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An evaluation of antipseudomonal dosing on the incidence of treatment failure

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Abstract

Introduction: Significant mortality is associated with delays in appropriate antibiotic therapy in *Pseudomonas aeruginosa* infections. The impact of empiric dosing on clinical outcomes has been largely unreported.

Methods: This retrospective cohort compared treatment failure in patients receiving guideline-concordant or guideline-discordant empiric therapy with cefepime, meropenem, or piperacillin/tazobactam. Patients with culture-positive *P. aeruginosa* between 1 July 2013 and 31 July 2019 were eligible for inclusion. Patients with cystic fibrosis, polymicrobial infection, and urinary or pulmonary colonization were excluded. The composite primary outcome was treatment failure, defined as (1) therapy modification due to resistance/perceived treatment failure, (2) increased/unchanged qSOFA, or (3) persistent fever 48 h after initiating appropriate therapy. Secondary outcomes included rate of infectious diseases consultation, all-cause inpatient mortality, mechanical ventilation requirement, and infection-related intensive care unit and hospital lengths of stay.

Results: In total, 198 patients were included: 90 guideline-concordant and 108 guideline-discordant. Baseline characteristics were balanced. Treatment failure was more common in the guideline-discordant than the guideline-concordant group (62% versus 48%; $p = 0.04$). This remained significant when adjusting for supratherapeutic dosing ($p = 0.02$). Infectious diseases consultation was higher in the guideline-discordant group (46% versus 29%, $p = 0.01$), while intensive care unit length of stay was longer in the guideline-concordant group (4.5 versus 3 days, $p = 0.03$). Additional secondary outcomes were similar.

Conclusion: Treatment failure was significantly higher in patients receiving guideline-discordant empiric antipseudomonal dosing. Guideline-directed dosing, disease states, and patient-specific factors should be assessed when considering empiric antipseudomonal dosing.

Keywords

Pseudomonas aeruginosa, cefepime, piperacillin/tazobactam, empiric therapy, treatment failure

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Introduction

An estimated 33,000 multidrug-resistant (MDR) *Pseudomonas aeruginosa* infections occur each year in the United States, with US$767 million in healthcare expenditure attributable to this drug-resistant organism.[1] However, this number likely underestimates the disease burden associated with *P. aeruginosa* infections as a whole, as it only accounts for those with MDR infections. The in-hospital mortality associated with these infections is high, reaching 40% in some cohorts.[2,3] As such, *P. aeruginosa* infections represent a serious cause of morbidity and mortality in hospitalized patients.

Early, appropriate empiric antibiotic therapy is critical to reduce morbidity and mortality associated with these infections. Previous studies pertaining to outcomes in *P. aeruginosa* infections have been limited in terms of scope and intervention, with at least some degree of conflicting results. Kang et al.[4] found that 30-day mortality was significantly lower in those patients who received effective, empirical antibiotics for *P. aeruginosa* bacteremia compared to those

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who did not (27.7% versus 44.9%; $p=0.049$). There was an additional trend toward higher mortality as the length of the delay increased. In contrast, a subsequent study by Osih et al.[5] assessed the impact of empiric, susceptible antibiotic therapy on in-hospital mortality and length of stay among patients with *P. aeruginosa* bacteremia. Time to susceptible antibiotic therapy was not found to be associated with an increase in in-hospital mortality or length of stay. Lodise et al.[6] attempted to further define the temporal association between delayed appropriate antibiotic therapy and mortality in those with *P. aeruginosa* bacteremia. The delayed treatment group (>52 h) experienced a significantly higher 30-day mortality (44% versus 19%, $p=0.008$).

Current studies evaluating risk factors for *P. aeruginosa* infection have done so primarily in those with bacteremia, and the dosing of antimicrobials has been largely unreported. To date, the majority of the research into risk factors for mortality and outcomes has focused on the time to initiation and activity of the empiric antibiotics employed. However, dose optimization strategies for β-lactam antibiotics have demonstrated reduced mortality and shorter hospital lengths of stay with specific agents.[7] Despite these data, significant variability exists in the dosing regimens recommended by the guidelines and those utilized in institutions. The primary objective of this study was to examine the morbidity and mortality associated with guideline-directed dosing of empiric antipseudomonal antibiotics and various infectious syndromes caused by *P. aeruginosa*.

