

Independent epidemiological role of carbapenem non-susceptibility in *Pseudomonas aeruginosa* infections

Tzach Aviv, Tsillia Lazarovitch, David Katz, Ronit Zaidenstein, Mor Dadon, Chen Daniel, Dror Marchaim

Sackler School of Medicine, Tel-Aviv University, Tel-Aviv. Unit of Infectious Diseases, Assaf Harofeh Medical Center, Zerifin, Israel



Introduction

- Carbapenems are considered amongst the agents of choice for invasive *Pseudomonas aeruginosa* infections.
- The rising incidence of carbapenem resistance among *Pseudomonas aeruginosa* (CRPA) offending strains has become a major source of concern, resulting in worse outcomes.
- The clinical impact of CRPA infections was not quantified using appropriate methodology and control groups (i.e., matched case-control design while strictly differentiating colonization from infection and controlling for delay in initiation of appropriate antimicrobial therapy).
- Our aim was to explore the independent role of carbapenem-resistance on clinical outcomes of patients with *P. aeruginosa* infection and to identify independent predictors for CRPA.

Methods

- Matched case-control study for adult patients with CRPA bloodstream infection (BSI) from 2007 to 2012 was executed at Assaf Harofeh medical center, Israel.
- Two additional patients were matched to each CRPA BSI case patient (in a 1:1:1 ratio); i.e., a case patient with carbapenem-susceptible *P. aeruginosa* BSI (CSPA), and an un-infected control patient.
- Matching criteria (in order of importance) were 1) time at risk, 2) admitting unit, and 3) calendar year.
- Multivariable matched analyses of predictors and outcomes were conducted by logistic regression and Cox regression, respectively.

Results

- The study cohort consisted of three matched groups of 85 patients each (overall 255).
- There were multiple predictors significantly associated with CRPA BSI (in comparison to un-infected controls); however, the majority was associated also with CSPA infections.
- In multivariable matched analysis, independent predictors of CRPA BSI were the presence of permanent devices and a shorter duration of time since the last administered antibiotic.

Multivariable model of risk factors for CRPA BSI

Variable	OR (95% CI); P-value
Permanent devices	11.4 (3.3-40); <0.001
Time from last antibiotics (in days)	0.96 (0.91-1.0); 0.05
Hypotension	1.8 (0.9-3.8); 0.096

➤ In univariate analyses, all measurable outcomes were associated with CRPA (i.e., mortality outcomes, length of stay, and morbidity outcomes).
 ➤ However, in separate multivariable outcome models, the carbapenem resistance determinant was not independently associated with any of the outcomes.
 ➤ On the contrary, timely initiation of appropriate antimicrobials were independently correlated with improved outcomes (p<0.05) for some of the multivariable outcome models.

Multivariate model of 14-days mortality

Variable	OR (95% CI); P-value
Carbapenem resistance <i>P. aeruginosa</i>	1.6 (0.7-3.9); 0.3
Malignancy (in the past or active)	4.1 (1.5-11.5); 0.007
Rapidly fatal McCabe score	3.7 (1.1-12.1); 0.03
Appropriate therapy administered (given 2 days before index day to 7 days after)	0.2 (0.1-0.6); 0.008
Pitt bacteremia score	1.3 (1.1-1.5); 0.004

*We chose to display this outcome because it was the primary study outcome

Multivariate model for discharged to long-term care facility (LTCF) after being admitted from home

Variable	OR (95% CI); P-value
Carbapenem resistance <i>P. aeruginosa</i>	0.2 (0.02-1.3); 0.09
Impaired cognition	14.7 (1.2-176.2); 0.03
Elderly (≥ 65 years old)	4.9 (0.7-34.5); 0.1
Pitt bacteremia score	1.8 (1.03-3.1); 0.04
ICU stay in current hospitalization	24.3 (2.2-265.6); 0.009

*We chose this outcome because it was the outcome parameter with the strongest association per univariable analysis between CRPA and CSPA (p=0.09).

Conclusions

- Carbapenem resistance was **not** independently associated with worse outcomes among patients with *P. aeruginosa* BSI, despite the correlations in univariable analyses.
- Appropriate antimicrobials are independently associated with improved outcomes.
- **The carbapenem resistance determinant of *P. aeruginosa* should not serve as a marker for the clinical and epidemiological significance of the pathogen.**
- Presence of permanent devices and recent exposure to antimicrobials should prompt the suspicion of CRPA, which might help to reduce delays in instituting appropriate therapy and improve patients' outcomes.