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Infections of cefotaxime-resistant and cefmetazole-susceptible *Escherichia coli* and *Klebsiella pneumoniae* in children

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A search of the computerized database at the National Taiwan University Hospital was made for cefotaxime-resistant and cefmetazole-susceptible isolates of *Escherichia coli* and *Klebsiella pneumoniae* (which may be extended-spectrum β-lactamase-producing strains) in pediatric wards and intensive care units between 1999 and 2001. Fourteen infectious episodes attributed only to study bacteria were identified, including 7 episodes of bacteremia. Nine patients (64.3%) had underlying medical conditions: 3 were premature babies, 3 were immunodeficient, 2 had malignancy, and 2 had a congenital heart disease with active heart failure even after surgery. Among the 7 patients with bacteremias, 5 may be catheter-related; 6 were treated with carbapenems and 1 was treated with cefmetazole successfully, with or without the removal of the catheter. Before the acquisition of the infection, a history of stay in an intensive care unit within 4 weeks was noted in 10 cases (71.4%); a history of use of extended-spectrum cephalosporins within 4 weeks was also noted in 6 cases (42.9%). Cefmetazole, with or without an aminoglycoside, was clinically effective in 6 cases (42.8%). Except for 1 episode of pneumonia that ended in mortality, all of the infectious episodes were successfully treated. The mortality rate was 7.1%.

Key words: Beta-lactam resistance, beta-lactamases, cefmetazole, *E.coli*, *K. pneumoniae,* treatment outcome

Gram-negative bacilli account for the majority of cases of nosocomial infection worldwide [1-6]. Cephalosporins are most common agents used in the empiric treatment of pediatric infections caused by Gram-negative bacilli. However, since the late 1980s, there have been increasing reports of nosocomial outbreaks caused by Gram-negative bacilli that exhibit extended-spectrum β-lactamases (ESBLs) [7]. Treatment with extended-spectrum cephalosporins (ESCs) for infections caused by ESBL-producing bacteria was associated with failure of therapy [8,9], and carbapenem became the drug of choice in such cases [2]. Previous reports also illustrated that inappropriate empiric antibiotic choice for critically ill patients may result in increased mortality related to infection caused by ESBL-producing bacteria [10].

The prevalence of ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* has been increasing in recent years in Taiwan. The percentage of ESBL-producing *E. coli* and *K. pneumoniae* in National Taiwan University Hospital (NTUH) was 2.5% and 3.4%, respectively, in 1993, and 6.7% and 10.3%, respectively, in 1997 [11]. Multicenter surveillance in intensive care units (ICUs) in Taiwan revealed that the percentage of ESBL-producing *E. coli* and *K. pneumoniae* in 2000 was 11.9% and 11.3%, respectively [6].

Antibiograms in these ESBL-producing bacteria usually show them to be resistant to ESCs and susceptible to cephamycins, including cefmetazole [12]. Bacteria with AmpC-producing β-lactamase, decreased outer membrane permeability or efflux mechanisms will show resistance to both cefotaxime and cefmetazole [13-15]. Therefore, bacteria that were resistant to cefotaxime and susceptible to cefmetazole were considered as ESBL-producing strains. The microbiologic characteristics of *E. coli* or *K. pneumoniae* that harbored this phenotype were recorded in this retrospective study. Also, the clinical characteristics of pediatric patients infected by such bacteria were analyzed.

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Materials and Methods

Study subjects

Cefotaxime-resistant and cefmetazole-susceptible *E. coli* and *K. pneumoniae* isolated from the pediatric wards and ICUs by disk diffusion method between 1999 and 2001 at NTUH were searched for on the computerized database. The pediatric wards included the oncology ward with 35 beds, where most of the patients were admitted for evaluation and management of malignant diseases, and the general ward with 50 beds, where patients were admitted for other diseases. The ICUs included the neonatal ICU, with 32 beds for premature babies, neonates or young infants, and the pediatric ICU, with 10 beds for other patients beyond the neonatal period. The medical charts of the patients enrolled in the study were reviewed and the characteristics of the isolates as well as the demographic data of the patients were analyzed. Infection or non-infection was judged based on clinical course.

Bacterial isolates

At the NTUH from 1999 to 2001, routine susceptibility testing was performed by disk diffusion method. Cefotaxime was the antibiotic representative of ESCs, as recommended by the National Committee for Clinical Laboratory Standards [16]. The double-disk synergy test, a standard test for defining ESBLs in *E. coli* and *K. pneumoniae*, was not yet routinely used in our laboratory then. Therefore, cefotaxime-resistant and cefmetazole-susceptible microorganisms were considered to be representative of ESBL-producing bacteria in our study.

Episodes of infection

Data were excluded from the final analysis if there were more than 1 bacterium isolated at the infection site such that the causative pathogen could not be determined clinically.