Methods

Setting and study population

This was a single-center, retrospective, observational cohort of patients from a 722-bed tertiary-care medical center. The study was approved by the hospital's Institutional Review Board. Electronic surveillance software was used to identify patients meeting the following criteria: 18 years of age or older, admission to the medical center between 1 July 2013 and 1 August 2019, confirmed *P. aeruginosa* by microbiologic culture, empiric and definitive treatment with an antipseudomonal β-lactam (cefepime, meropenem, and piperacillin/tazobactam). Patients were excluded if they carried a diagnosis of cystic fibrosis, were colonized with *P. aeruginosa*, had multiple organisms isolated from the same culture or infection site consistent with polymicrobial infection, or if they expired prior to receiving 48 h of appropriate antimicrobial therapy.

Data collection

Data collected consisted of basic demographic information (Table 1), clinical and laboratory assessment at the time of infection, infection characteristics (e.g. suspected site of infection, culture source), antipseudomonal β-lactam treatment (e.g. regimen, duration of therapy, additional antipseudomonal agents used for empiric double coverage, and changes in the maintenance dosing regimen due to isolate resistance pattern, treatment failure, or switch to an oral agent), antipseudomonal β-lactam treatment minimum inhibitory concentrations (MICs) as performed by VITEK 2 (bioMérieux), frequency of infectious diseases (ID) consultation at any point during admission, ventilation requirement, discharge disposition, and infection-related intensive care unit (ICU) and total hospital lengths of stay.

Definitions

Guideline-concordant (GC) therapy was defined as the initial dosing regimen of cefepime, meropenem, or piperacillin/tazobactam outlined as appropriate in guidelines pertaining to specific disease states or drug package inserts.[8–13] Assessment for GC dosing was done for scheduled regimens administered after renal function was known. A "one-time dose" prior to obtaining renal function was not considered guideline-discordant (GD). Every 8 h, extended infusion piperacillin/tazobactam was considered equivalent to every 6 h regimens, so long as the dose given was the same as those recommended in the guidelines (Table 2). Extended infusion meropenem employed the same dosing and renal adjustments as the 30-min infusion but was extended over 180 minutes. Extended infusion cefepime is not used at the authors' institution. Renal dose adjustments were considered concordant if the administered dose was indicated in the product labeling as a suggested dose for a patient's creatinine clearance. A dose greater than what was listed for a given indication and creatinine clearance was defined as supratherapeutic and considered GD. In addition, a pre-planned subgroup analysis was conducted merging the GC group with patients in the GD group who received supratherapeutic doses per guideline recommendations.

Colonization was assessed for all urinary and pulmonary isolates. A urine culture with *P. aeruginosa* without documentation of associated urinary symptoms (frequency, dysuria, burning, discomfort, pain in the flank, abdomen, stomach, or suprapubic area), a urinalysis without bacteria, or a urinalysis with less than 10 white blood cells (WBCs) was considered colonization. Pulmonary colonization was defined as a respiratory culture-positive for *P. aeruginosa* without the documentation of associated respiratory symptoms (cough, dyspnea, hypoxia, sputum production, or chest pain) or without a chest X-ray/computed tomography (CT) suggestive of an infectious process.

Outcomes

The primary outcome of treatment failure was a composite defined by the presence of one of the following: increased or unchanged quick sequential organ failure assessment (qSOFA) score from baseline to 48 h after the initiation of

Table 1. Population and infection characteristics.

