Klebsiella ESBL bacteremia-mortality and risk factors

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ABSTRACT

Background: Extended spectrum β-lactamase (ESBL)-producing bacteria have become recognized as a problem in South America. The aim of this study was to evaluate risk factors and mortality rate in bacteremia caused by ESBL-producing *Klebsiella pneumoniae* in a Brazilian hospital. **Methods:** A three-year retrospective cohort study with 104 cases of *K. pneumoniae* bacteremia (61 ESBL and 43 non-ESBL). Several clinical and laboratory variables were evaluated. The outcome of interest was 30-day mortality. The adequate treatment was evaluated according to antibiotic susceptibility. **Results:** Multivariable analysis showed that central venous catheter and mechanical ventilation were independent risk factors for ESBL. The duration of hospitalization before the bacteremia was not a risk factor. Mortality was similar in ESBL and non-ESBL and inadequate therapy was not shown to be a risk factor. **Conclusion:** ESBL-producing *Klebsiella* bacteremia can occur early, suggesting that a carbapenem should be included in the initial empirical therapy for bacteremia in patients under mechanical ventilation and/or central venous catheter in our institution.

Keywords: *Klebsiella pneumoniae*; beta-lactamases; bacteremia; carbapenems.

INTRODUCTION

Gram-negative rods are the leading cause of bloodstream infection in Brazilian hospitals with increasing incidence of extended spectrum β-lactamase (ESBL)–producing bacteria.[1] *Klebsiella pneumoniae* is the most important ESBL-producing bacteria, and the incidence has reached worrisome levels and continues to increase in South America.[2]

Mortality rate is evidently associated with inadequate empirical antibiotic choice for ESBL bacteria. Carbapenems are the drugs of choice for treatment of ESBL-producing *K. pneumoniae* (ESBL-KP), but this class of drugs is not always used as first option in empirical treatment for early nosocomial infection in developing countries. Inadequate restriction of carbapenems by some infection control programs may be associated with increasing mortality.

Considering the problem of inadequate treatment and mortality rate among patients with ESBL and non-ESBL strains of *K. pneumoniae* bacteremia, this study evaluated risk factors for mortality in patients with bloodstream infection caused by ESBL-KP in a Brazilian hospital with high incidence of this microorganism.

METHODS

A retrospective cohort was carried out at the Hospital Universitário Evangélico de Curitiba, a reference center for trauma, burn and renal transplant. This center is a 660-bed tertiary-care hospital in Curitiba, a city located in Southern Brazil with 60 intensive care beds.

From January 2006 to January 2009, 884 positive blood cultures were identified (excluding coagulase negative *Staphylococcus*) and 11.7% were positive for *K. pneumoniae*. All the patients with bacteremia caused by *K. pneumoniae* were included in our study. Patients with more than one positive blood culture were included only once. Only data associated with the first bacteremia and patients older than 12 years-old were evaluated.

Cultures were collected and processed using the BACT/Alert® (bioMérieux, Durham, USA). *Klebsiella* species were identified using biochemical analysis.[3] Susceptibility testing was performed by the disk diffusion method according to the CLSI guidelines.[4]

The following variables were evaluated for each patient: sex; age; previous hospital admission within 90 days; admission to the intensive

care unit; length of hospitalization before bacteremia; use of mechanical ventilation, central venous line, urinary catheter and surgery during the current hospitalization; underlying conditions such as *diabetes mellitus*, chronic renal failure, heart failure, neoplasm, acute renal failure, trauma and previous antibiotic use during current hospitalization. Previous infection or colonization with *K. pneumoniae* was evaluated. We assumed that the patients who were not cultured were negative for statistical analyses purposes.

Dynamic variables were included, as heart and respiratory rate, temperature, mean arterial pressure and Glasgow Coma Scale (GCS) in the day of the bacteremia. The following laboratory results were evaluated on the day of bacteremia: hemoglobin level, leukocyte and platelet counts, sodium, potassium, creatinine, urea, total billirubin and partial pressure of oxygen from arterial blood.

Thirty-day or in-hospital mortality was registered. Antibiotic treatment was classified as adequate or inadequate. Treatment of each patient was considered adequate if *K. pneumoniae* was susceptible to the antibiotic used during bacteremia and treatment was initiated within the first 48 hours of bacteremia diagnosis. Carbapenem (ertapenem, imipenem or meropenem) or polymyxin was considered the adequate antibiotic for ESBL-KP, when correct dose was administered. Tygecycline was not used and the hospital strains were not susceptible to aminoglycoside or fluoroquinolones during the period analyzed. The treatment for non-ESBL-KP was considered adequate if susceptible *in vitro*.

