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Antibiotic treatment and antimicrobial resistance in children with urinary tract infections

K. Vazouras[a,b,c,*], K. Velali[d], I. Tassiou[e], A. Anastasiou-Katsiardani[f], K. Athanasopoulou[g], A. Barbouni[h], C. Jackson[b], L. Folgori[i], T. Zaoutis[a,j], R. Basmaci[k], Y. Hsia[b,l]

[a] The Stavros Niarchos Foundation–Collaborative Center for Clinical Epidemiology and Outcomes Research (CLEO), University of Athens, Athens, Greece
[b] Paediatric Infectious Diseases Research Group, Institute for Infection and Immunity, St George's University of London, London SW17 0RE, UK
[c] Second Department of Pediatrics, Aghia Sophia Children's Hospital, Agia Sophia Hospital, Goudi, Athens, Greece
[d] First Department of Pediatrics, Aghia Sophia Children's Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[e] Paediatrics Department, University Hospital of Larissa, Larissa, Greece
[f] Paediatrics Department, Achillopouleion General Hospital of Volos, Volos, Greece
[g] Microbiology Department, Achillopouleion General Hospital of Volos, Volos, Greece
[h] Department of Public Health Policy, School of Public Health, University of West Attica, Athens, Greece
[i] Paediatric Infectious Disease Unit, Department of Paediatrics, Luigi Sacco Hospital, University of Milan, Milan, Italy
[j] Division of Infectious Diseases, Children's Hospital of Philadelphia, UPENN School of Medicine, Philadelphia, PA, USA
[k] Université de Paris, Infection, Antimicrobiens, Modélisation, Evolution, Unité Mixte de Recherche 1137, Institut National de la Santé Et de la Recherche Médicale, F-75018 Paris, France; Service de Pédiatrie-Urgences, Hôpital Louis-Mourier, Assistance Publique – Hôpitaux de Paris, F-92700 Colombes, France
[l] School of Pharmacy, Queen's University Belfast, Belfast, UK

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ABSTRACT

Objectives: The aim of this study was to describe antibiotic prescribing patterns and antimicrobial resistance rates in hospitalised children with febrile and afebrile urinary tract infections (UTIs).
Methods: Antibiotic prescriptions and antibiograms for neonates, infants and older children with UTI admitted to a general district hospital in Central Greece were evaluated. Data covering a 5-year period were collected retrospectively from the Paediatric Department's Electronic Clinical Archive. Patients were included based on clinical and microbiological criteria. Antimicrobial susceptibility was determined by the Kirby–Bauer disk diffusion method.
Results: A total of 230 patients were included in the study. Among 459 prescriptions identified, amikacin (31.2%) was the most common antibiotic prescribed in this population, followed by amoxicillin/clavulanic acid (17.4%) and ampicillin (13.5%). Children received prolonged intravenous (i.v.) treatments for febrile (mean ± S.D., 5.4 ± 1.45 days) and afebrile UTIs (mean ± S.D., 4.4 ± 1.64 days). A total of 236 pathogens were isolated. The main causative organism was *Escherichia coli* (79.2%) with high reported resistance rates to ampicillin (42.0%), trimethoprim/sulfamethoxazole (26.5%) and amoxicillin/clavulanic acid (12.2%); lower resistance rates were identified for third-generation cephalosporins (1.7%), nitrofurantoin (2.3%), ciprofloxacin (1.4%) and amikacin (0.9%). *Klebsiella* spp. isolates were highly resistant to cefaclor (27.3%).
Conclusion: High prescribing rates for amikacin and penicillins (± β-lactamase inhibitors) and prolonged i.v. treatments were observed. *Escherichia coli* was highly resistant to ampicillin, whilst third-generation cephalosporins exhibited greater in vitro efficacy. Establishment of antimicrobial stewardship programmes and regular monitoring of antimicrobial resistance could help to minimise inappropriate prescribing for UTIs.

1. Introduction

Urinary tract infections (UTIs) are common infections among children and are the most common proven bacterial infection in febrile infants without localising signs [1]. It has been estimated that the overall prevalence of childhood UTI is 7.0% and 7.8%,

* Corresponding author. Present address: The Stavros Niarchos Foundation–Collaborative Center for Clinical Epidemiology and Outcomes Research (CLEO), 5 Chatzigianni Mexi, Athens 11528, Greece.
E-mail address: k.vazouras@cleoresearch.org (K. Vazouras).