Population characteristics	Total ($n = 198$)	Concordant ($n = 90$)	Discordant ($n = 108$)	p value
Age (years), mean ± SD	55.9 ± 16.5	56.1 ± 15.1	55.8 ± 17.7	0.89
Sex (male) (%)	140 (70.7)	65 (72.2)	75 (69.4)	0.67
Race (%)				
Caucasian	88 (44.4)	43 (47.8)	45 (41.7)	0.39
African American	109 (55.6)	47 (52.2)	62 (57.4)	0.47
Asian	1 (0.5)	0 (0)	1 (0.9)	1.00
Weight (kg), mean ± SD	81.1 ± 22.5	81.9 ± 23.8	80.4 ± 21.4	0.65
Body mass index (kg/m^2), mean ± SD	26 ± 7.3	27.4 ± 8.1	26.6 ± 6.6	0.49
CrCl (mL/min), mean ± SD	71.2 ± 38.6	73.7 ± 42.7	69.1 ± 34.9	0.41
Suspected site of infection				
CNS (%)	2 (1)	1 (1.1)	1 (1)	1.00
Endovascular (%)	31 (15.7)	17 (18.9)	14 (13)	0.25
Pulmonary (%)	93 (47)	47 (52.2)	46 (42.6)	0.18
SSTI (%)	16 (8.1)	5 (5.6)	11 (10.2)	0.23
Intra-abdominal (%)	7 (3.5)	2 (2.2)	5 (4.7)	0.46
Urinary tract (%)	24 (12.1)	10 (11.1)	14 (13)	0.83
Bone/joint (%)	11 (5.6)	3 (3.3)	8 (7.4)	0.35
Miscellaneous (%)	14 (7.1)	5 (5.6)	9 (8.3)	0.45
Pseudomonas aeruginosa isolate MIC				
Cefepime (μg/mL), median [IQR]	2 [2–8]	2 [2–8]	2 [1–3.5]	0.06
Meropenem (μg/mL), median [IQR]	0.5 [0.25–7]	0.5 [0.25–6]	0.25 [0.25–6]	0.65
Piperacillin/tazobactam (μg/mL), median [IQR]	8 [8–16]	8 [7–16]	8 [8–16]	0.94

SD: standard deviation; CrCl: creatinine clearance; CNS: central nervous system; SSTI: skin and soft tissue infections; MIC: minimum inhibitory concentration; IQR: interquartile range.

Table 2. Guideline-concordant dosing.

	Drug	Doses (g)	Intervals	Routes
Central nervous system	Cefepime	2	Q8h	IV
	Meropenem	2	Q8h	IV
	Piperacillin/tazobactam	4.5	Q6h over 30 min	IV
	Piperacillin/tazobactam	4.5	Q8h over 4 h	IV
Endovascular/ bloodstream	Cefepime	2	Q8h	IV
	Meropenem	1	Q8h	IV
	Piperacillin/tazobactam	4.5	Q6h over 30 min	IV
	Piperacillin/tazobactam	4.5	Q8h over 4 h	IV
Pneumonia	Cefepime	2	Q8h	IV
	Meropenem	1	Q8h	IV
	Piperacillin/tazobactam	4.5	Q6h	IV
	Piperacillin/tazobactam	4.5	Q8h over 4 h	IV
Intra-abdominal	Cefepime	2	Q8h	IV
	Meropenem	1	Q8h	IV
	Piperacillin/tazobactam	4.5	Q6h over 30 min	IV
	Piperacillin/tazobactam	4.5	Q8h over 4 h	IV
Bone and joint	Cefepime	2	Q8–12h	IV
	Meropenem	1	Q8h	IV
	Piperacillin/tazobactam	4.5	Q6h	IV
	Piperacillin/tazobactam	4.5	Q8h over 4 h	IV
Skin and soft tissue	Cefepime	2	Q12h	IV
	Meropenem	1	Q8h	IV
	Piperacillin/tazobactam	4.5	Q6h	IV
	Piperacillin/tazobactam	4.5	Q8h over 4 h	IV

(Continued)

Table 2. (Continued)

	Drug	Doses (g)	Intervals	Routes
Urologic	Cefepime	2	Q12h	IV
	Meropenem	1	Q8h	IV
	Piperacillin/tazobactam	3.375	Q6h over 30 min	IV
	Piperacillin/tazobactam	3.375	Q8h over 4 h	IV

Table 3. Primary and secondary outcomes between concordant and discordant treatment groups.

