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PROPHETIC: Prospective Identification of Pneumonia in Hospitalized Patients in the Intensive Care Unit
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Abbreviations

HABP = hospital-acquired bacterial pneumonia

ICU = intensive care unit

FDA = Food and Drug Administration

PROPHETIC = Prospective Identification of Pneumonia in Hospitalized Patients in the Intensive Care Unit

VABP = ventilator-associated bacterial pneumonia

Abstract

Background: Pneumonia is the leading infection-related cause of death. Using simple clinical criteria and contemporary epidemiology to identify patients at high risk of nosocomial pneumonia should enhance prevention efforts and facilitate development of new treatments in clinical trials.

Research Question: What are the clinical criteria and contemporary epidemiology trends helpful in identifying patients at high risk of nosocomial pneumonia?

Study Design and Methods: Within the intensive care units of 28 United States hospitals, we conducted a prospective cohort study among adults hospitalized more than 48 hours and considered high risk for pneumonia (defined as treatment with invasive or noninvasive ventilatory support or high levels of supplemental oxygen). We estimated the proportion of high-risk patients developing nosocomial pneumonia. Using multivariable logistic regression, we identified patient characteristics and treatment exposures associated with increased risk of pneumonia development during the intensive care unit admission.

Results: Between February 6, 2016 and October 7, 2016, 4613 high-risk patients were enrolled. Among 1464/4613 (32%) high-risk patients treated for possible nosocomial pneumonia, 537/1464 (37%) met the study pneumonia definition. Among high-risk patients, a multivariable logistic model was developed to identify key patient characteristics and treatment exposures associated with increased risk of nosocomial pneumonia development (c-statistic 0.709, 95% confidence interval 0.686 to 0.731). Key factors associated with increased odds of nosocomial pneumonia included an admission diagnosis of trauma or cerebrovascular accident, receipt of enteral nutrition, documented aspiration risk, and receipt of systemic antibacterials within the preceding 90 days.

Interpretation: Treatment for nosocomial pneumonia is common among intensive care unit patients receiving high levels of respiratory support, yet more than half of patients treated do not fulfill standard diagnostic criteria for pneumonia. Application of simple clinical criteria may improve the feasibility of clinical trials of pneumonia prevention and treatment by facilitating prospective identification of patients at highest risk.

Hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) are the most common nosocomial infections and the leading reasons for antibiotic prescriptions in the intensive care unit (ICU).[1,2] HABP/VABP development is associated with high mortality and substantial short- and long-term morbidity.[3,4] Delayed effective antimicrobial therapy is associated with worse outcomes, so clinicians are compelled to treat promptly when HABP/VABP is suspected. Nevertheless, diagnosing HABP/VABP is inexact because diagnosis is based on a constellation of symptoms and clinical signs that are not sufficiently predictive of pneumonia.[5–7] HABP/VABP management is further complicated by frequent infection with multidrug resistant pathogens, few available antibiotics with demonstrated efficacy in HABP/VABP treatment, and a limited pipeline of new antibiotics undergoing evaluation in clinical trials.[8,9]

The low level of HABP/VABP antimicrobial development is a multifaceted problem driven in part by poor clinical trial feasibility, due to low enrollment.[10–12] Poor enrollment itself is a complex issue in which the relative contributions of changing HABP/VABP prevalence and high screening failure rates are unknown. Estimates of HABP/VABP prevalence are highly variable because consensus definitions are lacking and there is variability in interpretation of some criteria, such as the chest radiograph.[13] Epidemiologic definitions of HABP/VABP likely underestimate the true frequency of antibiotic prescribing for suspected nosocomial pneumonia in modern clinical practice. Furthermore, historical estimates of HABP/VABP burden may not capture the impact of recent VABP prevention efforts and implementation of ventilator-associated event monitoring and reporting.[14,15]

Improved understanding of contemporary HABP/VABP incidence using a definition employed in clinical trials may inform the design of more feasible trials. Evaluating risk for

HABP/VABP associated with patient characteristics and treatment exposures may help identify those patients at highest risk for disease acquisition, ultimately promoting the study of new treatments and prevention efforts by facilitating the conduct of efficient clinical studies focused on the patients most likely to benefit, while decreasing harm in those less likely to benefit.[16]

Using a large multicenter cohort of prospectively identified patients and a standard definition of HABP/VABP outlined in United States Food and Drug Administration (FDA) draft guidance to industry,[17] the Clinical Trials Transformation Initiative HABP/VABP studies team designed the Prospective Identification of Pneumonia in Hospitalized Patients in the ICU (PROPHETIC) study, which: 1) defined the contemporary incidence of HABP/VABP among patients at high-risk for this infection; and 2) identified demographic factors, comorbid conditions, and treatment exposures associated with increased risk of HABP/VABP development during ICU admission.

