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A cohort study of bacteremic pneumonia: The importance of antibiotic resistance and appropriate initial therapy?

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A cohort study of bacteremic pneumonia

The importance of antibiotic resistance and appropriate initial therapy?

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Abstract

Bacteremic pneumonia is usually associated with greater mortality. However, risk factors associated with hospital mortality in bacteremic pneumonia are inadequately described.

The study was a retrospective cohort study, conducted in Barnes-Jewish Hospital (2008–2015). For purposes of this investigation, antibiotic susceptibility was determined according to ceftriaxone susceptibility, as ceftriaxone represents the antimicrobial agent most frequently recommended for hospitalized patients with community-acquired pneumonia as opposed to nosocomial pneumonia. Two multivariable analyses were planned: the first model included resistance to ceftriaxone as a variable, whereas the second model included the various antibiotic-resistant species (methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae*).

In all, 1031 consecutive patients with bacteremic pneumonia (mortality 37.1%) were included. The most common pathogens associated with infection were *S aureus* (34.1%; methicillin resistance 54.0%), *Enterobacteriaceae* (28.0%), *P aeruginosa* (10.6%), anaerobic bacteria (7.3%), and *Streptococcus pneumoniae* (5.6%). Compared with ceftriaxone-susceptible pathogens (46.8%), ceftriaxone-resistant pathogens (53.2%) were significantly more likely to receive inappropriate initial antibiotic treatment (IIAT) (27.9% vs 7.1%; $P < 0.001$) and to die during hospitalization (41.5% vs 32.0%; $P = 0.001$). The first logistic regression analysis identified IIAT with the greatest odds ratio (OR) for mortality (OR 2.2, 95% confidence interval [CI] 1.5–3.2, $P < 0.001$). Other independent predictors of mortality included age, mechanical ventilation, immune suppression, prior hospitalization, prior antibiotic administration, septic shock, comorbid conditions, and severity of illness. In the second multivariable analysis that included the antibiotic-resistant species, IIAT was still associated with excess mortality, and *P aeruginosa* infection was identified as an independent predictor of mortality (OR 1.6, 95% CI 1.1–2.2, $P = 0.047$), whereas infection with ceftriaxone-resistant *Enterobacteriaceae* (OR 0.6, 95% CI 0.4–1.0, $P = 0.050$) was associated with lower mortality.

More than one-third of our patients hospitalized with bacteremic pneumonia died. IIAT was identified as the most important risk factor for hospital mortality and the only risk factor amenable to potential intervention. Specific antibiotic-resistant pathogen species were also associated with mortality.

Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation, CAP = community-acquired pneumonia, CfRE = ceftriaxone-resistant *Enterobacteriaceae*, GNB = Gram-negative bacteria, HAP = hospital-acquired pneumonia, HCAP = healthcare-associated pneumonia, IIAT = inappropriate initial antibiotic treatment, MDR = multidrug-resistant, MLR = multiple logistic regression, OR = odds ratio, VAP = ventilator-associated pneumonia.

Keywords: antibiotics, outcomes resistance, pneumonia

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1. Introduction

Pneumonia remains one of the most important infectious diseases affecting US adults.[1] It is associated with significant hospital length of stay, cost, morbidity, and mortality that does not seem to have improved over the past 2 decades despite important medical advances.[2] Bacteremia complicating pneumonia increases in prevalence among patients with greater severity of disease, becoming most common among critically ill patients.[3–7] Nosocomial bacteremic pneumonia seems to have the greatest risk of mortality and excess length of stay, especially ventilator-associated pneumonia (VAP) and healthcare-associated pneumonia (HCAP).[4,5,8–12] One important factor contributing to high mortality is the antimicrobial resistance patterns exhibited by the microbes responsible for pneumonia.[13] Increasing antimicrobial resistance promotes greater administration of inappropriate initial antibiotic treatment (IIAT) (i.e., an antibiotic regimen without activity against the offending pathogen as demonstrated by in vitro susceptibility testing).[14] This has resulted in the increasing empiric use of broad-spectrum

antimicrobial agents for the treatment of pneumonia to provide more appropriate initial treatment.

Recent studies have attempted to better define the risk factors for pneumonia attributed to antibiotic-resistant pathogens so that broad-spectrum antimicrobial therapy can be more accurately targeted.[15–20] Unfortunately, the identified risk factors overlap for antibiotic-resistant Gram-positive pathogens like methicillin-resistant *Staphylococcus aureus* (MRSA) and antibiotic-resistant Gram-negative bacilli (GNB), including *Pseudomonas aeruginosa*, *Acinetobacter* spp, and antibiotic-resistant *Enterobacteriaceae*. To date, few studies have attempted to establish specific risk factors or combinations of risk factors that predict ceftriaxone resistance, the cornerstone of antimicrobial therapy for community-acquired pneumonia (CAP). Predicting ceftriaxone resistance would implicitly modify empirical therapy in patients with suspected pneumonia. Therefore, we sought to identify risk factors for mortality in patients with bacteremic pneumonia and risk factors for various ceftriaxone-resistant microbes.

2. Methods

2.1. Study population and data Source

The study was conducted at Barnes-Jewish Hospital, an academic referral center of 1250 beds. This investigation was approved by the Washington University School of Medicine Human Studies Committee and the University of New Mexico Human Research Protections Office, and the need for informed consent was waived. All hospitalized patients between January 2008 and April 2015 with pneumonia complicated by secondary bacteremia were eligible for inclusion. Data were collected from the hospital's electronic health record system provided by the Center for Clinical Excellence, BJC Healthcare.

2.2. Study outcomes

The primary objective of this study was to determine whether markers of antibiotic resistance (ceftriaxone resistance) and specific antibiotic-resistant bacterial species (MRSA, *P aeruginosa*, ceftriaxone-resistant *Enterobacteriaceae* [CfRE]) are risk factors for mortality in patients with bacteremic pneumonia. The secondary objective of this study was to identify variables predicting bacteremic pneumonia due to specific antibiotic-resistant bacteria (MRSA, *P aeruginosa*, CfRE).

