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Original Article

Impact of Extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* on the Outcome of Community-onset Bacteremic Urinary Tract Infections

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BACKGROUND/PURPOSE: The number of community-onset bacteremic urinary tract infections (UTIs) caused by *Escherichia coli* and *Klebsiella pneumoniae* is increasing. However, the impact of extended-spectrum β-lactamase (ESBL)-producing *E. coli* and *K. pneumoniae* (ESBL-EK) on bacteremic UTI outcomes is unknown. The aim of this study was to retrospectively analyze the impact of ESBL-EK on community-onset bacteremic UTIs.

METHODS: Of the 58 patients enrolled, 12 suffered from ESBL-EK-caused community-onset bacteremic UTIs. Patients were categorized into ESBL ($n=12$) and non-ESBL ($n=46$) groups. Diagnosis was based on findings of concurrent bacteremia and bacteriuria caused by the same pathogen on admission.

RESULTS: The ESBL group had significantly more male patients (66.7% *vs.* 23.9%; $p=0.005$), indwelling urinary catheters (41.7% *vs.* 6.5%; $p=0.002$), patients admitted from other healthcare facilities (50.0% *vs.* 8.7%; $p=0.001$), and patients with higher Acute Physiology and Chronic Health Evaluation II scores (23.3±7.1 *vs.* 15.9±6.3; $p=0.001$) and intensive care unit admissions (41.7% *vs.* 4.4%; $p=0.003$) than the non-ESBL group. Multiple logistic regression analysis revealed that male gender (odds ratio=9.2; 95%, confidence interval=1.7–50.6) and healthcare facility residency (odds ratio=15.5; 95% confidence interval=2.4–98.9) were independent risk factors for ESBL-producer infections among bacteremic UTIs. Although the mortality rate of both groups was similar (8.3% *vs.* 4.4%; $p=0.403$), the ESBL group had longer hospital stays (16.3±9.3 days *vs.* 7.9±5.2 days; $p=0.010$) and higher antibiotic costs (615.1±423.5 USD *vs.* 252.8±269.2 USD, $p=0.014$).

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CONCLUSION: Male gender and healthcare facility residency are risk factors for ESBL-producer infections among patients with community-onset bacteremic UTIs. Patients with bacteremic UTIs caused by ESBL-EK also have prolonged hospital stays and higher antibiotic costs. Early detection of ESBLs and appropriate antibiotic coverage are likely to shorten hospital stays and reduce medical costs.

KEYWORDS: bacteremia, community, extended-spectrum β-lactamase, urinary tract infection

Introduction

Extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* were identified in the early 1980s following the introduction of oxyimino-β-lactam agents. *Escherichia coli* and *Klebsiella pneumoniae* are regarded as the predominant species of the ESBL producing *Enterobacteriaceae.*[1,2] *E. coli* and *K. pneumoniae* are major nosocomial pathogens that cause urinary tract infections (UTIs), intra-abdominal infections, and bacteremia.[3] ESBL-producing isolates of *E. coli* or *K. pneumoniae* are reported to be resistant to all penicillins and cephalosporins as well as to aztreonam by the Clinical and Laboratory Standards Institute.[4–6] UTIs are the most common infections seen in adults, and are treated with antibiotics. Some studies regard bacteremic incidence to be a marker of disease severity in UTIs.[7,8] Most studies on infections due to ESBL-producing *Enterobacteriaceae* have been performed in a hospital setting, and the number of studies involving a community setting is limited.[9–11] The aim of this study is to investigate the risk factors and treatment outcomes for bacteremic UTIs caused by *E. coli* and *K. pneumoniae,* with and without ESBL production.

Methods

Patients

This study was undertaken retrospectively by chart review and approved by the Institutional Review Board of the Tri-Service General Hospital (TSGHIRB Approval Number: 097-05-28), a 2,000-bed medical center in Taipei, Taiwan. We performed a search of our electronic medical record database for all patients with UTIs and bacteremia. From January 2006 to June 2008, 156 patients were diagnosed with bacteremic UTIs. We further screened the patients using the following criteria: adults aged ≥ 18 years with a concurrent bacteremia and bacteriuria due to the same pathogen, either *E. coli* or *K. pneumoniae*, within 48 hours of admission. From the medical charts, we collected demographic and clinical characteristics, including co-morbidities, clinical presentations, laboratory data, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, intensive care unit (ICU) admission, duration of hospital stay, prior invasive procedures, prior urinary catheterizations, and responses to treatment.

