Journal of Microbiology, Immunology and Infection (2018) 51, 723–731

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

Original Article

Extended-spectrum β-lactamase-producing *Escherichia coli* bacteremia: Comparison of pediatric and adult populations

Wan-Lin Tsai [a], Chih-Hsin Hung [b], Hui-An Chen [a,c], Jiun-Ling Wang [d], I-Fei Huang [a,c], Yee-Hsuan Chiou [a,c,e], Yao-Shen Chen [c,f], Susan Shin-Jung Lee [c,f], Wan-Yu Hung [b], Ming-Fang Cheng [a,c,e,*]

[a] *Department of Pediatrics, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, ROC*
[b] *Department of Chemical Engineering, Institute of Biotechnology and Chemical Engineering, I-Shou University, Kaohsiung, Taiwan, ROC*
[c] *School of Medicine, National Yang-Ming University, Taipei, Taiwan, ROC*
[d] *Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan, ROC*
[e] *Fooyin University, Kaohsiung, Taiwan, ROC*
[f] *Department of Internal Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, ROC*

Received 2 April 2017; received in revised form 5 July 2017; accepted 17 August 2017
Available online 31 August 2017

KEYWORDS
Adult;
Bacteremia;
Children;
E. coli;
Extended-spectrum β-lactamase

Abstract *Background/Purpose:* The prevalence of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* is increasing worldwide. This study investigated the clinical features and bacteriology of pediatric patients with ESBL-producing *E. coli* bacteremia and compared their characteristics with those of adult patients.
Methods: Clinical and laboratory data from all of the 41 patients aged ≤18 years diagnosed with *E. coli* bacteremia were collected over 5 years. Patients aged >18 years diagnosed with *E. coli* bacteremia, matched 1:1 for calendar time, were enrolled as the adult group. All *E. coli* isolates were tested for their blaCTX-M group and sequence type 131 (ST131). A novel seven-single nucleotide polymorphism-based clonotyping test was applied to detect the septatypes of each isolate.
Results: In the adult group, patients with ESBL-producing *E. coli* bacteremia had more previous hospitalizations and antimicrobial agent use than did those with non-ESBL-producing *E. coli* bacteremia, but these differences were not found in pediatric group. In the pediatric group, the proportion of isolates producing CTX-M group 9 was higher than that in the adult group (85.7% vs. 42.9%; $p < 0.05$). Among both groups, there were more *E. coli* ST131 in ESBL isolates

* Corresponding author. Department of Pediatrics, Veterans General Hospital-Kaohsiung, 386, Ta-Chung 1st. Rd., 813 Kaohsiung, Taiwan, ROC. Fax: +886 7 3468207.
E-mail address: mfcheng@vghks.gov.tw (M.-F. Cheng).

http://dx.doi.org/10.1016/j.jmii.2017.08.005

in than there were non-ESBL isolates. The distribution of septatypes was more homogenous in ESBL-producing *E. coli* among the pediatric patients than among the adult patients.
Conclusion: ST131 was the major clone causing *E. coli* bacteremia in both pediatric and adult populations. The pediatric population demonstrated a higher number of isolates producing CTX-M group 9 with more homogenous septatypes compared with the adult population.

Introduction

Since 2000, multidrug-resistant *Escherichia coli* that produces CTX-M enzymes has emerged globally as a critical pathogen. It causes both community- and hospital-onset infections, and is described as "the CTX-M pandemic."[1] These enzymes are synthesized by the Enterobacteriaceae family; in particular, extended-spectrum β-lactamase (ESBL)-producing *E. coli* that produces CTX-M-15, described as sero-group O25b-sequence type (ST) 131, was found in Europe, the Americas, Asia and the Middle East.[2] The *E. coli* O25b-ST131, which carries a broad range of virulence and resistance genes on transferable plasmids, has disseminated globally.[2–5] In addition, the number of asymptomatic healthy carriers without prior exposure to antimicrobial agents has increased.[6] Studies have identified the clinical features, demographic data, risk factors, and microbiology of variable ESBL-producing *E. coli* infections in adults.[7–10] However, information regarding *E. coli* bacteremia in children remains limited thus far. Moreover, as per our review of the relevant literature, no study has compared the children—adult disparities in *E. coli* bacteremia. In response, this study assessed the clinical features, demographic data, possible risk factors, and bacteriology of pediatric patients with ESBL-producing *E. coli* bacteremia and compared the pediatric and adult patient populations.

Methods

This study was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital (VGHKS; VGHKS15-CT9-12). From 2010 to 2014, all patients who were aged ≤18 years and diagnosed with either ESBL-producing or non-ESBL-producing *E. coli* bacteremia at VGHKS (a referral center located in southern Taiwan providing primary and tertiary medical care) were enrolled as the pediatric group. We also recruited an adult group of >18-year-old patients with ESBL-producing and non-ESBL-producing *E. coli* bacteremia, who were calendar year-month-, and number-matched with the pediatric group.

All 82 patients were analyzed using a structured recording form that focused on the clinical course of the infection according to information offered by primary care physicians and medical records. The diagnosis of the primary infection focus of bacteremia was based on clinical, microbiological, and radiological examination findings. Bacteremia was considered primary bacteremia if no infection focus could be established.

According to procedures described by Doumith et al.,[11] multiplex polymerase chain reaction (PCR) was used to define the four sequence types, namely ST131, ST95, ST73, and ST69, for all *E. coli* isolates. We added eight primers for four ST-specific regions into the PCR tubes to amplify four size patterns: 310, 200, 490, and 104 bp for ST131, ST95, ST73, and ST69, respectively. In addition, novel seven-single nucleotide polymorphisms (7-SNPs) for *fumC* and *fimH* were used for 7-SNP-based *E. coli* clonotyping. The results of the eight multiplex PCRs for *fumC* and *fimH* were divided into three groups: group 1 (comprising *fumC-63*, *fumC-248*, and *fumC-380*), group 2 (comprising *fimH-108*, *fimH-162*, and *fimH-233*), and group 3 (comprising only *fimH-483*). Notably, 7-SNP types and their corresponding clonotypes can help determine gene diversity.[12]

Phylogenetic groups A, B1, B2, and D were defined by amplifying the *chuA*, *yjaA*, and *TspE4C2* gene patterns of each bacterial strain.[13] Multiplex PCR was used to distinguish the blaCTX-M groups 1, 2, and 9.[14,15] Specific PCR was also performed to identify the common group 1 variants CTX-M-3 and CTX-M-15 and the group 9 variant CTX-M-14.[16,17]

All statistical analyses were performed on Stata/SE 12.1 for Windows (StataCorp., College Station, TX, USA). Clinical and laboratory data from patients were compared using the Wilcoxon rank sum test; these are expressed as medians and interquartile ranges. Categorical variables are presented herein as the percentage of each subgroup of patients, compared using the chi-squared test or Fisher exact test. All statistical analyses were two-sided, with significance set at $p < 0.05$.

