

Community-onset extended-spectrum β -lactamase producing *Escherichia coli* in urinary tract infections in children from 2015 to 2016

Prevalence, risk factors, and resistances

Iñigo Pérez Heras, MD*, Juan Carlos Sanchez-Gomez, MD, Pedro Beneyto-Martin, MD, Laura Ruano-de-Pablo, MD, Begoña Losada-Pinedo, MD

Abstract

Over the past 10 years, the resistances among microbes are increasing gradually in Europe and greater resistances are seen in southern countries. We studied the prevalence of community-onset ESBL-producing *Escherichia coli* urinary tract infections in children.

As secondary objectives, we analyzed associated risk factors and the resistance patterns in ESBL-producing *E coli* isolates.

Retrospective observational study in a tertiary care hospital about children ≤ 14 years old with community-onset *E coli* urinary tract infection. The variables studied were age, sex, ESBL-producing, antibiotic therapy 7 to 30 days before the infection, hospitalization 7 to 30 days before the infection, nefrourologic pathology, and vesicoureteral reflux.

Between January 1st, 2015 and December 31st, 2016, 229 isolates of *E coli* were obtained, of whom 21 (9.2%) were ESBL-producing *E coli*. Median age in non-ESBL-producing was 18 months versus 7 months in ESBL-producing group. Fourteen (66%) of the ESBL-producing group were men ($P = .001$), 5 (23.8%) were hospitalized 30 days before the infection ($P = .001$), 12 (57.1%) had nefrourological pathology ($P = .003$), 6 (28.5%) had vesicoureteral reflux ($P = .032$). Previous antibiotic therapy was not statistically significant. Multiple regression analyses between sex and 30 days previous hospitalization were $r = 3.51$ ($P = .0001$). Multidrug resistant isolates among ESBL-producing *E coli* was 12 (57%).

The retrospective study allowed assessing the problem of ESBL-producing isolates in the outpatient settings. Some risk factors from past studies were confirmed and a combined risk is suggested. The resistant spectrum should be taken into account when choosing antibiotic regimens.

Abbreviations: ESBL = extended-spectrum beta-lactamase, UTI = urinary tract infections.

Keywords: β -lactamases, community-acquired infections, *Escherichia coli*, Spain/epidemiology, urinary tract infections

1. Introduction

Over the past 10 years, the resistances among microbes are increasing gradually in Europe.^[1] This is especially important in Spain, where all the studies and reports suggest that our rates of antibiotic resistance are greater than other countries.^[1–3]

Most of the studies were made in adult population, or at least not specifically in children.^[4–12] This means that there is a gap of information that must be completed, in order to improve national health surveillance programs in our country.

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Department of Pediatrics, Hospital Virgen de la Salud, Toledo, Spain.

* Correspondence: Iñigo Pérez Heras, Ronda de Buenavista 28, bloque 2, 1°C, 45005, Toledo, Spain (e-mail: inigop30@gmail.com).

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On the other hand, the prevalence of urinary tract infections in children goes from 2% to 5%,^[4] with a risk of developing permanent renal damage in children below 2 years old.^[4]

Statistical data are quite different between countries. In the USA, reports show a prevalence of extended-spectrum β -lactamase (ESBL) producing *Escherichia coli* urinary tract infections (UTI) of 3%.^[5] In Mexico, the studies show a prevalence of 16.3%.^[6] In China, Iran, Saudi Arabia, and Israel, 10%,^[7] 30.3%,^[8] 41.9%,^[9] and 5%,^[10] respectively.

In Europe, greater resistances are seen in southern countries.^[11] In Germany, the studies show a prevalence of 8%.^[12] In France (very close to Spain) we can observe a prevalence of 3.3%^[11] as seen in 2013.

The data of Spain are very limited, but in 2000 a report showed that the prevalence of ESBL-producing *E coli* was about 0.5%,^[13] while in 2005 this number grew to 8.2%,^[14] which is 16 times greater.

Bearing in mind the lack of information in this matter in children in Spain, we tried to study the prevalence of community-onset ESBL-producing *E coli* urinary tract infections.

As secondary objectives, we analyzed associated risk factors and the resistance patterns in ESBL-producing *E coli* isolates.

2. Material and methods

We performed a retrospective observational study in a tertiary care hospital between January 1st, 2015 and December 31st,

Table 1

Analysis of risk factors in *E coli* isolates from January 2015 to December 2016 in children between 0 and 14 years old.

	Total N = 229	<i>E coli</i> N = 208	ESBL-producing <i>E coli</i> N = 21	P
Sex				
Male	80 (35%)	66 (31.7%)	14 (66%)	.001
Female	149 (65%)	142 (68.2%)	7 (33%)	
Previous hospitalization				
7 d	21	19	2	.023
15 d	25	21	4	.003
30 d	27	22	5	.001
Previous antibiotic therapy				
7 d	8	6	2	.16
15 d	27	24	3	.72
30 d	38	33	5	.35
Nefrourologic pathology				
Yes	66	54	12	.003
No	163	154	9	
Vesicoureteral reflux				
Yes	31	25	6	.035
No	198	183	15	

E. coli = *Escherichia coli*; ESBL: extended spectrum beta-lactamase.

2016. We collected data of all children ≤ 14 years old with community-onset *E coli* urinary tract infection who visited our emergency department in Toledo (Spain). Data for demographic characteristics, medical conditions, medication, and urinary isolates are from the patient medical record.

