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Major Article

Antipseudomonal monotherapy or combination therapy for older adults with community-onset pneumonia and multidrug-resistant risk factors: a retrospective cohort study

Obiageri O. Obodozie-Ofoegbu BPharm, MSc, PhD [a,b], Chengwen Teng PharmD, MS [a,b], Eric M. Mortensen MD, MSc, FACP [c], Christopher R. Frei PharmD, MSc, FCCP, BCPS [a,b,d,*]

[a] Pharmacotherapy Division, College of Pharmacy, The University of Texas at Austin, Austin, TX
[b] Pharmacotherapy Education and Research Center, Long School of Medicine, The University of Texas Health San Antonio, San Antonio, TX
[c] Division of Pulmonary and Critical Care Medicine, University of Connecticut School of Medicine, Farmington, CT
[d] South Texas Veterans Health Care System, San Antonio, TX

Key Words:
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Background: Infectious Diseases Society of America guidelines recommend empiric antipseudomonal combination therapy when *Pseudomonas* is suspected. However, combination antipseudomonal therapy is controversial. This study compares all-cause 30-day mortality in older patients who received antipseudomonal monotherapy (PMT) or antipseudomonal combination therapy (PCT) for the treatment of community-onset pneumonia.

Methods: This population-based, retrospective cohort study used data from over 150 Veterans Health Administration hospitals. Patients were classified as being at low, medium, or high risk of drug-resistant pathogens. In total, 31,027 patients were assigned to PCT or PMT treatment arms based on antibiotics received in the first 48 hours of hospital admission.

Results: The unadjusted 30-day mortality difference between PCT and PMT was most pronounced in the low-risk group (18% vs 8%), followed by the medium-risk group (24% vs 18%) and then the high-risk group (39% vs 33%). PCT was associated with higher 30-day mortality than PMT overall (adjusted odds ratio [aOR], 1.54; 95% confidence interval [CI], 1.43-1.66) in all 3 risk groups: low (aOR, 1.69; 95% CI, 1.50-1.89), medium (aOR, 1.30; 95% CI, 1.14-1.48), and high (aOR, 1.21; 95% CI, 1.04-1.40).

Conclusions: Older adults who received combination antipseudomonal therapy for community-onset pneumonia fared worse than those who received monotherapy. Empiric combination antipseudomonal therapy should not be routinely offered to all patients suspected of having pseudomonal pneumonia.

* Address correspondence to Christopher R. Frei, PharmD, FCCP, BCPS, Director, Pharmacotherapy Education and Research Center, Long School of Medicine, The University of Texas Health San Antonio, 7703 Floyd Curl Dr, MSC-6220, San Antonio, TX 78229.

E-mail address: freic@uthscsa.edu (C.R. Frei).

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BACKGROUND

Antibiotics are the mainstay of treatment for pneumonia; however, therapy is not "one size fits all." Furthermore, timely administration of antibiotics is critical, so initial empiric treatment, followed by pathogen-directed therapy, is required. One of the most controversial questions to date involves the choice of empiric antipseudomonal monotherapy (PMT) or antipseudomonal combination therapy (PCT) for patients suspected of having community-onset pneumonia due to *Pseudomonas*. Clinicians want to do what is best for their patients, including adequate coverage, to increase the probability of a positive outcome; however, they also want to limit their patients' exposure to broad-spectrum antibiotic therapies that may result in health complications and promote antibiotic resistance. Antibiotics are a precious resource, and prescribers want to be good stewards but lack high-quality evidence to inform this important decision. The available evidence comes from small, single-center studies and is often contradictory.[1] Clinicians are left to wonder, "Should I routinely prescribe PCT for my patients presenting with community-onset pneumonia and multidrug-resistant (MDR) risk factors?"

