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Mortality in patients with carbapenem-resistant *Pseudomonas aeruginosa* with and without susceptibility to traditional antipseudomonal β-lactams

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Background: Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) isolates can frequently retain susceptibility to traditional antipseudomonal β-lactams including cefepime, ceftazidime and piperacillin/tazobactam.

Objectives: This observational study aimed to determine the proportion of CRPA isolates that were susceptible to all tested other traditional antipseudomonal β-lactams (S-CRPA) and assess whether patients with S-CRPA had improved 30 day mortality compared with patients with NS-CRPA (non-susceptible to cefepime, ceftazidime or piperacillin/tazobactam).

Methods: Patients with CRPA isolated from normally sterile sites, urine, lower respiratory tracts and wounds were identified using active population- and laboratory-based surveillance through the Georgia Emerging Infections Program from August 2016 to July 2018 in Atlanta, GA, USA. Only unique patients who were hospitalized at the time of, or within 1 week of, culture were included. We excluded patients with cystic fibrosis. Multivariable logistic regression estimated the association between S-CRPA and 30 day mortality.

Results: Among 635 adults hospitalized with CRPA, 219 (34%) had S-CRPA. Patients with S-CRPA were more likely to be white (50% versus 38%, $P = 0.01$) and live in a private residence prior to culture (44% versus 28%, $P < 0.01$), and less likely to have required ICU care within the prior week (23% versus 36%, $P < 0.01$) compared with patients with NS-CRPA. Compared with those with NS-CRPA, patients with S-CRPA had an increased 30 day mortality (18% versus 15%, adjusted OR 1.9; 95% CI 1.2–3.1).

Conclusions: S-CRPA was associated with higher 30 day mortality than NS-CRPA in hospitalized patients. The reason for this observed increase in mortality deserves further investigation.

Introduction

Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) is the most common carbapenem-resistant Gram-negative organism isolated from hospitalized patients in the USA.[1] An estimated 10%–20% of all clinical *P. aeruginosa* cultures collected in US healthcare settings are resistant to at least one carbapenem, and in critical care settings 26% of both central line-associated bloodstream infections and ventilator-associated pneumonias caused by *P. aeruginosa* are resistant to carbapenems.[2,3] CRPA infections can be challenging to treat and are associated with a 17%–53% all-cause, in-hospital mortality.[4,5]

Unlike other carbapenem-resistant pathogens, many CRPA isolates are reported to be susceptible to other traditional antipseudomonal β-lactams (cefepime, ceftazidime and piperacillin/tazobactam).[6] This occurs because carbapenem resistance in *P. aeruginosa* is rarely due to carbapenemase production and is instead often mediated through a combination of mechanisms including decreased outer membrane permeability, overexpression of efflux pumps or AmpC β-lactamases and alterations in penicillin-binding proteins.[7,8] At some institutions, >50% of CRPA isolates are susceptible to at least one other traditional antipseudomonal β-lactam.[6] The clinical significance of this susceptible phenotype is unknown and not specifically addressed in the recent IDSA guidance on treatment of MDR Gram-negative organisms, which focused on difficult-to-treat resistant (DTR) *P. aeruginosa*

(non-susceptible [NS] to piperacillin/tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin and levofloxacin).[9]

In this study, we used active population- and laboratory-based surveillance data to (i) determine the proportion of CRPA isolates that were susceptible to all tested other traditional antipseudomonal β-lactams (cefepime, ceftazidime and piperacillin/tazobactam) (S-CRPA) and (ii) assess whether patients with S-CRPA had improved 30 day mortality compared with patients with NS-CRPA (NS to cefepime, ceftazidime or piperacillin/tazobactam).

Methods

Ethics

This study was done through the Georgia Emerging Infections Program and data collection and analysis were approved by the Emory University Institutional Review Board (IRB#0089004) with a waiver of patients' informed consent. This study was conducted in accordance with the Declaration of Helsinki as well as national and institutional standards.