Methods

Study Design

We conducted a multicenter, prospective, observational cohort study in ICUs of 28 United States hospitals. Enrolling sites comprised a diverse group of both community and tertiary academic medical centers with a median size of 727 (range 252, 1394) inpatient beds. All eligible adults admitted to participating ICUs were screened for the presence of predefined risk factors for HABP/VABP development (eFigure 1). Patients considered high risk for HABP/VABP development (defined as receiving invasive mechanical ventilation, noninvasive ventilation, or treatment with at least 50% fraction of inspired supplemental oxygen via high-flow, high-humidity nasal cannula, aerosol mask, partial or non-rebreather mask for a minimum of 12 hours

within any 24-hour period in the preceding 7 days) were enrolled and prospectively followed for development of signs or symptoms of possible pneumonia throughout their ICU course (study definitions are provided in the Supplementary Methods).

Adults ≥18 years old admitted to participating ICUs were eligible for enrollment if hospitalized for >48 hours or within 7 days of discharge from acute or chronic care facilities. Patients were excluded if pregnant or currently breastfeeding, currently receiving treatment for lung cancer or metastatic cancers with lung involvement, receiving comfort measures only, or previously treated for suspected pneumonia while enrolled in the study. The study protocol was approved and a waiver of informed consent was granted by Copernicus Group, an independent review board (CTTI_001, DCR2-15-710), or the institutional review board of the participating institution, when required.

Baseline demographics and treatment exposures were recorded for all patients at enrollment. High-risk patients were followed daily for development of clinical signs or symptoms of possible pneumonia or receipt of antibiotics to treat possible pneumonia. Antibiotic exposures and results of clinically obtained microbiologic testing were recorded for all patients receiving antibiotics for possible pneumonia.

Definitions

The high-risk population was defined as patients receiving high levels of respiratory support, but lacking study diagnostic criteria for pneumonia at the time of enrollment. The treated population was defined as the subset of high-risk patients receiving antibiotics for possible pneumonia, defined by documentation of antibiotic indications for pneumonia or undifferentiated sepsis for which pneumonia was considered a possible cause in the medical record, during their ICU

course. The HABP/VABP population included only the subset of treated patients fulfilling the study HABP/VABP definition, which required at least one criterion to be present from each diagnostic domain including radiographic criteria, respiratory signs and symptoms, systemic inflammation, and timing of symptom onset. The study HABP/VABP definition was consistent with that used in treatment guidelines and developed from inclusion criteria in antibacterial drug treatment trials for HABP/VABP outlined in FDA draft guidance for industry (full study definitions are provided in the Supplementary Methods).[3,17]

Microbiologic Testing

Clinically obtained microbiologic testing results were recorded in the case report form. No specific microbiologic testing or procedures were mandated by the study protocol. For positive microbiologic results, the organism name and reported antibiotic susceptibilities were recorded. Extended spectrum beta-lactamase production was captured when identified by each site's standard reporting protocol.

Outcomes

The primary outcome was the rate of study-defined HABP/VABP diagnosis in ICU patients meeting the predetermined high-risk criteria. The key secondary outcome was determination of risk factors associated with HABP/VABP development in ICU patients meeting prespecified high-risk criteria.

Statistical Analysis

All analyses were performed in predefined study populations. Patient characteristics were summarized as frequency and percentages for categorical variables, and medians with 25^{th} and 75^{th} percentiles for continuous variables. The cumulative percentage of patients developing VABP or HABP before study completion (due ICU discharge, transition to comfort measures, or death) was graphed as a function of time since high risk criteria were met. We performed risk modeling using multivariable logistic regression models and assessed relationships between 38 baseline risk factors and HABP/VABP development.

The aim of developing the multivariable logistic regression model was to identify patient characteristics and treatment exposures associated with increased risk for HABP/VABP development during the ICU course at the time the patient might be screened for enrollment in a HABP/VABP clinical trial. Patients who met the study definition of HABP/VABP at the time of enrollment were excluded from the model. Final predictors were identified using clinical guidance and a backward variable selection process at the 0.1 level of significance for model retention. These predictors were confirmed independently using a forward variable selection process. Collinearity was assessed by calculating the phi coefficient between prespecified covariates identified by clinical guidance as most likely to be associated. In a sensitivity analysis, we evaluated whether these predictors were also associated specifically with development of VABP, among the subset of high-risk patients receiving >48 hours of invasive mechanical ventilation. Discriminatory capacity of the multivariable models was assessed using the c-statistic. Calibration for each model was assessed graphically to display the level of agreement between observed and predicted rates of HABP/VABP and VABP respectively, by decile of risk. The out-of-sample performance of each model was evaluated using internal validation by

estimating the optimism-corrected c-statistic using 200 bootstrap samples. All analyses were performed using SAS version 9.4.