Community-onset infections were defined as infections diagnosed within 48 hours of admission, and were further classified as healthcare-associated infections if the patient fulfilled any of the following criteria: more than 48 hours of hospitalization within the past 90 days, receipt of hemodialysis, administration of intravenous medication or home wound care in the past 30 days, or residence in a nursing home or long-term care facility.[12] If none of these criteria were met, the patients were classified as having community-acquired infections. Antimicrobial therapy was defined as inappropriate if no *in vitro* active antimicrobial agent at the usual recommended dose was administered within the first 48 hours. For infections due to ESBL-EK (extended-spectrum β-lactamase producing *E. coli* and *K. pneumoniae* species), oxyimino-β-lactams (such as cefuroxime, cefotaxime, ceftriaxone, ceftazidime, cefepime, and aztreonam) were considered inappropriate therapy, regardless of *in vitro* susceptibility.

The primary outcome in this study was mortality rate at 21 days after admission (calculated as the total number of deaths/total number of cases) in both ESBL and non-ESBL groups. Antibiotic costs included antibiotics consumed during hospitalization, and the total amount was calculated in United States dollars (USD).

Microbiological methods

Antimicrobial susceptibility was determined by the disk diffusion method, and ESBL production was confirmed using Clinical and Laboratory Standards Institute criteria.[4–6]

Statistical analysis

Contingency data were analyzed using a two-tailed χ^2 test or Fisher's exact test. Continuous data were compared using Student's *t* test. A *p* value of <0.05 was considered significant (two-tailed). A multiple logistic regression analysis with stepwise selection was performed for risk factor analysis, with results presented as odds ratios with 95% confidence intervals. All statistical analyses were performed using the Statistical Analysis System for version 9.1.3 (SAS, Cary, North Carolina, USA).

Results

Fifty-eight patients with community-onset bacteremic UTIs caused by *E. coli* or *K. pneumoniae* fulfilled the study criteria. Of these, 12 (20.7%) were caused by ESBL-EK and 46 (79.3%) by non-ESBL-EK. The demographic and clinical characteristics of both groups are shown in Table 1. The most common underlying disease in both groups was diabetes [25.0% (3/12) and 34.8% (16/46), respectively], although there was no statistical significance between the two groups ($p=0.230$). The proportion of male patients was higher in the ESBL group than in the non-ESBL group, and was statistically significant [66.7% (8/12) *vs.* 23.9% (11/46); $p=0.005$]. There was no difference between the two groups in terms of clinical presentations such as fever, dysuria, frequency, and flank pain. The ESBL group had significantly more patients with indwelling urinary catheters [41.7% (5/12) *vs.* 6.5% (3/46); $p=0.002$], patients from healthcare facilities [50% (6/12) *vs.* 8.7% (4/46);

Table 1. Demographic and clinical characteristics of patients with community-onset bacteremic urinary tract infections[a]

Variables	ESBL ($n=12$)	Non-ESBL ($n=46$)	*p*
Age (yr)	74.2±14.3 (46–90)	72.3±13.9 (37–92)	0.690
Sex, male	8 (66.7)	11 (23.9)	0.005
Underlying disease			
Diabetes	3 (25.0)	16 (34.8)	0.230
Malignancy	0 (0)	6 (13.0)	0.231
Chronic liver disease	1 (8.3)	0 (0)	0.207
Heart failure	2 (16.7)	1 (2.2)	0.098
COPD	1 (8.3)	1 (2.2)	0.334
Renal disease	2 (16.7)	3 (6.5)	0.219
Prior antibiotic use in 30 days	1 (8.3)	5 (10.9)	0.406
Invasive procedure in 30 days[b]	0 (0)	1 (2.2)	0.793
Indwelling urinary catheter	5 (41.7)	3 (6.5)	0.002
Healthcare-associated	6 (50.0)	4 (8.7)	0.001
APACHE II score	23.3±7.1 (12–34)	15.9±6.3 (2–38)	0.001
Clinical presentations			
Fever	8 (66.7)	35 (76.1)	0.222
Dysuria	2 (16.7)	17 (37.0)	0.122
Frequency	2 (16.7)	6 (13.0)	0.323
Flank pain	0 (0)	6 (13.3)	0.225
ICU admission	5 (41.7)	2 (4.4)	0.003
Bacteria			
E. coli	7 (58.3)	28 (60.9)	
K. pneumoniae	5 (41.7)	18 (39.1)	0.873

[a]Data presented as mean±standard deviation (range) or *n* (%); [b]includes surgery or central catheter intervention. ESBL=Extended-spectrum β-lactamase; COPD=chronic obstructive pulmonary disease; APACHE II=Acute Physiology and Chronic Health Evaluation II; ICU=intensive care unit; *E. coli=Escherichia coli; K. pneumoniae=Klebsiella pneumoniae*.

