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Aminoglycosides for Treatment of Bacteremia Due to Carbapenem-Resistant *Klebsiella pneumoniae*

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Aminoglycoside treatment of carbapenem-resistant (CR) *Klebsiella pneumoniae* bacteremia was associated with a 70% rate (23/33) of 30-day survival. Successful treatment was associated with sources of bacteremia amenable to reliable aminoglycoside pharmacokinetics ($P = 0.037$), acute physiology and chronic health evaluation II (APACHE II) scores of <20 ($P = 0.16$), and nonfatal underlying diseases ($P = 0.015$). Success rates were 78% and 100% if ≥2 and all 3 factors were present, respectively. Clinicians may consider the use of aminoglycosides against CR *K. pneumoniae* bacteremia if strains are susceptible and the sources of infection are amenable to reliable pharmacokinetics.

Treatment options for carbapenem-resistant (CR) *Klebsiella pneumoniae* infections are limited. Aminoglycosides are active against ≥50% of CR *K. pneumoniae* isolates *in vitro* (1–3) and exhibit rapid bactericidal activity against susceptible strains during time-kill assays (2). Aminoglycosides have been shown to be more effective than polymyxin B or tigecycline in eradicating CR *K. pneumoniae* bacteriuria (4). Treatment with a regimen that included gentamicin was associated with reduced mortality among patients with sepsis, due to an outbreak strain of colistin-resistant, CR *K. pneumoniae* (5). The effectiveness of aminoglycosides against CR *K. pneumoniae* bacteremia in a nonoutbreak setting is unknown. Prior to the 1980s, aminoglycosides were reported to successfully treat ~70% of Gram-negative bacteremia cases (6). More recently, the availability of well-tolerated, broad-spectrum β-lactam antibiotics has relegated aminoglycosides to second-line status. Aminoglycoside therapy is limited by nephrotoxicity, a need for therapeutic drug monitoring, and poor penetration into abdominal and pulmonary sites of infection (7–10). The objective of this study was to review our clinical experience with aminoglycosides as primary therapy for CR *K. pneumoniae* bacteremia.

We conducted a retrospective study of patients at our center with CR *K. pneumoniae* bacteremia between February 2010 and September 2014. CR *K. pneumoniae* was defined by nonsusceptibility to a carbapenem and all third-generation cephalosporins (11). Patients with bacteremia who were initially treated with an aminoglycoside for ≥3 days were included. For patients with normal renal function, standard extended-interval aminoglycoside doses were recommended and adjusted according to the Hartford nomogram (7). Among patients with renal impairment, adjustments were made according to current recommendations (12). Bacteremia was classified as primary or secondary by the independent review of two investigators (13). Sources of bacteremia were considered amenable or unamenable to the achievement of reliable aminoglycoside pharmacokinetics at the site. Amenable sites were primary bacteremia, urine, and soft tissues (14, 15). Unamenable sites included the abdominal cavity, respiratory tract, and bone (8–10). Underlying diseases were classified as fatal or nonfatal, according to the criteria of McCabe and Jackson (16). Clinical success was defined as survival at 30 days following the onset of CR *K. pneumoniae* bacteremia, resolution of signs and symptoms of infection, sterilization of blood cultures within 7 days of treatment initiation, completion of planned antimicrobial therapy, and the absence of recurrent CR *K. pneumoniae* infections within 30 days. MICs were determined using reference Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods (17). Strains were tested for multilocus sequence type (ST) and *K. pneumoniae* carbapenemase (KPC) variants, as described previously (18). Comparisons between groups were made by Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables. Significance was defined as a P value of ≤0.05 (two-tailed).

