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ORIGINAL ARTICLE

Risk factors for gentamicin-resistant *E. coli* in children with community-acquired urinary tract infection

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Abstract

According to many guidelines, gentamicin is the empirical parenteral treatment for children with community-acquired urinary tract infection (CA-UTI). However, increasing resistance rates are reported. The purpose of this study is to analyze risk factors for presenting with a UTI caused by a community-acquired gentamicin-resistant *Escherichia coli* in children in our hospital and to describe their clinical outcome. A retrospective case-control local study was performed in a tertiary care hospital from January 2014 to December 2016. Cases and controls were children below 14 years old diagnosed in the Emergency Department with febrile CA-UTI caused by gentamicin-resistant and gentamicin-susceptible febrile *E. coli* strains, respectively. During the study period, 54 cases were included and compared with 98 controls. Patients with chronic conditions were more likely to present with a UTI due to gentamicin-resistant *E. coli* (OR 3.27; 95% CI 1.37–7.8, $p < 0.05$), as well as children receiving antibiotic prophylaxis (OR 3.5; 95% CI 1.2–10.1, $p < 0.05$). Cases had longer hospital stays than controls (5.8 ± 5 days vs. 4.4 ± 4 days, $p = 0.017$). Gentamicin-resistant strains associated higher rates of cefuroxime (29% vs. 3%), cefotaxime (27% vs. 0%), and quinolone resistance (40.7% vs. 6%) ($p < 0.01$) and produced more frequently extended-spectrum beta-lactamases (ESBL) (20% vs. 0%, $p < 0.01$) and carbapenemases (7.4% vs. 0%; $p = 0.015$). All gentamicin-resistant strains were amikacin-sensitive. The presence of chronic conditions and antibiotic prophylaxis could be potential risk factors for gentamicin-resistant *E. coli* CA-UTI in children. Simultaneous resistance to cephalosporins, quinolones, and ESBL/carbapenemase production is frequent in these strains.

Keywords Urinary tract infection · *E. coli* · Gentamicin · Drug resistance · Antimicrobial susceptibility · Extended-spectrum beta-lactamases

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Introduction

Community-acquired urinary tract infection (CA-UTI) is one of the most common infectious diseases in children, being *Escherichia coli* the most common uropathogen [1–3]. Therefore, its susceptibility pattern guides the empirical treatment.

Gentamicin is commonly recommended for treating children with UTIs that require parenteral therapy [2, 3]. However, recent pediatric series have reported increasing rates of nosocomial and CA-UTI caused by extended-spectrum beta-lactamases (ESBL) strains, many of which may associate gentamicin resistance [4–6]. The use of prophylactic antibiotics, presence of urinary malformations, recurrent UTIs, urinary catheterization, or recent hospitalization [6–11] has been suggested as potential risk factors for the selection of resistant strains.

Monitoring the susceptibility of the UTI-producing strains in children is generally recommended to guide local empiric treatment [6–11]. In 2014, the rate of gentamicin resistance among the strains of *E. coli* isolated in urine cultures collected at our Pediatric Emergency Department reached 15% [12], while in 2012, another hospital from our same geographic area reported gentamicin resistance rates lower than 5% in children with *E. coli* UTIs [1].

The aim of this study was to identify risk factors associated with gentamicin resistance that could explain the higher rate found in our center and that may be of interest for optimizing empirical treatment.

Patients and methods

A retrospective case-control local study was performed in a tertiary care hospital in Madrid, Spain. CA-UTI was defined as an infection detected at hospital admission or within the first 48 h of hospitalization [10]. Cases were episodes of febrile CA-UTI caused by a gentamicin-resistant *E. coli* diagnosed in children below 14 years of age between January 2014 and December 2016.

Urine specimens had been inoculated using calibrated loops on Columbia 5% sheep blood and MacConkey agars and incubated for 18 h to 24 h before quantitative reading. Identification and susceptibility tests were performed using Urine Combo type 69 Microscan® microdilution panels and WalkAway automatic system. Only when the confidence percentage of the identification was below 95%, final confirmation of the isolated bacteria was performed by MALDI Biotyper (Bruker Daltonik GmbH, Bremen, Germany). The EUCAST breakpoints [13] were used to interpret clinical categories. *E. coli* isolates with gentamicin resistance or intermediate category, minimum inhibitory concentration (MIC) 4 mg/l or greater, were used to define cases. ESBLs were phenotypically confirmed with the double-disk synergy method with cefotaxime, ceftazidime cefotaxime/clavulanate, and ceftazidime/clavulanate. Isolates having an MIC > 1 mcg/ml to imipenem or meropenem and > 0.5 mcg/ml to ertapenem were confirmed by PCR RealCycler® Universal OXVIKPND-G real-time PCR kit (Progenie Molecular, Spain).