We considered positive isolate when $>50,000$ colony-forming units in the urine sample obtained by urinary catheterization (those patients without urinary continence) or spontaneous urination. We excluded those cultures separated <7 days from the previous one (we consider them as a control of the evolution of the patient), and those who were receiving antibiotic prophylaxis.

E coli were identified by using biochemistry procedures. Resistance detection and in vitro susceptibility were made by broth microdilution (Siemens WalkAway, West Sacramento, CA).

The variables studied were age, sex, ESBL-producing, antibiotic therapy 7 days, 15 days, or 30 days before the infection, hospitalization 7 days, 15 days, or 30 days before the infection, nefrourologic pathology (defined as vesicoureteral reflux, intermittent catheterization, pyelectasis, multicystic renal dysplasia, and/or renal agenesis), and vesicoureteral reflux.

SPSS v23 (SPSS Inc., Chicago, IL) was used for analysis. $P < .05$ was considered statistically significant.

Previous hospitalization, antibiotic therapy, and pyelectasis were analyzed using Fisher exact test. Sex, nefrourologic pathology, and vesicoureteral reflux were analyzed with Chi-squared test. Student *t* test was used for age analysis.

Sex and 30 days previous hospitalization combined were analyzed with multiple regression.

No ethical approval was needed because it is an observational study, all the data were obtained from the patient medical record, without any contact with them. It is also impossible to identify through the database any of the patients included.

3. Results

During the study period, 229 *E coli* isolates were identified from sterile samples from children in the emergency department. Twenty one (9.2%) of them were ESBL-producing *E coli*.

Table 2

Resistances among ESBL-producing *E coli* isolates from January 2015 to December 2016 in children between 0 and 14 years old.

Antibiotic	Resistance	Susceptibility	Intermediate
Ampicillin	21 (100%)	0	0
Amoxicillin/clavulanic acid	13 (62%)	8 (38%)	0
Piperacillin/tazobactam	6 (28.6%)	12 (57%)	3 (14.3%)
Cefuroxime	18 (85.7%)	3 (14.3%)	0
Cefoxitin	2 (9.5%)	18 (85.7%)	1 (4.8%)
Ceftazidime	17 (81.9%)	1 (4.8%)	3 (14.3%)
Cefotaxime	19 (90.5%)	2 (9.5%)	0
Imipenem	0	21 (100%)	0
Meropenem	0	21 (100%)	0
Ertapenem	0	21 (100%)	0
Gentamicin	8 (38%)	13 (62%)	0
Tobramycin	9 (42.8%)	9 (42.8%)	3 (14.3%)
Amikacin	0	19 (90.5%)	2 (9.5%)
Nalidixic acid	15 (71.4%)	5 (23.8%)	1 (4.8%)
Ciprofloxacin	15 (71.4%)	3 (14.3%)	3 (14.3%)
Norfloxacin	17 (81.9%)	4 (19%)	0
Levofloxacin	4 (19%)	17 (81.9%)	0
Trimethoprim/sulfamethoxazole	13 (62%)	8 (38%)	0
Fosfomicin	2 (9.5%)	19 (90.5%)	0
Nitrofurantoin	0	21 (100%)	0

The median age was 17 months in all isolates, 18 months in non-ESBL-producing *E coli*, and 7 months in ESBL-producing *E coli*.

The risk factors statistical analyses and results are detailed in Table 1.

Multiple regression analyses between sex and 30 days previous hospitalization were $r = 3.51$ ($P = .0001$)

The resistances observed in ESBL-producing *E coli* sample are detailed in Table 2.

Moreover, 7 (33%) of them were resistant to cephalosporins, aminoglycosides, and quinolones, and 5 (23.8%) to cephalosporins and quinolones, but not aminoglycosides. The total amount of multidrug resistant isolates among ESBL producing *E coli* was 12 (57%).

4. Discussion

We find that among children, the isolation of ESBL-producing *E coli* is becoming common across pediatric age groups in Spain, consistent with previous reports in adults,^[13,14] and children over the world.^[8,15]

The spread of ESBL is plasmid-mediated, and can be transferred to other Gram-negative bacteria.^[16] This fact is important to understand the easily spread of resistances in a country, and the need of national healthcare programs.

In 2015, the prevalence of ESBL-producing *E coli* among UTI caused by *E coli* was 7.1% versus 14.6% in 2016. As we can see, this rate is increasing very fast among pediatric population.

The upward trend in ESBL-producing isolates with age,^[10] is not seen in our study (median age of 7 months in ESBL-producing group vs 18 months in *E coli* isolates). This may be because the *E coli* behavior in children is different from adults.

As seen in previous studies, being male, hospitalization 30 days previous to infection,^[6,15] nefrourologic pathology and vesicoureteral reflux are proposed as risk factors.

Moreover, male sex and hospitalization 30 days before infection have a combined risk of 3.51 ($P = .0001$), which should be taken into account to choose the best antibiotic regime for these children.

In our sample, 57% of the ESBL-producing *E coli* were multidrug resistant, which means that at least 5.24% of the children included have a multidrug resistant infection. They remain highly susceptible to fosfomicin, nitrofurantoin, and carbapenems.

In conclusion, the retrospective study allowed assessing the problem of ESBL-producing isolates in the outpatient settings. Some risk factors from past studies were confirmed and a combined risk is suggested. The resistant spectrum should be taken into account when choosing antibiotic regimens.

Our study has the proper limitations of an observational study.

Further studies are needed to reveal the real impact of these microorganisms in national healthcare.

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