Thirty-six consecutive patients with CR *K. pneumoniae* bacteremia were evaluated; 3 patients died after 1 day of aminoglycoside therapy and were excluded. The data for the remaining 33 patients are summarized in Table 1. The median acute physiology and chronic health evaluation II (APACHE II) score was 17 (range, 3 to 35). Primary bacteremia was diagnosed in 39% (13/33) of patients; secondary bacteremia resulted from sites in the abdomen (42% [14/33]), respiratory tract (6% [2/33]), urinary tract (6% [2/33]), soft tissue (3% [1/33]), and bone (3% [1/33]). Forty-eight percent (16/33) of infections were amenable to reliable aminoglycoside pharmacokinetics. Thirty-one CR *K. pneumoniae* isolates were available for strain typing. Ninety percent (28/31) were sequence type 258 (ST-258); 81% (25/31) and 13% (4/31) expressed KPC-2 and KPC-3 carbapenemases, respectively.

Thirty percent (10/33) of patients received gentamicin monotherapy. Ninety-seven percent (32/33) of CR *K. pneumoniae* strains were susceptible to gentamicin, and all were susceptible to amikacin. All patients infected with a gentamicin-susceptible strain were treated with a regimen that included gentamicin; the

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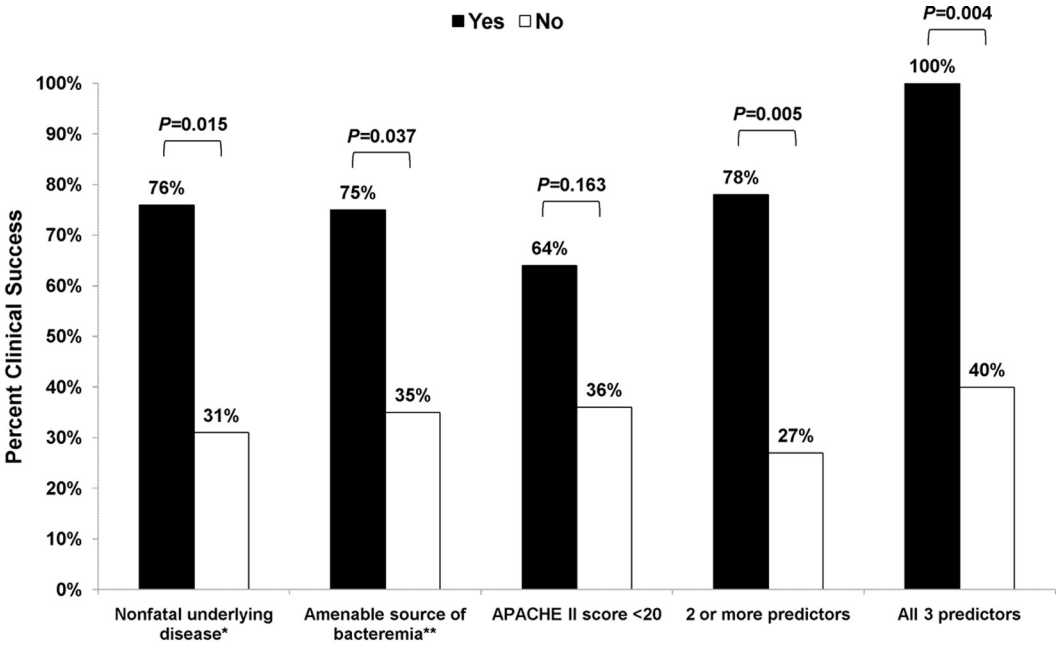
TABLE 1 Patient demographics, clinical characteristics, and outcomes of CR *K. pneumoniae* bloodstream infections