Urine cultures were considered positive if a single pathogen was isolated, with at least 10^5 colony-forming units (CFUs) of *E. coli* in spontaneous micturition, 10^4 CFUs in samples obtained by urethral catheterization, or 10^3 CFUs in samples obtained by suprapubic aspiration. When urine samples were obtained from urine collection bags, isolations were considered significant only in children with fever and pyuria with more than 10^5 CFUs identified in at least 2 different samples. Asymptomatic bacteriuria, nonsignificant counts, samples in which the gathering method was unknown, and isolations in samples obtained after 48 h of hospital admission were excluded.

Paired by date of sample collection, one to two *E. coli* UTI controls that fulfilled inclusion criteria were included per case, among isolations of gentamicin-sensitive *E. coli* strains corresponding to febrile CA-UTIs. The study protocol was approved by the Hospital's Ethics Committee.

The following epidemiological data were collected: age, gender, genitourinary malformations (grade III and IV vesicoureteral reflux (VUR), hydronephrosis, and other genitourinary malformations), other chronic diseases, previous UTIs, prophylactic antibiotic intake, hospitalization in the previous 6 months, and previous admission in the Pediatric Intensive Care Unit (PICU). Clinical variables included leukocytosis, C-reactive protein (CRP), need and length of hospitalization, failure of empirical treatment, antibiogram results including production of ESBL, and carbapenemases.

All statistical analyses were performed with SPSS 18.0 (SPSS Inc., Chicago, IL). Qualitative data were expressed as absolute frequencies and/or percentages; quantitative data were expressed either as a median and interquartile range, minimum-maximum range, or mean and standard deviation, depending on the data distribution. The association between risk factors and the presence of gentamicin-resistant strains was studied with the chi-square test or the Fisher exact test for categorical variables, and Student's t test or the Mann-Whitney U test for continuous variables according to data distribution.

To identify independent gentamicin resistance risk factors, a logistic regression model (Wald's test) was built, including the variables that were clinically relevant and/or statistically significant in the univariate analysis. If a patient had presented more than one UTI during the study period, only the first episode was considered when analyzing risk factors in the logistic regression model. A p value < 0.05 was considered as statistically significant.

Results

Between 2014 and 2016, 848 *E. coli* were isolated from urine samples obtained in the Pediatric Emergency Department. Eighty-one cases (9.5%) corresponded to gentamicin-resistant *E. coli* strains. The gentamicin resistance rate was 15% (30/201) in 2014, 5.3% (18/338) in 2015, and 10.6% (33/309) in 2016 ($p = 0.008$).

Out of 81 gentamicin-resistant isolates, 54 CA-UTI episodes diagnosed in 50 children met the inclusion criteria and were compared with 98 CA-UTI controls diagnosed in 95 children (152 total UTIs included). All gentamicin-resistant strains except one presented MIC > 8 mg/l or greater.

Regarding urine collection method, 51% (78/152) of urine samples corresponded to urethral or suprapubic catheterization, 47% (72/152) to clean catch urine collection, and 1.3% (2/152) to urine collection bags.

During the last 6 months, 27.8% cases (15/53) received prophylactic antibiotics, and 29.6% (16/54) were hospitalized at least once.

Eighteen patients had genitourinary malformations (33%; 18/54). Excluding genitourinary diseases, 20 children (37%) had some type of chronic disease, and 8 had at least two chronic conditions (15%). Half of these children presented fecal and/or urinary continence and needed clean intermittent catheterization (CIC) or manipulations of the distal digestive or urinary tracts (myelomeningocele/spina bifida with neurogenic bladder or distal digestive tract abnormalities). The second most frequent type of chronic conditions was encephalopathies or diseases with intellectual disability (congenital cytomegalovirus, cerebral palsy, or other syndromes) (45%; 9/20). Other less frequent chronic conditions were endocrine-metabolic diseases (4), congenital cardiopathies (2), and hematooncological diseases (1).

Cases and controls were comparable in terms of age although cases were more frequently male (51% vs. 31%, $p = 0.02$). The main characteristics of both groups are shown in Table 1. Children with *E. coli*-resistant CA-UTI were more likely to have previous history of UTI, genitourinary malformations, chronic diseases, antibiotic exposure, hospitalization in the previous 6 months, and PICU admission than controls ($p < 0.01$) (Table 1). In the multivariate analysis, the use of prophylactic antibiotics in the last 6 months and suffering from chronic diseases different to genitourinary malformations were independent risk factors for the development of gentamicin-resistant UTI (Table 2).

The need for empirical antibiotic change was more frequently observed in cases than controls (7/47; 15% vs. 3/90; 3.3%) ($p = 0.03$).