Results

Between February 6, 2016 and October 7, 2016, the study enrolled 5756 ICU patients; 4613 (80%) had high-risk factors for HABP/VABP development at enrollment and met study inclusion/exclusion criteria (Figure 1). Of the 4613 enrolled high-risk patients, 537 (12%) met the study HABP/VABP definition over a median follow-up of 7 days (Figure 2). Among 1464/4613 (32%) high-risk patients treated for possible pneumonia during their ICU course, 927/1464 patients, comprising 63% of the treated population, did not fulfill at least one domain of HABP/VABP diagnostic inclusion criteria recommended in FDA draft guidance (eTable 1). Of 1464 treated high-risk patients, 1181 (81%) were prescribed antibiotics for an indication of pneumonia and 523/1181 (44%) met the study HABP/VABP definition. Among 283/1464 (19%) high-risk patients treated with antibiotics for an indication of undifferentiated sepsis (for which pneumonia was being evaluated as a potential etiology) or for which no antibiotic indication was recorded, 14 (5%) met the study HABP/VABP definition.

Characteristics were similar of high-risk, treated, HABP, and VABP populations, including age, ICU type, hospital and ICU length-of-stay, and type of respiratory support (Table 1). In the HABP/VABP population, 502/537 (93%) patients were receiving invasive mechanical ventilation at the time of pneumonia diagnosis, including 108/537 (20%) patients with ventilated HABP (<48 hours of invasive mechanical ventilation at time of diagnosis) and 394/537 (73%) with VABP. The median duration of mechanical ventilation for high-risk patients that subsequently developed VABP was 8 days (interquartile range, 5–14) (Figure 3).

The multivariable logistic regression model was developed using 4613 high-risk patients. Key patient characteristics and treatment exposures associated with increased odds of pneumonia (meeting the study HABP/VABP definition) included an ICU admission diagnosis of trauma or cerebrovascular accident, receipt of enteral nutrition, documented aspiration risk, and receipt of systemic antibacterials within the preceding 90 days (Table 2). Collinearity that would impact stability of the multivariable model was not identified. The HABP/VABP logistic regression model demonstrated moderate discriminatory capacity and calibration (c-statistic 0.709 [0.686, 0.731]) (eFigure 2). The multivariable model yielded out-of-sample discrimination with an optimism-corrected c-statistic of 0.693 [0.670, 0.715]. The multivariable model was also evaluated in 3712/4613 (80%) patients at high risk for developing VABP (exposure to invasive mechanical ventilation >48 hours) and demonstrated similar discriminatory capacity and calibration (c-statistic 0.698 [0.671, 0.726], optimism-corrected c-statistic 0.677 [0.650, 0.705]) (eTable 2) (eFigure 3).

Microbiologic testing was collected and recorded in 477/537 (89%) patients fulfilling study HABP/VABP criteria. A bacterial pathogen was identified from at least one source in 306/477 (64%) of tested patients (eFigures 4 and 5). *Staphylococcus aureus* (102/477 [21%] patients) and *Pseudomonas aeruginosa* (52/477 [11%] patients) were the most frequently isolated bacterial pathogens among tested HABP/VABP patients (eFigures 6 and 7). Enterobacteriaceae were identified in 116/477 (24%) tested HABP/VABP patients. Extended spectrum beta-lactamase-producing bacteria were reported in 13/477 (3%) and carbapenem-resistant organisms in 3/477 (<1%) tested HABP/VABP patients.

Discussion

This large, contemporary, prospective cohort study made two pivotal observations. First, treatment for nosocomial pneumonia is common; 32% of prospectively identified high-risk patients received antibiotics for possible HABP/VABP, and 12% of these high-risk patients met case definitions for HABP/VABP consistent with FDA draft guidance for sponsors conducting interventional trials.[17] Second, we were able to identify common patient characteristics and treatment exposures associated with increased odds of HABP/VABP development among prospectively identified high-risk patients. Identification of these risk associations, in combination with the high-risk criteria we employed in this study, may help focus future prevention efforts, inform the design of more efficient clinical trials, and facilitate innovative enrollment strategies such as early screening or consent of patients at high-risk for developing HABP/VABP.

