AJIC brief report

Fluoroquinolone resistance in pediatric bloodstream infections because of *Escherichia coli* and *Klebsiella* species

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In pediatric bloodstream infections with fluoroquinolone (FQ)-resistant *Escherichia coli* and *Klebsielia* species, we noted an association between FQ resistance and extended-spectrum β-lactamase (ESBL) production (OR, 12; 95% CI: 2.28-83.8). A case control study revealed no significant risk factors (including prior antibiotic use) for FQ resistance among ESBL *E coli* and *Klebsiella* species (ESBL-EK). (Am J Infect Control 2008;36:70-3.)

Fluoroquinolones (FQs) are broad-spectrum antibiotics used widely in adults. Over the past decade, the prevalence of FQ-resistant *Enterobacteriaceae* has been increasing[1,2] and is independently associated with higher mortality in adults. FQ resistance in *Enterobacteriaceae* has been associated most consistently with prior FQ use.[3]

Because of joint toxicity seen in juvenile animals, ciprofloxacin was not approved initially for use in children. Recently, it was approved in children for inhalation anthrax or as a second-line agent for complicated urinary tract infections. To date, no study has investigated risk factors for FQ-resistant *Escherichia coli* or *Klebsiella* species in pediatric bloodstream infections (BSI). We examined the epidemiology of BSI with FQ-resistant *E coli* and *Klebsiella* species in children. We also studied mechanisms of FQ resistance among the isolates.

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METHODS

A case control study was conducted at the Children's Hospital of Philadelphia, a large, urban pediatric tertiary care center. Potential study patients were identified through the records of the clinical microbiology laboratory at the Children's Hospital of Philadelphia, which processes all specimens for the hospital. All patients with blood cultures positive for either *E coli* or *Klebsiella* species from May 1, 1999, to September 30, 2003, were eligible for inclusion. Only the first BSI for each patient was included for analysis. The minimum inhibitory concentrations were measured using the Microscan Gram-negative microtiter panel (Dade Behring, Deerfield, IL), and antibiotic susceptibilities were determined according to the Clinical Laboratory Standards Institute.

Because of an association between FQ resistance and extended-spectrum β-lactamase (ESBL) production, we defined cases as patients with BSI because of FQ-resistant ESBL-EK and controls as patients with BSI because of FQ-susceptible ESBL-EK. All eligible patients were included for comparison. Data on age, sex, race, hospital unit, inpatient antimicrobial therapy in the 30 days preceding infection, immunosuppressive medications, length of stay in the intensive care unit, underlying medical conditions, prior surgery, and presence of a

Table 1. Demographic and clinical characteristics, including prior inpatient antibiotic exposures of children with FQ-resistant and FQ-susceptible ESBL-EK BSI

Variable	FQ resistant*	FQ susceptible†	Odds ratio (95% CI)	*P* value
Age in year, mean (SD)	6.4 (8.38)	5.23 (6.26)		
Sex			0.6 (0.20-1.81)	.337
Male	3 (60%)	10 (33.3%)		
Infecting organism				
E coli	3 (60%)	5 (16.7%)		.01
Klebsiella species	1 (20%)	24 (80%)		
E coli and *Klebsiella*	1 (20%)	0 (0%)		
Hospitalized in prior 30 days	5 (100%)	23 (76.7%)	1.3 (1.07-1.59)	.559
Length of stay, median (IQR)‡	31 (NA)	25 (10-45)		
Malignancy	1 (20%)	11/29 (37.9%)	0.53 (0.086-3.23)	.635
Neutropenia§	1/3 (33%)	6/25 (24%)	1.39 (0.24-7.96)	1
Prior organ transplant	1 (20%)	10/29 (34.5%)	0.58 (0.09-3.59)	.65
Central venous catheter‖	3 (60%)	24 (80%)	0.75 (0.36-1.57)	.57
Mechanical ventilation¶	1 (20%)	9 (30%)	0.67 (0.11-4.18)	1
Total parenteral nutrition	1 (20%)	17/29 (59%)	0.34 (0.06-2.02)	.16
Immunosuppression in prior 30 days#	2 (40%)	17/28 (61%)	0.66 (0.22-2.01)	.63
Inpatient antibiotic exposure in prior 30 days				
Third-generation cephalosporins**	4 (80%)	15 (50%)	1.6 (0.91-2.82)	.35
Extended-spectrum penicillins††	1 (20%)	5 (16.7%)	1.2 (0.17-8.24)	1
Carbapenems‡‡	1 (20%)	2 (6.7%)	3 (0.33-27.23)	.38
Aminoglycosides§§	4 (80%)	21 (70%)	1.14 (0.70-1.88)	1
Antianaerobic agents‖‖	4 (80%)	21 (70%)	1.14 (0.70-1.88)	1
Fluoroquinolones	1 (20%)	1 (3.3%)	6 (0.44-81.20)	.27

