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Urinary Tract Infections in Children: Changing Trends in Etiology and Local Resistance Patterns over a Three-Year Period

Infeções do Trato Urinário em Pediatria: Evolução da Etiologia e Padrões de Resistências Locais ao Longo de Três Anos

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ABSTRACT

Introduction: Urinary tract infections are common in pediatrics. Knowledge of local resistance patterns is crucial to guide empirical antibiotic therapy. We aimed to review the pathogens implicated in urinary tract infections, local resistance patterns, and the impact of switching first-line empirical antibiotic regimens.
Methods: We conducted a cross-sectional study including pediatric patients performing urine cultures in a hospital in northern Portugal over two periods: 2019 (group 1) and 2022 (group 2). Between time periods, an internal guideline was implemented recommending cefuroxime as the first-line choice for empirical treatment of urinary tract infections, according to local resistance patterns. Uropathogens, empirical antibiotic choices and resistance patterns were compared among groups.
Results: The final sample included 402 cases of urinary tract infections in group 1 and 398 in group 2. *Escherichia coli* was the most common uropathogen (79.4 - 83.3%), followed by *Proteus mirabilis* and *Klebsiella spp*. The most common empirical antibiotic in group 1 was amoxicillin-clavulanate (A-C), as opposed to cefuroxime in group 2 ($p < 0.001$). The most common resistance was to ampicillin (39.3% - 39.7%). Resistance to A-C slightly decreased (33.1% *vs* 27.4%, $p = 0.079$), while resistance to cefuroxime (4.7% *vs* 3.3%, $p = 0.292$) and trimethoprim-sulfamethoxazole (TMP-SMX) remained similar (15.2% *vs* 14.1%, $p = 0.659$). Resistances to nitrofurantoin (9.0% *vs* 0.3%, $p < 0.001$) and fosfomycin (1.7% *vs* 0.3%, $p < 0.036$) significantly decreased from group 1 to group 2.
Conclusion: *E.coli* remains the predominant pathogen in pediatric urinary tract infections. Resistance to A-C in our sample was high (33.1%). The switch from A-C to cefuroxime as first-line agent resulted in a decreasing trend in A-C resistance, while cefuroxime resistance remained low and even slightly lower.
Keywords: Child; Drug Resistance, Bacterial; Urinary Tract Infections/drug therapy; Urinary Tract Infections/etiology; Urinary Tract Infections/microbiology

RESUMO

Introdução: As infeções do trato urinário são comuns em idade pediátrica. Conhecer a etiologia e os padrões de resistência locais é fundamental na determinação do tratamento empírico. Propusemo-nos a rever os patógenos implicados nas infeções do trato urinário, os padrões de resistência locais e o impacto do ajuste da antibioterapia de primeira-linha de acordo com as mesmas.
Métodos: Conduzimos um estudo transversal que incluiu os doentes pediátricos que realizaram urocultura num hospital do Norte de Portugal durante dois períodos: 2019 (grupo 1) e 2022 (grupo 2). Entre estes dois períodos, foi instituído um protocolo interno de atuação clínica que recomendava a utilização de cefuroxima como antibioterapia empírica de primeira linha, de acordo com a epidemiologia local. Os grupos foram comparados quanto aos uropatógenos identificados, respetivos padrões de resistência a antimicrobianos e antibioterapia empírica instituída.
Resultados: Foram identificados 402 casos de infeções do trato urinário no grupo 1 e 398 no grupo 2. A *Escherichia coli* (*E. coli*) foi o uropatógeno mais comum (79,4% - 83,3%), seguido do *Proteus mirabilis* e da *Klebsiella spp*. No grupo 1, o antimicrobiano empírico mais frequentemente selecionado foi a amoxicillina-clavulanato (A-C), enquanto no grupo 2 foi a cefuroxima ($p < 0.001$). A resistência mais frequentemente identificada foi à ampicilina (39.3% - 39.7%). A resistência a A-C não mostrou alterações estatisticamente significativas entre grupos (33,1% *vs* 27,4%, $p = 0{,}079$), tal como a resistência à cefuroxima (4,7% *vs* 3,3%, $p = 0{,}292$) e ao trimetoprim-sulfametoxazol (TMP-SMX) (15,2% *vs* 14,1%, $p = 0{,}659$). As resistências à nitrofurantoína (9,0% *vs* 0,3%, $p < 0.001$) e à fosfomicina (1,7% *vs* 0,3%, $p < 0{,}036$) diminuíram significativamente entre o grupo 1 e o grupo 2.
Conclusão: A *E.coli* mantém-se como o principal agente de infeções do trato urinário em pediatria. A resistência a A-C na nossa amostra é elevada (33,1%). A alteração de antibioterapia empírica de primeira-linha de A-C para cefuroxima resultou numa tendência de diminuição da resistência à A-C, sem aumento da resistência a cefuroxima.
Palavras-chave: Criança; Infeções do Trato Urinário/etiologia; Infeções do Trato Urinário/microbiologia; Infeções do Trato Urinário/tratamento farmacológico; Resistência Bacteriana a Medicamentos

