Urinary Tract Infections Caused by Community-Acquired Extended-Spectrum β-Lactamase-Producing and Nonproducing Bacteria: A Comparative Study

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Objective To study the clinical characteristics and associated risk factors of urinary tract infections (UTIs) caused by community-acquired extended-spectrum β-lactamase (CA-ESBL)-producing *Enterobacteriaceae.*

Study design A case-control study at a large community hospital in northern Israel, comparing children who had UTI due to CA-ESBL (n = 25) and CA non-ESBL (n = 125) in 2008-2011. Data were collected from medical charts, telephonic questionnaires administered to all participants, and groups were compared.

Results During the study period, the yearly incidence of CA-ESBL UTI increased significantly. There were no significant differences between the CA-ESBL and CA non-ESBL groups in demographics and clinical outcome. Compared with CA non-ESBL UTI, children with CA-ESBL UTI had a longer hospital stay (5.9 ± 3.3 vs 3.9 ± 2.3 days; $P = .003$) and higher rates of recent hospitalization (28% vs 4%; $P = .001$), previous UTI (40% vs 13%; $P = .003$), urinary tract anomalies (32% vs 5%; $P < .001$), UTI prophylaxis with cephalexin (32% vs 2%; $P < .005$), and aminoglycoside resistance. In a multivariate analysis, UTI prophylaxis (OR 12.5 [CI 2.7-58]), recent hospitalization (OR 4.8 [CI 1.1-21]), and *Klebsiella* spp. UTI (OR 4.7 [CI 1.3-17]), were risk factors for CA-ESBL UTI.

Conclusions Children prescribed UTI prophylaxis (due to urinary tract anomalies or recurrent UTI) with cephalexin and those with previous hospitalizations are at increased risk for CA-ESBL UTI. Although not associated with higher rates of complications, the multidrug resistant phenotype of CA-ESBL isolates poses a challenge in choosing appropriate empiric and definitive therapy and prolongs hospital stay. *(J Pediatr 2013;163:1417-21).*

Urinary tract infection (UTI) is the most common cause of bacterial infection among febrile infants and young children with fever without a source. The most common UTI pathogens are *Escherichia coli* and *Klebsiella* spp.[1-3] However, the initial antimicrobial therapy for UTI is empiric until the results of culture and antibiotic susceptibility are available. Recently, the American Academy of Pediatrics (AAP) published new guidelines for diagnosis and management of the initial UTI in febrile infants and children 2-24 months of age. Empiric therapy, according to the guidelines, should be based on local antimicrobial susceptibility patterns; examples for oral treatment include cephalosporins (third, second, and first generation), trimethoprim-sulfamethoxazole (Trimet/Sulfa) or amoxicillin-clavulanate, whereas third generation cephalosporins, aminoglycosides and piperacillin are recommended for the parenteral route.[4] *E coli* and *Klebsiella* spp have variable antimicrobial resistance mechanisms, which may include the production of extended-spectrum β-lactamases (ESBLs). ESBL are capable of degrading the β-lactam ring of most of the penicillins and cephalosporins. Additionally, other genes encoding resistance to other antimicrobial agents, such as aminoglycosides and fluoroquinolones, are often found in proximity to the genes encoding ESBL on bacterial plasmids, thereby conferring multidrug resistance patterns.[5]

ESBL-producing bacteria were mainly encountered, until recently, in hospitalized patients as hospital-acquired infections. However, community-acquired ESBL (CA-ESBL)-producing bacteria are emerging as a cause of UTI worldwide.[6-14] Several studies describe risk factors for CA-ESBL UTI in the general population; however, data about risk factors and clinical characteristics in children with CA-ESBL UTI have been scarce.[7,9] We recently noticed a substantial increase in the prevalence of CA-ESBL UTI among children in our institution (in *E coli* and *Klebsiella* strains) prompting us to investigate and compare clinical characteristics and possible risk factors in children with CA-ESBL UTI with those of children with CA UTI caused by non-ESBL-producing *Enterobacteriaceae* (CA non-ESBL UTI).

AAP	American Academy of Pediatrics
CA	Community-acquired
ESBL	Extended-spectrum β-lactamase
Trimet/Sulfa	Trimethoprim-sulfamethoxazole
UTI	Urinary tract infection
WGH	Western Galilee Hospital

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Methods

This was a case-control study conducted in Western Galilee Hospital (WGH) in Nahariya, Israel. WGH is a large secondary-care community hospital serving the population (600 000, including 220 000 children) of the Western Galilee region of northern Israel, and it is the only hospital serving this area. Children 0-18 years old hospitalized or seen at the emergency room with *E coli* or *Klebsiella* spp. UTI from 2008-2011 were eligible. These children were identified from a computerized microbiology database. During the study period, 736 children had UTI caused by *E coli* or *Klebsiella* spp. Of these 736, 25 children with CA-ESBL UTI were defined as the study group (3% of total UTI) and 125 children with CA non-ESBL UTI, chosen randomly by a computer-generated program, served as a control group. Data were collected from medical charts for all participating children using a standardized questionnaire and included demographics, past medical history, and clinical and laboratory data pertinent to previous and current UTI (such as previous UTI, UTI antimicrobial prophylaxis, renal abnormalities, and previous hospitalizations). Additional telephonic questionnaires were administered to all participating children; these did not differ from the questionnaire used to collect data from charts but focused on verifying the data acquired. Data acquired from medical charts and telephonic questionnaires were compared between both groups.