2.3. Definitions and study design

Adult patients (age >18 years) were identified retrospectively with bacteremic pneumonia in accordance with the American Thoracic Society's position statement on nosocomial pneumonia.[21] The diagnosis included presence of a new or progressive radiographic infiltrate and at least 2 of the following clinical features: fever greater than 38°C, leukocytosis ($>10 \times 10^9$ cells/L), leukopenia ($\leq 4 \times 10^9$ cells/L), or purulent secretions. 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 were reviewed by 1 of the investigators to confirm the radiographic findings (MHK) and to identify patients meeting the case definition for pneumonia (CVG, STM). Patients also had to have bacteremia defined as presence of at least 1 positive blood culture for true pathogens. Septic shock was defined as the need for vasopressors (norepinephrine, dopamine, vasopressin, epinephrine, phenylephrine). Only the first episode of bacteremic pneumonia was recorded. Antimicrobial treatment was classified as appropriate if the regimen had in vitro activity demonstrated against the isolated pathogens and as IIAT if the regimen did not demonstrate in vitro activity. In vitro antimicrobial susceptibility relied on standard published breakpoints.[22] Patients with pneumonia and bacteremia due to a nonpneumonic source (e.g., patient with *P aeruginosa* pneumonia and MRSA catheter-associated blood stream infection) were excluded from the study cohort.

Immunosuppression was defined as the acquired immune deficiency syndrome, solid organ or bone marrow transplant, hematologic malignancies, solid cell cancers treated with chemotherapy or radiation, long-term corticosteroids (>10 mg/d), and other immunosuppressive drugs (e.g., biologics for rheumatologic disorders). For purposes of this investigation, antibiotic susceptibility was determined according to ceftriaxone susceptibility, as ceftriaxone represents the antimicrobial agent most frequently recommended for hospitalized patients with CAP as opposed to nosocomial pneumonia.[2,21] Multidrug-resistant (MDR) pathogens had to demonstrate in vitro resistance to at least 1 agent from 3 distinct classes of antimicrobials that would normally have activity against that bacterium.[23]

2.4. Antimicrobial monitoring

From January 2002 through the present, Barnes-Jewish Hospital utilized an antibiotic control program to help guide antimicrobial therapy for bacterial infections. During this time, the use of cefepime, gentamicin, or vancomycin was unrestricted. However, initiation of intravenous ciprofloxacin, imipenem, meropenem, piperacillin/tazobactam, linezolid, or daptomycin was restricted and required preauthorization from either a clinical pharmacist or infectious diseases physician. Each intensive care unit (ICU) had a clinical pharmacist who reviewed all antibiotic orders to insure that dosing and interval of antibiotic administration was adequate for individual patients based on body size, renal function, and the resuscitation status of the patient. After daytime hours, the on-call infectious diseases physician reviewed and approved the antibiotic orders.

The initial antibiotic dosages employed for the treatment of bacterial infections at the Barnes-Jewish Hospital were as follows: cefepime, 1 to 2 g every 8 hours; piperacillin–tazobactam, 4.5 g every 6 hours; imipenem, 0.5 g every 6 hours; meropenem, 1 to 2 g every 8 hours; ciprofloxacin, 400 mg every 8 hours; gentamicin, 5 mg/kg once daily; vancomycin, 15 mg/kg every 12 hours; linezolid, 600 mg every 12 hours; and daptomycin, 6 mg/kg every 24 hours (daptomycin was not prescribed for pneumonia).

2.5. Antimicrobial susceptibility testing

The microbiology laboratory performed antimicrobial susceptibility of the bacterial isolates using the disk diffusion method according to guidelines and breakpoints established by the Clinical Laboratory and Standards Institute and published during the inclusive years of the study.[22] All classifications of antibiotic resistance were based on in vitro susceptibility testing using these established breakpoints.

2.6. Data collection and statistical analyses

We collected demographic characteristics (age, race, sex, nursing home residence), comorbidities of interest (hemodialysis, immunosuppression, Charlson score, previous hospitalizations within 90 days, previous bacteremia within 90 days, and prior

antibiotics within 30 days), clinical features (Acute Physiology and Chronic Health Evaluation [APACHE] II, need for vasopressors or mechanical ventilation, central vein catheter, duration of hospitalization before bacteremia), microbiology data (culture results and antibiotic susceptibility), treatment variables, and outcome data (hospital mortality and discharge location).

The sample size was determined by a convenience sample of all the patients with bacteremic pneumonia identified at our institution during the study period. Continuous variables were expressed as means and standard deviations (SDs), or medians and interquartile range (IQR), when appropriate. The *t* test and 1-way analysis of variance (ANOVA) tests were used to analyze normally distributed continuous variables, whereas the Mann–Whitney *U* and Kruskal–Wallis tests were used to analyze non-normally distributed continuous variables. Categorical data were reported as frequency distributions, and analyzed using the chi-square test or McNemar test. We performed univariable and stepwise backward automatic elimination multivariable logistic regression (MLR) analyses to determine variables associated with mortality and variables that contributed to infections caused by MRSA, *P aeruginosa*, and CfRE. We analyzed 2 MLR models for mortality. The first model included resistance to ceftriaxone as a variable, whereas the second model included the various antibiotic-resistant species (MRSA, *P aeruginosa*, and *Enterobacteriaceae*). All variables that reached a significance threshold of ≤ 0.2 in univariable analyses were entered in the multivariable models. We performed diagnostics for colinearity and tested for interactions. Missing values were 7.7% and were handled by multiple imputations. Goodness of fit was estimated using the Hosmer–Lemeshow c-statistic. *P* values less than 0.05 were considered statistically significant, and all tests were 2-tailed. All analyses were done using STATA/SE 13.1 (STATA Corp LP, College Station, TX).

3. Results

One thousand thirty-one consecutive patients with bacteremic pneumonia were identified (Fig. 1). The majority were white males admitted from home, with 10% of the patients residing in a nursing home before admission (Table 1). There were 159 (15.4%) patients with CAP (mortality 27.0%) and 429 (41.6%) patients with HAP (mortality 41.5%). Risk factors for potential infection with antibiotic-resistant pathogens included hemodialysis (9.8%), immunosuppression (34.1%), prior hospitalization (44.7%), and prior antibiotic use (53.1%). The median duration of hospitalization at which the diagnosis of bacteremic pneumonia occurred was hospital day 1 (IQR 0–9 days). The most common pathogens were *S aureus* (34.1%; methicillin resistance 54.0%), *Enterobacteriaceae* (28.0%), *P aeruginosa* (10.6%), anaerobic bacteria (7.3%), and *Streptococcus pneumoniae* (5.6%). Extended-spectrum β-lactamase (ESBL)-producing bacteria and carbapenemase-producing bacteria were uncommon. However, ceftriaxone-resistant bacteria accounted for 53.2%.

