Brazilian Journal of Microbiology (2021) 52:1913–1919
https://doi.org/10.1007/s42770-021-00551-x

CLINICAL MICROBIOLOGY - RESEARCH PAPER

Amikacin for the treatment of carbapenem-resistant *Klebsiella pneumoniae* infections: clinical efficacy and toxicity

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Received: 2 February 2021 / Accepted: 21 June 2021 / Published online: 30 June 2021

Abstract

Infections by carbapenem-resistant *Klebsiella pneumoniae* (CR*Kp*) are an increasing global threat with limited therapeutic options. Our objective was to evaluate clinical and microbiological outcomes of patients treated with amikacin for CR*Kp* infections. We did a retrospective cohort of patients > 18 years old, with CR*Kp* infections treated with amikacin in two tertiary care hospitals in Porto Alegre, Brazil. The impact of clinical factors, antibiotic treatment, and amikacin minimum inhibitory concentration (MIC) on patients' 30-day mortality was assessed. Microbiological clearance and nephrotoxicity (assessed by RIFLE score) were evaluated as secondary outcomes. A Cox regression analysis was done for mortality. We included 84 patients for analysis. Twenty-nine (34.5%) patients died in 30 days. Amikacin MIC values ranged from 0.125 to 8 µg/mL and did not influence on mortality, regardless of the prescribed dose of this antibiotic ($P = 0.24$). Bacterial clearance occurred in 17 (58.6%) of 29 patients who collected subsequent cultures. Two (16.6%) of the 12 persistently positive cultures changed the amikacin susceptibility profile from susceptible to intermediate. Twenty-nine (37.2%) patients developed acute kidney injury (AKI): risk 13, injury 11, and failure 5. Risk factors for AKI were higher baseline eGFR ($P < 0.01$) and combination therapy with colistin ($P = 0.02$). Comparing patients who received combination with colistin vs polymyxin B, AKI occurred in 60.0% vs 20.6%, respectively, $P < 0.01$. Fifteen of the 16 (16.6%) patients who developed renal injury or failure were receiving colistin. In conclusion, amikacin was an effective treatment for CR*Kp* infections. Within susceptible range, amikacin MIC values did not influence on clinical outcomes. Combination therapy of amikacin and colistin was highly nephrotoxic and should be used with caution.

Keywords Amikacin · CRE · Carbapenem-resistant *Klebsiella pneumoniae* · Acute kidney injury · Nephrotoxicity · Mortality

Introduction

Infections by carbapenem-resistant *Klebsiella pneumoniae* (*CRKp*) are an increasing global threat, due to the few therapeutic options against these bacteria [1]. Combination therapy with susceptible antibiotics has shown clinical benefit in many studies [2–4]. Amynoglicosides (AG) are old drugs that gained importance in this scenario because they retain in vitro activity for most *CRKp* isolates and can be synergic to other classes of antibiotics such as polymyxins. AG permeabilize the outer membrane of Gram-negative bacteria, likely enhancing the target site penetration of other antibiotics, and reduce protein synthesis [1]. Amikacin is a commonly used AG for this purpose.

The main concerns about the use of amikacin are difficulty to achieve pharmacokinetic (PK)/pharmacodynamic

Responsible Editor: Mara Correa Lelles Nogueira

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(PD) target with usual doses, nephrotoxicity, and development of resistance during treatment [5]. Amikacin optimal antibacterial activity is difficult to achieve in bacteria with amikacin MIC near or at the susceptibility breakpoint. Increasing the dose may be prohibitive due to nephrotoxicity [6]. Moreover, combination therapy with drugs such as polymyxins may increase its nephrotoxicity potential.

The purpose of this study was to determine the impact of amikacin dose regimens and combinations, MIC values and clinical factors on mortality, nephrotoxicity, and bacterial clearance of patients with *CRKp* infections.