*N=5, except where otherwise noted.
†N=30, except where otherwise noted.
‡Length of stay prior to BSI measured in days.
§Absolute neutrophil count less than 500 cells/mm^3.
‖Presence of central venous catheter at time of BSI.
¶Mechanical ventilatory support with endotracheal intubation at time of BSI.
#Received systemic corticosteroids for at least 2 weeks in the antecedent 30 days or received cyclosporine, tacrolimus, sirolimus, azathioprine, mycophenalate mofetil at any time.
**Includes cefotaxime, ceftriaxone, ceftazidime or cefepime.
††Includes ampicillin/sulbactam, ticarcillin, piperacillin, ticarcillin/clavulanate, piperacillin/tazobactam.
‡‡Includes imipenem/cilastin, meropenem.
§§Includes gentamicin, tobramycin, amikacin.
‖‖Includes ampicillin/sulbactam, ticarcillin/clavulanate, piperacillin/tazobactam, imipenem/cilastin, meropenem, metronidazole, clindamycin.

central venous catheter or a urinary catheter at the time of infection were abstracted from the medical record using a standardized data collection form. Antibiotic exposure in the 30 days prior to infection was assessed using the following drug classifications (not mutually exclusive categories): third/fourth-generation cephalosporins (eg, cefotaxime, cefepime), extended-spectrum penicillins (eg, piperacillin), carbapenems, aminoglycosides, antianaerobic agents (eg, β-lactam/β-lactamase inhibitor combinations, carbapenems, metronidazole, clindamycin), trimethoprim-sulfamethoxazole, and FQs.

For the univariate statistical analysis, categorical variables were compared using Fisher exact test, and continuous variables were compared using the Wilcoxon rank-sum test. For all calculations, a 2-tailed *P* value less than .05 was considered to be significant. The tests were performed using Stata (version 8.0; Stata Corporation, College Station, TX).

We studied mechanisms of FQ resistance in 31 of the 35 total ESBL-EK available for analysis. Specific target mutations in the quinolone resistance determining regions of *gyrA* and *parC* were detected as previously described.[4-6] Organic solvent tolerance (OST) was used to detect FQ resistance mediated by active efflux mechanisms, in accordance with prior reports.[4] FQ-resistant ESBL-producing *E coli* were examined by pulsed-field gel electrophoresis.[7]

RESULTS

During the study period, 271 bloodstream isolates of *E coli, Klebsiella pneumoniae*, and *Klebsiella oxytoca* were isolated from 268 patients. Eight isolates were resistant to ciprofloxacin and levofloxacin (2.9%): 6 *E coli*, 1 *K pneumoniae*, 1 *K oxytoca*. In addition, 35 of 271 (12.9%) also produced an ESBL: 8 *E coli*, 17 *K pneumoniae*, and 10 *K oxytoca*. Of the 8 FQ-resistant isolates, 5 also produced an ESBL (OR, 12.6; 95% CI: 2.28-83.8, $P < .01$): 4 *E coli*, 1 *K pneumoniae*.

Because of this association, we performed a case control study defining patients with FQ-resistant ESBL-EK BSI as cases and those with FQ-susceptible ESBL-EK