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ORIGINAL ARTICLE

Clinical characteristics of urosepsis caused by extended-spectrum beta-lactamase-producing *Escherichia coli* or *Klebsiella pneumonia* and their emergence in the community

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KEYWORDS
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Background: The purpose of this study is to delineate clinical characteristics of urosepsis caused by extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* (ESBL-EK) in different clinical settings, with an emphasis on community-acquired infections.
Methods: A retrospective study was conducted at two medical centers in Taiwan. From May 2002 to August 2007, clinical data of adults with urosepsis caused by ESBL-EK were collected. Patients were categorized into three groups according to the place of acquisition. Baseline characteristics, microbiological data and clinical outcomes were compared.
Results: Ninety-three cases of ESBL-EK urosepsis were included. Their mean age was 69.4 years, and 48.4% were men. Eleven (11.8%), 41 (44.1%), and 41 (44.1%) patients were categorized as

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having community-acquired, healthcare-associated, and hospital-acquired infections, respectively. Cases of ESBL-EK urosepsis from different settings shared similar characteristics in terms of age, gender, comorbidity and resistance profiles of bacterial strains. Of the bacterial isolates, 75% and 38.7% were resistant to fluoroquinolones and aminoglycosides, respectively. Cases of community-acquired urosepsis had a lower disease severity than those acquired in healthcare facilities or hospitals. Of note, there was no case fatality in 11 cases of community-acquired urosepsis and, in contrast, a crude mortality rate of 41.5% was found among adults with hospital-acquired urosepsis ($p < 0.001$).

Conclusion: A limited number of adults with community-acquired urosepsis caused by ESBL-EK in the present study had a favorable outcome. Nonetheless, clinicians should be cautious of the emergence of urinary tract infections caused by ESBL-producers in the community setting.

Introduction

Since an extended-spectrum beta-lactamase (ESBL)-producing organism was first reported in Germany in 1983,[1] the worldwide spread of pathogens harboring this characteristic phenotype, hydrolyzing most broad-spectrum beta-lactam agents, had a serious impact on the clinical management of infection diseases.[2] ESBL-producer infection has been known to be associated with a worse outcome than non-ESBL producer infection.[3] Besides, patients with ESBL-producer infections were more likely to receive inappropriate empirical antimicrobial therapy, which would be associated with a grave outcome.[3]

Escherichia coli and *Klebsiella pneumoniae* are two common ESBL-producing *Enterobacteriaceae* found worldwide,[4] and cause various infections, such as urinary tract infections (UTIs), intra-abdominal infections, and bacteremia in both nosocomial and community settings.[3,5,6] Yu et al summarized the published data about the epidemiology of ESBL-producing *Enterobacteriaceae* in Taiwan; the prevalence of the ESBL-producing phenotype among clinical *E. coli* or *K. pneumoniae* isolates ranged from 1.5% to 29.8% before 2005.[7] A recent study conducted in a tertiary center in Taiwan has shown that ESBL-producing *E. coli* and *K. pneumoniae* (ESBL-EK) accounted for 20.7% of the pathogens causing bacteremic community-onset UTIs.[8] Without exception, the increasing prevalence of ESBL-production among clinical *E. coli* and *K. pneumoniae* isolates was noted in our hospital (data not shown). Therefore, clinicians should be aware of potential treatment failure for community-acquired infections caused by ESBL-producing pathogens, as empirical use of cephalosporins is a common practice in Taiwan. The present study is focused on urosepsis and designed to depict the clinical specialty of ESBL-producer infections originating from the community by comparing with those of healthcare-associated and hospital-acquired urosepsis.