Results

During the 5-year study period, a total of 41 pediatric patients with *E. coli* bacteremia were enrolled in the pediatric group: 14 (34.1%) blood samples showed ESBL-producing *E. coli*, and the remaining 27 (65.9%) showed non-ESBL-producing *E. coli*. For comparison, we enrolled 14 ESBL-producing *E. coli* isolates and 27 non-ESBL-producing *E. coli* isolates from adult patients with bacteremia, matched 1:1 for calendar time with the pediatric group. The demographic data, clinical features, health-associated risk factors, and outcomes of the pediatric and adult patients are summarized in Table 1. Urinary tract infection (UTI), particularly non-Foley catheter-related UTI, was the most common cause of secondary bacteremia in both the pediatric and adult groups. The underlying diseases, healthcare-associated risk factors, laboratory data, and

Table 1 Clinical characteristics of pediatric and adult patients with ESBL-producing and non-ESBL-producing *E. coli* bacteremia.

Characteristics	No. (%) of pediatric patients		*p* Value	No. (%) of adult patients		*p* Value
	ESBL-producing *E. coli* ($n = 14$)	Non-ESBL-producing *E. coli* ($n = 27$)		ESBL-producing *E. coli* ($n = 14$)	Non-ESBL-producing *E. coli* ($n = 27$)	
Median age (days/years) (IQR)	9.5 (0—93)	116 (8—846)	0.046	67.3 (60.1—76.6)	66.2 (53.4—78.0)	0.441
Newborn (<28 day-old)	8 (57.1)	8 (29.6)	0.087			
Prematurity	5 (35.7)	4 (14.8)	0.231			
Males	10 (71.4)	12 (44.4)	0.100	8 (57.1)	15 (55.6)	0.923
Fever days (IQR)	1.5 (1—3)	2 (1—3)	0.955	2 (0—4)	2 (1—2)	0.466
Hospitalization days (IQR)	15.5 (12—60)	12 (6—20)	0.182	16.5 (11—25)	13 (8—17)	0.265
Initial proper antimicrobials	9 (64.3)	23 (85.2)	0.231	5 (35.7)	26 (96.3)	<0.001
Underlying diseases						
Cardiovascular disease	3 (21.4)	7 (25.9)	1.000	7 (50.0)	12 (44.4)	0.735
Chronic hepatitis	0 (0.0)	1 (3.7)	1.000	2 (14.3)	5 (18.5)	1.000
Malignancy	0 (0.0)	2 (7.4)	0.539	3 (21.4)	9 (33.3)	0.494
Vesicoureteral reflux	3 (21.4)	1 (3.7)	0.107			
Diabetes mellitus				6 (42.9)	13 (48.2)	0.747
ESRD				5 (35.7)	1 (3.7)	0.013
Healthcare-associated risk						
Community onset	7 (50.0)	16 (59.3)	0.571	8 (57.1)	20 (74.1)	0.307
Hospitalization in prior 3 months	1 (7.1)	4 (14.8)	0.645	8 (57.1)	8 (29.6)	0.087
Antimicrobials exposure in prior 3 months	1 (7.1)	3 (11.1)	1.000	7 (50.0)	3 (11.1)	0.017
ETT + MV	3 (21.4)	5 (18.5)	1.000			
Nasogastric tube use	5 (35.7)	6 (22.2)	0.463	6 (42.9)	1 (3.7)	0.004
Central line use	6 (42.9)	7 (25.9)	0.307	1 (7.1)	1 (3.7)	1.000
Foley catheter use	1 (7.1)	0 (0.0)	0.341	4 (28.6)	2 (7.4)	0.157
Primary bacteremia	0 (0.0)	6 (22.2)	0.079	3 (21.4)	5 (18.5)	1.000
Infection syndrome	14 (100.0)	21 (77.8)	0.079	11 (78.6)	22 (81.5)	1.000
UTI, catheter-related	0 (0.0)	1 (3.7)	1.000	4 (28.6)	2 (7.4)	0.157
UTI, non-catheter related	6 (42.9)	11 (40.7)	0.896	5 (35.7)	14 (51.9)	0.326
Intraabdominal infection	2 (14.3)	1 (3.7)	0.265	2 (14.3)	5 (18.5)	1.000
Laboratory data						
Bandemia (>10%)	4 (28.6)	5 (18.5)	0.692	2 (14.3)	5 (18.5)	1.000
Thrombocytopenia (<10k)	2 (14.3)	3 (11.1)	1.000	6 (42.9)	5 (18.5)	0.140
CRP (median, mg/dL) (IQR)	5.6 (1.8—8.5)	4.2 (1.8—9.7)	0.826	7.9 (6.1—17.2)	7.5 (3.1—23.0)	0.687
CRP (>5 mg/dL)	8 (57.1)	12 (44.4)	0.440	11 (91.7)	16 (66.7)	0.219
Shock	2 (14.3)	3 (11.1)	1.000	5 (35.7)	2 (7.4)	0.035
Mortality	3 (21.4)	4 (14.8)	0.673	3 (21.4)	1 (3.7)	0.107

ESBL, extended-spectrum β-lactamase; IQR, interquartile range; ESRD, end-stage renal disease; ETT, endotracheal tube; MV, mechanical ventilation; UTI, urinary tract infection; CRP, C-reactive protein. For median age variables, the pediatric and adult patients are recorded as days and years, respectively. For CRP variable, the ESBL and non-ESBL adult groups have 2 and 3 missing values, respectively.

outcomes were similar between patients with ESBL-producing and non-ESBL-producing *E. coli* bacteremia in the pediatric group. However, the tendency toward ESBL-producing *E. coli* bacteremia was higher in adult patients with end-stage renal disease (35.7% vs. 3.7%, $p = 0.013$) or with other health-associated risk factors, including antimicrobial agent use in the previous 3 months (50.0% vs. 11.1%, $p = 0.017$) and nasogastric tube use (42.9% vs. 3.7%, $p = 0.004$) than adults patients with non-ESBL-producing *E. coli* bacteremia.

