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Original Article

Clinical implications and risk factors of extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* infection in children: a case-control retrospective study in a medical center in southern Taiwan

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Background and Purpose: Infections caused by extended-spectrum beta-lactamase (ESBL)-producing Gram-negative bacilli constitute a growing problem worldwide. However, studies focusing on children are limited.
Methods: We have observed an increase in cases of ESBL-producing *Klebsiella pneumoniae* (ESBL-KP) infections in the past 6 years in our hospital in southern Taiwan. Using a case-control study design, we compared the clinical characteristics between 54 patients infected by ESBL-KP and 54 frequency-matched controls infected by non-ESBL-producing isolates.
Results: Risk factors associated with the infection of ESBL-KP were mainly longer pre-infection hospital stay and recent antibiotic exposure (within 30 days before the episode). Other potential risk factors included recent surgery, the application of mechanical ventilation, nasogastric tubes and central venous catheter insertion. ESBL-KP-related infection cases had a longer hospital stay than controls, and also had a higher mortality rate, although not significantly so.
Conclusions: Recent antibiotic exposure was by far the most important predisposing factor associated with infection of ESBL-KP. Unnecessary antibiotic use should be avoided both in the hospital and community, especially ceftazidime, vancomycin/teicoplanin, aminoglycosides and ampicillin. In our study, carbapenem antibiotics remained the most active drugs against ESBL-KP in pediatric patients, while flomoxef and ciprofloxacin were suitable alternative choices.

Key words: beta-Lactamases; beta-Lactam resistance; Carbapenems; *Klebsiella pneumoniae*; Risk factors

Introduction

The National Nosocomial Infection Surveillance System report of America from January 1992 to April 2000 showed the growing problem of antibiotic resistance in the past decades [1]. There were many mechanisms of antimicrobial resistance, of which resistance due to beta (β)-lactamase production was the most important [2]. During the past two decades, strains that produced plasmid-mediated extended-spectrum β-lactamases (ESBLs) have emerged among the *Enterobacteriaceae*, especially *Klebsiella pneumoniae* and *Escherichia coli*. ESBLs confer clinically significant resistance to broad-spectrum penicillins, monobactams and cephalosporins, including β-lactamase inhibitor combinations. ESBLs have been classified into many types by their amino acid sequences. TEM and SHV types were most common among ESBL-producing *K. pneumoniae* (ESBL-KP); however, OXA mutant or CTX-M types were also reported [3-6]. Since ESBL-KP was first isolated in Germany in 1983 [7], many outbreaks caused by the multidrug-resistant strains have been reported all over the world. *K. pneumoniae* was the most predominant organism in ESBL-producing *Enterobacteriaceae* [2,8-10].

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Infections caused by ESBL-KP have caused great concern for many reasons. First, inappropriate empiric antibiotics were often chosen initially in clinical practice [11]. Second, ESBL-KP isolates were multidrug-resistant and difficult to treat [11,12]. Third, patients with ESBL-KP were usually relatively immunocompromised with significantly longer hospital stays and thus relatively easily colonized by many multidrug-resistant organisms [13,14].

Most studies of epidemiology and risk factors of ESBL-KP infection have been conducted in adult populations, whereas data are limited in children. The purpose of this study was to compare and evaluate the clinical characteristics and risk factors of ESBL-KP infection among hospitalized pediatric patients.

Methods

Subjects

This case-control study was conducted at the Chang Gung Memorial Hospital, Kaohsiung (CGMH-K), a medical center with 170 ward beds and 53 intensive care unit (ICU) beds for children in southern Taiwan. From January 1, 2000 to October 31, 2005, all *K. pneumoniae* isolates identified by the microbiological laboratory were collected. They were divided into case and control groups, and the data retrospectively reviewed and compared.

The case group included those patients with ESBL-producing *K. pneumoniae*. If *K. pneumoniae* was isolated many times from a patient, only the first episode was enrolled. Case and control patients were matched 1:1. Case and control groups were matched for specimen source and date of isolation as closely as possible. The control group comprised those who acquired non-ESBL-producing *K. pneumoniae* during the same period. Only those patients defined as active infection were enrolled in this study. Each patient was included as either case or control only once. All study subjects were followed throughout their hospital stay.