Patient	Age (yr) (sex)[a]	Underlying disease(s)[b]	McCabe and Jackson score[c]	APACHE II score[d]	Time to BSI (days)[e]	Type of bacteremia	Source control (day)[f]	Duration of BSI (days)[g]	Time to initiation of therapy (h)[h]	Antimicrobial regimen (days of therapy)	MIC (μg/ml) for[i]:			Patient outcome[j]	Time to death in days
											Aminoglycoside	Carbapenem	Other		
22	58 (F)	Lung transplant	3	13	17	Primary	Catheter removal (2)	1	87	Gentamicin (9)	1	NA	NA	Clinical success	Alive
29	28 (M)	Pancreatitis, DM	3	3	25	Primary	Catheter removal (1)	1	110	Gentamicin (14)	2	NA	NA	Clinical success	Alive
103	64 (M)	Parkinson's disease, cholangitis	3	19	16	Secondary abdominal	IR-guided drainage of pancreatic abscess (2)	1	65	Gentamicin (13)	0.5	NA	NA	Clinical success	Alive
140	45 (F)	Multivisceral transplant	3	17	0	Primary	Port and catheter removal (4)	7	114	Gentamicin + doripenem (21)	1	8	NA	Clinical success	Alive
88	85 (F)	Pancreatitis	3	8	4	Secondary abdominal	None	1	52	Gentamicin + ertapenem (14)	0.5	8	NA	Clinical success	Alive
116	56 (F)	Liver transplant	3	20	1	Secondary abdominal	Biliary stent removal (11)	1	64	Gentamicin + doripenem (14)	1	32	NA	Clinical success	Alive
117	55 (M)	Liver transplant	3	10	1	Secondary abdominal	None	1	67	Gentamicin + doripenem (10)	0.5	8	NA	Clinical success	Alive
79	53 (M)	ESRD	2	14	25	Secondary wound	Bedside debridement	1	22	Gentamicin + doripenem (14)	0.5	8	NA	Clinical success	Alive
138	63 (M)	AML, febrile neutropenia	3	14	48	Primary	Catheter removal (4)	2	36	Gentamicin + ciprofloxacin + meropenem (14)	0.5	2	Cipro, 0.06	Clinical success	Alive
144	33 (M)	Paraplegia	3	9	8	Primary	Catheter removal (2 and 7)	6	63	Gentamicin (3) + meropenem-RPX7009 (8)	0.5	8	NA	Clinical success	Alive
142	70 (M)	DM s/p cardiac arrest	2	29	1	Secondary respiratory tract	None	1	75	Gentamicin (7) + inhaled gent (7) meropenm (14)	0.5	2	NA	Clinical success	Alive
119	57 (M)	Kidney transplant	3	15	48	Secondary urinary tract	Foley catheter removed (1)	5	31	Gentamicin + doripenem (18)	1	4	NA	Clinical success	Alive
120	58 (M)	ESLD, CCA	2	16	3	Secondary abdominal	PTC catheter exchange (6)	2	60	Gentamicin + doripenem (15)	1	256	NA	Clinical success	33 (due to underlying disease)
69	69 (M)	HIV, Burkitt's lymphoma	2	26	12	Primary	None	1	59	Gentamicin (10) + colistin (8) + meropenem (12)	0.5	256	Colistin, 0.25	Clinical success	81 (due to *Pseudomonas* BSI)
66	74 (M)	CHF, DM	2	12	7	Primary	Catheter removal (3)	2	94	Gentamicin (6)	1	NA	NA	Clinical success	84 (due to underlying disease)
49	65 (M)	Liver transplant and ESRD	2	19	5	Primary	Catheter removal (2)	5	86	Gentamicin (14)	2	NA	NA	Clinical success	73 (due to underlying disease)
30	30 (M)	Lung transplant	3	21	72	Primary	Catheter removal (4)	3	95	Gentamicin (7)	0.25	NA	NA	Clinical success	564 (due to underlying disease)
121	32 (M)	Multivisceral transplant	3	11	91	Primary	Catheter exchange over wire (1), and then removed (3)	3	55	Gentamicin + doripenem (15)	0.5	256	NA	Clinical success	126 (due to relapse CR-*K. pneumoniae* BSI)

