2017

A prospective one-year microbiologic survey of combined pneumonia and respiratory failure

Kristen Fisher
Washington University School of Medicine in St. Louis
Tracy Trupka
Washington University School of Medicine in St. Louis
Scott T. Micek
St. Louis College of Pharmacy
Paul Juang
St. Louis College of Pharmacy
Marin H. Kollef
Washington University School of Medicine in St. Louis

SURGICAL INFECTIONS
Volume 18, Number 7, 2017

DOI: 10.1089/sur.2017.111

A Prospective One-Year Microbiologic Survey of Combined Pneumonia and Respiratory Failure

Kristen Fisher,[1] Tracy Trupka,[1] Scott T. Micek,[2] Paul Juang,[2] and Marin H. Kollef[1]

Abstract

Background: Pneumonia and respiratory failure are common problems in the intensive care unit (ICU) setting, often occurring together. The relative prevalence of pneumonia types (community acquired, hospital acquired, ventilator associated) and causative pathogens is not well described in patients with respiratory failure.
Methods: This was a prospective observational cohort study conducted in the medical ICU (34 beds) of Barnes-Jewish Hospital, an academic referral center of 1,300 beds from January 2016–December 2016. All patients who were prospectively adjudicated to have respiratory failure and pneumonia (RFP) regardless of pneumonia type were classified into one of four microbiologic categories: pathogen negative, antibiotic-susceptible pathogen (according to ceftriaxone susceptibility), antibiotic-resistant pathogen, and viruses. The primary outcomes assessed were the hospital mortality rate and inappropriate initial antibiotic therapy (IIAT) for non-viral pathogens.
Results: Among 364 consecutive patients with RFP, 63 (17.3%) had organisms that were antibiotic susceptible, 104 (28.6%) had antibiotic-resistant organisms, 118 (32.4%) were pathogen negative, and 79 (21.7%) had viral infections. For these categories, IIAT occurred in 3.2%, 21.2%, 0.8%, and 0, respectively ($p < 0.001$). Vasopressor-requiring shock was present in 61.9%, 72.1%, 68.6%, and 67.1%, respectively ($p = 0.585$), and the hospital mortality rates were 27.0%, 48.1%, 31.4%, and 36.7%, respectively ($p = 0.020$). Multivariable logistic regression analysis identified IIAT as an independent predictor of in-hospital death (adjusted odds ratio 5.28; 95% confidence interval 2.72–10.22; $p = 0.012$). Male gender, increasing Acute Physiology and Chronic Health Evaluation (APACHE) II scores, greater age, and the presence of shock also predicted death.
Conclusions: Microbiologic categorization of patients with RFP suggests that antibiotic-resistant pathogens and viruses are associated with the highest mortality rates. Vasopressor-requiring shock was common regardless of the microbiologic categorization of RFP. Future development and use of rapid diagnostics and novel therapeutics targeting specific RFP pathogens may allow more timely administration of appropriate antimicrobial therapy and enhance antibiotic stewardship practices.

Keywords: outcomes; pneumonia; respiratory failure

Pneumonia is the second most common diagnosis among patients requiring hospitalization and accounts for about 2.8% of all hospital stays [1]. Similarly, respiratory failure is one of the most common medical conditions in hospitalized patients, with increasing growth in prevalence over the past decade [1,2]. Therefore, it is not surprising that respiratory failure and pneumonia (RFP) often occur together, with either pneumonia precipitating respiratory failure or complicating the occurrence of respiratory failure from other causes.

There are limited data on the types of pneumonia, pathogen distribution, and clinical outcomes in patients with respiratory failure. Most studies of pneumonia in critically ill patients have focused on a specific type, such as community-acquired pneumonia (CAP) or ventilator-associated pneumonia (VAP) [3–9]. The impact of initial empiric therapy on the outcomes of patients with RFP, segregated according to the pathogens associated with the pneumonia, also is not well described. Moreover, the most recent guidelines from the Infectious Diseases Society of America and the American Thoracic Society recommend avoidance of the term ''healthcare-associated pneumonia'' (HCAP), adding potential confusion in terms of how patients coming from the

[1]Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, Missouri.
[2]Division of Pharmacy Practice, St. Louis College of Pharmacy, St. Louis, Missouri.

community with healthcare-associated risk factors should be treated empirically [10,11]. Therefore, we performed a prospective observational study to better understand the occurrence of RFP, regardless of pneumonia type (community acquired, hospital acquired, ventilator associated), at our institution in order to describe the etiologic agents associated with pneumonia and their relation to clinical outcomes.