Bacteremic pneumonia was associated with MRSA in 190 (18.4%) patients, *P aeruginosa* in 109 (10.6%) patients, and CfRE in 110 (10.7%) patients, with these 3 pathogens accounting for 74.5% of the ceftriaxone-resistant group. Patients infected with ceftriaxone-resistant pathogens were significantly more likely to be immunosuppressed, previously hospitalized or treated with antibiotics, admitted from a nursing home, have longer hospital stays before the onset of infection, require hemodialysis,

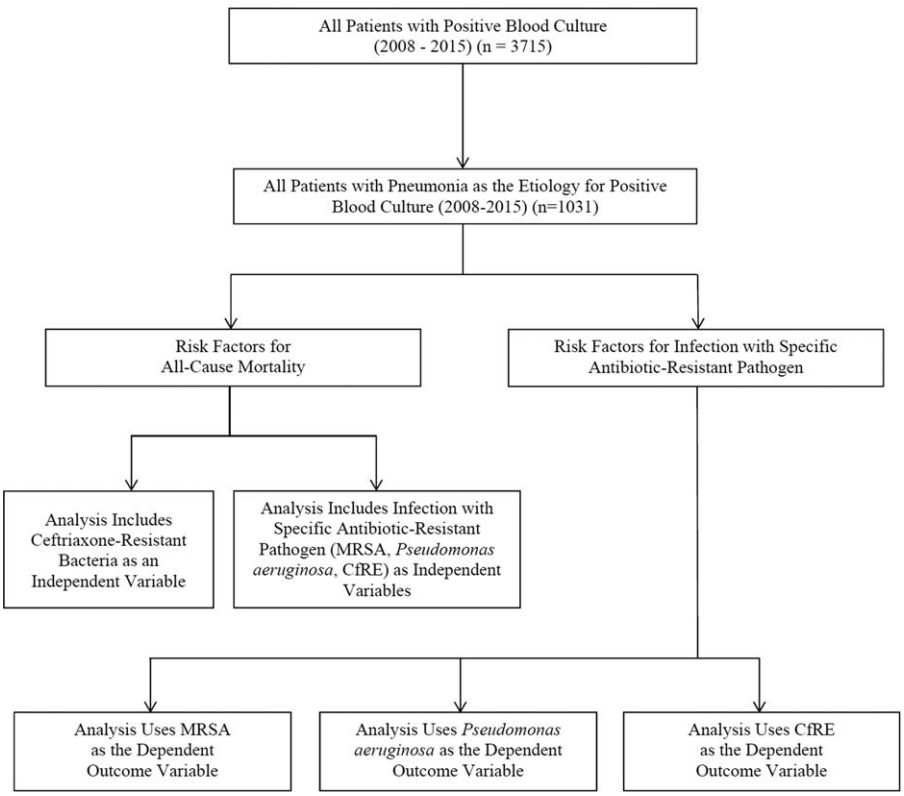

Figure 1. Analysis plan. CfRE = ceftriaxone-resistant *Enterobacteriaceae*, MRSA = methicillin-resistant *Staphylococcus aureus*.

Table 1

Demographics, clinical characteristics, microbiology, and hospital course among 1031 patients diagnosed with bacteremia secondary to pneumonia between 2008 and 2015.

Characteristic	All patients (N = 1031)
Age, y, mean ± SD	58.7 ± 16.1
Sex: male	600 (58.2%)
Race*	
White	678 (65.8%)
African American	305 (29.6%)
Hispanic	1 (0.1%)
Admission source†	
Admission from nursing home	103 (10.0%)
Admission from home	701 (68.0%)
Transferred from a different hospital	215 (20.9%)
Pneumonia type	
CAP	159 (15.4%)
HAP	429 (41.6%)
Duration of hospitalization before infection, d, median (IQR)	1 (0–9)
Bacteria species	
Staphylococcus aureus	352 (34.1%)
MRSA	190 (18.4%)
VISA	15 (1.5%)
Enterobacteriaceae‡	289 (28.0%)
Anaerobes§	75 (7.3%)
Streptococcus pneumoniae	57 (5.6%)
Pseudomonas aeruginosa	109 (10.6%)
Acinetobacter spp	21 (2.0%)
Stenotrophomonas maltophilia	25 (2.4%)
Resistance to ceftriaxone	549 (53.2%)
ESBL producers	16 (1.6%)
Carbapenemase producers	3 (0.3%)
Comorbidities	
Hemodialysis	101 (9.8%)
Immunosuppression	351 (34.0%)
Charlson score	5.5 ± 3.4
Prior hospitalization	461 (44.7%)
Prior antibiotics	547 (53.1%)
Recent surgery	
Abdominal surgery	86 (8.3%)
Nonabdominal surgery	160 (15.5%)
Central vein catheter	493 (47.8%)
Mechanical ventilation	452 (43.8%)
ICU	682 (66.2%)
Septic shock	561 (54.4%)
Peak WBC × 10^3, cells/μL, median (IQR)	17.4 (10.1–29.7)
APACHE II score, mean ± SD	16 ± 6.3
Inappropriate initial antibiotic treatment	187 (18.1%)
Disposition	
Discharge to home	274 (26.6%)
Discharge to nursing home/ rehabilitation	343 (33.3%)
Mortality	382 (37.1%)

Community-acquired pneumonia: patients were admitted from home, no previous hospitalizations within 90 days, no previous antibiotics, no chronic hemodialysis, duration of hospitalization before bacteremic pneumonia of ≤2 days.

HAP definition: duration of hospitalization before bacteremic pneumonia >2 days.

APACHE = Acute Physiology and Chronic Health Evaluation, CAP = community-acquired pneumonia, ESBL = extended spectrum beta-lactamase, HAP = hospital-acquired pneumonia, ICU = intensive care unit, IQR = interquartile range, MRSA = methicillin resistant *Staphylococcus aureus*, SD = standard deviation, VISA = vancomycin-intermediate *Staphylococcus aureus*, WBC = white blood cell count.

* Also Asian, native American, unknown.

† Also prison, unknown.

‡ *Enterobacteriaceae*: *Serratia*, *Enterobacter*, *Citrobacter*, *Klebsiella*, *Escherichia coli*, *Proteus* species.

