Communication/Comunicação

# Epidemiology of extended spectrum β-lactamase producing *Enterobacter* bacteremia in a Brazilian hospital

## Epidemiologia de bacteremia causadas por *Enterobacter* produtores de β-lactamases de espectro estendido em um hospital brasileiro

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**ABSTRACT**

**Introduction:** *Enterobacter* can be included in the group of extended spectrum β-lactamases (EBSL)-producing bacteria, though few studies exist evaluating risk factors associated with this microorganism. A retrospective cohort study was conducted to determine risk factors associated with ESBL-producing-*Enterobacter* and mortality. **Methods:** A retrospective cohort study with 58 bacteremia caused by ESBL-producing-*Enterobacter* (28 cases) and non-ESBL (30 cases). **Results:** Risk factors associated with ESBL-*Enterobacter* were trauma, length of hospitalization, admission to the intensive care unit, urinary catheter and elective surgery ($p< 0.05$). The survival curves were similar for ESBL and non-ESBL. **Conclusions**: ESBL-producing-*Enterobacter* bacteremia is prevalent and the survival curve was similar to non-ESBL-producing strains.

**Key-words**: Extended spectrum β-lactamases. Enterobacter. Bacteremia.

**RESUMO**

**Introdução:** *Enterobacter* pode ser incluído no grupo de bactérias produtoras de β-lactamases de espectro estendido (ESBL), mas existem poucos estudos avaliando fatores de risco para ESBL. Nós realizamos uma coorte retrospective para determiner fatores de risco associados com Enterobacter produtores de ESBL. **Métodos:** Uma coorte retrospectiva com 58 bacteremias por Enterobacter ESBL (28 casos) e não-ESBL (30 casos). **Resultados:** Fatores de risco para ESBL-*Enterobacter* foram trauma, tempo de internação, admissão em UTI, sonda vesical e cirurgia eletiva ($p<0.05$). A mortalidade foi similar entre ESBL e não-ESBL. **Conclusões**: Enterobacter produtor de ESBL é prevalente e a curva de mortalidade foi semelhante com o grupo não-ESBL.

**Palavras-chaves**: β-lactamases de espectro estendido. Enterobacter. Bacteremia.

Infections caused by extended spectrum β-lactamases (ESBL) producing bacteria has increased mortality in hospitalized patients[1]. Invasive procedures, admission to intensive care units and previous use of antibiotics are the most common risk factors for ESBL-producing bacteria[2]. *Enterobacter* is a microorganism associated with Amp-C gene resistance that confers resistance to third generation cephalosporins. However, our group has observed a progressive decrease in susceptibility to fourth generation cephalosporin in our institution, suggesting the increase of ESBL-producing strains. *Enterobacter* can be included in the group of EBSL-producing bacteria, though few studies exist evaluating risk factors associated with this microorganism.

Even though the treatment of infections caused by ESBL strains is the same for non-ESBL *Enterobacter*, we believe that certain clinical and/or laboratorial findings or previous antibiotic use could be risk factors for ESBL-producing *Enterobacter*. Thus, a retrospective cohort study was conducted to determine risk factors associated with ESBL strains of *Enterobacter* sp.

The retrospective cohort study was conducted at the Hospital Universitario Evangelico de Curitiba. This center is a 660-bed tertiary hospital in Curitiba, a City located in southern Brazil. From January 2006 to January 2009, 884 bacteremia were identified (excluding coagulase negative *Staphylococcus*) and 58 (6.5%) were caused by *Enterobacter* sp. All the patients with bacteremia caused by *Enterobacter* were included only once using data from the first bacteremia. Only patients older than 12 years of age were evaluated.

Cultures were collected according to the standard protocol used in the hospital and were processed using the BACT/Alert® (bioMerieux, Durham, USA). *Enterobacter* was identified using biochemical analysis[3]. Susceptibility testing was performed by the disk diffusion method, in accordance with CLSI guidelines, and ESBL was defined using cefepime with amoxicillin/clavulanate disk approximation method[4].

The following variables were evaluated for each patient: sex; age; previous hospital admission within the preceding 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, cancer; acute renal failure trauma and previous antibiotic use during current hospitalization; previous colonization by *Enterobacter*. The following laboratorial results were evaluated on the day of diagnosis: hemoglobin, leukocyte, platelet counts, sodium, potassium, creatinine, urea, total billirubin and partial pressure of oxygen from arterial blood.

Thirty-day and in-hospital mortality were registered. Antibiotic treatment was classified as adequate or inadequate. Treatment of each patient was considered adequate if *Enterobacter* was susceptible to the antibiotic used during bacteremia and treatment was initiated within the first 48 hours of bacteremia diagnosis. For ESBL strains, the only antibiotic considered adequate was carbapenem.

Patients with ESBL-producing *Enterobacter* bacteremia were compared with patients with non-ESBL bacteremia to determine

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factors associated with 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 the $\chi^2$ test and the Mann-Whitney test was used for continuous variables. Significance level was set at 0.05. Odds 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-producing *Enterobacter* and the difference was assessed using the log-rank test. Significance was determined when *P* value was lower than 0.05.

