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Clinical and Microbiological Characterization of Pediatric Patients with Urinary Tract Infection in a Fourth-Level Hospital in Bogotá, Colombia, over a Period of Four Years

Caracterización clínica y microbiológica de pacientes pediátricos con infección de vías urinarias en un hospital de cuarto nivel en Bogotá (Colombia) en un periodo de cuatro años

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ABSTRACT

Introduction: Urinary tract infection (UTI) is one of the most frequent infectious diseases in the pediatric population. There is no updated data available in literature of the pathogens responsible for complicated and uncomplicated UTI in children and their antimicrobial resistance profiles at the San Ignacio University Hospital or in the city of Bogotá. **Objective:** To carry out a demographic and clinical characterization of pediatric patients with UTI and a microbiological characterization of the resistance pattern of its main etiological agents. **Materials and methods:** A cross-sectional study was carried out with all pediatric patients under ten years of age with UTI confirmed by urine culture who came to our institution between January 2014 and December 2017. Redcap was used to register data corresponding to demographic variables, clinical manifestations, isolated microorganisms with their antibiograms, complications, and recurrence rate of UTI. Subsequently, a data analysis was performed. **Results:** A registry of 675 patients under ten years of age with urinary tract infection was obtained. The majority were females, two years old or younger and had fever as the cardinal sign of infection. A relevant comorbidity was constipation, and 15.3% of the children had a urinary tract malformation. Three-point five percent had a history of previous urological surgical intervention and 73.2% were experiencing

their first UTI episode. Ninety-eight-point four percent of the infections were community acquired and, regardless of their origin, the most common isolated agent was *Escherichia coli* (73%). The most frequent resistance patterns were penicillinase-producing (41.5%), followed by multi-sensitive (32.1%) and cephalosporins resistance (26%). Regarding the treatment established, cephalosporins were used in 92% of the cases, especially of first (61%) and third (38%) generation. **Conclusions:** We obtained similar results to those found in older studies in Bogotá and the San Ignacio University Hospital. Characterizing our population showed us that, through 2014–2017 and compared to the previous six years, the sensitivity of *Escherichia coli* to first-generation cephalosporins was stable, which indicates they are still a viable treatment option in our case, according to the local resistance profile.

Keywords
urinary tract infections; pediatrics; anti-bacterial agents; drug resistance; antibiogram; etiology; microbiology.

RESUMEN
Introducción: La infección de vías urinarias (IVU) es una de las patologías infecciosas más frecuentes en la población pediátrica. No existen datos actualizados disponibles en la literatura sobre los patógenos responsables de las IVU complicadas y no complicadas en niños y sus perfiles de resistencia a los antimicrobianos en el Hospital Universitario San Ignacio ni en la ciudad de Bogotá. **Objetivo:** Realizar una caracterización demográfica y clínica de los pacientes pediátricos con IVU, y una caracterización microbiológica y del patrón de resistencia de sus principales agentes etiológicos. **Diseño del estudio:** Estudio transversal que incluyó todos los pacientes pediátricos menores de 10 años con IVU confirmada por urocultivo que consultaron a nuestra institución entre enero de 2014 y diciembre de 2017. Se utilizó Redcap para el registro de datos correspondientes a variables demográficas, manifestaciones clínicas, microorganismos aislados, antibiogramas, complicaciones y tasa de recurrencia. Posteriormente, se realizó un análisis de los datos. **Resultados:** Se obtuvo un registro de 675 pacientes menores de 10 años con IVU. La mayoría eran niñas, tenían 2 años o menos y presentaron fiebre como signo cardinal de la infección. Una comorbilidad relevante en la población fue el estreñimiento y el 15,3 % de los niños presentaba alguna malformación del tracto urinario. El 3,5 % de los pacientes tenía antecedente de intervención quirúrgica urológica previa y el 73,2 % de los niños estaba cursando con el primer episodio de IVU. El 98,4 % de las infecciones fueron adquiridas en la comunidad e independiente de su origen el agente aislado con más frecuencia fue la *Escherichia coli* (73 %). Los patrones de resistencia más frecuentes fueron productores de penicilinasa (41,5 %) seguido de multisensibles (32,1 %) y resistentes a cefalosporinas (26 %). En cuanto al tratamiento establecido, se utilizaron cefalosporinas en el 92 % de los casos; principalmente de primera generación (61 %) y de tercera (38 %). **Conclusiones:** Se obtuvieron resultados similares a los presentados en estudios anteriores en Bogotá y el Hospital Universitario San Ignacio. Durante el periodo 2014-2017 y en comparación con los 6 años anteriores, la sensibilidad de *Escherichia coli* a las cefalosporinas de primera generación se mantuvo estable, lo que indica que sigue siendo una opción de tratamiento viable en nuestro caso, de acuerdo con el perfil de resistencia local.

