RESEARCH PAPER

Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae Causing Community-Acquired Urinary Tract Infections in Children in Colombia

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Objective: To characterize the pediatric patients presenting at the two pediatric centers in Bogotá, with first isolate urine culture of community-acquired extended-spectrum β-lactamase (ESBL)-producing enterobacteriaceae. **Methods:** Review of microbiological data of children between January, 2012 and December, 2018, obtained using the WHONET software. **Results**: A total of 2657 *Escherichia coli, Klebsiella spp and Proteus mirabilis* - positive urine cultures were obtained within a 6-year period; data of 132 patients were finally selected. Frequency of ESBL-producing bacteria infections in community-acquired urinary tract infections (UTI) was 5%: 123 *E. coli* (93.2%), 7 *K. pneumoniae* (5.2%), 1 *K. oxytoca* (0.8%), and 1 *P. mirabilis* (0.8%). **Conclusion:** A predominance of female sex, preschool children, and lower tract urinary infections were found, as well as a low frequency of comorbidities. Adequate sensitivity to amikacin and nitrofurantoin was found in this study.

Keywords: *Escherichia coli, Klebsiella spp, Management, Prevalence, Sensitivity.*

Gram-negative bacteria are a common cause of urinary tract infections (UTIs) in children, and are frequently being reported as extended-spectrum β-lactamase (ESBL)-producing bacteria [1]. Actual incidence of urinary infections due to ESBL-producing bacteria in children is difficult to estimate; however, over the last 10 years, resistance has been gradually increasing around the world [2].

Adult studies report a prevalence of 3% to 16.3% among all UTI patients [1], whereas a prevalence of 10.9% has been reported in a pediatric study [3]. There are few pediatric studies, estimating the prevalence and the incidence of ESBL-producing enterobacteriaceae in community-acquired UTIs. We report the frequency and the clinical characteristics of children presenting with urinary infections and a urine culture with community-acquired ESBL-producing bacteria in two hospitals of Bogotá.

METHODS

A hospital record review of patients younger than 18 years was done from the emergency department of Hospital de San José and Hospital Infantil Universitario de San José in Bogotá. Children included were those with urinary symptoms or febrile condition without focus and initially an ESBL-producing bacteria was isolated for the first time in the urine culture from January, 2012 to December, 2018. Those with positive urine cultures for healthcare-associated infections (defined as hospital-acquired infections during treatment or care for a medical condition) and reinfections (two or more UTI by ESBL-producing bacteria) were excluded. Socio-demographic and clinical variables were evaluated, including additional diagnoses, underlying pathologies, inpatient manage-ment, and characteristics related to antibiotic treatment. Information was collected using an instrument developed by the investigators, which was completed based on the review and selection of medical records that met the inclusion criteria. Microbiological information was obtained using the WHONET 5.6 software (World Health Organization). Minimum inhibitory concentrations (MIC) were also rated and interpreted in accordance with the recommendations of the Clinical and Laboratory Standards Institute (CLSI) of 2017 [4], measured based on the MicroScan (Baxter) parameters in Hospital San José and on the VITEK2 (bioMerieux) automated method, in the Hospital Infantil Universitario de San José.

Statistical analyses: Information was stored in a database to be then validated selecting 10% of the records, and compared against the instruments. A descriptive analysis

of the information was conducted in STATA 12; qualitative variables were presented with absolute and relative frequencies, while quantitative variables included central tendency and scatter measurements, in accordance with the distribution of the data. This study was submitted and approved by the ethics and the research on humans committees in both hospitals.

