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Original article

Emergence of extended-spectrum β-lactamase producing *Enterobacter* spp. in patients with bacteremia in a tertiary hospital in southern Brazil

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ABSTRACT

Background: Extended-spectrum β-lactamases (ESBLs) are increasingly prevalent in *Enterobacter* spp., posing a challenge to the treatment of infections caused by this microorganism. The purpose of this retrospective study was to evaluate the prevalence, risk factors, and clinical outcomes of inpatients with bacteremia caused by ESBL and non ESBL-producing *Enterobacter* spp. in a tertiary hospital over the period 2004–2008.
Methods: The presence of bla_{CTX-M}, bla_{TEM}, bla_{SHV}, and bla_{PER} genes was detected by polymerase chain reaction (PCR) and nucleotide sequence analysis. Genetic similarity between strains was defined by pulsed-field gel electrophoresis (PFGE).
Results: *Enterobacter* spp. was identified in 205 of 4907 of the patients who had positive blood cultures during hospitalization. Of those cases, 41 (20%) were ESBL-producing *Enterobacter* spp. Nosocomial pneumonia was the main source of bacteremia caused by ESBL-producing *Enterobacter* spp. The presence of this microorganism was associated with longer hospital stays. The ESBL genes detected were: CTX-M-2 (23), CTX-M-59 (10), CTX-M-15 (1), SHV-12 (5), and PER-2 (2). While *Enterobacter aerogenes* strains showed mainly a clonal profile, *Enterobacter cloacae* strains were polyclonal.
Conclusion: Although no difference in clinical outcomes was observed between patients with infections by ESBL-producing and non-ESBL-producing strains, the detection of ESBL in *Enterobacter* spp. resulted in the change of antimicrobials in 75% of cases, having important implications in the decision-making regarding adequate antimicrobial therapy.

Emergencia de *Enterobacter* spp. productores de β-lactamasas de espectro extendido en pacientes con bacteriemia en un hospital terciário del sur del Brasil

Palabras clave:
Bacteriemia
Enterobacter
Beta-lactamasas de espectro extendido
BLEE

RESUMEN

Antecedentes: Las β-lactamasas de espectro extendido (BLEE) son cada vez más frecuentes en *Enterobacter* spp., lo que representa un desafío para el tratamiento de infecciones causadas por este microorganismo. El propósito de este estudio fue evaluar los factores de riesgo y los resultados clínicos de pacientes ingresados con bacteriemia causada por *Enterobacter* spp. productores de BLEE en un hospital terciario durante los años 2004-2008.
Métodos: La presencia de los genes bla_{CTX-M}, bla_{TEM}, bla_{SHV}, e bla_{PER} se detectó mediante la reacción en cadena de la polimerasa (PCR) y análisis de la secuencia de nucleótidos. La similitud genética entre las cepas fue definida por electroforesis en gel de campo pulsado (PFGE).

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Resultados: *Enterobacter* spp. fue identificado en 205 pacientes de un total de 4.907 que tenían cultivos positivos de sangre durante la hospitalización. De esos 205 casos, 41 (20%) eran *Enterobacter* spp. productores de BLEE. La neumonía nosocomial fue la principal fuente de bacteriemia causada por *Enterobacter* spp. productores de BLEE. La presencia de este microorganismo se asoció con una mayor estancia hospitalaria. Las BLEE detectadas fueron: CTX-M-2 (23), CTX-M-59 (10), CTX-M-15 (1), SHV-12 (5) y PER-2 (2). Mientras que las cepas de *Enterobacter aerogenes* presentaron un perfil principalmente clonal, *E. cloacae* fueron policlonales.
Conclusiones: Si bien no fueron observadas diferencias en los resultados clínicos entre los pacientes con infecciones causadas por cepas productoras de BLEE y no productoras de BLEE, la detección de BLEE en *Enterobacter* spp., resultó en el cambio de los antimicrobianos en el 75% de los casos, habiendo implicaciones importantes en la toma de las decisiones con respecto a la terapia antimicrobiana adecuada.