Palabras clave
infección de vías urinarias; pediatría; agentes antibacterianos; resistencia bacteriana; antibiogramas; etiología; microbiología.

Introduction

Urinary tract infection (UTI) is one of the most common infectious diseases in the pediatric population. It is estimated that at the age of seven, 2% of boys and 8% of girls have had at least one episode of UTI and up to 30% of them had a recurrence between the first six to twelve months after the first infection (1-4).

These infections are classified as complicated or uncomplicated. Complicated UTIs include patients with structural or functional alterations and/or infections caused by unusual pathogens (5,6). These two are closely related, since having an abnormality of the urinary tract and/or an alteration of the urinary flow increases the possibilities of an uncommon etiological agent (7).

The most frequent causal microorganisms are bacteria, and some of the most commonly isolated are *Escherichia coli* (*E. coli*) (in up to 80% of cases), followed by *Klebsiella pneumoniae, Proteus mirabilis, Enterobacter* spp., *Enterococcus* spp., and *Pseudomonas* spp. (5). There are variations according to age and gender; it has been reported that during the first year of life, the prevalence is higher in males (3.7%) than in females (2%), and after that year, the ratio is inverted (5). Adolescent girls are more affected by *Staphylococcus*spp. and uncircumcised boys by *Proteus* spp. (6).

Another classification of urinary tract infections is based on whether or not it is recurrent; term used for patients who have experienced two or more episodes of pyelonephritis, one episode of pyelonephritis and

one or more episodes of cystitis, or three or more episodes of cystitis (8,9). Recurrent infection has been associated, throughout history, with the presence of vesicoureteral reflux, among other urinary tract abnormalities (10). In fact, evidence has shown that, in up to 30% of pediatric patients with a urological malformation, the first manifestation is a urinary tract infection (11).

Recurrent urinary tract infections can lead to long-term progressive kidney damage and scarring, which can precede proteinuria, hypertension, and, ultimately, chronic kidney failure (6,12). This was the main reason why antibiotic prophylaxis was proposed, on which there is currently contradictory evidence, since it is not clear if it really generates a protective effect on the recurrence of a urinary infection (13), but an increase in bacterial resistance has been described, that complicates treatment and reduces the available therapeutic arsenal (2).

Prompt treatment of the infection is essential, and the choice of antibiotics for empirical management of patients should be based on local data on susceptibility to antibiotics (14). Due to the growing resistance of microorganisms to traditionally used antibiotics, the proposed management has changed over time (3). A meta-analysis reported that the resistance of *E. coli* to ampicillin and trimethoprim sulfamethoxazole (TMP SMX) in both developing and developed countries is 72–78% and that of *Klebsiella* spp. to gentamicin and third-generation cephalosporins is 60–66% (6).

Colombia is no exception, since it has been necessary to modify management guidelines in recent years due to growing bacterial resistance (15). Now, in the city of Bogotá, a mandatory registration program of resistance patterns is being carried out in district hospitals by the Bacterial Resistance Control Group (GREBO), to which its results are expected to define the different patterns of resistance presented in the multiple hospitals of the city.