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KEY MESSAGES

- *E.coli* remains the predominant pathogen in pediatric UTI.
- Antibiotic resistance patterns are crucial in guiding treatment selection.
- In our sample, uropathogen resistance to amoxicillin-clavulanate (A-C) was high (33.1%).
- Switching from A-C to cefuroxime as the first-line option to treat pediatric UTI resulted in a decreasing trend in A-C resistance, although not statistically significant. Cefuroxime resistance remained low.
- The continued use of cefuroxime as first-line option should help decrease A-C resistance in our population. Further studies would be of interest to evaluate the impact of this measure.

INTRODUCTION

Urinary tract infections (UTI) occur when microorganisms multiply in the urinary tract, causing an inflammatory response.[1] This is an important cause of hospital admissions and morbidity in pediatrics.[2] UTIs can affect the lower urinary tract, resulting in cystitis, or the upper urinary tract, resulting in pyelonephritis.[3] Because pyelonephritis typically presents with fever, as opposed to cystitis, the terms 'febrile' and 'afebrile' UTI are widely used to refer to each type of infection.[4]

Girls are more commonly affected, except during the first year of life.[5] Up to 11% of girls and 4% of boys experience a UTI before the age of 16 years.[3]

The presenting signs and symptoms are usually nonspecific, which can contribute to a delayed diagnosis.[6] Fever is commonly the only symptom in children under the age of two, but it may also be accompanied by irritability, lethargy, vomiting, and diarrhea.[4] In older, particularly, potty-trained children, dysuria, urinary frequency, urgency, and suprapubic or flank pain may be present.[3]

The most common pathogens causing UTIs are *Escherichia coli* (*E. coli*), *Proteus* spp., *Staphylococcus saprophyticus*, *Klebsiella* spp., and other Enterobacteriaceae.[7-9] Bacteria typically reach the urinary tract by the ascending route, as the most frequent UTI agents are present in the gastrointestinal tract.[10] However, hematogenous spread can also occur, particularly in newborns.[10]

Diagnosis is confirmed by the proliferation of a single microorganism in a urine culture.[11] A late diagnosis can lead to short-term complications, such as renal abscess and sepsis, and long-term complications such as renal scarring, hypertension, and renal failure.[10,12] Therefore, early empirical antibiotic treatment should be started upon a strong suspicion of UTI.[13] However, antibiotic overuse, especially of a broader than necessary spectrum, can lead to an increase in antibiotic-resistant pathogens.[14]

The most commonly recommended antibiotics include trimethoprim-sulfamethoxazole (TMP-SMX), nitrofurantoin, ciprofloxacin, cephalosporins, and amoxicillin-clavulanate (A-C).[15] In Portugal, A-C and cefuroxime are both acceptable first-line choices for empirical treatment.[16] The choice of antibiotics should take into consideration local data on antibiotic resistance patterns, which vary greatly according to geographical location and population characteristics.[17,18] Hence, local surveillance of antibiotic resistance is crucial for determining the pattern of antimicrobial resistance and guiding empirical and directed therapy.[19]

In this study, we aimed to determine the resistance patterns of the most common pathogens causing UTIs in the pediatric population treated in a district-level hospital in the north of Portugal, before and after a guideline guided by local epidemiological data was implemented. Secondary outcomes included the clinical and demographic characterization of patients presenting with UTI.

