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Carbapenem-resistant *Klebsiella pneumoniae* is associated with poor outcome in hemodialysis patients

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Summary *Background:* Hemodialysis (HD) units have become a source of resistant bacteria. One of the most alarming developments is the emergence of carbapenem-resistant *Klebsiella pneumoniae* (CRKP). Risk factors and outcomes of CRKP isolation in HD patients have not been previously studied.
Methods: A nested case—control study was conducted in maintenance HD patients between January 1st 2006 and June 30th 2009. CRKP-positive patients were matched with randomly selected CRKP-negative HD patients. Demographics, clinical and laboratory data were collected for 24 months prior to the specimen collection. Multivariate analyses identified independent risk factors for CRKP. A prospective follow-up determined CRKP-associated outcome.
Results: Demographics associated with CRKP acquisition in HD patients were age between 65 and 75 and having no living offspring. Clinical conditions associated with CRKP were previous hospitalization, temporary HD catheter and previous isolation of vancomycin-resistant enterococcus. CRKP-related outcome was poor: median survival of one month and a hazard ratio [95% CI] of 5.9 [3.2—11.0] for mortality.

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Conclusions: Temporary HD catheters and previous treatment for VRE may predict subsequent CRKP isolation. A microbiological diagnosis of CRKP in HD patients is highly associated with imminent mortality. Meticulous measures to control the spread of CRKP bacteria among HD patients appear particularly warranted.

Introduction

Sepsis-related mortality rates in dialysis patients are significantly higher than in the general population even after accounting for comorbidities[1–3] and are reported by the USRDS (United States Renal Data System) as the second most common cause of mortality among these patients.[4] The spread of antibiotic resistance is a major threat to dialysis patients. Among hemodialysis (HD) outpatients, up to 28% may be colonized with drug-resistant bacteria including multi-drug-resistant Gram-negative bacteria (MDRGN). In some HD units MDRGN may account for up to 25% of all blood stream infections in HD patients.[5] Furthermore, infections caused by MDRGN bacteria may have a higher mortality rate than drug-susceptible Gram-negative bacteria.[6–8]

In the general population, after *Escherichia coli*, *Klebsiella pneumoniae* is the second most common cause for hospital- and community-acquired Gram-negative blood stream infections.[6] In intensive care units, *K. pneumoniae* comprises the fourth and fifth most common causes of pneumonia and bacteremia, respectively.[9] HD patients have been demonstrated to be particularly prone to develop *K. pneumoniae* infections[6] in addition to resistant *Pseudomonas aeruginosa* infections.[10]

Emergence of *K. pneumoniae* producing extended spectrum beta-lactamase (ESBL) has advanced the use of carbapenem-based antibiotics. However, in the last decade carbapenem-hydrolyzing beta-lactamases have been detected in Enterobacteriaceae. One particular group of transmissible plasmid-encoded carbapenemase enzymes, designated *K. pneumoniae* carbapenemase (KPC), confers carbapenem-resistance to *K. pneumoniae* strains (CRKP).[11]

CRKP strains pose a significant threat due to both an almost pan-antibiotic resistance and to a rapid nosocomial spread. Incidence of CRKP in some USA centers rose from 1% to 8% of all nosocomial *K. pneumoniae* isolates within 7 years.[12–14] KPC has also spread to *E. coli*, *P. aeruginosa* and *Acinetobacter baumannii* and thus, what was once considered a clonal spread, has now become a global problem of interspecies dispersion.[15,16]

As of 2006, almost all major hospitals in Israel reported a sharp increase in the number of clinical isolates of CRKP.[17–19] CRKP has been associated with increased mortality (up to 50%) in the general hospital population, with a possible direct causal role in mortality.[20] To date, no studies have addressed the risk factors and prognosis for CRKP colonization and infection in HD patients, contrasting with the ample data available in HD patients for other MDRGN[4,5] or MRSA.[21,22] The aims of this study were thus to identify risk factors for CRKP among HD patients and to measure its outcome.

Methods

Setting

The study was conducted at the Hadassah-Hebrew University Medical Center, Jerusalem, Israel, a 1100-bed hospital serving as a referral center for approximately 500 maintenance HD patients in the Jerusalem vicinity. The study was approved by the institutional review board.

Patients

Only maintenance HD patients were included in the study, defined as patients referred to chronic HD by the nephrology team and treated for at least 14 days. Exclusion criteria were dialysis for acute kidney injury (AKI), age younger than 18 years and diagnosis of CRKP before the onset of HD.

Matched control cases, using the same exclusion criteria, were randomly selected from the total maintenance HD population treated during the study period on the basis of their national identification number displaying an odd digit located one before the last digit. In accordance with previous recommendations for epidemiologic studies in drug-resistant bacteria, case patients were defined as all patients colonized or infected with CRKP while the control patients were randomly selected from all eligible HD patients not found to be colonized or infected with CRKP.[23–25] Colonized cases were defined are patients from whom CRKP was isolated only from stool cultures, whereas all other specimen sources (blood, urine, sputum, wound, etc.) positive for CRKP were taken to have clinical significance and thus these patients were defined as infected.

Study design

In order to assess risk factors for CRKP isolation in HD patients, we performed a nested case—control analysis after frequency matching an index date for the two groups. The index date was defined as the date of the first CRKP isolation for the case patients and the date of an equivalent hospital admission within two months for the control patients (Figure 1).

In order to assess the prognostic implication of CRKP isolation we performed a prospective cohort study, where we measured prognosis since index date, again using the matched cases and controls.

Data collection

The period of data collection for identification of CRKP-positive HD patients began on January 1st 2006 (the year