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Brief communication

KPC-producing *Enterobacter aerogenes* infection



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ABSTRACT

Background: *Enterobacter* is a common nosocomial microorganism and its carbapenem's resistance has increased. The management of these cases is unclear.

Objective: We evaluated 16 patients with KPC-producing *Enterobacter aerogenes* infections, detailing the site of infection, therapy, clinical and epidemiological data.

Methods: A retrospective and descriptive study. Clinical data were revised and KPC-2 detection was by molecular methods. Risk factors associated with mortality were compared using appropriate tests according to variable type with a significance level of 0.05.

Results: The 30-day mortality rate was 37.5% with no association with inadequate treatment. Age ($p=0.004$) and Charlson score of comorbidities ($p=0.048$) were independent risk factors associated with death in the multivariate analysis. The odds ratio for age >43 years was 3.00 (95% CI: 1.02–9.32) and for Charlson score >3 was 2.00 (95% CI: 1.08–3.71). Five strains were pan-resistant based on automated susceptibility tests. All patients were treated with monotherapy.

Conclusion: The clinician should be alert to carbapenem-resistant *Enterobacteriaceae* infection in older patients with comorbidities. The mortality is high and we believe that prompt and adequate therapy must be employed.

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Enterobacter is a microorganism associated with third generation cephalosporins resistance due to overexpression of Amp-C gene. However, we have observed a progressive decrease in susceptibility to fourth generation cephalosporin, suggesting increase of ESBL-producing strains.¹ ESBL-producing *Enterobacter* are usually susceptible

only to carbapenems, and these drugs have been the treatment of choice for severe infections. More recently, the emergence of carbapenemase-producing *Enterobacteriaceae* has severely challenged antimicrobial therapy, since it confers a distinct level of resistance to carbapenems.² The most common carbapenemase identified in the world was first

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described in *Klebsiella pneumoniae*, which is called *Klebsiella pneumoniae* carbapenemase (KPC).³

KPC-producing *Enterobacteriaceae* are spreading throughout the world, not only in *K. pneumoniae*, but also in *Escherichia coli*, *Enterobacter*, *Citrobacter*, *Serratia* and others.² KPC-producing *Enterobacter* has been described in some series of *Enterobacteriaceae*, and recently Satlin and Jenkins published a case of KPC-producing *Enterobacter gergoviae* infection in an immunosuppressed patient with a poor outcome despite adequate therapy.⁴

Considering the importance of *Enterobacter* as a nosocomial bacteria and the current resistance panorama, we evaluated 16 patients with KPC-producing *Enterobacter aerogenes* infections, detailing the site of infection, therapy, and epidemiological data.

This was a case-series study with 16 patients with *E. aerogenes* infection who received care between January 2013 and September 2013 in a general tertiary hospital in Curitiba, Brazil (Hospital Universitario Evangelico de Curitiba). The hospital has 660 beds and it is a reference center for trauma, burn, and renal transplant.

E. aerogenes identification and susceptibility tests were performed with Vitek 2 (Biomérieux, Marcy-L'Étoile, France) according to the CLSI guidelines.⁵ Isolates showing reduced susceptibility to ertapenem/meropenem were tested for detection of production of carbapenemase using the modified Hodge test (MHT).⁵ Isolates with positive MHT were submitted to PCR for *bla*_{KPC} using EasyQ KPC (Biomérieux, Marcy-L'Étoile, France) as previously described.⁶ The amplicon was fully sequenced until 900 pb. Minimal inhibitory concentration (MIC) for meropenem, tigecycline, and colistin was determined by E-test.⁷

KPC-producing *Enterobacteriaceae* isolates were examined using automated rep-PCR-based typing system (DivesiLab™, Biomérieux, Athens, GA, USA).⁸ The results were analyzed and interpreted with the DiversiLab web-bases software using Pearson Correlation method. Clonally related isolates were defined as those with $\geq 95\%$ homology.