§ Anaerobes: *Moraxella, Morganella, Prevotella, Fusobacterium, Bacteroides, Clostridium* species.

central vein catheters, and mechanical ventilation (Table 2). Patients infected with ceftriaxone-resistant pathogens were also more likely to receive IIAT (27.9% vs 7.1%; $P < 0.001$) and to have greater hospital mortality (41.5% vs 32.0%; $P = 0.001$).

Among the patients infected with ceftriaxone-resistant pathogens, *P aeruginosa* was associated with the highest rates of immunosuppression and prior hospitalization, whereas infection with CfRE was associated with the highest rates of prior antibiotic exposure, duration of hospitalization before infection, and presence of a central vein catheter (Table 3). Bacteremic pneumonia due to CfRE had the highest rate of IIAT, whereas *P aeruginosa* was associated with the greatest risk of mortality. Independent risk factors associated with MRSA, *P aeruginosa*, and CfRE are shown in Table 4, confirming the associations observed in the univariable analyses for *P aeruginosa* and CfRE (see Supplemental Tables 1 through 4 for the univariate analyses, http://links.lww.com/MD/B237).

3.1. Logistic regression analysis for hospital mortality

The 2 MLR analyses performed to identify factors associated with hospital mortality, along with the univariable analyses, are shown in Table 5. The first logistic regression analysis for hospital mortality, which included resistance to ceftriaxone as an independent variable, identified IIAT with the greatest odds ratio (OR) for hospital mortality (OR 2.2, 95% confidence interval [CI] 1.5–3.2, $P < 0.001$) (Table 5). Other independent predictors of hospital mortality included age, mechanical ventilation, immune suppression, prior hospitalization, prior antibiotic administration, septic shock, comorbid conditions, and severity of illness. Resistance to ceftriaxone was not independently associated with mortality. The second MLR analysis, which included specific pathogens (*P aeruginosa*, CfRE, MRSA) as independent variables, also found IIAT to be associated with the greatest OR for hospital mortality (OR 2.3, 95% CI 1.6–3.2, $P < 0.001$) and demonstrated that infection with *P aeruginosa* was independently associated with greater mortality, whereas CfRE infection was associated with a lower risk of mortality (Table 5).

4. Discussion

In our study, we found that more than one-third of patients with bacteremic pneumonia died during their hospitalization. IIAT was identified as the most important risk factor for hospital mortality and the only risk factor potentially amenable to intervention. We also identified differences in risk factors for infection with various ceftriaxone-resistant bacteria. However, the risk factors were general markers of disease severity or tended to overlap between pathogens as shown by prior hospitalization being associated with *P aeruginosa* infection and prior antibiotic use predicting infection with CfRE. These findings support the clinical importance of timely appropriate antibiotic treatment to optimize clinical outcomes regardless of the antibiotic-resistant pathogen causing bacteremic pneumonia.

Several earlier studies have attempted to develop prediction models for infection attributed to antibiotic-resistant bacteria in patients with pneumonia. The definitions used for antibiotic-resistant pathogens were either similar to ours centering on resistance to drugs empirically used in the treatment of CAP,[17] whereas others were more stringent including only MRSA, *P aeruginosa*, and ESBL or carbapenemase-producing *Enterobacteriaceae*.[15,16,18,20] From a practical treatment perspective determining which empiric antibiotic regimen to administer to patients with pneumonia usually hinges on whether the clinician considers the offending pathogens to be resistant to the typical empiric regimen prescribed for CAP (ceftriaxone plus a macrolide

Table 2

Comparison between ceftriaxone-susceptible and ceftriaxone-resistant bacteria.

Characteristic	Ceftriaxone-susceptible (n = 482)	Ceftriaxone-resistant (n = 549)	*P*
Age, y, mean ± SD	58.9 ± 16.4	58.4 ± 15.8	0.636
Male sex	287 (59.5%)	313 (57.0%)	0.411
Race*			0.775
White	310 (64.3%)	368 (67.0%)	
African American	150 (31.1%)	155 (28.2%)	
Pneumonia type			
CAP	107 (22.2%)	52 (9.5%)	<0.001
HAP	163 (33.8%)	266 (48.5%)	<0.001
Nursing home residence	37 (7.7%)	66 (12.0%)	0.020
Hemodialysis	36 (7.5%)	65 (11.8%)	0.018
Immunosuppression	147 (30.5%)	204 (37.2%)	0.026
Prior hospitalization	184 (38.2%)	277 (50.5%)	<0.001
Prior antibiotics	209 (43.4%)	338 (61.6%)	<0.001
Charlson score	5.5 ± 3.5	5.5 ± 3.4	0.872
Central vein catheter	187 (38.8%)	306 (55.7%)	<0.001
Surgery			0.004
Abdominal	39 (8.1%)	47 (8.6%)	
Nonabdominal	56 (11.7%)	104 (18.9%)	
Duration of hospitalization before bacteremia, d, median (IQR)	0 (0–5)	2 (0–14)	0.001†
Mechanical ventilation	191 (39.6%)	261 (47.5%)	0.011
ICU	308 (63.9%)	374 (68.1%)	0.153
Septic shock	261 (54.1%)	300 (54.6%)	0.873
APACHE II score, mean ± SD	15.9 ± 6.2	16.1 ± 6.4	0.555
Peak WBC × 10^3, cells/μL, median (IQR)	18 (11–31)	17 (9.1–28.5)	0.045†
Inappropriate initial antibiotic treatment	34 (7.1%)	153 (27.9%)	<0.001
Discharge to skilled nursing facility	157 (32.6%)	186 (33.9%)	0.657
Mortality	154 (32.0%)	228 (41.5%)	0.001

Resistant to ceftriaxone: methicillin-resistant *Staphylococcus aureus*: 190 (34.6%); *Pseudomonas aeruginosa*: 109 (19.9%); *Acinetobacter* species: 20 (3.6%); *Stenotrophomonas maltophilia*: 25 (4.6%); Ceftriaxone-resistant *Enterobacteriaceae*: 110 (20.0%); others (*Achromobacter*, *Burkholderia*, anaerobes, *Enterococcus* species, *Candida* species [isolated from respiratory secretions and pleural fluid]): 89 (16.2%).

HAP definition: duration of hospitalization before bacteremic pneumonia >2 days.

