2018

Importance of site of infection and antibiotic selection in the treatment of carbapenem-resistant Pseudomonas aeruginosa sepsis

Nicholas S. Britt
Barnes-Jewish Hospital

David J. Ritchie
St. Louis College of Pharmacy

Marin H. Kollef
Washington University School of Medicine in St. Louis

Carey-Ann D. Burnham
Washington University School of Medicine in St. Louis

Michael J. Durkin
Washington University School of Medicine in St. Louis

See next page for additional authors

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

CLINICAL THERAPEUTICS

Importance of Site of Infection and Antibiotic Selection in the Treatment of Carbapenem-Resistant *Pseudomonas aeruginosa* Sepsis

Nicholas S. Britt,[a]* David J. Ritchie,[a,b] Marin H. Kollef,[c] Carey-Ann D. Burnham,[d,e,f] Michael J. Durkin,[g] Nicholas B. Hampton,[h] Scott T. Micek[a,b]

[a]Department of Pharmacy, Barnes-Jewish Hospital, St. Louis, Missouri, USA

[b]Department of Pharmacy Practice, St. Louis College of Pharmacy, St. Louis, Missouri, USA

[c]Department of Medicine, Division of Pulmonary and Critical Care Medicine, Washington University School of Medicine, St. Louis, Missouri, USA

[d]Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri, USA

[e]Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri, USA

[f]Department of Molecular Microbiology, Washington University School of Medicine, St. Louis, Missouri, USA

[g]Department of Medicine, Division of Infectious Diseases, Washington University School of Medicine, St. Louis, Missouri, USA

[h]Center for Clinical Excellence, BJC HealthCare, St. Louis, Missouri, USA

ABSTRACT In a retrospective analysis of 215 patients with carbapenem-resistant *Pseudomonas aeruginosa* sepsis, we observed a significantly higher risk of mortality associated with respiratory tract infection (risk ratio [RR], 1.20; 95% confidence interval [CI], 1.04 to 1.39; $P = 0.010$) and lower risk with urinary tract infection (RR, 0.80; 95% CI, 0.71 to 0.90; $P = 0.004$). Aminoglycoside monotherapy was associated with increased mortality, even after adjusting for confounders (adjusted RR, 1.72; 95% CI, 1.03 to 2.85; $P = 0.037$), consistent across multiple sites of infection.

KEYWORDS carbapenem resistance, *Pseudomonas aeruginosa*, multidrug resistance, sepsis

Infections due to carbapenem-resistant Gram-negative organisms represent an emerging threat to public health worldwide (1). The majority of carbapenem-resistant Gram-negative infections are caused by nonfermenters, most commonly, *Pseudomonas aeruginosa* (2). Multidrug-resistant *P. aeruginosa* is classified as a serious threat according to the most recent U.S. Centers for Disease Control and Prevention report, and 20% to 30% of clinical isolates are carbapenem resistant (1, 3). Mortality associated with these infections is high (20% to 50%), making optimal and timely treatment essential (4, 5). Unfortunately, the treatment of choice for carbapenem-resistant *P. aeruginosa* infection remains uncertain, and management is primarily based on pathogen-directed susceptibility patterns (6, 7).

We conducted a single-center retrospective cohort study at Barnes-Jewish Hospital (St. Louis, MO, USA), a 1,315-bed tertiary care academic medical center, to evaluate the comparative effectiveness of antibiotic agents used in the management of sepsis due to carbapenem-resistant *P. aeruginosa* infection (2012 to 2015). Inclusion criteria were age ≥18 years, hospital admission, carbapenem-resistant *P. aeruginosa* isolated from any site, and sepsis, defined as ≥2 systemic inflammatory response syndrome (SIRS) criteria (8). Exclusion criteria were cystic fibrosis (CF), polymicrobial infection, recurrent infection (only first case analyzed), and discharge to home alive without receiving appropriate targeted antibiotic therapy. Carbapenem resistance was defined as phe-

Received 22 November 2017 **Returned for modification** 13 December 2017 **Accepted** 19 January 2018

Accepted manuscript posted online 29 January 2018

Citation Britt NS, Ritchie DJ, Kollef MH, Burnham CA, Durkin MJ, Hampton NB, Micek ST. 2018. Importance of site of infection and antibiotic selection in the treatment of carbapenem-resistant *Pseudomonas aeruginosa* sepsis. Antimicrob Agents Chemother 62:e02400-17. https://doi.org/10.1128/AAC.02400-17.