When *Pseudomonas* pneumonia is suspected, American Thoracic Society and Infectious Diseases Society of America pneumonia guidelines recommend PCT with 2 or more antipseudomonal therapies, including beta-lactam plus aminoglycoside, beta-lactam plus fluoroquinolone, or aminoglycoside plus fluoroquinolone.[2] Nevertheless, several studies have failed to observe additional benefit with PCT versus PMT in the setting of *Pseudomonas* pneumonia.[3-7] Early studies were promising for PCT,[8] but more recent studies have not been able to reliably confirm those findings.[9-11] Additional studies have demonstrated a mortality benefit only for the sickest pneumonia patients,[12] including those with *Pseudomonas* bacteremia, or as definitive treatment.[13,14]

Because clinicians rarely know if a patient has *Pseudomonas* bacteremia on admission, and timely empiric therapy is critical, it is helpful to use prediction rules to decide who gets any type of empiric antipseudomonal therapy (PMT or PCT). One of our prior studies confirmed that such rules can be used effectively to identify patients likely to benefit from empiric antipseudomonal therapy.[15] However, it is unclear if such rules can also be used to identify patients who might experience additional benefit from PCT (vs PMT); therefore, the objective of this study was to compare all-cause 30-day mortality in older patients who received PCT (vs PMT) for the treatment of community-onset pneumonia, stratified based on risk level of having pseudomonal pneumonia.

METHODS

This population-based, retrospective cohort study used data from over 150 hospitals and 1400 clinics in the Veterans Health Administration (VHA) system between fiscal years 2002 and 2007. The methods used to build the database and define the study population have been previously published.[16-19] Briefly, data for this study were obtained from the VHA electronic medical record system and include administrative, clinical, laboratory, and pharmacy data. These data were generated during the course of care and billing for VHA patients and not for research; however, the study investigators used these pieces of data to construct variables that can be used for research. For example, comorbidities were defined using International Classification of Diseases codes. It is important to note that this was not a sample or subset of the VHA population; rather, this was a population-based study of all patients in the VHA system. The institutional review board of The University of Texas Health Science Center at San Antonio and the South Texas Veterans Health Care System Research and Development committee approved this study.

Patients were included if they were ≥65 years of age and had either a primary discharge diagnosis of pneumonia/influenza (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 480.0-483.99 or 485-487) or a secondary discharge diagnosis of pneumonia/influenza plus a primary diagnosis of respiratory failure (ICD-9-CM code 518.81) or sepsis (ICD-9-CM code 038.xx). Comorbid conditions were determined using ICD-9-CM codes from outpatient and inpatient care in accordance with the Charlson comorbidity scoring system.[20,21] If patients were admitted more than once during the period of study, only the first episode qualified for inclusion in the study. Patients who did not receive antipseudomonal therapy and those who received it after 48 hours post-admission were excluded.

The risk score tool and variables for the stratification of these patients was based on the risk score developed by Ma et al[22] and modified for our database, as earlier defined.[17] Briefly, the risk-level groups (low, 0.0-2.0; medium, 2.5-7.0; high, 7.5-21.5) were generated based on the number of points a patient had, as contributed by the total score from the comorbidities presented by the individual. A total of 31,027 patients received antipseudomonal therapy in the first 48 hours of admission and were stratified into PMT or PCT arms for each risk group. Antipseudomonal therapies were defined as the receipt of specific beta-lactams, fluoroquinolones, or aminoglycosides with *in vitro* activity against *Pseudomonas*. Table 1 provides a complete list of all antibiotics considered in this study, as well as definitions of guideline-concordant community-acquired pneumonia (GC-CAP) therapy, *Pseudomonas* therapy, and methicillin-resistant *Staphylococcus aureus* (MRSA) therapy.

The primary study outcome was all-cause 30-day mortality, which has been shown to be most closely associated with pneumonia-related mortality.[23] Mortality was assessed using the VHA Vital Status file, which is in close agreement (98%) with the National Death Index.[24]

Statistical analyses

The 30-day all-cause mortality was compared for patients who received PMT or PCT. All statistical analyses were conducted using JMP 10.0 (SAS; Cary, NC). Categorical variables were compared by Fisher exact test or χ^2. Continuous variables were compared using the Wilcoxon rank-sum test (Table 2). For bivariable statistical tests, *P* values of ≤.05 were considered to be statistically significant, and all tests were 2-tailed.