APACHE = Acute Physiology and Chronic Health Evaluaton, CAP = community-acquired pneumonia, HAP = hospital-acquired pneumonia, ICU = intensive care unit, IQR = interquartile range, SD = standard deviation, WBC = white blood cell count.

* Race also includes: Hispanic, Asian, Native American, unknown.

† By the Mann–Whitney *U* test.

Community-acquired pneumonia: patients were admitted from home, no previous hospitalizations within 90 days, no previous antibiotics, no chronic hemodialysis, duration of hospitalization before bacteremic pneumonia of ≤2 days.

or a respiratory quinolone).[2] These earlier studies have attempted to guide this decision-making process by identifying risk factors for antibiotic resistance. However, they primarily attempted to juxtapose CAP and HCAP among patients directly admitted to the hospital with pneumonia, excluding cases of HAP and VAP. Although the models in these studies seemed to perform well in the initial cohorts from which they were developed, their predictive accuracy was less robust when applied to other cohorts of pneumonia patients.[24,25]

The majority of risk factors previously identified for antibiotic resistance in patients with pneumonia converge towards previous antibiotic or hospital exposures, impaired functional status, and the acuity of the clinical presentation. It is usually not 1 single risk factor, with the possible exception of immunosuppression, but the presence of 2 or more risk factors that increases the hazard for drug-resistant pathogens.[15–18,20] Understanding that the same risk factors might carry different weights and interact differently in a prediction model, some studies have tried to examine the predisposing conditions for bacterial species of interest, with MRSA and *P aeruginosa* being commonly targeted.[18,26–29] Unfortunately, none of these prediction scores have been validated in prospective studies aimed at guiding the administration of empiric antibiotic treatment for suspected pneumonia.

Our study attempts to expand upon earlier studies by identifying risk factors for bacteremic pneumonia attributed to CfRE. The rate of previous antibiotic use was high across all resistant pathogens in our study population, but was highest for CfRE (74.5%). CfRE infections were also more likely to occur later during the hospitalization. However, only prior antibiotic exposure and presence of a central vein catheter were found to independently predict the presence of CfRE infection. Antibiotic-resistant *Enterobacteriaceae* (ESBL or carbapenemase-producing strains) originating in the community setting have recently been found to be an important etiology of inappropriately treated infections, making clinical prediction of such pathogens problematic.[30–32] Moreover, the presence of immunosuppression is associated with infection attributed to all resistant pathogens including MRSA and Gram-negative bacilli (*P aeruginosa*, *Acinetobacter baumanii*, *Stenotrophomonas maltophilia*, *Klebsiella* spp, *Serratia* spp).[19] In our population, immunosuppression characterized bacteremic pneumonia caused by *P aeruginosa*, whereas earlier studies identified *Pseudomonas* pneumonia to develop as a secondary infection after previous hospitalization, in immunocompromised hosts with damaged lungs, in previously colonized patients, and in those with debilitating comorbidities like cerebrovascular disease.[33–39]

Table 3

Comparison of methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and ceftriaxone-resistant *Enterobacteriaceae* bacteremic pneumonia.

Characteristic	MRSA (n = 190)	*Pseudomonas aeruginosa* (n = 109)	CfRE (n = 110)	*P* value
Age, y, mean ± SD	56.9 ± 15.5	59 ± 14.7	59.2 ± 16.5	0.483*
Male sex	105 (55.3%)	67 (61.5%)	64 (58.2%)	0.575
Nursing home residence	25 (13.2%)	14 (12.8%)	14 (12.7%)	0.993
Hemodialysis	23 (12.1%)	9 (8.3%)	16 (14.5%)	0.356
Immunosuppression	43 (22.6%)	67 (61.5%)	44 (40.0%)	0.001
Prior hospitalization	85 (44.7%)	71 (65.1%)	50 (45.5%)	0.005
Prior antibiotics	93 (49.0%)	68 (62.4%)	82 (74.5%)	0.001
Charlson score	5 ± 3.4	6 ± 3.4	5.5 ± 3.3	0.901*
Central vein catheter	74 (38.9%)	68 (62.4%)	81 (73.6%)	0.001
Surgery				0.096
Abdominal	12 (6.3%)	5 (4.5%)	12 (10.9%)	
Nonabdominal	30 (15.8%)	20 (18.3%)	27 (24.5%)	
Duration of hospitalization before bacteremia, d, median (IQR)	0 (0–6)	2 (0–12)	8.5 (0–19)	0.001*
Mechanical ventilation	88 (46.3%)	49 (45.0%)	56 (50.9%)	0.642
Septic shock	97 (51.1%)	65 (59.6%)	56 (50.9%)	0.302
APACHE II score, mean ± SD	15.8 ± 6.2	18 ± 6.9	15.5 ± 6	0.322*
Peak WBC × 10^3, cells/μL, median (IQR)	19.1 (11.3–30)	15.0 (4.2–28)	16.8 (9.5–28.3)	0.015*
Resistance to piperacillin–tazobactam		9 (8.3%)	97 (88.2%)	0.001
Resistance to cefepime		8 (7.3%)	16 (14.5%)	0.100
Resistance to meropenem		16 (14.7%)	5 (4.5%)	0.009
Inappropriate initial antibiotic treatment	27 (14.2%)	19 (17.4%)	31 (28.2%)	0.011
Discharge to skilled nursing facility	67 (35.3%)	29 (26.6%)	47 (42.7%)	0.043
Mortality	67 (35.3%)	59 (54.1%)	34 (30.9%)	0.001

APACHE = Acute Physiology and Chronic Health Evaluaton, CfRE = ceftriaxone resistant *Enterobacteriaceae*, IQR = interquartile range, MRSA = methicillin-resistant *Staphylococcus aureus*, SD = standard deviation, WBC = white blood cell.

* By the Kruskal–Wallis test for nonparametric data expressed as the median and IQR and by 1-way ANOVA for parametric data expressed as mean ± SD.

Taken together, these studies highlight the difficulty in using clinical variables to identify specific pathogen types.

