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

Tzach Aviv[1], Tsillia Lazarovitch[1], David Katz[2], Ronit Zaidenstein[3], Mor Dadon[1], Chen Daniel[1], Dror Marchaim*[4]

[1]*Assaf Harofeh Medical Center*

[2]*Shaare Zedek Medical Center; Internal Medicine*

[3]*Assaf Harofeh Medical Center; Infectious Diseases*

[4]*Assaf Harofeh Medical Center; Infection Control and Prevention*

Background: Carbapenems are considered amongst the agents of choice for *Pseudomonas aeruginosa* infections, as long as the pathogen is susceptible; however, the incidence of infections caused by carbapenem-resistant *P. aeruginosa* (CRPA) is increasing, resulting in worse outcomes. This association however, was not derived using appropriate control groups (i.e., case-case-control) or while controlling for certain confounders (e.g., time to appropriate therapy, differentiation between colonization and infection). Hospitals are frequently instituting infection control measures (e.g., contact isolation precautions, screening policies) only when isolates becomes non-susceptible to carbapenems. The independent role of the carbapenem resistance determinant has not been analyzed while using a controlled design. Our objectives were to: 1) determine the independent role of carbapenem-resistance on clinical outcomes of patients with *P. aeruginosa* infections, and 2) identify independent predictors for CRPA.

Material/methods: A matched case-case-control study was conducted at the Assaf Harofeh Medical Center for calendar years 2007-2012, for adult (>18 years) patients with monomicrobial CRPA bloodstream infections (BSI). 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) included: 1) time at risk (time from admission to infection), 2) admitting unit, and 3) calendar year. Demographic, microbiological and

clinical data were extracted from all available records and national registries. Multivariable matched analyses of predictors and outcomes were conducted by logistic regression (risk factors) and Cox regression (outcomes).

Results: The study cohort consisted of three matched groups of 88 patients (overall 264). There were multiple predictors significantly associated with CRPA BSI (in comparison to un-infected controls); however, the majority was associated also with CSPA. In the multivariable matched analysis, the only independent predictors of CRPA BSI, as opposed to CSPA BSI, were the presence of permanent devices (aOR=11.4, $p<0.001$) and a shorter duration of time since the last administered antibiotic ($p=0.05$). Per univariate analyses, all measurable outcomes were associated with CRPA (i.e., mortality outcomes, length of stay, and morbidity outcomes). Seven separate outcome models were constructed. The carbapenem resistant determinant was not independently associated with any of the outcomes; however, delay in initiation of appropriate antimicrobials (DAAT) was independently correlated with worse outcomes ($p<0.05$) in all models.

Conclusions: Carbapenem resistance was not independently associated with worse outcomes among patients with *P. aeruginosa* BSI, despite significant correlations in univariable analyses. DAAT was independently associated with worse outcomes. The Carbapenem resistance status of *P. aeruginosa* should not be a determinant of its clinical and epidemiological significance. Presence of permanent devices and recent exposure to antimicrobials should prompt the suspicion of CRPA, which might help to reduce DAAT and improve patient's outcomes.