METHODS

We performed a single-center, cross-sectional study including two groups separated by a three-year period. Firstly, we included patients between the ages of 29 days and 17 years and 364 days with urine cultures registered in our microbiology laboratory between January 1, 2019 and December 31, 2019. Only pure growth > 10^3 CFU/mL in samples collected by bladder catheterization and > 10^5 CFU/mL in samples collected by urinary midstream were included. Urine samples obtained by urine bag or to which the sampling method was not specified were excluded, as well as samples in which more than one microorganism was identified.

For included subjects, clinical records were examined to retrieve information on sex, age, sampling method, CFU/mL counts, identified microorganism, antibiogram, empirical antibiotic regimen, febrile/afebrile infection, chemoprophylaxis during infection, history of urologic abnormalities, discharge destination, and follow-up. These participants were labeled as group 1.

Based on the primary results, in January 2021 we implemented an internal guideline stating cefuroxime was the first-line choice for empirical antibiotic therapy for our population. This guideline also reviewed the appropriate urine collecting methods and indications for follow-up in a pediatric nephrology consult.

In 2023, we then identified all urine cultures registered in our microbiology laboratory between January 1, 2022 and December 31, 2022 and collected data on the aforementioned variables, with the same inclusion criteria as the previous cohort. These participants consisted of group 2.

This study was approved by the institutional Ethics Committee.

Statistical analyses were performed using the statistical software R, version 4.4.2, and the packages 'glmmTMB' and 'interactions'.

The significance level was set at 0.1. In this study, the significance level between 0.05 and 0.1 is called 'marginal' and, roughly speaking, it corresponds to weaker effects. All significant results have been assessed through regression modeling. When compared to traditional statistical tests, regression models have several advantages such as: incorporating a family of distributions suitable for the dependent variable, performing multivariable analyses (including interactions), discarding *p*-value adjustment for multiple comparisons, and providing graphical complementary analyses. We used logistic models for dichotomous data, and Conway-Maxwell-Poisson models for count data.

RESULTS

Clinical and demographic characteristics

The final sample consisted of 402 cases of UTI in group 1 and 398 in group 2. Table 1 summarizes the clinical demographic characteristics of both groups.

Mean age was 4.7 (SD 5.56) years in group 1 and 3.0 (SD 4.67) years in group 2 ($p < 0.001$). There was a higher prevalence of the female sex in both groups, with a 4:1 distribution in the first and 2:1 distribution in the second ($p < 0.001$). Mean age was significantly lower in male patients in group 1 ($p = 0.023$) and in female patients in group 2 ($p < 0.001$).

Regarding the type of infection, in group 1, 226 (56.2%) were febrile and 176 (43.8%) were afebrile; in group 2, 272 (68.3%) were febrile and 126 (31.7%) were afebrile

Table 1 – Clinical and demographic characteristics

	Group 1 (n = 402)		Group 2 (n = 398)		*p*-value
Age (years)	4.7 (5.56)		3.0 (4.67)		< 0.001***
Sex – male (female)	78 (19.4%)		130 (32.7%)		< 0.001***
Febrile UTI (afebrile UTI)	226 (56.2%)		272 (68.3%)		0.004***
Collecting method – In-out catheterization (midstream)	171 (42.5%)		231 (58.0%)		< 0.001***
< 2 years-old	162 out of 213 (76.1%)		225 out of 279 (80.6%)		0.219
Uropathy	63 (15.7%)		56 (14.1%)		0.525
Chemoprophylaxis	8 (2.0%)		15 (3.8%)		0.139
Inpatient treatment	24 (6.0%)		38 (9.5%)		0.061^
Non-family doctor follow-up					
Pediatric nephrology consult (general paediatrician)	112 out of 185 (27.9%)		51 out of 198 (12.8%)		< 0.001***
Age (years)					
Male patients	3.6 (5.01)	0.023*	1.7 (3.27)	< 0.001***	*
Female patients	4.9 (5.66)		3.6 (5.10)		
Inpatient	2.3 (4.25)	0.002**	0.4 (1.17)	<0.001***	
Outpatient	4.8 (5.60)		3.3 (4.81)		
Febrile infections					
Male patients	40 (51.3%)	0.328	89 (68.5%)	0.972	
Female patients	186 (57.4%)		183 (68.3%)		
In-out catheterization					
Male patients	16 (20.5%)	< 0.001***	163 (60.8%)	0.107	
Female patients	155 (47.8%)		68 (52.3%)		