Patients and Methods

Study population and data source

The study was conducted in the two medical intensive care units (ICUs) (34 beds) at Barnes-Jewish Hospital, an academic referral center of 1,300 beds. The medical ICUs are geographically co-located closed units with shared physician, nursing, pharmacist, and respiratory therapist staffs. This investigation was approved by the Washington University School of Medicine Human Studies Committee, and the need for informed consent was waived (IRB No. 201509075). All mechanically ventilated patients (January 2016–December 2016) with pneumonia were eligible for inclusion. All mechanically ventilated patients were assessed daily (weekdays) for possible study finclusion and data were collected prospectively from the hospital's electronic health record system and from treating physicians and pharmacists.

Study outcomes/objectives

The primary objective of this study was to categorize RFP according to one of four microbiologic categories: pathogen negative, antibiotic susceptible, antibiotic resistant, and viral. The primary outcomes assessed were hospital mortality rate and inappropriate initial antibiotic therapy (IIAT) for non-viral pathogens. Secondary outcomes were hospital length of stay (LOS), duration of mechanical ventilation, occurrence of a secondary pneumonia, and 90-day readmission.

Definitions and study design

Adult patients (age >18 y) were identified prospectively as having pneumonia in accordance with the American Thoracic Society's position statement on nosocomial pneumonia [12]. The criteria were the presence of a new or progressive radiographic infiltrate and at least two of the following clinical features: Fever >38°C, leukocytosis ($>10\times10^9$ cells/L), leukopenia ($\leq4\times10^9$ cells/L), or purulent secretions. The presence of a new or progressive radiographic infiltrate was based on the interpretation of the chest radiographs by board-certified radiologists blinded to the study. All patient records were reviewed by at least one of the investigators to confirm the radiographic findings and to identify patients meeting the case definition for pneumonia. Patients were classified as having CAP if they met the pneumonia criteria within 24 h of arrival at the hospital, whereas patients meeting the pneumonia criteria more than 24 h after hospital admission were classified as having hospital-acquired pneumonia (HAP). Patients were classified as having VAP if they met the pneumonia criteria more than 24 h after the start of mechanical ventilation.

For purposes of this investigation, antibiotic-susceptible RFP was determined according to ceftriaxone susceptibility, as ceftriaxone represents the antimicrobial agent most frequently recommended for hospitalized U.S. patients with pneumonia coming from the community setting [13]. Septic shock was defined as the need for vasopressors (norepinephrine, dopamine, vasopressin, epinephrine, phenylephrine). A secondary pneumonia was defined as a distinct clinical episode meeting the pneumonia definition occurring >48 h after completion of a course of appropriate antimicrobial therapy for the initial episode of pneumonia. Antimicrobial treatment was classified as IIAT if the initial regimen had no in vitro activity against the isolated bacterial or fungal pathogen.

Immunosuppression was defined as the acquired immunodeficiency syndrome, solid organ or bone marrow transplant, hematologic malignancies, solid-tumor cancers treated with chemotherapy or radiation, long-term corticosteroids (>10 mg/d), and other immunosuppressive drugs (e.g., biologics for rheumatologic disorders). Multidrug-resistant (MDR) pathogens had to demonstrate resistance in vitro to at least one agent from three distinct classes of antimicrobials that normally would have activity against that bacterium [14].

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 azithromycin, ceftriaxone, cefepime, gentamicin, and vancomycin was unrestricted. However, initiation of intravenous ciprofloxacin, imipenem, meropenem, piperacillin/tazobactam, ceftolozone/tazobactam, ceftazidime/avibactam, linezolid, or ceftaroline required authorization from either a clinical pharmacist or an infectious diseases physician. Each ICU had a clinical pharmacist who reviewed all antibiotic orders to ensure that dosing and interval of administration were adequate for individual patients based on body size, renal function, and resuscitation status.

