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Major Article

Clinical epidemiology of carbapenem-resistant gram-negative sepsis among hospitalized patients: Shifting burden of disease?

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Background: Infections caused by carbapenem-resistant gram-negative bacilli are an emerging public health threat. However, there is a paucity of data examining comparative incidence rates, risk factors, and outcomes in this population.

Methods: This single-center retrospective cohort study was conducted at an urban tertiary-care academic medical center. We included patients admitted from 2012 to 2015 who met the following criteria: i) age ≥ 18 years; and ii) culture positive for carbapenem-resistant *Enterobacteriaceae* (CRE) or carbapenem-resistant non-*Enterobacteriaceae* (CRNE) from any site. Exclusion criteria were: i) < 2 systemic inflammatory response criteria; ii) cystic fibrosis; and iii) no targeted treatment. We evaluated hospital survival by Cox regression and year-by-year differences in the distribution of cases by the Cochran-Armitage test.

Results: 448 patients were analyzed (CRE, n = 111 [24.8%]; CRNE, n = 337 [75.2%]). CRE sepsis cases increased significantly over the study period ($P < .001$), driven primarily by increasing incidence of *Enterobacter* spp. infection ($P = .004$). No difference was observed in hospital survival between patients with CRE versus CRNE sepsis (hazard ratio [HR], 1.29; 95% confidence interval [CI], 0.83-2.02; $P = .285$), even after adjusting for confounding factors (adjusted HR, 1.08; 95% CI, 0.62-1.87; $P = .799$).

Conclusions: Clinical outcomes did not differ between patients with CRE versus CRNE sepsis. Dramatic increases in CRE, particularly *Enterobacter* spp., appear to be causing a shift in the burden of clinically significant carbapenem-resistant gram-negative infection.

Infections caused by multidrug-resistant gram-negative bacilli (MDR-GNB) are becoming an increasingly common clinical problem.[1-4] According to the latest report from the U.S. Centers for Disease Control and Prevention (CDC), carbapenem-resistant *Enterobacteriaceae* (CRE) represent an urgent threat to public health.[5] While CRE infections are an important concern, infections caused by non-fermenting MDR-GNB, such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* complex, are also on the rise.[5,6] Whether carbapenem-resistant non-*Enterobacteriaceae* (CRNE) infections affect different patient populations than CRE has not been extensively evaluated.

Resistance mechanisms and production of virulence factors differ significantly between CRE and CRNE.[7] *P. aeruginosa* in

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particular is able to produce many exotoxins that may influence clinical outcomes.[8,9] Carbapenemase production is an emerging plasmid-mediated resistance mechanism in CRE but is rare in non-*Enterobacteriaceae*.[4,10] Although carbapenem resistance has been associated in multiple meta-analyses with worse clinical outcomes in patients with gram-negative infections, whether outcomes differ between CRE and CRNE infections is unclear.[11-13] The objectives of this study were to quantify the burden of carbapenem-resistant gram-negative sepsis in a cohort of hospitalized patients and to compare risk factors and clinical outcomes between patients with CRE or CRNE infections.

METHODS

This single-center retrospective cohort study was conducted at Barnes-Jewish Hospital, an urban tertiary-care academic medical center in St. Louis, Missouri, USA. The design was chosen to allow for comparison of CRE versus CRNE and most accurately quantify and evaluate trends in the epidemiology of these infections. All adult hospitalized patients (age ≥ 18 years) with a gram-negative organism isolated from any site were initially screened for inclusion. We included those patients with a corresponding clinical isolate from January 2012 through December 2015 that displayed phenotypic non-susceptibility to any carbapenem agent tested (ertapenem, doripenem, imipenem, or meropenem) in accordance with the current CRE definition endorsed by the CDC.[14] For patients with infections caused by *Proteus* spp., *Providencia* spp., or *Morganella* spp., which are known to have intrinsic reduced susceptibility to imipenem, resistance to another carbapenem agent was required for the isolate to be deemed carbapenem resistant.[14] Inclusion dates were chosen to allow for evaluation of carbapenem-resistant cases after the 2012 carbapenem breakpoint revisions by the Clinical and Laboratory Standards Institute (CLSI).[15] To limit analysis to cases of true infection rather than colonization, we excluded patients without sepsis, defined as ≥2 systemic inflammatory response syndrome (SIRS) criteria.[16] Furthermore, we excluded patients with cystic fibrosis and those who were discharged to home alive without ever having received targeted antimicrobial therapy.[16] We also excluded patients with polymicrobial infection (>1 organism isolated); and in cases of recurrent infection, only the first case encountered during the study period was analyzed.