RESULTS

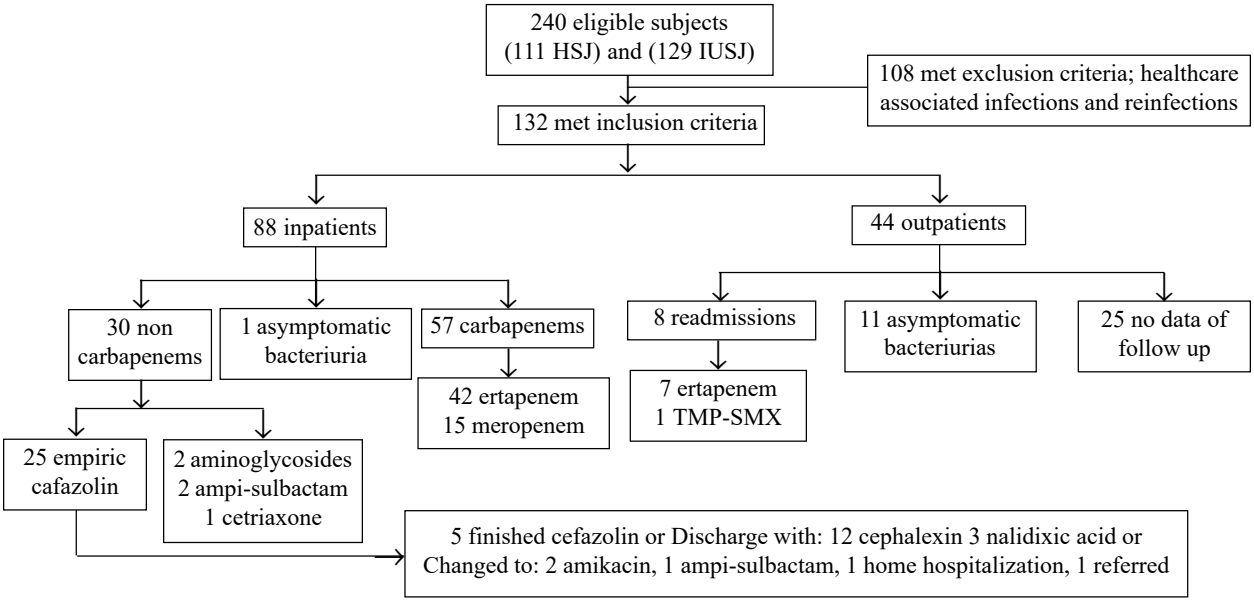
A total of 2657 positive urine cultures were obtained, of which 240 were reported as ESBL-producing bacteria; the medical records were reviewed, and in the end, 132 (81.8% girls) patients were eligible for the final analysis (**Fig. 1**). Frequency of community-acquired ESBL-producing bacteria isolates in first UTI was 5%. Of the 132 community-acquired ESBL-producing bacteria isolates, 123 (93.2%) were from *E. coli*, 7 (5.2%) from *K. pneumoniae*, and 1 (0.8%) each from *K. oxytoca,* and *Proteus mirabilis.*

The median (IQR) age of girls and boys age 4 (1-6.5) year and 0.5 (0.2-1) year, respectively. Other characteristics of the population are shown in **Table I**.

Additionally, 49 patients (37.1%) had a previous history of UTIs, 25 patients (18.9%) had UTI-associated congenital malformations, 19 (76%) had renal or urologic conditions (hydronephrosis (n=9), pyelectasis (n=5), horseshoe kidney (n=2), renal hypoplasia (n=1), duplex collector system (n=1) and renal duplication (n=1) and 6 patients (24%) presented with neurological malformations (myelomeningocele (n=5), hydrocephalus (n=1). Among this group of malformations, 18 (69.2%) presented a history of previous UTI. Furthermore, four patients (3.0%) were in immunosuppressive therapy: two cases of nephrotic syndrome, one case of systemic lupus erythe-matous and one due to chronic kidney failure. Nine patients (6.8%) exhibited an additional risk because of self-medication with amoxicillin, cephalexin, trimethoprim sulfamethoxazole (TMP-SMX) or metronidazole. 50 patients (37.9%) had no relevant history or risk factors for UTI.

Imaging findings showed 92 (69.6%) patients undergoing kidney and urinary tract ultrasound, of which 52 (56.5%) had normal results, 13 (14.1%) exhibited enlarged kidneys, 9 (9.8%) had evidence of pyelocaliceal-ectasia, 7 (7.6%) with kidney atrophy, 6 (6.5%) sediments in urine, 3 (3.2%) hydronephrosis, 1 (1.1%) duplicated pyelocaliceal system, and 1 (1.1%) neurogenic bladder). Out of 24 patients undergoing cystouretrography, 12 (50%) were normal, 7 (29.2%) had vesicoureteral reflux, and 2 (8.3%) bladder diverticula; the remaining three patients (12.5%) had penile hypospadias, postvoid residual urine, and decreased posterior urethral diameter. Finally, of 22 patients undergoing renal gammagraphy, 12 (54.5%) had documented pyelonephritis, 8 (36.4%) were normal, and 2 (9.1) had kidney scarring.

Sensitivity profiles and co-resistance for *E. coli* and *K. pneumoniae* are illustrated in **Table II**.



TM-SMX: trimethoprim-sulfamethoxazole; HSJ: Hospital de San José; IUSJ: Hospital Infantil Universitario de San José.