In Bogotá, various studies have also been carried out with the objective of identifying the main etiological agents in certain hospitals. During 2006–2007 Granados et al. observed the microbiological characteristics and antimicrobial resistance of isolates from urine cultures of children at the Santa Fe Foundation, and the most commonly isolated microorganisms were *E. coli* (62%), *Proteus mirabilis* (17%), and *Enterococcus faecalis* (*E. faecalis*) (6%). They reported an *E. coli*'sresistance profile of 50% for ampicillin, 41% for TMP SMX and 17% for ampicillin sulbactam. On the other hand, *Proteus mirabilis*had a 96% resistance towards nitrofurantoin, and *E. faecalis* had a 76% resistance for clindamycin and 100% for ampicillin, nitrofurantoin, linezolid and vancomycin (16). In 2014, Océn and Corredor (17) analyzed urinary tract infections in pediatric patients at Bosa Hospital, and the main isolated etiological agents were *E. coli* (95%), *Klebsiella ozaenae* (4%), *Klebsiella pneumoniae* (2%), and *Proteus mirabilis* (2%), with a resistance profile of *E. coli* of 72% for ampicillin sulbactam, 8% for gentamicin, and 8% for cefazolin (17).

At the San Ignacio University Hospital (HUSI), a microbiological and antimicrobial resistance characterization was carried out in urine culture isolates in children aged one month to five years between January 2008 and February 2013 by Estrada et al., reporting a distribution by sex of 75% for females and 25% for males, in which the age range with the highest prevalence was between two and twelve months. The most frequent etiological agents were *E. coli* (78.3%), *Proteus mirabilis* (8.7%), and *Klebsiella pneumoniae* (3.9%), and the sensitivity of *E. coli* for treatment with cefazolin was 80.1%, 79.3% with ceftriaxone, and nitrofurantoin with 86.7%, on which the institution's management guidelines have been based since their publication.

In most cases, the antibiotic management of urinary tract infection must be established empirically, and this must be based on the antimicrobial resistance patterns typical of the hospital where it is prescribed. If not, the risk of short-term complications such as bacteremia and long-term complications such as chronic hypertension, kidney scarring, and end-stage kidney disease may increase. Additionally, the inappropriate use of antibiotics can modify the bacterial flora and induce resistance, which is

already a latent and serious problem in our population (3,18).

There is no up-to-date data available in literature about the responsible pathogens of complicated and uncomplicated urinary tract infections in pediatric patients and their antimicrobial resistance profiles at the San Ignacio University Hospital, nor in the city of Bogotá (19). Additionally, the ones available are focused on infants. Therefore, our objective was to carry out a retrospective observational study considering all pediatric patients with confirmed urinary tract infection who were treated at the HUSI from 2014 to 2017. This is in order to determine the main isolated microorganisms and their susceptibility patterns according to the urine cultures and antibiograms, which can lead to propose empirical treatment schemes and prevention strategies at our community.

Materials and methods

A cross-sectional retrospective study was carried out. It was approved by the ethical committee of San Ignacio University Hospital, and inclusion criteria involved all patients under the age of ten who were treated at the institution between 2014 and 2019 and had a diagnosis of complicated or not complicated UTI (confirmed by positive urine culture). The method used to obtain the urine sample was defined in terms of age; depending on the case, it was taken by urethral catheterization or clean catch midstream urine sample. All the included patients were diagnosed and treated at HUSI.

To collect the data, we filtered pediatric patients with ICD-10 (International Classification of Diseases), code N390, which stands for UTI diagnosis. We reviewed clinical records and used REDCap (Research Electronic Data Capture) software, which is a secure web application for building and managing databases, in order to register data. The purpose was to characterize the population in demographic terms, if they had history of previous urological surgical intervention, their clinical presentation, and to identify the main etiological agents of infection and their resistance pattern based on the antibiogram. It also aimed to identify the antibiotic managements, the complications found, and the recurrence ratio of UTI. The results were compared with other studies of UTI in pediatric patients.

Results

From January 2014 to December 2017, 675 children under ten years of age were diagnosed with urinary tract infection at the San Ignacio University Hospital. The majority were females and two years old or younger (Table 1).

Table 1
Age and gender distribution among the studied pediatric population

Age (years)	Male n (%)	Females n (%)	Total n (%)
<1 year	110 (56.1)	125 (26.1)	235 (34.8)
1–2 years	58 (29.6)	178 (37.2)	236 (35)
3–5 years	23 (11.7)	152 (31.7)	175 (25.9)
6–10 years	5 (2.6)	24 (5)	29 (4.3)
Total	196 (29)	479 (71)	675 (100)

Source: Own elaboration.