More adult patients with non-ESBL-producing *E. coli* bacteremia received proper initial antimicrobial treatment after hospitalization than did adult patients with ESBL-producing *E. coli* bacteremia (35.7% vs. 96.3%, $p < 0.001$). Moreover, adult patients with ESBL-producing *E. coli* bacteremia had a higher chance of developing shock than did adult patients with non-ESBL-producing *E. coli* bacteremia (35.7% vs. 7.4%, $p = 0.035$). Mortality rate between the patients with ESBL-producing *E. coli* and non-ESBL-producing *E. coli* bacteremia was not statistically significant in both pediatric and adult populations. Only one pediatric patient with non-ESBL-producing *E. coli* bacteremia in this study had *E. coli* bacteremia-attributed death. Adult patients with ESBL-producing *E. coli* bacteremia also

showed higher tendencies of cardiovascular diseases ($p = 0.022$), end-stage renal disease ($p = 0.041$), diabetes mellitus ($p = 0.016$), previous hospitalization ($p = 0.013$), and 3-month-prior antimicrobial agent use ($p = 0.033$) than did pediatric patients with ESBL-producing *E. coli* bacteremia (Table 2).

Among the 14 pediatric patients with ESBL-producing *E. coli* bacteremia, CTX-M group 9 genes were found in 12 (85.7%) isolates, of which 10 (83.3%) were confirmed to be CTX-M-14; 1 (7.1%) had CTX-M group 1 genes, which encoded CTX-M-3 and CTX-M-15 simultaneously; and one (7.1%) had no CTX-M gene. By contrast, of the 14 adult patients

Table 2 Clinical characteristics and resistance mechanisms of pediatric and adult patients with ESBL-producing *E. coli* bacteremia.

	No. (%) of patients		*p* Value
	Children ($n = 14$)	Adults ($n = 14$)	
Median age (years) (IQR)	0.026 (0–0.255)	67.3 (60.1–76.6)	<0.001
Males	10 (71.4)	8 (57.1)	0.695
Fever days (IQR)	1.5 (1–3)	2 (0–4)	0.605
Initial proper antimicrobials	9 (64.3)	5 (35.7)	0.131
Underlying diseases			
Cardiovascular disease	3 (21.4)	9 (64.3)	0.022
COPD	0 (0.0)	1 (7.1)	1.000
Chronic hepatitis	0 (0.0)	2 (14.3)	0.481
Vesicoureteral reflux	3 (21.4)	0 (0.0)	0.222
ESRD	0 (0.0)	5 (35.7)	0.041
Diabetes mellitus	0 (0.0)	6 (42.9)	0.016
Dementia	0 (0.0)	2 (14.3)	0.481
Malignancy	0 (0.0)	3 (21.4)	0.222
Health care-associated risk			
Community onset	7 (50.0)	8 (57.1)	0.705
Hospitalization to general ward in prior 3 months	1 (7.1)	8 (57.1)	0.013
Antimicrobials exposure in prior 3 months	1 (7.1)	7 (50.0)	0.033
Previous operation in prior 3 months	1 (7.1)	1 (7.1)	1.000
ETT + MV	3 (21.4)	0 (0.0)	0.222
Nasogastric tube use	5 (35.7)	6 (42.9)	0.699
Central line use	6 (42.9)	1 (7.1)	0.077
Foley catheter use	1 (7.1)	4 (28.6)	0.326
Primary bacteremia	0 (0.0)	3 (21.4)	0.222
Infection syndrome			
UTI, non-catheter related	6 (42.9)	5 (35.7)	0.699
UTI, catheter related	0 (0.0)	4 (28.6)	0.098
Intraabdominal infection	2 (14.3)	2 (14.3)	1.000
Laboratory data			
WBC (median, mg/dL) (IQR)	10,780 (3060–13,780)	10,555 (4460–13060)	0.927
Bandemia (>10%)	4 (28.6)	2 (14.3)	0.648
Thrombocytopenia (<10k)	2 (14.3)	6 (42.9)	0.209
CRP (median, mg/dL) (IQR)	5.6 (1.8–8.5)	7.9 (6.1–17.2)	0.090
CRP (>5 mg/dL)	8 (57.1)	11 (91.7)	0.081
Shock	2 (14.3)	5 (35.7)	0.385
Mortality	3 (21.4)	3 (21.4)	1.000
ESBL-resistance mechanism			
CTX-M group 9	12 (85.7)	6 (42.9)	0.018
CTX-M-14	10 (71.4)	6 (42.9)	0.127
CTX-M group 1	1 (7.1)	4 (28.6)	0.326
CTX-M-3	1 (7.1)	4 (28.6)	0.326
CTX-M-15	1 (7.1)	4 (28.6)	0.326
CTX-M group 1 + CTX-M group 9	0 (0.0)	1 (7.1)	1.000
CTX-M group 2 + CTX-M group 9	0 (0.0)	1 (7.1)	1.000
Unidentified	1 (7.1)	2 (14.3)	1.000

For CRP variable, the adult group has 2 missing values. ESBL, extended-spectrum β-lactamase; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; ETT, endotracheal tube; MV, mechanical ventilation; UTI, urinary tract infection; WBC, white blood cell; CRP, C-reactive protein.

with ESBL-producing *E. coli* bacteremia, six (42.9%) isolates were producers of CTX-M group 9, with all of them encoding CTX-M-14 ($p = 0.018$; Table 2). Among the 14 ESBL-producing *E. coli* isolates in the pediatric and adult groups, nine (64.3%) and 10 (71.4%) belonged to the ST131 clonal group, respectively. By contrast, among the 27 non-ESBL-producing *E. coli* isolates in the pediatric and adult groups, three (11.1%) and two (7.4%) belonged to the ST131 clonal group, respectively. In the pediatric group, all ESBL-producing *E. coli* belonging to the ST131 clonal group produced CTX-M-14. By contrast, in the adult group, β-lactamases produced by the ST131 clonal group were more diverse than that in the pediatric group: CTX-M-14 was the most prevalent, followed by CTX-M-15 and then CTX-M-3.

