Risk Factors for Treatment Failure of Polymyxin B Monotherapy for Carbapenem-Resistant *Klebsiella pneumoniae* Infections

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Polymyxins are reserved for salvage therapy of infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP). Though synergy has been demonstrated for the combination of polymyxins with carbapenems or tigecycline, *in vitro* synergy tests are nonstandardized, and the clinical effect of synergy remains unclear. This study describes outcomes for patients with CRKP infections who were treated with polymyxin B monotherapy. We retrospectively reviewed the medical records of patients with CRKP infections who received polymyxin B monotherapy from 2007 to 2011. Clinical, microbiology, and antimicrobial treatment data were collected. Risk factors for treatment failure were identified by logistic regression. Forty patients were included in the analysis. Twenty-nine of 40 (73%) patients achieved clinical cure as defined by clinician-documented improvement in signs and symptoms of infections, and 17/32 (53%) patients with follow-up culture data achieved microbiological cure. End-of-treatment mortality was 10%, and 30-day mortality was 28%. In a multivariate analysis, baseline renal insufficiency was associated with a 6.0-fold increase in clinical failure after adjusting for septic shock (odds ratio [OR] = 6.0; 95% confidence interval [CI] = 1.22 to 29.59). Breakthrough infections with organisms intrinsically resistant to polymyxins occurred in 3 patients during the treatment. Eighteen of 40 (45%) patients developed a new CRKP infection a median of 23 days after initial polymyxin B treatment, and 3 of these 18 infections were polymyxin resistant. The clinical cure rate achieved in this retrospective study was 73% of patients with CRKP infections treated with polymyxin B monotherapy. Baseline renal insufficiency was a risk factor for treatment failure after adjusting for septic shock. Breakthrough infections with organisms intrinsically resistant to polymyxin B and development of resistance to polymyxin B in subsequent CRKP isolates are of concern.

Infections caused by carbapenem-resistant *Klebsiella pneumoniae* (CRKP) have been associated with poor outcomes. An overall mortality rate of 48% is reported for patients with CRKP, compared to 26% for those with carbapenem-susceptible *K. pneumoniae* infections (1). CRKP isolates confer resistance through the production of *K. pneumoniae* carbapenemases (KPCs), which are able to hydrolyze all currently available β -lactams, including carbapenems (2). Due to additional mechanisms of resistance commonly found in KPC-producing isolates, they often demonstrate resistance to other antimicrobial classes, including fluoroquinolones and aminoglycosides (2, 3). This limits therapeutic choices, as polymyxins (polymyxin B or colistin) and tigecycline may be the only antibiotics that retain *in vitro* and *in vivo* microbiological activity.

CRKP infections are often treated with combination therapy (4, 5); however, the choice of agents is both limited and challenging. Combination therapy with aminoglycosides, if susceptibility is preserved, carries an increased risk of nephrotoxicity. Due to a high volume of distribution, low blood levels, and high MIC, tigecycline is a “last resort” option, particularly for bloodstream infections. High MICs of carbapenems preclude achieving therapeutic levels even with pharmacodynamically optimized dosing strategies. Although *in vitro* synergy against CRKP has been observed when polymyxin B is used in combination with rifampin, cefepime, aminoglycosides, carbapenems, or tigecycline, testing methods are nonstandardized, and therefore the clinical effect of synergy remains unclear (3, 6–8). Limited data have demonstrated survival benefits of combination therapy using polymyxin B or colistin with carbapenems and/or tigecycline for patients with CRKP bacteremia (4, 5). Given the frequently encountered challenges of combination therapy, we aimed to describe the out-

comes for patients with CRKP infections treated with polymyxin B monotherapy and to identify risk factors for treatment failure.

MATERIALS AND METHODS

Study design. This was a retrospective study in a tertiary care academic medical center in New York City. The study population included adult patients (aged ≥ 18 years) with CRKP infections who received polymyxin B monotherapy for ≥ 72 h. Only the first treatment course was included.

Microbiology. Cases were identified from a microbiology lab report of CRKP isolates from 1 January 2007 to 15 August 2011 and by review of medical records. The Vitek-2 system (bioMérieux) used by our microbiology laboratory has built-in analysis software (version R05.01) that enables it to identify resistance phenotypes. Isolates were included if the ertapenem/imipenem MIC was reported as resistant by Vitek-2. For tigecycline and polymyxin B, susceptibility was defined as an MIC of ≤ 2 mg/liter by Etest, according to Food and Drug Administration (FDA) breakpoints for *Enterobacteriaceae* and Clinical and Laboratory Standards Institute (CLSI) breakpoints for *Acinetobacter baumannii*, respectively.