In addition to identifying risk factors for particular drug-resistant pathogens, we also tried to assess the impact of drug resistance on mortality in this very well-defined cohort. It is interesting that even though CfRE infections more likely received IIAT, due to the higher rates of resistance to piperacillin–-tazobactam and cefepime, patients infected with *P aeruginosa* had significantly higher mortality—a finding that was confirmed in the multivariable analysis even after correcting for inappropriate antibiotics and severity of disease. This finding is consistent with earlier studies highlighting the virulence of *P aeruginosa* as a pneumonia pathogen[33,40,41] and our earlier study showing that *P aeruginosa* bacteremia had the lowest number needed to treat with appropriate antibiotic therapy (2.5, 95% CI 2.1–3.1) to save 1 additional life.[42]

The association between MDR status and increased mortality is well-described, but differs across infections and across bacterial species. In the case of *S aureus*, large epidemiological studies found increased case fatality rates for patients with MRSA bloodstream infections.[43–45] However, in most of these population-based studies, the authors were unable to control for the appropriateness of initial antibiotic therapy or acuity of illness, and their results have not been fully replicated in comprehensive cohort studies that have found no differences in mortality between MRSA and MSSA across races, age groups, and healthcare systems.[46–48] A small study looking specifically at MRSA bacteremic pneumonia during an MRSA outbreak underlined the importance of adequately matching the 2 groups.[49] Similarly, a recent multicenter, multinational study of pneumonia caused by *P aeruginosa* found that MDR status was independently associated with mortality.[50] Two other

Table 4

Variables associated with methicillin-resistant *Staphylococcus aureus*, *Pseduomonas aeruginosa*, and ceftriaxone-resistant *Enterobacteriaceae* bacteremic pneumonia in multivariable logistic regression analyses.

	MRSA		*Pseduomonas aeruginosa*		CfRE	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age, y*	0.99 (0.98–0.99)	0.011				
Immunosuppression	0.6 (0.4–0.9)	0.011	2.8 (1.8–4.4)	0.001		
Central vein catheter	0.7 (0.5–0.95)	0.025			2.9 (1.8–4.9)	0.001
Admitted from home	0.5 (0.4–0.75)	0.000				
APACHE II score*			1.1 (1.03–1.1)	0.001		
Prior hospitalization			2 (1.2–3.2)	0.003		
Prior antibiotics					2.3 (1.4–3.8)	0.001

APACHE = Acute Physiology and Chronic Health Evaluation, CfRE = ceftriaxone-resistant *Enterobacteriaceae*, CI = confidence interval, MRSA = methicillin-resistant *Staphylococcus aureus*, OR = odds ratio.

* 1-point increments in age (years) and in APACHE II score.

Table 5

Variables associated with hospital mortality in univariable and multivariable logistic regression analyses including resistance to ceftriaxone and MRSA, *Pseudomonas aeruginosa*, and CfRE.

	Analysis including resistance to ceftriaxone*				Analysis including MRSA, *Pseudomonas aeruginosa*, and CfRE†			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age, y	1.02 (1.01–1.03)	<0.001	1.01 (1.00–1.02)	0.012	1.02 (1.01–1.03)	0.001	1.01 (1.00–1.02)	0.019
White race	1.4 (1.0–1.8)	0.020			1.4 (1.0–1.8)	0.020		
African American race	0.7 (0.6–1.0)	0.030			0.7 (0.6–1.0)	0.030		
Resistance to ceftriaxone	1.5 (1.2–2.0)	0.002						
Mechanical ventilation	1.7 (1.3–2.2)	0.001	1.6 (1.1–2.1)	0.006	1.7 (1.3–2.2)	0.001	1.5 (1.1–2.0)	0.007
Nursing home residence	1.7 (1.1–2.5)	0.010			1.7 (1.1–2.5)	0.010		
Immunosuppression	2.4 (1.8–3.1)	0.001	2.2 (1.6–3.1)	0.001	2.4 (1.8–3.1)	0.001	2.3 (1.7–3.1)	0.001
Prior hospitalization	1.9 (1.4–2.4)	0.001	1.4 (1.0–1.8)	0.043	1.9 (1.4–2.4)	0.001		
Septic shock	2.2 (1.7–2.8)	0.001	1.6 (1.2–2.2)	0.003	2.2 (1.7–2.8)	0.001	1.7 (1.2–2.2)	0.001
Prior antibiotics	1.3 (1.0–1.7)	0.040	1.4 (1.0–1.9)	0.027	1.3 (1.01–1.7)	0.040	1.4 (1.0–1.8)	0.039
APACHE II score	1.1 (1.0–1.1)	0.001	1.04 (1.01–1.06)	0.002	1.1 (1.0–1.1)	0.001	1.04 (1.0–1.1)	0.003
Charlson score	14.4 (11.2–18.4)	0.001	1.07 (1.00–1.10)	0.012	14.4 (11.2–18.4)	0.001	1.1 (1.0–1.1)	0.005
Inappropriate antibiotics	2.3 (1.7–3.2)	0.001	2.2 (1.5–3.2)	0.001	2.3 (1.7–3.2)	0.001	2.3 (1.6–3.2)	0.001
MRSA					0.9 (0.7–1.3)	0.600	1.2 (0.8–1.7)	0.394
Pseudomonas aeruginosa					2.2 (1.5–3.3)	0.001	1.6 (1.1–2.5)	0.047
CfRE					0.7 (0.5–1.1)	0.178	0.6 (0.4–1.0)	0.050

Variables not significantly associated with mortality considered in the univariable analysis: sex, other race (Asian, native American), prior bacteremia, duration of hospitalization before bacteremic pneumonia, admission source, hemodialysis, total parenteral nutrition, central vein catheter, type of surgery, peak white blood cell count.

APACHE = Acute Physiology and Chronic Health Evaluation, CfRE = ceftriaxone-resistant *Enterobacteriaceae*, CI = confidence interval, MRSA = methicillin-resistant *Staphylococcus aureus*, OR = odds ratio.

* Hosmer–Lemeshow goodness of fit = 0.55.

† Hosmer–Lemeshow goodness of fit = 0.600.

studies focusing on *Pseudomonas* bacteremia also found that MDR infection remained as an independent predictor for mortality even after adjusting for IIAT.[51,52] The higher mortality rates observed with *Pseudomonas* bacteremic pneumonia compared with CfRE bacteremic pneumonia is likely due to the virulence of the pathogen and the compromised health status of the infected patients.[53,54] This is also supported by the recent findings of Peña et al[55] who found that specific virulence factors in *P aeruginosa* bloodstream infections such as type III secretion system genotypes were associated with high early mortality.