Potential confounding was minimized using multivariate logistic regression. Separate multivariable logistic regression models were constructed to determine whether any association existed between

Table 1
Definitions of antibiotic therapy

Guideline-concordant community-acquired pneumonia therapy
Ward patients
Beta-lactam* plus (macrolide† or doxycycline)
Respiratory fluoroquinolone‡
Intensive care unit patients
Beta-lactam* plus (macrolide† or doxycycline)
Beta-lactam* plus respiratory fluoroquinolone‡
Pseudomonas therapy
Antipseudomonal beta-lactam§
Antipseudomonal fluoroquinolone‖
Aminoglycoside¶
Methicillin-resistant *Staphylococcus aureus* therapy
Vancomycin
Linezolid

*Beta-lactam includes cefotaxime, ceftriaxone, ampicillin-sulbactam, ertapenem, or aztreonam.
†Macrolide includes azithromycin, clarithromycin, or erythromycin.
‡Respiratory fluoroquinolone includes moxifloxacin, levofloxacin, or gatifloxacin.
§Antipseudomonal beta-lactam includes cefepime, ceftazidime, imipenem-cilastatin, meropenem, piperacillin-tazobactam, ticarcillin-clavulanate, or aztreonam.
‖Antipseudomonal fluoroquinolone includes ciprofloxacin or levofloxacin.
¶Aminoglycoside includes gentamicin, tobramycin, or amikacin.

Table 2
Baseline characteristics for patients with antipseudomonal monotherapy or antipseudomonal combination therapy

	PMT (n = 23,916)	PCT (n = 7111)	*P* value
Patient age (yr), median (IQR)	78 (72-82)	78 (72-83)	.39
Male, %	98	99	.0093
Race, %			
White	83	80	.0002
Black	12	13	.70
Other	5	7	<.0001
Hispanic ethnicity, %	6	10	<.0001
MDR risk score variables, %			
Respiratory organ failure (14 points)	8	21	<.0001
Hospitalization in the past 90 days (5 points)	24	38	<.0001
Invasive mechanical ventilation (2 points)	4	17	<.0001
Healthcare-associated pneumonia risk factor (0.5 points)	35	50	<.0001
MDR risk score, median (IQR)	0 (0-5.5)	5.5 (0-5.5)	<.0001
Low (0.0-2.0), %	70	48	<.0001
Medium (2.5-7.0), %	21	30	<.0001
High (7.5-21.5), %	9	22	<.0001
Charlson comorbidity score, median (IQR)	2 (1-4)	3 (1-4)	<.0001
Comorbid conditions, %			
Myocardial infarction	7	8	<.0001
Heart failure	26	26	.86
Chronic obstructive pulmonary disease	53	52	.0097
Liver disease	1	1	.17
Renal disease	12	15	<.0001
Diabetes	33	35	.0039
Neoplastic disease	26	30	<.0001
HIV/AIDS	<1	<1	.13
Medication use within 90 days, %			
Cardiovascular medications	71	65	<.0001
Antidiabetic medications	23	22	.53
Inhaled corticosteroids	24	21	<.0001
Systemic corticosteroids*	24	25	.37
Pulmonary medications	39	36	<.0001
Vasopressors, %	3	12	<.0001
Invasive mechanical ventilation, %	4	17	<.0001
Noninvasive mechanical ventilation, %	3	7	<.0001
Hemodialysis, %	15	20	<.0001
Organ failure, %			
Any organ failure, %	21	39	<.0001
Respiratory	8	21	<.0001
Cardiovascular	5	9	<.0001
Neurological	2	3	<.0001
Renal	11	21	<.0001
Hematologic	2	5	<.0001
Hepatic	<1	<1	.0012
Antibiotic therapy, %			
Guideline-concordant CAP therapy	85	67	<.0001
MRSA therapy	49	59	<.0001
Pseudomonas diagnosis code by discharge	1 (179)	7 (504)	<.0001

CAP, community-acquired pneumonia; *HIV/AIDS*, human immunodeficiency virus/acquired immunodeficiency syndrome; *IQR*, interquartile range; *MDR*, multidrug-resistant; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *PCT*, antipseudomonal combination therapy; *PMT*, antipseudomonal monotherapy.
*Includes oral and/or injectable corticosteroids.

PMT or PCT and 30-day mortality in the overall population and additionally in each of the 3 risk groups. The dependent variable was 30-day mortality, and the independent variable was PMT or PCT. Covariates included all characteristics from Table 2. The independent variable and all covariates were entered into the model simultaneously. Adjusted odds ratios (aORs) and 95% confidence intervals (95% CIs) were calculated; those 95% CIs not crossing 1 were considered to be statistically significant.