Statistical analysis

Patients with ESBL-KP bacteremia were compared with those with non-ESBL-KP bacteremia to determine factors associated with carbapenem resistance. A second analysis was performed comparing patients who died during hospitalization with those who survived. Continuous data were expressed as mean ± standard deviation (SD) or median with ranges. Frequencies were expressed as percentages. Dichotomous variables were compared using Chi-square and Mann Whitney test was used for continuous variables. Significance level was set at 0.05. Variables with $p < 0.10$ in the univariated analysis were included in the multivariable analysis. Multivariate analysis was performed using binary logistic regression model. Odd ratios (OR) with 95% confidence intervals (95% CI) were calculated for each variable. Variables in which 95% CI did not include 1.0 were maintained in the final model.

Kaplan–Meier survival estimates were calculated to evaluate the role of adequate treatment in the outcome of bacteremia caused by ESBL-KP, and the difference was assessed using the log-rank test.

All data were stored using the software Excel (Microsoft, New York, USA) and statistical analysis was performed using the software SPSS 11.5 (SPSS, Chicago, USA). Kaplan–Meier survival estimates were determined with GraphPad Prism 4.0 (GraphPad, La Jolla, USA).

RESULTS

One hundred and four patients were included in this study. Sixty-three patients were enrolled as ESBL-KP (60%) and 41 patients with non-ESBL-KP (40%). The median age of all patients included was 43.0 years (range, 12-86) and 43% were female. The mean length of hospitalization was 45.87 ± 36.60 days and the mean duration of hospitalization until first *K. pneumoniae* bacteremia was 18.8 ± 17.81 days. Characteristics of the patients and laboratory data are described in the Table 1.

In the univariate analysis, factors associated with ESBL included invasive procedures as mechanical ventilation ($p = 0.007$), the use of central venous catheter ($p = 0.009$), and elective surgery ($p = 0.023$). Other risk factors associated with ESBL were male sex ($p = 0.027$), *diabetes mellitus* ($p = 0.043$), and admission to the intensive care unit ($p = 0.017$). Previous use of fourth generation cephalosporin ($p = 0.003$) was a risk factor as well. Although resistant strains were associated to longer stay in the hospital, hospitalization length until the bacteremia was not a risk factor for ESBL infection (Figure 1). Even though these finding supports the association with ESBL infection, only mechanical ventilation ($p = 0.022$) and central venous line ($p = 0.017$) turned out to be independent risk factors for ESBL-KP bacteremia in the multivariate analysis. All other investigated risk factors were significant only in the univariate analysis.

Global ESBL-KP and non-ESBL-KP mortality rates were similar (49.2% vs. 41.9%, $p = 0.43$). Kaplan–Meier estimates of survival were also similar for ESBL-KP and non-ESBL-KP infected patients (Figure 2A). There was no independent risk factor associated with higher mortality rate at the multivariate analysis.

Only 55 patients (52.9%) received adequate treatment within 48 hours of bacteremia. Mortality of patients receiving adequate treatment was 50.9% (28 of 55 patients), and 40.8% in patients with inadequate antibiotic therapy (20 of 49 patients). Mortality of *Klebsiella* bacteremia was not attributed to inadequate treatment as demonstrated in the Kaplan-Meier curve (Figure 2B). Patients infected by either ESBL or non-ESBL strains who received adequate therapy had similar mortality rates ($p = 0.43$).

DISCUSSION

In our study, 58% of the *Klebsiella* strains were ESBL-producing. Marra et al.[5] found similar rate, showing 52% of ESBL-KP in another Brazilian hospital. Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) study described a different panorama in North America, Asia and

Table 1. Clinical and laboratory characteristics of 104 patients with* K. pneumoniae *bacteremia