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respectively, in infants and children presenting to health services with fever and/or other symptoms of UTI [2]. UTIs have been identified as the second most common reason for antibiotic prescribing (most frequently cephalosporins and penicillins), after respiratory tract infections, in paediatric outpatients in Greece [3].

Appropriate treatment of UTIs has become challenging due to high resistance to commonly prescribed antibiotics (e.g. aminopenicillins) [4] and the globally increasing prevalence of multidrug-resistant organisms causing UTIs [5], including in Greece. Evidence has shown a high prevalence of multidrug resistance in Gram-negative organisms, which are the most common cause of UTIs [6,7]. However, there is limited evidence regarding antibiotic-resistant UTIs in infants and children in Greece, and most available data are from case reports [8–11]. Overall resistance to ampicillin and trimethoprim/sulfamethoxazole (SXT) has been estimated to be as high as 51% and 29%, respectively, among Greek children [4]. The exact burden of antimicrobial resistance (AMR) in children in Greece is poorly understood as the paediatric population is not adequately represented in the established national surveillance programme [12]. Nevertheless, UTIs are key to understanding the magnitude of AMR owing to the increasing isolation of resistant strains in urine [5].

The aims of this study were (i) to describe the antibiotic prescribing patterns for treatment of UTIs, including information on dosing, duration and route of administration, and (ii) to investigate the antimicrobial resistance rates of uropathogens isolated from hospitalised children with UTI in a Greek general district hospital over a 5-year period.

2. Materials and methods

2.1. Data source

A retrospective cohort study was performed in Achillopouleion General Hospital of Volos, a general district hospital in Central Greece, from August 2010 to September 2015, including neonates (aged <29 days), infants and toddlers (aged 29 days up to <2 years) and older children (aged 2 to <5 years or ≥5 years). This paper reports a cross-sectional analysis of the baseline data from the cohort study. Patients' medical notes were retrieved from the Paediatric Department's Electronic Clinical Archive and patients with UTI were identified using a comprehensive approach including ICD-10 codes and free-text information. Demographic data, diagnoses, medical history and antibiograms were extracted from the database. Atypical UTIs were identified according to the UK National Institute for Health and Care Excellence (NICE) guidelines [13]. Information on antibiotic prescribing (drug, dose, frequency and duration) was also extracted. Dosing was compared with recommendations from the Greek National Formulary for Medicines (last updated in 2007) [14] and the '*British National Formulary for Children*' [15].

2.2. Inclusion criteria

Children from birth to 18 years of age with either a febrile or afebrile UTI were included in the study. Febrile UTIs (fUTIs) had to fulfil all three of the following criteria: (i) fever with a temperature of ≥38 °C for children older than 12 months or ≥37.4 °C for infants younger than 12 months; (ii) positive urine culture with pathogen growth ≥10 000 CFU/mL for catheter specimens or suprapubic aspiration or ≥100 000 CFU/mL for clean-catch specimens; and (iii) pyuria (≥5 white blood cells per high-power field) in centrifuged urine OR positive dipstick (nitrites or leukocyte esterase). In the absence of fever, UTIs were identified as afebrile UTIs (aUTIs). Children with a positive blood culture with the same pathogen or a positive acute dimercaptosuccinic acid (DMSA) scan as well as a positive urine culture were included even in the absence of pyuria or substantial pathogen growth. Children with recurrent episodes were included if the admissions were separated by an interval of ≥2 months.

2.3. Laboratory methods

Antibiograms were performed with the Kirby–Bauer disk diffusion method using antibiotic-impregnated disks as recommended by the Clinical and Laboratory Standards Institute (CLSI) [16]. In cases of inconclusive results or highly resistant strains, bacterial identification and antimicrobial susceptibility testing were performed using an automated VITEK® 2 identification and resistance testing system (bioMérieux, Marcy-L'Étoile, France). Antibiogram results are reported as susceptible, intermediate or resistant in general; here intermediate and resistant isolates were considered collectively as non-susceptible (hereafter referred to as resistant). Extended-spectrum β-lactamase (ESBL)-producing strains were identified using the double-disk synergy test [16]. Proportions of resistance were reported for pathogen–antibiotic combinations with ≥10 tests reported.

