Original

Aetiology and antibiotic resistance in paediatric urinary tract infection. A multicentre study in primary carea

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Abstract

Introduction: empirical treatment of urinary tract infection (UTI) requires knowledge of antibiotic resistance in the most prevalent uropathogens. The aim of the study was to analyse the pathogens involved in community-acquired paediatric UTIs, their drug resistance profile and the association between resistance and the studied variables.

Patients and methods: nationwide, multicentre, prospective, longitudinal and descriptive study carried out in primary care paediatrics clinics. We included all UTI episodes identified in patients aged 0-15 years in the caseloads of 187 collaborating paediatricians (187 058 patients), regardless of the setting where they were diagnosed or treated, between 1/10/2019 and 31/12/2020.

Results: there were 588 identified UTI episodes. *Escherichia coli* was the most frequently isolated uropathogen (79.67%), followed by *Proteus* spp., *Klebsiella* spp. and *Enterococcus* spp. Extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae* were isolated in 1.52% of episodes. The lowest prevalences of resistance to oral antibiotics corresponded to third-generation cephalosporins, cefuroxime and fosfomycin (3.88%, 4.81% and 6.30%, respectively). The proportions of resistance to first-generation cephalosporins, gentamicin and amikacin were 8.69%, 7.55% and 3.23% respectively. The prevalence of resistance was 23.85% for amoxicillin-clavulanic acid (34.51% in males) and 23.40% for cotrimoxazole.

Conclusions: *E. coli* was the most frequently isolated uropathogen. Amoxicillin-clavulanic acid and cotrimoxazole should not be used empirically due to the high prevalence of resistance. Second and third generation cephalosporins and fosfomycin could be adequate empirical therapy depending on age and the type of infection. Local susceptibility to first-generation cephalosporins should be tested.

Key words:
- Antibiotic resistance
- Antimicrobial stewardship programmes
- Urinary tract Infection

Etiología y resistencia a los antibióticos en la infección urinaria pediátrica. Estudio multicéntrico desde Atención Primaria

Resumen

Introducción: el tratamiento empírico de la infección urinaria (IU) requiere conocer las resistencias a antibióticos de los uropatógenos más frecuentes. El objetivo de este estudio fue identificar los patógenos responsables de IU pediátricas comunitarias, analizar sus resistencias a antibióticos y su relación con las variables estudiadas.

Pacientes y métodos: estudio descriptivo, longitudinal, prospectivo y multicéntrico de ámbito nacional realizado desde las consultas de Pediatría de Atención Primaria. Se recogieron los episodios de IU identificados en los cupos pediátricos (0 a 15 años) de 187 colaboradores (187 058 pacientes), independientemente del lugar en el que se diagnosticaron o trataron, entre el 1/10/2019 y el 31/12/2020.

Resultados: se registraron 588 episodios de IU. *Escherichia coli* fue el patógeno más frecuente (79,67%), seguido de *Proteus* spp., *Klebsiella* spp. y *Enterococcus* spp. En el 1,50% de los casos, se aislaron enterobacterias productoras de betalactamasas de espectro extendido (BLEE). Los antibióticos orales con menor porcentaje de resistencia fueron cefalosporinas de tercera generación, cefuroxima y fosfomicina (3,88%, 4,81% y 6,30%, respectivamente). Las resistencias a cefalosporinas de primera generación, gentamicina y amikacina fueron 8,69%, 7,55% y 3,23%, respectivamente. Las resistencias a amoxicilina-clavulánico fueron del 23,85% (34,51% en varones) y del 23,40% a cotrimoxazol.

Conclusiones: *E. coli* fue el patógeno más frecuentemente aislado. Amoxicilina-clavulánico y cotrimoxazol no deben utilizarse empíricamente. Cefalosporinas de segunda y tercera generación y fosfomicina podrían ser (según la edad y el tipo de infección) el antibiótico empírico de elección. Es necesario testar la sensibilidad local a cefalosporinas de primera generación.

Palabras clave:
- Infección tracto urinario
- Programa optimización antimicrobianos
- Resistencia a antibióticos

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INTRODUCTION

Urinary tract infection (UTI) is defined as microbial growth in the urinary tract accompanied by compatible clinical manifestations.[1] It is one of the most common types of bacterial infections in the paediatric age group. Approximately 2% of boys and 8% of girls experience at least one episode of UTI in the first 7 years of life.[2] The incidence is higher in male infants under 6 months and girls from age 1 year.[1-4] The rates of recurrence, which are particularly high in infants under 1 year and patients with urinary tract malformations, reach 10 to 15% in the first 6 to 12 months after the initial episode.