Materials and methods

Study design, settings, and participants

We conducted a retrospective cohort study from January 2018 to June 2019, in two tertiary care hospitals in Porto Alegre, Brazil, with 833 and 674 beds each.

Samples and eligibility criteria

Patients with cultures that tested positive for *CRKp* were evaluated for inclusion and exclusion criteria.

Inclusion criteria

We included patients ≥ 18 years old receiving intravenous amikacin treatment for > 48 h for CR*Kp* infection, according to medical record review.

Exclusion criteria

We excluded surveillance swab samples, samples with in vitro resistance to amikacin, and patients with lower urinary tract infections.

Bacterial identification

Routine samples were identified by biochemical tests or by Vitek® (bioMérieux) automated system. The samples of interest for the research were separated and subcultured in MacConkey culture mediums. *Klebsiella pneumoniae* carbapenemase (KPC) identification was done by phenotypic tests [7] or molecular test [8]. When ethylenediamine tetraacetic acid (EDTA) test was positive in phenotypic tests, samples were sent for confirmation by multiplex real-time polymerase chain reaction (PCR).

Amikacin susceptibility testing

Amikacin (Sigma-Aldrich, USA) susceptibility tests were performed by broth microdilution technique. The broth microdilution technique was evaluated in a 96-well microdilution plate, where 50 µL of bacterial suspension adjusted to 1.5×10^8 CFU/mL and 50 µL of amikacin antibiotic were pipetted at the different concentrations tested. The American Type Culture Collection (ATCC) strain was used for control. MIC results were interpreted after 18–24 h incubation at 37 °C, according to the Clinical and Laboratory Standards Institute (CLSI) cutoff points [9]. Polymyxin MICs were routinely done at the local microbiology laboratory of each institution by microdilution technique or Etest® (bioMérieux).

Variables and definitions

Our primary outcome was 30-day mortality. Secondary outcomes were nephrotoxicity and biological clearance. Nephrotoxicity was assessed by RIFLE score [10]. We classified as acute kidney injury (AKI) only patients that lost renal function during amikacin treatment and did not spontaneously recover it before the end of therapy, to avoid misclassification due to transitory variations of estimated glomerular filtration rate (eGFR) values.

Variables potentially related to clinical and microbiological outcomes were assessed: demographic variables (age, gender, weight), comorbidities (underlying diseases of patients and Charlson comorbidity score [11]), site of infection (respiratory, abdominal, urinary, and bloodstream material), severity (intensive care unit (ICU) admission, and vasopressor use), use of combination therapy with in vitro susceptibility or resistance, therapy duration, antimicrobial dose (average daily dose of amikacin used in milligram/kilogram/day) and adequate amikacin dose adjustment according to eGFR as follows: eGFR ≥ 50 mL/min dose of 15 mg/kg/day, eGFR 10–49 mL/min dose of 7.5 mg/kg/day, and eGFR < 10 mL/min- dose of 7.5 mg/kg/day every 48 h [12].

Statistical analysis

All statistical analyses were performed using SPSS for Windows, Version 18.0. The assessment of patients' baseline characteristics was performed by calculating the median and interquartile range (IQR) for ordinal or non-normally distributed variables, mean and standard deviation (SD) for continuous variables of normal distribution, and total and percentage value for categorical variables. All tests were two-tailed and P value ≤ 0.05 was considered statistically significant. A Cox regression analysis was performed for

mortality. Variables with $P < 0.2$ in the univariate analysis were included in forward-stepwise model and retained if $P < 0.05$. A subgroup analysis was done in patients receiving amikacin monotherapy.

Ethical approval

The research complied with the recommendations of Resolution No. 196 of 10/10/96—National Health Council for Scientific Research in Human Beings. The project was carried out after its approval by the institution's Research Ethics Committee number 2.687.149 and 2.476.428.