Continuous variables are represented as mean (SD) and categorical variables as counts (percentage). *p*-values were calculated using adequate regression modelling (logistic for dichotomous data, and Conway-Maxwell-Poisson for count data).
Each item assessed with a different model (a total of 13 models).
^*p* < 0.1; **p* < 0.05; ***p* < 0.01; ****p* < 0.001.

(*p* < 0.001). For both groups, and in both sexes, febrile infections were more frequent.

For children under the age of two, in both groups, in-out catheterization was the most frequent urine-collecting method (*p* = 0.219). In group 1, 20.5% of male and 47.8% of female patients had a urine sample collected by in-out catheterization (*p* < 0.001). In group 2, the percentage of in-out catheterization was 60.8% in male and 52.3% in female patients (*p* = 0.107).

There was no statistically significant difference between groups regarding the presence of urologic abnormalities (15.7% *vs* 14.1%, *p* = 0.525) or chemoprophylaxis use (2.0% *vs* 3.8%, *p* = 0.139).

Most children were treated as outpatients and only 24 (6.0%) in group 1 and 38 (9.5%) in group 2 were admitted (*p* = 0.061). Median age was lower for inpatients in both groups (*p* < 0.001).

Most patients were followed-up by their family doctor: 217 (54.0%) in group 1 and 200 (50.3%) in group 2. In group 1, the second most common referral for follow-up was the pediatric nephrology consultation (27.9%), whereas in group 2, the second most common referral was to the general pediatrician (36.9%), with the difference being statistically significant (*p* < 0.001).

Microorganisms

Table 2 describes the relative frequency of the identified pathogens, and Fig. 1 represents the relative frequency of the most common bacteria according to type of infection. For afebrile infections, *E. coli* (n = 132, 75.0%), *Proteus mirabilis* (n = 25, 14.2%) and *Staphylococcus saprophyticus* (n = 12, 6.8%) were the most common pathogens in group 1. In group 2, *E. coli* (n = 87, 69.0%), *Proteus mirabilis* (n = 24, 9.0%) and *Klebsiella* spp. (n = 6, 4.8%) were the most common agents identified.

For febrile infections, the most commonly isolated microorganisms were *E. coli* (n = 203, 89.8%), *Proteus mirabilis* (n = 10, 4.4%) and *Klebsiella* spp. (n = 9, 4.0%) in group 1 as well as group 2: *E. coli* (n = 229, 84.2%), *Proteus mirabilis* (n = 21, 7.7%) and *Klebsiella* spp. (n = 12, 4.4%). For these microorganisms, there were no statistically significant differences between groups.

Empirical antibiotic regimen

Empirical antibiotic regimen choice is detailed in Table 3, and Fig. 1 shows the most frequently prescribed antibiotics according to type of infection. Amoxicillin-clavulanate was the most common antibiotic choice in group 1 for both febrile (51.8%) and afebrile infections (61.4%), as opposed to cefuroxime becoming the preferred drug in group 2 (*p* < 0.001), also for both febrile (67.6%) and afebrile infections (46.8%). Cefotaxime in febrile infections and fosfomycin in afebrile infections remained the third most frequent choice in both groups.