We evaluated Charlson comorbidity index score, age, length of hospitalization before bacteremia, and antibiotic use during infection. The site infection criteria were defined according to the Brazilian Health Surveillance Agency.⁹

Continuous data were expressed as mean with standard deviation of interquartile (25–75%). Frequencies were expressed as percentages. All data were stored using the software Excel (Microsoft, New York, USA) and statistical analysis was performed using the software SPSS 16 (SPSS, Chicago, USA). Univariate analysis was performed separately for each of the variables. *p*-Values were calculated using the chi-square test or Fisher's exact test for categorical variables and Student's *t*-test or Wilcoxon rank-sum test for continuous variables. Variables for which the *p*-value was ≤ 0.10 in univariate analysis were included in a forward stepwise logistic regression model. Variables were checked for confounding and collinearity. A *p*-value of 0.05 was set as the limit for acceptance or removal of the new terms in the model. Goodness-of-fit was assessed by Hosmer-Lemeshow test. All tests were two-tailed, and a *p*-value ≤ 0.05 was considered significant. Therapy was considered adequate when the microorganism was susceptible to the drug tested.

All strains were compatible with KPC-2 type. The data are detailed in Table 1. The mean age was 56 years (IQ 25–75%: 39–75). The thirty-day mortality was 37.5%, and the global in-hospital mortality was 62.5%.

Adequate therapy was prescribed for only seven patients (43.7%). Adequate therapy was not associated with a better outcome in univariate analysis. Age (*p* = 0.004) and Charlson score of comorbidities (*p* = 0.048) were risk factors associated with death, but not gender or site of infection. These two continuous variables were categorized in order to perform a binary logistic regression. In the multivariate analysis, both risk factors were independently associated with death: age > 43 years (odds ratio = 3.00; 95% confidence interval (CI) 1.02–9.32) and Charlson score > 3 (odds ratio = 2.00; 95% CI 1.08–3.71).

All patients were treated with antibiotic monotherapy but always with maximal dosage adjusted for renal function, except tigecycline and polymyxin. Tigecycline was used with doubled dose and the dose of polymyxin was 25,000–30,000 IU every 12 h. Five strains were pan-resistant considering automated susceptibility tests. One strain had MIC > 16 mg/L for colistin, but 8 mg/L for meropenem MIC and 2 mg/L for tigecycline.

In some infections, like urinary tract, it was hard to differentiate colonization from infection. Thus, it was not possible to conclude that fosfomycin was effective in treating KPC-producing *Enterobacter*, although this approach has been described previously by our group.¹⁰

A patient was considered treated when the drug used was active *in vitro*. However, recommendation for tigecycline in ventilator-associated pneumonia was not possible based on data presented in Table 1.

The repPCR identified two clones (Fig 1) suggesting a clonal dissemination among 12 patients. Only 12 strains were tested because four samples were unavailable.

KPC enzymes in *Enterobacteriaceae* have become endemic in many regions worldwide, especially among *K. pneumoniae* isolates in Brazil.⁶ The emergence of KPC among these bacteria has severely challenged antimicrobial therapy, since they confer high level resistance to all beta-lactams and distinct levels of resistance to the carbapenems. Several retrospective studies tried give support for combined therapy against KPC-producing *Enterobacteriaceae*, without consistent results.¹¹ In this study, we confirmed that the outcome is determined by conditions other than adequate therapy. Advanced age was an independent risk factor for KPC-producing *Enterobacteriaceae* in a previous study,⁶ but not a risk factor for mortality. Fosfomycin has been used for severe infection, as urinary tract infection in our service, but resistance has increased as previously reported.¹⁰ Clinical breakpoints have not been established for fosfomycin, but some authors have used the same values established for *E. coli*, although these values are off label.¹⁰

Clinicians should reevaluate the aggressive therapy (several combinations and large dosages) in patients with advanced age with several comorbidities, once adequate therapy may not be sufficient to modify the outcome. The most important side effect of current therapies against carbapenem-resistant *Enterobacteriaceae* (polymyxin and aminoglycosides) is renal failure. Acute renal failure increases mortality by 40%, a percentage that can outweigh

Table 1 – Clinical data of 16 patients with KPC-producing *Enterobacter aerogenes*.

