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Concise Communication

The epidemiological impact and significance of carbapenem resistance in *Pseudomonas aeruginosa* bloodstream infections: a matched case–case-control analysis

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Abstract

A case–case-control investigation (N = 255 patients) explored the epidemiology of carbapenem-resistant *Pseudomonas aeruginosa* (CRPA). Recent exposure to carbapenems and a rapidly fatal condition should prompt practitioners to shorten delays in initiating appropriate therapy, which can adversely impact CRPA outcomes, as opposed to the isolated impact of the carbapenem resistance determinant.

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Carbapenems are effective and safe; they are the mainstay of therapy for serious *Pseudomonas aeruginosa* infections.[1–3] However, there is a significant association between carbapenem nonsusceptibility and adverse clinical outcomes.[4] Carbapenem-resistant *P. aeruginosa* (CRPA) is a major epidemiological threat, specifically in countries where the new antipseudomonal β-lactam agents (eg, ceftolozane-tazobactam and ceftazidime-avibactam) are not yet available.

Currently, prevention efforts frequently target CRPA strains. Contact isolation precautions are utilized for CRPA carriers, and screening programs are frequently aimed at CRPA strains.[2] However, the mechanisms of resistance of *P. aeruginosa* to carbapenems are frequently mediated through chromosomal genes.[2] Therefore, it might be appropriate to target the prevention of transmission of all *P. aeruginosa* strains. In addition, the studies that have reported on the association between CRPA and poor outcomes have major limitations: (1) many were not conducted using the matched case–case-control study design,[4] (2) many did not strictly adhere to infection definitions that differentiate infection from asymptomatic carriage,[3] and (3) many have not controlled for delay in initiation of appropriate antimicrobial therapy (DAAT).[4] All of these factors might have led to the overestimation of the independent association between resistance to carbapenems and poor clinical outcomes. For CRPA prevention programs to be effective, it is important to differentiate DAAT from the isolated impact of the resistance determinant to appropriately allocate prevention resources. Moreover, exploring the independent predictors of CRPA using an appropriate design can help guide stewardship interventions aimed at reducing DAAT and improving outcomes.

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Methods

A retrospective matched case–case-control analysis was conducted among adults (>18 years old) at the Assaf Harofeh Medical Center, Israel, from 2007 to 2012. The institutional ethics committee approved the study. Resistant cases were defined as patients with bloodstream infections (BSIs) due to *P. aeruginosa* that were not susceptible to either meropenem or imipenem (MIC ≥ 4 μg/dL for both).[5] Susceptible cases were defined as patients with *P. aeruginosa* BSIs that were susceptible to both meropenem and imipenem. The uninfected control group consisted of patients without *P. aeruginosa* infection or BSI. Patients were included in the analysis only once. A susceptible case and an uninfected control were matched to a resistant case (1:1:1 ratio) according to time at risk,[6] hospital unit, and calendar year. Eligible susceptible cases and uninfected controls were randomly selected (Excel software, Microsoft, Redmond WA).

Data were collected from available records. Posthospitalization deaths were captured from a national registry. The primary outcome was 14-day mortality. Assuming a 21% mortality rate among cases and 10% among controls,[3] we calculated that a population of 225 patients would be needed to provide adequate power (β = 0.8) to detect significant differences between cases and controls. Logistic and Cox regressions were used to capture predictors and outcomes of CRPA infections. All models were assessed for collinearity and were controlled for confounding. A matched analysis was performed comparing resistant cases and uninfected controls. We forced 2 variables into each outcome model: carbapenem resistance and DAAT (as a continuous variable and DAAT > 48 hours, whichever statistical association was stronger). All tests were 2-tailed.

Results

We matched 85 CRPA BSI cases to 85 case patients with carbapenem-susceptible *P. aeruginosa* (CSPA) BSI (from 491 eligible patients) and to 85 uninfected control patients (from 2,046 eligible patients). In total, 255 patients were enrolled. The study population consisted of elderly (69%) and functionally dependent (48%) individuals,[7] with high Charlson's comorbidity indices (5.7 ± 3.1).[8]

Predictors of CRPA BSI

Most bivariate predictors associated with CRPA BSI, primarily certain demographics and background conditions, were also associated with CSPA BSI (Table 1). The distribution of the infectious syndromes was similar. Acute illness indices were more severe among patients with CRPA infections (Table 1).

