Diagnostic Microbiology and Infectious Disease 78 (2014) 172–177

Contents lists available at ScienceDirect

Diagnostic Microbiology and Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Risk factors and treatment outcomes of bloodstream infection caused by extended-spectrum cephalosporin-resistant *Enterobacter* species in adults with cancer☆,☆☆

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ARTICLE INFO

Article history:
Received 19 February 2013
Received in revised form 22 October 2013
Accepted 5 November 2013
Available online 14 November 2013

Keywords:
Enterobacter
Bacteremia
Cephalosporin resistance
Risk factor
Treatment outcome

ABSTRACT

Treatment of *Enterobacter* infection is complicated due to its intrinsic resistance to cephalosporins. Medical records of 192 adults with cancer who had *Enterobacter* bacteremia were analyzed retrospectively to evaluate the risk factors for and the treatment outcomes in extended-spectrum cephalosporin (ESC)–resistant *Enterobacter* bacteremia in adults with cancer. The main outcome measure was 30-day mortality. Of the 192 patients, 53 (27.6%) had bloodstream infections caused by ESC-resistant *Enterobacter* species. Recent use of a third-generation cephalosporin, older age, tumor progression at last evaluation, recent surgery, and nosocomial acquisition were associated with ESC-resistant *Enterobacter* bacteremia. The 30-day mortality rate was significantly higher in the resistant group. Multivariate analysis showed that respiratory tract infection, tumor progression, septic shock at presentation, *Enterobacter aerogenes* as the culprit pathogen, and diabetes mellitus were independent risk factors for mortality. ESC resistance was significantly associated with mortality in patients with *E. aerogenes* bacteremia, although not in the overall patient population.

1. Introduction

Enterobacter species are emerging as important pathogens. *Enterobacter* is the eighth most common pathogen in healthcare-associated infections in the United States (Hidron et al., 2008) and constitutes 2.9% of healthcare-associated bloodstream infections in Korea (Son et al., 2010). Intrinsic resistance to penicillin and early cephalosporins is mediated by a chromosomal ampC beta-lactamase and often complicates *Enterobacter* treatment. Furthermore, derepression and hyperproduction of ampC result in rapid inducible resistance upon exposure to beta-lactams and carbapenems, resulting in *Enterobacter* isolates that initially tested susceptible to cephalosporins developing resistance during therapy (Chow et al., 1991).

Even though patients with malignancy are at risk for *Enterobacter* infection, there have been few studies on the microbiological and clinical characteristics of *Enterobacter* infection in this population. Previous treatment with antibiotics, prior invasive procedure, and a stay in the intensive care unit (ICU) are reported risk factors for infection with *Enterobacter* that is resistant to extended-spectrum antibiotics (Kang et al., 2005; Ye et al., 2006), but no study has focused exclusively on patients with cancer. Studies on *Enterobacter* infection outcomes in patients with cancer are also lacking, despite infection being a common complication of malignancy that appears to be associated with significant morbidity and mortality.

We conducted a retrospective observational study to elucidate the risk factors for infection with extended-spectrum cephalosporin (ESC)–resistant *Enterobacter* species and the impact of ESC resistance on outcomes in adults with cancer.

2. Materials and methods

2.1. Patients and microbiologic tests

A database at Samsung Medical Center, a 1960-bed tertiary care hospital with a comprehensive cancer center, was reviewed to identify patients diagnosed with cancer who also had *Enterobacter* bacteremia. A review of the medical records was conducted of patients with an episode of *Enterobacter* bacteremia between January 2004 and December 2011. Patients aged 16 years and older were enrolled if they had a diagnosis of *Enterobacter* bacteremia and were being treated for cancer or had been diagnosed with cancer within 1 year prior to the bacteremia onset. Only the first episode of

☆ Financial support: This study was supported by Samsung Biomedical Research Institute Grant #SBRI GL1-B2-031-1.
☆☆ Potential conflicts of interest: All authors report no conflicts of interest relevant to this article.
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http://dx.doi.org/10.1016/j.diagmicrobio.2013.11.002

bacteremia for each patient was included in the analysis. Species identification was performed using VITEK II (bioMerieux, Hazelwood, MO, USA), a standard identification card. Antimicrobial susceptibility testing was performed using the broth microdilution method or the disk diffusion method, following the recommendations of the CLSI (2010). Phenotypic or genetic tests for extended-spectrum beta-lactamase production were not performed as per routine protocol of our institution.

2.2. Data collection

We reviewed the medical records to collect the following data: age, sex, type of malignancy, cancer status at the last evaluation prior to the bacteremic event, comorbidities, administration of antibiotics within 3 months prior to the onset of bacteremia, site of infection, severity of illness (presentation with septic shock and Pitt bacteremia score), and initial and definitive antimicrobial regimens. Other conditions were also identified, including neutropenia, nosocomial acquisition, use of corticosteroids and immunosuppressants not included in the chemotherapy regimen, presence of an indwelling catheter, mechanical ventilation, surgery within 3 months, and invasive procedures performed during the 72 hours prior to bacteremia onset.

The primary outcome measure was all-cause 30-day mortality rate. Additionally, clinical response at 72 hours and 7 days and all-cause mortality rate at 90 days were assessed. Clinical response was classified as complete response (resolution of fever, bacteremia, and all other signs of infection), partial response (improvement of the above, but not complete resolution), and failure (persistent fever or bacteremia, clinical deterioration, or death).