Address correspondence to Nicholas S. Britt, nbritt@ku.edu.

* Present address: Nicholas S. Britt, Department of Pharmacy Practice, University of Kansas School of Pharmacy, Kansas City, Kansas, USA.

notypic nonsusceptibility to meropenem or imipenem. Clinical data were collected retrospectively from the electronic medical record. Comorbidities were identified by diagnosis codes as recorded by a treating physician. The primary outcome was all-cause in-hospital mortality. Baseline characteristics were compared by using the chi-squared test or Fisher's exact test for categorical data and Student's *t* test or the Mann-Whitney *U* test for continuous data. Multivariable log-binomial regression analysis was conducted to determine variables associated with mortality. Susceptibility testing was performed during routine clinical care using the disk diffusion method according to Clinical Laboratory and Standards Institute (CLSI) guidelines current at the time of infection (9). The Washington University in St. Louis institutional review board approved this study, and a P value of <0.05 was considered statistically significant.

A total of 2,736 patients with carbapenem-resistant Gram-negative infections were screened. Patients were excluded if they had <2 SIRS criteria ($n = 1{,}700$), CF ($n = 91$), recurrent infection ($n = 392$), lack of appropriate treatment before discharge alive ($n = 64$), and infection due to a Gram-negative organism other than *P. aeruginosa* ($n = 274$). A total of 215 patients with carbapenem-resistant *P. aeruginosa* sepsis were included in the final analysis. Overall, in-hospital mortality was 21.4% (46/215). Factors associated with mortality are shown in Table 1. The most common site of infection was the respiratory tract, which was associated with a greater risk of mortality than other sites of infection (28.8% [30/104] versus 14.4% [16/111]; risk ratio [RR], 1.20; 95% confidence interval [CI], 1.04 to 1.39; $P = 0.010$). The reason for this observation is unclear but may be related to difficulty in organism identification, leading to delayed appropriate therapy or suboptimal antibiotic penetration into the lung parenchyma. Conversely, urinary tract infections were associated with a lower risk of mortality than other sites of infection (6.5% [3/46] versus 25.4% [$n = 43/169$]; RR, 0.80; 95% CI, 0.71 to 0.90; $P = 0.004$), underscoring the importance of infection site on outcomes among patients with carbapenem-resistant *P. aeruginosa* infection.

The most commonly utilized treatment modality was monotherapy with cefepime ($n = 88$). At our institution, cefepime is the treatment of choice for empirical therapy due to suspected *P. aeruginosa* infection, and dual Gram-negative coverage is not routinely utilized because of cefepime susceptibility rates of ~90% among non-CF *P. aeruginosa* isolates. These susceptibility rates consistently exceed those of meropenem by 5% to 10%, and it is not uncommon to encounter cases of infection due to carbapenem-resistant *P. aeruginosa* with retained susceptibility to other antipseudomonal β-lactam agents, including cefepime or piperacillin-tazobactam (our unpublished data). In a recent study at the University of Pittsburgh Medical Center, 68% of carbapenem-resistant *P. aeruginosa* bloodstream isolates were susceptible to cefepime, and 57% were susceptible to piperacillin-tazobactam (7). Whether treatment of infections due to this susceptibility pattern requires use of more-toxic agents, such as aminoglycosides or polymyxins; more-expensive agents, such as novel β-lactam/β-lactamase inhibitors; or combinations of multiple active agents remains unclear (10). In the present study, we did not observe increased mortality associated with use of cefepime monotherapy (15.9% [14/88] versus 25.2% [32/127]; RR, 0.89; 95% CI, 0.77 to 1.02; $P = 0.102$) or piperacillin-tazobactam monotherapy (17.4% [8/46] versus 22.5% [38/169]; RR, 0.94; 95% CI, 0.80 to 1.10; $P = 0.455$) compared with mortality with all other therapies, suggesting that these agents may still be of utility in the management of select cases of carbapenem-resistant *P. aeruginosa* infection. There was no difference in mortality between patients receiving combination therapy and those receiving monotherapy (27.3% [3/11] versus 21.1% [43/204]; RR, 1.09; 95% CI, 0.75 to 1.57; $P = 0.705$), albeit this was a limited sample. Previous literature suggested a benefit of definitive treatment with combination therapy in carbapenem-resistant *Enterobacteriaceae* infection, but the data do not appear to support increased effectiveness against multidrug-resistant *P. aeruginosa*, consistent with our findings (10).