Pneumonia is defined as abnormality in chest X-ray studies, including obvious infiltration, patchy lesions or consolidation, with compatible clinical symptoms or signs. If the sputum smear and the culture result were compatible, the condition was categorized into "probable pneumonia". If only the culture result was available, it was categorized as "possible pneumonia".

Bacteremia was divided into "bacteremic pneumonia", if the patient had concomitant pneumonia, or "primary bacteremia (may be catheter-related)", if there was no other obvious infectious focus and the blood specimen was sampled from the catheter, including arterial catheter, central venous catheter or port-A catheter. Whether the bacteremia was catheter-related or not could not be differentiated since there was only limited clinical information in this retrospective chart review. If the port of entry of a catheter became infected, or a catheter tip culture revealed confluent growth of bacteria with clinical signs of systemic infection, this was categorized as "catheter-related infection other than bacteremia".

Urinary tract infection (UTI) is defined by colony counts of a single pathogen in a urine specimen of more than 10^5, 10^4 or any colony forming units per mL by voiding urine, catheterized urine, or urine from suprapubic aspiration, respectively. If there was no evidence of upper UTI, it was categorized as "simple UTI".

The origins of isolates were considered community-acquired if they were recovered from inpatients within 3 days after admission, or nosocomial if recovered beyond 3 days after admission.

Results

Characteristics of the study subjects

From 1999 to 2001, 13 patients with 14 episodes of infections fulfilled our inclusion criteria. Another 14 episodes of infections were excluded because the culture revealed polymicrobial bacteria and it was not known whether or not the study bacteria was solely responsible for the infection. Most cases excluded were pneumonia (4 cases), catheter-related infection other then bacteremia (4 cases) and wound infections (3 cases). Among 14 episodes of infections, 6 were male and 8 were female. The mean age of the patients was 2.7 years (range, 0.1-14.6 years) while the median age was 4.2 months. The mean length of hospitalization when the bacterial isolate was obtained was 32 days (range, 0-63 days).

There were 13 nosocomial infections (92.8%). Before the acquisition of the study bacteria, a history of stay in an ICU within 4 weeks was noted in 10 cases (71.4%); 9 of them only occurred in an ICU. A history of use of ESCs within 4 weeks was also noted in 6 cases (42.9%), and ceftazidime was used in 4 of them. Colonization of pathogens with similar antibiogram before the infection was observed in 3 cases (21.4%).

Two episodes were infected by *E. coli* and the rest by *K. pneumoniae*. The underlying diseases and data on the different episodes of infections are summarized in Table 1.

Table 1. Underlying medical conditions and the classification of infections

Classification of infections	Prematurity	Underlying medical conditions							
		Malignancy		Immunodeficiency			CHD with heart failure	Nil	Total
		ALL	Osteo-sarcoma	WAS s/p BMT	RAI and asplenia	ACTH therapy			
Bacteremia									
Bacteremic pneumonia	2								2
Possibly catheter-related	1	1	1				1	1	5
Catheter-related infection other than bacteremia					1		1		2
Pneumonia without bacteremia									
Probable						1		1	2
Possible								1	1
Urinary tract infection									
Lobar nephronia								1	1
Simple UTI				1					1

Abbreviations: ALL = acute lymphoblastic leukemia; WAS = Wiscott-Aldrich syndrome; BMT = bone marrow transplantation; RAI = right atrial isomerium; ACTH = adrenocorticotrophic hormone; CHD = congenital heart disease; UTI = urinary tract infection

Clinical features during treatment

Except for 1 episode of probable pneumonia, which ended in mortality, all of the infectious episodes were successfully treated. Among the 7 patients with bacteremias, carbapenems (either meropenem or imipenem) were the main treatment in 4 patients and treatment was initiated within 3 days of onset of the infection. One patient did not receive adequate antibiotics within 3 days; cefmetazole (day 4) and then meropenem (day 5) was prescribed later after the culture results were known. Amikacin and cefmetazole respectively, were the only effective treatment in the other 2 patients. The latter 3 patients may be catheter-related bacteremia and the catheter was removed early in the treatment course. Two patients with probable pneumonia were treated with meropenem within 3 days. The other patient with possible pneumonia was treated with amikacin and cefmetazole. The patient with simple UTI was treated with cefmetazole while the patient with lobar nephronia was treated with cefmetazole initially and gentamicin was added later. In the latter, fever subsided on day 8, after cefmetazole was started. The treatment was successful. The only mortality was a patient with probable pneumonia who developed infantile spasm under adrenocorticotrophic hormone therapy. Ceftazidime was started on day 1 of the fever. The antibiotics were shifted to meropenem on day 4, however, the patient died the same day due to septic shock.

