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MAJOR ARTICLE

PROPHETIC EU: Prospective Identification of Pneumonia in Hospitalized Patients in the Intensive Care Unit in European and United States Cohorts

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Background. The prospective identification of patients at high risk for hospital-acquired/ventilator-associated bacterial pneumonia may improve clinical trial feasibility and foster antibacterial development. In a prior study conducted in the United States, clinical criteria were used to prospectively identify these patients; however, these criteria have not been applied in a European population.

Methods. Adults considered high risk for pneumonia (treatment with ventilation or high levels of supplemental oxygen) in the intensive care units of 7 European hospitals were prospectively enrolled from June 12 to December 27, 2017. We estimated the proportion of high-risk patients developing pneumonia according to US Food and Drug Administration guidance and a subset potentially eligible for antibacterial trial enrollment. We compared patient characteristics, treatment exposures, and pneumonia incidence in a European cohort and a previously described US cohort.

Results. Of 888 high-risk patients, 211/888 (24%) were treated for possible pneumonia, and 150/888 (17%) met the Food and Drug Administration definition for hospital-acquired/ventilator-associated bacterial pneumonia. A higher proportion of European patients treated for possible pneumonia met the pneumonia definition (150/211 [71%] vs 537/1464 [37%]; $P < .001$). Among patients developing pneumonia, a higher proportion of European patients met antibacterial trial eligibility criteria (124/150 [83%] vs 371/537 [69%]; $P < .001$).

Conclusions. Clinical criteria prospectively identified high-risk patients with high rates of pneumonia in the European cohort. Despite higher rates of established risk factors and incident pneumonia, European patients were significantly less likely to receive antibiotics for possible pneumonia than US patients. Different treatment practices may contribute to lower rates of antibacterial trial enrollment in the United States.

Keywords. antibacterial agent; bacterial pneumonia; health care–associated pneumonia; intensive care unit; mechanical ventilator.

New antibacterial agents with proven efficacy in the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) are needed to combat increasing rates of infection caused by antimicrobial-resistant pathogens [1, 2]. Additionally, unanticipated limitations of currently available antibacterial drugs initially approved for other clinical indications underscore the need to rigorously evaluate new antibacterial agents in well-designed HABP/VABP clinical trials [3–6]. Despite the urgent need, few registrational trials evaluating new antibacterial agents for HABP/VABP treatment have been completed over the past decade [7–12]. Multiple contributors to the economic inefficiencies of HABP/VABP antibacterial development have been identified [13]. Declining rates of nosocomial pneumonia and high rates of screening failure, partially due to prolonged exposure to potentially effective prior antibacterial drug therapy, are commonly implicated drivers of excessive clinical trial cost [14, 15].

We recently reported findings from a large cohort of critically ill patients hospitalized in 28 US centers who were prospectively identified as high risk for developing HABP/VABP [16].

Received 18 January 2022; editorial decision 25 April 2022; accepted 06 May 2022; published online 9 May 2022

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https://doi.org/10.1093/ofid/ofac231

Of the 4613 patients enrolled, 32% received antibacterials for treatment of possible nosocomial pneumonia and 12% developed HABP or VABP during their intensive care unit (ICU) course. Whether these findings are applicable in critically ill populations outside the United States, where different epidemiology or treatment practices exist, is unknown. In contemporary antibacterial drug registrational trials, the vast majority of patients are enrolled outside the United States [7, 17]. The underlying drivers of the higher HABP/VABP clinical trial enrollment rates observed in Europe, vs the United States, are not well characterized.

The Clinical Trials Transformation Initiative (CTTI) HABP/VABP studies team designed this multicenter cohort study of prospectively identified patients in Europe, which (1) defined the incidence of HABP/VABP in a cohort of critically ill patients fulfilling previously described high-risk clinical criteria; (2) estimated the proportion of HABP/VABP patients eligible for enrollment in nosocomial pneumonia antibacterial drug trials; and (3) compared patient characteristics and treatment exposures in contemporary European and US cohorts to better understand observed differences in HABP/VABP incidence and clinical trial eligibility.

METHODS

Study Design

This multicenter, prospective, observational cohort study was conducted in the ICUs of 7 European hospitals before the COVID-19 pandemic. Enrolling sites comprised a diverse group of community and academic medical centers with a median size (range) of 850 (600–1300) inpatient beds located in Belgium (1), Spain (2), and the Netherlands (4). The study protocol was identical to that employed in the CTTI US cohort study and has been previously described [16]. Briefly, eligible adult patients admitted to the ICUs of participating centers were screened for the presence of predefined risk factors for HABP/VABP development. Patients meeting the study-defined high-risk criteria were enrolled and prospectively followed through their ICU stay for exposure to antibacterial drugs administered for treatment of possible nosocomial pneumonia.

Patient Consent

The study protocol was approved, and a waiver of informed consent was granted by an independent review board (Copernicus Group, CTTI_001, DCR2-15-710) or, when required, the institutional review board of participating US institutions, and by ethics committees from each country in Europe.

