%) cases of NVHAP. Viruses were identified in 42 patients (24.1%) (19 rhinovirus, seven influenza A, six parainfluenza virus, five coronavirus, four human metapneumovirus, and four respiratory syncytial virus), gram-negative bacteria were isolated in 25 patients (14.4%) (nine *P aeruginosa*, four *Escherichia coli*, four *Haemophilus species*, three *Klebsiella pneumoniae*, two *Enterobacter species*, two *Stenotrophomonas maltophilia*, and 1 each for *Moraxella catarrhalis*, *Citrobacter koseri*, and *Achromobacter xylosoxidans*), and gram-positive bacteria were found in 20 patients (11.5%) (17 *S aureus*, two beta-hemolytic streptococci group F, and 1 *Streptococcus pneumoniae*). Among *S aureus* isolates, nine were methicillin resistant (52.9%), whereas 12 of the gram-negative isolates (48.0%) were resistant to ceftriaxone (representing an antibiotic typically prescribed for pneumonia in patients without risk factors for antibiotic resistance).

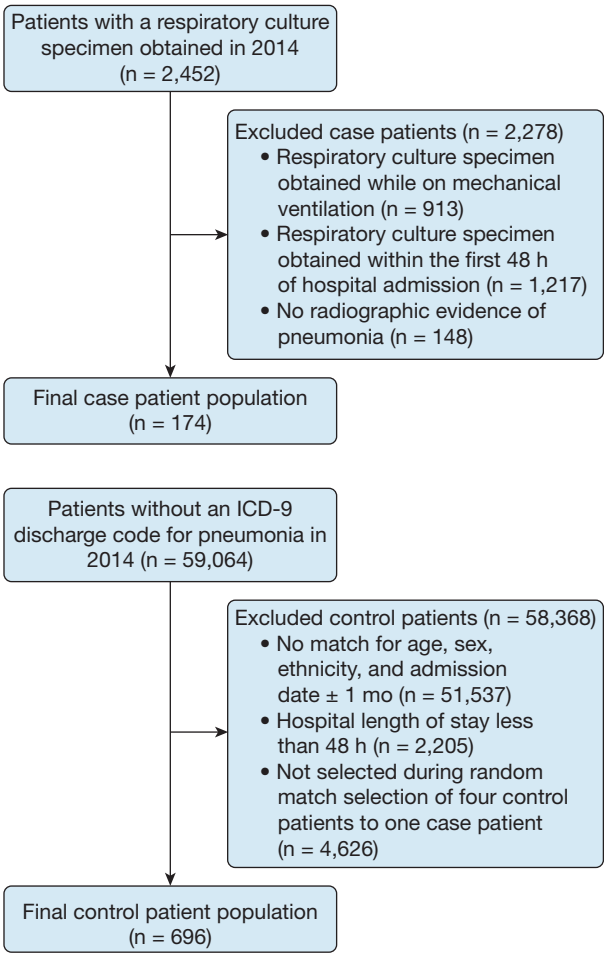

Figure 1 – *Study flow diagram. Case and control patients were selected from the Barnes-Jewish Hospital Informatics Repository. ICD-9 = International Classification of Diseases, Ninth Revision.*

The mean duration to occurrence of NVHAP was on hospital day 4.2 ± 3.8. Characteristics of case patients and control subjects are listed in Table 1. Patients with NVHAP were more likely to have higher baseline comorbidity on admission based on the Charlson comorbidity index and to have chronic obstructive pulmonary disease. Patient outcomes are shown in Table 2. Patients with NVHAP were statistically more likely to die during their hospital stay compared with patients without NVHAP (15.5% vs 1.6%; $P < .01$). Similarly, patients with NVHAP were more likely to require transfer to an ICU (56.3% vs 22.8%; $P < .01$) and mechanical ventilation (19.0% vs 3.9%; $P < .01$) and to have a longer hospital length of stay (median, 15.9 vs 4.4 days; $P < .01$). Thirty-day hospital readmission rates were similar between the two study groups.

Adjusted odds ratios by conditional logistic regression for variables evaluated for their association with hospital mortality are presented in Table 3. NVHAP with an adjusted OR of 8.4 (95% CI, 5.6-2.5) along with mechanical ventilation and increasing Charlson comorbidity scores were associated with a greater risk of hospital mortality. The Hosmer-Lemeshow test suggests that our model fit the data ($P = .76$). Mortality was greater for patients with NVHAP stratified by Charlson comorbidity index (Fig 2).