Since this study was developed to inform design of more efficient clinical trials, we used a HABP/VABP definition consistent with recommended clinical trial inclusion criteria in FDA draft guidance.[17] Although national surveillance data suggest a decreasing incidence of nosocomial pneumonia, this study demonstrates HABP and VABP remain common nosocomial infections.[18] The higher rates of pneumonia observed in this study may be partially due to using a HABP/VABP definition similar to that recommended in clinical practice guidelines, rather than an epidemiologic definition.[3,19,20] To minimize risk of underestimating HABP/VABP among high-risk patients treated with antibiotics for unclear indications, we included patients prescribed antibiotics for undifferentiated sepsis if pneumonia was considered a possible cause. Even if high-risk patients treated with antibiotics for a clinical indication of undifferentiated sepsis were excluded, 26% of the high-risk population was treated with antibiotics for a clinical indication of

pneumonia and only 44% of these patients ultimately met the study HABP/VABP definition; this discrepancy highlights diagnostic uncertainty in the management of HABP/VABP, as well as the urgent need for new tools to improve the accuracy and consistency of HABP/VABP diagnosis.[13,21]

Discordance between treatment and diagnostic confirmation may reflect clinicians' reluctance to base treatment decisions upon imprecise chest radiography, insensitive HABP/VABP diagnostic criteria, or variability within treatment practices.[22–24] Though impossible to confidently evaluate within the design of this study, the frequency of antibiotic prescribing for clinical syndromes not fulfilling the study HABP/VABP definition also raises concern for antibiotic overprescription in this high-risk population. Such concerns emphasize the need for prospective evaluation of patient-centered outcomes associated with antibacterial exposure in the management of suspected HABP/VABP using criteria of increasing stringency, particularly since receiving antibiotics is itself a risk factor for developing pneumonia, carries risk of adverse events, and may preclude eligibility for HABP/VABP trial enrollment.[25] Nevertheless, this study does provide evidence that ICU patients receiving high levels of respiratory support do frequently receive antibiotics for HABP/VABP and fulfill recommended inclusion criteria for enrollment in antibacterial drug trials.

A key result of this study was identification of common patient characteristics and treatment exposures associated with increased odds of HABP/VABP development. Our model identified several clinical characteristics and potentially modifiable risk factors (receipt of systemic antibacterials within the preceding 90 days or antacid medications during the current hospitalization) previously associated with increased odds of HABP/VABP.[26–29] The findings from this large prospective cohort validate previous risk associations and may also inform future

development of a more comprehensive HABP/VABP risk prediction tool used to design efficient clinical trial enrollment strategies or effectively steward costly or higher-risk prevention strategies that cannot be practically or safely implemented universally. Development of a comprehensive risk prediction tool could complement real-time monitoring systems to effectively identify patients developing nosocomial pneumonia as early and efficiently as possible.[30] Prospective identification of patients at high-risk for HABP/VABP, using the high-risk criteria employed in this study, potentially enhanced by more comprehensive risk prediction tools, may also help focus clinical trial screening efforts on patients at highest risk, facilitating enrollment in more efficient clinical trials and furthering evaluation of early informed consent trial designs whereby patients or their surrogates may be approached about enrollment in HABP/VABP clinical trials before developing nosocomial pneumonia.[31]

Limitations

This study has some limitations. First, since only United States adult ICUs were included, our study may not be generalizable to other populations; therefore, our findings have been evaluated in a pediatric ICU cohort, and analysis of data from a European cohort is ongoing.[32] Second, candidate risk factors for HABP/VABP were only evaluated in patients meeting prespecified high-risk criteria, so odds of pneumonia could not be evaluated in patients who did not receive high levels of respiratory support and were presumably at lower risk for developing HABP/VABP. Third, since this study was only conducted in ICU patients, 85% of whom received invasive mechanical ventilation during their ICU course, nonventilated HABP is underrepresented. Epidemiologic studies suggest HABP is increasingly common and accounts for the majority of nosocomial pneumonias.[33,34] The clinical characteristics and treatment

exposures associated with increased odds of HABP/VABP in our study may not have similar associations with nonventilated HABP, especially HABP that develops outside the ICU setting. Since this study was developed to inform design of efficient HABP/VABP clinical trials in the ICU setting, we evaluated risk associated with a combined HABP/VABP endpoint. We did not observe significant differences in the prevalence of candidate risk factors between HABP and VABP populations or in performance of the multivariable model when evaluating only the subgroup of high-risk patients at risk for VABP, but this does not diminish the fact that HABP and VABP are distinct clinical entities and an evaluation of risk factors for nonventilated HABP would require a broader inclusion of hospitalized patients outside the ICU. Fourth, because some variables required to calculate standard severity of illness scores were not collected upon study enrollment, we could not include these patient characteristics in the multivariable model. Finally, although the proportion of cases with a bacterial pathogen detected (64%) was consistent with prior studies, we could not accurately estimate the burden of nosocomial pneumonia associated with viral pathogens, which have been associated with nosocomial pneumonia in several single-center studies.[8,35,36]

Interpretation

In conclusion, the burden of HABP and VABP among critically ill patients is substantial. Treatment for possible nosocomial pneumonia is exceedingly common among patients receiving high levels of respiratory support, yet most of these patients do not fulfill standard clinical definitions of HABP/VABP. Prospective identification of patients at high-risk for HABP/VABP using simple clinical criteria may facilitate conduct of innovative and efficient clinical trials to

promote development of optimal preventive, diagnostic, and treatment strategies to improve management of this disease.