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 bacteremic pneumonia given the constraints of our definition. Second, the data were derived from a single center, and this necessarily limited 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, we did not address antibiotic pharmacokinetics as a potential contributor to mortality in this cohort. Another limitation of our study is that some of the variables identified as risk factors for infection with specific pathogens are not intuitively linked with those pathogens. For example, the presence of a central vein catheter, known to be associated with MRSA bloodstream infections, was found to be linked to infection with CfRE. This may be due to the presence of a central vein catheter being a marker for infection with CfRE rather than playing a direct role in the pathogenesis of CfRE bacteremic pneumonia. Finally, we did not include a control group of patients without bacteremic pneumonia.

In summary, our study represents the largest study of patients with bacteremic pneumonia published to date. We found that IIAT seems to be the most important independent determinant of mortality and is the only identified mortality predictor amenable to intervention. Moving forward, clinicians need to develop novel approaches for the treatment of patients with bacteremic pneumonia that achieve timely application of appropriate antibiotic therapy while avoiding the unnecessary use of antibiotics, especially broad-spectrum agents. Advances in new antibiotic development along with rapid diagnostics offer approaches for achieving this important balance.[56]

References

[1] Smith SB, Ruhnke GW, Weiss CH, et al. Trends in pathogens among patients hospitalized for pneumonia from 1993 to 2011. JAMA Intern Med 2014;174:1837–9.

[2] Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med 2015;373:415–27.

[3] Sligl W, Taylor G, Brindley PG. Five years of nosocomial Gram-negative bacteremia in a general intensive care unit: epidemiology, antimicrobial susceptibility patterns, and outcomes. Int J Infect Dis 2006;10:320–5.

[4] Agbaht K, Diaz E, Muñoz E, et al. Bacteremia in patients with ventilator-associated pneumonia is associated with increased mortality: a study comparing bacteremic vs. nonbacteremic ventilator-associated pneumonia. Crit Care Med 2007;35:2064–70.

[5] Magret M, Lisboa T, Martin-Loeches I, et al. Bacteremia is an independent risk factor for mortality in nosocomial pneumonia: a prospective and observational multicenter study. Crit Care 2011;15:R62.

[6] Taylor GD, Buchanan-Chell M, Kirkland T, et al. Bacteremic nosocomial pneumonia. A 7-year experience in one institution. Chest 1995;108:786–8.

[7] Bryan CS, Reynolds KL. Bacteremic nosocomial pneumonia. Analysis of 172 episodes from a single metropolitan area. Am Rev Respir Dis 1984;129:668–71.