Primary outcome	Total ($n = 198$)	Concordant ($n = 90$)	Discordant ($n = 108$)	p value
Treatment failure (%)	110 (55.6)	43 (47.8)	67 (62)	0.044
Increased/unchanged qSOFA (%)	79 (71.8)	31 (72.1)	48 (71.6)	0.959
Persistent fever (%)	27 (24.5)	18 (41.9)	9 (13.4)	<0.001
Modification due to perceived resistance or failure (%)	51 (46.3)	17 (39.5)	34 (50.7)	0.25
Secondary outcomes	**Total ($n = 198$)**	**Concordant ($n = 90$)**	**Discordant ($n = 108$)**	**p value**
ID consult after initiation of empiric antipseudomonal therapy (%)	76 (39.9)	26 (28.9)	50 (46.3)	0.012
ICU LOS (days) (%)	10.6 ± 16.0	13.4 ± 18.9	8.2 ± 12.7	0.026
Ventilation requirement (%)	97 (49)	47 (52.2)	50 (46.3)	0.40
Discharge disposition (%)				
Home (%)	101 (51)	49 (54.4)	52 (48.1)	0.38
SNF/LTAC (%)	58 (29.3)	26 (28.9)	32 (29.6)	0.91
Rehab (%)	16 (8.1)	6 (6.7)	10 (9.3)	0.51
Hospice (%)	4 (2)	2 (2.2)	2 (1.9)	1.00
Death (%)	19 (9.6)	7 (7.8)	12 (11.1)	0.43

qSOFA: quick sequential organ failure assessment; ID: infectious diseases; ICU LOS: intensive care unit length of stay; SNF/LTAC: skilled nursing facility/long-term acute care facility.

empiric antibiotic therapy active against *P. aeruginosa*, persistence of fever >100.4°F or 38°C 48 h after initiation of empiric antibiotic therapy active against *P. aeruginosa*, or modification of antibiotic therapy due to resistance or perceived treatment failure (Table 3). Modification of antibiotic therapy was at the discretion of the primary treating team and could be due to resistance development during therapy, demonstrated with increased MICs on subsequent cultures or to perceived treatment failure, demonstrated by increasing or persistently elevated WBC counts, fever, new-onset hypotension, increasing respiratory requirements, or failure of skin/wounds to demonstrate healing. Secondary outcomes consisted of all-cause inpatient mortality, mechanical ventilation requirement, discharge disposition, as well as infection-related ICU, and total hospital lengths of stay.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (SPSS Inc., Chicago, IL, USA).[14] Chi-square and Fisher's exact test were used for the analysis of nominal variables, while continuous variables were analyzed using the student's *t*-test or Mann–Whitney *U* test, as appropriate. Comparisons between multiple groups were analyzed using Wilcoxon rank sum or analysis of variance (ANOVA), pending data type. A p value less than 0.05 was used to determine statistical significance.

Results

Baseline characteristics

A total of 2037 patients met study inclusion criteria. After excluding 1839 patients, 198 patients were included in the study. Considerations for exclusion are addressed in Figure 1. In total, 90 patients (45.5%) received GC therapy, and 108 patients (54.5%) received GD therapy. Of the 108 patients categorized as GD, 16 received supratherapeutic dosing. Baseline characteristics were similar between groups with respect to demographics, infection characteristics, suspected site of infection, and *P. aeruginosa* MICs (Table 1). Pulmonary infections were the most frequent suspected site of infection (47%); however, *P. aeruginosa* was more commonly isolated from suspected urinary tract infections in the GC group (10% versus 1%; $p = 0.006$). Other culture sources did not vary significantly between treatment groups. Secondary bacteremia