2.3. Definition

Enterobacter bacteremia was defined as the isolation of *Enterobacter* species in blood culture, regardless of the number of positive cultures. Since *Enterobacter sakazakii* and *Enterobacter agglomerans* have previously been included in studies of *Enterobacter* infection, they were considered *Enterobacter* species for the purposes of this study despite the recent reclassification. ESC resistance was defined as *in vitro* resistance to any one of the following cephalosporins: cefotaxime, ceftazidime, and ceftriaxone. The date of onset of bacteremia was considered the first day on which a blood culture returned positive for *Enterobacter* species. Nosocomial infection was defined as an infection that occurred either more than 48 hours after admission to the hospital or after acquisition in another hospital and subsequent transfer to our hospital. Respiratory tract infection was defined as a sepsis with new or progressive infiltrate on chest x-ray compatible with noncardiac etiology and/or those with isolation of *Enterobacter* species from lower respiratory tract specimens without other identifiable source. Gastrointestinal and pancreatohepatobiliary infections included those with corresponding focus of infection identified by symptoms, laboratory findings, or imaging studies. Patients with intraabdominal focus other than gastrointestinal or pancreatohepatobiliary tracts (e.g., intraabdominal abscess) were classified as having intraabdominal infection. Patients without any identifiable source of infection were classified as primary bacteremia. Healthcare-associated infection was defined for the purposes of this study as has been previously described (American Thoracic Society and Infectious Diseases Society of America, 2005), except for attendance at a hospital within the prior 30 days, which was excluded as a risk factor for healthcare-associated infection. This was excluded because almost all patients in this study had visited a hospital at least every 30 days for cancer management. ICU stay was defined as current stay in ICU at the onset of bacteremia, regardless of previous history of ICU admission. Neutropenia was defined as an absolute neutrophil count of $<500/mm^3$ within 48 hours after the onset of bacteremia (Freifeld et al., 2011). Septic shock was defined as sepsis with systolic blood pressure <90 mm Hg that did not respond to adequate fluid resuscitation and necessitated the use of a vasopressor. A Pitt bacteremia score at the sampling for blood culture was calculated (Paterson et al., 2004).

Antimicrobial therapies were classified as empirical or definitive. Empirical therapy was defined as those antibiotics used within 24 hours after the onset of sepsis. Definitive therapy was defined as the antibiotics used after the results of susceptibility testing had been reported. Antimicrobial therapy was considered appropriate if the treatment regimen included 1 or more antibiotic shown to be active *in vitro* in appropriate doses for the indicated use.

2.4. Statistical analysis

We compared the patients with ESC-susceptible *Enterobacter* bacteremia and those with ESC-resistant infection and also compared the patients who died within 30 days with those who survived. For each analysis, Student's *t* test and Mann-Whitney *U* test were used to compare continuous variables, and χ^2 or Fisher's exact test was used for categorical variables. To identify independent risk factors for resistant infection and mortality, a multiple logistic regression model with stepwise backward selection was used. Factors with $P < 0.10$ on univariate analysis were included in multivariate analysis. In multivariate analysis of the group with *Enterobacter aerogenes* bacteremia, Firth's bias reduction method was used to resolve a complete separation problem (Heinze and Schemper, 2002). All *P* values are 2-tailed, and $P < 0.05$ was considered statistically significant. SPSS Statistics, version 19.0 (IBM, Armonk, NY, USA) and SAS Enterprise Guide 4 (SAS Institute, Cary, NC, USA) were used for analyses.

3. Results

3.1. Study population

One hundred ninety-two adults diagnosed with cancer and with *Enterobacter* bacteremia were identified. Species of *Enterobacter* isolated from the blood culture were as follows: *Enterobacter cloacae* (n = 130, 67.7%), *E. aerogenes* (n = 56, 29.2%), *Enterobacter asburiae* (n = 4, 2.1%); *E. sakazakii* (n = 2, 1.0%), and *Enterobacter cancerogenus* (n = 1, 0.5%). One patient had both *E. cloacae* and *E. aerogenes* isolated from a single blood culture. One hundred thirty-three (69.3%) patients had solid tumors, of which gastrointestinal and hepatobiliary were the predominant origins (n = 90, 75.2%). Among 59 patients with hematologic malignancy, leukemia (n = 30, 50.8%) and lymphoma (n = 20, 33.9%) comprised the majority.

3.2. Risk factors for bloodstream infections caused by ESC-resistant Enterobacter species

Enterobacter species from 53 patients (27.6%) were resistant to ESCs and were classified as the resistant group. The remaining 139 isolates were ESC susceptible. The demographics and clinical characteristics of each group are shown in Table 1. Appropriateness of antimicrobial regimen and their classes were also shown in Table 1, but they are excluded from further analysis as they cannot be risk factors for resistant infection. Factors associated with resistant infection in univariate analysis were older age, solid tumor, the presence of liver disease, no chemotherapy within previous 30 days, surgery within the previous 3 months, a non-neutropenic state, and the presence of percutaneous drainage. Administration of antibiotics within the previous 3 months was also associated with resistant *Enterobacter* bacteremia ($P < 0.001$). Among the different classes of antibiotics used within the previous 3 months, the use of third-