The final list of covariates included patient age, race, Hispanic ethnicity, myocardial infarction, heart failure, chronic obstructive pulmonary disease, liver disease, renal disease, diabetes, neoplastic disease, cardiovascular medications, antidiabetic medications, inhaled corticosteroids, systemic corticosteroids, pulmonary medications, vasopressors, invasive and non-invasive mechanical ventilation, respiratory failure, cardiovascular failure, neurological failure, renal failure, hematological failure, hepatic failure, GC-CAP therapy, and MRSA therapy. When variables were collinear, only 1 of the variables was used. For example, most patients on hemodialysis also had renal failure; therefore, renal failure was chosen as the variable for the models, and the hemodialysis variable was excluded. The Charlson score and the "any organ failure" variables were excluded from the models because individual comorbidities and organ failures were already included in the models. Individual risk score variables were also excluded from the models because our study ran separate multivariable models for the 3 risk groups, and these individual characteristics were used to define those risk groups.

RESULTS

Overall population

Of the 31,027 patients who met study criteria, 23% received PCT and 77% received PMT. Patients belonged to low- (59%), medium- (24%), and high- (18%) risk groups. One or more health care–associated pneumonia criteria was the most common MDR risk score variable, followed by hospitalization in the past 90 days, respiratory organ failure, and invasive mechanical ventilation. The median (interquartile range) Charlson score was 2 (1-4), and common comorbidities included chronic obstructive pulmonary disease (53%), diabetes (33%), heart failure (26%), and neoplastic disease (26%). The most common medications used within 90 days prior to admission were cardiovascular (71%) and pulmonary (39%) medications. Organ failure occurred in 24% of patients. Finally, 80% of patients received GC-CAP therapy, and 34% received MRSA therapy.

Baseline characteristics

Patient age (median of 78 years), race (>80% white), and sex (>98% male) were similar for patients receiving PCT or PMT (Table 2); however, many comorbid conditions including diabetes, renal disease, and heart failure were more prevalent in the PCT arm. All of the MDR risk score variables were more prevalent in the PCT arm, and a greater proportion of patients in the PCT arm had organ failure. Of note, 70% of those on PMT were classified as low risk, compared to 50% of those on PCT. Conversely, 22% of those on PCT were high risk, as compared to 9% of those on PMT. Finally, PMT patients were more likely to have received guideline-concordant therapy, whereas PCT patients were more likely to have received MRSA therapy and to have had a positive *Pseudomonas* culture by discharge.

All-cause mortality

The 30-day mortality was 18% overall and increased among the risk groups: low (13%), medium (21%), and high (36%). The unadjusted mortality difference between PCT and PMT was most pronounced in the low-risk group (18% vs 8%; 10% absolute risk difference), followed by the medium-risk group (24% vs 18%; 6% difference) and the high-risk group (39% vs 33%; 6% difference) (Fig 1). PCT was associated with higher 30-day mortality than PMT overall (aOR, 1.54; 95% CI, 1.43-1.66) and in all 3 risk groups: low (aOR, 1.69; 95% CI, 1.50-1.89), medium (aOR, 1.30; 95% CI, 1.14-1.48), and high (aOR, 1.21; 95% CI, 1.04-1.40) (Table 3).

DISCUSSION

This study set out to determine if PCT (vs PMT) is associated with additional survival benefit in the high-risk group. Unfortunately, the study found no additional benefit with PCT in any of the risk groups, including the high-risk group. Our results favored PMT significantly,