Materials and methods

Patients

A retrospective study was conducted in two medical centers, National Taiwan University Hospital (Hospital A) and National Cheng Kung University Hospital (Hospital B), in Taiwan. The list of patients with ESBL-EK bacteremia between May 2002 and August 2007 was retrieved from the database of Clinical Microbiology Laboratories in the two study hospitals. Cases of ESBL-EK bacteremia fulfilling the following criteria were included for analysis: adults (aged older than 18 years) with either symptoms of lower UTIs or pyuria associated with the same pathogen as that found in the bloodstream (defined as the same bacterial species with the same antibiogram). For patients having more than one episode of bacteremia caused by the same isolate, only the first bacteremic episodes were included for analysis.

Antimicrobial susceptibility and ESBL detection of bacterial isolates

Blood samples collected in the commercially prepared bottles were incubated in blood culture system (BACTEC™ 9240, Beck Dickinson, New Jersey, USA). Urine samples were plated onto the chromogenic medium (ChromID CPS3, bioMérieux, Marcy l'Etoile, France). *E. coli* and *K. pneumoniae* isolates were identified by the colony/biochemical characters and confirmed by the Vitek identification system (bioMérieux).

Antimicrobial susceptibility of each isolate was determined by the disk diffusion method, employing the method and interpretative criteria recommended by the Clinical and Laboratory Standards Institute (CLSI).[9] Phenotypic confirmation for ESBL detection was performed by cephalosporin/clavulanate combination disks as suggested by the CLSI.

Collection of clinical information

Medical records of eligible cases were reviewed. Clinical information, including demographic data, comorbidities, disease severity, complication of bacteremia, laboratory and microbiology data, antimicrobial treatment, and clinical outcome, was collected using a standardized case form.

Definitions

UTIs with concurrent bacteremia caused by the same pathogen indicated the presence of urosepsis. Complicated

urosepsis was arbitrarily defined as urosepsis complicated by functional or structural lesions of the urinary tract, infections involving the prostate, or abscess formation.

Based on the place of acquisition, urosepsis was classified into three groups, i.e., community-acquired, healthcare-associated, or hospital-acquired urosepsis. The hospital-acquired urosepsis comprised adults with positive cultures that were obtained after more than 48 hours of hospitalization. Healthcare-associated infections followed the definition made by Friedman et al[10] In brief, individuals who had visited a hemodialysis clinic or received intravenous chemotherapy in the 30 days before the onset of bacteremia, were hospitalized in an acute care hospital for 2 days or more in the 90 days before bacteremia, or resided in a long-term care facility, were regarded to have healthcare-associated infections. Community-acquired urosepsis comprised patients unable to fulfill the definitions of health care-associated and hospital-acquired infections. Blood and/or urine samples with ESBL-EK had to be obtained within 48 hours of admission among adults with healthcare-associated or community-acquired urosepsis. ESBL-EK isolates conferring resistance to both fluoroquinolones (either ciprofloxacin or levofloxacin, or both) and aminoglycosides (either amikacin or gentamicin, or both) were defined as being multidrug resistant (MDR).

The severity of bacteremia was evaluated by the Pittsburgh bacteremia score, and patients with four points or more were regarded as having critical illness.[11] Organ dysfunctions involving cardiovascular, respiratory, renal, hepatic, neurological, or hematological systems were classed as having clinical worst conditions within the first 24 hours after bacteremia onset, and evaluated by the organ dysfunction and/or infection score.[12] Patients with dysfunction in two or more organs were categorized as having severe sepsis.

Empirical antimicrobial therapy was defined as the drugs administrated within 48 hours of bacteremia onset. Types of antimicrobial agents were classified into carbapenems, cephalosporins, cephamycins, fluoroquinolones, and β-lactam/β-lactamase inhibitor combinations. The definitive antimicrobial therapy was determined by the drugs administrated after the microbiological data were available. Antimicrobial agents were considered to be appropriate if the causative bacterium was susceptible to the agent, according to the antimicrobial susceptible data. The clinical outcomes considered in the study included mortality at discharge, 30-day crude mortality, and sepsis-related mortality, which was defined as the death of patients with persisting clinical evidences of active infection, excluding other causes of mortality.