Besides age and sex, there are other risk factors that include renal or congenital anomalies of the kidney or urinary tract (CAKUT), diseases that affect urine flow, vesicoureteral reflux, phimosis in male infants, labial adhesion in girls, urinary dysfunction, constipation, neurogenic bladder, urinary tract catheterization, nephroureterolithiasis and sexual activity in female adolescents.[1,3-5] The diagnosis of UTIs is not free of controversy. There is no consensus for the colony-forming unit (CFU) threshold considered diagnostic of UTI. Although in our study we adhered to the criteria published in the document *Recomendaciones sobre el diagnóstico y tratamiento de la infección urinaria* (Recommendations on the diagnosis and treatment of urinary tract infection),[6] other, more recent documents lower the threshold in case of "high likelihood" of a true UTI,[1,7] introducing a subjective component. There is consensus that urine bag specimens are not appropriate for urine culture.

Urinary tract infections are usually managed with empiric therapy before the pathogen and its antimicrobial susceptibility profile are known. For this reason, it is crucial to update periodically information on drug resistance in prevalence uropathogens involved in community-acquired infections, taking into account variations associated with patient age, sex, fever or risk factors.[3] The aim of our study was to identify the causative pathogens involved in paediatric UTI cases in the primary care (PC) setting and analyse their antimicrobial resistance profile.

PATIENTS AND METHODS

We conducted a nationwide multicenter prospective, longitudinal and observational descriptive study in primary care paediatrics (PCP) clinics. We engaged the collaboration of clinicians through an invitation letter distributed to the members of la Asociación Española de Pediatría de Atención Primaria (Spanish Association of Primary Care Pediatrics, AEPap) and contacts in the primary care pediatrician (PEDIAP) mailing list of the RedIRIS network, which amounted to 4009 members and 1020 contacts, respectively, at the time of the mailing.

From 1/10/2019 to 31/12/2020, we followed up a total of 187 paediatric caseloads in 15 autonomous communities (ACs) in Spain. The collaborating partners were directed to record any diagnosed episode of UTI in their caseloads, whether diagnosed in their clinic or any other setting (hospital, urgent care or private health care system).

Madrid and Castilla y León were the ACs with the largest representation (37.22% and 19.44%, respectively), followed by Galicia (6.67%), Canary Islands (6.11%), Aragón (5.57%) and Andalusia (5%). No clinicians from Murcia, Baleares, Ceuta or Melilla participated. All participants worked in the public health care system, and 76.33% were employed in urban settings. The mean number of patients in the caseloads of collaborating paediatricians was of 1039,21 patients (median, 1020), and all their caseloads cumulatively amounted to 187 058 patients.

Inclusion criteria:

The study universe consisted of children aged 0 to 15 years managed at some point of the diagnosis, treatment or followup in a PCP clinic, independently of the setting of diagnosis. We recorded all episodes with a diagnosis of UTI based on the criteria outlined in the document *Recomendaciones sobre el diagnóstico and tratamiento de la infección urinaria*: compatible clinical manifestations and growth of microorganisms in urine collected with sterile technique, applying the thresholds presented in **Table 1**.[6]

Table 1. Criteria for clinically significant bacteriuria

Type of sample	Colony count (CFU/mL)
Suprapubic puncture	Any
Urinary catheter	≥10 000
Spontaneous urine catch	≥100 000 Consider 10 000-50 000 in the case of a high likelihood of true urinary tract infection (fever + pyuria-bacteriuria or patients with renal disease)

Source: *Recomendaciones sobre el diagnóstico y tratamiento de la infección urinaria*[6].

Exclusion criteria:

Episodes in patients not allocated to the caseloads of the collaborating clinician, in which followup was not possible or for which informed consent (IC) could not be obtained.

The data were anonymized and collected through an online form (Google Forms platform).

Testing of collected samples (urine culture in every case, urine test strip, urinalysis and urine sediment examination) was conducted in primary care centers and microbiology reference laboratories following the protocols of each facility.

We collected data on the following variables: age, sex, presence of fever (axillary temperature >38 °C), risk factors, consumption of antibiotics in the past month, prophylaxis, isolated pathogen and antimicrobial susceptibility results (antibiogram). We considered the following risk factors: vesicoureteral reflux, renal disease, renal malformation, urinary catheterization, bladder dysfunction, constipation, phimosis, labial adhesions, previous history of UTI and hypercalciuria. There is evidence[8,9] suggesting potential differences in the etiological agents and prevalence of drug resistance in UTIs in patients with renal or urinary system disease. Therefore, with the aim of assessing for these potential differences in this case series, we made a separate analysis of episodes with risk factors potentially related to kidney and urinary tract disease (group 1); establishing a second group of episodes with presence of risk factors of a different nature (group 2) and a third group without risk factors (group 3).