2.4. Statistical analysis

Demographic and baseline characteristics of the study cohort were described for febrile and afebrile UTIs. Differences in baseline variables between the two groups were tested by two-tailed Fisher's exact test for categorical variables. Statistical analysis was performed using Stata Statistical Software: Release 14 (Stata Corp LP, College Station, TX, USA).

2.5. Ethical approval

Ethical approval was granted by the Scientific Committee of Achillopouleion General Hospital of Volos.

3. Results

3.1. Patient characteristics

A total of 314 children with a diagnosis of UTI were hospitalised during the study period, of whom 230 fulfilled the inclusion criteria and were included in the final analysis (Table 1). Of the 230 patients, 166 (72.2%) were female. The age of included children ranged from 3 days to 17 years (median 10 months, interquartile range 3–37 months). The majority of children (78.7%; 181/230) had no reported co-morbidities and 11.3% (26/230) had urinary tract-associated abnormalities. There were 96 children (41.7%) with an atypical UTI. No child developed signs/symptoms of UTI > 48 h after hospital admission. Ten children (4.3%) had been hospitalised within 2 months prior to the UTI episode and 29 children (12.6%) were treated with antibiotics (therapeutic or prophylactic) on admission or up to 1 month prior to admission, mostly (23/29; 79.3%) with a β-lactam.

3.2. Antibiotic prescribing patterns

During the study period, 459 antibiotic prescriptions were identified for the 230 included patients (Table 2). A total of 378 prescriptions were for fUTIs and 81 were for aUTIs, mostly (97.4%; 447/459) intravenously. Overall, the most commonly prescribed antibiotic was amikacin (32.8% of prescriptions for fUTIs and 23.5% of prescriptions for aUTIs prescriptions), followed by amoxicillin/clavulanic acid (AMC) (16.7% of fUTIs and 21.0% of aUTIs prescriptions). A carbapenem (imipenem) was prescribed in only one case, as targeted treatment, whilst no quinolones were

Table 1
Demographic characteristics and pathogen identification in patients with febrile and afebrile urinary tract infections (UTIs).[a]

	All UTIs (n = 230)	Febrile UTIs (n = 181)	Afebrile UTIs (n = 49)	P-value
Demographics				
Age (on admission)				
<29 days	15 (6.5)	12 (6.6)	3 (6.1)	0.07
29 days to <2 years	138 (60.0)	116 (64.1)	22 (44.9)	
2 years to <5 years	37 (16.1)	25 (13.8)	12 (24.5)	
≥5 years	40 (17.4)	28 (15.5)	12 (24.5)	
Sex				
Male	64 (27.8)	49 (27.1)	15 (30.6)	0.72
Female	166 (72.2)	132 (72.9)	34 (69.4)	
Medical history				
Previously healthy	181 (78.7)	141 (77.9)	40 (81.6)	0.70
Urinary tract abnormalities[b]	26 (11.3)	24 (13.3)	2 (4.1)	0.08
Other medical conditions[c]	24 (10.4)	17 (9.4)	7 (14.3)	0.30
Concurrent infections	11 (4.8)	11 (6.1)	0 (0.0)	0.13
Bacteraemic UTI	6 (2.6)	6 (3.3)	0 (0.0)	0.35
Recurrent UTI	40 (17.4)	35 (19.3)	5 (10.2)	0.20
Atypical UTI	96 (41.7)	78 (43.1)	18 (36.7)	0.74
Recent hospitalisation[d]	10 (4.3)	8 (4.4)	2 (4.1)	>0.99
Recent or concurrent antibiotics use[e]	29 (12.6)	27 (14.9)	2 (4.1)	0.05
Pathogens (n = 236)				
Escherichia coli	187 (79.2)	153 (81.8)	34 (69.4)	0.093
Klebsiella spp.	17 (7.2)	14 (7.5)	3 (6.1)	
Proteus spp.	12 (5.1)	6 (3.3)	6 (12.2)	
Pseudomonas aeruginosa	11 (4.7)	8 (4.4)	3 (6.1)	
Enterobacter spp.	4 (1.7)	2 (1.1)	2 (4.1)	
Citrobacter sp.	1 (0.4)	1 (0.5)	0 (0.0)	
Gram-positive cocci[f]	4 (1.7)	3 (1.6)	1 (2.0)	
Total	236 (100)	187 (100)	49 (100)	–