The initial antibiotic doses employed for the treatment of bacterial pneumonia were as follows: azithromycin 500 mg once daily; ceftriaxone 1–2 g daily; cefepime 1–2 g q eight h; piperacillin–tazobactam, 4.5 g q six h; imipenem 0.5 g q six h; meropenem, 1–2 g q eight h; ceftolozone/tazobactam 1.5 g q eight h; ceftazidime/avibactam, 2.5 g q eight h; ciprofloxacin, 400 mg q 8 h; levofloxacin 750 mg once daily; vancomycin, 15 mg/kg q 12 h; linezolid 600 mg q 12 h; and ceftaroline 600 mg q eight h. Subsequent dose and frequency were adjusted for decreased renal function, where appropriate.

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 [15]. All classifications of antibiotic resistance were based on in vitro susceptibility testing using these established breakpoints. Viral pathogens were identified using the FilmArray® Respiratory Panel (bioMèrieux, Durham, NC).

Statistical analyses

The sample size was determined by the number of patients with RFP admitted to the medical ICUs during the study period. Continuous variables were expressed as means and standard deviations (SDs) or medians and interquartile ranges

(IQRs) when appropriate. The Student *t* test and one-way analysis of variance (ANOVA) 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 are reported as frequency distributions and were analyzed using the χ^2 test. We performed univariable and stepwise backward automatic elimination multivariable logistic regression analyses to identify the variables associated with IIAT and death. All variables that reached a significance threshold of ≤0.2 in univariable analyses were entered in the multivariable model. We performed diagnostics for colinearity and tested for interactions. Goodness of fit was estimated using the Hosmer–Lemeshow c-statistic. P values <0.05 were considered statistically significant, and all tests were two-tailed. All analyses were done using SPSS Statistics 21 (IBM SPSS Statistics, Armonk, NY).

Results

Three hundred sixty-four consecutive patients with RFP were identified. The majority were white men admitted from home or transferred from an outside hospital, with 10% of the patients residing in a nursing home or rehabilitation facility before admission (Table 1). There were 237 (65.1%) patients admitted from the community (mortality rate 30.0%), 98 (26.9%) with hospital-acquired pneumonia (mortality rate 50.0%), and 29 (8.0%) with VAP (mortality rate 44.8%)