Results

A total of 187 patients had *CRKp* isolates recovered from routine cultures. One hundred and sixty-eight (89.8%) of these samples had in vitro susceptibility to amikacin, 4 (2.1%) were intermediate, and 15 (8.0%) were resistant. Seventy-seven patients were excluded for not receiving amikacin therapy, 23 patients for low urinary tract infection, and 3 for being < 18 years old. We included 84 patients for analysis.

KPC and NDM were the resistance mechanisms identified in 80 (95.2%) and 4 (4.8%) samples, respectively. Amikacin MIC ranged from 0.125 to 8 µg/mL. The MIC at which 50% and 90% of the isolates were inhibited was 1 µg/mL and 4 µg/mL, respectively.

Fifty-eight patients (69.1%) were treated with combination therapy, with at least one in vitro susceptible antibiotic plus amikacin. All the susceptible combination therapies included polymyxins (21 with colistin, 25 with polymyxin B, and 12 changed from one type of polymyxin to the other during treatment), and 2 patients also received tigecycline. For 26 (31.0%) patients, amikacin was the only in vitro susceptible drug prescribed. Infections with polymyxin-resistant strains occurred in 10 (11.9%) patients, with MIC ranging from 4 to 32 µg/mL. All these patients received polymyxins despite in vitro resistance. Forty-eight (57.1%) patients were treated with in vitro–resistant meropenem. Meropenem MICs were tested in only 9 samples and were all ≥ 32 µg/mL.

Twenty-nine (34.5%) patients died in 30 days, in a median time of 16 (10.5–23) days after bacterial recovery. Amikacin MIC did not significantly impact on patient's mortality, $P = 0.24$. Ten (83.3%) of the 12 patients with amikacin MIC ≥ 4 µg/mL received active combination therapy. Patients' characteristics, infection site, bacterial isolates, and therapy are described in Table 1, along with their impact on 30-day mortality. The only risk factor for mortality that remained in the final Cox regression model was use of vasoactive drugs, aHR 2.90, 95%CI 1.4–6.1, $P < 0.01$.

Twenty-nine (34.5%) patients developed AKI during amikacin therapy by RIFLE criteria (risk 13, injury 11, failure 5). Risk factors for AKI in univariate analysis were higher baseline eGFR, median (IQR) of 98 (52–146) vs 49 (23.5–78.5) mL/min ($P < 0.01$), and combination therapy with colistin 18 (48.6%) of 37 vs 11 (37.9%) of 47 ($P = 0.02$). Excluding the 12 patients that received both polymyxins at some point, patients that received only polymyxin B as combination therapy vs colistin had an AKI rate of 6/29 (20.6%) versus 15/25 (60.0%) respectively, $P < 0.01$. Fifteen of the 16 (16.6%) patients who developed renal injury or failure received combination with colistin and one patient received polymyxin B. The median (IQR) days number of days of amikacin therapy was higher in patients with AKI, although not statistically significant, 10 (5.5–16) vs 8 (4–12), $P = 0.07$. Figure 1 shows the RIFLE score of patients according to combination therapy prescribed.

Twenty-nine (34.5%) of 84 patients collected subsequent cultures in the first 14 days after bacteria recovery. Twelve of these 29 (41.4%) patients remained with positive cultures for the same bacteria despite antimicrobial therapy. Persistent infection sites were abdominal site infections (33.3%), blood (33.3%), respiratory tract infections (25%), and urinary tract infections (8.3%), $P = 0.30$. Two (16.6%) of the 12 persistently positive cultures changed the amikacin susceptibility profile from susceptible to intermediate, during therapy.

The 26 patients that received amikacin as the only in vitro susceptible therapy did not significantly differ from the patients that received combination therapy, except for a lower proportion of cardiovascular disease, 36.4% vs 60.3%, respectively, $P = 0.04$. The 30-day mortality was 23.1% in this group compared to 39.7% in patients who received susceptible combination therapy ($P = 0.21$). We performed a subgroup analysis of patients receiving amikacin as monotherapy. Higher mortality was related to ICU admission ($P = 0.02$) and vasopressor use ($P = 0.03$) at the beginning of therapy. None of the patients with urinary source infections died compared to 35.5% of the patients with other primary site infections ($P = 0.06$). Patients who received antibiotic combination with an in vitro–resistant polymyxin had higher absolute mortality (66.7% vs 33.3%), $P = 0.06$.

