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Mortality in *Klebsiella pneumoniae* bacteraemia: a systematic review of effects of carbapenem resistance and initial antibiotic therapy

Philipp Patrick Kohler^{*1}, Cheryl Volling², Karen Green³, Prakeshkumar Shah¹, Allison Mcgeer⁴

¹*Mount Sinai Hospital*

²*Mount Sinai Hospital; Room 210; Infection Control*

³*Mount Sinai Hospital; Microbiology*

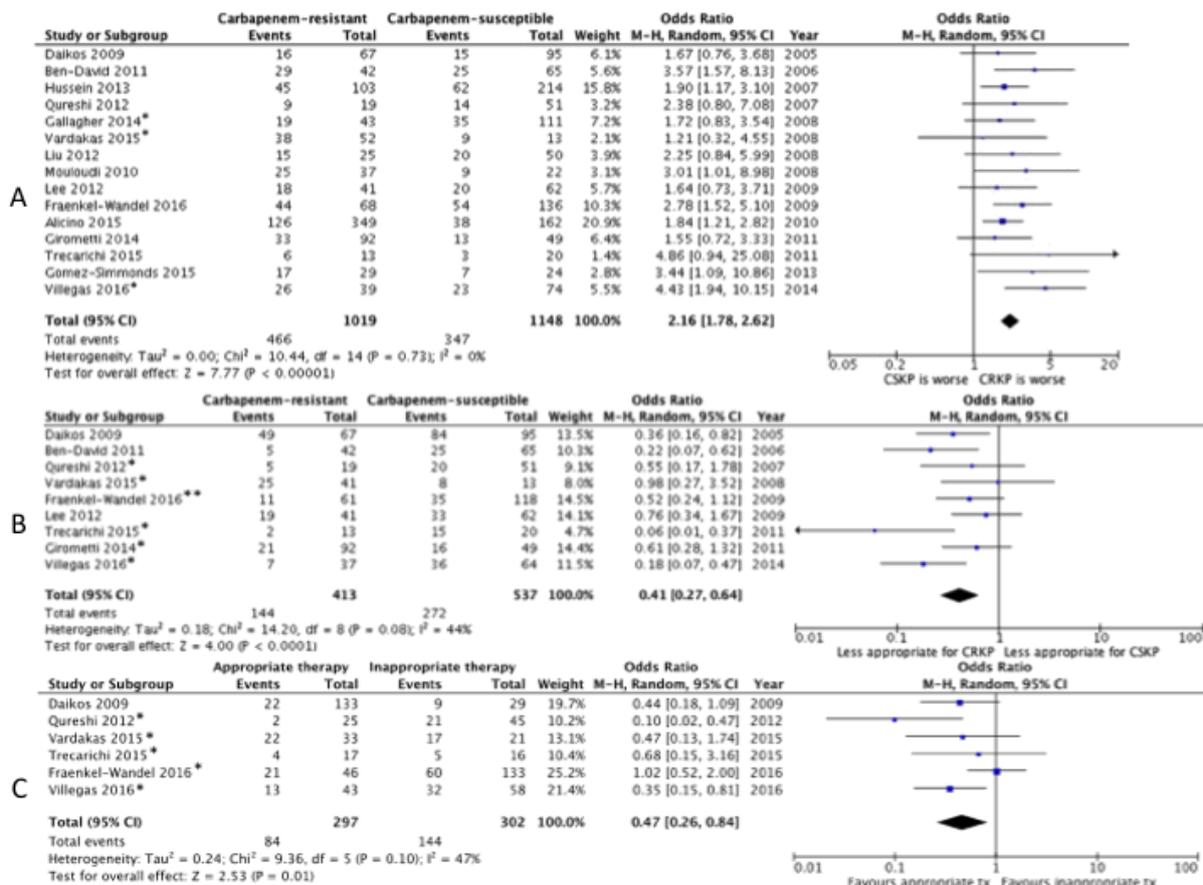
⁴*Mount Sinai Hospital; Infection Control and Microbiology*

Background: Mortality associated with infections caused by carbapenem-resistant Enterobacteriaceae is higher than that due to carbapenem-sensitive pathogens. We asked whether appropriateness of initial antibiotic therapy (IAT) might be responsible for the association between mortality and bacteremia caused by carbapenem-resistant (CRKP) or carbapenem-sensitive *Klebsiella pneumoniae* (CSKP), and whether changing appropriateness of IAT over time might alter the relationship.

Methods: MEDLINE, EMBASE, CINAHL and Wiley central database were searched for studies reporting on mortality among adult patients with CRKP or CSKP bacteremia. Carbapenem-resistance (CR) was defined as per CDC definitions: non-susceptibility to ≥ 1 carbapenem or carbapenemase production. Mortality was defined as in-hospital mortality or mortality within 14-30 days. A random effects model was used to estimate the association of carbapenem-resistance with mortality. The proportion of patients receiving appropriate IAT among CRKP and CSKP patients, and the mortality associated with appropriate versus non-appropriate IAT was compared.

Results: Among 11,654 records, we identified 15 studies (9 cohort and 6 case-control), all performed in high-risk countries for carbapenemases (Greece, Italy, Israel, Taiwan, Latin America, USA) between 2004 and 2014. CR was defined as non-susceptibility to carbapenems in 12 studies, and production of a carbapenemase in 3. Studies included 1,019 CRKP and 1,148 CSKP patients. The unadjusted OR for mortality associated with CRKP was 2.2 (95% CI 1.8-2.6) compared to patients with CSKP (Figure, panel A). Subgroup analysis of cohort versus case-control studies did not show any significant differences between groups. A pooled adjusted OR for mortality could not be calculated as adjustment differed in different studies; however, in 4 of 5 studies, the adjusted OR for mortality for CR versus CS infections was significantly greater than 1. CRKP patients were less likely to receive appropriate IAT (OR 0.41, 95% CI 0.27-0.64), and appropriate IAT was associated with a decreased OR for mortality of 0.47 (95% CI 0.26-0.84) (Figure, panel B and C). Neither the increased mortality in CRKP patients nor the proportion of patients with appropriate IAT did change over time (Figure, panel A and B, studies ordered by midyear of patient recruitment). On the study level, there was a strong negative correlation between the ratio of appropriate IAT in patients with CRKP vs CSKP and the odds for mortality with CRKP vs CSKP (R^2 0.89, $p=0.0002$, data not shown).

Conclusions: CR and lack of appropriate IAT were significantly associated with mortality among patients with *K. pneumoniae* bacteremia. The proportion of appropriate IAT has not improved over time. Measures aimed at identifying patients with increased risk for CRKP and delivery of appropriate IAT might reduce the observed difference in mortality compared to patients with CSKP bacteremia.



* Additional data were provided by the authors, not apparent in published article; ** Data provided by authors deviate slightly from data in published article