Variables	ESBL group (n = 63)	Non-ESBL group (n = 41)	OR (95% CI)	p
Age – yr				
Mean	38.3 ± 21.7	44.2 ± 25.3		0.79
Range	[12-85]	[12-86]		
Gender – n (%)				
Male	41 (65)	18 (44)	2.62 (1.16-5.93)	0.027
Female	22 (35)	23 (56)		
Coexisting diseases – n (%)				
Diabetes mellitus	7 (11)	11 (9)	2.24 (0.99-5.07)	0.043
Chronic renal failure	4 (10)	6 (21)	0.41 (0.10-1.61)	0.168
Heart failure	4 (10)	3 (11)	0.93 (0.19-4.50)	0.613
Arterial systemic hypertension	17 (42)	13 (46)	0.85 (0.32-2.25)	0.470
Neoplastic diseases	6 (15)	3 (11)	1.47 (0.34-6.45)	0.447
Chronic hemodialysis	3 (7)	4 (14)	0.48 (0.10-2.37)	
Trauma	11 (26)	4 (14)	2.28 (0.64-8.07)	0.160
Days before *K. pneumoniae*	20.2 ± 17.9	16.7 ± 17.5		0.053
Duration of hospitalization	52.2 ± 39.6	36.0 ± 29.4		0.117
Risk factor – n (%)				
Intensive care unit	49 (80)	23 (53)	3.55 (1.49-8.48)	0.017
Previous admission (< 90 days)	15 (24)	14 (32)	0.63 (0.26-1.50)	0.117
Previous *K. pneumoniae* colonization/infection	28 (46)	11 (20)	2.18 (0.93-5.11)	0.056
Acute renal failure	11 (28)	4 (14)	2.28 (0.64-8.07)	0.160
Mechanical ventilation	26 (40)	9 (22)	3.08 (1.37-6.96)	0.007
Central venous catheter	27 (41)	10 (28)	2.71 (1.21-6.06)	0.009
Urinary catheter	30 (75)	15 (53)	2.60 (0.93-729)	0.058
Elective surgery	28 (41)	12 (28)	3.11 (1.14-8.53)	0.003
Laboratory findings – mean ± SD				
Hemoglobin (g/dL)	10.2 ± 2.0	10.5 ± 2.1		0.594
Leucocytes (1000x cells/mm^3)	17.6 ± 13.0	18.4 ± 28.0		0.856
Immature cells (%)	17.0 ± 13.0	19.0 ± 14.9		0.685
Platelets (1000x cells/mm^3)	176.8 ± 154.2	176.2 ± 120.6		0.151
Creatinine (mg/dL)	1.7 ± 1.5	1.6 ± 1.9		0.800
Partial oxygen pressure (mmHg)	97.5 ± 39.4	86 ± 28.3		0.328
Billirubin (mg/dL)	3.3 ± 4.2	3.8 ± 2.6		0.234
Heart rate (max)	119.0 ± 33.6	104.8 ± 40.0		0.300
Respiratory rate (max)	27.9 ± 16.6	24.5 ± 10.9		0.915
GCS	10.0 ± 4.6	10.3 ± 5.7		0.919
Previous antibiotic use				
Third generation cephalosporin	13 (21)	3 (7)	3.61 (0.96-13.57)	0.05
Fourth generation cephalosporin	22 (35)	4 (9)	5.50 (1.73-17.44)	0.001
Vancomycin	12 (19)	9 (20)	0.93 (0.35-2.44)	0.42
Carbapenem	18 (29)	7 (16)	2.15 (0.81-5.73)	0.13

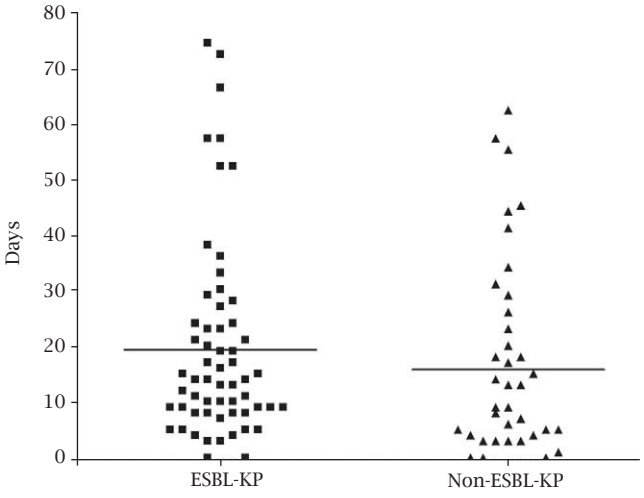

Figure 1: Hospital lengh and bacteremia caused by ESBL strains and non-ESBL strains.