Definitions

The high-risk population was defined as patients receiving high levels of respiratory support (invasive mechanical ventilation, noninvasive ventilation, or treatment with at least 50% fraction of inspired supplemental oxygen delivered by partial or nonrebreather mask, aerosol mask, or high-flow, high-humidity nasal cannula for a minimum of 12 hours within any 24-hour period in the 7 days before enrollment) (Supplementary Table 1). Additionally, high-risk patients lacked criteria to fulfill the study HABP/VABP definition upon enrollment. The treated population was defined as the subset of high-risk patients with antibacterials for treatment of possible pneumonia ordered in the electronic health record before ICU discharge. Antibacterial drug indications were assigned by review of clinician documentation and indications associated with antibacterial drug orders. Antibacterial drugs administered for the treatment of clinically suspected pneumonia or suspected pneumonia-induced sepsis were included. The HABP/VABP population was defined as the subset of the treated population fulfilling the study HABP/VABP definition. The HABP/VABP study definition required the presence of at least 1 criterion from the radiographic criteria, systemic inflammation, timing of symptom onset, and respiratory signs and symptoms domains (Supplementary Table 2). The study HABP/VABP definition was identical to the US PROPHETIC study definition previously developed for consistency with treatment guidelines and the US Food and Drug Administration's (FDA's) draft guidance to industry for HABP/VABP drug development [16, 18, 19]. Because this study was designed to estimate the number of high-risk patients who might be eligible for enrollment in antibacterial trials submitted to the US FDA in support of approval of new HABP/VABP treatments, European regulatory agency recommendations were not incorporated into a modified study HABP/VABP definition.

Outcomes

The primary outcome was the proportion of prospectively identified high-risk patients meeting the study HABP/VABP definition. The key secondary outcome was the proportion of HABP/VABP patients meeting FDA-recommended eligibility criteria for enrollment in an HABP/VABP antibacterial trial.

Statistical Analyses

All statistical analyses were performed in the prespecified study populations. Patient characteristics and treatment exposures were summarized as frequencies and percentages for categorical variables and as medians with 25th and 75th percentiles for continuous variables. The Wilcoxon rank-sum test was used to compare the continuous variables of interest between the European and US populations. The Pearson chi-square test or Fisher exact test was used for the categorical variables. Utilizing the same methodology employed in the US cohort, a multivariable logistic regression model was developed to evaluate and compare patient characteristics and treatment exposures associated with an increased risk of HABP/VABP development during the ICU course [16]. Briefly, only variables

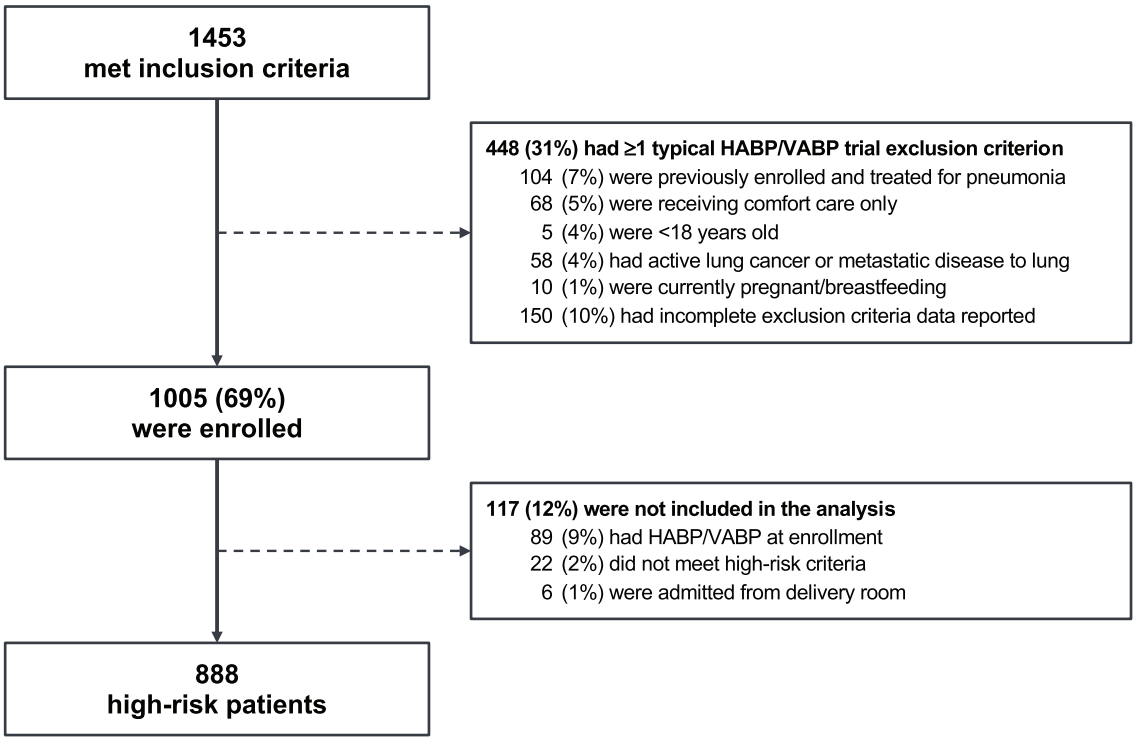


Figure 1. Screening, eligibility, and enrollment of ICU patients at risk for nosocomial pneumonia. Abbreviations: HABP/VABP, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia; ICU, intensive care unit.

documented upon enrollment into the high-risk population were evaluated in the multivariable model. Final predictors identified using clinical guidance and a backward variable selection process at the .1 level of significance for model inclusion were confirmed independently using a forward variable selection process. The discriminatory capacity of the multivariable model was assessed using the c-statistic. Goodness of fit for the multivariable model was assessed with the Hosmer-Lemeshow test. SAS, version 9.4, was used for all analyses.

