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Antimicrobial Susceptibility Study

Carbapenem-resistant *Klebsiella pneumoniae* bacteremia: factors correlated with clinical and microbiologic outcomes☆

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Abstract

We undertook a retrospective cohort study describing general outcomes and specific factors associated with positive outcomes in bacteremia due to carbapenem-resistant *Klebsiella pneumoniae* (CRKP). Forty-eight patients were included, of which 42% died at 30 days. Forty-two percent of patients were in septic shock at the time of the first positive blood culture, and 42% were recipients of solid organ transplants. Lack of microbiologic eradication at 7 days was independently associated with 30-day mortality. Adjunctive procedures performed for source control and microbiologic eradication at 7 days were associated with a favorable clinical response at 7 days. Time to initiation and receipt at any time of antimicrobials with in vitro activity against CRKP were not associated with improved survival. Breakthrough bacteremia occurred in 8 cases, all in patients receiving tigecycline. Our data suggest that severity of illness, rapid microbiologic eradication, and source control are crucial factors in the outcomes of patients with CRKP bacteremia.

Keywords: Polymyxin; Tigecycline; Carbapenem; Klebsiella

1. Introduction

Carbapenems have traditionally been considered one of the last lines of defense against infections due to multidrug-resistant Gram-negative organisms (MDRO), especially for those pathogens that produce extended-spectrum β-lactamases. Unfortunately, *Klebsiella pneumoniae* isolates producing a carbapenem-hydrolyzing β-lactamase (called KPC) first emerged in North Carolina and have become endemic to hospitals in New York City (Bradford et al., 2004; Bratu et al., 2005a, 2005b; Nordmann et al., 2009; Yigit et al., 2001). At NewYork-Presbyterian Hospital, Columbia University Medical Center (CUMC), New York, NY, a review of *K. pneumoniae* susceptibility data demonstrates a significant rise in carbapenem resistance, from 2% in 1999 to 26% in 2007 (P. Della-Latta, unpublished data).

KPC-producing *K. pneumoniae* isolates are resistant to not only all β-lactam antimicrobials, but also frequently to other classes of antimicrobials, such as aminoglycosides and fluoroquinolones (Bratu et al., 2005b, 2005c). As such, infections due to these organisms present significant therapeutic challenges to clinicians. Not surprisingly, patient outcomes are generally poor, and the optimal therapeutic regimen has not been established. According to a 2005 study, the 14-day mortality rate of bacteremia due to KPC-producing isolates approaches 50% (Bratu et al., 2005a). Because of insufficient clinical data, practitioners often must determine treatment regimens based on anecdotal experience, or in some instances, unstandardized in vitro synergy tests. Such tests suggest that combinations such as polymyxin B plus rifampin or cefepime might be therapeu-

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tically useful (Bratu et al., 2005c). Our study seeks to identify significant factors that correlate with outcomes in patients with bacteremia due to carbapenem-resistant *K. pneumoniae* (CRKP).

2. Materials and methods

2.1. Study design

A retrospective cohort study was performed at CUMC, a 1134-bed tertiary care medical center in New York City. Adult inpatients with bacteremia due to CRKP from January 1, 2004, to September 1, 2008, were identified from the microbiology laboratory database. For patients with multiple episodes of bacteremia, only the first episode was included. Patients with concomitant bacteremia due to another organism within 48 h of first positive blood culture were excluded, with the exception of coagulase-negative staphylococci. The study was approved by the CUMC Institutional Review Board.

2.2. Microbiologic methods

CRKP isolates were identified by review of the microbiology laboratory database. From 2004 to 2005, isolates were included if the meropenem/imipenem MIC was >8 mg/L. From 2006 to 2008, *K. pneumoniae* isolates were initially screened for carbapenem resistance with ertapenem because it is a better indicator of KPC production than the other carbapenems (Bratu et al., 2005b). As such, during this period, isolates that were ertapenem resistant were included. Antimicrobial susceptibility testing (AST) for ertapenem, polymyxin B, and tigecycline was conducted using Etest strips (bioMérieux, Rockland, MA) following manufacturer recommendations. Although the presence of the KPC gene was not confirmed for each isolate, >90% of ertapenem-resistant strains at CUMC are KPC producers, as confirmed by polymerase chain reaction. Seventy percent of KPCs from 2006 to 2008 were found to be KPC-2 and 30% KPC-3 (P. Della-Latta, unpublished data). A recent analysis of a collection of 14 clinical isolates from our institution found these strains to be generally nonclonal (Gootz et al., 2009). AST for all other antimicrobial agents was performed with the Vitek instrument (bioMérieux). The MICs of antimicrobial agents used as interpretative breakpoints of susceptibility and resistance followed the appropriate Clinical and Laboratory Standards Institute guidelines (CLSI, Performance Standards for Antimicrobial Susceptibility Testing, M100; CLSI, Wayne, PA).

2.3. Clinical analysis

Data were collected by a review of medical, laboratory, and pharmacy records. Because all acute physiology and chronic health evaluation (APACHE) II variables were not always available for all patients, a modified APACHE II score was used. This score excludes variables that are frequently absent from non-intensive care unit (ICU) patients (Glasgow coma score and oxygenation parameters), thus, standardizing collected variables across the entire patient population (Thom et al., 2008). Likewise, because arterial pH is not available in all patients, serum bicarbonate levels were substituted in the score (Knaus et al., 1995). The data collected at time of the first positive blood culture included demographics, underlying diseases, duration of hospital stay prior to onset of bacteremia, corticosteroid therapy, and the presence of central venous catheters (CVCs), indwelling urinary catheters, renal replacement therapy, or mechanical ventilation. The following comorbid conditions were also documented: absolute neutrophil count <500/mm^3, care in the ICU, and septic shock.

Clinical parameters collected within 24 h of first positive blood culture included the peak white blood cell (WBC) count and temperature and the lowest mean arterial pressure (MAP). These parameters were also collected 7 days after the first positive blood culture. Information regarding antimicrobial administration 3 days prior to and 7 days after the first positive blood culture was collected and included the following agents: tigecycline, polymyxin B, gentamicin, amikacin, tobramycin, levofloxacin, meropenem, imipenem, cefepime, rifampin, and sulfamethoxazole/trimethoprim. Microbiologic data, including cultures positive for CRKP from sites other than blood, were collected from the period 7 days prior to 7 days after the first positive blood culture. Adjunctive source control procedures (including CVC removal, urinary catheter removal, wound debridement, abscess, and body fluid drainage) performed within 5 days after first positive blood culture were also documented in patients with CRKP isolated from the respective alternate site(s).

The primary outcome of the study was to identify factors associated with patient survival at 30 days. Secondary outcomes included 1) identification of factors associated with microbiologic eradication of blood (7 days after the first positive blood culture), 2) identification of factors associated with a favorable clinical response 7 days after the first positive blood culture, and 3) determining whether the time to initiation of antimicrobials with in vitro activity against CRKP influenced 30-day mortality.

2.4. Definitions

Bacteremia was defined as the identification of CRKP in a blood culture specimen. Breakthrough bacteremia was defined as the development of bacteremia after ≥48 h of susceptible antimicrobial therapy. Septic shock was defined as the presence of sepsis and the need for vasoactive agents.

Antimicrobial regimens were classified as either empiric or definitive. Empiric antimicrobial agents were defined as those administered on the day of the first positive blood culture collection. In cases of renal insufficiency, renally dosed antimicrobials administered prior to the first positive blood culture were also accepted if the day of culture collection fell within the allotted dosing interval (institu-