Poster 1811, October 3-7, 2018

The University of Texas at Austin College of Pharmacy

# Empiric Pseudomonal Monotherapy versus Combination Therapy for Community-Onset Pneumonia in Older Adults

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## Abstract

**Background:** Patients with pseudomonal pneumonia have a poor prognosis; therefore, IDSA guidelines recommend empiric antipseudomonal combination therapy when *Pseudomonas* is suspected, at least until treatment can be adjusted based on susceptibilities. 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 cohort study used data from over 150 Veteran Health Administration hospitals. Patients were classified as low, medium, or high risk of drug-resistant pathogens according to a published rule. Patients were assigned to PCT or PMT groups based on antibiotics received in the first 48 hours of hospital admission. Separate multivariable logistic regression models were constructed to determine if the choice of PCT or PMT was associated with 30-day mortality, after accounting for divergent baseline characteristics. Adjusted odds ratios (aORs) and 95% confidence intervals (95%CI) were calculated for the overall, low, medium, and high risk groups.

**Results:** 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. 30-day mortality was 18% overall, and increased among the groups: low (13%), medium (21%), and high (36%). Patient age (median of 78 years), race (>80% white), and sex (>98% male) were similar for patients receiving PCT and PMT. 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 (24% vs. 18%, 6% difference) and high (39% vs. 33%, 6% difference) risk groups. PCT was associated with higher 30-day mortality than PMT overall (aOR, 1.54; 95%CI, 1.43-1.66), and in all three 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).

**Conclusion:** Older adults who received empiric 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.

## Introduction

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. A major challenge in treating pneumonia is the involvement of *Pseudomonas aeruginosa* as a pathogen. 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 (COP) due to *Pseudomonas*.

When *Pseudomonas* pneumonia is suspected, ATS/IDSA pneumonia guidelines recommend PCT with two or more antipseudomonal therapies[1]. Nevertheless, several studies have failed to observe additional benefit with PCT versus PMT in the setting of pseudomonal pneumonia[2].

Timely empiric antipseudomonal therapy is critical to survival in pseudomonal pneumonia and clinicians rarely know if a patient has *Pseudomonas* bacteremia on admission, it is helpful to use prediction rules to decide who gets empiric antipseudomonal therapy. Previous studies from our team have confirmed that such rules can be used effectively to identify patients likely to benefit from empiric antipseudmonal therapy[3] but it is unclear if such rules can also be used to identify patients who might benefit from PCT versus PMT.

## Objective

The objective of this study is to compare all-cause 30-day mortality in older patients who received PMT or PCT for the treatment of community-onset pneumonia, stratified based on risk level of having pseudomonal pneumonia.

## Methods

This is a population-based, retrospective, cohort study. Data was obtained from the VHA electronic medical record system from over 150 hospitals and 1,400 clinics in the Veterans Health Administration (VHA) system between fiscal years 2002 and 2007. The methods used to build the database have been previously published[4].

Eligible patients had to be ≥ 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[5,6].

The risk score tool and variables for the stratification of these patients has been earlier defined[4]. 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 shows the complete list of all antibiotics considered in this study, definitions of guideline-concordant CAP therapy, *Pseudomonas* therapy, and MRSA therapy. Primary study outcome was all-cause 30-day mortality. Mortality was assessed using the VHA vital status file.

**Table 1**. Definitions of antibiotic therapy

| Guideline-Concordant CAP therapy | |
|---|---|
| **Ward patients** | **ICU patients** |
| • Beta-lactam[1] plus (macrolide[2] or doxycycline)<br>• Respiratory fluoroquinolone[3] | • Beta-lactam[1] plus (macrolide[2] or doxycycline)<br>• Beta-lactam[1] plus respiratory fluoroquinolone[3] |
| **Pseudomonas therapy** | |
| • Antipseudomonal beta-lactam[4]<br>• Antipseudomonal fluoroquinolone[5]<br>• Aminoglycoside[6] | |
| **MRSA therapy** | |
| • Vancomycin<br>• Linezolid | |