RESULTS

From June 12 to December 27, 2017, a total of 1005 ICU patients were enrolled: 888 (88%) met the prespecified study criteria and were included in the high-risk population (Figure 1). Among 1005 enrolled patients, 89 (9%) were excluded from the high-risk population because HABP/VABP was present at the time of study enrollment. Of 888 high-risk patients, 150 (17%) met the study HABP/VABP definition. The median hospital length of stay at the time of HABP/VABP development (range) was 8 (5–13) days (Figure 2). Among 142/150 (95%) patients meeting HABP/VABP criteria and exposed to invasive mechanical ventilation, 131 (92%) VABP and 11 (8%) ventilated HABP cases were identified. In the subset of high-risk patients developing VABP, the median duration of invasive mechanical ventilation at the time of VABP diagnosis (range) was 10 (6–15) days.

Demographics, medical comorbidities, and treatment exposures of European high-risk patients were compared with those observed in the contemporary US study cohort (Table 1). High-risk patients in the European cohort were older (63 [51.5–73] vs 61 [50–70] years; $P = .003$), had a lower body mass index (26.2 [23.5–29.9] vs 28.9 [24.1–35.0] kg/m^2; $P < .001$), and were more commonly admitted to a mixed medical–surgical ICU (85% vs 4%; $P < .001$). No significant differences were observed in the rates or duration of exposure to invasive or noninvasive ventilation. Excluding pharmacologic gastric acid suppression and documented aspiration risk, patient characteristics and treatment exposures associated with a higher risk of HABP/VABP development in the US cohort (ICU admission for trauma or cerebrovascular accident, receipt of enteral nutrition, and exposure to systemic antibacterials within the preceding 90 days) were observed in higher proportions of high-risk patients in the European cohort. Selective oropharyngeal decontamination (SOD) or selective decontamination of the digestive tract (SDD) was administered to 356/422 (84%) high-risk patients enrolled in the Netherlands and 4/466 (1%) high-risk patients enrolled in Spain or Belgium. None of the 28 sites enrolling in the United States reported use of SOD or SDD on a site questionnaire.

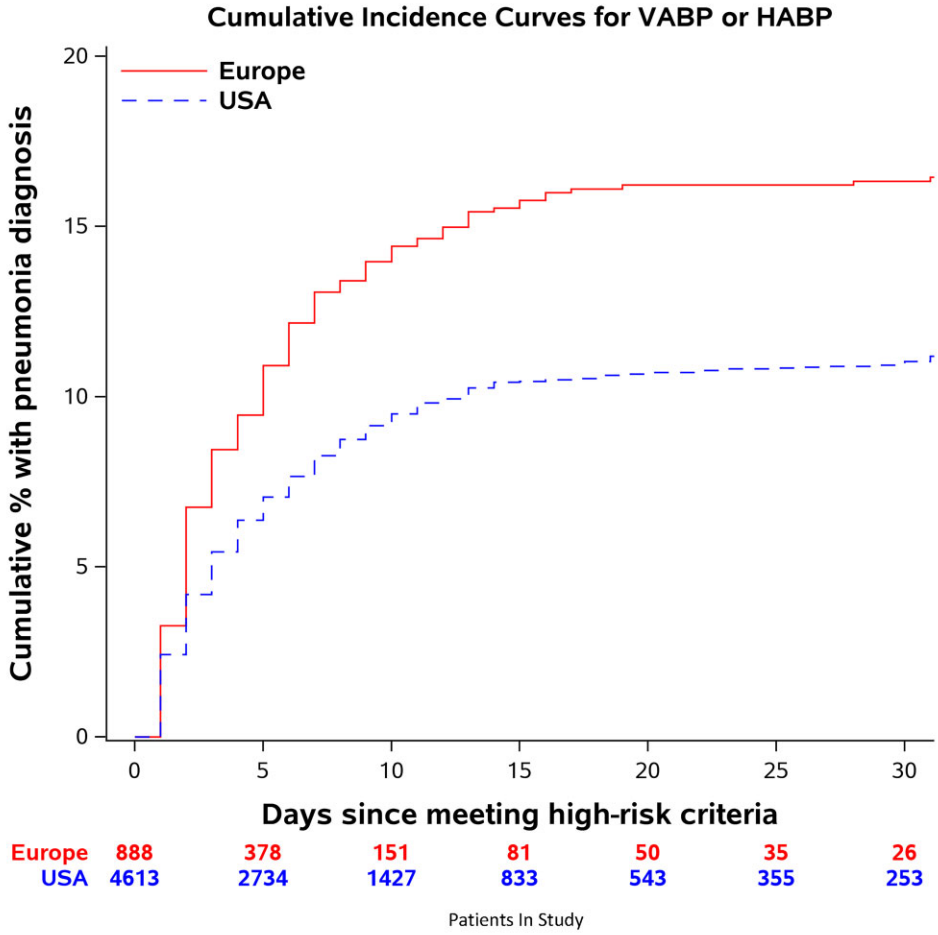


Figure 2. Cumulative incidence of HABP/VABP in Europe and the United States. Abbreviation: HABP/VABP, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia.

In the European high-risk population, 150 of 888 (17%) patients developed HABP/VABP, a significantly higher proportion than that observed in the US high-risk cohort (537/4613 [12%]; $P < .001$) (Figure 3A). Among high-risk patients in the European cohort, 211/888 (24%) received antibiotics for treatment of possible pneumonia, a significantly lower proportion than the 1464/4613 (32%) treated patients observed in the US high-risk cohort ($P < .001$). Whereas 150/211 (71%) high-risk patients treated for pneumonia in the European cohort met the study HABP/VABP criteria, 537/1464 (37%) treated patients in the US cohort fulfilled the HABP/VABP criteria ($P < .001$). In both cohorts, the most common reason that high-risk patients treated for pneumonia did not meet the study HABP/VABP definition was the lack of radiographic criteria (64% in both Europe and the United States). A significantly higher proportion of patients treated for possible pneumonia in the US cohort lacked diagnostic criteria across all required HABP/VABP diagnostic domains (Figure 3B).

