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Bacteremia due to carbapenem-resistant Enterobacteriaceae in neutropenic patients with hematologic malignancies

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Summary *Objectives:* To determine the prevalence, risk factors, treatments, and outcomes of bloodstream infections (BSIs) due to carbapenem-resistant Enterobacteriaceae (CRE) in adult neutropenic patients with hematologic malignancies.
Methods: We reviewed all BSIs between 2008 and 2012 in this population at two New York City oncology centers. A case-control study was conducted to identify CRE BSI risk factors, using three controls of non-CRE BSIs per case.
Results: CRE caused 43 (2.2%) of 1992 BSIs overall and 4.7% of Gram-negative bacteremias. Independent risk factors for CRE BSI were prior β-lactam/β-lactamase inhibitor (adjusted odds ratio [aOR] 3.2; $P = 0.03$) or carbapenem (aOR 3.0; $P = 0.05$) use, current trimethoprim-sulfamethoxazole (aOR 24; $P = 0.001$) or glucocorticoid (aOR 5.4, $P = 0.004$) use, and having a prior CRE culture (aOR 12; $P = 0.03$). Patients with CRE bacteremia had a median of 52 h from culture collection until receipt of active therapy. They had a 51% BSI-related mortality rate, with a median of 4 days from bacteremia onset until death.

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CRE-active empirical therapy was associated with a lower 30-day mortality rate (17% vs. 59%; $P = 0.08$).
Conclusions: CRE are lethal emerging causes of bacteremia in neutropenic patients. New strategies are needed to shorten the delay in administration of CRE-active agents and improve outcomes in this vulnerable population.

Introduction

Neutropenic patients with hematologic malignancies are uniquely threatened by multidrug-resistant Gram-negative bacteria because they rely on immediate bactericidal therapy to combat Gram-negative infections. Enterobacteriaceae are the most common causes of Gram-negative bacteremia in this population and have historically been susceptible to recommended β-lactam agents for the treatment of fever and neutropenia.[1,2] However, over the last decade, carbapenem-resistant Enterobacteriaceae (CRE) have emerged worldwide as lethal pathogens that are typically resistant to all β-lactam agents due to production of β-lactam-hydrolyzing enzymes such as *Klebsiella pneumoniae* carbapenemase (KPC).[3] Given that currently recommended empirical therapies are inactive against CRE, and identification of CRE by culture typically takes 2–3 days, the spread of CRE into neutropenic patients with hematologic malignancies could have devastating consequences because effective therapy would be delayed.[4]

We recently reported 18 patients with hematologic malignancies who developed bacteremia due to CRE.[5] Nine of 13 neutropenic patients in this study died, there were long delays until receipt of active therapy, and all deaths were related to CRE bacteremia. Given these preliminary findings, we sought to better understand the epidemiology of CRE in this patient population in an area where CRE are endemic nosocomial pathogens. Thus, we conducted a study at two large oncology centers in New York City, USA, a global epicenter for CRE, to determine the prevalence, risk factors, and outcomes of CRE bacteremia in neutropenic patients with hematologic malignancies.

Methods

Study design

The study was approved by the Institutional Review Boards of Weill Cornell Medicine and Memorial Sloan Kettering Cancer Center (MSKCC). We first identified all episodes of bloodstream infection (BSI) in adult (age ≥18 years) neutropenic patients (absolute neutrophil count ≤500 cells/mm^3) with hematologic malignancies at New York-Presbyterian Hospital/Weill Cornell Medical Center and MSKCC from 2008 to 2012. BSIs where the patient had a prior positive blood culture for the same organism(s) within the previous 30 days were excluded. Common skin commensals were designated causes of BSI if isolated from ≥2 blood culture sets from the same or consecutive days.[6] From this cohort, we determined the proportion of BSIs, Gram-negative bacteremias, and Enterobacteriaceae bacteremias that were due to CRE.

We performed two case-control analyses to identify risk factors for CRE bacteremia. In the primary analysis, we compared CRE cases to controls of BSIs due to pathogens other than carbapenem-resistant Gram-negative bacteria. In the secondary risk factor analysis, we designated BSI episodes due to carbapenem-susceptible Gram-negative bacteria as controls. For both control groups, we randomly selected three controls per case, matched by study center and year. Surveillance for detection of CRE colonization was not routinely performed at either study center.

We abstracted the following clinical data for cases and controls: demographics, comorbidities,[7] malignancy characteristics, healthcare exposures, prior infections, presence of sepsis,[8] Pitt bacteremia score,[9] antimicrobial therapies, time until receipt of an active agent (an agent to which the bloodstream isolate tested susceptible *in vitro*), 30-day mortality from BSI onset, and BSI-related mortality (death in a patient with ongoing bacteremia from the initial pathogen or who never recovered from septic shock associated with the BSI episode). Lastly, we reviewed episodes of monomicrobial bacteremia included in the case-control analyses and compared the 30-day survival by pathogen type.

Microbiologic methods

Species identification and antimicrobial susceptibility testing were performed by Vitek II (bioMérieux, Durham, NC, USA) or Microscan (Beckman Coulter, Brea, CA, USA). Carbapenem resistance was defined as resistance to any carbapenem based on updated Clinical and Laboratory Standards Institute interpretive breakpoints.[10] Extended-spectrum-β-lactamase (ESBL)/AmpC-producing Enterobacteriaceae were defined as being ceftriaxone-resistant and meropenem-susceptible, or testing positive for ESBL production.[10]

For available isolates, we performed broth microdilution testing using TREK panels (Thermo Fisher Scientific, Oakwood Village, OH, USA) and Etest (bioMérieux) for susceptibility to ceftazidime-avibactam. These results were used instead of automated susceptibility testing results, when available. CRE with polymyxin B or tigecycline minimum inhibitory concentrations (MICs) ≤2 μg/mL were considered susceptible to these agents.

In order to characterize the genetic basis of carbapenem resistance, we used a multiplexed PCR on available isolates to detect KPC, NDM, VIM, IMP, OXA-48-type, and CTX-M β-lactamase genes, followed by gene sequencing of positive results.[11–13] For carbapenem-resistant *K. pneumoniae* isolates, we also sequenced outer membrane porin genes.[14]

Statistical analysis

Categorical variables were compared using chi-square or Fisher's exact tests and continuous variables were