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The Impact of Carbapenem-Resistant Enterobacteriaceae Type on Clinical Outcomes After the Recovery of This Organism From Urine of Critically Ill Patients

To the Editor—Carbapenem-resistant Enterobacteriaceae (CRE) are a leading cause of nosocomial infections. In the CRE group, the *Klebsiella pneumoniae* carbapenemase (KPC) producers stand out among the others and have been associated with serious infections and high mortality rates, mainly in intensive care units.[1] Apart from that, antimicrobial resistance among these isolates has increased worldwide, therefore limiting the therapeutic alternatives against KPC.[2]

Early detection of colonized or infected patients is crucial for the rapid management of patients and to establish infection control practices in order to avoid further dissemination and to curb the rise of antimicrobial resistance.[2]

We conducted a prospective survey from July 1, 2013, through November 30, 2015, to assess the impact of CRE type involved on the clinical outcomes and the emergence of antimicrobial resistance among CRE urinary or bloodstream isolates in a cohort of critically ill patients from an adult intensive care unit of a tertiary hospital in Porto Alegre, Southern Brazil.

Patients were included at the time of their first urine culture in which CRE were recovered. Isolates with reduced susceptibility to carbapenems (meropenem, imipenem, and/or ertapenem) were identified by MicroScan Walkaway automated system (Beckman Coulter) and confirmed by Etest (AB Biodisk). The presence of carbapenemase was detected by phenotypic testing and by gene detection using a polymerase chain reaction procedure, as previously described.[3]

The primary outcomes (or clinical outcomes) were determined by result of a subsequent urine culture (negative or recurrent/subsequent bacteriuria) and/or blood culture with the same CRE within 90 days and mortality at 30 days. Development of antimicrobial resistance (which was the microbiologic outcome in this study) was evaluated comparing results from the first CRE isolate with those obtained in a subsequent sample (urine or blood) for amikacin, gentamicin, polymyxin B, tigecycline, and fosfomycin.

During the study period, a total of 109 patients were included. In 85 patients, KPC-2-producers (mostly *Klebsiella pneumoniae* [*Kp*]) were recovered whereas, in the remaining 24, a culture with carbapenemase nonproducers was obtained. Of the 85 patients with KPC-2-*Kp* bacteriuria, 19 died during the 30-day period, 27 had a negative urine culture or were discharged, 14 had bacteriuria with a microorganism other than KPC-2-producers, and 25 had a recurrent KPC-2-*Kp* bacteriuria. Moreover, 15 patients, including 5 patients who also had a recurrent urinary isolate, had an episode of bacteremia due to KPC-2-*Kp* and the 30-day mortality for these patients was 47% (Table 1). Regarding carbapenemase nonproducers, no patients were bacteremic, and only 4 of them had recurrent bacteriuria.

In 35 patients, a KPC-2-*Kp* isolate was recovered in a subsequent bacteriuria/bacteremia case and a minor increase in resistance was observed for polymyxin B (34% vs 43%), gentamicin (57% vs 69%), amikacin and tigecycline (14% vs 26%). For fosfomycin, used more often nowadays as therapy to treat urinary tract infections due to KPC producers, a significant increase in resistance was detected (11% vs 34%; OR, 4.04 [95% CI, 1.1–14.2], $P = 0.03$), driven by prior fosfomycin use, as previously described.[4] On the other hand, no increase of antimicrobial resistance was observed among isolates of carbapenemase nonproducers.

In this study, the urine specimen was used as a starting point for surveillance for KPC-2-*Kp* isolated during hospitalization because KPC-2-*Kp* was found most commonly in urine

TABLE 1. Microbiologic Characteristics and Clinical Outcomes After CRE Bacteriuria

CRE bacteriuria (n/total n, %)	Carbapenemase	Urinary outcome (n/total n, %)	Bacteremia (n/total n, %)	30-Day mortality (n/total n, %)
Klebsiella pneumoniae (82/109, 75%)	KPC-2	Recurrence (25/82, 30%)	Yes (15/82, 18%)	Yes (7/15, 47%)
Enterobacter cloacae (18/109, 17%)	None	NSC (13/18, 72%)	No	NA
K. pneumoniae (6/109, 6%)	None	NSC (4/6, 67%)	No	NA
Escherichia coli (3/109, 3%)	KPC-2	NSC (3/3, 100%)	No	NA

NOTE. CRE, carbapenem-resistant Enterobacteriaceae; NA, not applied; NSC, negative subsequent culture.

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culture. Criteria for asymptomatic bacteriuria, as reported by the Centers for Disease Control and Prevention/ National Healthcare Safety Network,[5] are primarily designed for surveillance purposes, and only patients with KPC-2-*Kp* bacteriuria who do not meet these criteria are thought to have urinary tract infection and receive treatment.

The results presented here show that the outcomes of CRE bacteriuria/bacteremia are influenced by both the choice of antimicrobial treatment and the CRE isolate type. The selective pressure imposed by antibiotic usage has been strongly associated with the emergence of resistance, as observed in this study and in previous reports regarding polymyxins,[6] tigecycline,[7] and fosfomycin,[4] which are considered "reappraised" therapeutic options to treat multidrug-resistant microorganisms.

Unequivocally, endemic KPC-2-*Kp* has become quite more competitive than multidrug-resistant noncarbapenemase isolates that proved to be self-limited, with neither bacteremia case nor development of resistance observed in this study (Table 1); KPC-2-*Kp* is probably favored by the presence of a more robust resistance mechanism, such as the production of carbapenemase, although $bla_{\text{KPC-2}}$ gene has not been associated with virulence by itself.[8]

In conclusion, KPC-2-*Kp* isolates presented with recurrent/subsequent bacteriuria as the main urinary outcome and as such developed cases of bacteremia with a high 30-day mortality rate being observed. Increase in resistance rates was observed for all agents evaluated, possibly driven by previous use similar to prior observations for KPC-2-*Kp* recovered from surveillance rectal swab samples.[9] These findings and the poor outcomes for KPC--2-*Kp* infection underscore the urgent need for better surveillance and stewardship programs to combat these antibiotic stains.

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Leandro Reus Rodrigues Perez, PhD

Affiliations: Hospital Mãe de Deus, Porto Alegre, Brazil; and Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.

Address correspondence to Leandro Reus Rodrigues Perez, PhD, Universidade Federal do Rio Grande do Sul, Faculdade de Farmácia, 2752 Ipiranga Ave, 90610-000, Porto Alegre–RS, Brazil (leandro.reus@gmail.com).

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The Chicken–Egg Dilemma: Legionnaires' Disease and Retrograde Contamination of Dental Unit Waterlines

To the Editor—On February 9, 2011, an 82-year-old Italian woman died from Legionnaires' disease (LD). Other than 2 appointments at a dental office, she had not been exposed to any obvious source of *Legionella* infection in the 2–10 days before symptom onset that occurred on February 7. On February 17, an epidemiologic field investigation in the dental office, performed by the regional healthcare agency, detected *Legionella pneumophila* serogroup 1 (sg1) in water samples from the cold-water tap (1500 CFU/L), the dental turbine (62000 CFU/L), and the cup filler (4000 CFU/L) of a dental unit, which had been routinely disinfected with H_2O_2. Strain typing revealed that the isolates from the environment and the patient's bronchial aspirate matched, suggesting that the dental unit waterlines (DUW) were the likely source of LD infection.[1]

In line with the guidelines for epidemiologic field investigation,[2] immediate control measures were taken.