We analysed and compared the isolated bacteria and the prevalence of resistance to different antimicrobials based on age, sex and the presence of fever and of risk factors.

Statistical analysis

The analysis was performed with the software JASP version 0.18.3, expressing quantitative variables in terms of percentages and the mean and standard deviation (SD). Qualitative data were compared using the χ^2 test. In the case of dichotomous variables, we used the Fisher exact test.

Ethical considerations

The study was carried out in adherence to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Hospital de Fuenlabrada, Madrid (APR 19/03). Patients were included after obtaining the IC of the parents/legal guardians of all patients in addition to the assent of patients aged more than 12 years.

RESULTS

We registered a total of 588 episodes corresponding to 519 patients. In 12 episodes, two pathogens were isolated, one of which was *Escherichia coli*. Of these 12 episodes, 9 occurred in children aged more than 2 years, 7 in female patients, 8 were afebrile, 4 occurred in patients without risk factors and 10 were the first UTI episode documented in the patient. There were a total of 600 bacterial isolations. During the period under study, 69 of the recorded episodes were recurrent (more than 1 episode in the same patient). **Table 2** summarizes the clinical characteristics of the UTI episodes and the patients.

Most frequent pathogens

In all analysed groups, *E. coli* was the most frequent pathogen. In the total sample, children of either sex, children aged more than 2 years and afebrile episodes, the pathogens following in

Table 2. Clinical characteristics of confirmed episodes of UTI and the corresponding patients

		Episodes of confirmed UTI	Patients with confirmed UTI
N		**N: 588 (%)**	**N: 519 (%)**
Sex	**Female**	439 (74.66)	380 (73.21)
Age	**< 2 years**	189 (32.14)	176 (33.91)
	<3 months	55 (9.35)	53 (10.21)
	3-11 months	99 (16.84)	93 (17.92)
	12-23 months	35 (5.95)	30 (5.78)
	>2 years	399 (67.86)	343 (66.09)
	2-5 years	202 (34.35)	171 (32.95)
	6-11 years	160 (27.21)	140 (26.98)
	>11 years	37 (6.29)	32 (6.17)
Mean age ± SD (months)		56.34 ± 47.26	55.35 ± 47.56
Continence	**Continent**	377 (64.12)	329 (63.39)
	Incontinent due to disease	6 (1.02)	3 (0.58)
	Incontinent due to age	205 (34.86)	187 (36.03)
Risk factor	**Total**	258 (43.88)	198 (38.16)
	VUR	39 (6.63)	24 (4.62)
	Renal malformation	36 (6.12)	28 (5.39)
	Previous UTI	161 (27.38)	106 (20.42)
	Constipation /encopresis	51 (8.67)	43 (8.29)
	Bladder dysfunction	27 (4.59)	13 (2.50)
	Urinary catheterization	4 (0.68)	1 (0.19)
	Labial adhesions	12 (2.73)*	10 (2.63)*
	Phimosis	47 (31.97)**	44 (32.12)**
	Hypercalciuria	3 (0.51)	2 (0.39)
	RF group 1	123 (20.92)	90 (17.34)
	RF group 2	135 (22.96)	108 (20.81)
	No RF	330 (56.12)	321 (61.85)
Fever		203 (34.52)	
Combined infection		12 (2.04)	12 (2.31)
Single episode		519 (88.27)	464 (89.40)
Previous prophylaxis		25 (4.25)	
Antibiotics in previous month		76 (12.93)	

*Over total female patients; **Over total male patients.
RF: risk factor (**RF group 1**: vesicoureteral reflux, renal disease, renal malformation, urinary catheterization, bladder dysfunction and constipation; **RF group 2**: phimosis, adhesions, previous history of UTI and hypercalciuria); **SD**: standard deviation; **UTI**: urinary tract infection; **VUR**: vesicoureteral reflux.

frequency were *Proteus* spp., *Klebsiella* spp. and *Enterococcus* spp.

In patients with no risk factors or group 2 risk factors, the second most frequent pathogen was also *Proteus* spp.

In children under 2 years, febrile episodes and patients with group 1 risk factors, *Klebsiella* spp. was the second most frequent pathogen.

Staphylococcus saprophyticus was isolated in 10 episodes. All these episodes were afebrile and occurred in patients aged more than 2 years, 8 occurred in girls, and all occurred in patients without risk factors saved for a mixed infection in a patient with a previous history of UTI, bladder dysfunction, urinary retention and constipation/encopresis. The urine specimens in all these episodes tested negative for nitrites in the urinalysis.