Discussion

This study found that the occurrence of NVHAP was associated with adverse outcomes, including a greater risk of hospital mortality. Hospital resource use was also found to be greater for patients in whom NVHAP developed, as evidenced by greater ICU admission, need for mechanical ventilation, and longer length of stay. Thirty-day hospital readmission was not found to be different between patients with and those without NVHAP. We also found that a viral cause for NVHAP was common, accounting for 24.4% of all cases. The case-control study identified a strong association between hospital mortality and NVHAP.

TABLE 1] Baseline Demographic and Clinical Characteristics

Characteristic	Cases With NVHAP (n = 174)	Control Subjects Without NVHAP (n = 696)	*P* Value
Age, y	57.5 ± 15.0	57.5 ± 14.9	1.0
Male sex, No. (%)	95 (54.6)	380 (54.6)	1.0
White, No. (%)	124 (71.3)	523 (75.4)	.27
African American, No. (%)	37 (21.3)	167 (24.1)	.44
Charlson comorbidity score	5.5 ± 3.2	4.8 ± 3.4	.02
Coronary artery disease, No. (%)	28 (16.1)	106 (15.2)	.78
Congestive heart failure, No. (%)	46 (26.4)	151 (21.7)	.18
Cerebrovascular disease, No. (%)	19 (10.9)	89 (12.8)	.50
COPD, No. (%)	89 (51.1)	225 (32.3)	< .01
Cirrhosis, No. (%)	36 (20.7)	114 (16.4)	.18
Diabetes, No. (%)	57 (32.8)	255 (36.6)	.34
Active malignancy, No. (%)	21 (12.1)	80 (11.5)	.83
Chronic kidney disease, No. (%)	38 (21.8)	162 (23.3)	.69
Surgical patient, No. (%)	75 (43.1)	291 (41.8)	.76
Medical patient, No. (%)	99 (56.9)	405 (58.2)	.75

Values expressed as mean ± SD or No. (percent). NVHAP = nonventilated hospital-acquired pneumonia.

Sopena and Sabrià[12] examined 12 Spanish hospitals over 10 years and were able to prospectively identify only 186 patients with non-ICU HAP, representing less than 20 cases per year. Among the 165 patients with a complete data set, there were 60 with a microbiological cause established (36.4%). Seven immunocompromised patients with pneumonia due to *Aspergillus* species were included, and no cases of viral HAP were identified. Kollef et al[13] examined 4,543 patients with pathogen-positive pneumonia admitted to 59 US hospitals between January 1, 2002 and December 31, 2003.[13] NVHAP accounted for 18.4% of the patients with pneumonia, and again there were no cases of viral pneumonia identified in this study. More recently, the importance of viruses as a cause of HAP has been recognized because of the availability of molecular probes for the identification of respiratory viruses. A single-center study from South Korea identified 59 patients with severe HAP attributed to a respiratory virus over a 2-year period, accounting for 22.5% of all their cases of severe HAP.[5] Over a 6-year period (August 2007 to September 2013), Andruska et al[17] identified 9,624 patients with a discharge diagnosis of pneumonia from Barnes-Jewish Hospital. Although viral pneumonia accounted for only 2.7% of all pneumonia cases during this period, it was associated with the second highest rate of hospital readmission (8.3%) after pneumonia attributed to potentially antibiotic-resistant bacteria (11.4%).

More recently, with the routine application of commercially available viral multiplex testing, Crotty

TABLE 2] Clinical Outcomes

Outcome	Cases With NVHAP n = 174	Control Subjects Without NVHAP n = 696	*P* Value
ICU admission, No. (%)	98 (56.3)	159 (22.8)	< .01
Mechanical ventilation, No. (%)	33 (19)	27 (3.9)	< .01
Hospital mortality, No. (%)	27 (15.5)	11 (1.6)	< .01
Hospital LOS, d, range[a]	15.9 (9.8-26.3)	4.4 (2.9-7.3)	< .01
Readmission 30 d after hospital discharge, No. (%)[b]	37 (25.2)	145 (21.2)	.29

LOS = length of stay. See Table 1 legend for expansion of other abbreviation.
[a]Median (interquartile range).
[b]Only hospital survivors considered: cases, n = 147; control subjects, n = 685.

TABLE 3] Conditional Logistic Regression Model of Hospital Mortality

Variable	Adjusted OR	95% CI	*P* Value
Hospital-acquired pneumonia	8.4	5.6-12.5	< .01
Mechanical ventilation	8.0	5.3-11.9	< .01
Charlson comorbidity index (1-point increments)	1.2	1.1-1.2	.01

Hosmer-Lemeshow goodness of fit, $P = .76$.

et al[18] identified 284 patients with viral pneumonia at Barnes-Jewish Hospital from March 2013 to November 2014. The majority of these patients (51.8%) were immunocompromised, and 84 patients (29.6%) were found to have coinfections, with 48 having a bacterial coinfection (57.6%). Overall hospital mortality was high (23.2%), and readmissions were common within 30 days and 90 days of discharge (21.1% and 36.7%, respectively).