Discussion

We evaluated clinical and microbiological outcomes of 84 patients who received amikacin to treat CR*Kp* infections. The main findings of our study are (a) amikacin retained susceptibility for most CR*Kp* isolates; (b) Amikacin MIC did not impact on 30 day mortality or bacterial *clearance*; (c) nephrotoxicity was related to higher baseline eGFR; (d) combination therapy with colistin, but not polymyxin B, was associated to higher rates of AKI, specially renal injury and

Table 1 Characteristics of patients and univariate analysis of risk factors for 30-day mortality

Variable	Total $N=84$	30-day mortality Yes, $N=29$	No, $N=55$	P value
Demographics				
Male gender	52 (61.9)	19 (65.5)	33 (60.0)	0.65
Age (years)	60.0 ± 21.1	64.5 ± 15.0	57.9 ± 14.9	0.06
Weight (kg)	67.7 ± 17.8	69.0 ± 14.0	70.5 ± 13.3	0.63
Comorbidities				
Cardiovascular disease	44 (52.4)	21 (72.4)	23 (41.8)	0.01
Chronic renal disease	17 (20.2)	10 (34.5)	7 (12.7)	0.02
Baseline estimated GFR	57.5 (28.5–106.5)	59.0 (27–99)	56.0 (32–128)	0.75
CNS	17 (20.2)	7 (24.1)	10 (18.2)	0.57
Diabetes	28 (33.3)	11 (37.9)	17 (30.9)	0.63
Digestive tract	24 (28.6)	7 (24.1)	17 (20.9)	0.62
Chronic liver disease	8 (9.5)	3 (10.3)	5 (9.1)	1.00
HIV	2 (2.4)	1 (3.4)	1 (1.8)	1.00
Cancer	27 (32.1)	8 (27.6)	19 (34.5)	0.63
Pulmonary disease	25 (29.8)	11 (37.9)	14 (25.5)	0.32
Charlson	4 (3–5)	4 (3–6)	4 (2–5)	0.19
Disease severity				
ICU admission	37 (44.0)	17 (58.6)	20 (36.4)	0.07
Vasoactive drug	25 (29.8)	14 (48.3)	11 (13.1)	0.01
Infection site				
Pulmonary	23 (27.4)	9 (31.0)	14 (25.5)	0.61
Abdominal	14 (16.7)	2 (6.9)	12 (21.8)	0.12
Upper urinary tract	25 (29.8)	8 (27.6)	17 (30.9)	0.80
Skin and soft tissue	4 (4.8)	1 (3.4)	3 (5.5)	1.00
Blood	18 (21.4)	9 (31.0)	9 (16.4)	0.16
Bacterial isolates				
Time from admission to bacterial isolation	28.1 (± 19.8)	22.2 (± 23.3)	16.4 (± 16.0)	0.19
Polymicrobial Infections	25 (29.8)	8 (27.6)	17 (30.9)	0.81
Polymyxin resistance	10 (11.6)	4 (13.8)	6 (10.5)	0.73
Amikacin MIC	0.5 (0.5–1)	1 (0.5–2)	1 (0.5–2)	0.24
Therapy				
Amikacin dose (mg/kg/dia)	13.1 ± 6.5	13.6 ± 6.1	13.3 ± 5.1	0.83
Adequate dose adjustment for eGFR	45 (53.2)	15 (51.7)	30 (54.5)	0.82
Time from bacterial isolation to start susceptible therapy (days)	3 (2–4)	3 (2–4)	3 (2–4)	0.72
Susceptible combination therapy	58 (69.0)	23(79.3)	35 (63.6)	0.21
Antibiotic combination				
Polymyxin	66 (78.6)	27 (93.1)	39 (70.9)	0.02
Polymixin B	41 (48.8)	17 (58.6)	24 (43.6)	0.25
Colistin	37 (44.0)	14 (48.3)	23 (41.8)	0.64
Meropenem	48 (57.1)	17 (58.6)	31 (56.4)	0.99
Tigecycline	2 (2.4)	1 (3.4)	1 (1.8)	0.99
Total time of amikacin therapy (days)	12 (8–17.0)	7 (2–10)	10 (6–14)	0.05
Development of AKI	29 (34.5)	10 (34.5)	19 (34.5)	0.99
Risk	13 (15.5)	4(13.8)	9 (16.4)	
Injury	11 (13.1)	5 (17.2)	6 (10.9)	
Failure	5 (5.8)	1 (3.4)	4 (7.3)	