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Author Contributions

SP Bergin: Dr. Bergin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Bergin contributed to the conception and design of the study, the data analysis, the data interpretation, the manuscript drafting, and the critical revision of the manuscript.

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VG Fowler Jr.: Dr. Fowler contributed to the conception and design of the study, the supervision, data interpretation, the manuscript drafting, and the critical revision of the manuscript.

TL Holland: Dr. Holland contributed to the conception and design of the study, the supervision, data acquisition, analysis and interpretation, the manuscript drafting, and the critical revision of the manuscript.

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Table 1. Characteristics of Key Study Populations

Characteristic	High-Risk Patients (N=4613)	Treated Patients (N=1464)	HABP Patients (N=143)	VABP Patients (N=394)
Demographics[a]				
Age, median (IQR), y	61.0 (50.0, 70.0)	60.0 (49.0, 70.0)	63.0 (55.0, 74.0)	58.0 (45.0, 69.0)
Female sex, No. (%)	2058 (44.6)	599 (40.9)	51 (35.7)	159 (40.4)
Body mass index, median (IQR), kg/m^2	28.9 (24.1, 35.0)	28.5 (23.8, 34.8)	26.1 (22.1, 31.6)	29.4 (25.1, 35.1)
Hospital length of stay, median (IQR), days	4.0 (3.0, 8.0)	5.0 (3.0, 9.0)	6.0 (3.0, 10.0)	5.0 (3.0, 9.0)
ICU length of stay, median (IQR), days	3.0 (2.0, 5.0)	4.0 (2.0, 6.0)	4.0 (2.0, 7.0)	3.5 (2.0, 6.0)
APACHE II Score, [b] median (IQR)			19.0 (15.0, 27.0)	23.0 (17.0, 28.0)
Treatment Exposures, [c] No. (%)				
Invasive mechanical ventilation	3908 (84.7)	1316 (89.9)	108 (75.5)	394 (100)
Noninvasive mechanical ventilation	751 (16.3)	258 (17.6)	36 (25.2)	42 (10.7)
Enteral nutrition	3035 (65.8)	1149 (78.5)	98 (68.5)	357 (90.6)
Vasopressor/inotropic therapy	2211 (47.9)	722 (49.3)	70 (49.0)	226 (57.4)
Biologic agents, current hospitalization	169 (3.7)	57 (3.9)	3 (2.1)	21 (5.3)
Corticosteroids, current hospitalization	589 (12.8)	226 (15.4)	32 (22.4)	54 (13.7)
PPI/H-2 blocker, current hospitalization	3475 (75.3)	1185 (80.9)	114 (79.7)	332 (84.3)
Blood product transfusion, prior 7 days	1062 (23.0)	332 (22.7)	33 (23.1)	132 (33.5)
Systemic antibacterials, prior 90 days	2832 (61.4)	1020 (69.7)	108 (75.5)	275 (69.8)
Mechanical circulatory support	220 (4.8)	69 (4.7)	4 (2.8)	29 (7.4)
Massive volume resuscitation	532 (11.5)	174 (11.9)	12 (8.4)	61 (15.5)
Active Medical Problems,[c,d] No. (%)				
Acute respiratory distress syndrome	686 (14.9)	332 (22.7)	36 (25.2)	66 (16.8)
Acute kidney injury	1078 (23.4)	410 (28.0)	32 (22.4)	88 (22.3)
Chronic kidney disease	541 (11.7)	173 (11.8)	13 (9.1)	45 (11.4)
End stage renal disease	270 (5.9)	70 (4.8)	8 (5.6)	15 (3.8)
Aspiration risk	605 (13.1)	325 (22.2)	31 (21.7)	100 (25.4)
Autoimmune disorder	194 (4.2)	68 (4.6)	7 (4.9)	21 (5.3)
Chemotherapy, prior 30 days	139 (3.0)	55 (3.8)	7 (4.9)	13 (3.3)
Diabetes mellitus	1304 (28.3)	393 (26.8)	24 (16.8)	91 (23.1)