Fever was the most common sign in the initial consult (Table 2); patients were hospitalized for four days in average, and 156 patients had more severe UTIs or complications, corresponding to 22.8% of the sample (pyelonephritis in 68.8% of the cases, sepsis in 18.2% and acute kidney injury in 2.6%, among others). A relevant comorbidity was constipation, which was found in 21.5% of the patients and regarding the previous history in terms of UTI, 73.2% were experiencing their first episode, and, of the remaining cases, 57.5% were on their second episode.

Table 2
Most common chief complaints among the studied pediatric population

Symptoms	n (%)
Fever	403 (59.7)
Dysuria	111 (16.4)
Emesis	38 (5.6)
Abdominal pain	24 (3.6)
Hematuria	12 (1.8)
Fetid urine	10 (1.5)
Hyporexia	9 (1.3)

Source: Own elaboration.

Fifteen-point-three percent of the children had a urinary tract malformation and the frequency of the most prevalent pathologies is exposed in Table 3. The diagnosis of the urinary tract malformations was made between 2014 and 2017 in 36.5% of the cases, and, in the rest of the patients, the diagnosis was made previously or the date of diagnosis was unknown. Three-point-five percent of the patients had a history of previous urological surgical intervention, and the most common procedures are specified in Table 4.

Table 3
Most common urological malformations in the studied pediatric population

Urinary tract malformation	n (%)
Renal anomaly	39 (37.9)
Vesicoureteral reflux grade III	14 (13.5)
Megaureter	13 (12.6)
Vesicoureteral reflux grade IV	8 (7.8)
Pyeloureteral obstruction	8 (7.8)
Vesicoureteral reflux grade I	7 (6.8)
Vesicoureteral reflux grade II	7 (6.8)
Ureterocele	7 (6.8)

Source: Own elaboration.

Table 4
Most common urological interventions in the studied pediatric population

Previous urological surgical interventions	n (%)
Vesicostomy	4 (16.6)
Correction of posterior urethral valves	3 (12.5)
Endoscopic resection of ureterocele	3 (12.5)
Vesicoureteral reimplantation	3 (12.5)
Double collecting system correction	2 (8.3)
Pyeloplasty	2 (8.3)
Nephroureterectomy	2 (8.3)

Source: Own elaboration.

In both cases (patients with infections acquired in the community and infections associated with healthcare), *E. coli* was the most frequent isolated microorganism (Table 5), and the most prevalent resistance patterns were penicillinase-producing (41.5%), followed by multi-sensitive (32.1%) and cephalosporins resistance (26%). The antibiotics to which *E.coli* had the higher resistance rates are presented in Table 6.

Table 5
Most frequently isolated microorganisms in the urine cultures of the pediatric population under study

Isolated microorganisms in community acquired UTI (n=664)	n (%)
E. coli	489 (73.6)
Proteus mirabilis	82 (12.3)
Klebsiella pneumoniae	32 (4.8)
Citrobacter	4 (0.6)
Pseudomona aeruginosa	3 (0.4)
Enterobacter	2 (0.3)
Isolated microorganisms in UTI associated with healthcare (n=11)	**n (%)**
E. coli	4 (36.4)
Klebsiella pneumoniae	3 (27.3)
Citrobacter	1 (9.1)
Proteus mirabilis	1 (9.1)
Pseudomona aeruginosa	1 (9.1)
Enterococcus faecalis	1 (9.1)

Table 6
Escherichia coli's resistance to antibiotics according to antibiograms of pediatric patients with urinary tract infection at San Ignacio University Hospital in Bogotá – Colombia