[a] Data are presented as n (%).
[b] Urinary tract abnormalities include vesicoureteral reflux and major anatomical urinary tract abnormalities.
[c] Other medical conditions include gastrointestinal diseases, heart defect, endocrinology disorders, syndromes, neurological conditions, haematological conditions and prematurity.
[d] Within 2 months.
[e] On admission or up to 1 month prior to admission.
[f] Two cases of *Enterococcus* spp. and one case of *Staphylococcus simulans* accounted for three febrile UTIs, whilst one afebrile UTI was caused by group B *Streptococcus*.

prescribed in this study population. The mean ± standard deviation duration of intravenous (i.v.) treatment for fUTIs was 5.4 ± 1.45 days, whilst aUTIs were treated intravenously for a mean of 4.4 ± 1.64 days (Table 2).

Information on dosing could be identified in 37.7% (173/459) of prescriptions. The results on the main antibiotics used (for which at least five prescriptions could be found) are presented in Table 3. High doses, exceeding the upper limit of the available guidance [14,15], were observed for AMC in one neonate, whilst ceftriaxone was consistently prescribed in the upper-high range (75–80 mg/kg/day), as usually recommended for severe infections. Finally, piperacillin/tazobactam (TZP) was prescribed outside the proposed range in two of the three available prescriptions.

3.3. Pathogen identification and antimicrobial susceptibility patterns

A total of 236 pathogens were isolated from 230 patients. The most commonly identified pathogen was *Escherichia coli* (79.2%; 187/236), followed by *Klebsiella* spp. (7.2%; 17/236), *Proteus* spp. (5.1%; 12/236) and *Pseudomonas aeruginosa* (4.7%; 11/236) (Table 1). *Enterobacter* spp. (1.7%; 4/236), *Citrobacter* sp. (0.4%; 1/236) and Gram-positive cocci (1.7%; 4/236) were the least frequent isolates in this population. The characteristics of the pathogens are presented in Table 1.

Among the 157 *E. coli* isolates tested, 66 (42.0%) were resistant to ampicillin, whereas resistance to AMC and ampicillin/sulbactam (SAM) was 12.2% and 19.3%, respectively (see Supplementary Table S1 for full details, including the number of isolates tested for resistance to each antibiotic). *Escherichia coli* also showed high resistance to TZP amongst the 58 isolates tested (12.1%). The resistance rates for first- and second-generation cephalosporins (2GCs) ranged from 3.3% for cefoxitin to 28.8% for cefalotin. Only 1.7% of *E. coli* isolates were resistant to third-generation cephalosporins (3GCs) and fourth-generation cephalosporins (4GCs). High resistance rates were identified to SXT (26.5%), whilst only 2.3% of isolates were resistant to nitrofurantoin. Aminoglycosides appeared to be active against most *E. coli* isolates: 5.9% were resistant to gentamicin and only 0.9% to amikacin. Low levels of resistance were also reported for quinolones (1.4% for ciprofloxacin), whilst all *E.coli* isolates were fully susceptible to carbapenems.

Proteus spp. isolates (n = 12) showed no resistance to 2GCs. A few were resistant to SXT (8.3%) as well as to 3GCs, 4GCs, aminoglycosides and carbapenems. Among a total of 17 *Klebsiella* spp. isolates, resistance rates to SAM and AMC were 28.6% and 13.3%, respectively. Resistance rates for *Klebsiella* spp. against 2GCs ranged from 14.3% for cefuroxime to 30.0% for cefalotin. *Pseudomonas aeruginosa* showed no resistance to TZP, ceftazidime, aminoglycosides or quinolones. The full susceptibility results are provided in Supplementary Table S1.

Data for the Gram-positive pathogens are presented in Supplementary Table S2.