Characteristic	High-Risk Patients (N=4613)	Treated Patients (N=1464)	HABP Patients (N=143)	VABP Patients (N=394)
Immunocompromised	545 (11.8)	170 (11.6)	23 (16.1)	38 (9.6)
Chronic respiratory failure	129 (2.8)	39 (2.7)	4 (2.8)	10 (2.5)
Congestive heart failure, NYHA class IV	141 (3.3)	41 (3.1)	3 (2.4)	6 (1.7)
Cirrhosis or gastrointestinal bleeding	467 (10.1)	150 (10.2)	16 (11.2)	40 (10.2)
Cerebrovascular accident	400 (8.7)	162 (11.1)	14 (9.8)	46 (11.7)
Substance abuse	1289 (27.9)	422 (28.8)	34 (23.8)	115 (29.2)
HIV infection	54 (1.2)	10 (0.7)	2 (1.4)	3 (0.8)
Delirium or altered mental status	1276 (27.7)	455 (31.1)	40 (28.0)	112 (28.4)
Seizures	417 (9.0)	163 (11.1)	6 (4.2)	42 (10.7)
Chronic obstructive pulmonary disease	804 (17.4)	262 (17.9)	25 (17.5)	52 (13.2)
Myocardial infarction	337 (7.3)	115 (7.9)	11 (7.7)	24 (6.1)
Chronic dialysis (any type)	490 (10.6)	145 (9.9)	14 (9.8)	35 (8.9)
Intensive care unit type, No. (%)				
Medical	2468 (53.5)	837 (57.2)	84 (58.7)	188 (47.7)
Surgical/trauma	852 (18.5)	215 (14.7)	22 (15.4)	97 (24.6)
Cardiac/cardiac surgery	769 (16.7)	194 (13.3)	18 (12.6)	50 (12.7)
Neurosciences	350 (7.6)	139 (9.5)	9 (6.3)	42 (10.7)
Mixed	174 (3.8)	79 (5.4)	10 (7.0)	17 (4.3)
Intensive care admission source, No. (%)				
Emergency department	2729 (59.2)	926 (63.3)	97 (67.8)	225 (57.1)
Skilled nursing, long term acute care	177 (3.8)	69 (4.7)	11 (7.7)	18 (4.6)
Scheduled procedure	488 (10.6)	79 (5.4)	8 (5.6)	26 (6.6)
Non-procedure; clinic or direct admission	812 (17.6)	282 (19.3)	18 (12.6)	83 (21.1)
Other	407 (8.8)	108 (7.4)	9 (6.3)	42 (10.7)
Intensive care admission diagnosis, No. (%)				
Acute hypercapnic respiratory failure	233 (5.1)	77 (5.3)	4 (2.8)	13 (3.3)
Acute hypoxemic respiratory failure	893 (19.4)	348 (23.8)	40 (28.0)	69 (17.5)
Acute myocardial infarction	124 (2.7)	41 (2.8)	6 (4.2)	7 (1.8)
Acute renal failure or severe electrolyte abnormality	45 (1.0)	12 (0.8)	1 (0.7)	2 (0.5)

Characteristic	High-Risk Patients (N=4613)	Treated Patients (N=1464)	HABP Patients (N=143)	VABP Patients (N=394)
Altered mental status	337 (7.3)	118 (8.1)	10 (7.0)	23 (5.8)
Cardiogenic shock	86 (1.9)	32 (2.2)	2 (1.4)	11 (2.8)
Cerebrovascular accident	191 (4.1)	70 (4.8)	7 (4.9)	23 (5.8)
Hemorrhagic shock or severe hemorrhage	94 (2.0)	27 (1.8)	0 (0.0)	11 (2.8)
Other hypovolemic shock	17 (0.4)	3 (0.2)	1 (0.7)	1 (0.3)
Planned post-operative ICU admission	475 (10.3)	82 (5.6)	9 (6.3)	32 (8.1)
Sepsis or septic shock	337 (7.3)	99 (6.8)	12 (8.4)	23 (5.8)
Shock	41 (0.9)	11 (0.8)	1 (0.7)	3 (0.8)
Frequent/refractory seizures	94 (2.0)	39 (2.7)	1 (0.7)	14 (3.6)
Trauma	275 (6.0)	101 (6.9)	10 (7.0)	60 (15.2)
Other	1371 (29.7)	404 (27.6)	39 (27.3)	102 (25.9)

Abbreviations: APACHE = acute physiology and chronic health evaluation; H2 = histamine blocker; HABP = hospital-acquired bacterial pneumonia; ICU = intensive care unit; IQR = interquartile range; PPI = proton pump inhibitor; VABP = ventilator-associated bacterial pneumonia

[a]Characteristics recorded at the time of high-risk population enrollment.

[b]Some variables required for APACHE II score calculation were only recorded when pneumonia diagnosis confirmed

[c]Characteristics recorded when pneumonia diagnosis confirmed or upon ICU discharge (for patients not developing HABP/VABP).

[d]Diagnoses included in the active medical problem categories defined in supplement.