As shown in Table 3, all ESBL-producing *E. coli* isolates from the pediatric and adult patients were susceptible to amikacin, imipenem, and tigecycline. Other susceptible antimicrobial agents were cefoxitin (85.7% and 78.6% in the pediatric group and adult groups, respectively) and minocycline (85.7% and 78.6% in the pediatric and adult groups, respectively). In addition to cephalosporins, non-ESBL-producing *E. coli* isolates were more susceptible to gentamicin, piperacillin, and ampicillin/sulbactam than were ESBL-producing *E. coli* isolates in both the pediatric and adult groups. Notably, ESBL-producing *E. coli* isolates in the pediatric group were more susceptible to ciprofloxacin than were those in the adult group (50% and 14.3% in the pediatric and adult groups, respectively), although the *p* value did not reach statistical significance.

No significant differences in the antimicrobial susceptibility were noted between ESBL-producing *E. coli* ST131 and non-ST131 colonies in the pediatric and adult isolates. There was no yearly change of the prevalence of the multidrug-resistant *E. coli* colony, ST-131, in both pediatric and adult isolates during the study period. A majority of the ESBL-producing *E. coli* isolates were derived from the phylogenetic group B2 in both groups [pediatric, 85.7% ($n = 12$); adult, 64.3% ($n = 9$)]. The remaining two ESBL-producing *E. coli* isolates in the pediatric group belonged to groups A and B1. In the adult group, the second most common phylogenetic group of ESBL-producing *E. coli* was group D [28.6% ($n = 4$)]; for the remaining isolate, no definitive group was identified (Fig. 1).

The 7-SNP-based clonotyping revealed that SNP761 was the most dominant septatype in all patients with ESBL-producing *E. coli* bacteremia, comprising 78.6% and 42.9% of all isolates in the pediatric and adult patients, respectively. The distribution of the septatypes was more homogenous in ESBL-producing *E. coli* than in non-ESBL-producing *E. coli* (Fig. 2).

Discussion

This study compared the demographic data, clinical features, outcomes, antimicrobial susceptibility, and microbiology of ESBL-producing *E. coli* between pediatric and adult patients. Most of the patients in both groups had community-onset ESBL-producing *E. coli* bacteremia and no

Table 3 Nonsusceptibility rates and *E. coli* sequence type in pediatric and adult patients with *E. coli* bacteremia.

Antimicrobial agents	No. (%) of patients					
	Children			Adults		
	ESBL[a] ($n = 14$)	Non-ESBL ($n = 27$)	*p* Value	EBSL[a] ($n = 14$)	Non-ESBL ($n = 27$)	*p* Value
Amikacin	0 (0.0)	1 (3.7)	1.000	0 (0.0)	0 (0.0)	NA
Ceftazidime	14 (100.0)	2 (7.4)	<0.001	14 (100.0)	1 (3.7)	<0.001
Ciprofloxacin	7 (50.0)	7 (25.9)	0.170	12 (85.7)	4 (14.8)	<0.001
Ceftriaxone	14 (100.0)	2 (7.4)	<0.001	14 (100.0)	0 (0.0)	<0.001
Cefazolin	14 (100.0)	5 (18.5)	<0.001	14 (100.0)	5 (18.5)	<0.001
Cefepime	14 (100.0)	1 (3.7)	<0.001	14 (100.0)	0 (0.0)	<0.001
Cefoxitin	2 (14.3)	3 (11.1)	1.000	3 (21.4)	5 (18.5)	1.000
Gentamicin	10 (71.4)	5 (18.5)	0.001	10 (71.4)	8 (29.6)	0.011
Imipenem	0 (0.0)	1 (3.7)	1.000	0 (0.0)	0 (0.0)	NA
Minocycline	2 (14.3)	8 (29.6)	0.447	3 (21.4)	3 (11.1)	0.393
Piperacillin	14 (100.0)	16 (59.3)	0.007	14 (100.0)	16 (59.3)	0.007
Ampicillin/ Sulbactam	14 (100.0)	13 (48.2)	0.001	14 (100.0)	9 (33.3)	<0.001
TMP/SMZ	6 (42.9)	11 (40.7)	0.896	7 (50.0)	11 (40.7)	0.571
Tigecylcine	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Sequence type						
ST131	9 (64.3)	3 (11.1)	0.001	10 (71.4)	2 (7.4)	<0.001
ST95	0 (0.0)	3 (11.1)	0.539	0 (0.0)	0 (0.0)	NA
ST73	0 (0.0)	1 (3.7)	1.000	0 (0.0)	1 (3.7)	1.000
ST69	0 (0.0)	1 (3.7)	1.000	0 (0.0)	0 (0.0)	NA

NA, nonapplicable; TMP/SMZ, trimethoprim/sulfamethoxazole; ST, sequence type.
[a] No significant differences in the antimicrobial susceptibility between ESBL-producing *E. coli* in the pediatric and adult groups.