Antibiotics	2014 (n=114)	2015 (n=104)	2016 (n=117)	2017 (n=158)
Cefazolin	10.5% (12)	11.5% (12)	13.6% (16)	3.7% (6)
Ceftriaxone	8.7% (10)	8.6% (9)	7.6% (9)	4.4% (7)
Ampicillin	64.9% (74)	68.2% (71)	62.3% (73)	45.5% (72)
Amp / sulbactam	32.4% (37)	42.3% (44)	37.6% (44)	28.4% (45)
Cefuroxime	2.6% (3)	0% (0)	0% (0)	3.7% (6)
Trimet / Sulfa	46.4% (53)	48% (50)	51.2% (60)	50.6% (80)
Ertapenem	0% (0)	0% (0)	0% (0)	0% (0)
Meropenem	0% (0)	0% (0)	0% (0)	0% (0)
Amikacin	0% (0)	0% (0)	0% (0)	0% (0)
Pip / Tazo	0% (0)	0.9% (1)	1.7% (2)	2.5% (4)
Gentamicin	13.1% (15)	18.2% (19)	18.8% (22)	22.7% (36)
Aztreonam	7.8% (9)	8.6% (9)	5.9% (7)	5% (8)
Nitrofurantoin	2.6% (3)	3.8% (4)	0.8% (1)	0% (0)
Cefoxitin	2.6% (3)	0% (0)	0% (0)	0.6% (1)
Cefepime	7.8% (9)	8.6% (9)	7.6% (9)	8.8% (14)
Cefotaxime	8.7% (10)	8.6% (9)	7.6% (9)	5% (8)
Ciprofloxacin	20.1% (23)	11.5% (12)	17% (20)	4.4% (7)
Ceftazidime	8.7% (10)	7.6% (8)	6.8% (8)	5% (8)
Cephalothin	1.7% (2)	8.6% (9)	5.1% (6)	29.7% (47)

The average days of treatment with antibiotics were 8.5. In 92% of the cases, a cephalosporin was used; first generation in 61% of cases, and third generation in 38%. Ertapenem was used in 7% of the patients and 5% had received prophylactic management at some point of their lives, especially with cephalexin, nitrofurantoin, nalidixic acid or trimethoprim sulfamethoxazole, with a frequency of 55.9%, 17.6%, 8.8%, and 8.8%, respectively.

Conclusions

In conclusion, the results were similar to those obtained in previous years in studies carried out in Bogotá. Compared with the Santa Fe Foundation article written during 2006 and 2007, the first two etiological agents remained the same (*E.coli* and *Proteus mirabilis*); however, in the present study, a lower proportion of *Enterococcus faecalis* infection was found. It is important to mention that, in general, an increase in the resistance of *E.coli* to different antibiotics was evidenced between these two institutions from 2006 to 2008, which can be observed in Table 7. As to the 2014 study by Océn and Corredor (17), which was carried out in Bosa Hospital and included 164 patients whose profiles showed higher resistance for gentamicin (8% vs. 13.1% in 2014, 18.2 in 2015, 18.8 in 2016, and 22.7 in 2017), cefazolin (8% vs. 10.4% in 2014, 11.5% in 2015, and 13.6% in 2016), and ampicillin (50% vs. 64.9% in 2014, 68.2% in 2015, and 62.3% in 2016), as well as less frequency of infection by *Klebsiella ozaenae* (16).

In Medellín, the resistance profile of *E. coli* in pediatric patients with UTI was evaluated in 2010 and 2011, and the results were similar to those shown in Bogotá in previous years (TMP SMX: 43% v. 42.4% in 2008–2013 and 46.4% in 2014; gentamicin: 12% v. 8.4% in 2008–2013 and 13.1% in 2014; cefepime: <10% v. 13.8% in 2008–2013, and 7.8% in 2014, among others) (20). In Cali, a similar study was developed during 2004 and 2005, in which they found higher resistance patterns when set side by side with the results presented in Table 7 (ampicilin: 79.7%; ampicillin sulbactam: 69.1%; cefazolin: 44.7%; TMP SMX: 52.8%), which corroborates that there are significant differences in bacterial resistance depending on the moment, city and institution where it is evaluated (21).

Table 7
Comparison of Escherichia coli's resistance to antibiotics from 2006 to 2017 in two different institutions in Bogotá, Colombia

Antibiotics	FSFB (%)	HUSI (%)	HUSI (%)			
	2006-2007 n=262	2008-2013 n=483*	2014 n=114	2015 n=104	2016 n=117	2017 n=158
Ampicillin	50	57.2	64.9	68.2	62.3	45.5
Amp / sulb	17.6	31.5	32.4	42.3	37.6	28.4
Cefazolin	5.7	13	10.4	11.5	13.6	3.7
Ceftriaxone	0.4	9.1	8.7	8.6	7.6	4.4
Ceftazidime	0.4	4.6	8.7	7.6	6.8	5
Cefepime	0.4	13.8	7.8	8.6	7.6	8.8
Gentamicin	3.1	8.4	13.1	18.2	18.8	22.7
Aztreonam	0.8	6.3	7.8	8.6	5.9	5
Trimet / Sulfa	41.2	42.4	46.4	48	51.2	50.6
Nitrofurantoin	0.8	8.2	2.6	3.8	0.8	0
Ciprofloxacin	4.2	15.5	20.1	11.5	17	4.4