Data collection and study population

We used active population- and laboratory-based surveillance data of CRPA isolated from normally sterile sites (includes blood, bone, cerebrospinal fluid, deep tissue/internal abscess, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid or other normally sterile sites), urine, lower respiratory tract (includes sputum, tracheal aspirate, bronchoalveolar lavage or other lower respiratory tract sample) and wounds, collected by the CDC-funded Georgia Emerging Infections Program from August 2016 to July 2018 in Atlanta, GA, USA (population ∼4 million). CRPA was defined as having an MIC ≥8 mg/L for doripenem, imipenem or meropenem. The MIC was determined by the respective local clinical laboratory's automated testing instrument. Cases were identified by routine queries of laboratory automated testing instruments in the catchment area. MICs were interpreted according to the CLSI 2020 guidelines. Patient demographics (age, sex, race) and clinical characteristics (residence prior to culture, Charlson comorbidity index [CCI], length of stay, admission to the ICU in the week prior to culture, specimen source and discharge location) were obtained through medical record review. All-cause 30 day mortality data was supplemented by review of Georgia Vital Statistics records.

We retrospectively analysed all adults without cystic fibrosis (CF) with their first incident CRPA case where they were hospitalized at the time of, or within 1 week of, culture collection (Figure S1, available as Supplementary data at *JAC-AMR* Online). Incident cases were defined as the first CRPA isolate from a patient during a 30 day period that met the surveillance definition. We excluded cases with incomplete medical record review and those without susceptibility testing for at least one of the other traditional antipseudomonal β-lactams.

Statistical analysis

We determined the proportion of patients with S-CRPA and compared patients with S-CRPA with those with NS-CRPA using χ^2 tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. The CCI was dichotomized based on the median value in the analysis. Multivariable logistic regression estimated the association between S-CRPA (exposure) and 30 day mortality (outcome). All demographic and clinical characteristic variables that were consistent with our *a priori* directed acyclic graph and significant ($P < 0.2$) for both the exposure (S-CRPA phenotype) and outcome (30 day mortality) in the univariable analyses were included in the model as possible confounders. Length of stay variables were not included in the model as these were considered to be on the causal pathway. All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Of the 1733 incident CRPA cases, 779 were from adults without CF and who were hospitalized at the time of or within 1 week of CRPA culture. In total, 635 unique patients had isolates with susceptibility testing for at least one of the other traditional antipseudomonal β-lactams (cefepime, ceftazidime and piperacillin/tazobactam) (Figure S1). The median age was 63 years (IQR 53–75) and 384 (61%) were male. Most ($n = 421$, 66%) resided in a hospital or long-term care facility 4 days prior to culture and nearly one-third ($n = 201$, 32%) were admitted to the ICU within the week prior to culture. The most common culture sources were the respiratory tract ($n = 224$, 35%) and urine ($n = 243$, 38%) (Table 1).

Non-susceptibility to multiple antibiotic classes[7] (defined in Table S1) occurred frequently with 522 (82%) NS to ≥3 classes and 214 (34%) NS to ≥5 classes of antibiotics. A total of 219 (34%) patients had S-CRPA. Patients with S-CRPA were more likely to be white (50% versus 38%, $P = 0.01$) and live in a private residence prior to culture (44% versus 28%, $P < 0.01$), and less likely to have been in the ICU in the week prior (23% versus 36%, $P < 0.01$) than patients with NS-CRPA (Table 1).

Forty (18%) patients with S-CRPA died within 30 days of culture, compared with 62 (15%) patients with NS-CRPA (unadjusted OR 1.3, 95% CI 0.8–2.0). In a multivariable analysis, S-CRPA was significantly associated with 30 day mortality (adjusted OR 1.9, 95% CI 1.2–3.1) after controlling for age, CCI, place of residence and admission to the ICU prior to culture, which were all independent risk factors for 30 day mortality (Table 2).