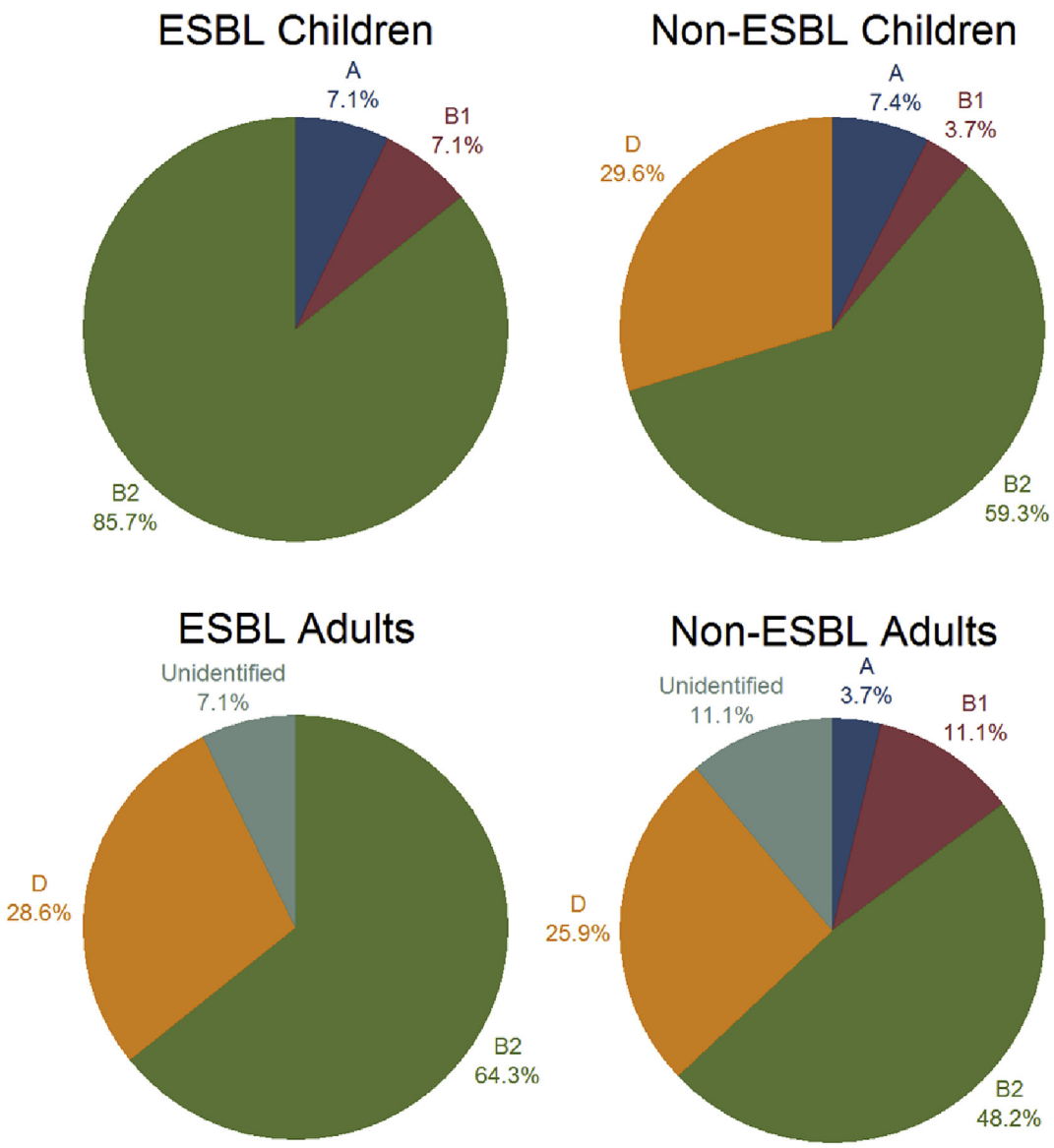

Figure 1. Phylogenetic groups of *E. coli* isolates in pediatric and adult patients with *E. coli* bacteremia. ESBL, extended-spectrum β-lactamase.

ESBL-producing *E. coli* outbreak was reported during the study period. Previous studies focusing on UTIs have revealed that children aged <1 year are more likely to have ESBL-producing *E. coli* infections than are older children.[18] By contrast, old age is a significant risk factor in adult populations that age ≥60 years was found to be an independent risk factor for ESBL-producing bacterial infection.[19]

Several studies conducted on children and adults have reported that having underlying renal or nonrenal diseases, previous UTI episodes, UTI prophylaxis, previous hospitalization, or antimicrobial agent use within the previous 3 months are risk factors for ESBL-producing *E. coli* infection.[8,20–24] In the present study, a majority of the pediatric patients were healthy and lacked apparent health-associated risk factors. However, underlying diseases, previous hospitalization, and antimicrobial agent use within the previous 3 months were risk factors for ESBL-producing *E. coli* bacteremia in the adult patients.

E. coli ST131 has been identified as a global pathogen causing various infection syndromes. In this study, most of the pediatric and adult patients were infected with ESBL-producing *E. coli* ST131. The risk factors for *E. coli* ST131 infection differ from the conventional ones for ESBL-producing *E. coli* infections[9]; *E. coli* ST131 has been recognized as a major pathogen causing community- and hospital-acquired infections worldwide.[2–5,25–28] Contact with either companion[29] or noncompanion[30] animals, contamination of food[31] or water sources, colonization of the human gut,[32] transmission through healthcare facilities,[33] and travel from countries with high prevalence of *E. coli* ST131[34,35] may explain the emergence of multidrug-resistant isolates.

In the present study, we detected *E. coli* ST131 colonies by using multiplex PCR and performing a novel 7-SNP-based clonotyping to obtain a total of 82 isolates. Among the pediatric patients, 64.3% ($n = 9$) and 11.1% ($n = 3$) had