The medical records of the patients reviewed included demographic characteristics, comorbid diseases (central nervous system damage, congenital disease, respiratory distress or pulmonary parenchyma infection, gastrointestinal tract disease, genitourinary tract disease, cancer), source of specimen (blood, urine, pus and others), date of collection and admission, recent antibiotic therapy, recent hospitalization and surgery, catheter intervention (endotracheal tube, nasogastric tube, central venous catheter, Foley catheter, etc.), laboratory data (leukocyte and platelet count, etc.) and clinical outcome (length of hospital stay and in-hospital mortality). Drug sensitivity testing of the isolated bacteria was also reviewed.

Microbiological testing

Bacterial susceptibility to antimicrobial agents was determined according to criteria of the National Committee for Clinical Laboratory Standards [15]. ESBL-producing *K. pneumoniae* was suspected if the disk-diffusion susceptibility test showed the inhibition zone of ceftriaxone ≤25 mm or ceftazidime ≤22 mm. These isolates were subjected to cefotaxime (30 μg)-cefotaxime/clavulanate (30/10 μg) and ceftazidime (30 μg)-ceftazidime/clavulanate (30/10 μg) disk testing. An increase of 5 mm or more in diameter of the inhibition zone when either of the oxymino-cephalosporins were combined with clavulanate was considered evidence of ESBL production [15]. The reference strains were *E. coli* American Type Culture Collection (ATCC) 25922 and *K. pneumoniae* ATCC 700603.

Variable definition

All variable definitions were established prior to data collection. All the *K. pneumoniae* isolates from enrolled case and control groups were further subdivided into two groups: community-acquired infection and nosocomial infections. Nosocomial infection was determined according to the Centers for Disease Control and Prevention definition issued in 1988 [1]. Previous hospitalization was defined as admission to any hospital within 30 days prior to this admission. Recent surgery was defined as any surgical intervention within 30 days. Previous antibiotic therapy was defined as antibiotics for at least 2 days within 30 days before the bacteria was isolated. Past antibiotic use was defined as antibiotic use for at least 2 days within 30-60 days before specimen collection. If the patient died within 30 days after the date of specimen collection, the death was related to this episode of infection in our definition. Pre-infection hospital stay was the interval between the date of admission and specimen collection. However, post-infection hospital stay was the interval between the specimen collection and discharge or death.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) for Windows (Version 13.0; SPSS Inc., Chicago, IL, USA) was used for analysis of data. Student's *t* test was used for analysis of continuous variables with a normal distribution, chi-squared test (or Fisher's exact test

if the expected frequency in any cell of a contingency table was <5) was used for analysis of categorical variables. All tests used were two-tailed. A p value <0.05 was considered as statistically significant. Multivariate analysis was applied to all key variables to identify those significantly associated with the outcome in the univariate analysis (p<0.05), by use of a logistic regression model.

Results

A total of 274 *K. pneumoniae* isolates from blood, urine, pus, central venous catheter tip and bronchioalveolar lavage culture were collected. There were 78 ESBL-KP isolates identified, with a prevalence of 28.4% (78/274). Only 54 cases were finally enrolled, excluding 20 strains being repeated isolation, and four strains of asymptomatic colonization or no available data. There was no *K. pneumoniae*-related cluster found during the period. Of these 54 *K. pneumoniae* isolates, seventeen isolates were from blood, six from central venous catheter tip, 22 from urine, eight from pus, and one from bronchioalveolar lavage. Fifty four non-ESBL-KP isolates were matched in a 1:1 ratio for comparison. However, case numbers from central venous catheter tip were not sufficient to match with the control group, and six isolates from blood were used instead.