The antibiogram of all strains is shown in Fig. 1, according to study group. The percentage of amoxicillin-clavulanate resistance was not significantly higher in cases than controls (18/54; 33% vs. 27/98; 27.6%) ($p > 0.05$), but resistance to cefuroxime, cefixime, cefotaxime, and quinolones was higher in cases ($p < 0.01$) (Fig. 1). Gentamicin-resistant strains were more frequently ESBL ($p < 0.01$) and carbapenemase producers ($p = 0.015$). All gentamicin-resistant strains were sensitive to amikacin.

Discussion

In this study, the presence of chronic conditions, especially those affecting fecal and/or urinary continence, as well as

Table 1 Clinical features and laboratory data of gentamicin-resistant and nonresistant febrile UTI episodes

	Cases ($n = 54$)	Controls ($n = 98$)	p
Age (months)	11.15 m (IQR 3.7–31)	11.85 m (IQR 4–47.2)	> 0.05
Male % (no.)	50% (27)	31.6% (31)	*0.02*
Leukocytes (cell/ml)	17,580 (IQR 12,100–21,950)	16,100 (IQR 12,900–20,175)	> 0.05
Neutrophils (cell/ml)	10,150 (IQR 7840–13,420)	9115 (IQR 5800–12,220)	> 0.05
CRP (mg/dl)	59 mg/l (IQR 25–95)	65 mg/l (IQR 21–115)	> 0.05
Previous UTIs % (no.)	37% (20)	20.4% (20)	< *0.01*
Rate of hospital admission % (no.)	39% (21)	32.7% (32)	> 0.05
Length of hospital admission (days)	5.8 ± 5 days	4.4 ± 4 days	*0.017*
Cases requiring at least 5 days of admission % (no.)	66% (14)	34% (11)	*0.02*
Genitourinary malformations % (no.)	33.3% (18)	16.5% (16)	< *0.01*
Antibiotic prophylaxis exposure (previous 6 months) % (no.)	27.8% (15)	7% (7)	< *0.01*
Hospitalization (previous 6 months) % (no.)	29% (16)	20% (20)	< *0.01*
Previous PICU stay % (no.)	29.6% (12)	4% (4)	< *0.01*
Chronic condition % (no.)	37% (20)	12.2% (12)	< *0.01*

All expressed as median (IQR) except otherwise specified. *Significance: p<0.05*

Table 2 Risk factors for gentamicin resistance; multivariate analysis results

Potential risk factors	OR (95% CI)	*p* value
Antibiotic prophylaxis (previous 6 months)	**3.27 (1.2–10.1)**	**0.016**
Chronic condition	**2 (1.37–7.8)**	**0.08**
Male	1 (0.98–4.31)	*> 0.05*
Genitourinary malformations	0.8 (0.32–3.51)	*> 0.05*
Previous PICU stay	1.17 (0.52–9.19)	*> 0.05*
Hospitalization (previous 6 months)	0.7 (0.46–2.9)	*> 0.05*
Previous UTI history	1.27 (0.35–2)	*> 0.05*

Significance: p<0.05

previous antibiotic exposure, was associated to gentamicin-resistant *E. coli* CA-UTI.

Gentamicin resistance is of concern, particularly as it often associates ESBL production [4, 7, 8, 10, 14–16]. Data on the prevalence of ESBL-producing bacteria among CA-UTI in children in our country is scarce, although it seems to have increased lately [4]. A recently published series shows a 3.5% prevalence of ESBL-producing strains in febrile pediatric CA-UTIs that required hospitalization, *E. coli* being responsible for 84% of them [4].

Antibiotic exposure has been identified in different settings as a major determinant for the selection of resistant strains. In our study, the use of prophylactic antibiotics in the last 6 months was a risk factor for the development of gentamicin-resistant UTI. Beta-lactam antibiotics seem to play a role in selecting ESBL-producing bacteria [6–8, 10, 16, 17]. A recent meta-analysis has shown how the risk of developing a multidrug-resistant UTI is sixfold greater among children receiving prophylaxis [18]. This fact has important implications in the risk-benefit assessment of prophylaxis and in the selection of empirical treatment in patients receiving prophylaxis that present with a UTI.

Chronic conditions have also been suggested as potential risk factors for the isolation of resistant strains in children with UTI [6]. In our study, this factor was also associated with gentamicin resistance after multivariate analysis. In fact, up to 70% of our cases presented some type of chronic disease, including genitourinary malformations. Our hospital is a tertiary care center that attends children with many and varied chronic medical conditions, and presents higher rates of gentamicin-resistant *E. coli* CA-UTI than other hospitals in the same geographic area [1, 12]. These differences emphasize the importance of identifying risk factors for resistant UTI to optimize local empirical treatment in certain patients.

Most of our cases with chronic conditions associated different grades of bowel and/or bladder dysfunction, and/or needed CIC. Recently, Foster et al. have published high rates of resistance to third-generation cephalosporins and CRE in children who needed CIC (rates of ESBL of 7.8 to 10.4%) [19]. In addition, the increase rate of resistance to third-generation cephalosporins in patients who required CIC was higher than that in patients who did not need it [19].