Among 150 HABP/VABP patients in the European cohort, 124 (83%), or 14% of the enrolled high-risk population (n = 888), had been exposed to <24 hours of potentially effective antibacterial therapy at the time of HABP/VABP diagnosis, fulfilling the FDA-recommended eligibility criteria for enrollment in HABP/VABP antibacterial trials (Figure 4). In the US cohort, 371/537 (69%) HABP/VABP patients, or 8% of the entire high-risk population, met the recommended HABP/VABP trial eligibility criteria ($P < .001$). Of the 124 HABP/VABP patients meeting recommended eligibility criteria in Europe, 45 (36%) had at least 1 additional exclusion criterion commonly employed in HABP/VABP clinical trials—a significantly lower proportion than the 212/371 (57%) HABP/VABP patients otherwise meeting recommended eligibility criteria in the US cohort ($P < .001$).

The multivariable logistic regression model included all 888 high-risk patients from the European cohort. Consistent with the US model, ICU admission diagnoses of trauma or

Table 1. Characteristics of European and United States Populations at High Risk for Pneumonia

Characteristic	Europe High-Risk Patients (n = 888)	United States High-Risk Patients (n = 4613)	*P* Value
Demographics[a]			
Age, median (IQR), y	63.0 (51.5–73.0)	61.0 (50.0–70.0)	.003
Female sex, No. (%)	302 (34.0)	2058 (44.6)	<.001
Body mass index, median (IQR), kg/m^2	26.2 (23.5–29.9)	28.9 (24.1–35.0)	<.001
Hospital length of stay, median (IQR), d	2.0 (2.0–5.0)	4.0 (3.0–8.0)	<.001
ICU length of stay, median (IQR), d	2.0 (1.0–2.0)	3.0 (2.0–5.0)	<.001
Treatment exposures, No. (%)[b]			
Invasive mechanical ventilation	735 (82.8)	3908 (84.7)	.143
Noninvasive mechanical ventilation	144 (16.2)	751 (16.3)	.962
Enteral nutrition[c]	681 (76.7)	3035 (65.8)	<.001
Vasopressor/inotropic therapy	690 (77.7)	2211 (47.9)	<.001
Biologic agents, current hospitalization	12 (1.4)	169 (3.7)	<.001
Corticosteroids, current hospitalization	142 (16.0)	589 (12.8)	.010
PPI/H-2 blocker, current hospitalization[c]	631 (71.1)	3475 (75.3)	.007
Blood product transfusion, prior 7 d	361 (40.7)	1062 (23.0)	<.001
Systemic antibacterials, prior 90 d[c]	579 (65.2)	2832 (61.4)	.032
Mechanical circulatory support	51 (5.7)	220 (4.8)	.219
Massive volume resuscitation	149 (16.8)	532 (11.5)	<.001
Active medical problems, No. (%)[b,d]			
Acute respiratory distress syndrome	55 (6.2)	686 (14.9)	<.001
Acute kidney injury	174 (19.6)	1078 (23.4)	.014
Chronic kidney disease	59 (6.6)	541 (11.7)	<.001
End-stage renal disease	6 (0.7)	270 (5.9)	<.001
Aspiration risk[c]	49 (5.5)	605 (13.1)	<.001
Autoimmune disorder	32 (3.6)	194 (4.2)	.408
Chemotherapy, prior 30 d	11 (1.2)	139 (3.0)	.003
Diabetes mellitus	190 (21.4)	1304 (28.3)	<.001
Immunocompromised	78 (8.8)	545 (11.8)	.009
Chronic respiratory failure	37 (4.2)	129 (2.8)	.029
Congestive heart failure, NYHA class IV	45 (5.3)	141 (3.3)	.006
Cirrhosis or gastrointestinal bleeding	55 (6.2)	467 (10.1)	<.001
Cerebrovascular accident	114 (12.8)	400 (8.7)	<.001
Substance abuse	212 (23.9)	1289 (27.9)	.013
HIV infection	9 (1.0)	54 (1.2)	.687
Delirium or altered mental status	97 (10.9)	1276 (27.7)	<.001
Seizures	49 (5.5)	417 (9.0)	<.001
Chronic obstructive pulmonary disease	108 (12.2)	804 (17.4)	<.001
Myocardial infarction	65 (7.3)	337 (7.3)	.988
Dialysis (any type)	60 (6.8)	490 (10.6)	<.001
Intensive care unit type, No. (%)			
Medical	34 (3.8)	2468 (53.5)	<.001
Surgical/trauma	18 (2.0)	852 (18.5)	<.001
Cardiac/cardiac surgery	61 (6.9)	769 (16.7)	<.001
Neurosciences	21 (2.4)	350 (7.6)	<.001
Mixed	754 (84.9)	174 (3.8)	<.001
Intensive care admission source, No. (%)			
Emergency department	553 (62.3)	2729 (59.2)	.083
Skilled nursing, long-term acute care	33 (3.7)	177 (3.8)	.863
Scheduled procedure	184 (20.7)	488 (10.6)	<.001
Nonprocedure; clinic or direct admission	37 (4.2)	812 (17.6)	<.001
Other	81 (9.1)	407 (8.8)	.774
Intensive care admission diagnosis, No. (%)			
Acute hypercapnic respiratory failure	25 (2.8)	233 (5.1)	.003
Acute hypoxemic respiratory failure	152 (17.1)	893 (19.4)	.123
Acute myocardial infarction	30 (3.4)	124 (2.7)	.253
Acute renal failure or severe electrolyte abnormality	1 (0.1)	45 (1.0)	.004