Data collection. Patients' demographic information, baseline characteristics, clinical data on the day of positive culture (type of infection, modified APACHE [mAPACHE] score, intensive care unit [ICU] admission, and presence of septic shock), and microbiology and antimicrobial data were collected by chart review. Clinical response, microbiological

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cure, end-of-treatment (EOT) mortality, 30-day mortality, and nephrotoxicity were evaluated by two investigators.

Definitions. Clinical infections were defined by one of the following criteria: a positive blood culture; the presence of systemic inflammatory response syndrome (SIRS) plus a positive culture from a nonsterile site; a clinical pulmonary infection score (CPIS) of >6 for pneumonia; or the presence of urinary symptoms, pyuria, and $>10^5$ CFU/ml for urinary tract infection (UTI). Clinical response was defined as a clinician-documented improvement in signs and symptoms of infection, and clinical failure was defined as persistence or deterioration in clinical parameters or death. Cases were reviewed independently by two investigators to validate the classification as a clinical response or failure. Microbiological clearance was evaluated for patients who had follow-up cultures during antibiotic treatment. Patients were defined as having baseline renal insufficiency if the initial serum creatinine (SCr) level was ≥ 1.6 mg/dl or they had reported chronic kidney or end-stage renal disease or received hemodialysis. Nephrotoxicity due to polymyxin B was defined as a decrease in baseline creatinine clearance (CL_{CR}) of $\geq 50\%$ or doubling of baseline SCr in patients with normal renal function or an increase of baseline SCr of $\geq 50\%$ or decrease of CL_{CR} of 20% in patients with abnormal baseline renal function.

Statistical analysis. Initial univariate comparisons were conducted using chi-square or Fisher's exact test for categorical variables and the Student *t* test or the Mann-Whitney U test for continuous variables. Variables with *P* values of ≤ 0.2 were included in a stepwise (backward selection) conditional multivariate logistic regression model to identify factors associated with treatment failure. All analyses were performed using SPSS, version 20.

RESULTS

From 2007 to 2011, a total of 505 patients with CRKP isolates were identified from a hospital-wide microbiology report generated by our clinical microbiology laboratory. We excluded 457 patients: 330 patients received a treatment regimen that did not include polymyxin B, and 127 patients received polymyxin B in combination with other agents. Forty-eight patients received polymyxin B monotherapy. Eight patients were excluded due to one of the following reasons: receiving polymyxin B for less than 72 h ($n = 3$), having polymicrobial infections with multidrug-resistant (MDR) *Acinetobacter baumannii* ($n = 2$), having CRKP isolates with intermediate susceptibility to polymyxin B ($n = 2$), or having a hospital stay prior to initiation of electronic records ($n = 1$).

Polymyxin B dosing at our institution was standardized in January 2009. Prior to 2009, nonstandardized dosing of polymyxin B was based on 15,000 to 25,000 units/kg of body weight/day in two divided doses, with adjustment for renal function at the treating physician's discretion. From January 2009 onwards, polymyxin B dosing was based on the hospital protocol established by our antimicrobial stewardship program: a loading dose of 25,000 units/kg was given on day 1, followed by 25,000 units/kg given every 24 h in patients with normal renal function. Subsequent doses and the dosing interval were adjusted based on CL_{CR} (9).

The ages of patients ranged from 21 to 92 years, with a median age of 76 years. Among 40 infections, there were 14 (45%) bacteremias (sources of bacteremia were catheter [$n = 3$], urinary [$n = 4$], pulmonary [$n = 4$], and intra-abdominal [$n = 3$] sources), 12 (30%) UTI, 7 (17.5%) pneumonias, 4 (10%) skin and soft tissue infections, 2 (5%) intra-abdominal infections, and 1 (2.5%) case of osteomyelitis.