Resistance patterns

In vitro resistance patterns for the microorganisms identified in both groups are represented in Table 4 and were similar in both groups. The most commonly identified resistances were to ampicillin (39.3% in group 1 *vs* 39.7% in group 2, *p* = 0.909), A-C and TMP-SMX. Resistance to cefuroxime was 4.7% in group 1 and 3.3% in group 2, *p* = 0.295). Resistance to A-C was 33.1% in group 1 and 27.4% in group 2 (*p* = 0.078). Resistance to TMP-SMX, the most common agent in chemoprophylaxis, remained similar (15.2% in group 1 *vs* 14.1% in group 2, *p* = 0.659). Resistances to nitrofurantoin (9.0% *vs* 0.3%, *p* < 0.001) and fosfomycin (2.0% *vs* 0.3%, *p* < 0.0496) decreased significantly from group 1 to group 2.

Table 5 describes the *in vitro* resistance patterns to the two most frequent empirically prescribed antibiotics of the three most commonly isolated bacteria.

In both groups, resistance patterns were similar regardless of a history of urologic abnormalities (Table 4).

Resistance to cotrimoxazole was significantly higher in children under chemoprophylaxis in both groups (Table 4).

DISCUSSION

In this study, we analyzed the epidemiology of UTIs in children, regarding the pathogens involved and their resistance patterns. We compared two time periods, before and after an internal guideline was published with cefuroxime

Table 2 – Pathogens identified in urine culture

Pathogen	Group 1	Group 2	*p*-value
Escherichia coli	335 (83.3%)	316 (79.4%)	0.457
Proteus mirabilis	35 (8.7%)	45 (11.3%)	0.265
Klebsiella spp.	13 (3.2%)	16 (4.0%)	0.578
Staphyloccus saprophyticus	12 (3.0%)	3 (0.8%)	**0.032***
Other pathogens	7 (1.7%)	18 (4.5%)	**0.034***

p-values were calculated using a unique logistic regression model with 'group' as dependent variable and 'microorganism' as independent variable.
Percentages have been rounded and thus may not add up to 100%.
^*p* < 0.1; **p* < 0.05; ***p* < 0.01; ****p* < 0.001.