Among the 236 pathogens, 4 ESBL-producing isolates (3 *E. coli* and 1 *Klebsiella* sp.) as well as 1 *Klebsiella* sp. with a phenotype of potential high-level cephalosporinase-producer were identified. All of these pathogens had caused a fUTI in female patients. The age of patients with a UTI caused by an ESBL-producer ranged from 5 months to 3 years. Two of these children had a history of recurrent UTIs and a background of major urinary tract abnormality, being under prophylaxis (SXT or cefaclor). The other three patients were healthy prior to admission with an unremarkable medical history. The ESBL-producing isolates exhibited resistance to penicillins and

Table 2
Antibiotic prescriptions for treatment of febrile and afebrile urinary tract infections (UTIs).

Antibiotic	No. (%) of prescriptions	Age (on admission)				Treatment duration in days (mean ± S.D.)
		<29 days	29 days to <2 years	2 years to <5 years	≥5 years	
Febrile UTIs (n = 378)						
Penicillin G	1 (0.3)		1			–
Ampicillin	53 (14.0)	10	37	4	2	3.9 ± 2.7
SAM	34 (9.0)		21	4	9	4.8 ± 1.7
AMC	63 (16.7)	1	45	10	7	5.8 ± 2.1
TCC	1 (0.3)	1				8
TZP	7 (1.9)	1	5		1	7.4 ± 4.0
Cefaclor	1 (0.3)		1			–
Cefprozil	1 (0.3)		1			–
Cefoxitin	2 (0.5)		2			3.7
Cefuroxime	25 (6.6)		14	3	8	4.3 ± 1.9
Cefotaxime	42 (11.1)	8	25	5	4	6.7 ± 2.7
Ceftriaxone	17 (4.5)		10	4	3	8.4 ± 2.2
Ceftazidime	3 (0.8)		2		1	6.7
Imipenem	1 (0.3)				1	9
Netilmicin	1 (0.3)		1			5
Amikacin	124 (32.8)	10	82	14	18	4.4 ± 1.9
SXT	2 (0.5)		2			–
aUTIs (n = 81)						
Ampicillin	9 (11.1)	2	6		1	4.9 ± 4.0
Amoxicillin	1 (1.2)			1		
SAM	5 (6.2)		2	2	1	3.4 ± 1.5
AMC	17 (21.0)	1	12	1	3	4.0 ± 2.3
TZP	3 (3.7)		2		1	7.7 ± 0.3
Cefaclor	3 (3.7)			2	1	
Cefprozil	4 (4.9)			2	2	1.3 ± 0.3
Cefuroxime	13 (16.0)		7	3	3	3.6 ± 1.6
Cefotaxime	3 (3.7)	1	2			7.7 ± 2.5
Ceftriaxone	1 (1.2)				1	
Ceftazidime	1 (1.2)		1			
Netilmicin	2 (2.5)		2			4.5 ± 3.5
Amikacin	19 (23.5)	3	14	1	1	5.0 ± 2.5

S.D., standard deviation; SAM, ampicillin/sulbactam; AMC, amoxicillin/clavulanic acid; TCC, ticarcillin/clavulanic acid; TZP, piperacillin/tazobactam; SXT, trimethoprim/sulfamethoxazole.

Table 3
Intravenous antibiotic dosing stratified by age.

Age/antibiotic	No. of prescriptions	Dose (mg/kg/day)		Recommended dosing (mg/kg/day)	
		Mean ± S.D	Range	EOF[a,b,c]	BNFc[a,c]
<29 days					
Ampicillin	8	199 ± 11.4	177–219	25–200	60–120 (<7 days) 90–180 (7–20 days) 120–240 (21–28 days)
Cefotaxime	7	142 ± 18.7	100–150	50–100 (<7 days) 75–150 (7–28 days)	50–100 (<7 days) 75–150 (7–20 days) 75–200 (21–28 days)
Amikacin	8	15 ± 1.1	13–17	15	15
29 days to <2 years					
Ampicillin	21	199 ± 2.9	190–200	50–400	100–200
SAM	7	157 ± 18.9	148–200	150	N/A
AMC	8	90 ± 1.2	89–92	75	60 (<3 months) 90 (≥3 months)
Cefuroxime	8	101 ± 45.6	20–150	30–100	60–240
Cefotaxime	14	149 ± 2.4	143–153	50–200	100–200
Ceftriaxone	7	80 ± 9.4	73–100	50–100	50–80
Amikacin	24	15 ± 2.1	14–25	15	15
2 to <5 years					
Cefuroxime	5	108 ± 25.9	80–150	30–100	60–240
Amikacin	6	16 ± 2.9	15–22	15	15
≥5 years					
SAM	6	135 ± 16.2	114–153	150	N/A
Amikacin	8	15 ± 0.4	14–15	15	15 (<5 years) 15–22.5 (>12 years)