Patients were classified into CRE or CRNE groups for analysis. The primary outcome was hospital survival. We hypothesized that survival would be lower for patients with CRNE sepsis compared to CRE sepsis due to the virulence of this group of organisms and known differences in mechanisms of resistance.[17,18] Thus, the CRNE sepsis group was designated as the comparator group for all tests. Secondary outcomes were 7-day, 28-day, and 90-day all-cause mortality, chosen to evaluate the comparative risk of death at early, intermediate, and late timepoints. All outcomes were assessed from the beginning of CRE or CRNE sepsis, defined at the time of index-positive culture while meeting sepsis criteria.

Clinical data recorded during routine care were abstracted by a bioinformatics specialist (N.B.H.) via electronic query of a database available at our institution and audited by the primary investigator (N.S.B.) to ensure accuracy and concordance with the electronic medical record. Variables collected included patient demographics, setting of onset (hospital-acquired infection defined as culture date >48 hours after admission), comorbidities and Charlson comorbidity index (defined according to diagnosis codes), invasive devices and procedures, previous antimicrobial exposures, previous hospitalizations, immunosuppression, vital signs, microbiologic data, laboratory data, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and vital status.[19,20] Prior to 2013, bacterial identification was performed using phenotypic methods, typically VITEK2. After 2013, organism identification was performed using the Bruker Biotyper matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) system.[21,22] Susceptibility testing was performed during routine clinical care using the disk diffusion method, according to CLSI guidelines current at the time. *Enterobacteriaceae* isolates that were phenotypically non-susceptible to our reference carbapenem agent (meropenem) were further characterized using polymerase chain reaction to detect carbapenemase genes[23,24]

Baseline characteristics were compared using the chi-squared test for categorical data and Student's t-test or Mann-Whitney *U* test for continuous data. We analyzed year-by-year differences in the distribution of sepsis cases caused by CRE versus CRNE infection using the Cochran-Armitage test for trend. Hospital survival was first evaluated by univariable Cox regression. Two multivariable Cox proportional hazards models for hospital survival were then derived. In the first, CRNE sepsis was forced into the model as the exposure variable of interest. Other variables associated with CRNE sepsis or hospital survival ($P < .2$) were entered into the model manually using an iterative process as described by Hosmer et al.[25] Only variables that were significant confounders (≥10% change in the associated hazard ratio [HR]) were retained in the final parsimonious model.[25] In the second, CRNE sepsis was not forced into the model, and factors independently associated with hospital survival ($P < .05$) were identified using a backward stepwise approach. Dichotomous secondary outcomes were compared by chi-squared test. A subgroup analysis evaluating the effect of carbapenemase production on hospital survival of patients with CRE sepsis was also performed. Statistical analyses were performed using SPSS software (version 22; IBM Corporation; Armonk, New York, USA) and GraphPad Prism software (version 7; GraphPad, La Jolla, California, USA). For all statistical tests, the level of significance was designated as .05. The Washington University in St. Louis institutional review board approved this study.

RESULTS

A total of 84,955 patients met inclusion criteria and were assessed for eligibility over the course of the study period. Patients were excluded because of carbapenem-susceptible infection (n = 82,260), <2 SIRS criteria (n = 1700), recurrent or polymicrobial infection (n = 392), cystic fibrosis (n = 91), and lack of treatment prior to discharge (n = 64). A total of 448 patients were included in the final analysis, including 124 patients (27.7%) in 2012, 98 patients (21.9%) in 2013, 92 patients (20.5%) in 2014, and 134 patients (29.9%) in 2015. Overall, CRNE infections were more common than CRE infections (75.2% [n = 337/448] versus 24.8% [n = 111/448]) over the 4-year study period. However, a significant shift in the distribution of CRE and CRNE cases occurred from 2012 to 2015 (Fig 1; $P < .001$). CRE infections comprised only 13/124 (10.5%) of carbapenem-resistant gram-negative infections in 2012, but this increased to 56/134 (41.8%) by 2015 (Fig 1).

Baseline characteristics of patients with CRE or CRNE sepsis were compared, and multiple factors distinguished these groups of patients (Table 1). Genitourinary infections were significantly more common in patients with CRE sepsis (41.4% [46/111] versus 20.5% [69/337]; $P < .001$), whereas respiratory tract infections were significantly more common in patients with CRNE sepsis (26.1% [29/111] versus 49.0% [165/337]; $P < .001$; Table 1). Patients with CRE sepsis also experienced significantly longer delays in initiation of appropriate antimicrobial therapy than patients with CRNE sepsis (Table 1). Conversely, patients with CRNE sepsis were significantly more likely to have been admitted to the intensive care unit (ICU), to have been mechanically ventilated, to have been previously hospitalized within the preceding 6 months, and to have had previous