Vesicoureteral reflux (VUR), recent UTI, or hospitalization and specifically PICU stay has been described as risk factors for bacterial resistance in UTI [4, 6–8, 11, 16, 20]. They were considered for the analysis, but did not

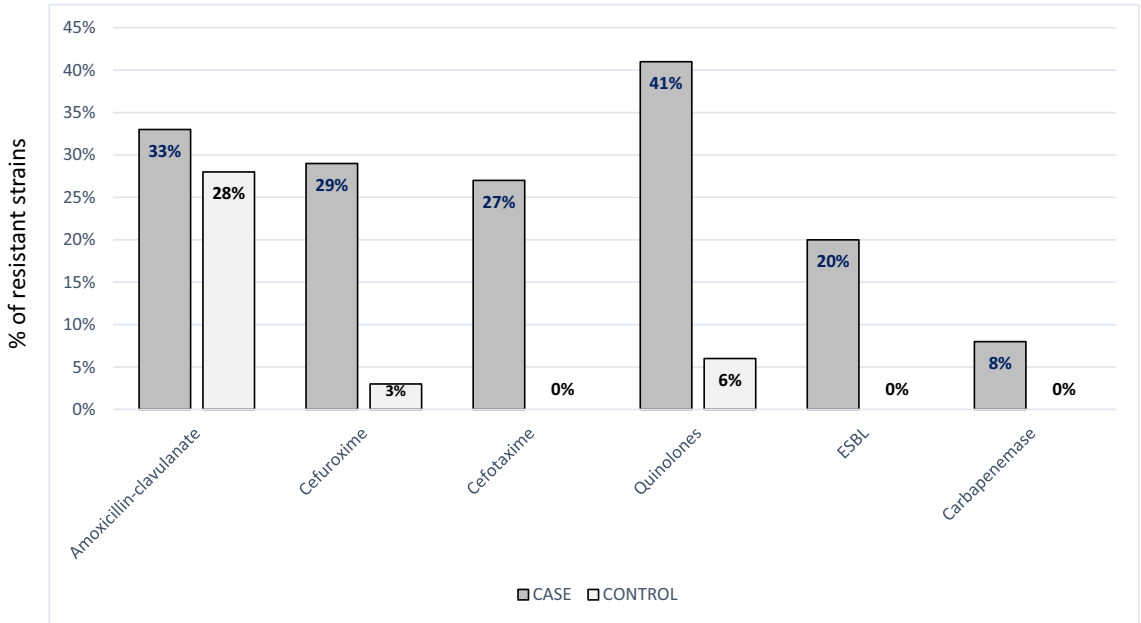

Fig. 1 Resistance patterns to other antibiotics cases vs. controls

maintain statistical significance after adjustment by potential confounders. These factors are usually present in children recurrently exposed to antibiotics, which could be the real reason for the increased resistance rates observed in this group of patients by many authors.

The increase in cephalosporin and gentamicin resistance is an important limitation for empirical antibiotic treatment of UTI in children [4, 7, 16, 20, 21]. Avoiding the prescription of cephalosporins as prophylaxis and using short-course antimicrobial regimens [4, 22] have been suggested as potential strategies to reduce antibiotic pressure. In addition, empirical use of intravenous amikacin in at-risk populations has been suggested by some authors [4, 5, 7, 11, 14, 16]. This aminoglycoside does not present cross resistance with gentamicin and provides appropriate coverage against other uropathogens, with an excellent diffusion to renal parenchyma [5, 6, 23, 24]. In our study, 100% of gentamicin-resistant strains were amikacin-sensitive, supporting the use of this antibiotic as an excellent alternative for patients with risk factors for gentamicin resistance. Apart from carbapenems, antibiotics such as fosfomycin have also been suggested as effective treatment for children suffering from UTI caused by ESBL-producing organisms, in order to reserve carbapenems for selected cases [25].

The main limitation of this study lies in its retrospective design, which has not allowed us to thoroughly collect data regarding the previous use of antibiotics, or the exact length and type of antibiotic prophylaxis. The relatively small sample size and the local feature of our study as well as the diversity of patients included are important limiting factors in allowing us to draw definite and generalizable conclusions.

In conclusion, our data suggest that isolation of gentamicin-resistant *E. coli* in CA-UTI could be more frequent in children with chronic diseases and/or previous antibiotic exposure. As the presence of a resistant strain may impact on the clinical outcome, identification of risk factors and adjustment of local empiric treatment according to epidemiological surveillance data should be implemented in clinical protocols. Prospective, longitudinal studies are needed to identify risk factors and resistance rates in high-risk populations.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors. The study protocol was approved by the La Paz Hospital's Ethics Committee.

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