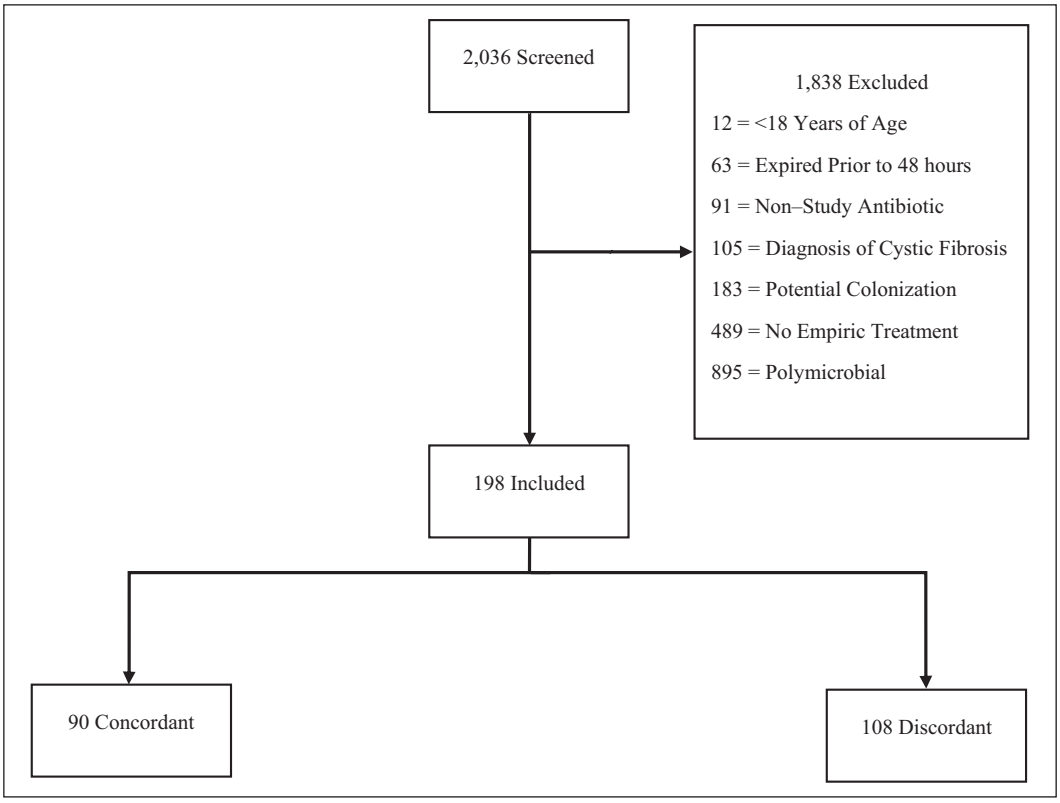

Figure 1. Study flowchart.

occurred most frequently in those with pulmonary (54%) and urinary tract (48%) infections. Cefepime (41.1% versus 27.8%; $p=0.048$) and meropenem (21.1% versus 6.5%; $p=0.002$) were prescribed significantly more often in the GC group, with piperacillin/tazobactam prescribed significantly more frequently in the GD group (65.7% versus 37.7%; $p<0.001$). However, four patients in the GC group received extended infusion regimens, all of meropenem. No patients in the GD group received extended infusion regimens ($p=0.04$).

The median qSOFA score at baseline was 2 [interquartile range (IQR): 0–2] in the GC group and 1 [1–2] in the GD group, with a median qSOFA score of 1 [0–2] in both groups at 48 h after the initiation of treatment. GC temperature at baseline (37.4°C ± 1.2) and at 48 h (36.8°C ± 1.2) did not differ significantly from those observed in the GD group (37.4°C ± 1.1 baseline, 36.9°C ± 0.8 at 48 h; $p=0.14$ and 0.28, respectively). WBC count did not differ significantly between treatment groups at baseline (GC—12.6 ± 10.9 versus GD—13.9 ± 9.9; $p=0.41$) or at 48 h (GC—10.6 ± 8.2 versus 11.9 ± 7.4; $p=0.24$).