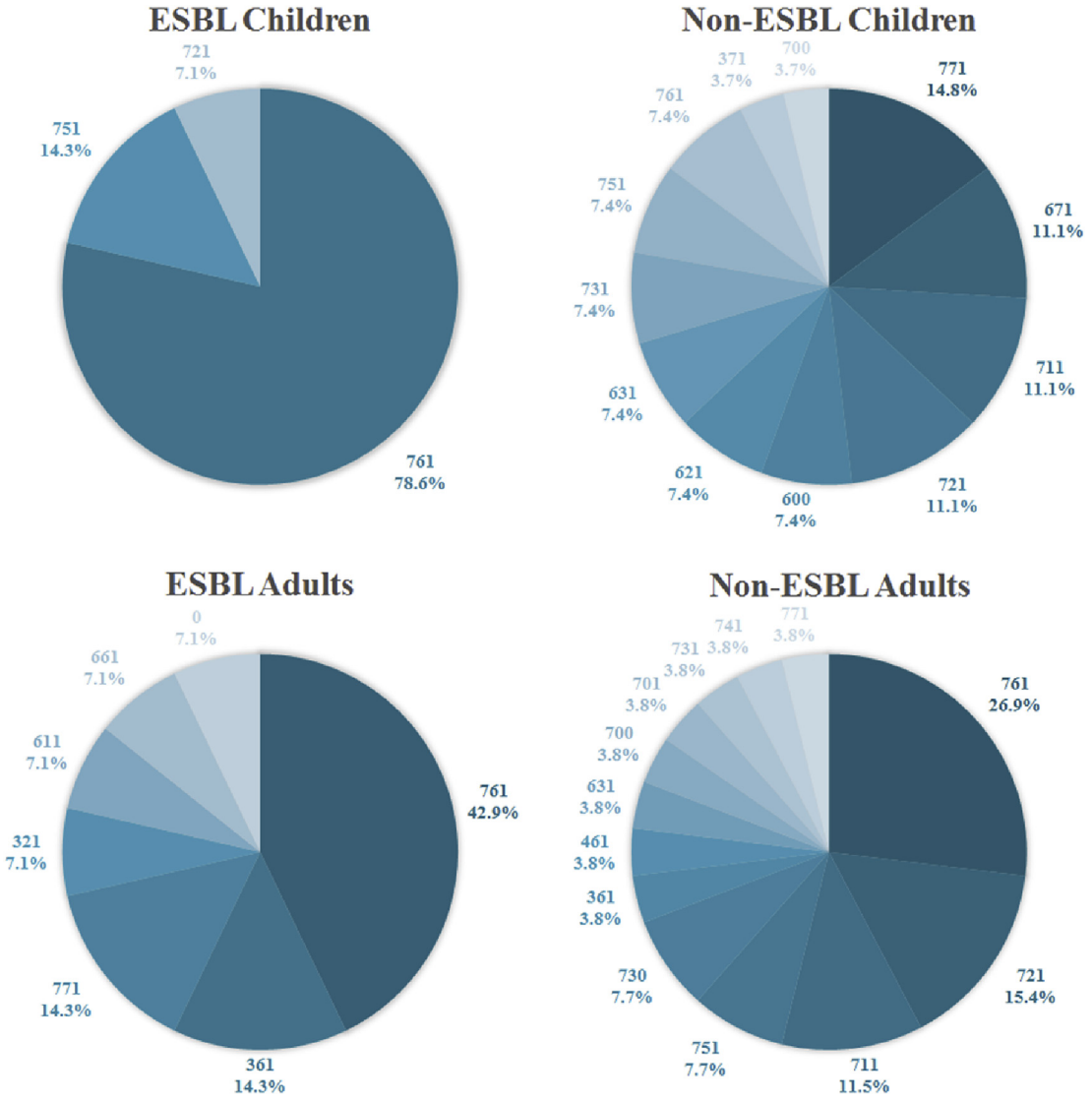

Figure 2. Comparison of diversity detected using 7-SNP typing of ESBL-producing and non-ESBL-producing *E. coli* isolates from pediatric and adult patients. ESBL, extended-spectrum β-lactamase; 7-SNP, seven-single nucleotide polymorphism.

bacteremia caused by ESBL-producing and non-ESBL-producing *E. coli* ST131, respectively ($p = 0.001$). Similarly, among the adult patients, *E. coli* ST131 colonies were isolated from 71.4% ($n = 10$) of the patients with ESBL-producing *E. coli* bacteremia, but only 7.4% ($n = 2$) of the patients with non-ESBL-producing *E. coli* bacteremia ($p < 0.001$). Furthermore, 88.9% ($n = 8$) of *E. coli* ST131 isolates were identified in the pediatric group, with ESBL-producing *E. coli* bacteremia observed in patients age <1 years; this corroborates a previous study that *E. coli* ST131 is a major pathogen in infants in pediatric UTI.[28] Moreover, *E. coli* ST131 was predominantly derived from the phylogenetic group B2, which often carries more virulence determinants than do other non-B2 phylogenetic groups, in both pediatric and adult populations; these results are similar to those of a study from the United States.[3]

Two previous longitudinal nationwide surveillance data showed that the prevalence of ESBL-producing *E. coli* increased from 4% in 2002–2004 increased to 10.7% in 2010–2012[36] and 19.5% of *E. coli* isolates from patients in intensive care units at 10 major teaching hospitals were ESBL-producing in 2007,[37] respectively. The two major β-lactamases, CTX-M-14 and CTX-M-15, are mainly synthesized by ESBL-producing *E. coli* in Taiwan, Canada,[38] Spain,[39] and New Zealand.[40] In the present study, a majority of the isolates from both the pediatric and adult groups produced CTX-M-14. As reported in previous studies in Taiwan,[9,28] the distribution of CTX-M-14 is higher in the pediatric group than in the adult group. Moreover, here, we observed that the β-lactamases produced by the *E. coli* ST131 clonal group in the adult population were more diverse than those in the pediatric group. Among Northeast Asian countries, a regional study in Japan revealed that the prevalence of CTX-M-14-producing *E. coli* ST131 increased from 2002 to 2010,[41] and a study in South Korea reported that CTX-M-14-producing *E. coli* ST131 is the second most prevalent ESBL-producing *E. coli*.[42]

In this study, all ESBL-producing *E. coli* isolates were susceptible to amikacin, imipenem, and tigecycline; they also had a high susceptibility rate for cefoxitin and minocycline. CTX-M-14-producing *E. coli* from the pediatric patients accounted for a higher proportion of ESBL-producing *E. coli* than those from the adult patients. Ciprofloxacin is not commonly used in the pediatric population. Moreover, CTX-M-14-producing *E. coli* are likely to be more susceptible to ciprofloxacin than are CTX-M-15-producing *E. coli*,[40] which may partially account for the higher non-susceptibility of ESBL-producing *E. coli* to ciprofloxacin in the adult group than of that in the pediatric group, though the *p* value did not reach statistical significance.

This study has some limitations. First, this was a single-center study in southern Taiwan comprising a small sample size; thus, the results of this study may not be applicable worldwide. In addition, adults generally tend to have more underlying diseases and exposure to multiple health-care-associated risk factors than do children. In this study, the largest clonal group, ST131, corresponds to different septatypes from those in a study in the United States[12]; this may result from the geographic diversity of ESBL-producing *E. coli* strains with variable virulence and resistance mechanisms. Unlike those in Canada,[38] New Zealand,[40] and South Korea,[42] ESBL-producing *E. coli* strains in Taiwan express CTX-M-14 more dominantly than they do CTX-M-15.

In conclusion, adults with ESBL-producing *E. coli* bacteremia were associated with more underlying diseases and health-care-associated risk factors than were pediatric patients with ESBL-producing *E. coli* bacteremia. ST131 was the major clone in both the adult and pediatric ESBL bacteremia patients. Moreover, CTX-M-14 was the most prevalent β-lactamase produced by *E. coli* in Taiwan, regardless of patient age, and accounted for a higher proportion of the ESBL-producing *E. coli* strains in the pediatric patients than in the adult patients. The prevalence of multidrug-resistant *E. coli* infections has increased in the recent years; in our series, most patients with ESBL-producing *E. coli* bacteremia were previously healthy with no apparent risk factors, particularly in the pediatric group. Future national surveillance studies focusing on environmental exposure, human carriage, household spread, and animal contact are warranted.