Table 3. Isolates in the overall sample of episodes, by sex and by age

	Isolates in total sample	Isolates by sex N: 598[†]		Isolates by age N: 600	
Pathogen	N: 600	Male	Female	<2 years	>2 years
		152	446	192	408
	Total (%)	Total (%)	Total (%)	Total (%)	Total (%)
E. coli	478 (79.67)	107 (70.39)	369 **(82.74)****	162 (84.38)	316 (77.45)
Proteus spp.	44 (7.33)	19 **(12.5)***	25 (5.61)	3 (1.56)	41 **(10.05)*****
Klebsiella spp.	30 (5)	8 (5.26)	22 (4.93)	16 **(8.33)***	14 (3.43)
Enterococcus spp.	18 (3)	7 (4.61)	11 (2.47)	4 (2.08)	14 (3.43)
S. saprophyticus	10 (1.67)	2 (1.32)	8 (1.79)	0 (0)	10 **(2.45)***
Citrobacter spp.	6 (1)	3 (1.97)	3 (0.67)	2 (1.04)	4 (0.98)
Other GNB	9 (1.5)	5 **(3.29)***	4 (0.91)	5 (2.60)	4 (0.98)
Other GP cocci	5 (0.83)	1 (0.66)	4 (0.91)	0 (0)	5 (1.23)

[†]The sex was not documented in 2 patients. **p* <0.05; ***p* <0.005; ****p* < 0.001.
GNB: gram-negative bacilli (include *Edwardsiella tarda, Enterobacter asburiae, Haemophilus parainfluenzae, Enterobacter cloacae, Pseudomonas* spp.); **GP:** gram positive. **Other gram-positive cocci:** include *Aerococcus Urinae, group B Streptococcus,* coagulase-negative *Staphylococcus*.

Table 4. Distribution of pathogens isolated in febrile and afebrile episodes and based on the presence of risk factors

Pathogen	Isolate distribution based on presence of fever		Isolate distribution based on risk factors		
	Afebrile episodes	Febrile episodes	Episodes with group 1 risk factors	Episodes with group 2 risk factors	Episodes without risk factors
	N: 393	N: 207	N: 128	N: 138	N: 334
	Total (%)	Total (%)	Total (%)	Total (%)	Total (%)
E. coli	298 (75.83)	180 **(86.96)****	93 (72.66)	111 (80.43)	274 (82.04)
Proteus spp.	41 **(10.43)****	3 (1.45)	6 (4.69)	12 (8.70)	26 (7.78)
Klebsiella spp.	17 (4.33)	13 (6.28)	11 **(8.59)***	9 (6.52)	10 (2.99)
Enterococcus spp.	13 (3.31)	5 (2.42)	8 **(6.25)***	2 (1.45)	8 (2.40)
S. saprophyticus	10 **(2.54)***	0	1 (0.78)	0	9 (2.69)
Citrobacter spp.	4 (1.01)	2 (0.97)	2 (1.56)	1 (0.72)	3 (0.90)
Other GNB	6 (1.53)	3 (1.45)	4 **(3.13)***	3 (2.17)	2 (0.60)
Other GP cocci	4 (1.02)	1 (0.48)	3 (2.34)	0	2 (0.60)

**p* <0.05; ***p* <0.001.
Group 1 risk factors defined as one or more of the following: vesicoureteral reflux, renal disease, renal malformation, urinary catheterization, bladder dysfunction or constipation. **Group 2 risk factors** defined as one or more of the following: phimosis, adhesions, history of previous UTI or hypercalciuria. **GNB:** gram-negative bacilli (include: *Edwardsiella tarda, Enterobacter asburiae, Haemophilus parainfluenzae, Enterobacter cloacae, Pseudomonas* spp.). **GP:** gram-positive **(**other GP cocci include: *Aerococcus urinae*, group B streptococcus, coagulase-negative *Staphylococcus*).

Tables 3 and 4 present the pathogen distributions in the different groups.

Prevalence of antimicrobial resistance

Tables 5 and 6 and Figure 1 present the proportion of isolates resistant to the antibiotics used most widely for treatment of UTIs in the total episodes, by group and in the episodes involving the most frequent etiological agent (*E. coli*).

In the overall sample of episodes, third-generation cephalosporins, cefuroxime and fosfomycin were the oral antibiotics with the lowest prevalence of resistance (3.88%, 4.81% and 6.30%, respectively).