Fig. 1 Flowchart of the study.

Table I Clinical and Demographic Characteristics of Children With First Episode of Urinary Tract Infection by Community-Acquired ESBL-Producing Enterobacteriaceae (*N*=132)

Characteristics	*No.* (%)
Age (mo)	
<12	28 (21.2)
13-24	22 (16.7)
25-60	45 (34.1)
61-144	30 (22.7)
>145	7 (5.3)
Comorbidities	
Renal and urological comorbidities[a]	18 (13.6)
Other comorbidities[b]	15 (11.4)
Diagnosis	
Asymptomatic bacteriuria	12 (9.1)
Lower UTI	102 (77.3)
Upper UTI	18 (13.6)
History of hospitalization[c]	28 (21.2)
History of surgery[c]	8 (6.1)
Previous antibiotic therapy[c]	50 (37.9)
UTI[d]	49 (37.1)
Congenital malformation[e]	26 (19.7)
Hospital stay (d), median (IQR)	9 (6-11)

UTI: Urinary tract infection; ESBL; Extended spectrum beta lacta-mase; [a]Renal and urological comorbidities: hydronephrosis, pyelectasis, horse-shoe kidney, nephrotic syndrome, bladder diverticula, vesicoureteral reflux, kidney transplant and nephrostomy; [b]Other comorbidities: my-elomeningocele, anemia, chromosomo-pathy, cholestasis, hydrocephalus, systemic lupus erythematous, pulmonary hypertension. [c]3 months prior to ED visit; [d]due to ESBL non-producing germs; [e]predisposing to UTI.

Supplementary Fig. 1 shows the detailed MICs for *E. coli* for the most important antibiotics, using automated methods and their relationship to the CLSI to define sensitivity and resistance.

After the initial assessment 44 patients, empiric outpatient therapy was administered with cephalexin in 39 cases (88.7%), nalidixic acid in 2 cases (4.5%), no antibiotic therapy was prescribed in 2 cases (4.5%), while TMP-SMX was used in 1 case (2.3%). Of these patients, 8 (18.2%) relapsed and were admitted for ertapenem treatment (7) and 1 was discharged with TMP-SMX. The remaining 36 patients (81.8%); 11 were considered to develop asymptomatic bacteriuria and 25 patients had no outpatient follow-up information available.

88 patients received hospitalized management, 70 (79.5%) were initially treated with cephalosporins, 7 (7.9%) with aminoglycosides, and 11 (12.6%) received other antibiotic therapies. Once the results of the urine culture were available, 57 (64.8%), received specific therapy with carbapenems: ertapenem (*n*=42) and mero-penem (*n*=15); 31 patients (35.2%) received another betalactamic antibiotic therapy (*n*=28) and aminogly-cosides (*n*=3).

Of the 107 patients followed, 12 were considered asymptomatic bacteriurias, and 95 received empirical treatment. Of these 95 patients, 74 (77.8%) required switching over to carbapem management and 21 (22.2%) patients experienced no change in their antibiotic treatment.

In terms of outcomes, one 7-month old patient died, with Down syndrome admitted with a diagnosis of upper

Table II Specific Sensitivity CLSI 2017 of Each Antibiotic According to the ESBL-Producing Bacteria Isolated in Positive Urine Culture (*N*=130)[a]

	Escherichia coli			*Klebsiella pneumoniae*		
Antibiotic	*Sensitive*	*Intermediate*	*Resistant*	*Sensitive*	*Intermediate*	*Resistant*
Ampicillin sulbactam, *n*=130	46 (35.4)	25(19.2)	52 (40)	3 (2.3)	0	4 (3.1)
Piperacillin-tazobactam, *n*=68	56 (82.4)	3 (4.4)	5 (7.4)	4 (5.8)	0	0
Amikacin, *n*=130	121 (93)	1 (0.8)	1 (0.8)	7 (5.4)	0	0
Gentamicin, *n*=130	88 (67.7)	1 (0.8)	34 (26.1)	6 (4.6)	0	1 (0.8)
TMP-SMX, *n*=128	33 (25.8)	0 (0.0)	88 (68.8)	3 (2.3)	0	4 (3.1)
Nitrofurantoin, *n*=129	92 (71.3)	28 (21.7)	2 (1.5)	5 (3.9)	1 (0.8)	1 (0.8)
Fosfomycin, *n*=57	52 (91.3)	0	1 (1.7)	3 (5.3)	0	1 (1.7)
Ciprofloxacin, *n*=129	59 (45.7)	2 (1.6)	61 (47.3)	4 (3.1)	0	3 (2.3)
Meropenem, *n*=130	130 (100)	0	0	130 (100)	0	0

[a]One case each of P. mirabilis and K.oxytoca were excluded; Values in no. (%); all n not equal to 130 because not all isolates had the disks for that antibiotic in the antibiogram.

