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Treatment heterogeneity in *Pseudomonas aeruginosa* pneumonia

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ABSTRACT

Background: Serious bacterial infections present a unique challenge for studies of real-world evidence. Often, the causative organism is unknown during the initial period of treatment and clinical symptoms change day-to-day, which lead to multiple changes in therapy. While it is assumed approaches to treating specific infectious diseases are mostly similar, we've previously identified substantial treatment heterogeneity, even among organism-specific and site-specific infections.

Objective: To quantify treatment heterogeneity among patients with positive *P. aeruginosa* lung cultures in the national Veterans Affairs (VA) Healthcare System.

Methods: Our retrospective cohort study included inpatients with positive *P. aeruginosa* from sputum and bronchoalveolar lavage cultures collected during VA medical center stays from 01/15-04/18. We included the first positive culture during the admission per patient. Daily antibiotic exposures were mapped from 3 days prior to the culture collection date until discharge or 30 days for longer stays. Heterogeneity was defined as patterns of antibiotic treatment (drug and duration) not shared by any other patient.

Results: Our study included 5,300 patients and 87.4% of patients had different patterns of antibiotic drug and duration. Among patients with changes in therapy (84.4%), 96.8% had different antibiotic treatment patterns, with a median time to first change of 1 day and median of 3 changes. When restricting the analysis to antibiotic classes (rather than drug), Gram-negative antibiotics, and anti-pseudomonal antibiotic classes, heterogeneity was 82.0%, 52.3%, and 48.8%, with median time to first change of 1, 3, and 3 days, and a median of 3, 2, and 2 changes, respectively.

Conclusion: Among inpatients with positive *P. aeruginosa* lung cultures, substantial heterogeneity was observed in the national VA Healthcare System. Even at the class level, and restricting the analysis to anti-pseudomonal antibiotic classes, approximately 50% of patients had different treatment patterns during their inpatient stay. Current methods to assess treatment, including intent-to-treat, as-treated, and even time-dependent exposures, do not adequately account for the extensive heterogeneity observed in infectious diseases.

***Updated to exclude long-term care admissions (n=135).**

BACKGROUND

Even in the presence of clinical guidelines, society guidelines, and/or hospital protocols to guide treatment in order to best manage serious bacterial infections, our study team has noted substantial treatment heterogeneity. We are therefore assessing whether heterogeneity persists in infections where such guidelines and/or consensus are absent or less clear.

METHODS

- Hospitalizations with first *P. aeruginosa* positive lung cultures, Jan 2015-April 2018. Culture could be anytime during admission.
- Exposure mapping identified all antibiotics from 3 days prior to culture until discharge, or 30 days from culture for longer hospital stays. Assessed combination therapy, duration of therapy, and changes in therapy.

RESULTS

Treatment patterns		All antibiotics (n=5,300)	Gram-negative antibiotics (n=4,479)	Anti-pseudomonal antibiotic classes (n=4,510)
Change in therapy	Number with change, n (%)	4,473 (84.4%)	2,560 (57.2%)	2,575 (57.1%)
	Day of change from culture, median (IQR)	1 (0-2)	3 (1-5)	3 (1-5)
	Number of changes, median (IQR)	3 (2-5)	2 (1-3)	2 (1-3)
	Unique change patterns with length of therapy, n (%)	4,331 (96.8%)	2,166 (84.6%)	2,063 (80.1%)
	Unique change patterns without length of therapy, n (%)	3,889 (86.9%)	1,145 (44.7%)	904 (35.1%)
No change in therapy	Number without change, n (%)	827 (15.6%)	1,919 (42.8%)	1,935 (42.9%)
	Unique non-change patterns with length of therapy, n (%)	304 (36.8%)	177 (9.2%)	137 (7.1%)
	Unique non-change patterns without length of therapy, n (%)	115 (13.9%)	30 (1.6%)	15 (0.8%)

IQR = interquartile range. Gram-negative antibiotics included amikacin, cefepime, ceftazidime/avibactam, ceftolozane/tazobactam, ciprofloxacin, colistin, gentamicin, imipenem, levofloxacin, meropenem, Piperacillin/tazobactam, tobramycin). Anti-pseudomonal antibiotic classes included aminoglycosides (amikacin, gentamicin, tobramycin), carbapenems (imipenem, meropenem, doripenem), extended-spectrum cephalosporins (cefepime, ceftazidime), fluoroquinolones (ciprofloxacin, levofloxacin), piperacillin (piperacillin, piperacillin/tazobactam).

RESULTS

Outcomes	Change in pattern (n=4,473)	No change in treatment pattern (n=827)	No change, monotherapy (n=591)	No change, combination therapy (n=236)
Inpatient mortality, n (%)	**765 (17.1%)**	**85 (10.3%)**	**35 (5.9%)**	**50 (21.2%)**
Mortality within 30 days of culture[1], n (%)	**891 (19.9%)**	**138 (16.7%)**	**67 (11.3%)**	**71 (30.1%)**
Readmission within 30 days of discharge, n/n (%)	808/3,708 (21.8%)	155/742 (20.9%)	121/556 (21.8%)	34/186 (18.3%)
Persistent positive *P. aeruginosa* culture[2], n/n (%)	**679/1,781 (38.1%)**	**14/153 (9.2%)**	12/120 (10.0%)	2/33 (6.1%)
P. aeruginosa reinfection within 30 days of discharge, n/n (%)	244/3,708 (6.6%)	40/742 (5.4%)	30/556 (5.4%)	10/186 (5.4%)

[1]Inpatient or outpatient mortality. [2]Positive culture for *Pseudomonas aeruginosa* after 7 days of treatment. Denominator only includes patients with follow-up cultures. Bolded indicates p-value <0.05, for change compared to no change, and no change monotherapy versus no change combination therapy.

CONCLUSIONS

Among hospitalized patients with positive *P. aeruginosa* respiratory cultures, 87.5% has different antibiotic treatments, in terms of the specific antibiotic, timing of receipt of each antibiotic (which day of admission), and duration of therapy. Treatment heterogeneity even remained high, at approximately 50%, when restricting the analysis to Gram-negative antibiotics only and anti-pseudomonal antibiotic classes only. Mortality was highest among those initially receiving combination therapy and continuing with that same combination therapy (no changes), and lowest among those receiving only monotherapy (no changes), which could represent less complex patients / less severe infection, and/or improved outcomes with appropriate initial therapy. Persistent positive *P. aeruginosa* cultures occurred in more than one-third of patients who had changes in therapy. Reinfection and readmission were similar across the different treatment patterns. Current methods to assess treatment, including intent-to-treat, as-treated, and even time-dependent exposures, do not adequately account for the extensive heterogeneity observed in the treatment of infectious diseases. This misclassification has important implications as clinical outcomes vary significantly between heterogeneous treatment approaches and would be difficult to attribute outcomes to one specific treatment.

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