Acknowledgments

This study was supported by grants from the National Science Council, Executive Yuan, Taiwan (MOST 104-2314-B-075B-003-MY3) and Kaohsiung Veterans General Hospital in Taiwan (VGHKS 105-107).

References

1. Canton R, Coque TM. The CTX-M beta-lactamase pandemic. *Curr Opin Microbiol* 2006;**9**:466—75.
2. Rogers BA, Sidjabat HE, Paterson DL. *Escherichia coli* O25b-ST131: a pandemic, multiresistant, community-associated strain. *J Antimicrob Chemother* 2011;**66**:1—14.
3. Johnson JR, Johnston B, Clabots C, Kuskowski MA, Castanheira M. *Escherichia coli* sequence type ST131 as the major cause of serious multidrug-resistant *E. coli* infections in the United States. *Clin Infect Dis* 2010;**51**:286—94.
4. Peirano G, Pitout JD. Molecular epidemiology of *Escherichia coli* producing CTX-M beta-lactamases: the worldwide emergence of clone ST131 O25:H4. *Int J Antimicrob Agents* 2010;**35**:316—21.
5. Platell JL, Cobbold RN, Johnson JR, Heisig A, Heisig P, Clabots C, et al. Commonality among fluoroquinolone-resistant sequence type ST131 extraintestinal *Escherichia coli* isolates from humans and companion animals in Australia. *Antimicrob Agents Chemother* 2011;**55**:3782—7.
6. Spellberg B, Doi Y. The rise of fluoroquinolone-resistant *Escherichia coli* in the community: scarier than we thought. *J Infect Dis* 2015;**212**:1853—5.
7. Lin HC, Lai LA, Wu JY, Su YM, Chang SP, Hsueh YM. Risk factors for acquiring extended-spectrum beta-lactamase-producing Enterobacteriaceae in geriatric patients with multiple comorbidities in respiratory care wards. *Geriatr Gerontol Int* 2013;**13**:663—71.
8. Wu YH, Chen PL, Hung YP, Ko WC. Risk factors and clinical impact of levofloxacin or cefazolin nonsusceptibility or ESBL production among uropathogens in adults with community-onset urinary tract infections. *J Microbiol Immunol Infect* 2014;**47**:197—203.
9. Chung HC, Lai CH, Lin JN, Huang CK, Liang SH, Chen WF, et al. Bacteremia caused by extended-spectrum-beta-lactamase-producing *Escherichia coli* sequence type ST131 and non-ST131 clones: comparison of demographic data, clinical features, and mortality. *Antimicrob Agents Chemother* 2012;**56**:618—22.
10. Park SH, Choi SM, Chang YK, Lee DG, Cho SY, Lee HJ, et al. The efficacy of non-carbapenem antibiotics for the treatment of community-onset acute pyelonephritis due to extended-spectrum beta-lactamase-producing *Escherichia coli*. *J Antimicrob Chemother* 2014;**69**:2848—56.
11. Doumith M, Day M, Ciesielczuk H, Hope R, Underwood A, Reynolds R, et al. Rapid identification of major *Escherichia coli* sequence types causing urinary tract and bloodstream infections. *J Clin Microbiol* 2015;**53**:160—6.
12. Tchesnokova V, Avagyan H, Billig M, Chattopadhyay S, Aprikian P, Chan D, et al. A novel 7-single nucleotide polymorphism-based clonotyping test allows rapid prediction of antimicrobial susceptibility of extraintestinal *Escherichia coli* directly from urine specimens. *Open Forum Infect Dis* 2016;**3**:ofw002.
13. Clermont O, Bonacorsi S, Bingen E. Rapid and simple determination of the *Escherichia coli* phylogenetic group. *Appl Environ Microbiol* 2000;**66**:4555—8.
14. Pitout JD, Hossain A, Hanson ND. Phenotypic and molecular detection of CTX-M-beta-lactamases produced by *Escherichia coli* and *Klebsiella* spp. *J Clin Microbiol* 2004;**42**:5715—21.
15. Ensor VM, Livermore DM, Hawkey PM. A novel reverse-line hybridization assay for identifying genotypes of CTX-M-type extended-spectrum beta-lactamases. *J Antimicrob Chemother* 2007;**59**:387—95.
16. Chia JH, Chu C, Su LH, Chiu CH, Kuo AJ, Sun CF, et al. Development of a multiplex PCR and SHV melting-curve mutation detection system for detection of some SHV and CTX-M beta-lactamases of *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* in Taiwan. *J Clin Microbiol* 2005;**43**:4486—91.
17. Sidjabat HE, Paterson DL, Adams-Haduch JM, Ewan L, Pasculle AW, Muto CA, et al. Molecular epidemiology of CTX-M-producing *Escherichia coli* isolates at a tertiary medical center in western Pennsylvania. *Antimicrob Agents Chemother* 2009;**53**:4733—9.
18. Kizilca O, Siraneci R, Yilmaz A, Hatipoglu N, Ozturk E, Kiyak A, et al. Risk factors for community-acquired urinary tract