Aminoglycoside monotherapy was associated with an increased risk of mortality compared to other monotherapies (38.5% [15/39] versus 17.0% [28/165]; RR, 1.35; 95%

TABLE 1 Characteristics associated with all-cause in-hospital mortality among patients with sepsis due to carbapenem-resistant *Pseudomonas aeruginosa*

Characteristic[a] (*n* = 215)	Survivor (*n* = 169)	Nonsurvivor (*n* = 46)	*P* value
Age, median (yr [IQR])	58 (44–67)	61 (52–70)	0.060
Age ≥65 yr (*n* [%])	59 (34.9)	19 (41.3)	0.424
Yr of infection (*n* [%])			0.224
2012	59 (34.9)	17 (37.0)	0.797
2013	42 (24.9)	7 (15.2)	0.167
2014	28 (16.6)	13 (28.3)	0.073
2015	40 (23.7)	9 (19.6)	0.556
ICU admission (*n* [%])	86 (50.9)	31 (67.4)	0.046
Length of stay (median days [IQR])[b]	3 (1–18)	10 (1–29)	0.034
Hospital-acquired infection (*n* [%])[c]	93 (55.0)	33 (71.7)	0.041
Time to appropriate treatment (mean ± SD h)[d]	16.3 ± 27.6	28.5 ± 77.5	0.302
Antibiotic treatment (*n* [%])[e,f]			0.089
Aminoglycoside monotherapy	24 (14.2)	15 (32.6)	0.004
Colistin monotherapy	13 (7.7)	1 (2.2)	0.311
Cefepime monotherapy	74 (43.8)	14 (30.4)	0.102
Fluoroquinolone monotherapy	10 (5.9)	4 (8.7)	0.505
Piperacillin-tazobactam monotherapy	38 (22.5)	8 (17.4)	0.455
Aztreonam monotherapy	1 (0.6)	1 (2.2)	0.383
Ceftolozane/tazobactam monotherapy	1 (0.6)	0 (0.0)	>0.999
Combination therapy	8 (4.7)	3 (6.5)	0.705
Infection site (*n* [%])			0.081
Intraabdominal	9 (5.3)	3 (6.5)	0.754
Respiratory tract	74 (43.8)	30 (65.2)	0.010
Bloodstream/endovascular	17 (10.1)	4 (8.7)	>0.999
Urinary tract	43 (25.4)	3 (6.5)	0.004
Skin/soft tissue/osteomyelitis	26 (15.4)	6 (13.0)	0.692
Previous hospitalization (*n* [%])[g]	151 (89.3)	46 (100)	0.015
Invasive surgical procedure (*n* [%])[h]	86 (50.9)	23 (50.0)	0.915
Central venous catheter (*n* [%])[h]	133 (78.7)	32 (69.6)	0.194
Urinary catheter (*n* [%])[h]	107 (63.3)	32 (69.6)	0.432
Other invasive device (*n* [%])[h]	37 (21.9)	11 (23.9)	0.771
Mechanical ventilation (*n* [%])	105 (62.1)	43 (93.5)	<0.001
Previous antibiotic exposure (*n* [%])[i]	131 (77.5)	42 (91.3)	0.036
Carbapenem[i]	81 (47.9)	27 (58.7)	0.195
Vasopressor requirement (*n* [%])	70 (41.4)	41 (89.1)	<0.001
Immunosuppression (*n* [%])	56 (33.1)	28 (60.9)	0.001
Solid organ transplantation	14 (8.3)	7 (15.2)	0.160
Stem cell transplantation	18 (10.7)	5 (10.9)	>0.999
Acute kidney injury (*n* [%])[j]	48 (28.4)	13 (28.3)	0.985
SIRS criteria (median [IQR])	3 (2–3)	3 (2–3)	0.541
Charlson comorbidity index (median [IQR])	6 (3–8)	7 (5–11)	0.007
APACHE II score (median [IQR])	13 (10–17)	15 (12–19)	0.030