In total, 85 patients (78.7%) in the GD group had their maintenance regimens changed to alternative antipseudomonal agents, compared with 53 patients (58.9%) in the GC group ($p=0.003$). Those in the GC group requiring changes in their maintenance regimens were more likely to be due to demonstrated resistance to the empiric agent (20.7% versus 4.7%; $p=0.005$), while those with changes to their maintenance regimen in the GD group were more likely to be due to perceived treatment failure (34.1% versus 13.2%; $p=0.007$). There were no significant differences between groups in the rate of double coverage (22.2%—GC, 18.5%—GD) or agents used for empiric double coverage, which included ciprofloxacin, levofloxacin, gentamicin, and tobramycin. Levofloxacin was the most commonly used agent in both groups (65%).

When stratified by β-lactam, those receiving meropenem had a significantly higher qSOFA score of 2 [IQR: 1–2] 48 h after initiating appropriate antibiotic therapy, as compared to those receiving cefepime or piperacillin/tazobactam, with a qSOFA score of 1 [IQR: 0–2] ($p=0.019$). Infections with a suspected urinary source were significantly more likely to have received piperacillin/tazobactam (19%) as compared to cefepime or meropenem (4.5% versus 3.8%; $p=0.005$). Cefepime recipients were more likely to have a suspected endovascular source of infection compared to meropenem or piperacillin/tazobactam (29.9% versus 15.4% versus 6.7%; $p<0.001$). Patients receiving meropenem had a numerically greater number of suspected pulmonary infections compared to cefepime or piperacillin/tazobactam (69.2% versus 43.2% versus 43.8%; $p=0.054$). Culture sources were not significantly different between agents, with the exception of significantly more respiratory isolates in the meropenem group as compared to cefepime or piperacillin/tazobactam (64.4% versus 38.8% versus 37.1%; $p=0.028$).

Outcomes

Treatment failure occurred in approximately 55% of the study population (Table 3). By treatment group, the GD group experienced a significantly higher rate of treatment failure than the GC group (62% versus 47.8%; $p=0.044$). Of the 110 patients who experienced treatment failure, the most common cause was an increased or unchanged qSOFA 48 h after the initiation of antibiotic therapy (71.8%), which was consistent across the GC and GD groups. Modification of the treatment regimen due to resistance or perceived treatment failure occurred in 51 patients (46.3%) overall. Persistent fever 48 h after the initiation of antibiotics occurred in 27 patients (24.5%) and was significantly more common in the GC treatment group ($p=0.001$). Approximately 40% (76 patients) of the study population received an ID consult after initiation of empiric antipseudomonal therapy, which was significantly more common in the GD as compared to the GC group ($p=0.012$). Overall, ICU length of stay was 10.6 days in the study population, and significantly longer in the GC group as compared to the GD group ($p=0.026$). Discharge home was the most common disposition overall ($n=101$) and did not differ significantly between groups ($p=0.38$). Inpatient mortality was comparable between the two groups, at 7.8% ($n=7$) in the GC group and 11.1% ($n=12$) in the GD group ($p=0.43$)

Primary and secondary outcomes were also further assessed among individual β-lactam agents. Treatment failure did not differ significantly between β-lactams. ID consultation was significantly more frequent in the cefepime (38.8%) and piperacillin/tazobactam (43.8%) groups as compared to the meropenem group (15.4%; $p=0.028$). ICU length of stay was significantly higher in the meropenem group than either the cefepime or piperacillin/tazobactam groups (16.3 ± 14.5 versus 12 ± 18.7 versus 8.2 ± 14 days; $p=0.006$). Mechanical ventilation requirement was significantly higher in the meropenem group (80.8%; $p=0.001$) as compared to cefepime (49.3%) or piperacillin/tazobactam (41%). The meropenem group was also significantly less likely to be discharged home (23.1%; $p=0.007$) compared to those receiving cefepime (52.2%) or piperacillin/tazobactam (57.1%). Skilled nursing facility (SNF) and long-term acute care hospital (LTAC) placement were also significantly more likely in the meropenem group (53.8%; $p=0.017$) compared to those receiving cefepime (23.9%) or piperacillin/tazobactam (26.7%). Inpatient mortality was not significantly different among the β-lactam antibiotics ($p=0.10$).