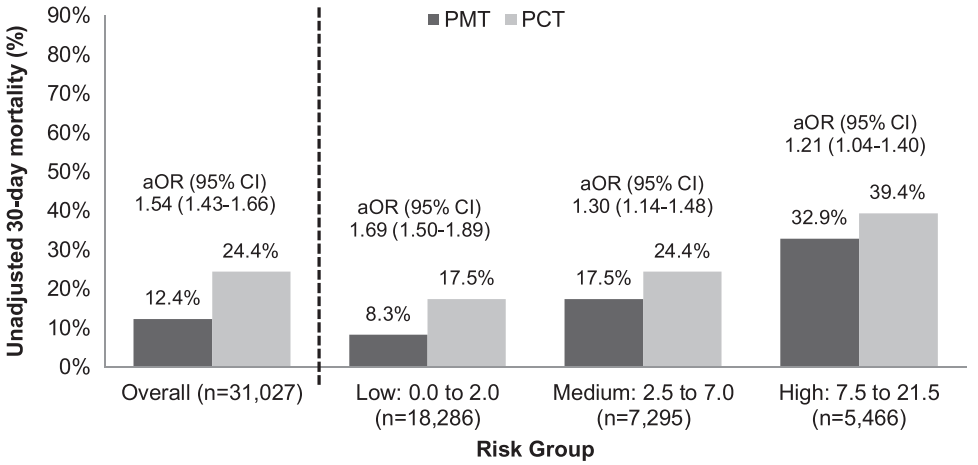

Fig 1. Comparison of 30-day mortality in patients who received PMT or PCT. *aOR*, adjusted odds ratio; *CI*, confidence interval; *PCT*, antipseudomonal combination therapy; *PMT*, antipseudomonal monotherapy.

Table 3
Multivariable models to identify risk factors for 30-day mortality, including antipseudomonal monotherapy or antipseudomonal combination therapy

	Adjusted odds ratio (95% confidence interval)			
Risk score	All (n = 31,027)	0.0-2.0 (low risk) (n = 18,286)	2.5-7.0 (medium risk) (n = 7295)	7.5-21.5 (high risk) (n = 5466)
PCT vs PMT	**1.54 (1.43-1.66)**	**1.69 (1.50-1.89)**	**1.30 (1.14-1.48)**	**1.21 (1.04-1.40)**
Age (1-yr increments)	0.91 (0.90-0.92)	0.89 (0.88-0.91)	0.92 (0.90-0.94)	0.92 (0.90-0.94)
Race	0.99 (0.90-1.10)	0.93 (0.80-1.08)	**1.09 (0.92-1.30)**	0.94 (0.75-1.16)
Hispanic ethnicity	0.97 (0.85-1.10)	**1.06 (0.88-1.27)**	0.80 (0.63-0.99)	**1.04 (0.79-1.36)**
Comorbid conditions				
Myocardial infarction	**1.13 (1.00-1.29)**	**1.12 (0.89-1.40)**	**1.02 (0.84-1.23)**	0.99 (0.76-1.29)
Heart failure	**1.05 (0.97-1.14)**	0.98 (0.87-1.12)	0.99 (0.87-1.14)	1.00 (0.85-1.18)
Chronic obstructive pulmonary disease	0.95 (0.88-1.03)	0.95 (0.84-1.06)	0.92 (0.80-1.06)	0.92 (0.78-1.09)
Liver disease	**1.32 (0.97-1.80)**	0.88 (0.46-1.54)	**1.20 (0.72-1.92)**	**1.86 (1.03-3.37)**
Renal disease	0.94 (0.85-1.05)	0.89 (0.75-1.05)	0.90 (0.76-1.06)	**1.01 (0.82-1.25)**
Diabetes	**1.03 (0.93-1.14)**	**1.06 (0.91-1.23)**	0.98 (0.82-1.17)	**1.04 (0.84-1.27)**
Neoplastic disease	**1.64 (1.52-1.76)**	**1.50 (1.35-1.67)**	**1.79 (1.58-2.03)**	**1.42 (1.21-1.67)**
Medication use, by class				
Cardiovascular medications	0.74 (0.68-0.79)	0.68 (0.61-0.76)	0.71 (0.61-0.81)	0.88 (0.75-1.03)
Antidiabetic medications	0.90 (0.80-1.01)	0.78 (0.65-0.93)	**1.03 (0.84-1.26)**	0.96 (0.76-1.22)
Inhaled corticosteroids	0.71 (0.65-0.79)	0.67 (0.57-0.78)	0.69 (0.58-0.82)	0.88 (0.72-1.07)
Systemic corticosteroids	**1.11 (1.02-1.20)**	**1.07 (0.94-1.23)**	**1.05 (0.91-1.22)**	1.00 (0.83-1.19)
Pulmonary medications	0.99 (0.91-1.09)	0.99 (0.87-1.14)	1.00 (0.85-1.17)	0.91 (0.76-1.09)
Vasopressors	**1.66 (1.45-1.91)**	**2.37 (1.81-3.09)**	**2.02 (1.46-2.81)**	**1.30 (1.08-1.57)**
Mechanical ventilation				
Invasive	0.88 (0.77-1.01)	2.71 (2.01-3.66)	0.85 (0.44-1.58)	0.73 (0.62-1.34)
Non-invasive	**1.47 (1.28-1.70)**	**2.26 (1.73-2.91)**	**1.62 (1.13-2.29)**	**1.11 (0.92-0.86)**
Organ failure				
Respiratory	**2.55 (2.29-2.84)**	N/A	N/A	0.86 (0.59-1.25)
Cardiovascular	**1.47 (1.30-1.66)**	**1.42 (1.15-1.72)**	**1.28 (1.00-1.62)**	**1.69 (1.39-2.07)**
Neurological	**1.36 (1.12-1.65)**	**1.30 (0.95-1.76)**	**1.47 (1.01-2.11)**	**1.24 (0.87-1.74)**
Renal	**1.58 (1.45-1.73)**	**1.88 (1.65-2.15)**	**1.42 (1.20-1.68)**	**1.33 (1.12-1.57)**
Hematologic	**1.58 (1.34-1.86)**	**1.44 (1.11-1.86)**	**1.40 (1.01-1.92)**	**2.00 (1.48-2.72)**
Hepatic	**2.55 (1.51-4.30)**	**2.92 (1.23-6.59)**	**1.97 (0.69-5.22)**	**2.78 (1.09-7.67)**
Antibiotic therapy				
Guideline-concordant community-acquired pneumonia therapy	0.53 (0.49-0.57)	0.49 (0.44-0.56)	0.59 (0.52-0.67)	0.78 (0.67-0.90)
Methicillin-resistant *Staphylococcus aureus* therapy	**1.22 (1.14-1.31)**	**1.22 (1.10-1.34)**	**1.19 (1.05-1.34)**	**1.06 (0.90-1.25)**
Pseudomonas diagnosis code by discharge	0.66 (0.53-0.82)	0.71 (0.47-1.04)	0.65 (0.42-0.98)	0.65 (0.46-0.90)