Table 2. High-Risk Patient Characteristic and Treatment Exposure Associations with Pneumonia Development

Factor	Type 3 Wald Chi-Square	Beta Coefficient	Adjusted Odds Ratio (95% CI)	P-Value
ICU admission diagnosis	53.10			
Acute hypercapnic respiratory failure		-0.31	0.73 (0.38, 1.39)	0.336
Acute hypoxemic respiratory failure		0.13	1.14 (0.74, 1.76)	0.552
Acute myocardial infarction		0.12	1.12 (0.55, 2.28)	0.749
Altered mental status or seizures		-0.06	0.94 (0.57, 1.55)	0.815
Cerebrovascular accident		0.51	1.67 (0.95, 2.94)	0.073
Sepsis or septic shock		-0.12	0.88 (0.52, 1.49)	0.646
Trauma		1.16	3.19 (1.96, 5.20)	<.001
Shock (excluding septic shock)		0.06	1.06 (0.62, 1.83)	0.822
Other		0.10	1.11 (0.73, 1.68)	0.629
Planned post-operative ICU admission			reference	
Enteral nutrition	41.26	0.87	2.38 (1.83, 3.11)	<.001
Aspiration risk	39.18	0.74	2.10 (1.66, 2.65)	<.001
Systemic antibacterials within 90 days	16.78	0.44	1.56 (1.26, 1.92)	<.001
Admission source	13.53			
Skilled nursing, long term acute care		0.60	1.82 (1.17, 2.82)	0.007
Non-procedure; clinic or direct admission		0.19	1.20 (0.93, 1.55)	0.152
Scheduled procedure		-0.37	0.69 (0.45, 1.06)	0.089
Other		0.14	1.15 (0.83, 1.61)	0.396
Emergency department			reference	
Diabetes mellitus	6.44	-0.29	0.75 (0.59, 0.94)	0.011
Invasive mechanical ventilation	5.96	0.49	1.63 (1.10, 2.40)	0.015
Noninvasive mechanical ventilation	4.57	0.30	1.35 (1.03, 1.78)	0.032
Proton pump inhibitor therapy/H2-blocker therapy	4.36	0.27	1.30 (1.02, 1.67)	0.037
Blood product transfusion in the last 7 days	3.80	0.21	1.24 (1.00, 1.53)	0.051
Corticosteroids at current hospitalization	2.96	0.23	1.26 (0.97, 1.65)	0.086
Female sex	2.70	-0.16	0.85 (0.70, 1.03)	0.101
ICU length of stay (days), per 1-day increase	2.31	0.01	1.01 (1.00, 1.03)	0.128

Abbreviations: CI = confidence interval; ICU = intensive care unit; OR = odds ratio
Characteristics and treatment exposures recorded at time of high-risk population enrollment.
4613 patients included in analysis.
Risk factors selected using backward selection with α=0.1 for model inclusion and clinical expertise.
C-statistic: 0.709 (0.686, 0.731)

Figure Legends

Figure 1. Patients at Risk for Nosocomial Pneumonia

Screening, eligibility, and enrollment of patients at risk for nosocomial pneumonia.

Abbreviations: HABP, hospital-acquired bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia; ICU, intensive care unit

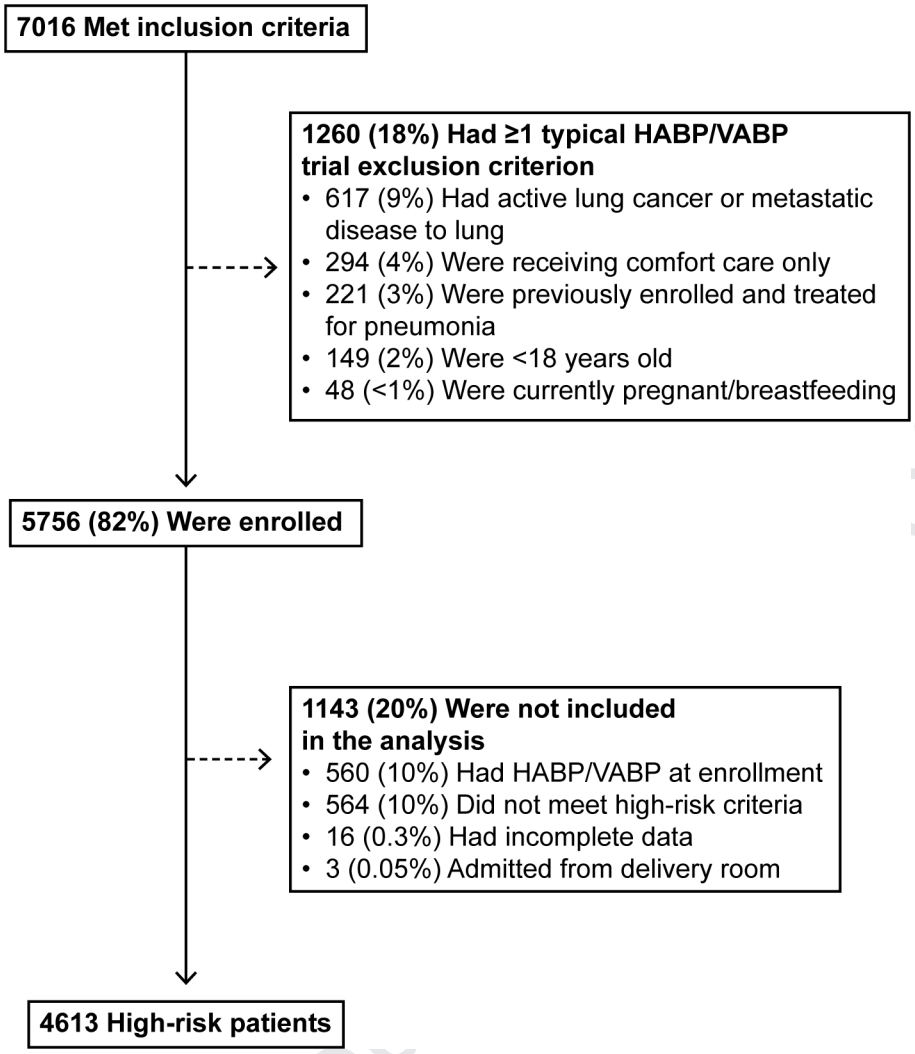
Figure 2. Study Outcome for High-Risk Patients