UTI and *E. coli* isolate. The patient received empirical treatment with ampicillin sulbactam, which was switched on day three to ertapenem, based on the urinary culture results. However, the condition of the patient progressed to septic shock.

Hospitalization in last three months (n=28, 21.2%), recurrent urinary tract infection (n=49, 37.1%), previous use of antibiotics (n=50, 37.9%) and urinary tract abnormalities were findings for ESBL producing community-acquired UTI.

DISCUSSION

This study presents the frequency of UTI associated with community acquired ESBL-producing bacteria similar to the levels reported in the international literature [1,5]. Demographic characteristics include a higher frequency of females, with an age group distribution similar to the reported in the world literature [6,7]. The factors related with ESBL-producing bacteria UTIs are: a history of a previous UTI non ESBL-producing bacteria, urinary tract malformations, hospitalization, or antibiotic therapy during the last 3 months (40% first generation cephalosporins) [5,8,9]. In terms of comorbidities, surprisingly most patients were previously healthy (without any comorbidities), which correlates with the circulation of ESBL-producing enterobacteriaceae phenotype in the community.

Median for hospital days is high, similar to previous studies [10], in addition to a more than two-fold increase in costs [9,11]. This may be due to the fact that patients with infections from ESBL-producing bacteria have a higher risk of hospitalization because of their past history [6]. Findings of imaging studies were mostly normal and among the most frequent ultrasound alterations were enlarged kidneys, followed by pyelectasis; the number of patients who underwent cystouretrographies and renal gammagraphies was low in contrast with literature [6] as for most in our population it was their first infection [12].

The most commonly isolated bacteria was *E. coli,* so a more detailed analysis was performed of the resistance to 8 antibiotics. A very high sensitivity was found to fosfomycin, nitrofurantoin and amikacin, with similar findings to those in the spanish study by Pérez, et al. [1]. A variable sensitivity and resistance was also identified in the group of betalactamase inhibitors, with a higher resistance in the ampicillin sulbactam group and intermediate sensitivity, with MIC approaching the resistance to piperacillin-tazobactam. It is therefore hypothesized that these are not sound therapeutic options in this scenario, because of the risk if increased resistance as has been stated by other authors [11,13]. A proportion of inpatients were treated with initial empirical management with cephazolin, achieving a satisfactory clinical evolution with a negative control urine culture. The correlation of urinary concentrations that the drug can reach should be studied [14]. In this series of patients, the typical risk factors described in the literature were uncommonly seen [7,15].

It can be suggested that this pathology may be underdiagnosed or even treated incorrectly, impacting on bacterial resistance and as a result in prognosis; forcing health professionals treating this disease to explore the presence of ESBL in a non-hospital population and without the risk factors specified in the literature. Other studies should be done to confirm if there are strains of multi-resistant bacteria circulating in the community.

Taking into account the observational nature of this study and the retrospective collection of data, it is not possible to determine causality. However, this drawback was offset using different sources of information. Further analytical and experimental studies are needed to validate the hypotheses herein discussed and propose an analytical study to confirm if there are strains of multi-resistant bacteria circulating in the community. Another limitation of study was that discs of antibiotic for antibiogram were not uniformly available for all cases.

UTIs from community acquired ESBL-producing enterobacteriaceae are a serious public health issue as a result of the increasing number of cases over the last decade. This population presents a frequency of 5% for *E. Coli* and *K. pneumoniae*. A predominance of low urinary infection was found in previously healthy girls of preschool age. The typical risk factors associated with ESBL-producing bacteria infections in community acquired UTI were low in this population. This study reveals the epidemiological and microbiological profile of these hospitals, good sensitivity was found in this population for amikacin and nitrofurantoin, so as to select an adequate treatment and to design alternative non-carbapenem antibiotic protocols for outpatients, with a view to promote the rational use of antibiotics. Fosfomycin, piperacillintazobactam, and other antibiotics require further investigation.

Ethics Clearance: Ethics and the research on humans committees in both hospitals. Hospital ethics review board (Comité de ética en investigación con sereshumanos Hospital de San José, CEISH-HSJ). No. 0369-2018, dated September 17, 2018.

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