Table 1. Baseline Characteristics

Characteristic	*Antibiotic susceptible* (n = *63*)	*Antibiotic resistant* (n = *104*)	*Pathogen negative* (n = *118*)	*Viral* (n = *79*)	p
Age	58.2 ± 16.0	58.7 ± 14.2	59.0 ± 15.9	56.0 ± 15.1	0.600
Male	31 (49.2)	63 (60.6)	68 (57.6)	41 (51.9)	0.437
Race					
African American	27 (42.9)	27 (26.0)	42 (35.6)	21 (26.6)	0.075
Caucasian	36 (57.1)	73 (70.2)	75 (63.6)	57 (72.2)	0.198
Other	0	4 (3.8)	1 (0.8)	1 (0.8)	0.196
Location prior to admission					
Home	**25 (39.7)**	**23 (22.1)**	**46 (39.0)**	**20 (25.3)**	**0.014**
Nursing facility	**12 (19.04)**	**17 (16.3)**	**8 (6.8)**	**4 (5.1)**	**0.008**
Outside hospital transfer	9 (14.3)	29 (27.9)	35 (29.7)	23 (29.1)	0.120
Lower level of care/lateral ICU	17 (27.0)	35 (33.7)	29 (24.5)	32 (40.5)	0.093
Medical history					
Congestive heart failure	13 (20.6)	8 (7.7)	15 (12.7)	11 (13.9)	0.115
Chronic obstructive lung disease	20 (31.7)	29 (27.9)	22 (18.6)	22 (27.9)	0.191
Interstitial lung disease	0	5 (4.8)	4 (3.4)	5 (6.3)	0.244
Diabetes mellitus	24 (38.1)	24 (23.1)	27 (22.9)	27 (34.2)	0.059
End-stage renal disease	3 (4.8)	12 (11.5)	7 (5.9)	6 (7.6)	0.328
Cirrhosis	1 (1.6)	10 (9.6)	8 (6.8)	6 (7.6)	0.257
Cystic fibrosis	0	4 (3.9)	1 (0.8)	0	0.075
Bronchiectasis	1 (1.6)	2 (1.9)	0	0	0.305
Malignancy	27 (42.9)	34 (32.7)	40 (33.9)	31 (39.2)	0.503
Stem cell transplant	**2 (3.2)**	**10 (9.6)**	**6 (5.1)**	**16 (20.3)**	**<0.001**
Solid organ transplant	2 (3.2)	10 (9.6)	3 (2.5)	4 (5.1)	0.098
Charlson Score	3 [2, 6]	3 [1.3, 5]	2 [1, 4]	3 [1, 5]	0.441
APACHE II	22 [19, 28]	25 [21.3, 31]	24 [19, 28.5]	23 [18, 27]	0.154
CPIS Score	**9 [7, 10]**	**9 [7, 10]**	**7 [6, 9]**	**6 [5, 7]**	**<0.001**
Prior hospitalization (90 d)	37 (58.7)	71 (68.3)	64 (54.2)	50 (63.3)	0.193
Antibiotics within 30 days	**25 (39.7)**	**74 (71.2)**	**70 (59.3)**	**55 (69.6)**	**<0.001**
Tracheostomy on admission	**6 (9.5)**	**16 (15.4)**	**2 (1.7)**	**1 (1.3)**	**<0.001**
Mechanical ventilation (90 d)	**10 (15.9)**	**21 (20.2)**	**13 (11.0)**	**5 (6.3)**	**0.003**
Immune status					
Steroids	**6 (9.5)**	**39 (37.5)**	**20 (16.9)**	**22 (27.9)**	**<0.001**
Other Immunosuppressant	**3 (4.8)**	**21 (20.2)**	**13 (11.0)**	**16 (20.3)**	**0.013**
Chemotherapy (90 d)	19 (30.2)	21 (20.2)	17 (14.4)	18 (22.8)	0.154
Radiation (90 d)	6 (9.5)	4 (3.8)	2 (1.7)	8 (10.1)	0.078
HIV	6 (9.5)	3 (2.9)	5 (4.2)	3 (3.8)	0.234
Prior pneumonia classification					
Hospital acquired	13 (20.6)	25 (24.0)	35 (29.7)	25 (31.6)	0.384
Ventilator associated	**3 (4.8)**	**22 (21.2)**	**2 (1.7)**	**2 (2.5)**	**<0.001**
Community acquired	47 (74.6)	57 (54.8)	81 (68.6)	52 (65.8)	0.052

Values are expressed as medians [interquartile range], means (± SD), or number (percent). Singificant differences are in **boldface** type.
APACHE = Acute Physiology and Chronic Health Evaluation; CPIS = Clinical Pulmonary Infection Score; ICU = intensive care unit; HIV = human immunodeficiency virus.

Table 2. Pathogen Distribution for Antibiotic Susceptible, Antibiotic Resistant, and Viral Pneumonia[a]

Antibiotic susceptible (n = *63*)		*Antibiotic resistant* (n = *104*)		*Viral* (n = *79*)[d]	
Staphylococcus aureus	32 (50.8)	*Staphylococcus aureus*	28 (26.9)	Rhinovirus/enterovirus	20 (25.3)
Streptococcus pneumoniae	9 (14.3)	*Pseudomonas aeruginosa*	23 (22.1)	Influenza A	12 (15.2)
Klebsiella pneumoniae	8 (12.7)	*Stenotrophomonas maltophilia*	10 (9.6)	Respiratory syncytial virus	11 (13.9)
Haemophilus influenzae	4 (6.3)	*Enterobacter* spp.	10 (9.6)	Coronavirus	11(13.9)
Escherichia coli	3 (4.8)	*Aspergillus fumigatus*	7 (6.7)	Metapneumovirus	8 (10.1)
Moraxella catarrhalis	3 (4.8)	*Escherichia coli*	5 (4.8)	Parainfluenza virus	7 (8.9)
Proteus spp.	3 (4.8)	*Klebsiella pneumoniae*	3 (2.9)	Adenovirus	6 (7.6)
Other *Streptococcus* spp.	3 (4.8)	*Acinetobacter baumannii*	3 (2.9)	Cytomegalovirus	5 (6.3)
Morganella morganii	2 (3.2)	*Achromobacter* spp.	3 (2.9)	Influenza B	1 (1.3)
Citrobacter koseri	1 (1.6)	*Providencia* spp.	3 (2.9)		
Providencia stuartii	1 (1.6)	*Legionella pneumophila*	3 (2.9)		
Multiple pathogens[b]	11 (17.5)	*Enterococcus* spp.[c]	2 (1.9)		
		Pneumocystis jiroveci	2 (1.9)		
		Histoplasma capsulatum	2 (1.9)		
		Serratia marcescens	1 (1.0)		
		Mycobacterium tuberculosis	1 (1.0)		
		Streptomyces sp.	1 (1.0)		
		Trichosporium	1 (1.0)		
		Blastomyces dermatitidis	1 (1.0)		
		Chryseobacterium	1 (1.0)		
		Paecilomyces	1 (1.0)		
		Multiple pathogens[b]	15 (14.4)		