$p=0.001$], prior ICU admissions [41.7% (5/12) *vs.* 4.4% (2/46); $p=0.003$], and higher APACHE II scores (23.3±7.1 *vs.* 15.9±6.3; $p=0.001$) than the non-ESBL group.

Patients in the ESBL group were further divided into healthcare-associated and community-acquired groups. There was no statistical significance in the demographic and clinical characteristics between these two groups (Table 2).

The mortality rate of the ESBL group was similar to that of the non-ESBL group [8.3% (1/12) *vs.* 4.4% (2/46); $p=0.403$]. However, the ESBL group had longer hospital stays (16.3±9.3 days *vs.* 7.9±5.2 days; $p=0.010$), was more likely to receive inappropriate antibiotic treatment [75.2% (9/12) *vs.* 0% (0/46); $p<0.001$], and had higher antibiotic costs (615.1±423.5 USD *vs.* 252.8±269.2 USD; $p=0.014$) (Table 3). In addition, the ESBL group tended to have defervescence later (3.6±3.5 days *vs.* 1.8±1.8 days; $p=0.106$), although the difference was not statistically significant. Multiple logistic regression analysis revealed that male gender (odds ratio=9.2; 95% confidence interval=1.7–50.6) and healthcare facility residency (odds ratio=15.5; 95% confidence interval=2.4–98.9) were independent risk factors for bacteremic UTIs caused by ESBL-EK.

Discussion

In our study, the incidence of ESBL producers among community-onset bacteremic UTIs caused by *E. coli* and *K. pneumoniae* between January 2006 and June 2008 was

Table 2. Demographic and clinical characteristics of healthcare-associated and community-acquired bacteremic urinary tract infections caused by extended-spectrum β-lactamase producing *Escherichia coli* and *Klebsiella pneumoniae*[a]

Variables	Healthcare-associated ($n=6$)	Community-acquired ($n=6$)	p
Age (yr)	78.7±10.1 (59–88)	67.9±17.3 (46–90)	0.297
Sex, male	4 (66.7)	4 (66.7)	0.455
Underlying disease			
Diabetes	1 (16.7)	2 (33.3)	0.409
Malignancy	0 (0)	0 (0)	–
Chronic liver disease	0 (0)	1 (16.7)	0.500
Heart failure	2 (33.3)	0 (0)	0.227
COPD	0 (0)	1 (16.7)	0.500
Renal disease	1 (16.7)	1 (16.7)	0.546
Prior antibiotic use in 30 days	1 (16.7)	0 (0)	0.500
Invasive procedure in 30 days[b]	0 (0)	0 (0)	–
Indwelling urinary catheter	3 (50.0)	2 (33.3)	0.379
APACHE II score	27.3±3.3 (22–32)	19.3±7.8 (12–34)	0.056
Clinical presentations			
Fever	3 (50.0)	5 (83.3)	0.242
Dysuria	0 (0)	2 (33.3)	0.227
Frequency	0 (0)	2 (33.3)	0.227
Flank pain	0 (0)	0 (0)	–
ICU admission	3 (50.0)	2 (33.3)	0.379
Bacteria			
E. coli	2 (33.3)	5 (83.3)	
K. pneumoniae	4 (66.7)	1 (16.7)	0.114

[a]Data presented as mean±standard deviation (range) or *n* (%); [b]includes surgery or central catheter intervention. COPD=Chronic obstructive pulmonary disease; APACHE II=Acute Physiology and Chronic Health Evaluation II; ICU=intensive care unit; *E. coli=Escherichia coli; K. pneumoniae=Klebsiella pneumoniae*.