NOTE: Odds ratios greater than 1 indicate an increased risk of 30-day mortality; odds ratios less than 1 indicate a decreased risk of 30-day mortality. Race was ordered as black vs non-black. The bolded numbers indicate when the odds ratio and associated confidence interval convey statistical significance (i.e., the 95% confidence interval does not cross one).
N/A, not applicable; *PCT*, antipseudomonal combination therapy; *PMT*, antipseudomonal monotherapy.

with 33% mortality in the monotherapy arm versus 39% in the combination therapy arm (aOR, 1.21; 95% CI, 1.04-1.40).

Other studies have also demonstrated a lack of additional benefit with combination therapy versus monotherapy in community-onset pneumonia and other infections.[9,11,25] A 2004 systematic review evaluating beta-lactam monotherapy versus beta-lactam plus aminoglycoside combination therapy for sepsis found no advantage to combination therapy among patients with Gram-negative infections, including *Pseudomonas aeruginosa* infections.[9] The authors reported that patients with pneumonia had significantly fewer failures with monotherapy and there was no advantage to combination therapy. In another study, combination therapy was not associated with

improved survival in patients with Gram-negative bacteremia (OR, 0.96; 95% CI, 0.70-1.32),[11] possibly due to inadequate sample size. In another study, hospital mortality was numerically higher for PCT patients (37%) compared with PMT patients (29%) ($P = .17$).[25] Though not statistically significant, the findings suggest that PCT might have been associated with poorer outcome than PMT had the study authors included a larger sample size. Several additional studies have reported no survival benefit for empiric PCT versus PMT.[26-29] The mortality rates in our study are greater than most of the prior studies, likely because our population is older with a greater proportion of patients who are male and have serious comorbidities. Nevertheless, the association observed in our study is consistent with that observed in prior studies. Furthermore, because of our large sample size, we are able to observe not only the same association (ie, numerically better survival with PMT vs PCT) but also a statistically significant difference in favor of PMT over PCT. Although our study is not the first to demonstrate this lack of additional benefit with PCT versus PMT, it is the first to do so among high-risk patients—the group that is considered most likely to benefit from PCT and a group that has previously been shown to benefit from antipseudomonal therapy in general.[17]