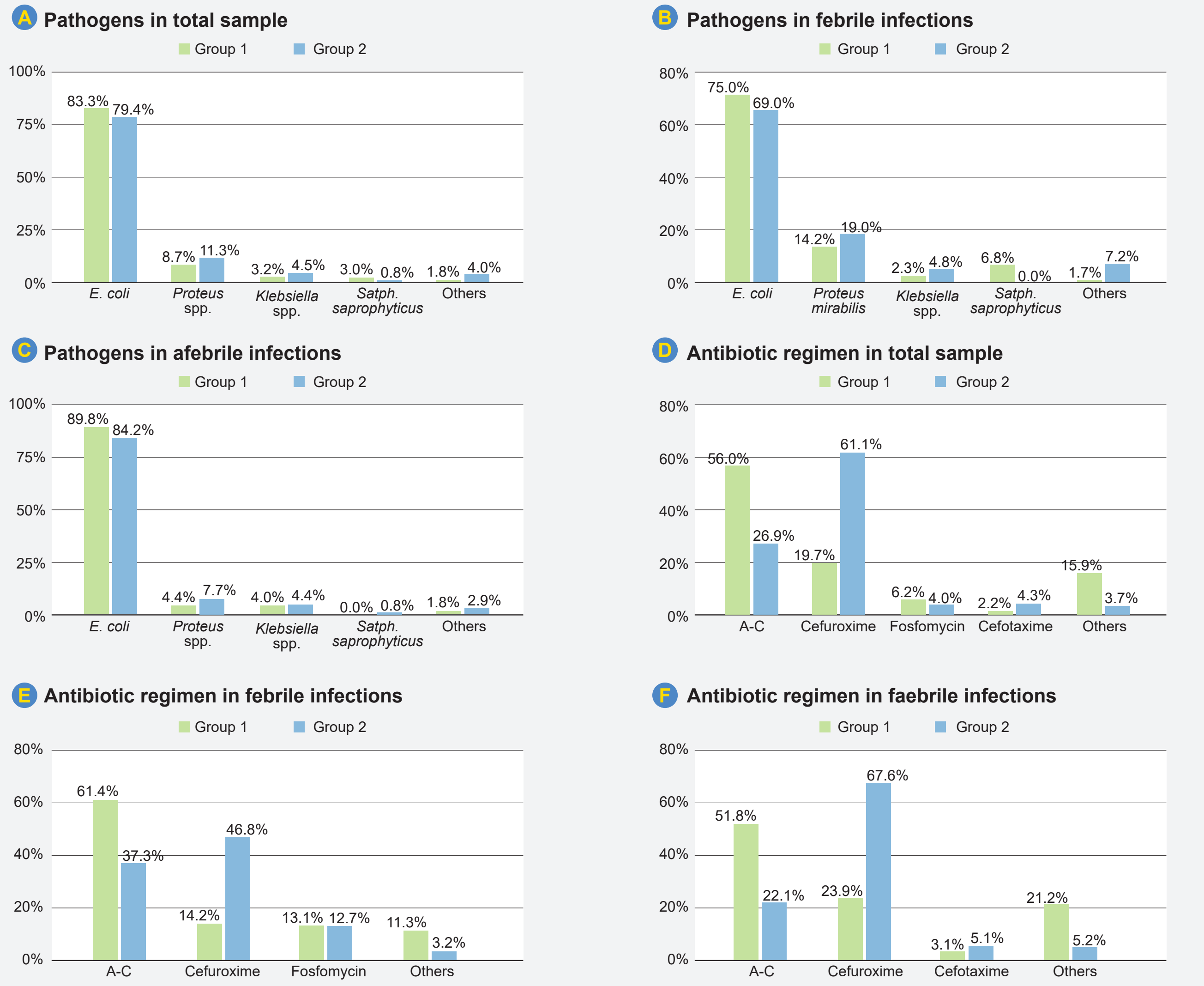

Figure 1 – Relative frequency of the pathogens identified according to type of infection. (A) Pathogens in total sample; (B) Pathogens in febrile infections; (C) Pathogens in afebrile infections; (D) Antibiotic regimen in total sample; (E) Antibiotic regimen in febrile infections; (F) Antibiotic regimen in febrile infections.
Numbers represent percentages.

Table 3 – Empirical antibiotics prescribed in both groups

Antibiotic	Group 1	Group 2	*p*-value
Amoxicillin-Clavulanate	225 (56.0%)	107 (26.9%)	**< 0.001*** **
Cefuroxime	79 (19.7%)	243 (61.1%)	**< 0.001*** **
Fosfomycin	25 (6.2%)	16 (4.0%)	0.163
Cefotaxime	9 (2.2%)	17 (4.3%)	0.123
Others	14 (3.5%)	12 (3.0%)	0.695
None	50 (12.4%)	3 (0.8%)	**< 0.001*** **

p-values were calculated using a unique logistic regression model with ‘group’ as dependent variable and ‘empirical_antibiotic’ as independent variable.
Percentages have been rounded and thus may not add up to 100%.
^*p* < 0.1; **p* < 0.05; ***p* < 0.01; ****p* < 0.001.

Table 4 – Resistance patterns to the 6 most frequent empirical antibiotic choices