Statistic analysis

Variables of clinical information were computed and were analyzed with SPSS software for Windows, version 13.0. Categorical variables were expressed as percentages of each subgroup of patients, and compared by the X^2 test with or without Fisher exact test or Yate's continuity correction. The variables with a p value less than or equal to 0.1 in the univariate analysis were put into the multivariable analysis. A p value less than 0.05 was considered to be statistically significant, and all tests were two-tailed.

Results

During the study period, 93 patients fulfilling the eligible criteria were analyzed. Their mean age was 69.4 years and 48.4% were male. With respect to the clinical settings where ESBL-EK urosepsis developed, 11(11.8%) were community-acquired, 41 (44.1%) were healthcare-associated, and 41 (44.1%) were hospital-acquired. Baseline characteristics of 93 patients with ESBL-EK urosepsis are shown and compared in Table 1. There was no difference in age, gender, or comorbid conditions between groups. Diabetes mellitus and chronic kidney disease were common underlying diseases in the three groups. In patients with healthcare-associated and hospital-acquired infections, debilitating comorbidities

Table 1 Baseline characteristics of 93 patients with extended-spectrum beta-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae* urosepsis acquired in different clinical settings

Variables	Number of cases (%)			p
	Community-acquired (n = 11)	Healthcare-associated (n = 41)	Hospital-acquired (n = 41)	
Gender (male)	5 (45.5)	18 (43.9)	22 (53.7)	0.662
Elderly (>65 years)	7 (63.6)	24 (58.5)	30 (73.2)	0.374
Comorbidities	8 (72.7)	34 (82.9)	34 (82.9)	0.713
Diabetes mellitus	5 (45.5)	18 (43.9)	21 (51.2)	0.796
Chronic kidney disease	4 (36.4)	15 (36.6)	18 (43.9)	0.771
Malignancy	2 (18.2)	13 (31.7)	12 (29.3)	0.680
Regular dialysis	0	5 (12.2)	11 (26.8)	0.034
Immunosuppressant therapy	0	4 (9.8)	8 (19.5)	0.167
Chemotherapy	0	3 (7.3)	2 (4.9)	0.622
Steroid	0	1 (2.4)	5 (12.2)	0.129
Organ transplantation	0	0	2 (4.9)	0.274
Chronic hepatitis	0	6 (14.6)	3 (7.3)	0.274
Liver cirrhosis	0	6 (14.6)	3 (7.3)	0.274
HIV infection	0	0	1 (2.4)	0.527

other than diabetes mellitus and chronic kidney disease, such as malignancies, immunosuppressant therapy, or liver cirrhosis, were noted more often than in patients with community-acquired infections (51.2% and 63.4% vs. 18.2%, respectively, $p = 0.028$).

In total, 59 patients were from Hospital A and 34 from Hospital B. There were no differences between cases from Hospitals A and B in terms of age, gender, and comorbidities. The proportions of *E. coli* and *K. pneumoniae* were similar in the two hospitals. Ten (91%) of 11 cases with community-acquired infection were noted in Hospital A. However, infections in patients from Hospital B were more severe than in those from Hospital A, as indicated by a Pittsburgh bacteremia score ≥ 4 (35.3% vs. 15.3%, $p = 0.039$). More patients from Hospital A received empirical carbapenem therapy than from Hospital B (39.0% vs. 17.6%, $p = 0.038$).

Carbapenems were empirically prescribed to treat the bloodstream infections in 36.4% of community-acquired infections, 24.4% of health care-associated infections and 36.6% of hospital-acquired infections ($p = 0.455$). Microbiological characteristics of those ESBL-EK isolates are shown in Table 2. The MDR phenotype was present in 37.6% of 93 isolates. More bacterial isolates from healthcare-associated infections were resistant to either aminoglycosides (51.2% vs. 27.3% or 29.3%) or fluoroquinolones (82.9% vs. 54.5% or 73.2%) than those from community-acquired infections or hospital-acquired infections, though the differences were not statistically significant ($p = 0.088$ and 0.14, respectively; Table 2).