Table 1. Continued

Characteristic	Europe High-Risk Patients (n = 888)	United States High-Risk Patients (n = 4613)	*P* Value
Altered mental status	97 (10.9)	337 (7.3)	<.001
Cardiogenic shock	27 (3.0)	86 (1.9)	.028
Cerebrovascular accident[c]	76 (8.6)	191 (4.1)	<.001
Hemorrhagic shock or severe hemorrhage	26 (2.9)	94 (2.0)	.103
Other hypovolemic shock	6 (0.7)	17 (0.4)	.248
Planned postoperative ICU admission	174 (19.6)	475 (10.3)	<.001
Sepsis or septic shock	94 (10.6)	337 (7.3)	<.001
Shock	15 (1.7)	41 (0.9)	.042
Frequent/refractory seizures	49 (5.5)	94 (2.0)	<.001
Trauma[c]	68 (7.7)	275 (6.0)	.056
Other	155 (17.5)	1371 (29.7)	<.001

Abbreviations: H2, histamine blocker; HABP, hospital-acquired bacterial pneumonia; ICU, intensive care unit; IQR, interquartile range; NYHA, New York Heart Association; PPI, proton pump inhibitor; VABP, ventilator-associated bacterial pneumonia.

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

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

[c]Items associated with higher odds of HABP/VABP development in the US cohort.

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

cerebrovascular accident and receipt of enteral nutrition were identified as key patient characteristics and treatment exposures associated with increased odds of meeting the study HABP/VABP end point (Supplementary Table 3). In contrast to the US multivariable model, source of ICU admission, diabetes mellitus, and type of mechanical ventilation exposure were not retained in the final model. No collinearity that would compromise the stability of the model was identified. The multivariable model demonstrated discriminatory capacity, calibration (c-statistic, 0.751 [0.708–0.794]), and no significant lack of fit ($\chi^2 = 7.66$; $P = .468$). SOD/SDD exposure was subsequently added to the multivariable logistic regression model. In the model incorporating this new variable, SOD/SDD exposure was associated with a lower risk of developing HABP/VABP (adjusted odds ratio, 0.56 [0.34–0.93]; $P = .024$). The discriminatory capacity of the multivariable model incorporating SOD/SDD was similar (c-statistic, 0.756 [0.713–0.799]), but the model fit and calibration were less satisfactory than the main model ($\chi^2 = 14.28$; $P = .075$) (Supplementary Table 4).

Microbiologic culture results were reported in 148/150 (99%) high-risk patients meeting the study HABP/VABP definition. At least 1 bacterial pathogen was identified in 104/129 (81%) patients meeting the study criteria for VABP, a significantly higher proportion than in the US cohort (235/357 [66%]; $P = .002$) (Supplementary Table 5). A higher proportion of VABP patients in the European cohort had lower respiratory tract culture results reported (Supplementary Table 6). At least 1 bacterial pathogen was identified in 12/19 (63%) patients meeting the study criteria for HABP (Supplementary Table 7). *Klebsiella* species were most commonly isolated from high-risk patients meeting the VABP criteria in the European cohort. In contrast, *Staphylococcus aureus* was

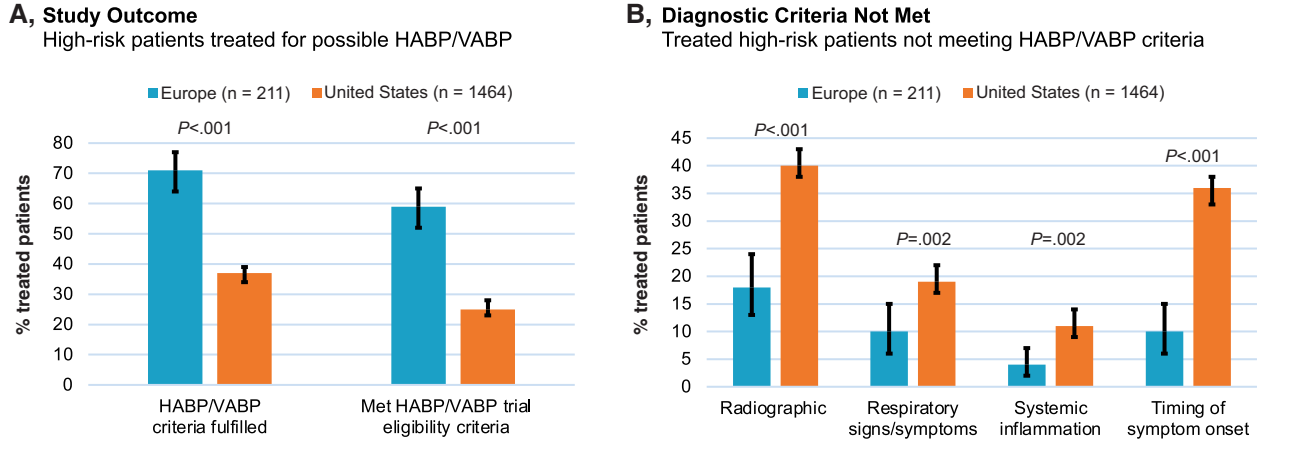
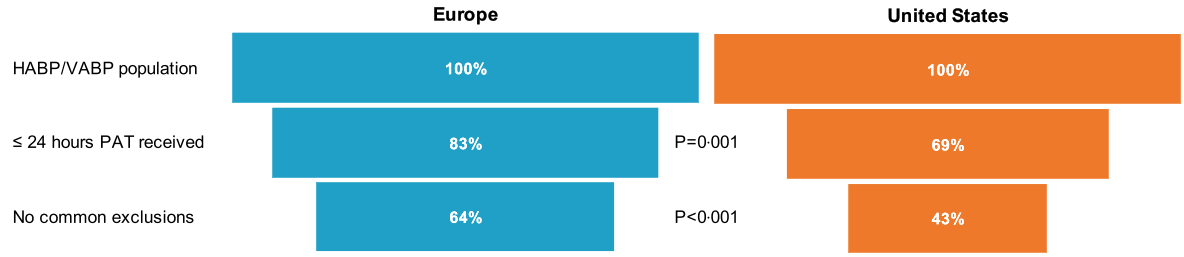


Figure 3. Summary of study outcome (A) and patients lacking diagnostic criteria (B) for high-risk patients treated for possible HABP/VABP. Abbreviation: HABP/VABP, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia.