Antibiotic	**Group 1**			**Group 2**			***p*-value**
Ampicillin	158 (39.3%)			158 (39.7%)			0.909
A-C	133 (33.1%)			109 (27.4%)			**0.078**^
Cotrimoxazol	61 (15.2%)			56 (14.1%)			0.659
Nitrofurantoine	36 (9.0%)			1 (0.3%)			**< 0.001*****
Cefuroxime	19 (4.7%)			13 (3.3%)			0.295
Fosfomycin	8 (2.0%)			1 (0.3%)			**0.0496***
None of these	206 (51.2%)			228 (57.3%)			**0.087**^
Urologic abnormalities							
	Yes 63	No 339	*p*-value	Yes 56	No 342	*p*-value	
Ampicillin	30 (47.6%)	128 (37.8%)	0.143	26 (46.4%)	132 (38.6%)	0.268	
A-C	26 (41.3%)	107 (31.6%)	0.134	21 (37.5%)	88 (25.7%)	**0.069**^	
Cotrimoxazol	13 (20.6%)	48 (14.2%)	0.191	11 (19.6%)	45 (13.2%)	0.199	
Nitrofurantoine	3 (4.8%)	33 (9.7%)	0.215	-	1 (0.3%)	0.988	
Cefuroxime	16 (25.4%)	3 (0.9%)	0.988	4 (7.1%)	9 (2.6%)	0.091	
Fosfomycin	7 (11.1%)	1 (0.3%)	0.804	-	1 (0.3%)	0.992	
Chemoprophylaxis							
	Yes 8	No 394	*p*-value	Yes 15	No 383	*p*-value	
Ampicillin	4 (50.0%)	154 (39.1%)	0.535	10 (66.7%)	148 (38.6%)	**0.038***	
A-C	4 (50.0%)	129 (32.7%)	0.314	8 (53.3%)	101 (26.4%)	**0.029***	
Cotrimoxazol	4 (50.0%)	57 (14.5%)	**0.014***	6 (40.0%)	50 (13.1%)	**0.007****	
Nitrofurantoine	1 (12.5%)	35 (8.9%)	0.724	-	1 (0.3%)	0.991	
Cefuroxime	-	19 (4.8%)	0.987	1 (6.7%)	12 (3.1%)	0.461	
Fosfomycin	-	7 (1.8%)	0.995	-	1 (0.3%)	0.994	

p-values were calculated using logistic regression models, one for each row.
Percentages have been rounded and thus may not add up to 100%.
^$p < 0.1$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

being the first-line choice for empirical antibiotic treatment.

The mean age was lower in the second group. This could be related to the increasing awareness for older children with UTI symptoms and no red flags to seek medical care in primary care as opposed to hospital settings. This could also justify the increased prevalence of febrile infections in group 2.

As expected, febrile infections were more common than afebrile infections and the female sex was more prevalent in both groups, with a 4:1 distribution in the first and 2:1 distribution in the second.[5] Mean age was significantly lower in males in both groups, as UTIs in boys occur more frequently in the first year of life.[14]

For children under the age of two, in both groups, in-out catheterization was the most frequent urine collecting method, as it provides a sterile sample, is painless, and both parents and professionals prefer it to suprapubic aspiration.[20] The percentage of catheterization increased in group 2, particularly in male patients (from 20.5% to 60.8%). This is likely due to the continuous efforts in educating professionals on this procedure, as lack of training is a major concern reported by professionals for the resistance in using this collecting method.[20]

As expected, the hospital admission rate was low, as most children with UTI can be discharged home without complications.[2] Mean age was significantly lower in inpatients for both groups, as the main reason for inpatient treatment in UTIs is younger age.[2]

We observed a significant decrease in the percentage of patients followed-up in the pediatric nephrology clinic. Since the prevalence of urologic abnormalities was similar, we believe this is due to the continuous education programs on adequate UTI follow-up aimed at primary care doctors and general pediatricians.

E.coli was the most significant uropathogen identified in both groups, with a relative frequency of 79.4% - 83.3%,

Table 5 – Comparison of resistance patterns of the three most common microorganisms to the two most frequent empirical antibiotic choices

Microorganism	Antibiotic	Group 1	Group 2	*p*-value
E. coli		335 (83.3%)	316 (79.4%)	
	A-C	121 (36.1%)	94 (29.7%)	**0.084^**
	Cefuroxime	15 (4.5%)	8 (2.5%)	0.185
Klebsiella spp.		13 (3.2%)	16 (5.1%)	
	A-C	4 (30.8%)	8 (50.0%)	0.300
	Cefuroxime	2 (15.4%)	3 (18.8%)	0.812
Proteus mirabilis		35 (8.7%)	45 (14.2%)	
	A-C	6 (17.1%)	4 (8.9%)	0.276
	Cefuroxime	2 (5.7%)		0.987

p-values were calculated using logistic regression models, one for each antibiotic, which assessed the effect of the interaction 'microorganism * group' in A-C, cefuroxime, and ampicillin.
Percentages have been rounded and thus may not add up to 100%.
^$p < 0.1$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

similar to that reported by several studies performed in Turkey, Israel, and France.[14,21,22] Other frequently identified pathogens were *Proteus mirabilis*, *Klebsiella* spp. and *Staphylococcus saprophyticus*.