Concerning the severity of the bloodstream infections, fewer cases with community-acquired ESBL-EK urosepsis presented with organ dysfunction than those in the other two groups (Table 3). In contrast, hospital-acquired infections were more often associated with acute renal dysfunction ($p = 0.001$) or respiratory failure ($p = 0.005$). In terms of sepsis-related mortality, no fatality occurred in cases with community-acquired infections, compared to 4.9% of patients with healthcare-associated infections and 14.6% of patients with hospital-acquired infections, though the difference did not reach the statistical significance ($p = 0.161$). Likewise, there were no significant differences in the 30-day mortality rates between the three groups. This was despite a higher 30-day mortality rate of 17.1% in cases with hospital-acquired infections compared to those with healthcare-associated (7.3%) or community-acquired (0%) infections ($p = 0.171$). As for the discharge mortality rate, hospital-acquired infection was significantly higher (41.5%) than healthcare-associated (9.8%) or community-acquired infections (0%) ($p < 0.001$).

To identify the prognostic factors of clinical aspects, clinical data of survival cases and fatal cases associated with sepsis are compared in Table 4. A high Pittsburgh bacteremia score (≥ 4) [odds ratio (OR) 20.55, 95% confidence interval (CI) 3.31−127.37, $p = 0.001$], shock (OR 9.86, 95% CI 1.17−83.01, $p = 0.04$), and neurological failure (OR 11.29, 95% CI 1.62−78.88, $p = 0.02$), were independently associated with sepsis-related mortality. In contrast, male gender (OR 0.08, 95% CI 0.01-0.79, $p = 0.031$) was related to a favorable outcome. Appropriateness of empirical or definitive therapy was not significantly related to a favorable outcome in terms of sepsis-related mortality.

Discussion

Bacteremia caused by ESBL-producing *Enterobacteriaceae* has been known to be associated with a longer hospital stay

Table 2 Empirical antibiotics prescribed for patients with extended-spectrum beta-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae* urosepsis and microbiological characteristics of causative isolates

Variables	Number of cases (%)			*p*
	Community-acquired (n = 11)	Healthcare-associated (n = 41)	Hospital-acquired (n = 41)	
Empirical treatment				
Cephalosporins	3 (27.3)	24 (58.5)	18 (43.9)	0.136
Carbapenems	4 (36.4)	10 (24.4)	15 (36.6)	0.455
Fluoroquinolones	2 (18.2)	1 (2.4)	4 (9.8)	0.164
β-lactam/β-lactamase inhibitors combinations	1 (9.1)	5 (12.2)	2 (4.9)	0.497
Cephamycins	1 (9.1)	0	2 (4.9)	0.230
Others	0	1 (2.4)	0	0.527
Appropriate empirical therapy	4 (36.4)	11 (26.8)	19 (46.3)	0.186
Appropriate definitive therapy	9 (81.8)	30 (73.2)	31 (75.6)	0.838
Microbiological characteristics				
Species				0.403
E. coli	9 (81.8)	25 (61.0)	25 (60.9)	
K. pneumoniae	2(18.2)	16 (39.0)	16 (39.0)	
Polymicrobial bacteremia	1 (9.1)	11 (26.8)	7 (17)	0.335
Multidrug resistance	3 (27.3)	20 (48.8)	12 (29.3)	0.143
Fluoroquinolone resistance [a]	6 (54.5)	34 (82.9)	30 (73.2)	0.140
Aminoglycoside resistance [b]	3 (27.3)	21 (51.2)	12 (29.3)	0.088

[a] Resistant to levofloxacin or ciprofloxacin.
[b] resistant to amikacin or gentamicin.

