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

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Received 26 May 2021; accepted 16 November 2021

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. 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. CRPA infections can be challenging to treat and are associated with a 17%–53% all-cause, in-hospital mortality.

Unlike other carbapenem-resistant pathogens, many CRPA isolates are reported to be susceptible to other traditional antipseudomonal β-lactams (cefepime, ceftazidime and piperacillin/tazobactam). 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. At some institutions, >50% of CRPA isolates are susceptible to at least one other traditional antipseudomonal β-lactam. 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.
obtained through medical record review. All-cause 30 day mortality data was
collected at each of the 21 ICUs in the week 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 classes7 (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-lacta-
mases.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 alterna-
tive 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.
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 \textit{P. aeruginosa} but unique to carbapenem-resistant organisms. Our observational

### Table 1. Characteristics and outcomes of hospitalized patients with CRPA in metropolitan Atlanta, stratified by susceptibility to traditional antipseudomonal \(\beta\)-lactams

|                        | All CRPA (n = 635) | S-CRPA\(^a\) (n = 219) | NS-CRPA\(^b\) (n = 416) | \(P\) value\(^c\) |
|------------------------|-------------------|------------------------|------------------------|-----------------|
| **Age category (years)** |                   |                        |                        |                 |
| 19–49                  | 124 (20)          | 37 (17)                | 87 (21)                | 0.09            |
| 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)**     |                   |                        |                        | 0.39            |
| 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 \(\chi^2\) 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 \textit{P. aeruginosa} but unique to carbapenem-resistant organisms. Our observational
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.

Acknowledgements
A portion of this work was presented at IDWeek in October 2020 (Poster 834).

We are grateful to all of the Georgia Emerging Infections Program staff who collect and maintain these data.

Funding
Surveillance of carbapenem-resistant P. aeruginosa was funded through the Centers for Disease Control and Prevention Emerging Infection Program (US0CK000485). J.H.-A. was supported by the Antibacterial Resistance Leadership Group fellowship (National Institute of Allergy and Infectious Diseases UM1AI104681). Funding agencies were not involved in the study design, data analysis, interpretation of results or drafting of the manuscript.

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

|                          | Alive (n = 533) | Dead (n = 102) | P valuea | Unadjusted OR (95% CI) | Adjusted OR (95% CI)b |
|--------------------------|----------------|---------------|----------|------------------------|-----------------------|
| S-CRPAc                  | 179 (34)       | 40 (39)       | 0.27     | 1.3 (0.8-2.0)          | 1.9 (1.2-3.1)         |
| Age category (years)     |                |               |          |                        |                       |
| 19–49                    | 115 (22)       | 9 (9)         | <0.01    | 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)           |                |               |          |                        |                       |
| Black                    | 281 (57)       | 52 (53)       | 0.87 (0.6-1.3)c | —                   |
| 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 facilityd | 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.

aCompared those alive versus dead at 30 days using χ² tests.
bFinal 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.
cCRPA isolates susceptible to all of the following tested antibiotics: cefepime, ceftazidime and piperacillin/tazobactam.
dOR was calculated comparing black race with any other race.
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| Black                    | 281 (57)       | 52 (53)       | 0.87 (0.6-1.3)c | —                   |
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| Multiracial or other     | 11 (2)         | 3 (3)         | Reference | —                     |
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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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