All seven isolates tested for susceptibility to meropenem by Etest demonstrated an MIC of 32 mg/liter. The median MIC for amikacin was 64 mg/liter (interquartile range [IQR], 16 to 64 mg/

liter), and that for gentamicin was 4 mg/liter (IQR, 4 to 16 mg/liter). Eleven isolates were tested by Etest for susceptibility to tigecycline and polymyxin B, with median MICs of 3 mg/liter (IQR, 2 to 4 mg/liter) and 1.5 mg/liter (IQR, 1 to 1.5 mg/liter), respectively. Only 40% of isolates were susceptible to tigecycline. The median length of hospital stay prior to CRKP-positive culture for all patients was 16.5 days (IQR, 4.5 to 41 days), the median time to start of polymyxin B from day of positive culture was 3.5 days (IQR, 2 to 4 days), and the median duration of polymyxin B therapy was 10.5 days (IQR, 7.3 to 14.8 days).

Twenty-nine of 40 (73%) patients attained clinical cure. Overall, 32 patients had follow-up culture data, and 17 of 32 (53%) patients had documented microbiological clearance. The clinical cure rate was 83% for UTI, 82% for bacteremia, and 43% for pneumonia. Clinical characteristics of the clinical cure and clinical failure groups are shown in Table 1. Significant differences in age, gender, Charlson score, mAPACHE score, median days to appropriate therapy, and duration of therapy were not observed between the two groups. Patients with clinical failure were more likely to have baseline renal insufficiency (odds ratio [OR], 5.50; 95% confidence interval [CI], 1.23 to 24.51), require ICU admission (OR, 3.28; 95% CI, 0.72 to 14.94), present with septic shock (OR, 4.0; 95% CI, 0.87 to 18.45), or have pneumonia (OR, 4.9; 95% CI, 0.89 to 27.49). Except for baseline renal insufficiency, these differences were not statistically significant. In multivariable analysis, the only independent risk factor for treatment failure was baseline renal insufficiency (OR, 6.0; 95% CI, 1.22 to 29.59), after adjustment for septic shock on the day of positive culture. The overall EOT mortality and 30-day mortality rates were 10% (4 of 40 patients) and 18% (7 of 40 patients), respectively. Four (10%) patients developed nephrotoxicity. Nineteen patients had a subsequent positive culture with CRKP a median of 23 days after completing the treatment course. Among these 19 patients, 18 had isolates tested for polymyxin B susceptibility, and 3 of 18 isolates were resistant to polymyxin B. In addition, three breakthrough infections with polymyxin-resistant organisms occurred during polymyxin B treatment, including a *Proteus mirabilis* wound infection on day 8 in a patient with initial CRKP UTI, a *P. mirabilis* UTI on day 12 in a patient with initial CRKP bacteremia, and a *Providencia stuartii* bacteremia on day 13 in a patient with initial CRKP pneumonia. All 3 patients required ICU admission for their initial CRKP infections, and none developed nephrotoxicity during polymyxin treatment.

DISCUSSION

Our study reports a treatment success rate of 73% for CRKP infections with polymyxin B monotherapy. Nephrotoxicity developed in 10% of patients. The only identified independent risk factor for treatment failure was renal insufficiency at baseline. To our knowledge, this is the largest cohort describing treatment outcomes of polymyxin B monotherapy for CRKP infections in the United States. Most studies with polymyxins have evaluated the pharmacokinetics (PK) and pharmacodynamics (PD) of colistin or have reported the clinical outcomes of colistin treatment with or without combination therapy (10, 11).

The 30-day mortality rate of 18% in our study is lower than those in recent studies, which have reported mortality rates of 39 to 54% for CRKP bloodstream infections (4, 5). A possible explanation for this difference is the types of infection included and the choice of antibiotics that patients received. Our study was not