Introduction

Enterobacter spp. has been recognized as nosocomial pathogens, mainly affecting patients in the intensive care unit (ICU). *E. cloacae* and *E. aerogenes* are the most common species found in human infections. The frequency of bacteremia has increased in the last decade, and the rate of infection is approximately 1/1000 admissions in university hospitals or tertiary-care centers.[1] In general, the mortality associated with bacteremia caused by *Enterobacter* spp. is as high as bacteremia caused by other enteric bacilli, with mean rates of 20–35%.[1]

β-Lactam resistance in *Enterobacter* spp. challenges the treatment of infections caused by this organism and is associated with unfavorable clinical outcomes.[2] The main resistance mechanism in these organisms is the expression of chromosomally encoded AmpC cephalosporinase,[1] leading to treatment failure when third-generation cephalosporins are used.[2] Moreover, the frequency of extended-spectrum β-lactamase (ESBL) expression is increasing in these species as an important cause of broad-spectrum cephalosporin resistance.[2]

While AmpC cephalosporinase is chromosomally encoded, ESBLs are mediated by transferable plasmids. Therefore, detection of ESBL genes is recommended for the adoption of control measures to prevent spread of resistance.[3]

Several reports have described the high mortality, time, and cost of hospitalization as well as delays in choosing the appropriate antibiotic therapy associated with infections caused by *Klebsiella pneumoniae*, *Escherichia coli*, and *Proteus mirabilis* ESBL-producing microorganisms.[4–6] However, studies evaluating the effects of ESBL production in *Enterobacter* spp. are rare. One report compared the clinical significance of ESBLs produced in *Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., and *Morganella morganii* and found no differences in the outcome of bacteremia between those microorganisms.[7] However, further clinical studies are hindered by the difficulty of detecting ESBLs in species that also express genes encoding inducible AmpC, since the latter may mask the detection of the former.[8]

This study evaluated the prevalence, risk factors, and clinical outcomes of bacteremia caused by ESBL- and non-ESBL-producing *Enterobacter* spp. strains.

Materials and methods

Study setting

This study was conducted at the Clinics Hospital of Federal University of Paraná (HC/UFPR), a 643-bed teaching hospital located in Curitiba, Brazil, over a 5-year period (January 2004–December 2008). Over the past 10 years, HC/UFPR has had an average of 18,699 admissions per year, including 159 ICU admissions, per year. The Clinics Hospital offers a broad range of complex care including bone marrow transplants, liver transplants, cardiovascular surgery, chemotherapy, and other high-risk procedures.

The study was approved by the Institutional Review Board of the HC/UFPR (project number 2288.182/2010-07). All patients received an individual identification number, and their names were not disclosed to maintain confidentiality.

Study design and bacterial strains

A retrospective comparative study was performed to assess risk factors and clinical outcomes of nosocomial infection by ESBL-producing *Enterobacter* spp. vs. non-ESBL-producing *Enterobacter* spp. strains. All patients included in this study developed bacteremia after 48 h of hospitalization and yielded positive blood culture for *Enterobacter* spp. (either ESBL-producing or non-producing strains). One isolate per patient was included in the study. The total number of patients with positive blood culture collected during the period of study was considered to assess prevalence.

Clinical data were obtained from medical records of the patients. The following clinical data were evaluated: age and sex, underlying disease (cancer, digestive tract diseases, respiratory diseases, heart diseases, central nervous system diseases, or kidney disease), invasive procedures (central venous catheter, mechanical ventilation, tracheotomy, surgery, transplant, or urinary catheter), ward and/or intensive care unit (ICU) admission, use of antimicrobial agents, immunosuppressant or chemotherapy prior to culture, primary focus of bacteremia, length of hospital stay (days), before and after blood culture results (with ESBL or non-ESBL producing *Enterobacter* spp.), changes in antimicrobial therapy after physicians were informed of the ESBL results, and clinical outcome (death, discharge, or related death).

Definitions

Patients with ESBL-producing *Enterobacter* spp. were defined as “group 1” and patients with non-ESBL-producing *Enterobacter* spp. were defined as “group 2”. Death was considered related to infection when the cause of death was septic shock and the last microorganism isolated from blood cultures was identified as *Enterobacter* spp. Antimicrobial therapy with carbapenems for ESBL-producing *Enterobacter* spp., and carbapenem or fourth-generation cephalosporins for non-ESBL *Enterobacter* spp. was considered appropriate therapy. Third-generation cephalosporins were considered inadequate therapies for both groups, and other antibiotics were deemed appropriate or not according to the antimicrobial susceptibility test.

Microbiology studies

Blood cultures were performed with the BactAlert® system (bioMérieux, Hazelwood, MO). The Vitek system (bioMérieux) was used for species identification (ID 32 GN card) and antimicrobial