[a]Values are expressed as number (percent).
[b]Including co-infection with viral pathogens
[c]Associated with concomitant isolation from pulmonary source and blood.
[d]Represents patients with only viruses identified as causative pathogen for pneumonia.

(p = 0.002 for mortality rate comparison). Among patients admitted from the community, the risk factors for infection with antibiotic-resistant pathogens were immunosuppression (16.0%), prior hospitalization (within 90 d) (55.7%), prior intravenous antibiotics (within 30 d) (51.5%), and admission from a nursing care facility (14.8%). Sixty-three (17.3%) patients were classified as having antibiotic-susceptible pneumonia, 104 (28.6%) had antibiotic-resistant organisms, 118 (32.4%) were pathogen negative, and 79 (21.7%) were infected with viruses. The pathogens identified are shown in Table 2, and the culture specimens obtained are shown in Supplementary Table 1. *Staphylococcus aureus* (15.1%; methicillin resistant 41.8%) was the most common pathogen associated with RFP followed by *Pseudomonas aeruginosa* (6.3%), rhinovirus (5.6%), and influenza A (3.3%). The Enterobacteriaceae as a class accounted for 11.0% of RFP cases.

Inappropriate antimicrobial therapy was identified in 3.2% of patients with antibiotic-susceptible infections, 21.2% with antibiotic-resistant infections, and 0.8% of pathogen-negative infections (one patient who did not have an antibiotic order entered) (p < 0.001) (Table 3). Patients with antibiotic-resistant infections were statistically more likely to receive IIAT than were those with antibiotic-susceptible infections (p < 0.001). The in = hospital mortality rate was

Table 3. Clinical Outcomes for Mechanically Ventilated Patients with Pneumonia According to Pathogen Type

	Antibiotic susceptible (n = *63*)	*Antibiotic resistant* (n = *104*)	*Pathogen negative* (n = *118*)	*Viral* (n = *79*)	p
Deaths	17 (27.0)	50 (48.1)	37 (31.4)	29 (36.7)	0.020
Length of stay	15 [8, 25]	18.5 [11, 30.8]	11 [6.50, 20.5]	18 [9.5, 28.75]	0.002
Intensive care unit length of stay	8 [4, 16]	9 [6, 17]	6 [4, 12]	8 [4, 18.25]	0.025
Ventilator d	4 [3, 11]	7.5 [4, 15]	4 [2, 8.5]	6 [2, 13]	0.003
Antibiotic d	10 [7, 14]	11 [7, 14]	7 [5, 9.3]	7 [4, 11]	<0.001
Vasopressor d	3 [2, 5]	4 [2, 8]	3 [2, 4]	4 [2, 11.5]	0.014
Inappropriate initial antimicrobial therapy	2 (3.2)	22 (21.2)	1 (0.8)	0 (0)	0.000
Second pneumonia	12 (19.0)	12 (11.5)	9 (7.6)	9 (11.4)	0.154
90-d readmission	15 (23.8)	17 (16.3)	25 (21.1)	11 (13.9)	0.559

Values are expressed as medians [interquartile range] or number (percent).