Table 1. Selected Bivariable Analyses Comparing Risk Factors Associated With Resistant Case Patients, Susceptible Case Patients, and Uninfected Control Patients (n = 85 patients in each group)

Parameter	CRPA No. (%)[a]	CSPA No. (%)[a]	Uninfected Controls No. (%)[a]	CRPA vs Uninfected		CSPA vs Uninfected		CRPA vs CSPA	
				OR (95% CI)	*P* Value	OR (95%)	*P* Value	OR (95% CI)	*P* Value
Demographics									
Age (years), mean ± SD	69.7 ± 16.2	72.7 ± 13.4	66.3 ± 15.97		.17		**.005**		.17
Female gender	45 (52.9)	42 (49.4)	37 (43.5)	1.4 (0.8–3.3)	.22	1.3 (0.7–2.5)	.40	1.1 (0.6–2.0)	.65
Background conditions and comorbidities									
Partially or fully dependent[7]	48 (56.5)	43 (50.6)	30 (35.3)	2.5 (1.3–5)	**.006**	2.0 (1.1–3.3)	**.04**	1.3 (0.7–2.5)	.44
Impaired cognition	35 (41.2)	27 (31.8)	18 (21.2)	2.5 (1.3–5)	**.005**	1.7 (0.8–3.3)	.12	1.4 (0.8–2.5)	.20
Permanent residency at a LTCF or direct transfer from another hospital	29 (34.1)	14 (16.7)	18 (21.2)	2 (1.0–3.3)	.06	0.8 (0.3–1.7)	.45	2.5 (1.3–5.0)	**.009**
Ischemic heart disease	16 (18.8)	19 (22.4)	32 (37.6)	0.4 (0.2–0.8)	**.006**	0.5 (0.2–0.9)	**.03**	0.8 (0.4–1.7)	.60
Diabetes mellitus	27 (31.8)	40 (47.1)	38 (44.7)	0.6 (0.3–1.1)	.08	1.1 (0.6–2)	.8	0.5 (0.3–1)	**.04**
Malignancy (in the past or active)	15 (17.6)	16 (18.8)	14 (16.5)	1.1 (0.5–2.5)	.84	1.1 (0.5–2.5)	.70	0.9 (0.4–2)	.80
Charlson combined condition score,[8] mean ± SD	5.3 ± 2.7	6.2 ± 2.9	5.5 ± 3.5	0.77		0.11			**.03**
Overall immunosuppression[b]	30 (35.3)	29 (34.1)	14 (16.5)	2.5 (1.4–5)	**.005**	2.5 (1.3–5)	**.008**	1.1 (0.6–2)	.90
Exposures to healthcare settings and antibiotics prior to isolation									
ICU stay in previous 3 mo	57 (67.1)	49 (57.6)	9 (10.6)	16.7 (7.7–50)	**<.001**	10 (5–33)	**<.001**	1.4 (0.8–2.5)	.20
Invasive procedure in previous 3 mo	69 (81.2)	69 (81.2)	15 (17.6)	20 (10–50)	**<.001**	20 (10–50)	**<.001**	1.0 (0.5–2.2)	> .99
Permanent devices[c]	72 (84.7)	58 (68.2)	16 (18.8)	25 (11.1–50)	**<0.001**	10 (4.5–20)	**<.001**	2.5 (1.3–5)	**.01**
Received antibiotics in previous 3 mo	72 (84.7)	66 (77.6)	23 (27.1)	14.3 (7.1–33.3)	**<.001**	9.1 (5–20)	**<.001**	1.7 (0.7–3.3)	.20
Time from last antibiotics, median d (range)	1.0 (0–38)	3.5 (0–76)	6 (0–76)		**.02**		.60		**.007**
BLBLIs in preceding 3 months	34 (46.6)	33 (49.3)	4 (16)	5 (1.4–14.3)	**.008**	5(1.6–16.7)	**.004**	0.9 (0.5-1.7)	.80
Carbapenems in previous 3 mo	51 (69.9)	22 (32.8)	2 (8.3)	25 (5–100)	**<.001**	5 (1.2–25)	**.03**	5.0 (2.5-10)	**<.001**
Severity of illness indices at time of isolation									
Hypotension[d]	43 (50.6)	21 (25.3)	12 (14.1)	6.2 (2.9–13.1)	**<.001**	2 (0.9–4.4)	.08	3.1 (1.6-6)	**<.001**
Mechanical ventilation	55 (64.8)	47 (56.6)	11 (12.9)	12.3 (5.7–26.7)	**<.001**	8.3 (3.9–17.9)	**<.001**	1.5 (0.8–2.7)	.20
Pitt bacteremia score,[10] median (range)	6 (0–13)	4 (0–14)	0 (0–12)		**<.001**		**<.001**		**.015**
Rapidly fatal McCabe score[9]	58 (68.2)	41 (48.8)	10 (11.8)	16.7 (7.1–33.4)	**<.001**	10.0 (3.3–16.7)	**<.001**	2.5 (1.3–5.0)	**.01**