Descriptive statistics and univariate analysis

The demographic data are listed in Table 1. Case patients were significantly younger than controls (p=0.025), with a mean difference of 17 months. There were no significant differences in age distribution, gender, previous hospitalization and past antibiotics use between the two groups. The case group had longer hospital stay both in pre-infection and post-infection periods (p<0.001). The duration of pre-infection hospital stay was longer in case patients and was longer than two weeks in 60% (32/54) of them. Case patients usually had significantly longer stays in ICUs (p<0.001) and greater incidence of nosocomial infection (p=0.001). This retrospective study also found 11 community-acquired ESBL-KP infections. There was no significant difference in comorbid conditions except respiratory distress and central nervous system damage (Table 2). The presence of mechanical ventilator use, central venous catheter, nasogastric tube or recent surgery at the time of infection was a significant predictor for ESBL-KP infection on univariate analysis (Table 2).

Previous antibiotics within 30 days before specimen collection was also assessed (Table 3). Exposure to third-generation cephalosporins, ceftazidime, ampicillin, aminoglycosides and vancomycin/teicoplanin were significantly associated with ESBL-KP infection. There was a higher rate of metronidazole and first and

Table 1. Demographic characteristics and potential risk factors among cases and controls

Variable	Cases (n = 54)	Controls (n = 54)	p
Age (years)			
0-3	45	39	0.165
4-7	4	3	0.696
>8	5	12	0.064
Gender			0.847
Male	29	30	
Female	25	24	
Past antibiotic use[a]	31	21	0.054
Previous antibiotic therapy[b]	53	30	<0.001
Previous hospitalization	16	15	0.832
Admission to ICU	44	19	<0.001
Length of pre-infection hospital stay (mean ± SD) [days]	37.5 ± 5.4	11.9 ± 2.6	<0.001
Nosocomial infection	43	26	0.001
Laboratory data (most recent specimen)			
WBC (mean ± SD) [x 10^9cell/L]	13.1 ± 0.1	11.3 ± 1.3	0.288
PLT (mean ± SD) [x 10^4/mm^3]	28.9 ± 3.3	22.1 ± 2.4	0.102
Hospitalization (mean ± SD) [days]	72.8 ± 8.5	26.25 ± 4.4	<0.001
Length of post-infection hospital stay (mean ± SD) [days]	34.4 ± 5.1	14.3 ± 2.3	<0.001
Death	8	7	0.781

Abbreviations: ICU = intensive care unit; SD = standard deviation; WBC = white blood cell; PLT = platelet

[a]Antibiotic exposure within 30-60 days before isolates were collected.

[b]Antibiotic exposure within 30 days before isolates were collected.

Table 2. Comorbidity and interventions among cases and controls

Variable	Cases (n = 54)	Controls (n = 54)	*p*
Comorbidity			
CNS	18	7	0.021
CHD	13	9	0.474
Respiratory distress	22	11	0.036
GI disease	19	16	0.537
GU disease	24	27	-
Cancer	2	11	-
Intervention			
CVC	30	15	0.006
Mechanical ventilation	26	11	0.004
Foley	6	3	0.489
NG tube	36	14	<0.001
Recent surgery	20	9	0.017

Abbreviations: CNS = central nervous system; CHD = congenital heart disease; GI = gastrointestinal; GU = genitourinary; CVC = central venous catheter; NG = nasogastric

second-generation cephalosporin exposure among the ESBL infection cases, but the differences were not statistically significant (Table 3).

Multivariate analysis

Forward logistic regression analysis showed that only two risk factors significantly associated with ESBL-KP infection (Table 4). One was the duration of hospital stay (adjusted odds ratio (OR), 1.06; 95% confidence interval (CI), 1.02-1.09; $p<0.001$), and the other was antibiotic therapy within 30 days before the specimen collection (adjusted OR, 0.003; 95% CI, 0.00-0.12; $p=0.003$).

Antibiotics susceptibility profile of ESBL-KP and non-ESBL-KP

The antibiograms of the 108 isolates with ESBL-KP and non-ESBL-KP are shown in Fig. 1. Imipenem was the only antibiotic agent to which all isolates were susceptible. Isolates of ESBL-KP were more resistant to aminoglycosides, cephalosporins, amoxicillin-elavulanate and piperacillin than isolates of non-ESBL organisms.