Regarding empirical antibiotic selection, A-C was the most common antibiotic choice in group 1 for both febrile (51.8%) and afebrile infections (61.4%), as opposed to cefuroxime becoming the preferred drug in group 2 ($p < 0.001$), also for both febrile (67.6%) and afebrile infections (46.8%). This suggests the intervention implemented between groups was effective in guiding empirical UTI treatment. Cefotaxime in febrile infections and fosfomycin in afebrile infections remained the third most frequent choice in both groups.

As expected, the most commonly identified *in vitro* resistance was to ampicillin, which remained similar among groups (39.3% - 39.7%).[7,23,24] We found a resistance rate to A-C in group 1 of 33.1%. Studies in France and Turkey reported resistance rates as high as 93%.[22,24] Studies in Israel, Greece, and Spain reported lower to similar rates, as well as an increase from 12% to 24% in a decade.[7,9,25] A previous study conducted in Portugal in 2009 - 2010 found an 18% rate of A-C resistance in pediatric UTIs.[26] These concerns prompted our internal guideline stating cefuroxime should be the first-line choice for our population. In the second group, recruited at least a year after guideline implementation, we observed a slight decrease in A-C resistance (27.4%). Conversely, cefuroxime resistance did not increase, displaying a decreasing trend from 4.7% to 3.3%. There were no statistically significant differences in resistance to TMP-SMX, the most common agent used in chemoprophylaxis (15.2% in group 1 *versus* 14.1% in group 2, $p = 0.659$).[27] Resistance to nitrofurantoin and fosfomycin remained low and significantly decreased from group 1 to group 2, as opposed to the increasing trend noted in previous studies.[24] Although 14.1% - 15.7% of our patients had a history of urologic abnormalities, only 2.0% - 3.8% were under chemoprophylaxis. The judicious use of chemoprophylaxis may have contributed to the finding of no evidence of increased resistance in patients with a history of urologic abnormalities, as opposed to that reported by Parry *et al*.[28] However, as expected, in both groups, resistance to TMP-SMX was significantly higher in children under chemoprophylaxis. Although antibiotic chemoprophylaxis for the prevention of recurrent UTI has proven successful,[29] its widespread use raises concerns of increased antibiotic resistance, supported also by this study.[23]

There are some limitations to our study. The single-center nature of this investigation limits the generalizability of our data to national and international populations. The sample size also limited the statistical power of some comparisons. However, our data provides useful information on resistance pattern trends of uropathogens, particularly to geographically neighboring populations. National and international multicenter studies such as the ESCAPE study are key to continuously monitoring antibiotic resistance in UTIs and update guidelines accordingly.[21]

In this study, we recognized the problem of A-C resistance in our population and evaluated the impact of switching to cefuroxime as first-line agent. Also, including all months of the year in the analysis prevented the effect of seasonal differences and including both in- and outpatients allowed for a representative sample regarding the distribution of sex, age and UTI severity.

CONCLUSION

Although overall more frequent in female children, UTIs are more prevalent in male patients at a younger age. *E.coli* remains the predominant pathogen in pediatric UTI. The uropathogens resistance to A-C in our population is approximately of one-third. The switch from A-C to cefuroxime as first-line agent resulted in a decreasing trend in A-C resistance while cefuroxime resistance remained low and even slightly lower. The continued use of cefuroxime as first-line option should help decrease A-C resistance in our population. Further studies in the future would be of interest to evaluate the increased impact of this measure.

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AUTHOR CONTRIBUTIONS

PS: Study design, data acquisition and analysis, writing of the manuscript.

LD: Data acquisition and analysis.

SCO, CP: Data acquisition.

ÂD: Writing of the manuscript.

ACT: Study design.

All authors approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

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