Discussion

Here we identified that approximately one-third of patients with CRPA in Atlanta, GA have S-CRPA, and these individuals have almost double the odds of dying compared with those with NS-CRPA. This association was only significant after controlling for other expected risk factors for 30 day mortality in this patient population including age, increased number of comorbidities and recent healthcare or ICU exposure. While we are not aware of prior studies specifically investigating S-CRPA, one study analysed a similar phenotype of *P. aeruginosa* only resistant to carbapenems (but susceptible to all other antibiotic classes) and reported a high all-cause, 30 day mortality rate of 72%.[10]

Differences in antibiotic treatment regimens may help explain the increase in observed mortality in S-CRPA. We hypothesize that patients with S-CRPA are frequently treated with other traditional antipseudomonal β-lactams reported as susceptible. However, evolving β-lactam resistance during therapy with cefepime and ceftazidime has been described in both clinical and *in vitro* studies due to increased expression of efflux pumps and AmpC β-lactamases.[7,11–13] Development of additional β-lactam resistance could lead to clinical failure and contribute to increased mortality. While we did not have data on antibiotic use in this study, we believe that evaluating treatment regimens used in this patient population and determining if specific patterns of antibiotic use are associated with mortality are important next steps. An alternative hypothesis is that the observed decrease in mortality rates was lower in patients with NS-CRPA if they had more prior antibiotic exposure and thus may be more likely to have a mild infection or a positive culture that only represents colonization.

Table 1. Characteristics and outcomes of hospitalized patients with CRPA in metropolitan Atlanta, stratified by susceptibility to traditional antipseudomonal β-lactams

	All CRPA ($n = 635$)	S-CRPA[a] ($n = 219$)	NS-CRPA[b] ($n = 416$)	*P* value[c]
Age category (years)				0.09
19–49	124 (20)	37 (17)	87 (21)	
50–64	187 (29)	64 (29)	123 (30)	
65–79	229 (36)	75 (34)	154 (37)	
>79	95 (15)	43 (20)	52 (12)	
Male ($n = 634$)	384 (61)	127 (58)	257 (62)	0.39
Race ($n = 595$)				0.01
Black	333 (56)	97 (48)	236 (60)	
White	248 (42)	101 (50)	147 (38)	
Multiracial or other race	14 (2)	6 (3)	8 (2)	
Charlson comorbidity index >2	307 (48)	98 (45)	209 (50)	0.19
Residence 4 days prior to culture				<0.01
Hospital inpatient	277 (44)	80 (37)	197 (47)	
Long-term facility (LTCF or LTACH)	144 (23)	42 (19)	102 (25)	
Private residence	214 (34)	97 (44)	117 (28)	
Location of culture collection				0.69
Hospital	485 (76)	163 (74)	322 (77)	
Long-term facility (LTCF or LTACH)	17 (3)	6 (3)	11 (3)	
Outpatient location	133 (21)	50 (23)	83 (20)	
ICU in 7 days prior to culture	201 (32)	50 (23)	151 (36)	<0.01
Culture source				0.11
Sterile site[d]	52 (8)	17 (8)	35 (8)	
Lower respiratory tract	224 (35)	64 (29)	160 (39)	
Urine	243 (38)	94 (43)	149 (36)	
Wound	116 (18)	44 (20)	72 (17)	
Time from admission to discharge/death, days, median (IQR)	13 (6–38)	10 (5–28)	16 (7–42)	<0.01
Time from culture to discharge/death, days, median (IQR)	9 (4–19)	7 (3–14)	10 (5–21)	<0.01
Outcome at 30 days[e]				
Death	102 (16)	40 (18)	62 (15)	0.27
Alive and still hospitalized	94 (15)	22 (10)	72 (17)	0.01
Alive and discharged	439 (69)	157 (72)	282 (68)	0.31
LTACH	56 (13)	20 (13)	36 (13)	
LTCF	145 (33)	41 (26)	104 (37)	
Private residence	233 (53)	94 (60)	139 (49)	
Other or unknown	5 (1)	2 (1)	3 (1)	

All values are presented as *n* (%) unless otherwise stated.
LTCF, long-term care facility; LTACH, long-term acute care hospital.
[a]CRPA isolates susceptible to all of the following tested antibiotics: cefepime, ceftazidime and piperacillin/tazobactam.
[b]CRPA isolates non-susceptible to at least one of cefepime, ceftazidime and piperacillin/tazobactam.
[c]Compared S-CRPA to NS-CRPA using χ^2 tests for categorical variables and Wilcoxon rank-sum tests for continuous variables.
[d]Sterile sites included cultures from blood, bone, cerebrospinal fluid, deep tissue/internal abscesses, pericardial fluid, peritoneal fluid, synovial fluid and pleural fluid.
[e]Outcome at 30 days has the following mutually exclusive categories: death, alive and still hospitalized, or alive and discharged. Of those who were alive and discharged, the categories for discharge were LTACH, LTCF, private residence or other/unknown.