A subgroup analysis was performed to assess any differences between those patients receiving GC and supratherapeutic dosing (GC + S; $n=106$) as compared to those who received GD ($n=92$) dosing (subtherapeutic). Treatment failure continued to occur significantly more frequently in the GD group as compared to the GC + S group (59 (64.1%) versus 51 (48.1%) $p=0.024$). Persistent fever was also more common in the GC + S group (20 (39.2%) versus 7 (11.9%) $p<0.001$). ID consultation occurred significantly more often in the GD as compared to the GC + S group (44 (47.8%) versus 31 (30.0%) $p=0.011$).

Discussion

To the authors' knowledge, this is one of the first studies to assess clinical outcomes related to the empiric dosing of antipseudomonal antibiotics. This study found GD antipseudomonal antibiotic dosing to be associated with significantly higher rates of treatment failure in patients with infections due to *P. aeruginosa*. The primary driver of treatment failure in the GD group, though not statistically significant, was the change in therapy due to perceived resistance or failure of the selected antipseudomonal therapy. This was not offset by the persistence of fever in the GC group. In addition, these same differences were sustained with the GC + S group compared to the GD (subtherapeutic) group. Modification of antibiotic therapy often depends on signs, symptoms, and clinical response to deem the treatment a failure, sometimes with minimal explanation in clinical documentation. While no clear association can be drawn from the data, subtherapeutic dosing of the selected antipseudomonal treatment could be the cause. Aggressive dosing and optimization strategies with extended infusion regimens can prolong the free drug concentrations above the MIC ($fT > MIC$), the pharmacodynamic parameter most associated with β-lactam treatment success. These strategies would be most beneficial for isolates with elevated MICs, where optimal pharmacokinetic/pharmacodynamic (PK/PD) targets are more difficult to obtain. However, the majority of *P. aeruginosa* isolates in this study were well within the susceptible range as defined by the Clinical Laboratory Standards Institute (CLSI).[15] Previous studies have reported a probability of target attainment (PTA) of approximately 80%–90% for cefepime, meropenem, and piperacillin/tazobactam with dosing regimens and MIC distributions similar to those found in this study.[16–18] With an expected PTA > 80% in almost all cases for the employed dosing regimens and *P. aeruginosa* MICs, the expected treatment failure rate for the GC and GD groups should be comparable. While there are significantly more extended infusion regimens in the GC group, it is unlikely that the small number (four patients) significantly impacted treatment failure. The difference in failure rates suggests that GC dosing, particularly the higher doses of cefepime and piperacillin/tazobactam, influences patient-specific factors and treatment response beyond what would be expected by PTA and $fT > MIC$.

Despite recommendations from guidelines included in this study for empiric double coverage of gram-negative organisms, evidence to suggest differences in outcomes is conflicting.[10,19,20] However, there does not seems to be a significant difference in terms of reported mortality between β-lactam + aminoglycoside and β-lactam + fluoroquinolone combination regimens.[21,22] *P. aeruginosa* susceptibilities at the authors' institution for the studied β-lactams are approximately 90% or greater, and empiric double coverage is relatively infrequent. This likely accounts for the relatively low overall rate of double coverage (~20%), despite > 60% of patients having either a suspected pulmonary or endovascular source. Antimicrobials prescribed for double coverage

did not differ between groups. The fluoroquinolones, ciprofloxacin, and levofloxacin were employed > 70% of the time, despite their lower empiric susceptibilities compared to aminoglycosides at our institution. Given the previous studies, it is unlikely that similar rates of empiric double coverage could explain the discrepancy in treatment failure observed between groups.