All data were recorded using the software Excel (Microsoft, New York, USA) and the 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).

A total of 58 patients were included in this study. Twenty-eight (48.2%) patients were enrolled as ESBL-producing *Enterobacter* strains and 30 (51.8%) patients were included as non-ESBL. The median age was 52.1 years-old (19 to 93) and 72.4% were male. The mean length of hospitalization was 43.9 days (±71.7). The mean duration of hospitalization until first *Enterobacter* was 20.7 days (±24.3). Patient characteristics and laboratorial data are described in **Table 1**. The most common species of *Enterobacter* was *E. aerogenes* (71%), followed by *E. gergoviae* (17%) and *E. cloacae* (12%).

Risk factors associated with ESBL-*Enterobacter* were trauma, length of hospitalization, admission to the intensive care unit, urinary catheter and elective surgery ($p< 0.05$).

The 30-day mortality of patients with *Enterobacter* bloodstream infection was 48.3%. The 30-day mortality was similar between ESBL and non-ESBL (51.7% vs 46.7%; $p= 0.29$). The global mortality showed the same tendency (53.4% vs 46.3, $p= 0.21$). In the univariated analysis, urinary catheter, previous use of cefepime, length of hospitalization, admission to the intensive care unit and mechanical ventilation were factors associated with high mortality ($p< 0.05$).

**TABLE 1 - Characteristics of 58 patients with *Enterobacter* bacteremia.**

| Characteristic | ESBL-*Enterobacter* (n=28) | Non-ESBL-*Enterobacter* (n=30) | OR (95% CI) | P |
|---|---|---|---|---|
| **Age - yr** | | | | |
| mean | 51.8±20.6 | 52.4±15.4 | 52.1±17.9 | 0,89 |
| range | [19 - 93] | [20 - 81] | [19 - 93] | |
| **Gender - n (%)** | | | | |
| male | 19 (68.0) | 23 (77.0) | 0.64 (0.20 - 2.05) | 0,34 |
| female | 9 (32.0) | 7 (23.0) | | |
| **Coexisting diseases - n (%)** | | | | |
| diabetes mellitus | 4 (14.0) | 6 (20.0) | 0.67 (0.17 - 2.67) | 0.14 |
| chronic renal failure | 2 (7.0) | 7 (23.0) | 0.25 (0.05 - 1.34) | 0.17 |
| heart failure | 6 (21.0) | 6 (20.0) | 1.09 (0.31 - 3.89) | 0,31 |
| arterial systemic hypertension | 6 (21.0) | 12 (40.0) | 0.41 (0.13 - 1.31) | 0,13 |
| neoplastic diseases | 5 (18.0) | 8 (26.0) | 0.60 (0.17 - 2.11) | 0,44 |
| trauma | 11 (26.0) | 4 (13.0) | 4.21 (1.15 - 15.39) | < 0.05 |
| **Days before *Enterobacter*** | 24.5±28.8 | 17.1±19.1 | | 0,25 |
| **Duration of hospitalization** | 61.2±81.3 | 27.7±23.6 | | < 0.05 |
| **Risk factor - n (%)** | | | | |
| intensive care unit | 20 (71.0) | 13 (43.0) | 3.27 (1.10 - 9.75) | < 0.05 |
| previous admission (< 90 days) | 18 (64.0) | 17 (56.0) | 1.38 (0.48 - 3.96) | 0,37 |
| mechanical ventilation | 20 (71.0) | 16 (53.0) | 2.19 (0.74 - 6.50) | 0,12 |
| central venous catheter | 22 (78.0) | 22 (73.0) | 1.33 (0.40 - 4.48) | 0,43 |
| vesical urinary catheter | 23 (82.0) | 17 (55.0) | 3.52 (1.05 - 11.76) | < 0.05 |
| elective surgery | 20 (71.0) | 14 (46.0) | 2.86 (0.96 - 8.49) | < 0.05 |
| **Laboratorial findings - mean ± SD** | | | | |
| hemoglobin (g/dL) | 10.6±2.0 | 9.9±5.4 | 10.3±5.4 | 0,22 |
| leucocytes (1,000x cells/mm$^3$) | 12.1±8.0 | 12.1±9.4 | 12.1±8.7 | 0,98 |
| immature cells (%) | 18.7±13.0 | 19.2±14.3 | 18.9±13.6 | 0,88 |
| platelets (1,000x cells/mm3) | 191.8±159.2 | 135.9±87.8 | 163.8±130.1 | 0,16 |
| creatinine (mg/dL) | 1.5±1.6 | 2.7±2.2 | 2.1±2.7 | 0,07 |
| partial pressure oxygen (mmHg) | 105.1±50.2 | 96.6±68.1 | 101.3±58.3 | 0,11 |
| billirubin (mg/dL) | 1.52±1.6 | 3.6±.5.7 | 1.7±2.1 | 0,14 |
| **Previous antibiotic use - n (%)** | 9 (32.0) | 13 (43.0) | 0.62 (0.21 - 1.81) | 0,67 |
| third generation cephalosporin | 3 (10.0) | 7 (23.0) | 0.39 (0.09 - 1.71) | 0,17 |
| fourth generation cephalosporin | 8 (28.0) | 3 (10.0) | 3.60 (0.85 - 15.31) | 0,07 |
| carbapenem | 4 (14.0) | 4 (13.0) | 1.08 (0.24 - 4.83) | 0,6 |