TABLE 1 Predictors of clinical failure

Variable	No. (%) of patients		Univariate analysis		Multivariate analysis	
	Clinical cure (<i>n</i> = 29)	Clinical failure (<i>n</i> = 11)	OR (95% CI)	<i>P</i> value	OR (95% CI)	<i>P</i> value
Baseline characteristics						
Age of ≥ 65 yr ^a	23 (79.3)	6 (54.5)	0.31 (0.07–1.39)	0.12		
Male gender	15 (51.7)	6 (54.5)	1.12 (0.28–4.5)	0.87		
Charlson score of ≥ 3	22 (78.6)	10 (90.9)	2.73 (0.29–25.75)	0.65		
Diabetes mellitus	13 (44.8)	5 (45.5)	1.03 (0.25–4.14)	0.97		
Coronary artery disease	16 (55.2)	7 (63.6)	1.42 (0.34–5.94)	0.63		
Baseline renal insufficiency ^a	7 (24.1)	7 (63.6)	5.50 (1.23–24.51)	0.02	6.0 (1.22–29.59)	0.028
Surgical infection within 30 days	7 (24.1)	2 (18.2)	0.70 (0.12–4.03)	0.69		
Prednisone (20 mg/day)	5 (17.2)	1 (9.1)	0.48 (0.05–4.65)	0.52		
Characteristics on day of positive culture						
mAPACHE score of ≥ 20	6 (21.4)	1 (9.1)	0.37 (0.04–3.46)	0.65		
ICU admission ^a	13 (44.8)	8 (72.8)	3.28 (0.721–14.94)	0.12		
Septic shock ^a	5 (17.2)	5 (45.5)	4.00 (0.87–18.45)	0.07	4.5 (0.83–24.5)	0.082
Polymicrobial infection	10 (34.5)	3 (27.3)	0.71 (0.15–3.30)	0.66		
Type of infection						
Bacteremia	11 (37.9)	3 (27.3)	0.61 (0.13–2.82)	0.72		
Urinary tract infection	10 (34.5)	2 (18.3)	0.42 (0.08–2.34)	0.45		
Pneumonia ^a	3 (10.3)	4 (36.4)	4.9 (0.89–27.49)	0.08		
Skin and soft tissue infection	3 (10.3)	1 (9.1)	0.87 (0.08–9.34)	0.91		
Intra-abdominal infection	1 (3.4)	1 (9.1)	2.8 (0.16–49.10)	0.48		
Osteomyelitis	1 (3.4)	0	0.72 (0.59–0.87)	0.53		
Treatment characteristic						
Polymyxin B loading dose	7 (24.1)	4 (36.4)	1.80 (0.40–8.00)	0.46		

^a Variable selected for multivariate analysis.

limited to bloodstream infections but also included infections from other sites. Patient cohorts with bloodstream infections in previous studies were likely to be more ill than our cohort. In a previous study, 41% of patients received tigecycline as monotherapy, which may be suboptimal for bloodstream infections due to its large volume distribution (12). Furthermore, the polymyxins that were used in previous studies varied, including the use of colistin or the mix of colistin and polymyxin B. Although colistin and polymyxin B are in the same family (polymyxins), colistin is administered as colistin methanesulfonate (CMS), which requires further conversion to the active moiety, colistin. In contrast, polymyxin B does not require conversion and is administered as an active drug. As there are no head-to-head comparisons between colistin and polymyxin B, it is unclear if this difference is clinically significant.

In our cohort, patients with pneumonia had the most unfavorable outcome, with a success rate of 43%. This is comparable to results of prior studies that evaluated colistin for MDR Gram-negative pneumonia, with treatment success rates ranging from 25 to 57% (13, 14). Interestingly, another study also identified that pneumonia, but not other sources of bacteremia, was associated with mortality in univariate analysis (4). However, these results cannot be compared directly to our study, as the previous studies were not limited to polymyxin B monotherapy. The poor outcomes for patients treated with polymyxin B for CRKP pneumonia may be explained partially by a low concentration of the drug at the target site. An early PK study in the 1980s showed a low level of free polymyxin B in lung tissue after intravenous polymyxin B

administration (15). A more recent study also reported an undetectable colistin level in bronchial lavage fluid 2 h after the start of CMS infusion due to extensive tissue binding and poor penetration into lung tissue (16). In contrast to the low clinical success rate for pneumonia, the high clinical response rate (83%) for UTI was unexpected given the low concentration of polymyxin B recovered from urine reported by a previous PK study (17). One small study reported that four of four patients with multidrug-resistant Gram-negative bacteriuria cleared the organism after intravenous polymyxin B therapy, and another study demonstrated a 64% microbiologic clearance rate for CRKP bacteriuria with polymyxin B, compared to 88% and 43% with aminoglycoside and tigecycline, respectively (18, 19). This suggests that polymyxin B still has activity against UTI despite its very low concentration in urine.

Nephrotoxicity has been a concern for polymyxin use. A previous study comparing colistin and polymyxin B showed similar rates of nephrotoxicity (26% and 27%, respectively) (20). In fact, the association between baseline renal insufficiency and treatment failure in our study raises the possibility of suboptimal doses of polymyxin B given to patients with baseline renal insufficiency. Higher doses (≥ 200 mg/day) of polymyxin B may be associated with lower in-hospital mortality, although at a higher cost of nephrotoxicity (21). Case reports and animal studies have suggested that renal adjustment might not be necessary for dosing of polymyxin B in renal failure (22, 23). Prospective PK and PD studies are urgently needed to guide dose adjustment of polymyxin B.