CAP: community-acquired pneumonia; ICU: intensive care unit
[1]Beta-lactam includes cefotaxime, ceftriaxone, ampicillin-sulbactam, ertapenem, or aztreonam
[2]Macrolide includes azithromycin, clarithromycin, or erythromycin
[3]Respiratory fluoroquinolone includes moxifloxacin, levofloxacin, or gatifloxacin
[4]Antipseudomonal beta-lactam includes cefepime, ceftazidime, imipenem-cilastatin, meropenem, piperacillin-tazobactam, ticarcillin-clavulanate, or aztreonam
[5]Antipseudomonal fluoroquinolone includes ciprofloxacin or levofloxacin
[6]Aminoglycoside includes gentamicin, tobramycin, or amikacin

**Statistical Analyses:** 30-day all-cause mortality was compared for patients who received PMT and PCT. All statistical analyses were conducted using JMP 10.0® (SAS Corp, Cary, NC). For bivariable statistical tests, *P* values of ≤ 0.05 were considered to be statistically significant, and all tests were two-tailed. Potential confounding was minimized using multivariate logistic regression. Separate multivariable logistic regression models were constructed to determine whether any association existed between PMT/PCT and 30-day mortality in the overall population and additionally in each of the three risk groups. Adjusted odds ratios (aORs) and 95% confidence intervals (95%CI) were calculated; those 95%CI not crossing 1 were considered to be statistically significant.

## Results

| | PMT (n=23,916) | PCT (n=7,111) | P-value |
|---|---|---|---|
| Patient age (years), median (IQR) | 78 (72-82) | 78 (72-83) | 0.3855 |
| Male, % | 98 | 99 | 0.0093 |
| Race, % | | | |
| White | 83 | 80 | 0.0002 |
| Black | 12 | 13 | 0.6996 |
| Other | 5 | 7 | <0.0001 |
| Hispanic ethnicity, % | 6 | 10 | <0.0001 |
| MDR risk score variables (points), % | | | |
| Respiratory organ failure (14pts) | 8 | 21 | <0.0001 |
| Hospitalization in the past 90 days (5pts) | 24 | 38 | <0.0001 |
| Invasive mechanical ventilation (2pts) | 4 | 17 | <0.0001 |
| Healthcare-associated pneumonia risk factor (0.5pts) | 35 | 50 | <0.0001 |
| MDR risk score, median (IQR) | 0 (0-5.5) | 5.5 (0-5.5) | <0.0001 |
| Low (0.0-2.0), % | 70 | 48 | <0.0001 |
| Medium (2.5-7.0), % | 21 | 30 | <0.0001 |
| High (7.5-21.5), % | 9 | 22 | <0.0001 |
| Charlson comorbidity score, median (IQR) | 2 (1-4) | 3 (1-4) | <0.0001 |
| Comorbid conditions, % | | | |
| Myocardial infarction | 7 | 8 | <0.0001 |
| Heart failure | 26 | 26 | 0.8637 |
| Chronic obstructive pulmonary disease | 53 | 52 | 0.0097 |
| Liver disease | 1 | 1 | 0.1739 |
| Renal disease | 12 | 15 | <0.0001 |
| Diabetes | 33 | 35 | 0.0039 |
| Neoplastic disease | 26 | 30 | <0.0001 |
| HIV/AIDS | <1 | <1 | 0.1292 |
| Medication use within 90 days, % | | | |
| Cardiovascular medications | 71 | 65 | <0.0001 |
| Anti-diabetic medications | 23 | 22 | 0.5289 |
| Inhaled corticosteroids | 24 | 21 | <0.0001 |
| Systemic corticosteroids[a] | 24 | 25 | 0.3673 |
| Pulmonary medications | 39 | 36 | <0.0001 |
| Vasopressors, % | 3 | 12 | <0.0001 |
| Invasive mechanical ventilation, % | 4 | 17 | <0.0001 |
| Noninvasive mechanical ventilation, % | 3 | 7 | <0.0001 |
| Hemodialysis, % | 15 | 20 | <0.0001 |
| Organ failure, % | | | |
| Any organ failure, % | 21 | 39 | <0.0001 |
| Respiratory | 8 | 21 | <0.0001 |
| Cardiovascular | 5 | 9 | <0.0001 |
| Neurological | 2 | 3 | <0.0001 |
| Renal | 11 | 21 | <0.0001 |
| Hematologic | 2 | 5 | <0.0001 |
| Hepatic | <1 | <1 | 0.0012 |
| Antibiotic therapy, % | | | |
| Guideline-concordant CAP therapy | 85 | 67 | <0.0001 |
| MRSA therapy | 49 | 59 | <0.0001 |
| Pseudomonas culture-positive by discharge | 1 (179) | 7 (504) | <0.0001 |

