Risk factors in the acquisition of extended-spectrum β-lactamase *Klebsiella pneumoniae*: a case–control study in a district teaching hospital in Taiwan

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Summary: A case–control study was performed to find the risk factors in the acquisition of extended-spectrum β-lactamase (ESBL) *Klebsiella pneumoniae*. From 1 May 2001 to 30 September 2001, 422 isolates of *K. pneumoniae* identified by the microbiological laboratory in Hsin-Chu hospital were collected, 59 of which were ESBL-producing strains. The prevalence rate was 14% (59/422). There were 43 case patients (ESBL-producing *K. pneumoniae*) and 86 controls (non-ESBL-producing *K. pneumoniae*). Tracheostomy, insertion of a Foley catheter, endotracheal tube, nasogastric tube and central venous catheter were found to be risk factors in the acquisition of *K. pneumoniae* with ESBLs by univariate analysis. Tracheostomy (odds ratio, 5.13; 95% CI, 1.24–21.1; $P = 0.023$) and ceftazidime use (odds ratio, 13.40; 95% CI, 1.21–148.85; $P = 0.035$) remained as risk factors by multivariate analysis with logistic regression. Other anti-pseudomonal agents should be used as empirical therapy to treat possible *Pseudomonas aeruginosa* infection in order to reduce ceftazidime use and thereby decrease the prevalence of ESBL producing strains of Enterobacteriaceae.

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Keywords: *K. pneumoniae*; ESBLs; risk factors; ceftazidime.

Introduction

The National Nosocomial Infections Surveillance System report of America from January 1992 to April 2000 showed the problem of antibiotic resistance has worsened in the past decade.[1] There are many mechanisms of antimicrobial resistance, but β-lactamase production is the most important mechanism for bacterial resistance to β-lactam antibiotics.[2] Since *Klebsiella pneumoniae* with extended-spectrum β-lactamase (ESBLs) was first isolated in Germany in 1983,[3] many outbreaks caused by multi-resistant strains have been reported all over the world.[4–7] With the general use of broad-spectrum β-lactam antibiotics, the ratio of ESBL-producing isolates among Enterobacteriaceae, of which *K. pneumoniae* is the most common, has become higher.[2,8–9]

ESBLs are plasmid-mediated enzymes that hydrolyze broad-spectrum β-lactams and are strongly inhibited by clavulanate. Most of them are derived from TEM or SHV, but some are OXA mutants or CTX-M types.[10–13] ESBL is not only transmitted by plasmids between bacteria, but is also

difficult to detect by routine antimicrobial suscepti-bility tests.[14–15] Thus clinical treatment failure occurs frequently.[16] If *K. pneumoniae* with ESBLs is suspected early by its clinical characteristics and risk factor analysis, it is possible to improve the outcome in ESBL-producing *K. pneumoniae* infection. In this study, we tried to find risk factors in the acquisition of ESBL-producing *K. pneumoniae*, and proposed some methods to reduce the prevalence of this highly resistant bacteria in hospitalized patients.

Patients and methods

Setting and subjects

This study was conducted at Hsin-Chu Hospital, a district teaching hospital with 679 ward beds and 38 intensive care unit beds located in northern Taiwan. From 1 May 2001 to 30 September 2001, all isolates identified by the microbiological laboratory as *K. pneumoniae* were collected. Bacterial suscepti-bility to all antimicrobial agents was determined according to criteria of the National Committee for Clinical Laboratory Standards by means of Kirby–Bauer disk diffusion method. *K. pneumoniae* for which the inhibition zones of ceftriaxone ≤ 25 mm or ceftazidime ≤ 22 mm were suspected of producing ESBL. These isolates were subjected to cefotaxime (30 µg)–cefotaxime/clavulanate (30/10 µg) and cefta-zidime (30 µg)–ceftazidime/clavulanate (30/10 µg) disk testing. Clavulanate enhancement of the dia-meter of the inhibition zone around either the oxyimino cephalosporin disk by at least 5 mm was regarded as presumptive evidence for the pre-sence of ESBL.[17–19] The reference strains were *Escherichia coli* ATCC 25922 and *K. pneumoniae* ATCC 700603.