61	84 (F)	ESRD, chronic respiratory failure, CAD	2	35	1	Primary	Catheter removed (1)	1	4	Gentamicin + meropenem (5)	1	8	NA	Failure due to death	6
999	64 (M)	Liver transplant	3	15	3	Secondary abdominal	Biliary balloon dilation (2)	7	72	Gentamicin + doripenem (4)	4	8	NA	Failure due to death	7
127	54 (M)	Liver transplant and AML	1	17	8	Secondary urinary tract	None	3	70	Gentamicin + colistin + meropenem (5)	0.5	4	Colistin, 16	Failure due to death	8
89	67 (F)	Rheumatoid arthritis	1	16	10	Secondary abdominal	None	1	66	Gentamicin (6)	0.25	NA	NA	Failure due to death	9
37	85 (F)	Chronic respiratory failure and CAD	2	20	2	Primary	Catheter removal (1)	1	26	Gentamicin (5)	1	NA	NA	Failure due to death	10
78	57 (M)	Alcoholic cirrhosis	2	25	14	Secondary respiratory tract	None	1	55	Gentamicin + colistin + doripenem (7)	0.25	128	Colistin, 4	Failure due to death	10
64	62 (F)	Pancreatic CA	1	8	69	Secondary abdominal	None	1	97	Gentamicin (6)	1	NA	NA	Failure due to death	14
128	66 (M)	ESLD, ESRD	2	26	19	Secondary abdominal	Chronic cholecystostomy tube	1	28	Gentamicin + doripenem (14)	0.5	128	NA	Failure due to death	19
74	61 (F)	ESRD	2	15	52	Secondary wound/bone	Multiple bedside debridements and wound vacuum	1	46	Gentamicin + meropenem (14)	0.5	128	NA	Failure due to death	22
131	73 (F)	Cholangiocarcinoma	2	26	3	Secondary abdominal	None	4	83	Amikacin + doripenem (23)	16	2	NA	Failure due to death	30
114	56 (M)	Liver transplant	3	25	1	Secondary abdominal	Biliary stent removal (2), biliary drainage and PTC catheter placement (12)	4	43	Gentamicin + doripenem (18)	1	16	NA	Failure due to persistent IAI	35
136	52 (M)	Pancreatic cancer	2	13	4	Primary	Port removed (2)	1	33	Gentamicin + meropenem (10)	1	8	NA	Failure due to recurrent BSI (day 20)	NA[k]
39	65 (M)	Liver transplant	2	18	1	Secondary abdominal	Balloon dilation of choledocojejuno-stomy to remove stone (6)	4	37	Gentamicin (10)	2	NA	NA	Failure due to recurrent BSI (day 10) and new IAI (day 11)	1,044
48	60 (M)	Liver transplant	2	22	61	Secondary abdominal	Abdominal washout (9)	11	127	Gentamicin + colistin + doripenem (8)	0.5	64	Colistin, 0.25	Failure due to persistent BSI requiring change of therapy	Alive
91	60 (M)	Pancreatitis	3	18	7	Secondary abdominal	Percutaneous drainage (3)	1	23	Gentamicin + doripenem (14)	0.5	16	NA	Failure due to persistent IAI requiring change of therapy	Alive

[a] F, female; M, male.
[b] DM, diabetes mellitus; ESRD, end-stage renal disease; AML, acute myeloid leukemia; s/p, status-post; ESLD, end-stage liver disease; CCA, cholangiocarcinoma; CHF, congestive heart failure; CAD, coronary artery disease; CA, cancer.
[c] As defined by the McCabe and Jackson classification of underlying diseases (16), where 1 = rapidly fatal, 2 = ultimately fatal, and 3 = nonfatal.
[d] At the onset of bloodstream infection.
[e] Time from hospital admission to positive blood culture. BSI, bloodstream infection (bacteremia).
[f] IR, infrared; PTC, percutaneous transhepatic cholangiography.
[g] Days of positive blood cultures.
[h] Time from collection of blood culture to first dose of combination therapy.
[i] NA, not available.
[j] IAI, intra-abdominal infection.
[k] Discharged to hospice, so date of death was not available.



* As defined by the McCabe-Jackson classification criteria (16).

** Amenable sources of bacteremia include vascular catheters, soft tissues, and urinary tract.

FIG 1 Factors associated with clinical success following aminoglycoside therapy for CR *K. pneumoniae* (CR-Kp) bacteremia.

patient infected with the gentamicin-nonsusceptible (MIC, 8 μg/ml) and amikacin-susceptible (MIC, 16 μg/ml) strain was treated with amikacin plus doripenem (Table 1, patient 131). Aminoglycoside therapy was initiated at a median of 63 h (range, 4 to 127 h) after the first positive blood culture was collected.