Prevalence of Common Sponsor-Mandated Exclusion Criteria Among HABP/VABP Patients Meeting Eligibility Criteria Recommended by the United States Food and Drug Administration

Exclusion criterion	Europe HABP/VABP patients (N=124)	United States HABP/VABP patients (N=371)	*P* value
≥1 common exclusion, N (%)	45 (36.2)	212 (57.1)	<.001
Participant in other clinical trial, N (%)	4 (3.2)	13 (3.5)	1
Impaired renal function, N (%)			
eGFR <50 mL/min/1.73m^2	31 (25.0)	142 (38.3)	.009
eGFR <30 mL/min/1.73m^2	20 (16.1)	89 (24.0)	.077
eGFR <10 mL/min/1.73m^2	1 (0.8)	12 (3.2)	.201
Receiving dialysis	6 (4.8)	19 (5.1)	.901
Immunocompromised, N (%)			
Receiving chemotherapy	1 (0.8)	9 (2.4)	.464
Stem cell transplant recipient	0 (0.0)	5 (1.3)	
Chronic pulmonary disease, N (%)			
Interstitial lung disease	2 (1.6)	10 (2.7)	.739
Cystic fibrosis	1 (0.8)	1 (0.3)	.439
Hepatic dysfunction, severe, N (%)	6 (4.8)	41 (11.1)	.041
Seizure disorder, N (%)	7 (5.6)	39 (10.5)	.106

Abbreviations: eGFR, estimated glomerular filtration rate; HABP, hospital-acquired bacterial pneumonia; PAT, prior antibacterial therapy; VABP, ventilator-associated bacterial pneumonia

Figure 4. Comparison of HABP/VABP patients eligible for trial enrollment. Abbreviation: HABP/VABP, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia.

most commonly isolated from patients meeting the study HABP or VABP criteria in the US cohort.

DISCUSSION

Three important observations were derived from this large contemporary, prospectively enrolled cohort of critically ill patients. First, HABP/VABP remains a common complication of critical illness. Application of simple clinical criteria effectively identified a cohort of patients at high risk; 17% of these prospectively identified high-risk patients met standard case definitions for HABP or VABP during their ICU course. Second, the majority of prospectively identified high-risk patients meeting the standard HABP/VABP diagnostic criteria are potentially eligible for enrollment in antibacterial clinical trials: 83% of patients in Europe and 69% of those in the US who met the study HABP/VABP definition also met the FDA-recommended eligibility criteria for enrollment in an antibacterial trial. Third, a higher HABP/VABP incidence in the European cohort, combined with lower rates of antibiotic prescription for patients not meeting the HABP/VABP diagnostic criteria, may underlie reported discrepancies in HABP/VABP antibacterial trial enrollment rates and feasibility between Europe and the United States. These pivotal observations advance our understanding of the contemporary burden of nosocomial pneumonia, the prevalence of common trial exclusion criteria in the HABP/VABP population, and differences in European and US high-risk populations, which may inform future HABP/VABP registrational trial design and feasibility.

Low enrollment rates underlying the poor feasibility of HABP/VABP antibacterial registrational trials are well documented and have not significantly changed over the past 2

decades [7, 13, 15]. A decreasing incidence of VABP has been proposed as a contributor to low enrollment rates. The CTTI HABP/VABP study team recently published findings from a large cohort of critically ill patients requiring significant respiratory support in the United States in which 32% of high-risk patients received antibacterial treatment for possible HABP/VABP and 12% of the high-risk population ultimately met the clinical criteria for HABP/VABP during their ICU course [16]. In this cohort of high-risk patients enrolled from the ICUs of 7 European hospitals, a significantly higher incidence of HABP/VABP was observed: 17% of the high-risk population met the study HABP/VABP definition. This observation stands in contrast to surveillance data suggesting declining rates of nosocomial pneumonia, providing additional evidence that HABP/VABP remains a common complication of critical illness, at least among patients already requiring significant respiratory support [1, 20]. This study was not designed to estimate the incidence of HABP outside the ICU setting, but the findings suggest that declining rates of HABP/VABP in critically ill patients are not a significant driver of low enrollment rates in HABP/VABP registrational trials.