Discussion

Colonization by *K. pneumoniae* is often a prerequisite of infection and several studies also showed that relationship between intestinal colonization and infection [8, 9,16,17]. However, Lucet et al [8] considered that risk factors for colonization differed from those for infection. Most studies have excluded those with colonization while analyzing the risk factors of acquisition with multidrug-resistant *K. pneumoniae* [18]. This study included patients with *K. pneumoniae* infection in CGMH-K for a 6-year period in order to find the risk factors associated with acquisition of ESBL-KP in pediatric patients.

In this study, cases were significantly younger than controls and mostly hospitalized in ICU. Outbreaks of ESBL-KP in our neonatal ICU and pediatric ICU before the study period may have contributed to our results. Despite strict infection control practices and control of such outbreaks, the rate of ESBL remains high in this unit.

The process of colonization or infection by ESBL-KP often begins following contact with colonized patients, staff and contaminated objects. Antibiotics increase colonization resistance by reducing the normal flora, whereas invasive manipulation may allow direct transmission of pathogens [14,19]. Our finding of the independent association between recent surgical intervention, present of central venous catheter and nasogastric tubes, and need for mechanical ventilation support with ESBL-KP are consistent with earlier studies [17,20]. The importance of these factors lies on the epidemiologic implications at the hospital level because the result suggested more nosocomial transmission of the infection and higher clinical severity

Table 3. Previous antibiotics within 30 days before specimen collection

Antibiotic	Cases (n = 54)	Controls (n= 54)	Unadjusted OR	*p*
Third-generation cephalosporins	22	10	3.02	0.020
Ceftazidime	13	5	3.11	0.039
Others[a]	9	3		0.066
Aminoglycoside	42	18	7.0	<0.001
Ampicillin	33	12	5.5	<0.001
Ciprofloxacin	1	0		
Metronidazole	7	2		0.161
Vancomycin/teicoplanin	26	12	3.25	0.005

Abbreviation: OR = odds ratio

[a]Others include ceftriaxone and cefotaxime.

Table 4. Adjusted risk factors for extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* infection in hospitalized children

Variable	Adjusted OR (95% CI)	*p*
Duration of pre-infection hospital stay	1.06 (1.02-1.09)	<0.001
Previous antibiotic therapy within 30 days before specimen collection	0.003 (0.00-0.12)	0.003

Abbreviations: OR = odds ratio; CI = confidence interval

scores at admission in our case group [21]. However, patient to patient transmission could not be substantiated in our study because no molecular fingerprinting was available for our ESBL-producing isolates to identify a clonal relationship.

Most recent data suggest that the risk imparted by previous antibiotic use was considerable. Lautenbach et al [14] in 2001 reported that total prior antibiotic exposure was the only independent risk factor for ESBL-KP. Some studies further corroborate that the previous use of antibiotics was the predictor of ESBL-producing organisms [21-24]. Our result was also in accordance with those reports in both univariate and multivariate analysis.

Of the various classes of antibiotics, third-generation cephalosporins had been the most incriminated in infection by ESBL-producing organisms [11,18,21,25]. Other antibiotics [26-28], such as fluoroquinolones, aminoglycosides, penicillin and second-generation cephalosporins have also been implicated, but to a lesser extent. In this study, the previous use of ampicillin and vancomycin/tiecoplanin in the case group was significantly higher than in the control group. Ampicillin was a common first-line antibiotic for the treatment of pediatric infections of the respiratory system, gastrointestinal and genitourinary tract, perinatal infection and sepsis. Monotherapy with ampicillin was shown to increase the risk of bacteremia due to *Klebsiella* in one study [29]. ESBL-KP was usually much more resistant to aminoglycosides and third-generation cephalosporins than the non-ESBL-producing *Enterobacteriaceae* [30,31]. Our study also revealed that vancomycin/teicoplanin — used empirically to treat suspected catheter infection due to multidrug-resistant *Staphylococcus or Streptococcus* spp. — was a potential risk factor. The reason could be that this treatment disrupted the anaerobic intestinal microflora and promoted intestinal colonization with ESBL-KP, which was proved in an animal model [32,33].