The antibiotic therapy was incorrect in 93.3% in the non-survival group and 82% in the survival group. The inadequate therapy was corrected in 70.7% of these patients. Kaplan-Meier survival showed a similar curve of mortality in ESBL and non-ESBL (**Figure 1**).

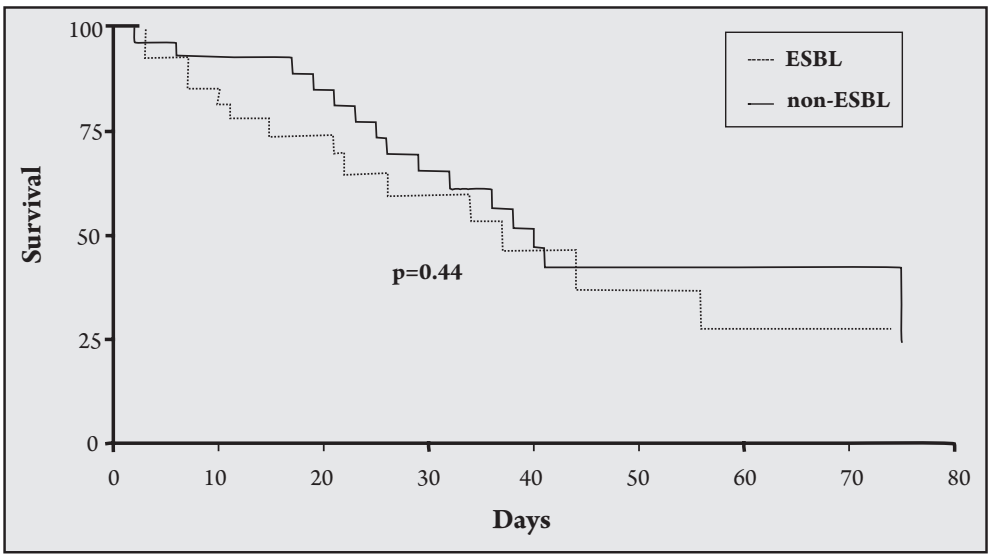


**FIGURE 1 - Mortality curve from patients with ESBL-producing *Enterobacter* bacteremia.**

*Enterobacter* is a less important microorganism than other ESBL-producing bacteria (*Escherichia coli* and *Klebsiella pneumoniae*) in the medical literature. The origin of *Enterobacter* infection is related with bacterial translocation from the gastrointestinal tract, the habitat of this pathogen. The incidence of ESBL-strains in our institute is high, achieving 60% in *Klebsiella pneumoniae* bacteremia.

Hospitalization time before *Enterobacter* bacteremia was similar between ESBL and non-ESBL (more than 15 days), suggesting that a prolonged stay in the hospital was not a condition for ESBL *Enterobacter*. In the univariated analysis, intensive care unit admission, urinary catheter, elective surgery and trauma were risk factors associated with ESBL-strains. All these conditions are related to the severe conditions of the patients, as well as use of large spectrum antibiotics. A published previously study verified irrelevant risk factors for *Enterobacter* bacteremia among other bacteria, but no comparison was performed regarding different resistance profile[5]. Chang et al[6] showed that fourth generation cephalosporin resistance was an independent risk factor of mortality in *Enterobacter* bacteremia[6]. The mortality curve showed a tendency of higher mortality in the first 15 days after bacteremia caused by ESBL strains, with no statistical significance.

Risk factors for death were similar to those determined for the ESBL-strain, mainly associated with invasive procedures, previous use of cefepime and admission to the intensive care unit.

The mortality of *Enterobacter* bacteremia is high and most patients in the death group were being administered inadequate therapy. The number of cases in this study does not permit a significant result to confirm this logical tendency. However, this demonstrated that the service needs to change its empirical therapy for patients with bacteremia, especially after 15 days of admission. In another study, 66% of inadequate empirical therapy had been used until final culture with further adequacy[6]. Most patients were using piperacillin/tazobactam or cefepime during bacteremia (data not shown) and carbapenem should be used empirically until final cultures, avoiding the *up-escalation* therapy shown in the present study, where most physicians corrected the therapy following final culture, increasing the spectrum of the antibiotic.

*Enterobacter* is a frequent pathogen in bacteremia, the mortality is high and ESBL-producing strains are prevalent in our hospital, following the tendency of other Enterobacteriaceae related with this mechanism of resistance, empirical use of carbapenem should be considered in this pattern of hospital, since this study demonstrated that ESBL strains can occur early.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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