FSFB: Santa Fé Foundation; HUSI: San Ignacio University Hospital.
*The results of this study include the resistance of all the microorganisms found. *E. coli* stands for 78.3% of the cases.

We also highlight, as one of the limitations of our study, the fact that it is monocentric, which generates a limitation to extrapolate and compare the results with other health centers, since the population characteristics may be different.

Regarding studies in our institution, although not published, an investigation was carried out prior to the years of the present study (2008–2013 v. 2014–2017), which was very useful to compare changes over time. However, it is important to emphasize that this was performed only in pediatric patients of five years or less and that the sample was larger in the present study (675 v. 483). The distribution by sex was very similar, in both cases being mostly girls (75% v. 71%) and, to a lesser extent, boys (25% v. 29%), which correlated with global epidemiology and has been associated historically with the anatomical differences between both sexes, especially the length of the urethra. The most frequent etiological agents of UTI persisted through the years, first being caused by *E. coli*, with a similar prevalence (73% v. 78.3%), followed by *Proteus mirabilis* (12.4% vs. 8.7%) and *Klebsiella pneumoniae* (4.7% v. 3.9%). These three microorganisms were also more sensitive and more resistant to the same antibiotics (they had higher sensitivity rates for ertapenem, meropenem, and amikacin, and lower sensitivity rates for ampicillin and ampicillin/sulbactam). Regarding the sensitivity pattern of the most common bacteria (*E. coli*), the present study showed a resistance profile to cefazolin that was like the one reported in previous years (13% in 2008–2013 v. 10.5% in 2014, 11.5% in 2015, and 13.6% in 2016) and, regarding ceftriaxone and nitrofurantoin, even higher sensitivities were found (79.3% v. 91.2%, 91.3%, 92.% and 86.7% v. 97.3%, 96.1%, 99.1%, and 98%, respectively) (Table 7).

Based on these results from 2008 to 2013, the institutional guide divided treatment recommendations in children younger than two years or older. Cefepime was recommended in newborns. In patients one to six months old with severity criteria ceftriaxone was recommended, and without severity criteria cefazolin. Patients that were older than six months were divided depending on whether or not they had fever. If they did, treatment again depended on whether or not they had severity criteria, and, if they didn't, they should receive treatment with cephalexin. In children with two years of age or more that had severity criteria, they promoted treatment with ceftriaxone, and, if they didn't have severity criteria but did have criteria for hospitalization, cefazolin. In outpatient management, cephalexin was recommended.

These recommendations are closely related to the results of the present study, since, in 92% of the cases, a cephalosporin was chosen for empirical treatment, which suggests that medical staff do follow the institutional guide recommendations.

In April 2021, a new institutional guide was published and reported that, due to the increased resistance of *E. coli* to first-generation cephalosporins and low resistance to second- and third-generation cephalosporins, and that, in some episodes of UTI, the patients required a change from antimicrobial management to one

with a broader spectrum, they decided to change the recommendation to use second-generation cephalosporins in the empirical treatment of pediatric patients with uncomplicated UTI, suggesting cefuroxime, in most cases, instead of cefazolin.

In our study, a stable resistance to first-generation cephalosporins was observed for *E. coli* from 2014 to 2017 and compared to the six previous years. Considering the importance of the institution's own resistance profile to guide the empirical management, we recommend evaluating in more detail whether it is justified to make the last changes. It is ideal to administer the least potent effective antibiotic in order to have the opportunity to escalate management in case the patient requires it, and to make a rational use of antibiotics to avoid the increase in antibiotic resistance rates. We also propose cost-effectiveness studies comparing cefazolin and cefuroxime, since second-generation cephalosporins imply a higher price and the impact of recommending them as first-line management in all patients with uncomplicated UTI should be evaluated.

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