**Table 2.** Baseline characteristics for patients with antipseudomonal monotherapy (PMT) or antipseudomonal combination therapy (PCT).

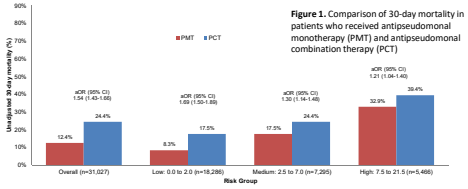


**Figure 1.** Comparison of 30-day mortality in patients who received antipseudomonal monotherapy (PMT) and antipseudomonal combination therapy (PCT)

## Discussion

- Our study found no benefit in the use of PCT over PMT in older adult patients with community-onset pneumonia. Similar to our findings, other studies have reported a lack of difference in the use of combination therapy over monotherapy in different bacteremia conditions, including CAP[7,8]. It is often expected that "more" is better, and in the concept of combination therapy in pneumonia, it is suggested that the effect of two or more agents combined, will be synergistic, achieving better treatment outcomes. However, this has frequently proven to be untrue in community-onset pseudomonal pneumonia.
- In our study, PCT was associated with worse outcomes than PMT overall and across all risk groups. Similar trends have been reported in the literature[9]. Hospital mortality was numerically higher for PCT patients (36.6%) compared with PMT patients (28.7%), and thirty-day mortality for the same group of patients were 23% and 20%, respectively[10].
- Severity of illness, which is often more prevalent in the PCT arm[11], has been suggested as the explanation for this observation. However, in our study, all the eight co-morbid conditions used in our Charlson score; myocardial infarction, COPD, renal disease, diabetes, and neoplastic disease, which are also independent risk factors associated with 30-day mortality, were adjusted for as confounding variables in multivariate and bivariate analyses.
- Notable in our study findings is that the mortality differences between PCT and PMT arms were numerically larger in the low-risk group, and smaller in the high-risk group. This finding is similar to the report by another group, that in the *Pseudomonas aeruginosa* bacteremia group, PCT showed a poorer outcome in patients at low-risk of *Pseudomonas bacteremia*[8]. Together, this evidence suggests that prescribers should avoid exposing this low-risk population to PCT even when pseudomonal pneumonia is suspected.

### Contributions to knowledge

Although several studies have reported no benefit in mortality for empiric PCT over empiric PMT, none has used our risk stratification approach for cohort identification and classification. We have previously reported that empiric antipseudomonal therapy offered a significant survival benefit to patients at high-risk of pseudomonal pneumonia, but not to the medium and low-risk groups. The present study adds to that knowledge with the findings that PCT may not produce additional benefit.

### Implications for Clinical Practice

The 2006 IDSA/ATS CAP guidelines recommend empiric PCT when *Pseudomonas* is suspected, at least until cultures and susceptibilities can be obtained, to prevent inappropriate initial therapy[1]. The observed outcome of our study does not support this notion, but rather supports the 2016 IDSA/ATS HAV/VAP guidelines, which recommend PMT for low-risk patients and PCT for those at high-risk of death (mortality risk >25%)[12].

## 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.

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## Acknowledgement

This study was supported by a grant from the NIH/NINR (R01NR010828). Dr. Frei was supported in part by a NIH KL2 career development award (NCRR 5KL2 RR025766 [2010-2012]and NCATS 8KL2 TR000118 [2013-2015]). Dr. Mortensen was supported in part by a grant from the AHRQ (R24 HS022418). This material is the result of work supported with resources and the use of facilities at the South Texas Veterans Health Care System.

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