A high prevalence of prior antibiotic exposure and medical comorbidities resulting in clinical trial ineligibility has also been implicated as a driver of low enrollment in HABP/VABP registrational trials. Prior effective antibacterial therapy can significantly confound the evaluation of study drug efficacy in pneumonia noninferiority trials [21]. US FDA guidance for industry recommends excluding patients exposed to >24 hours of potentially effective antibacterial therapy from enrollment in HABP/VABP registrational trials [18]. Because exposure to broad-spectrum antibacterials is common in critically ill patients, this exclusion criterion has been implicated as a significant determinant of clinical trial enrollment. Our findings suggest that exposure to prior effective antibiotic therapy would result in HABP/VABP registrational trial ineligibility in a minority of HABP/VABP patients. Among high-risk patients meeting the study HABP/VABP definition, 17% in the European cohort and 31% in the US cohort had been exposed to >24 hours of potentially effective antibiotic therapy at the time of HABP/VABP diagnosis. This observation may overestimate the number of patients excluded because of prior effective antibacterial therapy, as we were unable to estimate the proportion of HABP/VABP patients with progressive pneumonia despite prolonged exposure to antibacterials—for whom registrational trial enrollment would be appropriate because the prior antibacterial regimen failed. Although not required by regulatory agencies, additional exclusion criteria are commonly incorporated into HABP/VABP antibacterial trial protocols. Our observations suggest that these additional exclusion criteria may reduce registrational trial enrollment rates more than excessive prior antibacterial therapy exposure (Figure 4). Among enrolled patients meeting FDA-recommended registrational trial eligibility criteria, 36% of those enrolled in Europe and 57% of those from the US cohort had at least 1 additional exclusion criterion commonly incorporated into eligibility criteria for HABP/VABP registrational trials conducted over the past 2 decades. These findings advance our understanding of the impact of incorporating additional exclusion criteria into HABP/VABP registrational trial protocols, suggesting that design of pragmatic trials with fewer sponsor-mandated exclusion criteria may significantly improve antibacterial trial feasibility.

Contemporary comparisons of high-risk patient characteristics, treatment exposures, HABP/VABP incidence, and prevalence of common HABP/VABP registrational trial exclusion criteria are essential to understanding observed regional variation in clinical trial enrollment rates [7,17]. In this study, a significantly higher incidence of patients who met the HABP/VABP study criteria was observed in the European high-risk cohort: 17% vs 12% in the US cohort ($P < .001$). A higher prevalence of established risk factors for HABP/VABP in the European high-risk population (primary ICU admission diagnoses of trauma or cerebrovascular accident, receipt of enteral nutrition, receipt of systemic antibacterials within the preceding 90 days) may partially account for this difference. Whether other treatment exposures, specifically the threshold to administer empiric antibacterials for suspected nosocomial pneumonia, influence the observed differences in HABP/VABP incidence is unknown. Despite a lower incidence of HABP/VABP, high-risk patients in the US cohort were treated with antibiotics for possible nosocomial pneumonia significantly more than those patients in the European cohort: 32% vs 24% of high-risk patients ($P < .001$). In the US cohort, 63% of high-risk patients receiving antibacterials for possible nosocomial pneumonia did not meet the study criteria for HABP/VABP; a significantly lower proportion was observed in the European cohort (29%; $P < .001$). This diagnostic outcome discrepancy was driven primarily by the lack of radiographic criteria in treated high-risk US patients (40% vs 18% in the European cohort; $P < .001$). It is unknown if a lower threshold to treat ventilator-associated tracheobronchitis in the US cohort, which has been associated with a lower risk of progression to VABP, influenced the discrepancy in observed VABP rates [22]. Although the design of this study precludes direct evaluation, these observations raise concern for antibiotic overprescription for syndromes that do not fulfill the standard HABP/VABP criteria, which may increase the risk for adverse events and underlie observed differences in the proportion of HABP/VABP patients meeting FDA-recommended eligibility criteria for registrational trial enrollment.

This study has important limitations. First, because only ICU patients meeting predefined high-risk criteria (a requirement for high levels of respiratory support) were enrolled, nonventilated HABP, which comprises the largest proportion of

nosocomial pneumonia, is underrepresented [23]. The findings of this study may not apply to patients not meeting the study high-risk definition. Second, the observations derived from these cohorts enrolled in the United States and Western Europe may not be generalizable to high-risk patients in Eastern Europe or other parts of the world. The primary reason we enrolled patients in both the European Union and the United States was to evaluate drivers of documented regional variability in HABP/VABP incidence and HABP/VABP registrational trial enrollment [1, 13]. However, data from HABP/VABP registrational trials submitted to the US FDA since 2015 suggest that enrollment rates at Western European and North American sites are relatively similar and among the lowest observed worldwide [7]. Because we did not enroll patients from regions of the world associated with the highest HABP/VABP trial enrollment rates, we cannot evaluate key drivers of these discordant enrollment rates. While this study may not be generalizable to regions with historically higher registrational trial enrollment rates (Eastern Europe, Asia, South America), the findings significantly enhance our understanding of HABP/VABP trends and potentially eligible HABP/VABP patient populations in regions where these critical registrational trials are less feasible. Third, because this was an observational cohort study, other unmeasured differences between the enrolled European and US cohorts may have influenced the observed differences in treatment exposures, HABP/VABP incidence, and estimated rates of registrational trial eligibility. Fourth, it is possible that changes in patient characteristics or treatment practices since enrollment completion in 2017 diminish the applicability of these findings to the design of new HABP/VABP antibacterial drug trials. Fifth, the duration of study enrollment precluded an analysis of seasonal trends in HABP/VABP incidence and treatment exposures that may be impacted by prevalence of viral pneumonia [24]. Finally, whether enrollment of the European cohort in a different season and beginning ~9 months after completion of US enrollment contributed to observed differences in treatment patterns or HABP/VABP incidence is unknown.