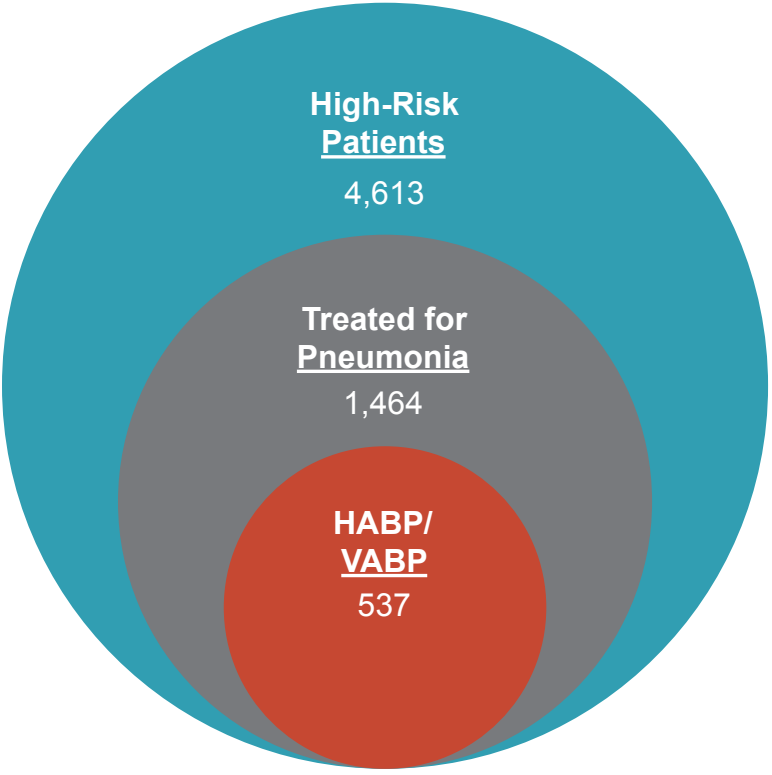
Of 4613 enrolled high-risk patients, 1464 (32%) were treated for possible pneumonia during their ICU course; of these, 537/1464 (37%) met the study HABP/VABP definition over a median follow-up of 7 days.

Abbreviations: HABP, hospital-acquired bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia; ICU, intensive care unit

Figure 3. Cumulative Incidence of Nosocomial Pneumonia for High-Risk Patients

Abbreviations: HABP, hospital-acquired bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia


7016 Met inclusion criteria
1260 (18%) Had ≥1 typical HABP/VABP trial exclusion criterion
• 617 (9%) Had active lung cancer or metastatic disease to lung
• 294 (4%) Were receiving comfort care only
• 221 (3%) Were previously enrolled and treated for pneumonia
• 149 (2%) Were <18 years old
• 48 (<1%) Were currently pregnant/breastfeeding
5756 (82%) Were enrolled
1143 (20%) Were not included in the analysis
• 560 (10%) Had HABP/VABP at enrollment
• 564 (10%) Did not meet high-risk criteria
• 16 (0.3%) Had incomplete data
• 3 (0.05%) Admitted from delivery room
4613 High-risk patients


High-Risk
Patients
4,613
Treated for
Pneumonia
1,464
HABP/
VABP
537

Cumulative Incidence Curves for VABP and HABP