The prevalence of resistance was 23.85% for amoxicillin-clavulanic acid (34.51% in male patients)

Table 5. Antibiotic resistance in UTI episodes, overall and by sex and age

	Resistance in total sample	Resistance by sex		Resistance by age	
Antibiotic	**N: 600**	**Male N: 152†**	**Female N: 446†**	**<2 years N: 192**	**>2 years N: 408**
	Antibiograms (% R)	**Antibiograms (% R)**	**Antibiograms (% R)**	**Antibiograms (% R)**	**Antibiograms (% R)**
Amoxicillin	517 (46.42 %)	123 **(54.47%)***	392 (43.88%)	166 (51.20%)	351 (44.16%)
Amoxicillin-clavulanic	457 (23.85 %)	113 **(34.51%)****	343 (20.41%)	148 (28.38%)	309 (21.68%)
Piper-tazobactam	94 (4.26 %)	26 (7.69 %)	68 (2.94%)	31 (0%)	60 (6.67%)
Cephalothin/Cefazoline	69 (8.69 %)	17 (11.76%)	52 (7.69%)	24 (12.5%)	45 (6.67%)
Cefoxitin	106 (7.55 %)	28 (7.41%)	78 (7.69%)	34 (14.71%)	72 (4.17%)
Cefuroxime	478 (4.81 %)	112 (6.25%)	364 (4.40%)	156 (4.49%)	322 (4.97%)
Cefotaxime Ceftriaxone	258 (3.88 %)	72 (2.78%)	185 (4.32%)	96 (3.13%)	162 (4.32%)
Ceftazidime	154 (3.90 %)	39 (5.13%)	115 (3.48%)	58 (3.45%)	96 (4.17%)
Cefepime	148 (2.70 %)	35 (5.71%)	112 (1.79%)	49 (2.04%)	99 (3.03%)
Fosfomycin	524 (6.30 %)	118 (9.32%)	404 (5.45%)	157 (3.82%)	367 (7.36%)
Nitrofurantoin	478 (8.37 %)	108 **(14.81%)***	368 (6.52%)	148 (5.41%)	330 (9.70%)
Cotrimoxazole	513 (23.40%)	124 (29.84%)	387 (21.45%)	160 (25.63%)	353 (22.38%)
Trimethoprim	44 (18.18%)	10 (30.00%)	34 (14.71%)	18 (22.22%)	26 (15.38%)
Ciprofloxacin Ofloxacin	314 (9.87%)	68 (10.29%)	245 (9.80%)	97 (6.19%)	217 (11.52%)
Norfloxacin	160 (13.13%)	34 (8.82%)	126 (14.29%)	46 (10.87%)	114 (14.04%)
Nalidixic acid	88 (23.86%)	15 (26.67%)	72 (23.61%)	26 (19.23%)	62 (25.81%)
Amikacin	93 (3.23%)	23 (4.35%)	70 (2.86%)	34 (0%)	59 (5.08%)
Gentamicin	477 (7.55%)	121 (10.74%)	354 (6.50%)	160 (6.25%)	317 (8.20%)
Vancomycin	25 (8.00 %)	4 (0%)	21 (9.52%)	11 (9.09%)	14 (7.14%)
Meropenem	128 (2.34 %)	31 (3.23%)	97 (2.06%)	48 (0%)	80 (3.75%)
Ticarcillin	30 (40%)	7 (42.86%)	23 (39.13%)	14 (21.43%)	16 (56.25%)
ESBL	9 (1.50%)	3 (2.08%)	6 (1.40%)	5 (2.70%)	4 (1.03%)

†Sex was not documented in 2 patients. **p* <0.05; ***p* <0.005.
ESBL: extended-spectrum beta-lactamase-producing strain; **R:** resistant.

and 23.40% for cotrimoxazole. Furthermore, the percentage of resistant isolates was 8.69% for first-generation cephalosporins, 8.37% for nitrofurantoin (14.81% in male patients); 7.55% for gentamicin and 3.23% for amikacin.

In the stratified analysis, we found that the percentages of resistance to amoxicillin, amoxicillin-clavulanic acid and nitrofurantoin were significantly higher in male patients. The percentages of resistance to fosfomycin and to nitrofurantoin were significantly greater in in afebrile episodes, the percentage of resistance to cefepime significantly greater in febrile episodes and the percentages of resistance to cefuroxime and amoxicillin significantly greater in patients with risk factors potentially related to renal disease.

We did not find any significant differences based on age.

Nine isolates (1.5% of episodes) corresponded to extended-spectrum beta-lactamase (ESBL)-producing enterobacteria. Only one of these episodes occurred in a patient currently receiving prophylaxis who had consumed antibiotics in the past month.

In 96 episodes (16.33% of the total), patients reported a history of antibiotic treatment and/or prophylaxis in the past month. In 20 episodes (3.40% of the total), the patient had received antibiotics for prophylaxis, but not for treatment, in the past month. And in 71 episodes (12.07% of the total), the patient had consumed antibiotics for treatment but not for prophylaxis.