Although we do not have data to comment on the development of resistance to polymyxin B during the treatment of CRKP, it is interesting that 17% of subsequent CRKP infections in our patients were resistant to polymyxin B. There were also 3 patients who developed breakthrough infections with an organism intrinsically resistant to polymyxin B after at least 8 days of monotherapy. A prior study also reported emergence of infections due to *Proteus* spp. 3 months after completion of treatment with colistin (24). Our study suggests that these breakthrough infections can occur during the treatment course. Further studies are needed to investigate whether using combination therapy with polymyxin B can be beneficial by preventing the development of polymyxin B resistance and emergence of breakthrough infections with organisms intrinsically resistant to polymyxins.

Our study shows a high treatment success and low 30-day mortality rate with polymyxin B monotherapy for CRKP infections. Caution should be taken in using polymyxin B monotherapy for the treatment of CRKP pneumonia. Baseline renal insufficiency is associated with treatment failure. More studies are needed to compare the treatment efficacies of polymyxin B monotherapy and combination treatments in prospective cohorts and to determine whether efficacy varies between colistin and polymyxin B.

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Y.D. and T.-Y.C. evaluated clinical responses, microbiological cure, EOT mortality, 30-day mortality, and nephrotoxicity, and they reviewed cases independently to validate the classification as a clinical response or failure.