Table 3 Severity of disease and mortality of 93 patients with extended-spectrum beta-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae* urosepsis in three different clinical settings

Variables	Number of cases (%)			*p*
	Community-acquired (n = 11)	Healthcare-associated (n = 41)	Hospital-acquired (n = 41)	
Severity				
Pittsburgh bacteremia score ≥4	0	9 (22.0)	12 (29.3)	0.118
Severe sepsis [a]	0	8 (19.5)	10 (24.4)	0.191
ODIN score[b] defined organ failure				
Respiratory failure	0	5 (12.2)	15 (36.6)	0.005
Shock	0	12 (29.3)	14 (34.1)	0.079
Hematological failure	1 (9.1)	7 (17.1)	7 (17.1)	0.796
Neurological failure	0	7 (17.1)	7 (17.1)	0.331
Renal failure	0	13 (31.7)	2 (4.9)	0.001
Hepatic failure	0	4 (9.8)	1 (2.4)	0.239
Complicated urosepsis[c]	3 (27.3)	7 (17.7)	6 (14.6)	0.569
Mortality				
Sepsis-related mortality	0	2 (4.9)	6 (14.6)	0.161
30-day crude mortality	0	3 (7.3)	7 (17.1)	0.171
Mortality at discharge	0	4 (9.8)	17 (41.5)	<0.001

[a] Two or more organ systems failure.
[b] Organ damage and/or infection score.
[c] Urosepsis complicated with structural or functional dysfunction, prostate involvement, or abscess formation. ODIN = organ dysfunction and/or infection.

and incomplete treatment response.[13] In the community-onset cases, it is also related to early in-hospital mortality.[3,8] Since the emergence of ESBL-producer infections in the community, a question is elicited: should clinicians prescribe antimicrobial agents with a more broad antibacterial spectrum to treat patients coming from the community? A major concern of such a clinical practice is that the extended use of broad-spectrum antimicrobial agents may contribute to the spread of antimicrobial resistant pathogens.[14] The balance between the pros and cons of antimicrobial treatment becomes an important issue. It is important to find clinical clues for early identifying people with infectious diseases caused by ESBL-producing *Enterobacteriaceae* and early initiation of appropriate antimicrobial therapy.

Risk stratification is important in the initial evaluation of clinical cases and subsequent management. However, the retrospective nature and study design of the present study made us unable to identify the risk factors of ESBL-producer infections among individuals with community-onset infections. In the literature, several risk factors for ESBL-producing bacterial infections have been well

Table 4 Variables associated with the sepsis-related mortality among patients with urosepsis caused by extended-spectrum beta-lactamase-producing *Escherichia coli* or *Klebsiella pneumoniae*

Variables	Number of cases (%)		Univariate analysis			Multivariate analysis		
	Fatal (n =8)	Surviving (n =85)	Odds ratio	95% confidence interval	*p*	Odds ratio	95% confidence interval	*p*
Gender (male)	1 (12.5)	44 (51.8)	0.13	0.02-1.13	0.060	0.08	0.01-0.79	0.031
Comorbidities other than DM or CKD	7 (87.5)	42 (49.4)	7.17	0.85-60.79	0.062			
Pittsburgh bacteremia score ≥4	6 (75)	15 (17.6)	14.00	2.57-76.23	0.001	20.55	3.31−127.37	0.001
Severe sepsis	7 (87.5)	11 (12.9)	47.09	5.28-420.31	<0.001			
Shock	6 (75)	20 (23.5)	9.75	1.82-52.16	0.005	9.86	1.17−83.01	0.023
Respiratory failure	4 (50)	16 (18.8)	4.31	0.97-19.11	0.062			
Hematological failure	4 (50)	11 (12.9)	6.73	1.47-30.88	0.022			
Neurological failure	5 (62.5)	9 (10.6)	14.07	2.87-68.97	<0.002	11.29	1.62−78.88	0.015
Hepatic failure	2 (25)	3 (3.5)	9.11	1.27-65.46	0.057			
Appropriate definitive therapy	3 (37.5)	67 (78.8)	0.16	0.04-0.74	0.021			
Appropriate empirical therapy	1 (12.5)	33 (38.8)	0.23	0.03-1.91	0.250			
Community-acquired infections	0	11 (12.9)	—	—	0.589			0.999