Table 6. Antibiotic resistance based on the presence of fever and risk factors

	Resistance based on presence of fever		Resistance based on risk factor		
Antibiotics	**Isolation in febrile episodes N: 207**	**Isolation in afebrile episodes N: 393**	**Isolation in episodes with group 1 risk factors N: 128**	**Isolation in episodes with group 2 risk factors N: 138**	**Isolation in episodes without risk factors N: 334**
	No. of antibiograms (%R)	**No. of antibiograms (%R)**	**No. of antibiograms (%R)**	**No. of antibiograms (%R)**	**No. of antibiograms (%R)**
Amoxicillin	179 (47.49%)	338 (45.86%)	110 **(57.27%)***	120 (37.50%)	287 (45.99%)
Amox-clavulanic	157 (26.11%)	300 (22.67%)	97 (26.80%)	104 (22.12%)	256 (23.44%)
Piperacillin-tazobactam	37 (2.70%)	57 (5.26%)	22 (9.09%)	23 (0.00%)	49 (4.08%)
Cephalothin/Cefazoline	31 (6.45%)	38 (10.53%)	15 (13.33%)	14 (14.29%)	40 (5.00%)
Cefoxitin	36 (13.89%)	70 (4.29%)	18 (11.11%)	26 (7.69%)	62 (6.45%)
Cefuroxime	167 (5.99%)	311 (4.18%)	97 **(9.28%)***	110 (2.73%)	271 (4.06%)
Cefotaxime Ceftriaxone	103 (5.83%)	155 (2.58%)	52 (5.77%)	58 (3.45%)	148 (3.38%)
Ceftazidime	66 (7.58%)	88 (1.14%)	35 (5.71%)	36 (0.00%)	83 (4.82%)
Cefepime	60 **(6.67%)***	88 (0.00%)	30 (6.67%)	37 (0.00%)	81 (2.47%)
Fosfomycin	175 (2.86%)	349 **(8.02%)***	107 (9.35%)	118 (2.54%)	299 (6.69%)
Nitrofurantoin	162 (4.32%)	316 **(10.44%)***	91 (8.79%)	114 (7.02%)	273 (8.79%)
Cotrimoxazole	167 (20.96%)	346 (24.57%)	101(29.70%)	116 (17.24%)	296 (23.65%)
Trimethoprim	23 (21.74%)	21 (14.29%)	5 (20.00%)	11 (9.09%)	28 (21.43%)
Ciprofloxacin Ofloxacin	111 (7.21%)	203 (11.33%)	58 (5.17%)	81 (13.58%)	175 (9.71%)
Norfloxacin	55 (14.55%)	105 (12.39%)	27 (7.41%)	42 (19.05%)	91 (12.09%)
Nalidixic acid	37 (16.22%)	51 (29.41%)	12 (25.00%)	16 (37.50%)	60 (20.00%)
Amikacin	39 (7.70%)	54 (0.00%)	20 (10.00%)	21 (0.00%)	52 (1.92%)
Gentamicin	168 (7.14%)	309 (7.77%)	102 (8.82%)	113 (7.08 %)	262 (7.25%)
Vancomycin	10 (20%)	15 (0.00%)	5 (20.00%)	2 (0.00%)	18 (5.56%)
Meropenem	55 (5.45%)	73 (0.00%)	31 (6.45%)	28 (0.00%)	69 (1.45%)
Ticarcillin	19 (26.32%)	11 (63.64%)	6 (50.00%)	6 (16.67%)	18 (44.44%)
ESBL	4 (2.02%)	5 (1.33%)	1 (0.82%)	3 (2.29%)	5 (1.55%)

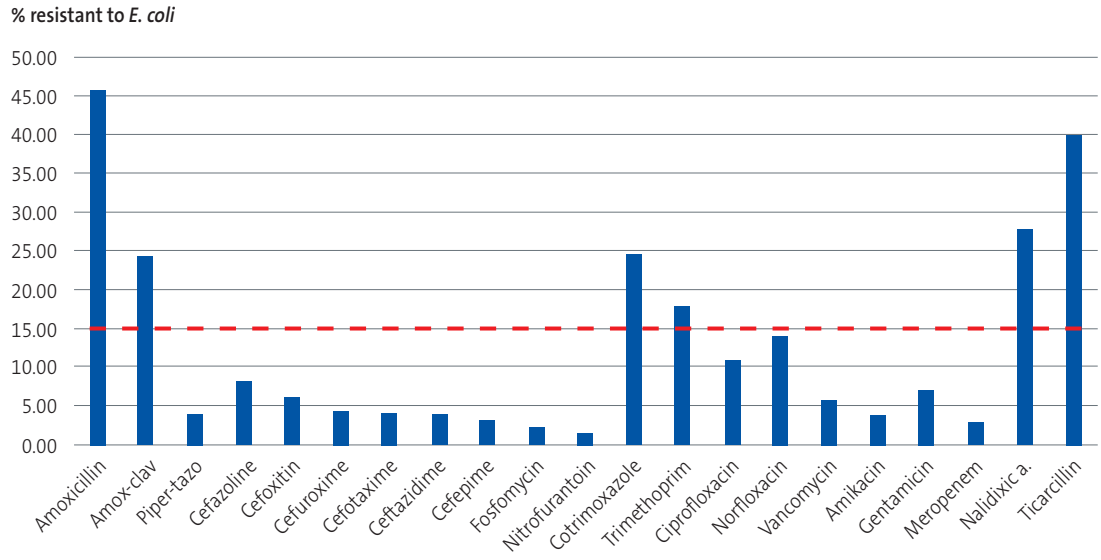
*p <0.05.
Group 1 risk factors defined as one or more of the following: vesicoureteral reflux, renal disease, renal malformation, urinary catheterization, bladder dysfunction or constipation. **Group 2 risk factors** defined as one or more of the following: phimosis, adhesions, history of previous UTI or hypercalciuria. **ESBL:** extended-spectrum beta-lactamase-producing strain; **R:** resistant.