REFERENCES

- Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP. 2008. Outcomes of carbapenem-resistant *Klebsiella pneumoniae* infection and the impact of antimicrobial and adjunctive therapies. *Infect. Control Hosp. Epidemiol.* 29:1099–1106.
- Hirsch EB, Tam VH. 2010. Detection and treatment options for *Klebsiella pneumoniae* carbapenemases (KPCs): an emerging cause of multidrug-resistant infection. *J. Antimicrob. Chemother.* 65:1119–1125.
- Bratu S, Tolaney P, Karumudi U, Quale J, Moorthy M, Nichani S, Landman D. 2005. Carbapenemase-producing *Klebsiella pneumoniae* in Brooklyn, NY: molecular epidemiology and in vitro activity of polymyxin B and other agents. *J. Antimicrob. Chemother.* 56:128–132.
- Qureshi ZA, Paterson DL, Potoski BA, Kilayko MC, Sandovsky G, Sordillo E, Polsky B, Adams-Haduch JM, Doi Y. 2012. Treatment outcome of bacteremia due to KPC-producing *Klebsiella pneumoniae*: superiority of combination antimicrobial regimens. *Antimicrob. Agents Chemother.* 56:2108–2113.
- Tumbarello M, Viale P, Viscoli C, Trearichi EM, Tumietto F, Marchese A, Spanu T, Ambretti S, Ginocchio F, Cristini F, Losito AR, Tedeschi S, Cauda R, Bassetti M. 2012. Predictors of mortality in bloodstream infections caused by *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae*: importance of combination therapy. *Clin. Infect. Dis.* 55:943–950.
- Bergen PJ, Forrest A, Bulitta JB, Tsuji BT, Sidjabat HE, Paterson DL, Li J, Nation RL. 2011. Clinically relevant plasma concentrations of colistin in combination with imipenem enhance pharmacodynamic activity against multidrug-resistant *Pseudomonas aeruginosa* at multiple inocula. *Antimicrob. Agents Chemother.* 55:5134–5142.
- Elemam A, Rahimian J, Doymaz M. 2010. In vitro evaluation of antibiotic synergy for polymyxin B-resistant carbapenemase-producing *Klebsiella pneumoniae*. *J. Clin. Microbiol.* 48:3558–3562.
- Pournaras S, Vriani G, Neou E, Dendrinos J, Dimitroulia E, Poulou A, Tsakris A. 2011. Activity of tigecycline alone and in combination with colistin and meropenem against *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Enterobacteriaceae* strains by time-kill assay. *Int. J. Antimicrob. Agents* 37:244–247.
- Esaian D, Dubrovskaya Y, Phillips M, Papadopoulos J. 2012. Effectiveness and tolerability of a polymyxin B dosing protocol. *Ann. Pharmacother.* 46:455–456.
- Dalfino L, Puntillo F, Mosca A, Monno R, Spada ML, Coppolecchia S, Miragliotta G, Bruno F, Brienza N. 2012. High dose, extended-interval colistin administration in critically ill patients: is this the right dosing strategy? A preliminary study. *Clin. Infect. Dis.* 54:1720–1726.
- Plachouras D, Karvanen M, Friberg LE, Papadomichelakis E, Antoniadou A, Tsangaris I, Karaikos I, Poulakou G, Kontopidou F, Armaganidis A, Cars O, Giamarellou H. 2009. Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by gram-negative bacteria. *Antimicrob. Agents Chemother.* 53:3430–3436.
- Meagher AK, Ambrose PG, Grasele TH, Ellis-Grosse EJ. 2005. The pharmacokinetic and pharmacodynamic profile of tigecycline. *Clin. Infect. Dis.* 41(Suppl 5):S333–S340.
- Garnacho-Montero J, Ortiz-Leyba C, Jimenez-Jimenez FJ, Barrero-Almodovar AE, Garcia-Garmendia JL, Bernabeu-Wittel IM, Gallego-Lara SL, Madrazo-Osuna J. 2003. Treatment of multidrug-resistant *Acinetobacter baumannii* ventilator-associated pneumonia (VAP) with intravenous colistin: a comparison with imipenem-susceptible VAP. *Clin. Infect. Dis.* 36:1111–1118.
- Levin AS, Barone AA, Penco J, Santos MV, Marinho IS, Arruda EA, Manrique EI, Costa SF. 1999. Intravenous colistin as therapy for nosocomial infections caused by multidrug-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*. *Clin. Infect. Dis.* 28:1008–1011.
- Ziv G, Nouws JF, van Ginneken CA. 1982. The pharmacokinetics and tissue levels of polymyxin B, colistin and gentamicin in calves. *J. Vet. Pharmacol. Ther.* 5:45–58.
- Imberti R, Cusato M, Villani P, Carnevale L, Iotti GA, Langer M, Regazzi M. 2010. Steady-state pharmacokinetics and BAL concentration of colistin in critically ill patients after IV colistin methanesulfonate administration. *Chest* 138:1333–1339.
- Zavascki AP, Goldani LZ, Cao G, Superti SV, Lutz L, Barth AL, Ramos F, Boniatti MM, Nation RL, Li J. 2008. Pharmacokinetics of intravenous polymyxin B in critically ill patients. *Clin. Infect. Dis.* 47:1298–1304.
- Pastewski AA, Caruso P, Parris AR, Dizon R, Kopec R, Sharma S, Mayer S, Ghitan M, Chapnick EK. 2008. Parenteral polymyxin B use in patients with multidrug-resistant gram-negative bacteremia and urinary tract infections: a retrospective case series. *Ann. Pharmacother.* 42:1177–1187.
- Satlin MJ, Kubin CJ, Blumenthal JS, Cohen AB, Furuya EY, Wilson SJ, Jenkins SG, Calfee DP. 2011. Comparative effectiveness of aminoglycosides, polymyxin B, and tigecycline for clearance of carbapenem-resistant *Klebsiella pneumoniae* from urine. *Antimicrob. Agents Chemother.* 55:5893–5899.
- Oliveira MS, Prado GV, Costa SF, Grimbaum RS, Levin AS. 2009. Polymyxin B and colistimethate are comparable as to efficacy and renal toxicity. *Diagn. Microbiol. Infect. Dis.* 65:431–434.
- Elias LS, Konzen D, Krebs JM, Zavascki AP. 2010. The impact of polymyxin B dosage on in-hospital mortality of patients treated with this antibiotic. *J. Antimicrob. Chemother.* 65:2231–2237.
- Abdelraouf K, He J, Ledesma KR, Hu M, Tam VH. 2012. Pharmacokinetics and renal disposition of polymyxin B in an animal model. *Antimicrob. Agents Chemother.* 56:5724–5727.
- Kwa AL, Abdelraouf K, Low JG, Tam VH. 2011. Pharmacokinetics of polymyxin B in a patient with renal insufficiency: a case report. *Clin. Infect. Dis.* 52:1280–1281.
- Paul M, Bishara J, Levkovich A, Chowers M, Goldberg E, Singer P, Lev S, Leon P, Raskin M, Yahav D, Leibovici L. 2010. Effectiveness and safety of colistin: prospective comparative cohort study. *J. Antimicrob. Chemother.* 65:1019–1027.