CONCLUSIONS

In conclusion, applying simple clinical criteria effectively identified a cohort of critically ill patients at high risk for developing HABP/VABP in Europe and the United States. Most prospectively identified high-risk patients developing nosocomial pneumonia met the recommended eligibility criteria for enrollment in HABP/VABP registrational drug trials. Differences in patient characteristics and treatment practices may contribute to observed differences in registrational trial enrollment. An improved understanding of these differences and applying simple clinical criteria to prospectively identify patients at high risk for HABP/VABP may improve registrational trial feasibility and foster development of new antibacterial treatments for nosocomial pneumonia.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

Financial support. This publication was supported by the Food and Drug Administration (FDA) of the US Department of Health and Human Services (HHS) as part of as part of an award totaling $3 778 241.33 with 15% financed with nongovernmental sources. Partial funding was also provided by pooled membership fees from CTTI's member organizations (https://www.ctti-clinicaltrials.org/membership). The contents are those of the authors and do not necessarily represent the official views of, nor an endorsement by, the FDA/HHS or the US Government. Dr. Fowler was supported by midcareer mentoring award K24-AI093969 from the National Institutes of Health.

Potential conflicts of interest. S. P. Bergin: Dr. Bergin reports consulting for Aridis Pharmaceuticals and C3J Therapeutics. S. B. Calvert: Dr. Calvert reports salary support from US FDA grant R18FD005292 and CTTI membership fees. J. Farley: Dr. Farley reports no conflicts related to this work. J.-L. Sun: Ms. Sun reports no conflicts related to this work. K. Chiswell: Dr. Chiswell reports no conflicts related to this work. W. Dieperink: Dr. Dieperink reports no conflicts related to this work. J. Kluytmans: Dr. Kluytmans reports no conflicts related to this work. J. C. Lopez-Delgado: Dr. Lopez-Delgado reports no conflicts related to this work. R. Leon-Lopez: Dr. Leon-Lopez reports no conflicts related to this work. M. J. Zervos: Dr. Zervos reports serving as a consultant for ContraFect and receiving research grants from Merck, Moderna, Janssen, Pfizer, and Serono. M. H. Kollef: Dr. Kollef reports support from the Barnes-Jewish Hospital Foundation. M. Sims: Dr. Sims reports grants from Aridis Pharmaceuticals Inc., Cidara Therapeutics, ContraFect, Cubist Pharmaceuticals Inc. (now Merck), Curetis Ag, Curetis GmBM, CutisPharma, DiaSorin Molecular LLC, Epigenomics Inc., EUROIMMUN US, Finch Therapeutics, Genentech USA Inc., Gilead Sciences, IBIS Biosystems, Iterum Therapeutics, Janssen Research and Development, LLC, Kinevant Sciences GmBH, Leonard-Meron Biosciences, Merck, Nabriva Therapeutics, NeuMoDx Molecular, Paratek Pharmaceuticals, Pfizer, Prenosis, Regeneron Pharmaceuticals, Sanofi Pasteur Inc., Seres Therapeutics Inc., Shire, Summit Therapeutics. B. A. Kabchi: Dr. Kabchi reports no conflicts related to this work. D. Rubin: Dr. Rubin reports no conflicts related to this work. J. Santiago: Dr. Santiago reports no conflicts related to this work. M. Natarajan: Dr. Natarajan reports no conflicts related to this work. P. Tenaerts: Dr. Tenaerts reports salary support from US FDA grant R18FD005292 and CTTI membership fees. V. G. Fowler Jr.: Dr. Fowler reports serving as chair of the V710 Scientific Advisory Committee (Merck); has received grant support from Cerexa/Actavis/Allergan, Pfizer, Advanced Liquid Logics, NIH, MedImmune, Basilea Pharmaceutica, Karius, ContraFect, Regeneron Pharmaceuticals, and Genentech; has NIH Small Business Technology Transfer/Small Business Innovation Research grants pending with Affinergy, Locus, and Medical Surface; has been a consultant for Achaogen, Astellas Pharma, Arsanis, Affinergy, Basilea Pharmaceutica, Bayer, Cerexa Inc., ContraFect, Cubist, Debiopharm, Durata Therapeutics, Grifols, Genentech, MedImmune, Merck, the Medicines Company, Pfizer, Novartis, NovaDigm Therapeutics Inc., Theravance Biopharma, and XBiotech; has received honoraria from Theravance Biopharma and Green Cross; and has a patent pending in sepsis diagnostics. T. L. Holland: Dr. Holland reports consulting for Basilea Pharmaceutica (ceftobiprole), Genentech (immunotherapeutic), Motif Bio (iclaprim), Aridis (monoclonal antibody), and Lysovant (lysin). M. J. Bonten: Mr. Bonten reports no conflicts related to this work. S. J. Hullegie: Mr. Hullegie reports grants from ZonMW outside the submitted work. All authors have submitted the ICMJE Form for

Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Author contributions. S.P.B., S.B.C., J.F., D.R., J.S., P.T., V.G.F., and T.H. conceptualized and contributed to the design of the study. S.P.B. wrote the original draft of the manuscript. S.P.B., S.B.C., J.L.S., K.C., and T.L.H. verified the underlying data in the manuscript. J.L.S. and K.C. formally analyzed the data. W.D., J.K., J.C.L.-D., R.L.-L., M.J.Z, M.H.K., M.S., and B.A.K. contributed to the investigation. S.P.B., S.B.C., T.L.H., S.H., P.T., V.G.F., and M.J.B were involved with project administration and supervision. All authors contributed to data interpretation and reviewed and edited the manuscript. All authors had full access to all the data in the study and accept final responsibility to submit for publication.

Data availability. Data collected for the study will be made publicly available via a data sharing platform. Data have been de-identified, and CTTI will take all necessary measures to ensure that patient privacy is safeguarded. A version of this article has been posted on a preprint server, which can be accessed via the following link: https://papers.ssrn.com/sol3/papers.cfm? abstract_id=3907471.

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