Gender	Age	Admission	Survival	Outcome	Charlson index	Source of infection	Treatment	Tigecycline MIC (mg/L) ^c	Meropenem MIC (mg/L) ^c	Colistin MIC (mg/L) ^c	Treatment
F	82	21	1	Death	1	Surgical site infection	Not treated	2	8	>16	None
F	54	214	88	Death	0	Ventilator pneumonia	Treated	4	8	<0.5	Tigecycline 100 mg q12h 14d
F	58	33	35	Death	5	Urinary	Not treated	4	>16	0.5	Meropenem 1000 mg q12h 4d
M	76	26	30	Death	4	Urinary	Treated	>8	>16	<0.5	Fosfomycin 3 g/day 17d
F	38	11	18	Survival	0	Ventilator pneumonia	Not treated	4	8	4	Meropenem 500 mg q8h 11d ^a
F	91	100	48	Death	6	Ventilator pneumonia	Treated	4	1	4	Tigecycline 100 mg q12h 11d
M	23	0	70	Survival	0	Surgical site infection	Not treated	4	>16	8	Tigecycline 100 mg q12 24d
M	90	25	1	Death	9	Blood	Treated	4	>16	2	Polymyxin B 1,000,000 q12 3d (died)
F	50	9	8	Death	2	Blood	Treated	4	>16	>16	Polymyxin B 1,000,000 q6h 8d
M	74	35	19	Death	5	Ventilator pneumonia	Treated	4	>16	>16	Polymyxin B 1,000,000 q12h 14d
M	51	58	43	Survival	1	Catheter	Not treated	4	>16	>16	Ampicillin/sulbactam 3 q6h 15d
M	30	8	8	Survival	0	Urinary	Treated	^b			Fosfomycin 3 g/day 7d
M	43	34	13	Death	0	Blood	Not treated	4	>16	>16	Tigecycline 100 mg q12h 14d
M	31	34	28	Survival	0	Catheter	Not treated	4	>16	>16	None
F	55	87	27	Survival	3	Urinary	Not treated	^b			Meropenem 1000 mg q8h 4d
M	51	54	0	Death	2	Ventilator pneumonia	Not treated	1	8	0.5	Ciprofloxacin 400 mg q12h 10d

See full text for treatment discussion.

^a Dosage adjusted to creatinine clearance.

^b The sample was not stored.

^c E-test.

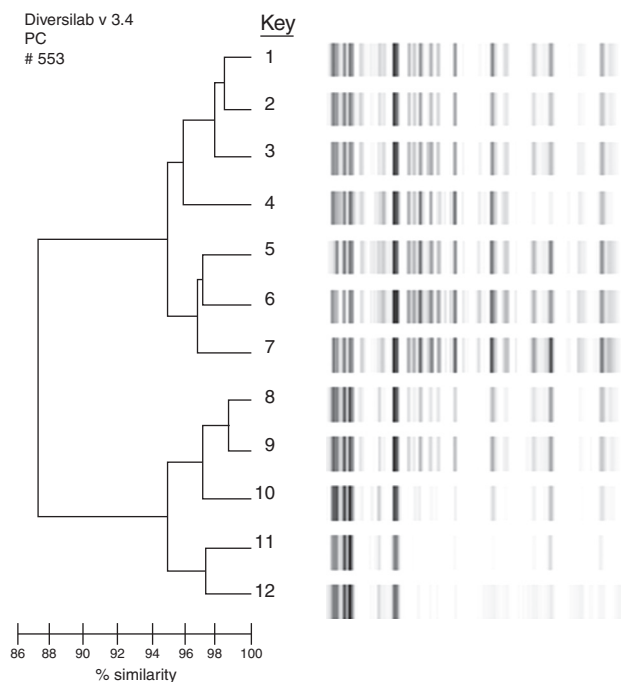


Fig. 1 – repPCR of 12 strains of KPC-producing *Enterobacter aerogenes*.

the benefits of therapy. This issue is controversial, but the clinician should be alert to carbapenem-resistant *Enterobacteriaceae* infection in immunosuppressed patients, as well as in older patients with comorbidities. The mortality is high and we believe that prompt and adequate therapy must be employed.

Despite uncertainty regarding the ideal treatment, infection control measures are fundamental to avoid spread of these bacteria in the hospital. Our study showed two clones out 16 strains. This suggests that cross-infections were responsible for this outbreak. From September through December, *Enterobacter* producing KPC were not identified in the hospital. Infection control measures were not employed specifically to this microorganism, suggesting a self-limited outbreak.

Conflicts of interest

The authors declare no conflicts of interest.

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