Clinical data

A case was defined as a patient with ESBL-producing *K. pneumoniae*. If *K. pneumoniae* with ESBLs in the same patient was isolated on many occasions, only the first episode was reviewed. Every case patient was matched in a 1:2 ratio with controls. Both case and control had the same specimen source and the closest date of isolation. If several controls were available for matching with a case, one with similar demographic data was chosen. The controls were those who acquired non-ESBL-producing *K. pneumoniae* during the same period. Recorded data of all the cases and controls included sex, age, co-morbid conditions, source site of specimen and date of collection, date of admission, antimicrobial therapy, management and surgery during hospitalization, laboratory data and clinical outcome.

Co-morbid conditions, which were considered as possible risk factors, included diabetes mellitus, uraemia, cirrhosis, malignancy, major trauma, cere-brovascular accident, shock, burns, chemotherapy and radiotherapy within one month before the spe-cimen collection. Specimen sources were categorized as blood, urine, sputum, pus, and others. Interven-tions that were possible risk factors were tracheost-omy, haemodialysis, endoscopy, surgery, total parenteral nutrition and insertion of an arterial line, Foley catheter, chest tube, central venous catheter, nasogastric tube, and endotracheal tube. Laboratory data included white blood cell count and creatinine level nearest the date of specimen collection. All antimicrobial therapy that was admi-nistered within the 30 days before specimen collec-tion was recorded.

Definition

All *K. pneumoniae* isolated from enrolled cases and controls were divided into three groups. They were isolates of colonization, isolates causing community-acquired infection and isolates causing hospital-acquired infection. If *K. pneumoniae* was present without producing any clinical symptoms, it was classified as an isolate of colonization. Nosocomial infection was determined by the CDC definition of nosocomial infection issued in 1988.[20] All infections other than hospital-acquired were considered community-acquired. Clinical outcomes were clas-sified as recovery or death. If the patient died within 30 days after the date of specimen collection, the death was thought to be related to this episode of infection. However all deaths of patients with colo-nization episodes were regarded as irrelevant.

Statistical analysis

All statistics were performed by software SPSS 8.0. Contingency table analysis was done by χ^2 test or two-tailed Fisher's exact test as appropriate. Con-tinuous or interval variable analysis was completed by *t*-test or Mann–Whitney test. Multivariate anal-ysis was applied to all the key variables, which were significantly associated with the outcome in the univariate analysis, by using a logistic regression

model to identify the risk factors in the acquisition of ESBL-producing *K. pneumoniae*. A *P*-value < 0.05 was considered statistically significant.

Results

During the study period, 422 isolates of *K. pneumonias* were collected. The infection control team of Hsin-Chu Hospital did not detect any outbreak due to *K. pneumoniae*. Six of them came from one patient. Three patients had four isolates, six patients had three isolates, and 26 patients had two isolates each. The other isolates came from different patients. Fifty-nine isolates were ESBL-producing. The prevalence was 14% (59/422). There were 43 cases and 86 controls. Of the isolates from the cases 90.7% (39/43) and 97.7% (42/43) were ceftazidime-resistant and ceftriaxone-resistant, respectively, while only 3.5% (3/86) of the isolates from the controls were ceftazidime-resistant and 4.7% (4/86) were ceftriaxone resistant. The specimen sources in the case patients were as follows: four isolates from blood, 12 isolates from urine, 17 isolates from sputum, three isolates from pus, two isolates from a central venous catheter tip, three isolates from pleural effusion and two isolates from bronchial washing. All controls were matched in a 1:2 ratio. But no isolates from pleural effusion could be matched with a control; three isolates from sputum were used instead. Of the 43 case patients, one was colonized by *K. pneumoniae* with ESBLs, 19 patients had nosocomial infection and 23 had community-acquired infection. Among the controls,

four were colonized by non-*K. pneumoniae* with ESBLs, 12 had hospital-acquired infection and 70 had community-acquired infection.