CKD = chronic kidney disease; DM = diabetes mellitus.

described.[3,13,15,16] In the clinical settings of community-onset infections, ESBL-producer infections were usually associated with old age,[3,16] urinary tract anomaly or catheter use,[3] previous hospitalization,[3,16] and recent exposure to antimicrobial agents.[3,15,16] These characters implicate the close linkage between cases and health care facilities. In our study, we applied the Friedman's definition for health care-associated infections. Cases with residence in health care facilities and/or a recent hospital stay would not be included in the group of community-acquired urosepsis. Therefore, our patients with community-acquired urosepsis can be regarded to acquire the infections in the community. Although diabetes mellitus and chronic kidney disease were frequently noted, fewer or no other debilitating conditions, such as malignancy, liver cirrhosis, or immunosuppressant therapy, were ever implicated in the cases of community-acquired infections. These conditions were, however, more commonly present in those with healthcare-associated or hospital-acquired infections. Fewer underlying illnesses may be partially associated with a favorable prognosis for community-acquired urosepsis in our study.

In this study, in accordance with previous studies,[17–19] Pittsburgh bacteremia score-defined critical illness was noted to be the independent prognostic factor, as well as the presence of shock and neurological failure. Of note, the severity of disease and frequencies of organ dysfunctions at the initial presentation of bacteremia were lower in the community-acquired group than the other two groups. There was no fatal case in the community-acquired group. Beyond these host factors, we speculate that the favorable outcome of the community-acquired infections may be partly contributed to the virulence factors of bacteria. A trade-off between the resistance and virulence[20] has been mentioned. That is, the more resistance, the less virulence. Another plausible explanation for favorable outcome in the community-acquired subgroup of ESBL-producer urosepsis is the absence of debilitating underlying conditions, which may play a critical role in determining the clinical outcome of bloodstream infections.

Previous clinical studies on community-onset infections caused by ESBL-producing *Enterobacteriaceae* have shown conflicted results regading the impact of the appropriateness of empirical therapy on mortality.[3,13,17,21] Diverse study designs and different categorization of clinical settings made the data incomparable. In our study, neither empirical nor definitive antimicrobial therapy were significantly related to the sepsis-related mortality. However, there was a trend for a better outcome in those treated by appropriate empirical or definitive antimicrobial therapy. The limited sample size made this study unable to clearly elucidate the role of antimicrobial therapy on the outcome of cases of ESBL-producer blood stream infections. However, at the present time it is too early to change the current recommendation for community-acquired UTIs with the increasing concern of ESBL-producer infections, since our patients with community-acquired urosepsis caused by ESBL-producers fared well in spite of about two-thirds of these patients not empirically receiving appropriate antimicrobial therapy.

ESBL production renders most beta-lactam agents ineffective, and the phenomenon of co-resistance to other classes of antimicrobial agents existing in these pathogens further limits the therapeutic choice of antimicrobial agents for ESBL-producer infections.[22,23] We found the co-resistance pattern of community-acquired ESBL-producers was similar to that of isolates obtained in healthcare-associated or hospital-acquired infections. Though not proven in the present study, it is possible that there is overflow of nosocomial ESBL-producers into the community.[24–26]

In conclusion, our study highlights that there was an emergence of urosepsis due to ESBL-producing Enterobacterieaceae in the community, and the affected subjects had clinical characteristics of lower disease severity, less chronic debilitating illness, and a favorable prognosis. More clinical observations are required to delineate the clinical impact of ESBL-producer infections in the community setting.

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