[a]IQR, interquartile range; SD, standard deviation; APACHE II, Acute Physiology and Chronic Health Evaluation II.
[b]Before index culture.
[c]Hospitalized >48 h before index culture without previous evidence of infection.
[d]Treatment with an agent to which the organism was phenotypically susceptible *in vitro*.
[e]Monotherapy defined as receipt of <2 antibiotics to which the organism was susceptible *in vitro* as definitive therapy for ≥48 h.
[f]Combination therapy defined as receipt of ≥2 antibiotics to which the organism was susceptible *in vitro* as definitive therapy for ≥48 h.
[g]Within the preceding 6 months.
[h]During the index hospitalization before index culture.
[i]Within the preceding 3 months.
[j]Determined by diagnosis code as recorded by a treating physician.

TABLE 2 Multivariable log-binomial regression model of variables associated with all-cause in-hospital mortality among patients with carbapenem-resistant *Pseudomonas aeruginosa* sepsis

Variable	Crude RR[a] (95% CI)	*P* value	Adjusted RR[a] (95% CI)	*P* value
Aminoglycoside monotherapy[a]	1.35 (1.04–1.75)	0.003	1.72 (1.03–2.85)	0.037
Vasopressor requirement	7.68 (3.16–18.69)	<0.001	6.85 (2.71–17.35)	<0.001
Charlson comorbidity index	1.15 (1.04–1.96)	0.005	1.16 (1.05–1.90)	0.001
APACHE II score	1.07 (1.01–1.13)	0.036	1.01 (0.98–1.04)	0.394

[a]RR, risk ratio. Comparator: all other monotherapies.

CI, 1.04 to 1.75; $P = 0.003$). This association persisted after adjusting for confounding factors in multivariable log-binomial regression (adjusted RR, 1.72; 95% CI, 1.03 to 2.85; $P = 0.037$) (Table 2). Other factors significantly associated with an increased risk of mortality were vasopressor requirement and comorbidity burden (Table 2). In subgroup analyses by site of infection, aminoglycoside monotherapy was associated with a significantly increased risk of mortality in skin and soft tissue infections/osteomyelitis (50.0% [3/6] versus 13.0% [3/23]; RR, 1.74; 95% CI, 0.77 to 3.92; $P = 0.047$). Aminoglycoside monotherapy was associated with a nonsignificantly increased risk of mortality among subgroups of urinary tract (20.0% [1/5] versus 5.0% [2/40]; RR, 1.19; 95% CI, 0.76 to 1.85; $P = 0.205$), bloodstream/endovascular (33.3% [1/3] versus 12.5% [2/16]; RR, 1.31; 95% CI, 0.58 to 2.98; $P = 0.364$), and intraabdominal (40.0% [10/25] versus 24.7% [21/85]; RR, 1.25; 95% CI, 0.89 to 1.77; $P = 0.135$) infections. Only one patient with respiratory tract infection was treated with aminoglycoside monotherapy. Although aminoglycosides distribute well into various tissues, pathophysiological perturbations in critically ill patients with sepsis leading to increased volume of distribution and augmented renal clearance may decrease systemic aminoglycoside concentrations and prevent attainment of pharmacokinetic/pharmacodynamic targets versus isolates displaying MICs near the susceptibility breakpoint, potentially leading to poorer outcomes (11).

The present study had limitations. This was a retrospective analysis at a single center and likely lacked sufficient power to detect differences between some antibiotic regimens. Thus, prospective comparative effectiveness analyses of antibiotic agents for carbapenem-resistant *P. aeruginosa* infection are warranted. We included culture results from all body sites to evaluate the influence of this variable on patient outcomes; however, cultures from nonsterile sites may represent colonization rather than true infection. We attempted to overcome this by limiting analyses to patients with sepsis only and excluding known colonizers (i.e., CF). Thus, we expect any degree of misclassification to be negligible. This study did not feature analyses of antibiotic dosing strategies, which may have influenced the results.