We also calculated frequencies of resistance for the different Acs, but due to the small number of episodes in some of the regions we were unable to obtain significant results.

DISCUSSION

The findings of this study carried out in the PC setting, in which 588 episodes of pediatric UTI were analysed, confirmed that *E. coli* was the leading uropathogen, responsible for nearly 80% of UTI episodes. This was consistent with recent studies conducted in Spain that reported percentages of 80.75%[10] and 76.9%[11], respectively, exceeding those of previous studies (58.9-64%).[12-15] This increase could be associated with the greater percentage of specimens collected at the PC level in our series (65.40%) compared to other studies (53%[13] or 55.1%[12]). The causative pathogens that followed in frequency, *Proteus* spp. and *Klebsiella* spp., were consistent with other studies conducted in Spain.[10-12]

Figure 1. Antibiograms performed in *E. coli* isolates. The red line marks the 15% resistance prevalence threshold above which the antibiotic is NOT recommended for empiric treatment



It should be noted that while *E. coli* was the most frequent uropathogen in all the groups considered in the analysis, there was a percentage of UTI episodes, which varied between groups and was almost as high as 30% in patients of male sex or with group 1 risk factors, in which the causative agent was a different pathogen.

In our study, we did not take into account the location of the UTI (upper *vs.* lower urinary tract), but we did consider the presence of fever (febrile *vs.* afebrile episodes). In agreement with other case series,[10] most episodes of febrile UTI were caused by *E. coli* (86.96%), followed by *Klebsiella* spp., with frequencies that far exceeded those of other pathogens.

E. coli was isolated in 72.66% of episodes occurring in patients with group 1 risk factors, followed in frequency by *Klebsiella* spp. (8.59%), *Enterococcus* spp. (6.25%) and *Proteus* spp. (4.69%). These findings were consistent with the distribution published by Chamorro *et al*.[8] and differed from those of the series published by Oltra-Benavent *et al*., in which the proportion of episodes caused by microorganisms other than *E. coli* was greater (46.8%).[9] Both series consisted of patients with pyelonephritis and renal or urologic disease, although in the latter, 25.5% of the episodes occurred in patients with a history of urologic surgery.

We did not find significant differences in the isolates between boys with and without phimosis.

S. saprophyticus accounted for 1.67% of isolates. Given its infrequent nitrite formation and more frequent involvement in sexually active female adolescents,[16] we propose considering performance of urine culture in this group when a UTI is suspected, even in the case of nitrite-negative results in the dipstick test.

In 2.04% of episodes, two pathogens were isolated from culture. Although the presence of 2 pathogens in a urine culture suggests contamination,[4,5] based on the literature, it is recommended that clinical features are taken into account to decide whether these results should be interpreted as a true UTI: complicated versus uncomplicated UTI, sample collection method, type of isolate (uropathogen or saprophyte), presence of pyuria, etc.[5,17] The frequency of mixed infection in our study was slightly larger than the frequency reported in another study conducted in Spain.[11]

The resistance rates for amoxicillin-clavulanic acid and cotrimoxazole were very high (23.85% and 23.40%), so these drugs should not be used for empiric therapy unless there is evidence of a lower prevalence of resistance at the local level. The best sensitivity profiles corresponded to cefuroxime, cefixime and fosfomycin, which therefore could be (depending on the age and type of infection) the first-line antibiotics while awaiting the results of the antibiogram.