Our study findings may surprise some readers. After all, the current guidelines for the management of patients with community-acquired pneumonia recommend PCT for suspected pseudomonal pneumonia.[2] In light of new evidence, from this study and our prior study,[17] we believe that the community-acquired pneumonia guidelines should be changed. We support the use of empiric PMT in high-risk patients, but we do not support the use of empiric PCT in pneumonia patients from any of the risk groups. PCT may be beneficial over PMT for patients with known *Pseudomonas* (ie, definitive therapy)—a question beyond the scope of this study—but PCT is not associated with additional benefit in patients simply suspected of having *Pseudomonas* (ie, empiric therapy).

Limitations

Despite the many strengths of our study, including its large sample size, risk stratification, and robust statistical methodologies to deal with dissimilar baseline characteristics, our study has limitations, most of which are inherent to all retrospective, observational studies. For example, this study design can only identify an association but not prove causation. It is possible that some unmeasured variable accounts for the lack of additional benefit with PCT. Given the retrospective nature of the study, we cannot ascertain the providers' rationale for their prescribing practices. The study only included patients who received antibiotics within 48 hours of admission. Because it generally takes longer than 48 hours for culture and sensitivity results to return, we can presume this is empiric therapy, but we do not know that for sure. In addition, we acknowledge that several variables that have been previously associated with greater disease severity in other pneumonia studies were more prevalent among patients who received PCT. That is why we stratified patients into 3 risk groups and used multivariable regression models to mitigate baseline differences between groups. Risk stratification is a practical strategy and one that is warranted, given that we saw a benefit with antipseudomonal therapy in the high-risk group in our prior study. Regression modeling has been shown to adequately adjust for confounders in observational studies and provides adequate control for these confounders when estimating the effect of treatment on outcomes.[30]

CONCLUSIONS

Older adults who received combination antipseudomonal therapy for community-onset pneumonia fared worse than those who received monotherapy. Combination therapy may be even more detrimental for low-risk patients than for medium- or high-risk patients. Empiric combination antipseudomonal therapy should not be routinely offered to all patients suspected of having *Pseudomonas aeruginosa* pneumonia.