In a retrospective analysis of patients with sepsis due to carbapenem-resistant *P. aeruginosa*, we evaluated associations between the site of infection and antibiotic choice on all-cause in-hospital mortality. We found an increased risk of mortality among patients with respiratory tract infection and a reduced risk of mortality among patients with urinary tract infection. Aminoglycoside monotherapy was associated with higher mortality than other treatments, and the magnitude of this effect was consistent across multiple infection sites. Although additional research is needed, the present study revealed important relationships between the site of infection, antibiotic selection, and mortality in patients with carbapenem-resistant *P. aeruginosa* infection, which should be considered in future studies.

ACKNOWLEDGMENTS

Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health (KL2TR002346 to M.J.D.) and the Barnes-Jewish Hospital Foundation (M.H.K.).

The funders had no role in the study design, data collection and interpretation, or the decision to submit the work for publication.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Barnes-Jewish Hospital Foundation.

N.S.B. has served as a consultant on research grants from Merck & Co. and Gilead Sciences. D.J.R. has received speaking honoraria from Allergan, Astellas Pharma, and Theravance Biopharma. C.A.B. has received research support from bioMérieux, Cepheid, Theravance Biopharma, Accelerate Diagnostics, and Aperture Bio and consulting fees from Thermo Fisher and Monsanto. All other authors declare no conflicts of interest.

REFERENCES

1. Centers for Disease Control and Prevention. 2013. Antibiotic resistance threats in the United States, 2013. Centers for Disease Control and Prevention, Atlanta, GA.
2. Cai B, Echols R, Magee G, Arjona Ferreira JC, Morgan G, Ariyasu M, Sawada T, Nagata TD. 2017. Prevalence of carbapenem-resistant Gram-negative infections in the United States predominated by Acinetobacter baumannii and Pseudomonas aeruginosa. Open Forum Infect Dis 4:ofx176.
3. Weiner LM, Webb AK, Limbago B, Dudeck MA, Patel J, Kallen AJ, Edwards JR, Sievert DM. 2016. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011-2014. Infect Control Hosp Epidemiol 37:1288–1301. https://doi.org/10.1017/ice.2016.174.
4. Liu Q, Li X, Li W, Du X, He JQ, Tao C, Feng Y. 2015. Influence of carbapenem resistance on mortality of patients with Pseudomonas aeruginosa infection: a meta-analysis. Sci Rep 5:11715. https://doi.org/10.1038/srep11715.
5. Zhang Y, Chen XL, Huang AW, Liu SL, Liu WJ, Zhang N, Lu XZ. 2016. Mortality attributable to carbapenem-resistant Pseudomonas aeruginosa bacteremia: a meta-analysis of cohort studies. Emerg Microbes Infect 5:e27. https://doi.org/10.1038/emi.2016.22.
6. Kanj SS, Kanafani ZA. 2011. Current concepts in antimicrobial therapy against resistant Gram-negative organisms: extended-spectrum beta-lactamase-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae, and multidrug-resistant Pseudomonas aeruginosa. Mayo Clin Proc 86:250–259. https://doi.org/10.4065/mcp.2010.0674.
7. Buehrle DJ, Shields RK, Clarke LG, Potoski BA, Clancy CJ, Nguyen MH. 2017. Carbapenem-resistant *Pseudomonas aeruginosa* bacteremia: risk factors for mortality and microbiologic treatment failure. Antimicrob Agents Chemother 61:pii=e01243-16. https://doi.org/10.1128/AAC.01243-16.
8. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. 1992. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 101:1644–1655.
9. Clinical and Laboratory Standards Institute. 2016. Performance standards for antimicrobial susceptibility testing; 26th informational supplement. CLSI document M100S-26. Clinical and Laboratory Standards Institute, Wayne, PA.
10. Hu Y, Li L, Li W, Xu H, He P, Yan X, Dai H. 2013. Combination antibiotic therapy versus monotherapy for Pseudomonas aeruginosa bacteraemia: a meta-analysis of retrospective and prospective studies. Int J Antimicrob Agents 42:492–496. https://doi.org/10.1016/j.ijantimicag.2013.09.002.
11. Varghese JM, Roberts JA, Lipman J. 2011. Antimicrobial pharmacokinetic and pharmacodynamic issues in the critically ill with severe sepsis and septic shock. Crit Care Clin 27:19–34. https://doi.org/10.1016/j.ccc.2010.09.006.