Results are presented as: mean ± standard deviation, median (interquartile range) or absolute value (percentage); *CNS*, central nervous system; *HIV*, human immunodeficiency virus; *MIC*, minimal inhibitory concentration; *eGFR*, estimated glomerular filtration rate

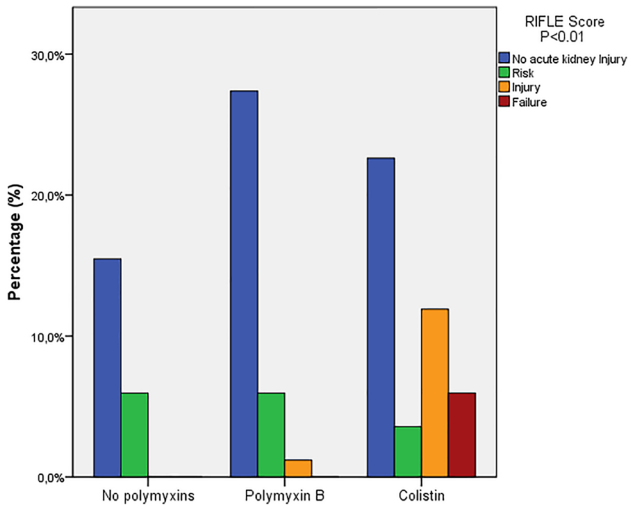

Fig. 1 RIFLE score in patients receiving amikacin for the treatment of carbapenem-resistant *Klebsiella pneumoniae* infections, according to combination therapy prescribed

failure; (e) amikacin monotherapy had better clinical results in urinary source infections.

AG have regained attention worldwide due to the maintenance of high susceptibility rates in CR*Kp* infections, and its potential synergistic effect with other antimicrobial agents [13, 14]. The majority (89.8%) of our bacterial isolates were susceptible to amikacin; however, only 84 (50.0%) were treated with this drug and therefore included for analysis. Patients had an overall mortality of 34.5%, lower when compared to other carbapenem-resistant Enterobacteriales (CRE)–related cohorts [3, 15]. This could be explained by the lower severity disease of patients or even by the fact that all of them received amikacin. According to the study by Freire et al., higher clinical success was achieved in patients who received combination therapy with aminoglycosides for CRE infections (78.9% versus 37.0%, $P < 0.01$) [15]. Also, Medeiros et al. found that combination therapy with two in vitro active agents, mostly polymyxin B plus amikacin, showed a survival benefit when compared to other regimens (42.5% vs 57.5% $P = 0.03$) [3].

Despite the favorable results described in patients treated with AG for CRE, the narrow therapeutic window of AG is still a major concern when using this class of antibiotics. It is difficult to achieve AG PK/PD target with regular recommended doses (especially in isolates with MICs at the upper limit of susceptibility), while increasing total dose may be prohibitive due to nephrotoxicity [5, 6]. In our cohort, most isolates presented low amikacin MICs: MIC50 and MIC90 of 1 µg/mL and 4 µg/mL, respectively. No impact of amikacin MIC was found on 30-day mortality, possibly because current prescribed doses of amikacin are effective for bacteria with these low MIC values. In fact, in previous Monte-Carlo simulations, CRE infections with amikacin MIC 16 µg/mL were the ones to show the worse results compared to samples with lower MIC, regarding achievement of adequate concentration above the MIC target [6]. Moreover, the use of susceptible combination therapy for most patients, particularly in those with infections presenting higher amikacin MICs (≥ 4 µg/mL), might have hidden the potential impact of eventual under target doses on mortality. Another explanation would be the ability of AG to be synergistic to other antibiotics on bacterial killing [6].