Table 3. Clinical outcomes of patients with bacteremic urinary tract infections caused by extended-spectrum β-lactamase-EK and non-extended-spectrum β-lactamase-EK[a]

	ESBL (n=12)	Non-ESBL (n=46)	p
Hospital stay (d)	16.3±9.3	7.9±5.2	0.010
Defervescence (d)	3.6±3.5	1.8±1.8	0.106
Inappropriate antibiotic treatment	9 (75.0)	0 (0)	<0.001
Mortality	1 (8.3)	2 (4.4)	0.403
Antibiotics cost (USD)	615.1±423.5	252.8±269.2	0.014

[a]Data presented as mean±standard deviation or *n* (%). ESBL-EK=extended-spectrum β-lactamase *E.coli* and *K. pneumoniae*; USD=United States dollars.

20.7% (12/58). Indeed, the community may be a reservoir for ESBL-producing pathogens.[10,13,14] In a survey conducted from 2001 to 2002 to determine the incidence of ESBL-producing *Enterobacteriaceae* in the stools of outpatients, the prevalence of ESBL carriers was found to increase from 2.1% to 7.5%.[14] In another study, the incidence of ESBL-producing *Enterobacteriaceae* bacteremia from the community was 4.1%.[11] The spread of multidrug-resistant Gram-negative bacteria in the community is a serious problem in public health. Recently, fecal carriage, intestinal colonization, international travel, and household member transmission were also determined to be contributing factors to the spread of ESBL-producing organisms.[15–18] Kang et al asserted that 34.2% (13/28) of the cases of community-onset ESBL-*E. coli* bacteremia originated from UTIs in South Korea.[11]

Worldwide, *Klebsiella* spp. remains the predominant organism producing ESBL. Colodner et al showed that *K. pneumoniae* infection was a risk factor for UTIs due to ESBL-producing bacteria in non-hospitalized patients.[10] In our study, the percentage of *K. pneumoniae* in both groups showed no statistical significance.

Rodríguez-Baño et al demonstrated that diabetes, previous antibiotic use, recurrent UTIs, previous hospital admission, old age, and male gender are potential risk factors for UTIs with ESBL-producing organisms in the community.[9] Moor et al indicated that healthcare facilities are significant reservoirs of ESBL in the community; indeed, 43% (42/98) of their cases were healthcare facility residents, and urine was indicated as the most common source (97%).[19] In our study, male gender and healthcare facility residency were identified as independent risk factors for bacteremic UTIs caused by ESBL-EK. Although 50% of the patients in the ESBL group were healthcare-associated, these patients came to the hospital from the community and were infected with ESBL-producing bacteria. For patients admitted to the hospital with community-acquired UTIs, the risk factors for acquiring ESBL-producing organisms should be considered before initiating treatment.

Apisarnthanarak et al studied community-onset ESBL-EK bloodstream infections in Thailand and found that UTIs were the most prevalent infections (56%). A higher mortality rate in ESBL patients than in non-ESBL patients [36% (13/36) *vs.* 15% (15/108)] was also noted, although the APACHE II scores on admission were similar in both groups (10 *vs.* 9).[20] However, no statistical significance with regard to the mortality rate was noted between the two groups in our study, even though both groups had higher APACHE II scores. Since the proportion of inappropriate antibiotic treatments was similar in both studies, the discrepancies in clinical outcome between our study and Apisarnthanarak's report cannot be completely explained by antibiotic treatment alone. There must have been other issues relating to medical care.

In our study, the ESBL group showed a higher incidence of inappropriate antibiotic treatments, higher ICU admission rate, and higher APACHE II scores than the non-ESBL group, thereby leading to longer hospital stays and higher antibiotic costs. Although there are not enough comparative clinical data to determine the best treatment for infections caused by ESBL-producing bacteria, carbapenems remain the first choice for treatment of serious bloodstream-associated infections.[21] Clinicians should prescribe antibiotics that are appropriate, depending on the local prevalence of ESBLs and disease severity in the patients, especially for those who are at high risk of infection due to ESBL-EK.

In conclusion, ESBL-EK infections are not uncommon in patients with community-onset bacteremic UTIs. Male gender and residence in a healthcare facility are independent risk factors of ESBL-producer infections. Patients with ESBL-EK infections are more likely to have been given inappropriate antibiotics, and have longer hospital stay and higher antibiotic costs. Clinical practitioners should be well informed regarding potential risk factors for ESBLs and should be cautious about the antimicrobial agents administered to decrease the rate of treatment failure and reduce antibiotic costs.

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