Patient data are presented in Table I. Case patients were significantly older than controls ($P = 0.024$). They also had higher white cell counts ($P = 0.008$) and longer hospitalization durations ($P < 0.001$). More case patients than controls were admitted to intensive care units ($P = 0.001$) or regarded as having hospital-acquired infections ($P < 0.001$). The interval between the date of admission and specimen collection was longer in case patients ($P < 0.001$), and was longer than two weeks in 53.5% (23/43). More control patients were not admitted during the course of the study period ($P = 0.020$). No statistical significance was observed in terms of co-morbid conditions between case and control patients (Table II). Risk factors found to be significantly associated with the acquisition of ESBL-producing *K. pneumoniae* on univariate analysis were tracheostomy ($P < 0.001$), insertion of a Foley catheter ($P < 0.001$), endotracheal tube ($P = 0.004$), central venous catheter ($P < 0.001$), and nasogastric tube ($P < 0.001$) (Table III). Cases had a high proportion of first-generation cephalosporins ($P = 0.031$), second-generation cephalosporins ($P = 0.045$), ceftazidime ($P < 0.001$) and aminoglycosides ($P = 0.001$) use (Table IV). Although cases had higher mortality than controls (12/43, 27.9% vs. 18/86, 20.9%), this was not statistically significant. Multivariate analysis was applied to all key variables by a logistic regression model to identify risk factors significantly associated with acquisition

Table I *Demographic data of the patients*

	Cases ($N = 43$) (range) [%]	Controls ($N = 86$) (range) [%]	Odds ratio	*P*-value
Age (years)	71.77 (22–88)	65.4 (1–99)	—	0.024 †
Female	17 [39.5]	39 [45.3]	0.79	0.530 *
Interval between date of specimen collection and admission day	16.6 (−1–77) §	6.1 (−3–77) §	—	<0.001 †
Not admitted	1 [2.3]	14 [16.3]	0.12	0.020 ‡
Admitted to ICU	30 [69.8]	33 [38.4]	3.71	0.001 *
Lab data				
WBC	13596 (2180–33380)	10812 (15–29660)	—	0.008 †
Creatinine	1.8 (0.6–9.2)	1.5 (0.6–5.5)	—	0.385 †
Nosocomial infection	19 [44.2]	12 [14.0]	4.88	<0.001 *
Hospitalization (days)	45.5 (0–143)	18.1 (0–82)	—	<0.001 †
Death	12 [27.9]	16 [18.6]	1.69	0.227 *

* Chi-square test.
† Mann–Whitney test.
‡ Fisher's exact test.
§ Minus means the specimens were collected before admission.

Table II *Co-morbid conditions of the patients*

	Cases (N = 43) (%)	Controls (N = 86) (%)	Odds ratio	P-value
DM	16 (37.2)	26 (30.2)	1.37	0.425*
Uraemia	3 (7.0)	2 (2.3)	3.15	0.332†
Liver cirrhosis	5 (11.6)	3 (3.5)	3.64	0.116†
Malignancy	1 (2.3)	10 (11.6)	0.18	0.099†
Trauma	1 (2.3)	1 (1.2)	2.02	1.000†
CVA	17 (39.5)	22 (25.6)	1.90	0.104*
Shock	6 (14.0)	15 (17.4)	0.77	0.613*
Burn	0 (0)	0 (0)	—	—
Chemotherapy	0 (0)	1 (1.2)	—	—
Radiotherapy	0 (0)	0 (0)	—	—

DM, diabetes mellitus; CVA, cerebrovascular accident.
*Chi-square test.
†Fisher's exact test.