Fifty-eight (69.1%) of the patients received in vitro susceptible combination therapy with polymyxins. Although polymyxin combination was significantly related to higher mortality in univariate analysis, it lost significance when controlled for vasopressor use. Prescription bias of combination therapy to severely ill patients in this cohort possibly justifies its absence of benefit, contrary to other observational studies [3, 13].

Twenty-nine (34.5%) patients of our cohort developed AKI. Opposed to what could be expected, higher baseline eGFR was related to higher nephrotoxicity. Previous studies have shown that amikacin reabsorption in renal tubules is a main step on kidney injury mechanism of this drug [14, 16, 17]. One hypothesis is that the higher the GFR, more absorption occurs in renal tubules leading to more proportional kidney damage. Active renal tubular reabsorption and consequent kidney damage also occurs with polymyxins [18]. Renal injury and failure occurred only in patients who used polymyxin combination, perhaps due to the sum of toxicity of these drugs or because those were more severe patients. One remarkable fact is that patients that received colistin presented significantly higher rates of AKI, compared to those who received polymyxin B. This finding has been previously described in the literature [19, 20] and may have been potentiated by the concomitant use of amikacin in this study.

Subsequent cultures were collected for 34.5% of the patients and bacterial clearance occurred in 58.6%. Two (16.7%) of 12 patients changed amikacin susceptibility profiles during therapy. In a previous study with kidney transplant patients, aminoglycoside resistance was developed over time in more than 65% of the analyzed strains [21]. Although our study had a low rate of resistance development during therapy, this should be closely monitored.

The subgroup analysis of patients treated with amikacin as the only in vitro susceptible therapy showed better results in urinary tract infections. This is in accordance with previous literature [22]. Combination with in vitro–resistant polymyxin showed no survival benefit.

Limitations of this study were the relatively small number of patients included and the low variability of MICs, which limits the validity of the conclusions to similar epidemiological scenarios. In addition, serum amikacin level was not

measured to calculate the final exposure of these patients to the drug. However, it has the strength of focusing specifically on the role of amikacin for the treatment of CR*Kp* and bringing important insights about nephrotoxicity issues related to this drug when combined to polymyxins.

In conclusion, amikacin retains high susceptibility and can be an important therapeutic option for CR*KP* infections. At low MIC values, no specific dose adjustments seem necessary. Combination therapy with colistin showed higher nephrotoxic rates than with polymyxin B and should be used with caution.

Author contribution Diógenes Rodrigues performed research, analyzed data, and wrote the paper; Giulia Soska Baldissera, Douglas Mathos, and Aline Sartori collected and analyzed data; Alexandre P. Zavascki analyzed data and wrote the paper; Maria Helena Rigatto conceived the study, performed research, analyzed data, and wrote the paper.

Funding This study was funded by Fundo de Incentivo à Pesquisa (FIPE) do Hospital de Clínicas de Porto Alegre. APZ is a research fellow of the National Council for Scientific and Technological Development (CNPq), Ministry of Science and Technology, Brazil.

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Ethics approval The project was carried out after its approval by the institution's Research Ethics Committee number 2.687.149 and 2.476.428.

Consent to participate As this was a retrospective study, the ethics committee waived the need for informed consent.

Consent for publication All authors agree on the publication of this manuscript.

Competing interests Alexandre P Zavascki receives research grants from Pfizer. The other authors declare no competing interests.

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