Table 4. Multivariable Logistic Regression Analysis with Hospital Morality Rate as the Dependent Variable

Variable	*aOR*	*95% CI*	p
Age (one-point increments)	1.05	1.03– 1.07	0.032
Male gender	3.67	2.02– 6.67	0.030
APACHE II score (one-point increments)	1.14	1.09– 1.19	0.003
Shock	10.69	5.21–21.93	0.001
Inappropriate initial antibiotic therapy	5.28	2.72–10.22	0.012

Removed from model for non-significance: Caucasian race, African-American race, congestive heart failure, interstitial lung disease, cirrhosis, underlying malignancy, stem cell transplant, Charlson score, prior hospitalization, prior antibiotic exposure, hospital-acquired pneumonia, community-acquired pneumonia, admission from home.

APACHE = Acute Physiology and Chronic Health Evaluation; aOR = adjusted odds ratio; CI = confidence interval.

Hosmer-Lemeshow goodness-of-fit = 0.547.

greatest for patients with an antibiotic-resistant infection (48.1%), followed by viral (36.7%), pathogen-negative (31.4%), and antibiotic-susceptible (27.0%) infections. The hospital LOS was significantly longer for patients with antibiotic-resistant and viral pneumonias. Antibiotic duration of therapy was significantly longer for pneumonia attributed to antibiotic-resistant and antibiotic-susceptible pathogens.

We found that 53 of the 79 patients (67.1%) with RFP attributed to a viral infection, with only 1 (1.3%) of these individuals having microbiologic evidence of a coexistent non-pulmonary bacterial infection, suffered shock necessitating vasopressor therapy. This was similar to the rate of shock seen in patients with antibiotic-susceptible infections (61.9%), antibiotic-resistant infections (72.1%), and pathogen-negative infections (68.6%) ($p = 0.585$ for the group comparison). However, patients with viral pneumonia and those with antibiotic-resistant infections had greater durations of vasopressor administration (Table 3).

The univariable analysis for in-hospital deaths is shown in Supplementary Table 2. Other outcomes according to hospital survivorship are shown in Supplementary Table 3. Nonsurvivors spent more time on mechanical ventilation, required more days of vasopressor therapy, and were significantly more likely to receive IIAT. The results of the multivariable analysis are shown in Table 4. Inappropriate initial antibiotic therapy was identified as an independent predictor of in-hospital death (adjusted odds ratio [AOR] 5.28; 95% confidence interval [CI] 2.72–10.22; $p = 0.012$). Male gender, increasing age, higher APACHE II scores, and the presence of shock also predicted death. A second multivariable analysis was conducted with IIAT as the dependent outcome variable. In this analysis, VAP (AOR 4.22; 95% CI 2.25–7.92; $p = 0.022$), shock (AOR 14.03; 95% CI 4.88–40.33; $p = 0.012$), and prior mechanical ventilation (90 days) (AOR 2.00; 95% CI 1.44–2.77; $p = 0.034$) predicted IIAT (Hosmer-Lemeshow goodness-of-fit score 0.871).

Discussion

Microbiologic categorization of patients with RFP suggests that antibiotic-resistant pathogens and viruses are associated with worse outcomes than are seen in patients with antibiotic-susceptible and pathogen-negative pneumonia. Disease attributed to antibiotic-susceptible pathogens and pathogen-negative cases had lower mortality rates and significantly lower rates of IIAT than patients with antibiotic-resistant infections despite similar severity of illness. Inappropriate initial antibiotic therapy and shock were the only potentially modifiable risk factors we identified that were associated with death. Interestingly, less than 10% of our entire cohort had VAP, with the majority of the RFP patients who subsequently developed respiratory failure being classified as either CAP or HAP. Nevertheless, the presence of VAP was a predictor of IIAT. We also found that most patients with viral pneumonia suffered shock and that the appearance of shock was similar to that observed in the other pathogen-based groupings of pneumonia. Interestingly, almost one quarter of patients with RFP classified as CAP had infection with antibiotic-resistant pathogens, implying a potential flaw with current guidelines suggesting that such patients be treated automatically with ceftriaxone or an equivalent agent [10].