Note. Significant associations are highlighted in bold. CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CSPA, carbapenem-susceptible *P. aeruginosa*; OR, odds ratio; CI, confidence interval; SD, standard deviation; LTCF, long-term care facility. ICU, intensive care unit; BLBLI, β-lactam–β-lactamase inhibitor combination; BSI, blood stream infection.

[a]Valid percent: count divided by the total number of valid (ie, nonmissing) observations.

[b]Immunosuppression includes any of the following: neutropenia at culture date (<500 neutrophils/mm^3), exposure to glucocorticoids in the previous month, chemotherapy in the previous 3 months, radiotherapy, posttransplantation of any kind, anti-TNF-α (tumor necrosis factor α) therapy in the previous 3 months, or (7) human immunodeficiency virus (HIV) infection.

[c]Permanent devices included tracheostomies, percutaneous endoscopic gastrostomy, pacemakers, central lines, urinary catheters, external orthopedic devices, drains. Not included: internal stents, prosthetic heart valve, and prosthetic joints. Permanent devices were in place at least 48 hours prior to the isolation.

[d]Hypotension was defined as a systolic blood pressure <90 mmHg, or administration of intravenous vasopressors, or an acute drop in systolic blood pressure >30 mmHg and/or diastolic blood pressure >20 mm Hg in the 48 hours preceding the culture time.

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Table 2. Bivariable Analyses Comparing Clinical Outcomes of Resistant Case Patients, Susceptible Case Patients, and Uninfected Control Patients (n = 85 patients in each group).

Parameter	CRPA No. (%)[a]	CSPA No. (%)[a]	Uninfected Controls No. (%)[a]	CRPA vs Uninfected		CSPA vs Uninfected		CRPA vs CSPA	
				OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Time to appropriate antimicrobial therapy parameters									
Hours to appropriate therapy, median (range)	31.3 (0–121)	7 (0–118)							**.034**
≥48 h DAAT	39 (58.2)	21 (30.4)						3.3 (1.7–5)	**.001**
Clinical outcomes									
In hospital mortality	45 (52.9)	46 (54.1)	24 (28.2)	2.5 (1.4–5)	**.001**	3.3 (1.7–5)	**.001**	>0.99 (0.5–1.7)	.90
14-d mortality	36 (42.4)	28 (32.9)	2 (2.4)	33.3 (7.1–100)	**<.001**	20.0 (4.8–100)	**<.001**	1.4 (0.8–2.5)	.20
90-d mortality	51 (60)	52 (61.2)	29 (34.1)	2.9 (1.6–5.3)	**.01**	3.3 (1.7–5.1)	**<.001**	0.9 (0.5–1.7)	.90
Among survivors of the index hospitalization only									
Functional deterioration	18 (46.2)	20 (51.3)	18 (29.5)	2.1 (0.9–5)	.09	2.5 (1.1–5.0)	**.03**	0.8 (0.3–2)	.70
Discharged to LTCF after being admitted from home	19 (65.5)	16 (44.4)	10 (19.2)	10 (2.9–20)	**<.001**	3.3 (1.4–10)	**.01**	2.5 (0.8–5)	.09
CDI isolation in the following 3 mo	1 (1.2)	2 (2.4)	1 (1.2)	1.0 (0.06–16.66)	>.99	2.0 (0.2–25)	>.99	0.5 (0.1–5)	>.99
Invasive procedure or surgery in the following 3 mo[b]	31 (36.9)	29 (34.5)	52 (61.2)	0.4 (0.2–0.7)	**.02**	0.3 (0.2–0.6)	**.001**	1.1 (0.6–2)	.70
Length of stay, median d (range)	37 (0–193)	35 (0–168)	21 (0–99)		**<.001**		**<.001**		.932

Note. CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CSPA, carbapenem-susceptible *P. aeruginosa*; OR, odds ratio; CI, confidence interval; LTCF, long-term care facility; CDI, *Clostridium difficile* infection. Significant associations are highlighted in bold.