Table III *Interventions during hospitalization*

	Cases (N = 43) (%)	Controls (N = 86) (%)	Odds ratio	P-value
Tracheostomy	14 (32.6)	6 (7.0)	6.44	<0.001*
Arterial catheter	1 (2.3)	1 (1.2)	2.03	1.000†
Foley catheter	37 (86.0)	48 (55.8)	4.88	<0.001*
Chest tube	3 (7.0)	3 (3.5)	2.08	0.400†
Endotracheal tube	25 (58.1)	27 (31.4)	3.03	0.004*
Haemodialysis	4 (9.3)	2 (2.3)	4.31	0.095†
Central venous catheter	26 (60.5)	24 (27.9)	3.95	<0.001*
Nasogastric tube	36 (83.7)	38 (44.2)	6.50	<0.001*
TPN	3 (7.0)	4 (4.7)	1.54	0.685†
Endoscopy	12 (27.9)	14 (16.3)	1.99	0.121*
Surgery	11 (25.6)	12 (14.0)	2.12	0.104*

*Chi-square test.
†Fisher's exact test.
TPN, total parenteral nutrition.

Table IV *Antibiotic use within 30 days before specimen collection*

	Cases (N = 43) (%)	Controls (N = 86) (%)	Odds ratio	P-value
First-generation cephalosporins	23 (53.5)	29 (33.7)	2.26	0.031*
Second-generation cephalosporins	8 (18.6)	6 (7.0)	3.05	0.045*
Ceftazidime	13 (30.2)	1 (1.2)	36.83	<0.001†
Other third-generation cephalosporins	2 (4.7)	3 (3.5)	1.35	1.000†
Aminoglycosides	26 (60.5)	26 (30.2)	3.53	0.001*
Quinolones	0	0	—	—
Penicillin group	9 (20.9)	13 (15.1)	1.49	0.408*

*Chi-square test.
†Fisher's exact test.

of *K. pneumoniae* with ESBLs. Only tracheostomy (odds ratio, 5.13; 95% CI, 1.24–21.1; $P = 0.023$) and ceftazidime use (odds ratio, 13.40; 95% CI, 1.21–148.85; $P = 0.035$) remained as risk factors.

Discussion

Colonization by *K. pneumoniae* is often a pre-requisite of infection.[6] Brun-Buisson *et al.*[21] reported that 64 of 210 patients (30.5%) acquired one or more hospital-acquired infections after colonization with multi-resistant Enterobacteriaceae during a study of 18 weeks in the medical intensive care unit. Their study concluded that intestinal decontamination could help control an outbreak of intestinal colonization and infection with multi-resistant Gram-negative bacilli.[21] However, while discussing the risk factors of cases with multi-resistant *K. pneumoniae*, most studies have excluded those with colonization.[22–24] Lucet *et al.*[6] thought risk factors for colonization differed from those for infection. In order to find the risk factors associated with the acquisition of *K. pneumoniae* with ESBLs, this study included all the *K. pneumoniae* isolates in Hsin-Chu Hospital during the five-month study period.

Any ESBL producer should be counted as ceftriaxone- or ceftazidime-resistant, irrespective of the disc results. In this study, four isolates of *K. pneumoniae* with ESBLs were judged as sensitive to ceftazidime and one isolate sensitive to ceftriaxone at NCCLS breakpoints. Reports such as these can mislead physicians who then choose inappropriate antibiotics to treat ESBL-producing *K. pneumoniae* infections. In fact, only few therapeutic choices for ESBL-producing *K. pneumoniae* infections are available. Carbapenem appears to be the drug of choice for serious infections due to *K. pneumoniae* with ESBLs. Other alternatives for treatment may have limitations. In a study of antibiotic resistance of *Klebsiella* spp. with ESBLs in Europe, 30% of putative ESBL producers were resistant to piperacillin/tazobactam.[25] Cephalomycins are also considered as therapy for ESBL-producing *K. pneumoniae* infections, but emergence of resistant isolates in patients receiving these agents may limit their use.[26] The incidence of *K. pneumoniae* with ESBLs resistant to quinolones is increasing, so this class of antibiotics is not recommended as a therapeutic choice.[27]

National Nosocomial Infections Surveillance of America from 1987 to 1991 revealed that ceftazidime-resistant *K. pneumoniae* increased from

1.5% (1987–1989) to 3.6% (1990–1991).[28] The percentage was even higher in intensive care units. Increases in rates of resistance to ceftazidime among isolates of *K. pneumoniae* (from 3.66% to 14.4%) were noted from 1990 to 1993.[29] In Taiwan, the percentage of *K. pneumoniae* with ESBLs ranged from 8.5% to 30.0% among hospitals in recent reports.[30–32] Our prevalence of 14% approached those of most of the institutions in this area.