Our data highlight the complexity of RFP because of the variability in the types of patients who develop this infection, as well as the variability in the associated pathogens. Traditional approaches for selecting empiric therapy for pneumonia have focused on the bacterial organisms associated with this infection [10]. Most authors suggest that the presence of specific risk factors predisposing to infection with potentially antibiotic-resistant bacteria, such as methicillin-resistant *S. aureus* (MRSA) and *Pseudomonas aeruginosa,* should prompt initial broader-spectrum empiric coverage for these pathogens [10,16]. However, this approach of ''clinical reasoning,'' even when supplemented by institution-specific algorithms developed for the prediction of infection with antibiotic-resistant bacteria, is of limited clinical utility [17]. This inaccuracy in clinical decision-making often leads to overtreatment with empiric broad-spectrum antibiotics but also the administration of IIAT [17,18]. The recent recommendation to eliminate the use of the term ''HCAP'' is in large part a response to the increasing use of empiric broad-spectrum antibiotics in patients with community-onset pneumonia [10,19]. However, minimizing the administration of IIAT is also an important determinant of outcome that clinicians should take into account when deciding which pathogens to cover with the initial empiric antimicrobial regimen [8].

Rapid microbiologic diagnostics represents a strategy that may improve the way antibiotic therapy is directed to patients with RFP, as well as how antibiotic therapy is provided to patients with pneumonia not complicated by respiratory failure. Such technologies have the capability of providing pathogen identification and true antibiotic susceptibility within six h from the time a specimen is logged in to the microbiology laboratory [20]. This could minimize the time that patients are exposed to IIAT. Moreover, the availability of rapid true susceptibility data also can be used to de-escalate empiric broad-spectrum antibiotic therapy at an earlier point in time. A recent meta-analysis of rapid microbiologic diagnostic assays suggests that when the clinical use of such technology is incorporated into antimicrobial stewardship programs,in- hospital mortality rates can be reduced [21].

Several limitations of our study should be recognized. First, it was performed at a single center and may not reflect the types of patients or pathogens seen at other hospitals. Barnes-Jewish Hospital has a regional referral pattern that includes community hospitals, 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 antibiotic-resistant bacteria and non-bacterial pathogens. This may explain the relatively high rates of infection with antibiotic-resistant gram-negative bacteria and MRSA in our cohort. Second, we had a relatively low rate of IIAT, which may reflect the long history of antimicrobial stewardship being practiced in these closed ICUs [22,23]. Third, the rate of observed VAP was low in our population. This may be a reflection of referral patterns to our hospital accounting for a much larger percentage of patients with CAP and HAP. It also may represent the presence of ICU protocols aimed at minimizing the occurrence of VAP [24,25]. Fourth, we cannot exclude the possibility that patients with pathogen-negative and viral pneumonia had a concomitant bacterial infection in some instances that was not detected by our conventional microbiology techniques [26]. Fifth, we included patients who were immunosuppressed in order to have a more representative picture of the types of patients and pathogens presenting to the ICU with RFP. Finally, we excluded antiviral therapies when determining the presence of IIAT given the limitations of available anti-viral drugs and their influence on patient outcomes.

In conclusion, we found that patients with RFP represent a heterogeneous group composed primarily of patients with CAP and HAP. Although the number of patients receiving IIAT was small, most of the IIAT was secondary to infection with antibiotic-resistant bacteria and non-bacterial pathogens. These findings have important implications for assessing and comparing the outcomes of patients with pneumonia from different institutions. Intuitively, it would not be fair to compare an ICU caring disproportionately for patients with antibiotic-resistant pathogens with one where patients with antibiotic-susceptible infections predominate. Moreover, our data suggest that advances in the development and utilization of rapid diagnostics targeting antibiotic-resistant bacterial, fungi, and viruses may help in directing the initial antimicrobial therapy of patients with RFP. Future development and clinical use of rapid diagnostics and novel therapeutics targeting specific RFP pathogens should allow more timely administration of appropriate antimicrobial therapies and enhanced antibiotic stewardship efforts.

Author Disclosure Statement

Dr. Kollef's effort was supported by the Barnes-Jewish Hospital Foundation. The remaining authors have no conflicts of interest to report.