A major strength of this study is use of active population- and laboratory-based surveillance data to systematically identify all CRPA cases throughout metropolitan Atlanta, GA, resulting in a large sample size of >600 non-CF adults with CRPA. Notable limitations include that we did not have antibiotic use data or a severity of illness score, which may limit the generalizability of our findings. Additionally, similar to other studies, we are not able to differentiate between colonization and infection.[14,15] We limited our sample to only patients that were hospitalized within 1 week of culture to capture patients more likely to have an active CRPA infection requiring treatment. Lastly, as with all observational studies, we could not control for unmeasured differences between S-CRPA and NS-CRPA patients.

The S-CRPA phenotype is common among *P. aeruginosa* but unique to carbapenem-resistant organisms. Our observational

Table 2. Factors associated with 30 day mortality in patients with CRPA

	Alive ($n = 533$)	Dead ($n = 102$)	*P* value[a]	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[b]
S-CRPA[c]	179 (34)	40 (39)	0.27	1.3 (0.8–2.0)	1.9 (1.2–3.1)
Age category (years)			<0.01		
19–49	115 (22)	9 (9)		Reference	Reference
50–64	160 (30)	27 (26)		2.2 (1.0–4.8)	2.4 (1.1–5.6)
65–79	185 (35)	44 (43)		3.0 (1.4–6.5)	2.9 (1.3–6.4)
>79	73 (14)	22 (22)		3.9 (1.7–8.8)	5.3 (2.1–13.0)
Male ($n = 634$)	327 (61)	57 (56)	0.3	0.8 (0.5–1.2)	—
Race ($n = 595$)			0.8		
Black	281 (57)	52 (53)		0.87 (0.6–1.3)[d]	—
White	205 (41)	43 (44)		Reference	—
Multiracial or other	11 (2)	3 (3)		Reference	—
Charlson comorbidity index >2	244 (46)	63 (62)	<0.01	1.9 (1.2–3.0)	1.7 (1.1–2.8)
Residence 4 days prior to culture			<0.01		
Private residence	204 (38)	10 (10)		Reference	Reference
Inpatient	219 (41)	58 (57)		5.4 (2.7–10.9)	4.3 (2.0–9.3)
Long-term care facility[e]	110 (21)	34 (33)		6.3 (3.0–13.2)	6.4 (2.9–14.0)
ICU in 7 days prior to culture	145 (27)	56 (55)	<0.01	3.3 (2.1–5.0)	3.5 (2.1–5.9)
Sterile site infection	38 (7)	14 (14)	0.03	2.1 (1.1–4.0)	—

All values are presented as *n* (%) unless otherwise stated.
[a]Compared those alive versus dead at 30 days using χ^2 tests.
[b]Final multivariable model was created to estimate the association between S-CRPA phenotype and 30 day mortality. Blank cells indicate the term was not included in the final model.
[c]CRPA isolates susceptible to all of the following tested antibiotics: cefepime, ceftazidime and piperacillin/tazobactam.
[d]OR was calculated comparing black race with any other race.
[e]This includes long-term care facilities and long-term acute care hospital.

study suggests that S-CRPA may represent an important phenotypic subgroup to consider when choosing antibiotics, similar to choosing treatment for patients with ceftriaxone- or cefoxitin-resistant Enterobacterales infections. We believe our findings are hypothesis generating and should motivate additional research on the treatment of patients with S-CRPA. As global concerns of antibiotic resistance continue to rise, selecting the narrowest spectrum but effective antibiotic for different phenotypic patterns of resistance remains a crucial, unanswered question.

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Transparency declarations

None to declare.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the Centers for Disease Control and Prevention or National Institutes of Health.

Supplementary data

Table S1 and Figure S1 are available as Supplementary data at *JAC-AMR* Online.

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