Boo et al published a case-control study on the risk factors associated with the rectal colonization of ESBL-producing *Klebsiella* species in newborn infants admitted to the neonatal ICU [17], and concluded that the duration of hospital stay was the independent risk factor of ESBL rectal colonization. This is consistent with our study, in which case patients had significantly longer pre-infection hospital stay than control patients. Schiappa et al's study [34] showed that patients with ESBL-KP infection had higher clinical severity (significantly higher Acute Physiology And Chronic Health Evaluation II score) at admission. Our case patients also had significantly more comorbid conditions and were mostly admitted to the ICU.

The antibiograms revealed a limited group of effective antibiotics for the treatment of ESBL-KP infection (Fig. 1). Carbapenem antibiotics are the most reliably effective empiric therapies for this infection from our data, similar to previous reports [27,32]. ESBL-KP were

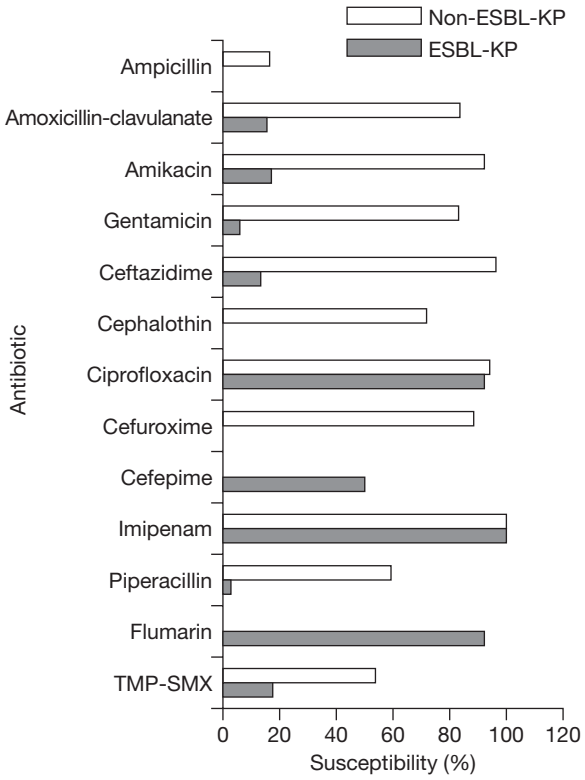

Fig. 1. Antimicrobial susceptibility of extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* (ESBL-KP) and non-ESBL-KP in pediatric patients at Chang-Gung Memorial Hospital, Kaohsiung. TMP-SMX = trimethoprim-sulfamethoxazole.

also highly susceptible to ciprofloxacin and flomoxef in children (92.59% and 92.49%), whereas ciprofloxacin susceptibility in the Taiwanese report of Liao et al [35] was only 36.6% in the general population. These drugs might have a role as alternative therapy for ESBL-KP, offering the possibility of reducing selection pressure for carbapenem-resistant organisms. In Taiwan, the cefepime susceptibilities of ESBL-KP ranged from 37% to 100% in vitro [36]. Cefepime susceptibility was only 50% in our data. Alternative therapy using cefepime against ESBL-KP strains in Taiwan could be reliable if appropriately guided by cefepime and ceftazidime MIC result [37].

In conclusion, we found that these case patients had a significantly higher rate of nosocominal infections and ICU admissions, and longer hospital stay in univariate analysis than control patients. They were also significantly more likely to have comorbidity and invasive interventions than controls.

Previous antibiotic therapy within 30 days preceding specimen isolation and longer pre-infection hospital stay were the two significant risk factors of acquisition with ESBL-KP infection in multivariate logistic regression analysis of our study. Antimicrobial agents associated with increased selection pressure for resistance not only included aminoglycosides and ceftazidime as in earlier studies, but also ampicillin and vancomycin/teicoplanin. Flomoxef and ciprofloxacin were reliable alternatives to carbapenems for children with ESBL-KP infection.

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