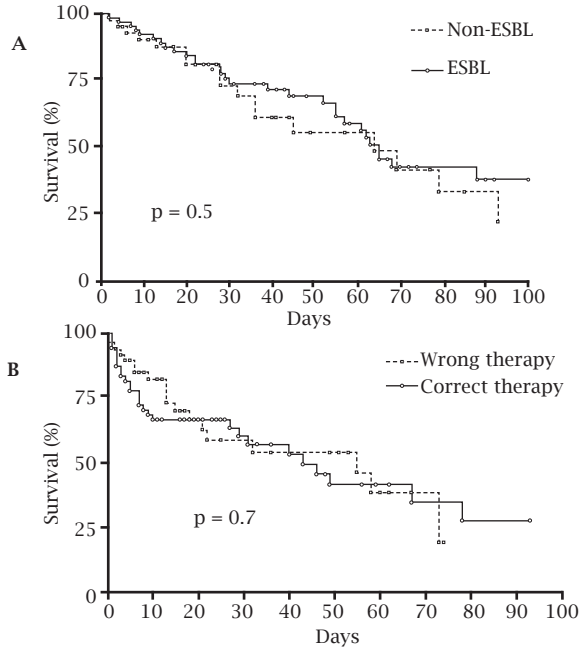

Figure 2: Mortality curve from patients with *K. pneumoniae* (ESBL vs. non-ESBL) **(A)**; and patients under correct or wrong therapy for *K. pneumoniae* bacteremia **(B)**.

Europe (Northern and Southern) in the SMART study with only 17% ESBL-producers *Klebsiella* spp.[6] Data from the MYSTIC study from South America showed 52% of resistance to cefepime, which can be a surrogate for ESBL strains.[7]

Use of beta-lactam antibiotics containing an oxyimino group (cefuroxime, ceftriaxone, cefotaxime, ceftazidime, or aztreonam) are risk factors for ESBL-KP.[8-11] Nevertheless, previous use of cefepime was a risk factor for ESBL in our study. This risk factor had not been confirmed previously.[12,13] In our hospital, cefepime is commonly used for the treatment of severe community pneumonia at the emergency room. The use of cefepime is a modifiable risk factor, and restriction of cefepime use could be an approach to decrease ESBL-KP in our institution. Other risk factors for ESBL strains were invasive procedures, which included central venous line and mechanical ventilation.

Previous studies showed a mortality rate between 20 and 40% in patients with bacteremia caused by *K. pneumoniae*.[14-16] The mortality rate in our study was high, when compared to other studies. Although no direct comparison to patients from other studies can be made, in our study patients were severely ill. The first explanation would be a higher proportion of patients with *K. pneumoniae* bacteremia receiving inadequate empirical therapy. Nonetheless, despite being elevated the rate of inadequate treatment was not associated with mortality of ESBL bacteremia patients. Du et al.[17] demonstrated that inadequate treatment was an isolated risk factor, justifying early and empirical use of carbapenems in patients with bacteremia in some hospitals. The cost of carbapenem restricts its use in developing countries, increasing mortality as demonstrated in Nigeria.[16] A previous publication of Paterson[18] underscored that early treatment with carbapenems is particularly important in seriously ill patients with nosocomial infections, mainly those caused by ESBL strains, decreasing the mortality rate. However, larger sample size of patients would be required to draw more definitive conclusions.

Some caveats must be considered in our study. It is a retrospective analysis from an isolated institution with particular characteristics, the infection control program includes strict restriction of carbapenems, the attributed mortality for ESBL-KP was not calculated and some variables were not included in the analysis, such as APACHE score. A clonal study should be performed to determine the strain as well as the type of the ESBL bacteria. One of the factors associated with ESBL-KP bacteremia was previous use of cefepime. This could be due to bias as ESBL-KP were compared with non-ESBL producing KP and this group of patients very probably did not use cefepime (as cefepime would have eradicated the susceptible microorganism).

CONCLUSION

In conclusion, mortality due to *K. pneumoniae* infection is high and more than 50% of patients were under inadequate treatment in the ESBL group, justifying the use of carbapenem as first choice in patients admitted to centers with high incidence of ESBL-producing species. We believe that a change in the empirical treatment is necessary, mainly in patients with sepsis during hospitalization, which can decrease the global mortality of patients infected by ESBL-KP. The

time to use this group of drugs should not be guided by hospitalization length, because we could not correlate increased resistance with duration of hospitalization. Our institution will change the carbapenem restriction and assess the long term benefits of this approach in the mortality of patients with ESBL infection as well as the effect on resistance profile. We believe that this approach must be implemented in other institutions according to local epidemiology. Although ESBL constituted < 10% of all bacteremia in our hospital, we can not neglect the 50% inadequate therapy for this group of bacteria.

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