[a]Valid percent: count divided by the total number of valid (ie, nonmissing) observations.

[b]Examples of invasive procedure other than surgery include endoscopy, percutaneous procedure, central line, urinary catheter, and drain insertion.

We conducted 2 multivariable risk factor analyses: resistant cases versus controls and susceptible cases versus controls. The independent predictors of CRPA were ischemic heart disease (aOR, 0.17; $P = .02$), recent (3 months) exposure to carbapenems (aOR, 17.4; $P = .001$), and rapidly fatal McCabe[9] condition (aOR, 12.1; $P = .001$). Independent predictors of CSPA were advanced age ($P = .02$), ischemic heart disease (aOR, 0.13; $P = .005$), and recent invasive procedure (aOR, 24; $P < .001$). Independent predictors associated with CRPA but not CSPA infection were recent exposure to carbapenems and a rapidly fatal McCabe score.[9]

Clinical outcomes of CRPA BSI

Of the 255 patients included in this study, 115 patients (45.1%) died during their index hospitalization, 66 patients (25.9%) died within 14 days (primary outcome), and 132 patients (51.8%) died within 90 days. Of patients who survived the hospitalization, the median duration of stay was 17 days (range, 0–149 days); 56 patients (40.3%) experienced functional deterioration,[7] and 45 patients (38.5%) were discharged to a long-term care facility (LTCF) after being admitted from home. Patients with CRPA or CSPA BSIs had significantly worse clinical outcomes compared to uninfected controls (Table 2). Clinical outcomes were similar between CRPA and CSPA cases. Time to initiation of appropriate therapy was significantly prolonged among CRPA BSIs compared to CSPA BSIs (Table 2).

Multivariable models were calculated for 2 clinical outcomes: 14-day mortality and discharge to an LTCF (Table 2). Independent factors associated with 14-day mortality were time to appropriate antimicrobial therapy ($P = .008$), malignancy (aOR, 4.1; 95% confidence interval [CI], 1.5–11.5; $P = .007$), rapidly fatal McCabe score (aOR, 3.7; 95% CI, 1.1–12.1; $P = .03$),[9] and a Pitt bacteremia score ≥4 (aOR, 1.3; 95% CI, 1.1–1.5; $P = .004$).[10] Independent factors associated with discharge to an LTCF were impaired cognition at baseline (aOR, 14.7; 95% CI, 1.2–176; $P = .03$), ICU stay during current hospitalization (aOR, 24.3; 95% CI, 2.2–266; $P = .009$), and Pitt bacteremia score ≥4 (aOR, 1.8; 95% CI, 1.03–3.1; $P = .04$).[10] Carbapenem resistance was not associated with these outcomes.

Discussion

Debate continues as to whether the associations between poor clinical outcomes and resistance are due to DAAT or to inherent properties of the resistance determinant of the offending strain.[1] This study addressed methodological limitations from prior studies evaluated CRPA infections and clinical outcomes.

This investigation confirmed that DAAT impacts outcomes of patients with multidrug-resistant organism (MDRO) infections.[1] This impact has been demonstrated in the past with *Acinetobacter baumannii*, carbapenem-resistant enterobacteriaceae (CRE), vancomycin-resistant enterococci (VRE), and methicillin-resistant *Staphylococcus aureus* (MRSA).[1] There is an urgent need to develop genuine measures to shorten DAAT (eg, via use of rapid diagnostics, efficacious predictive tools) to improve the outcomes of MDRO infections.[1]

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In contrast to prior investigations,[3,4] patients with CSPA BSIs did not suffer significantly worse outcomes compared to patients with CRPA BSI (Table 1). We believe this was due to the study design, which resulted in selecting a control group which was truly representative of the source population and also due to limitations in sample size and power in the current study (though it was powered to detect differences in the primary outcome).[6]

Our study had several limitations. It was a single-centered, retrospective with a relatively small sample size. However, by overcoming prior limitations, this study generated valuable data regarding stewardship and infection control aspects, pertaining to the management of *P. aeruginosa* infections in hospitalized patients. Results should be validated in other centers and on larger populations.

Based on these results, infection control programs should not focus solely on carbapenem resistance. The case–case-control study design identified independent predictors for CRPA (ie, recent exposure to carbapenems and a rapidly fatal McCabe score). This information can be used to develop successful stewardship interventions and to reduce DAAT and improve patient outcomes.

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