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ORIGINAL ARTICLE

Risk factors and clinical significance of bacteremia caused by *Pseudomonas aeruginosa* resistant only to carbapenems

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bacteremia;
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Background/purpose: Carbapenem-resistant *Pseudomonas aeruginosa* infections have been a challenge and issue in hospital settings. However, the clinical impact of *P. aeruginosa* blood isolates resistant only to carbapenems has never been discussed previously.
Methods: To assess the risk factors and clinical significance of bacteremia caused by carbapenem resistance only *P. aeruginosa* (CROPA), a 6-year retrospective case–control study was conducted. The CROPA strains were defined as isolates susceptible to ciprofloxacin, antipseudomonal penicillins and cephalosporins, and aminoglycosides but resistant to one antipseudomonal carbapenem (imipenem or meropenem) or both. The controls were selected among patients with bacteremia due to *P. aeruginosa* susceptible to all above classes of antipseudomonal antibiotics, which was defined as all-susceptible *P. aeruginosa*.
Results: Twenty-five patients had at least one blood culture positive for CROPA, and 50 controls had all-susceptible *P. aeruginosa* bacteremia. CROPA bacteremia had a high 30-day mortality rate (72.0%), as compared to 26.0% for the controls ($p < 0.001$). Through multivariate analysis, carbapenem exposure was the only risk factor for developing CROPA bacteremia ($p = 0.002$). A comparison between the surviving and deceased patients with CROPA bacteremia showed that nine (50%) of those who died, but none of the survivors, received carbapenems as the initial empirical therapy ($p = 0.027$).

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Conclusion: Carbapenem exposure was associated with emergence of CROPA infections. Repeated carbapenem use in such patients might increase rates of inappropriate initial empirical treatment and mortality. Prudent carbapenem use is important to reduce the emergence of CROPA.

Introduction

Pseudomonas aeruginosa is a leading cause of nosocomial infections in hospital settings.[1] The in-hospital mortality related to *P. aeruginosa* bloodstream infections is from 25.5% to 39%.[2,3] Imipenem is a mainstay in the treatment of severe *P. aeruginosa* infections, but the emergence of increasing imipenem resistance among clinical *P. aeruginosa* isolates has become a major concern of clinicians.[4,5] The average 30-day mortality of imipenem-resistant *P. aeruginosa* bacteremia was up to 41%, and these isolates were more likely to have cross-resistance to other common antipseudomonal agents.[3,6,7] The mechanisms of carbapenem resistance for *P. aeruginosa* are production of metallo-β-lactamase, overexpression of efflux, and loss of the outer membrane protein.[8–11] Either production of metallo-β-lactamase or overexpression of efflux could induce resistance to other antipseudomonal β-lactams.

During a 6-year period from 2004 to 2010, we noted the emergence of an unusual group of *P. aeruginosa* strains, which were resistant only to carbapenems (imipenem, meropenem, or both) via the disk diffusion method in accordance with the Clinical and Laboratory Standards Institute (CLSI) document M100-S22.[12] We defined this phenotype of *P. aeruginosa* strain as carbapenem resistance-only *P. aeruginosa* (CROPA),[13] which were susceptible to all antipseudomonal antibiotics tested (amikacin, gentamicin, piperacillin, piperacillin–tazobactam, aztreonam, ceftazidime, cefepime, and ciprofloxacin) but were resistant to carbapenems (imipenem, meropenem, or both). The percentage of CROPA strains among all the clinical *P. aeruginosa* blood isolates increased from 1.8% to 4.9% during the 6-year period from 2004 to 2010 at our hospital. The clinical impact of bacteremia caused by these CROPA strains has never been discussed in the English literature.

Thus, we conducted a 6-year retrospective case–control study to address the risk factors and clinical significance of CROPA bacteremia.

Materials and methods

Study site and ethical approval

Chang Gung Memorial Hospital Linkou is a 3715-bed university-affiliated medical center providing both primary and tertiary care in northern Taiwan. The ethical approval for this study was given by the hospital Institutional Review Board with a reference number of 100-0795B.

Study design and patients

A retrospective cohort 1:2 matched case–control study was conducted to collect cases with *P. aeruginosa* bacteremia between October 2004 and October 2010. We identified all the hospitalized patients with an age $\geq$18 years and at least one blood culture positive for CROPA by searching the microbiology laboratory database. Patients were considered cases if they had symptoms and signs suggestive of systemic infection with an imipenem or meropenem minimal inhibitory concentration (MIC) of their first isolate ≥ 4 μg/mL.[12] The symptoms and signs of infection included at least two of the following clinical characteristics: (1) temperature $<$ 36°C or $>$ 38°C; (2) heart rate $>$ 90 beats/min; (3) tachypnea: respiratory rate $>$ 20 breaths/min, or arterial partial pressure of carbon dioxide $<$ 32 mmHg; (4) white blood cell count $<$ 4.0×10^9 cells/L or $>$ 12.0×10^9 cells/L; or (5) the presence of $>$10% immature neutrophils. The controls were patients hospitalized during the study period with bacteremia due to *P. aeruginosa* susceptible to all the tested antipseudomonal agents, including amikacin, gentamicin, ciprofloxacin, aztreonam, ceftazidime, cefepime, piperacillin–tazobactam, piperacillin, imipenem, and meropenem. This type of *P. aeruginosa* strains were defined as all-susceptible *P. aeruginosa* (ASPA) and all the first isolates had MICs $<$ 4 μg/mL for both imipenem and meropenem.[12] For each patient with CROPA bacteremia, two matched controls were selected by a stepwise matching technique to identify the appropriate control patient matched to a case for gender, age $\pm$ 5 years, and the year of *P. aeruginosa* being isolated. Only the first episode of bacteremia was included for analysis. Patients with polymicrobial bacteremia were excluded to avoid the influence of multiple pathogens on the analysis of prognosis.

Data collection and definitions

Patients' demographics and clinical characteristics were obtained from their medical records, including age, sex, and length of hospital stay before *P. aeruginosa* bacteremia, laboratory data, and clinical outcomes. Variables as risk factors included comorbid illnesses (such as diabetes mellitus, liver cirrhosis, end-stage renal disease, chronic obstructive lung disease, solid tumors, hematological malignancies, and cerebral vascular accident), sources of bacteremia, Pittsburgh bacteremia scores for disease severity, and antibiotic exposure prior to bacteremia.

A nosocomial infection was considered if the infection was not evident until >48 hours of hospitalization. Severity of illness was evaluated on the 1st day of bacteremia onset by means of Pittsburgh bacteremia score.[14] The sources of