Discussion

Conventional disk diffusion method may not detect all of the ESBL-producing *Enterobacteriaceae*, including *E. coli* and *K. pneumoniae*. Therefore, the prevalence of ESBL-producing microorganisms may be higher than reported. Among cefotaxime- or ceftazidime-resistant *E. coli* and *K. pneumoniae*, 58.3% and 77.8%, respectively, possessed the ESBLs phenotype in Taiwan in 2000 [6]. In this study, we did not have the susceptibility data of the study bacteria to ceftazidime, and some cefotaxime-susceptible microorganism may be ESBL-producing strains [17]. Some strains with AmpC-producing β-lactamases, decreased outer membrane permeability or efflux mechanisms may also be ESBL-producing strains and yet cefmetazole resistant [13-15]. Therefore, the cefotaxime-resistant and cefmetazole-susceptible microorganism is one phenotype that could be representative of ESBL-producing bacteria, but the screening method used may not be sensitive enough to reveal all of the ESBLs-producing strains in our study.

If all clinical isolates were included whether they caused infection or colonization, high non-susceptibility rates were observed in both *E. coli* and *K. pneumoniae* to amikacin and trimethoprim-sulfamethoxazole (data not shown). The susceptibility of the study bacteria to amikacin was lower than that of the overall isolated bacteria in NTUH. However, little difference was noted when ciprofloxacin or trimethoprim-sulfamethoxazole was compared. There was no relationship between the susceptibility rates and the length of hospitalization (data not shown). These findings suggest that ESBL-producing *E. coli* or *K. pneumoniae* might already express multi-resistance to antibiotics, at least including ESCs and amikacin,

regardless of the time point of hospitalization. It should be noted that ESBLs genes are encoded in the plasmid, which also encodes other resistant genes. If the plasmid is transferred to other bacteria, it confers multi-resistance to the bacteria.

Proper treatment of ESBL-producing bacteria is mandatory. In a previous study, the outcome of patients infected with ESBL-producing bacteria was grave if appropriate antibiotics were not initiated within 3 days of the onset of infection [18]. Another study suggested that mortality was significantly lower when a carbapenem regimen rather than a non-carbapenem regimen was used in the first 5 days of bacteremia [19]. In this study, all of our patients with bacteremia were successfully treated with an effective antibiotic within 5 days. Two of them started with a non-carbapenem regimen, 1 with amikacin and the other with cefmetazole. However, these 2 cases may have been catheter-related bacteremia; the suspicious catheter was removed early in the treatment course. Early removal of suspicious catheters is as important as initiation of appropriate antibiotics, and may partly explain the good outcome in our cases.

Cephamycins, cefmetazole included, have been reported to have good inhibitory activity against ESBL-producing bacteria in vitro [12,20]. Treatment failure of infection caused by ESBL-producing bacteria with cephamycins has been reported [21], but the causative pathogen also showed resistance to cephamycins in vitro in the study. Some reports noted that ESBL-producing bacteria show resistance to cephamycins in vitro because these bacteria are associated with porin deficiency [22], or produce cephamycinases [23] or AmpC-producing β-lactamases [24]. Other data showed that minor infections, such as UTI, caused by these ESBL-producing bacteria, may resolve with ESCs [25]. There is no such report about cephamycin treatment of infections of ESBL-producing bacteria susceptible to cephamycin in vitro. Since the ESBL-producing bacteria resistant to ESCs may be treated with ESCs, cephamycins, to which ESBL-producing bacteria are susceptible, may also be effective in some minor infections. Our results suggest exactly this, especially for mild to moderate infections. However, our data are not sufficient to assert that sole treatment with cefmetazole is adequate for primary bacteremia. Whether or not monotherapy with cefmetazole is sufficient to treat ESBL-producing bacteria cannot be certain in view of the small number of cases and lack of a case-control design.

We found that a history of an ESC use, especially ceftazidime, was associated with recovery of an ESBL-producing strain. Since patients admitted to the ICU tend to have more severe diseases and receive more antibiotics and intervention with medical devices, it is not surprising that a high percentage of our patients also had a history of stay in an ICU. In this study, 21.4% of infectious episodes had a preceding history of colonization and this suggested that colonization is the precursor of clinical infections. In clinical practice, ESBL-producing strains should be considered the etiology of infection if colonization had been previously documented.

In summary, ESBL-producing *E. coli* and *K. pneumoniae* caused colonizations and infections in pediatric patients. More cases were seen in subjects who had concomitant underlying medical conditions. The most invasive infections occurred in premature babies and patients with malignant diseases. Most of the infections were nosocomial and manifested during the ICU stay. Removal of suspicious infected catheters, including arterial catheters, was important to the success of the treatment regimen. Carbapenem remained the drug of choice with which most patients were effectively treated. Amikacin was not reliable because most ESBL-producing bacteria were not susceptible to it. Cefmetazole was effective in some infections caused by ESBL-producing strains, but further study is needed in this regard.

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