infection caused by ESBL-producing bacteria in children. *Pediatr Int* 2012;**54**:858—62.
19. Colodner R, Rock W, Chazan B, Keller N, Guy N, Sakran W, et al. Risk factors for the development of extended-spectrum beta-lactamase-producing bacteria in nonhospitalized patients. *Eur J Clin Microbiol Infect Dis* 2004;**23**:163—7.
20. Topaloglu R, Er I, Dogan BG, Bilginer Y, Ozaltin F, Besbas N, et al. Risk factors in community-acquired urinary tract infections caused by ESBL-producing bacteria in children. *Pediatr Nephrol* 2010;**25**:919—25.
21. Azap OK, Arslan H, Serefhanoglu K, Colakoglu S, Erdogan H, Timurkaynak F, et al. Risk factors for extended-spectrum beta-lactamase positivity in uropathogenic *Escherichia coli* isolated from community-acquired urinary tract infections. *Clin Microbiol Infect* 2010;**16**:147—51.
22. Rodríguez-Baño J, Alcalá JC, Cisneros JM, Grill F, Oliver A, Horcajada JP, et al. Community infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli*. *Arch Intern Med* 2008;**168**:1897—902.
23. Fan NC, Chen HH, Chen CL, Ou LS, Lin TY, Tsai MH, et al. Rise of community-onset urinary tract infection caused by extended-spectrum beta-lactamase-producing *Escherichia coli* in children. *J Microbiol Immunol Infect* 2014;**47**:399—405.
24. Moor CT, Roberts SA, Simmons G, Briggs S, Morris AJ, Smith J, et al. Extended-spectrum beta-lactamase (ESBL)-producing enterobacteria: factors associated with infection in the community setting, Auckland, New Zealand. *J Hosp Infect* 2008;**68**:355—62.
25. Lau SH, Kaufmann ME, Livermore DM, Woodford N, Willshaw GA, Cheasty T, et al. UK epidemic *Escherichia coli* strains A-E, with CTX-M-15 beta-lactamase, all belong to the international O25:H4-ST131 clone. *J Antimicrob Chemother* 2008;**62**:1241—4.
26. Nicolas-Chanoine MH, Blanco J, Leflon-Guibout V, Demarty R, Alonso MP, Canica MM, et al. Intercontinental emergence of *Escherichia coli* clone O25:H4-ST131 producing CTX-M-15. *J Antimicrob Chemother* 2008;**61**:273—81.
27. Lopez-Cerero L, Navarro MD, Bellido M, Martin-Pena A, Vinas L, Cisneros JM, et al. *Escherichia coli* belonging to the worldwide emerging epidemic clonal group O25b/ST131: risk factors and clinical implications. *J Antimicrob Chemother* 2014;**69**:809—14.
28. Cheng MF, Chen WL, Hung WY, Huang IF, Chiou YH, Chen YS, et al. Emergence of extended spectrum-beta-lactamase-producing *Escherichia coli* O25b-ST131: a major community-acquired uropathogen in infants. *Pediatr Infect Dis J* 2015;**34**:469—75.
29. Johnson JR, Miller S, Johnston B, Clabots C, Debroy C. Sharing of *Escherichia coli* sequence type ST131 and other multidrug-resistant and Urovirulent *E. coli* strains among dogs and cats within a household. *J Clin Microbiol* 2009;**47**:3721—5.
30. Peirano G, van Greune CH, Pitout JD. Characteristics of infections caused by extended-spectrum beta-lactamase-producing *Escherichia coli* from community hospitals in South Africa. *Diagn Microbiol Infect Dis* 2011;**69**:449—53.
31. Vincent C, Boerlin P, Daignault D, Dozois CM, Dutil L, Galanakis C, et al. Food reservoir for *Escherichia coli* causing urinary tract infections. *Emerg Infect Dis* 2010;**16**:88—95.
32. Leflon-Guibout V, Blanco J, Amaqdouf K, Mora A, Guize L, Nicolas-Chanoine MH. Absence of CTX-M enzymes but high prevalence of clones, including clone ST131, among fecal *Escherichia coli* isolates from healthy subjects living in the area of Paris, France. *J Clin Microbiol* 2008;**46**:3900—5.
33. Kim YA, Kim JJ, Kim H, Lee K. Community-onset extended-spectrum-beta-lactamase-producing *Escherichia coli* sequence type 131 at two Korean community hospitals: the spread of multidrug-resistant *E. coli* to the community via healthcare facilities. *Int J Infect Dis* 2016;**54**:39—42.
34. Pitout JD, Campbell L, Church DL, Gregson DB, Laupland KB. Molecular characteristics of travel-related extended-spectrum-beta-lactamase-producing *Escherichia coli* isolates from the Calgary Health Region. *Antimicrob Agents Chemother* 2009;**53**:2539—43.
35. Islam S. High rates of ESBL-producing *Escherichia coli* in young children who traveled recently to India. *Pediatr Infect Dis J* 2012;**31**:1103.
36. Wang JT, Chang SC, Chang FY, Fung CP, Chuang YC, Chen YS, et al. Antimicrobial non-susceptibility of *Escherichia coli* from outpatients and patients visiting emergency rooms in Taiwan. *PLoS ONE* 2015;**10**:e0144103.
37. Jean SS, Lee WS, Bai KJ, Lam C, Hsu CW, Yu KW, et al. Relationship between the distribution of cefepime minimum inhibitory concentrations and detection of extended-spectrum beta-lactamase production among clinically important Enterobacteriaceae isolates obtained from patients in intensive care units in Taiwan: results from the Surveillance of Multicenter Antimicrobial Resistance in Taiwan (SMART) in 2007. *J Microbiol Immunol Infect* 2015;**48**:85—91.
38. Peirano G, Richardson D, Nigrin J, McGeer A, Loo V, Toye B, et al. High prevalence of ST131 isolates producing CTX-M-15 and CTX-M-14 among extended-spectrum-beta-lactamase-producing *Escherichia coli* isolates from Canada. *Antimicrob Agents Chemother* 2010;**54**:1327—30.
39. Mora A, Blanco M, Lopez C, Mamani R, Blanco JE, Alonso MP, et al. Emergence of clonal groups O1:HNM-D-ST59, O15:H1-D-ST393, O20:H34/HNM-D-ST354, O25b:H4-B2-ST131 and ONT:H21,42-B1-ST101 among CTX-M-14-producing *Escherichia coli* clinical isolates in Galicia, northwest Spain. *Int J Antimicrob Agents* 2011;**37**:16—21.
40. Freeman JT, Williamson DA, Heffernan H, Smith M, Bower JE, Roberts SA. Comparative epidemiology of CTX-M-14 and CTX-M-15 producing *Escherichia coli*: association with distinct demographic groups in the community in New Zealand. *Eur J Clin Microbiol Infect Dis* 2012;**31**:2057—60.
41. Matsumura Y, Johnson JR, Yamamoto M, Nagao M, Tanaka M, Takakura S, et al. CTX-M-27- and CTX-M-14-producing, ciprofloxacin-resistant *Escherichia coli* of the H30 subclonal group within ST131 drive a Japanese regional ESBL epidemic. *J Antimicrob Chemother* 2015;**70**:1639—49.
42. Graham SE, Zhang L, Ali I, Cho YK, Ismail MD, Carlson HA, et al. Prevalence of CTX-M extended-spectrum beta-lactamases and sequence type 131 in Korean blood, urine, and rectal *Escherichia coli* isolates. *Infect Genet Evol* 2016;**41**:292—5.