References

1. Pfunter A, Wier LM, Stocks C. Most Frequent Conditions in U.S. Hospitals, 2010. Healthcare Cost Utilization Project. Agency for Healthcare Research and Quality. *Available at:* https://www.hcup-us.ahrq.gov/reports/statbriefs/sb148.pdf Accessed February 19, 2017.
2. Wunsch H, Linde-Zwirble WT, Angus DC, et al. The epidemiology of mechanical ventilation use in the United States. Crit Care Med 2010;38:1947–1953.
3. Kollef MH, Chastre J, Fagon JY, et al. Global prospective epidemiologic and surveillance study of ventilator-associated pneumonia due to *Pseudomonas aeruginosa*. Crit Care Med 2014;42:2178–2187.
4. Bassi GL, Ferrer M, Marti JD, et al. V/entilator-associated pneumonia. Semin Respir Crit Care Med 2014;35:469–481.
5. Jain S, Self WH, Wunderink RG, et al. Community-acquired pneumonia requiring hospitalization among US adults. N Engl J Med 2015;373:415–427.
6. Cillóniz C, Gabarrús A, Ferrer M, et al. Community-acquired pneumonia due to multidrug- and non-multidrug-resistant *Pseudomonas aeruginosa*. Chest 2016;150:415–425.
7. de Miguel-Díez J, Jiménez-García R, Hernández-Barrera V, et al. Trends in hospitalizations for community-acquired pneumonia in Spain: 2004 to 2013. Eur J Intern Med 2016. pii:S0953-6205(16)30439-3.
8. Guillamet CV, Vazquez R, Noe J, et al. A cohort study of bacteremic pneumonia: The importance of antibiotic resistance and appropriate initial therapy? Medicine 2016;95: e4708.
9. Burgos J, Luján M, Nieves Larrosa M, et al. Risk factors for respiratory failure in pneumococcal pneumonia: The importance of pneumococcal serotypes. Eur Respir J 2014;43: 545–553.
10. Kalil AC, Metersky ML, Klompas M, et al. Executive Summary: Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016;63:575–582.
11. Sibila O, Rodrigo-Troyano A, Shindo Y, et al. Multidrug-resistant pathogens in patients with pneumonia coming from the community. Curr Opin Pulm Med 2016;22:219–226.
12. American Thoracic Society; Infectious 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.
13. Llop CJ, Tuttle E, Tillotson GS, et al. Antibiotic treatment patterns, costs, and resource utilization among patients with community-acquired pneumonia: A US cohort study. Hosp Pract 2017;45:1–8.
14. Magiorakos AP, 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;18:268–281.
15. 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.
16. Wunderink RG, Waterer GW. Clinical practice: Community-acquired pneumonia. N Engl J Med 2014;370:543–551.
17. 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: 730–740.
18. Attridge RT, Frei CR, Pugh MJ, et al. Health care-associated pneumonia in the intensive care unit: Guideline-

concordant antibiotics and outcomes. J Crit Care 2016;36: 265–271.
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;40:572–581.
20. Kollef MH, Burnham CA. Ventilator-associated pneumonia: The role of emerging diagnostic technologies. Seminar Respir Crit Care Med (in press)
21. Timbrook TT, Morton JB, McConeghy KW, et al. The effect of molecular rapid diagnostic testing on clinical outcomes in bloodstream infections: A systematic review and meta-analysis. Clin Infect Dis 2017;64:15–23.
22. Micek ST, Ward S, Fraser VJ, et al. A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. Chest 2004;125:1791–1799.
24. Crotty MP, Meyers S, Hampton N, et al. Impact of antibacterials on subsequent resistance and clinical outcomes in adult patients with viral pneumonia: An opportunity for stewardship. Crit Care 2015;19:404.
24. Nolley EP, Trevino SE, Babcock HM, et al. A targeted educational intervention to reduce ventilator-associated complications. Am J Infect Control 2016;44:1406–1407.
25. Babcock HM, Zack JE, Garrison T, et al. An educational intervention to reduce ventilator-associated pneumonia in an integrated health system: A comparison of effects. Chest 2004;125:2224–2231.
26. Resti M, Moriondo M, Cortimiglia M, et al. Community-acquired bacteremic pneumococcal pneumonia in children: Diagnosis and serotyping by real-time polymerase chain reaction using blood samples. Clin Infect Dis 2010;51: 1042–1049.

Address correspondence to:
Dr. Marin H. Kollef
Division of Pulmonary and Critical Care Medicine
Washington University School of Medicine
4523 Clayton Avenue, Campus Box 8052
St. Louis, MO 63110

E-mail: kollefm@wustl.edu