When comparing sites of infection among agents, the cefepime group had significantly more endovascular infections, while the piperacillin/tazobactam group had significantly more urinary sources. The meropenem group also had numerically greater pulmonary infections (69% versus ~43%). Despite differences in pharmacokinetic parameters and concerns regarding infection site penetration, our post hoc evaluation of outcomes by antipseudomonal β-lactam yielded no differences in treatment failure among the studied antimicrobials.[23–27] However, it is worth noting that the more frequent use of piperacillin/tazobactam in suspected urinary sources of infection may have influenced the failure rates in these cases. The overall difference in treatment failure between groups suggests a general dosing discordance among all three study β-lactams.

Population-based prescribing and bias is an additional concern when considering which patients may be most susceptible to *P. aeruginosa* infections. At the authors' institution, cefepime and meropenem are the primary antipseudomonal β-lactams employed in febrile neutropenia, which could frequently result in treatment failure as defined in this study. The recurrent fevers observed in febrile neutropenia, despite appropriate antibiotic coverage, may be more representative of the population than treatment failure of the β-lactam itself. Empiric meropenem use is more common in critically ill patients, those who have previously received broad spectrum antimicrobials, or those with a history of extended spectrum β-lactamase producers. This may help explain the persistently higher 48-h qSOFA scores and longer lengths of ICU stay in patients receiving that agent. Changes in β-lactam usage also occurred over the study time frame, with cefepime increasing in usage to now rival piperacillin/tazobactam. Extended infusion regimens of meropenem and piperacillin/tazobactam were adopted late in the study time frame, December 2018 and September 2019, respectively. As a result, any potential benefits offered by these dose optimization strategies may not have been seen due to low enrollment numbers.

There are several limitations to our study. As a single-center, retrospective study without randomization, information and selection bias are inherent. A power analysis and sample size calculation were also not performed due to the retrospective nature of our study. Given the initial 48-h time frame required for assessment of treatment failure, survivorship bias is also a significant concern. Patients who expired prior to this time were excluded from the study, which may select for an overall study population with a lower degree of disease severity. The lack of assessment and control for comorbid conditions, timing of antimicrobial administration, or confounding disease states could have also affected outcome assessment. In addition, while there was an increased rate of ID consult in GD patients, we did not assess recommendations, and their consultation could have been prompted by observed treatment failure or due to underlying infection severity. The use of qSOFA scoring as a metric for treatment failure is also difficult to reconcile with previously published literature on *P. aeruginosa* infections. Most studies have evaluated 30-day mortality or have used the more sensitive, but equally difficult to evaluate, SOFA scoring in their evaluations and analyses. Persistent fever has also been demonstrated for up to 4 days despite adequate therapy;[28] therefore, including persistent fever after 48 h may be too soon to call treatment failure. However, this would result in significantly less patients in the GC group experiencing treatment failure, further distinguishing subtherapeutic dosing within the GD group as the cause for treatment failure.

Conclusion and relevance

Our study found that GD dosing was associated with higher rates of treatment failure in those with infections due to *P. aeruginosa* receiving antipseudomonal treatment with cefepime, meropenem, or piperacillin/tazobactam. Though there were significant differences in antipseudomonal β-lactam usage between GC and GD groups, there was no association between individual antipseudomonal β-lactam usage and treatment failure. The lack of association between treatment failure and antipseudomonal β-lactam agents, as well as the diverse disease states and patients included in the study, suggests that early clinical response in *P. aeruginosa* infections could be optimized by employing more aggressive antipseudomonal β-lactam dosing, even in the absence of elevated MICs or drug resistance.

Authors' note

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Author contributions

B.K.H and J.L.W. contributed to conception, design, acquisition, analysis, and interpretation, drafted and critically revised the article. M.J.B.W. and K.R.S. contributed to conception and critically revised the article. D.A.C. and K.B.E. contributed to design, critically revised the article, and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interests

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