[8] Bordon JM, Fernandez-Botran R, Wiemken TL, et al. Bacteremic pneumococcal pneumonia: clinical outcomes and preliminary results of inflammatory response. Infection 2015;43:729–38.
[9] Capelastegui A, Zalacain R, Bilbao A, et al. Pneumococcal pneumonia: differences according to blood culture results. BMC Pulm Med 2014;14:128.
[10] Jover F, Cuadrado J-M, Andreu L, et al. A comparative study of bacteremic and non-bacteremic pneumococcal pneumonia. Eur J Intern Med 2008;19:15–21.
[11] Lin S-H, Lai C-C, Tan C-K, et al. Outcomes of hospitalized patients with bacteraemic and non-bacteraemic community-acquired pneumonia caused by *Streptococcus pneumoniae*. Epidemiol Infect 2011;139: 1307–16.
[12] Shorr AF, Zilberberg MD, Micek ST, et al. Outcomes associated with bacteremia in the setting of methicillin-resistant *Staphylococcus aureus* pneumonia: a retrospective cohort study. Crit Care 2015;19:312.
[13] Guillamet CV, Kollef MH. Update on ventilator-associated pneumonia. Curr Opin Crit Care 2015;21:430–8.
[14] Kollef MH, Zilberberg MD, Shorr AF, et al. Epidemiology, microbiology and outcomes of healthcare-associated and community-acquired bacteremia: a multicenter cohort study. J Infect 2011;62:130–5.
[15] Aliberti S, Di Pasquale M, Zanaboni AM, et al. Stratifying risk factors for multidrug-resistant pathogens in hospitalized patients coming from the community with pneumonia. Clin Infect Dis 2012;54: 470–8.
[16] Maruyama T, Fujisawa T, Okuno M, et al. A new strategy for healthcare-associated pneumonia: a 2-year prospective multicenter cohort study using risk factors for multidrug-resistant pathogens to select initial empiric therapy. Clin Infect Dis 2013;57:1373–83.
[17] Shindo Y, Ito R, Kobayashi D, et al. Risk factors for drug-resistant pathogens in community-acquired and healthcare-associated pneumonia. Am J Respir Crit Care Med 2013;188:985–95.
[18] Shorr AF, Zilberberg MD, Micek ST, et al. Prediction of infection due to antibiotic-resistant bacteria by select risk factors for health care-associated pneumonia. Arch Intern Med 2008;168:2205–10.
[19] Vallés J, Martin-Loeches I, Torres A, et al. Epidemiology, antibiotic therapy and clinical outcomes of healthcare-associated pneumonia in critically ill patients: a Spanish cohort study. Intensive Care Med 2014;40:572–81.
[20] Falcone M, Russo A, Giannella M, et al. Individualizing risk of multidrug-resistant pathogens in community-onset pneumonia. PloS One 2015;10:e0119528.
[21] American Thoracic SocietyInfectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388–416.
[22] M100-S24: Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fourth Informational Supplement: CLSI_M100-S24. pdf [Internet]. Available at: http://ncipd.org/control/images/NCIPD_ docs/CLSI_M100-S24.pdf. Accessed March 7, 2016.
[23] Magiorakos A-P, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012;18:268–81.
[24] Self WH, Wunderink RG, Williams DJ, et al. Comparison of clinical prediction models for resistant bacteria in community-onset pneumonia. Acad Emerg Med 2015;22:730–40.
[25] Shorr AF, Zilberberg MD, Reichley R, et al. Validation of a clinical score for assessing the risk of resistant pathogens in patients with pneumonia presenting to the emergency department. Clin Infect Dis 2012;54:193–8.
[26] Shorr AF, Myers DE, Huang DB, et al. A risk score for identifying methicillin-resistant *Staphylococcus aureus* in patients presenting to the hospital with pneumonia. BMC Infect Dis 2013;13:268.
[27] Blot S, Depuydt P, Vandewoude K, et al. Measuring the impact of multidrug resistance in nosocomial infection. Curr Opin Infect Dis 2007;20:391–6.
[28] Trouillet JL, Chastre J, Vuagnat A, et al. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med 1998;157:531–9.
[29] De la Calle C, Morata L, Cobos-Trigueros N, et al. *Staphylococcus aureus* bacteremic pneumonia. Eur J Clin Microbiol Infect Dis 2016;35: 497–502.
[30] Al-Hasan MN, Eckel-Passow JE, Baddour LM. Impact of healthcare-associated acquisition on community-onset Gram-negative bloodstream infection: a population-based study: healthcare-associated Gram-negative BSI. Eur J Clin Microbiol Infect Dis 2012;31:1163–71.
[31] Freeman JT, Sexton DJ, Anderson DJ. Emergence of extended-spectrum beta-lactamase-producing *Escherichia coli* in community hospitals throughout North Carolina: a harbinger of a wider problem in the United States? Clin Infect Dis 2009;49:E30–32.
[32] Gupta N, Limbago BM, Patel JB, et al. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. Clin Infect Dis 2011;53: 60–7.
[33] Kollef MH, Chastre J, Fagon J-Y, et al. Global prospective epidemiologic and surveillance study of ventilator-associated pneumonia due to *Pseudomonas aeruginosa*. Crit Care Med 2014;42:2178–87.
[34] Rello J, Rodriguez A, Torres A, et al. Implications of COPD in patients admitted to the intensive care unit by community-acquired pneumonia. Eur Respir J 2006;27:1210–6.
[35] von Baum H, Welte T, Marre R, et al. CAPNETZ study group-Community-acquired pneumonia through *Enterobacteriaceae* and *Pseudomonas aeruginosa*: diagnosis, incidence and predictors. Eur Respir J 2010;35:598–605.
[36] Sibila O, Laserna E, Maselli DJ, et al. Risk factors and antibiotic therapy in *Pseudomonas aeruginosa* community-acquired pneumonia. Respirology 2015;20:660–6.
[37] Luna CM, Sarquis S, Niederman MS, et al. Is a strategy based on routine endotracheal cultures the best way to prescribe antibiotics in ventilator-associated pneumonia? Chest 2013;144:63–71.
[38] Arancibia F, Bauer TT, Ewig S, et al. Community-acquired pneumonia due to gram-negative bacteria and *Pseudomonas aeruginosa*: incidence, risk, and prognosis. Arch Intern Med 2002;162:1849–58.
[39] Venier AG, Gruson D, Lavigne T, et al. Identifying new risk factors for *Pseudomonas aeruginosa* pneumonia in intensive care units: experience of the French national surveillance, REA-RAISIN. J Hosp Infect 2011;79:44–8.
[40] Garnacho-Montero J, Sa-Borges M, Sole-Violan J, et al. Optimal management therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia: an observational, multicenter study comparing monotherapy with combination antibiotic therapy. Crit Care Med 2007;35: 1888–95.
[41] Zhuo H, Yang K, Lynch SV, et al. Increased mortality of ventilated patients with endotracheal *Pseudomonas aeruginosa* without clinical signs of infection. Crit Care Med 2008;36:2495–503.
[42] Vazquez-Guillamet C, Scolari M, Zilberberg MD, et al. Using the number needed to treat to assess appropriate antimicrobial therapy as a determinant of outcome in severe sepsis and septic shock. Crit Care Med 2014;42:2342–9.
[43] Laupland KB, Ross T, Gregson DB. *Staphylococcus aureus* bloodstream infections: risk factors, outcomes, and the influence of methicillin resistance in Calgary, Canada. J Infect Dis 2008;198: 336–43.
[44] Morgan M, Salmon R, Keppie N, et al. All Wales surveillance of methicillin-resistant *Staphylococcus aureus* (MRSA): the first year's results. J Hosp Infect 1999;41:173–9.
[45] Ibelings MM, Bruining HA. Methicillin-resistant *Staphylococcus aureus*: acquisition and risk of death in patients in the intensive care unit. Eur J Surg 1998;164:411–8.
[46] Yaw LK, Robinson JO, Ho KM. A comparison of long-term outcomes after meticillin-resistant and meticillin-sensitive *Staphylococcus aureus* bacteraemia: an observational cohort study. Lancet Infect Dis 2014;14: 967–75.
[47] Nickerson EK, Hongsuwan M, Limmathurotsakul D, et al. *Staphylococcus aureus* bacteraemia in a tropical setting: patient outcome and impact of antibiotic resistance. PloS One 2009;4:E4308.
[48] Tong SYC, Bishop EJ, Lilliebridge RA, et al. Community-associated strains of methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible *S. aureus* in indigenous Northern Australia: epidemiology and outcomes. J Infect Dis 2009;199:1461–70.
[49] González C, Rubio M, Romero-Vivas J, et al. Bacteremic pneumonia due to *Staphylococcus aureus*: a comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. Clin Infect Dis 1999;29: 1171–7.
[50] Micek ST, Wunderink RG, Kollef MH, et al. An international multicenter retrospective study of *Pseudomonas aeruginosa* nosocomial pneumonia: impact of multidrug resistance. Crit Care 2015;19: 219.
[51] Tam VH, Rogers CA, Chang K-T, et al. Impact of multidrug-resistant *Pseudomonas aeruginosa* bacteremia on patient outcomes. Antimicrob Agents Chemother 2010;54:3717–22.
[52] Tumbarello M, Repetto E, Trecarichi EM, et al. Multidrug-resistant *Pseudomonas aeruginosa* bloodstream infections: risk factors and mortality. Epidemiol Infect 2011;139:1740–9.

[53] Morata L, Cobos-Trigueros N, Martínez JA, et al. Influence of multidrug resistance and appropriate empirical therapy on the 30-day mortality rate of *Pseudomonas aeruginosa* bacteremia. Antimicrob Agents Chemother 2012;56:4833–7.
[54] Micek ST, Kollef MH, Torres A, et al. *Pseudomonas aeruginosa* nosocomial pneumonia: impact of pneumonia classification. Infect Control Hosp Epidemiol 2015;36:1190–7.
[55] Peña C, Cabot G, Gómez-Zorrilla S, et al. Influence of virulence genotype and resistance profile in the mortality of *Pseudomonas aeruginosa* bloodstream infections. Clin Infect Dis 2015;60:539–48.
[56] Kollef MH, Micek ST. Rational use of antibiotics in the ICU: balancing stewardship and clinical outcomes. JAMA 2014;312: 1403–4.