Co-morbid conditions of the patients were not related to the acquisition of *K. pneumoniae* with ESBLs in this study. One study showed the patients with ESBL-producing *K. pneumoniae* infection had higher clinical severity scores at admission.[33] In this study, the case patients also had higher white blood cell counts.

The process of colonization or infection by *K. pneumoniae* with ESBLs often begins following contact with colonized patients, staff or contaminated objects. Then antibiotics decrease colonization resistance by reducing the normal flora whereas invasive manipulation may allow direct transmission of pathogens.[33–34] Previous studies suggested that Foley catheters,[4,6,22,33–34] central venous catheters,[22,34] arterial catheters,[6,33] endotracheal tubes,[35] emergency abdominal surgery,[4] respirators,[4,33] and total parenteral nutrition[33] could be related to colonization or infection with ESBL-producing Enterobacteriaceae. This study found that tracheostomy, insertion of a Foley catheter, endotracheal tube, nasogastric tube and central venous catheter were risk factors in the acquisition of *K. pneumoniae* with ESBLs by univariate analysis.

In Taiwan, physicians face many limitations in the use of broad-spectrum antibiotics because of constrictive healthcare insurance budgets. Therefore, although as many as 69.8% and 38.4% of case and control patients had been admitted to intensive care units in this study respectively, most received first-generation cephalosporins and gentamicin for infections as empirical antibiotics. If the clinical condition deteriorated, physicians often then used ceftazidime as empirical therapy for fear of *Pseudomonas aeruginosa* infection. It is recognized that the use of ceftazidime is related to an increase in ESBL-producing *K. pneumoniae* infection. Lautenbach *et al.*[34] reported that total exposure to antimicrobial agents was the only independent predictor of infection with ESBL-producing *E. coli* and *K. pneumoniae*. This study showed case patients had a high probability of receiving first- and second-generation cephalosporins, ceftazidime and aminoglycosides. In the four categories of antibiotics, the use of ceftazidime was still a significant risk factor by logistic regression multivariate analysis.

Pena *et al.*[7] reported a significant role in the rigorous restriction of oxyimino-β-lactam use in the management and successful control of a large nosocomial ESBL-producing *K. pneumoniae* outbreak. Therefore, if *P. aeruginosa* infection is suspected clinically, other groups of anti-pseudomonas agents should be used as empirical therapy to treat *P. aeruginosa* infection and reduce the total amount of ceftazidime use to decrease the prevalence of *K. pneumoniae* with ESBLs.

Patients with ESBL-producing *K. pneumoniae* have longer durations of hospitalization,[22] this study had the same conclusion. Fifty-three percent of the specimens of case patients were collected two weeks or more after admission. This meant that the longer the patients were hospitalized, the more likely they were to acquire *K. pneumoniae* with ESBLs, perhaps because they received more invasive interventions and antibiotics. But if treated adequately, both groups had similar outcomes.[24]

One limitation of this study was incomplete records of antibiotic use before admission. It was uncertain that whether antibiotic use 30 days before specimen collection represented true selection pressure. Besides, this study was done in a district hospital, where no strain typing was done for the isolates due to lack of facility. A large-scale study is needed for definite conclusions.

Risk factors in the acquisition of *K. pneumoniae* with ESBLs include tracheostomy and ceftazidime use. By analysing relevant data and clinical characteristics, physicians should realize when multi-resistant micro-organisms can affect this group of patients. In conclusion, we encourage reasonable and judicious use of ceftazidime and early removal of unnecessary interventional apparatus to decrease the prevalence of *K. pneumoniae* with ESBLs.

Acknowledgements

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