The 14- and 30-day survival rates were 78% (26/33) and 70% (23/33), respectively. Clinical success was achieved in 54% (18/33) of the patients. Clinical success was more likely for patients with primary rather than secondary bacteremia (77% [10/13] versus 40% [8/20], respectively; $P = 0.07$), amenable rather than unamenable sources of bacteremia (75% [12/16] versus 35% [6/17], respectively; $P = 0.037$), and APACHE II scores of <20 rather than ≥20 at the onset of bacteremia (64% [14/22] versus 36% [4/11], respectively; $P = 0.16$). Success rates were higher among patients with underlying diseases that were classified as nonfatal rather than fatal (76% [13/17] versus 31% [5/16], respectively; $P = 0.015$). Overall, the clinical success rate was 78% (14/18) for patients in whom ≥2 factors linked to favorable outcomes were present (amenable source, APACHE II score <20, and/or nonfatal underlying disease), compared to 27% (4/15) for other patients ($P = 0.005$). For patients in whom all 3 favorable factors were present, the clinical success rate was 100% (8/8) compared to 40% (10/25) for others (Fig. 1; $P = 0.004$). Other variables, including time to initiation of treatment and aminoglycoside combination therapy, were not associated with clinical responses. For combination therapy, success rates were comparable against infections caused by strains that exhibited carbapenem MICs of ≤8 μg/ml and >8 μg/ml (62% [8/13] versus 40% [4/10], respectively; $P = 0.41$). Outcomes did not differ by strain ST or KPC subtype.

Thirty-six percent (9/25) developed acute kidney injury (AKI) at some point during aminoglycoside therapy (defined as a 1.5-fold increase in serum creatinine level from baseline [19]), with one patient requiring renal replacement therapy. The median time to AKI was 10 days (range, 2 to 18 days). One patient receiving gentamicin monotherapy had a recurrent bloodstream infection (11 days from initial bacteremia) due to an aminoglycoside-resistant, CR *K. pneumoniae* strain; otherwise, the emergence of aminoglycoside resistance was not identified.

Taken together, our data demonstrate that aminoglycosides are effective in treatment against CR *K. pneumoniae* bacteremia, provided the causative strain is aminoglycoside susceptible and the infection originates from a site amenable to targeted aminoglycoside concentrations. In these settings, our clinical success rate of 75% is comparable to pooled response rates reported for patients with CR *K. pneumoniae* infections who received two or more *in vitro* active agents (20–22). This success rate is also similar to the 80% rate we previously reported at our center for patients with CR *K. pneumoniae* bacteremia treated with a carbapenem and colistin, if both agents were active (carbapenem MIC, ≤8 μg/ml) (23).

Our findings support and extend those of a recent study that showed a survival advantage among patients with colistin-resistant, CR *K. pneumoniae* sepsis who were treated with gentamicin-based regimens (5). The earlier study focused exclusively on sepsis caused by an outbreak-associated ST-512, KPC-3-producing strain over a 9-month period. In contrast, our data were collected over a 4-year period and were not outbreak associated. Moreover, most of our patients were infected with KPC-2- or KPC-3-producing CR *K. pneumoniae* strains of the predominant international clonal group ST-258. Therefore, the utility of aminoglycosides against CR *K. pneumoniae* infections is not limited by strain

ST but rather by drug susceptibility and pharmacokinetic considerations.

In both studies, there were no differences in outcomes for patients who received aminoglycoside monotherapy or those who received combination regimens. Tigecycline was the agent used in combination in the earlier study, as opposed to a carbapenem in this study. The different regimens and small sample sizes preclude us from drawing definitive conclusions about the usefulness of aminoglycoside mono- or combination therapy. Nevertheless, our data indicate that aminoglycoside activity is a major driver of clinical outcomes, since the success rates for combination therapy were comparable for strains with carbapenem MICs of ≤8 μg/ml or >8 μg/ml.