References

1. Tang SY, Zhang SW, Wu JD, et al. Comparison of mono- and combination antibiotic therapy for the treatment of *Pseudomonas aeruginosa* bacteraemia: a cumulative meta-analysis of cohort studies. Exp Ther Med 2018;15:2418-28.
2. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44(Suppl 2):S27-72.
3. Hilf M, Yu VL, Sharp J, Zuravleff JJ, Korvick JA, Muder RR. Antibiotic therapy for *Pseudomonas aeruginosa* bacteremia: outcome correlations in a prospective study of 200 patients. Am J Med 1989;87:540-6.
4. Leibovici L, Paul M, Poznanski O, et al. Monotherapy versus beta-lactam-aminoglycoside combination treatment for gram-negative bacteremia: a prospective, observational study. Antimicrob Agents Chemother 1997;41:1127-33.
5. Tamma PD, Turnbull AE, Harris AD, Milstone AM, Hsu AJ, Cosgrove SE. Less is more: combination antibiotic therapy for the treatment of gram-negative bacteremia in pediatric patients. JAMA Pediatr 2013;167:903-10.
6. Paul M, Leibovici L. Editorial commentary: combination therapy for *Pseudomonas aeruginosa* bacteremia: where do we stand? Clin Infect Dis 2013;57:217-20.
7. Postma DF, van Werkhoven CH, van Elden LJ, et al. Antibiotic treatment strategies for community-acquired pneumonia in adults. N Engl J Med 2015;372:1312-23.
8. Anderson ET, Young LS, Hewitt WL. Antimicrobial synergism in the therapy of gram-negative rod bacteremia. Chemotherapy 1978;24:45-54.
9. Paul M, Benuri-Silbiger I, Soares-Weiser K, Leibovici L. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomised trials. BMJ 2004;328:668.
10. Heyland DK, Dodek P, Muscedere J, Day A, Cook D. Canadian Critical Care Trials Group. Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. Crit Care Med 2008;36:737-44.
11. Safdar N, Handelsman J, Maki DG. Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis. Lancet Infect Dis 2004;4:519-27.
12. Traugott KA, Echevarria K, Maxwell P, Green K, Lewis JS 2nd. Monotherapy or combination therapy? The *Pseudomonas aeruginosa* conundrum. Pharmacotherapy 2011;31:598-608.
13. Park SY, Park HJ, Moon SM, et al. Impact of adequate empirical combination therapy on mortality from bacteremic *Pseudomonas aeruginosa* pneumonia. BMC Infect Dis 2012;12:308.
14. Chamot E, Boffi El Amari E, Rohner P, Van Delden C. Effectiveness of combination antimicrobial therapy for *Pseudomonas aeruginosa* bacteremia. Antimicrob Agents Chemother 2003;47:2756-64.
15. Teshome BF, Lee GC, Reveles KR, et al. Application of a methicillin-resistant *Staphylococcus aureus* risk score for community-onset pneumonia patients and outcomes with initial treatment. BMC Infect Dis 2015;15:380.
16. Attridge RT, Frei CR, Restrepo MI, et al. Guideline-concordant therapy and outcomes in healthcare-associated pneumonia. Eur Respir J 2011;38:878-87.
17. Frei CR, Rehani S, Lee GC, et al. Application of a risk score to identify older adults with community-onset pneumonia most likely to benefit from empiric *Pseudomonas* therapy. Pharmacotherapy 2017;37:195-203.
18. Mortensen EM, Halm EA, Pugh MJ, et al. Association of azithromycin with mortality and cardiovascular events among older patients hospitalized with pneumonia. JAMA 2014;311:2199-208.
19. Mortensen EM, Nakashima B, Cornell J, et al. Population-based study of statins, angiotensin II receptor blockers, and angiotensin-converting enzyme inhibitors on pneumonia-related outcomes. Clin Infect Dis 2012;55:1466-73.
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
21. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613-9.
22. Ma HM, Ip M, Woo J, Hui DS. Development and validation of a clinical risk score for predicting drug-resistant bacterial pneumonia in older Chinese patients. Respirology 2014;19:549-55.
23. Sohn MW, Arnold N, Maynard C, Hynes DM. Accuracy and completeness of mortality data in the Department of Veterans Affairs. Popul Health Metr 2006;4:2.
24. Fisher SG, Weber L, Goldberg J, Davis F. Mortality ascertainment in the veteran population: alternatives to the National Death Index. Am J Epidemiol 1995;141:242-50.
25. Bowers DR, Liew YX, Lye DC, Kwa AL, Hsu LY, Tam VH. Outcomes of appropriate empiric combination versus monotherapy for *Pseudomonas aeruginosa* bacteremia. Antimicrob Agents Chemother 2013;57:1270-4.
26. Paulsson M, Granrot A, Ahl J, et al. Antimicrobial combination treatment including ciprofloxacin decreased the mortality rate of *Pseudomonas aeruginosa* bacteraemia: a retrospective cohort study. Eur J Clin Microbiol Infect Dis 2017;36:1187-96.

27. Deconinck L, Meybeck A, Patoz P, et al. Impact of combination therapy and early de-escalation on outcome of ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*. Infect Dis (Lond) 2017;49:396-404.
28. Kim YJ, Jun YH, Kim YR, et al. Risk factors for mortality in patients with *Pseudomonas aeruginosa* bacteremia; retrospective study of impact of combination antimicrobial therapy. BMC Infect Dis 2014;14:161.
29. Yoon YK, Kim HA, Ryu SY, et al. Tree-structured survival analysis of patients with *Pseudomonas aeruginosa* bacteremia: a multicenter observational cohort study. Diagn Microbiol Infect Dis 2017;87:180-7.
30. Spiegelman D, Zhou X. Evaluating public health interventions: 8. Causal inference for time-invariant interventions. Am J Public Health 2018;108: 1187-90.