CA UTI (ESBL or non-ESBL) was defined as *E coli* or *Klebsiella* spp positive urine culture from the emergency department (if the child was discharged) or within 72 hours from hospital admission. Exclusion criteria were asymptomatic bacteriuria (defined as a positive urine culture without any clinical manifestations of infection), culture taken >72 hours after admission, hospitalization within the previous week, admission from chronic care facilities, use of permanent urinary catheters or intermittent catheterization, UTI in the neonatal intensive care unit, and positive urine culture results not conforming with AAP UTI criteria.[3,15] Bacterial quantification in the urine specimens were defined by AAP guidelines at the time of the study: any bacterial growth for suprapubic aspiration, $>10^5$ colony forming units for urethral catheterization, and $>10^5$ colony forming units for 2 midstream collections. Urine bags were not used for specimen collection for urine culture.[15] Cases of UTI included pyelonephritis and cystitis, characterized by appropriate clinical symptoms (any or all of the following: back or flank pain, fever, nausea and vomiting for pyelonephritis and dysuria, urgency, frequency, suprapubic pain, and incontinence without fever for cystitis).[3] Antibiotic susceptibility and the presence of the ESBL phenotype were determined by using an automated susceptibility system (VITEK2; bioMérieux, Durham, North Carolina) according to the Clinical and Laboratory Standards Institute guidelines.[16] These methods remained unchanged during the study period. The appropriateness (in terms of antimicrobial resistance profiles) of the standard protocol used in the WGH of ampicillin plus gentamicin for pyelonephritis was evaluated. The combination of ampicillin plus gentamicin was implemented in 2007; at that time, it provided adequate coverage for 97% of the urinary pathogens in the pediatric division (of note, 10% of UTI cases were caused by *Enterococcus* spp). The study was approved by the Institutional Review Board of WGH.

Statistical Analyses

The calculation of the control group's size was done by using Sample Power v 1.2 (SPSS Inc, Chicago, Illinois). We estimated a 30% difference in administration of UTI antimicrobial prophylaxis between the CA-ESBL UTI and the CA non-ESBL UTI groups. Based on χ^2 test, 2-sided analysis, for 25 patients (the size of our study group) and a calculated power of 90% and α error rate of 5%, 125 patients were needed in the control group.

Statistical analysis was performed by using χ^2 test or Fisher exact tests to compare qualitative data between the study and control groups. To examine differences between the groups in quantitative data, independent sample *t* test or Wilcoxon rank sum test was used. Wilcoxon rank sum test was also used for comparisons of ordinal variables between the groups. Significant level of difference was defined as 2-sided *P* value of <.05. Variables were tested for inclusion in the multivariate logistic regression analysis if they were found to be associated with differences between the groups in unadjusted analyses ($P <$ .2) or were considered potentially clinically significant. Analysis was performed by using SPSS software, v 19.0 (IBM, Chicago, Illinois). *P* for trend of the yearly incidence of CA-ESBL UTI was calculated using http://www.vassarstats.net/.

Results

The phenomenon of CA-ESBL UTI among children with UTI at our institution was evident in every year of the study (2008-2011) and also in adjacent years with a yearly incidence of 1.2%-5.8% and a significant trend for increased incidence (**Figure 1**).

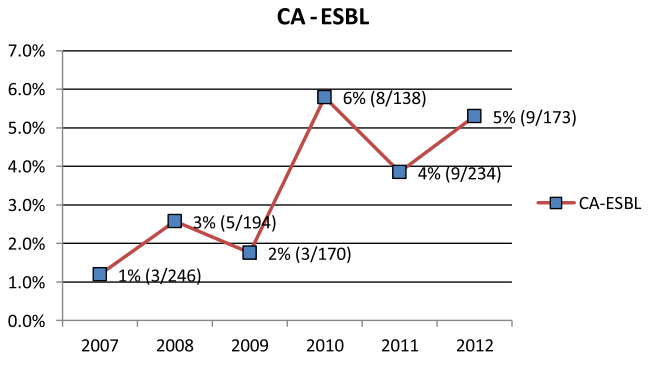

Figure 1. Incidence of CA ESBL-producing UTIs (% of total UTI) during the study period (2008-2011) and adjacent years.