It is notable that our previously reported success rate in treating CR *K. pneumoniae* bacteremia with carbapenem-colistin combination therapy was only 30% if colistin was the sole active agent (23). Indeed, the presence of either a major *ompK36* mutation or a doripenem MIC of ≤8 μg/ml predicted a lack of CR *K. pneumoniae* responsiveness to doripenem and colistin *in vitro* (24). Polymyxins alone or in combination have been linked to suboptimal treatment responses among patients with CR *K. pneumoniae* infections in another study (25). The emergence of colistin resistance during treatment is a well-recognized limitation of this agent (26–28). In contrast, aminoglycosides are rapidly and durably bactericidal *in vitro* (1, 2), and the emergence of resistance was uncommon in our clinical experience. Aminoglycosides and colistin are each limited by nephrotoxicity, which we observed for a minority of patients in this study. Given these data, we generally recommend an aminoglycoside-containing rather than colistin-containing regimen at our center if the causative strain is susceptible to both agents and the infected sites are amenable to aminoglycoside pharmacokinetics. On the other hand, larger cohort studies have failed to show superiority of aminoglycoside- versus colistin-based regimens (21). Thus, we encourage centers to internally audit patient outcomes prior to selecting preferred therapeutic approaches against CR *K. pneumoniae* bacteremia. Such approaches should be prospectively tailored to include new antimicrobial agents as they become available.

Our findings are plausible based on aminoglycoside pharmacokinetics. Aminoglycoside peak concentrations of 10× the MIC against the infecting pathogen are associated with optimal bactericidal killing (29) and suppression of aminoglycoside resistance (30). Peak serum concentrations range from 14 to 24 μg/ml among patients receiving extended-interval dosing regimens (7). This concentration range approximates 10× the MIC against 94% (31/33) of CR *K. pneumoniae* isolates in our study, including all isolates from patients with primary bacteremia. Aminoglycoside concentrations in urine are even higher (15). On the other hand, aminoglycoside concentrations in bile are 25 to 50% of those of serum and are virtually undetectable in the presence of biliary obstruction or hepatic damage (8, 10). Likewise, less than one-third of gentamicin serum concentrations are detectable in the alveolar lining fluid and respiratory secretions of critically ill patients (9, 31). In keeping with our experience, aminoglycosides are less efficacious than comparator agents for the treatment of intra-abdominal infections (32).

Optimal antimicrobial therapy is not the sole determinant of outcomes among patients with CR *K. pneumoniae* bacteremia (18). Underlying diseases and severity of illness at the onset of infection are also major predictors of mortality (21, 22, 33). Indeed, we found that clinical response rates were only 31% and 36% among patients with fatal underlying diseases and APACHE II scores of ≥20, respectively. When these factors were combined with unamenable sources of bacteremia, clinical response rates dropped to 22% and 29%, respectively. An important avenue of future investigation will be whether outcomes can be improved with newer agents, such as ceftazidime-avibactam, which is active against *Enterobacteriaceae* that produce KPC and other β-lactamases (34).

Primary bacteremia and bacteremia that was secondary to intra-abdominal sources predominated in our study. All patients with bacteremia stemming from intra-abdominal sources underwent an interventional procedure, but it is possible that the higher aminoglycoside failure rate in the population was due to suboptimal source control. Our results cannot necessarily be extrapolated to other types of infection. Based on pharmacokinetic and clinical data, it is reasonable to anticipate that aminoglycosides will be useful against bacteremia due to urinary sources (4, 8, 15). We also cannot exclude that clinician biases in choosing aminoglycoside-based regimens may have influenced our findings. Last, 70% of patients received an aminoglycoside in combination with another antimicrobial agent; thus, the value of aminoglycoside monotherapy for CR *K. pneumoniae* bacteremia is not clear.

In conclusion, despite a small sample size, our study provides much-needed insight into the potential roles for aminoglycoside treatment against CR *K. pneumoniae* bacteremia. As new agents against CR *K. pneumoniae* and other highly drug-resistant Gram-negative bacteria enter the clinic, it will be imperative to employ them judiciously to preserve their long-term utility. In this regard, it is critical to understand where older agents, like aminoglycosides, have useful roles. Moving forward, it will be important to determine if aminoglycosides can be used in combination with newer agents to improve efficacy and limit the emergence of resistance.

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