Our findings regarding the prevalence of isolates resistant to different antibiotics were consistent with or, in some cases, exceeded the previously reported figures.[11-16,18.] It is worth noting the high prevalence of resistance to amoxicillin-clavulanic acid, which exceeded 30% in some groups, probably due to its widespread use on account of either inappropriate prescription or shortages of antibiotics with a narrower spectrum. This percentage would preclude its use for empiric treatment of UTIs based on the recommendation to avoid antibiotics exceeding the resistance prevalence threshold of 15%.[1] Based on our findings, amoxicillin, amoxicillin-clavulanic acid, cotrimoxazole, trimethoprim and nalidixic acid should not be used for empiric treatment of UTI.

Treatment options for UTI are currently limited by recurrent shortages in cefuroxime axetil and restrictions for the use of fosfomycin, which has a good susceptibility profile but is only recommended from age 12 years,[19] and nitrofurantoin (which is only approved by the Spanish Agency of Medicines and Medical Devices [AEMPS] for treatment of uncomplicated cystitis in female patients aged more than 3 months).[20] As a result, in children aged less than 12 years, third-generation cephalosporins become the default first-line agent for empiric treatment, even in the case of lower UTI.

In this context, we ought to highlight the rates of resistance to first-generation cephalosporins observed in our study, which were lower compared to the previous literature,[13,18] although the low frequency with which these agents were included in the antibiogram (67 compared to 474 for second-generation cephalosporins) calls for caution and evinces the need to perform further studies to obtain local prevalence data to guide the prescription of empiric antibiotherapy, as recommended in the Clinical Practice Guideline recently published in Spain.[21]

We also found a lower prevalence of resistance to amikacin (3.33%) compared to gentamicin (7.55%), probably due to the more restricted use of the former.

When it came to quinolones, we found a significant prevalence of resistance despite their exceptional use in paediatric patients.

A particular trend in the broader problem of antimicrobial drug resistance is the increase in the frequency of community-acquired UTIs caused by ESBL-producing *E. coli*. Some studies have found an increase of up to 3.54% in recent years, corresponding to an annual increase of 0.51%.[22] The increase observed in our study (1.50%) is consistent with previously published data for Spain,[12-14,18] although frequencies as high as 17% have been reported in series with a large proportion of patients with renal or urologic disease.[9,23]. Of the 9 such isolates in our study, only one corresponded to a patient with renal or urologic disease.

With regard to the prevalences of drug resistance in the different CAs, we observed variations, but the small number of samples in some of these regions limits the generalizability of the results.

There are limitations to our study: the data obtained may not be representative of all the ACs due to uneven participation. Of a total of 404 clinicians that initially agreed to collaborate, only 187 were able to participate in the study. This was partly due to administrative barriers, a common hurdle in multicenter studies,[24] despite the observational design of the project.

There was variation in the number of antibiograms that included each of the antibiotics, although the numbers can be considered sufficient for the antibiotics used most frequently for treatment of community-acquired infections.

A large portion of the study period coincided with the COVID-19 pandemic. The state of alert was de-

clared 5 months after the start of followup and changes in health care could have affected data collection, the management of the episodes and the total number of UTIs diagnosed appropriately. In the final months of the study, UTI episodes may have been underrecorded on account of the excessive burden placed on the health care system by the resumption of in-person care delivery, concurrent to the different waves of the pandemic.

Although staying up to date with local drug resistance data is recommended, in practice it is very difficult to have a sufficient number of pediatric cultures in an area close to the patient. It is more common for reported data to be aggregated and not broken down by age or origin of the specimens (community vs hospital). For this reason, we believe that the data collected in our study, despite its limitations, are relevant for the practice of primary care paediatricians.

CONCLUSION

To conclude, the most prevalent uropathogen causing UTI continues to be *E. coli*, although in certain groups it may be necessary to consider other bacteria. Amoxicillin, amoxicillin-clavulanic acid, cotrimoxazole, trimethoprim and nalidixic acid should not be used for empiric treatment. Local patterns of sensitivity should be evaluated for first-generation cephalosporins, which are currently not considered for first-line treatment.

CONFLICTS OF INTEREST

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AUTHORSHIP

Author contributions: drafting of manuscript (MRAB, ACS), statistical analysis of the data (RJA), study design, coordination of collaborating partners, literature search and final revision of the manuscript (all).

Partial preliminary data from this study were presented as a communication at the 19th Congreso de Actualización en Pediatría (Paediatrics Update Congress) of the AEPap in 2023.

ABBREVIATIONS

AC: autonomous community • **CFU:** colony-forming unit • **ESBL:** extended spectrum beta-lactamase • **GNB:** gram-negative bacilli • **GP:** gram-positive • **IC** informed consent • **PC:** primary care • **PCP:** primary care paediatrics • **SD:** standard deviation • **UTI:** urinary tract infection.

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