The clinical importance of NVHAP has been demonstrated by comparing outcomes with VAP. Esperatti et al[14] examined patients in the ICU setting in whom either NVHAP or VAP developed.[14] Despite a lower proportion of identified pathogens in the patients with NVHAP compared with those with VAP, the type of microbiological isolates and clinical outcomes were similar regardless of whether pneumonia was acquired during or without mechanical ventilation. This finding would suggest that patient-specific findings, such as severity of illness and immune function, may be more important factors predisposing to nosocomial pneumonia than previous intubation. Moreover, both types of patients should receive similar empirical antibiotic treatment and benefit from preventive measures that are preferentially directed at intubated individuals. Hospital-based quality-improvement initiatives have primarily focused on preventing the occurrence of VAP and not NVHAP.[19,20] However, it has been difficult to demonstrate attributable mortality from VAP because of the overall severity of illness in the "at risk" ventilated patient population.[6] This may account for the inability of the majority of VAP prevention studies to demonstrate reductions in mortality. Our data suggest that NVHAP is associated with significant morbidity and mortality excess and that the prevention of NVHAP could potentially improve patient outcomes.

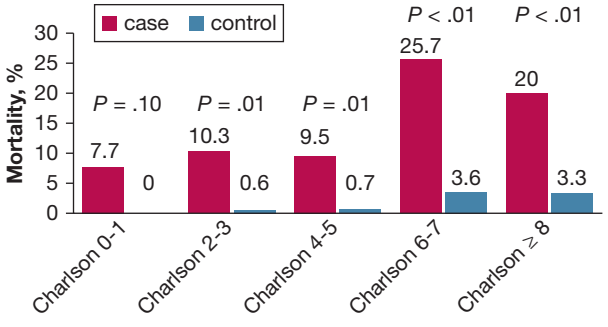

Figure 2 – *Hospital mortality for patients with (cases) and without (control subjects) nonventilated hospital-acquired pneumonia stratified by Charlson comorbidity index.*

The emergence of MDR pathogens as a cause of HAP has also resulted in greater administration of inappropriate initial antimicrobial therapy, which is associated with excess patient mortality.[21] MDR infection in NVHAP is increasingly common in many parts of the world, resulting in the delayed administration of appropriate antibiotic therapy.[22-24] Moreover, attributable mortality from HAP may be greater than that associated with VAP because of the lower severity of illness existing at baseline in patients with HAP compared with those with VAP.[25]

Several limitations of our study should be recognized. First, the retrospective design did not allow for determination of the cause of mortality. Furthermore, it is possible that we did not identify all cases of NVHAP given that we used respiratory culture results and not International Classification of Diseases, Ninth Revision codes to screen for study entry. This was purposely done to obtain a patient cohort for whom the treating physicians had a high enough suspicion for pneumonia to obtain microbiological cultures. Second, the data are derived from a single center, and this necessarily limits the generalizability of our findings. As such, our results may not reflect what one might see at other institutions. For example, Barnes-Jewish Hospital has a regional referral pattern that includes community hospitals, regional long-term acute care hospitals, nursing homes, and chronic wound, dialysis, and infusion clinics. Patients transferred from these settings are more likely to be infected with potentially antibiotic-resistant bacteria.

This may explain the relatively high rates of infection with potentially antibiotic-resistant gram-negative bacteria and *S aureus*. Third, given our sample size, we may have lacked power to identify all important confounders that could affect our mortality end point. Fourth, we did not use a protocol for obtaining specific types of culture samples in all patients, rather deferring this evaluation to the treating physicians. This may have contributed to sampling errors in identifying cases of NVHAP. Fifth, we limited the number of matching variables to maximize the number of patients with NVHAP in our study analysis. This may have contributed to unidentified differences in the case and control populations, such as severity of illness or admission diagnoses, which may have contributed to the outcome differences observed. Finally, we cannot exclude the possibility that bacterial coinfection was present among patients with a viral cause of NVHAP. Antibiotic administration may have limited the ability of conventional culture methods to identify antibiotic-susceptible bacteria in that setting.

In summary, our data suggest that the occurrence of NVHAP is associated with adverse patient outcomes and can be caused by both bacterial and viral pathogens. Interventional studies aimed at the prevention of NVHAP are required to determine whether the consequences of NVHAP can be avoided and patient outcomes improved.

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