S.D., standard deviation; EOF, Greek National Organisation for Medicines; BNFc, British National Formulary for Children; SAM, ampicillin/sulbactam; AMC, amoxicillin/clavulanic acid; N/A, not available; UTI, urinary tract infection.
[a] Range according to severity of UTI.
[b] Doses are not specified for UTIs from the EOF.
[c] For children with normal renal function.

β-lactamase-inhibitors (BLIs) (except for TZP) and were mostly susceptible to carbapenems (3/3 susceptible isolates), nitrofurantoin (3/4) and amikacin (3/4). No carbapenem resistance was identified in the study population.

4. Discussion

4.1. Principal findings

In this study population of hospitalised children with UTIs, amikacin, penicillins (± BLIs), cefuroxime and 3GCs were the most commonly prescribed antibiotics. The majority of children in this hospital received prolonged i.v. treatment. *Escherichia coli* was the most common pathogen causing UTIs in children, exhibiting high resistance rates to β-lactams (± BLIs). Lower resistance rates were observed against nitrofurantoin, cefuroxime, cefoxitin, quinolones and carbapenems.

4.2. Strengths and limitations

To our knowledge, this is the first large-scale study assessing antibiotic prescribing in childhood UTIs in Greece. In its '*Global action plan on antimicrobial resistance*', the World Health Organization (WHO) suggested the collection and reporting of data on the use of antimicrobial agents in order to tackle AMR [17]. Despite the presence of global [18,19] and national [3] data on antibiotic prescribing, there are currently no observational studies on antibiotic prescribing for specific paediatric infectious syndromes in district hospitals in Greece. In the present study, we provide a comprehensive description of antibiotic prescribing for UTIs in a regional hospital setting. ESBL-producing Enterobacteriaceae and other resistant infections, particularly UTIs, represent a growing threat to children [5,20]. Therefore, appropriate antibiotic prescribing in childhood UTIs is important to reduce the risk of AMR, and understanding current practice and resistance patterns can help inform future policy decisions.

However, there are several limitations of this study that need to be addressed. First, the study cannot be generalised to other Greek healthcare settings as childhood UTI management may vary across hospitals in Greece. Second, a substantial proportion (62.3%; 286/459) of prescriptions did not include dosing information. Thus, we were unable to fully evaluate appropriate dosing for UTI treatment in the study population. However, recording was complete regarding the number, class and route of antibiotics given, and the duration of treatment was missing in only 5 (1.1%) records. In addition, antimicrobial susceptibility testing of pan-susceptible isolates was limited with regard to TZP, newer quinolones (e.g. ciprofloxacin) and carbapenems (especially ertapenem), thus resistance rates apply mainly to isolates that were resistant to the more commonly tested antibiotics. It is also likely that some ESBL-producing cases may have been treated in other centres or in the community, so case numbers in this study may not fully reflect those in the local population. Characteristics of children with fUTIs and aUTIs were compared but we were unable to formally compare resistance rates between these two groups owing to the small numbers. Future work could further investigate differences between these clinical presentations and the implications for antibiotic management. Finally, a limited number of resistance rates for non-*E. coli* pathogens were provided owing to their limited frequency in the study population.

4.3. Implications for selection of empirical treatment

The American Academy of Pediatrics recommends AMC, SXT and 2GCs for oral empirical treatment of fUTIs [21]. 3GCs and aminoglycosides are mostly selected for parenteral treatment of fUTIs [21]. The updated Greek national guidance on treatment of fUTIs [22] suggests the use of 2GCs or 3GCs.

In the current study population, SXT and penicillins (± BLIs) appear not to be the optimal treatment options given the observed in vitro resistance rates. The WHO's recent recommendation that 3GCs should be the first parenteral choice for hospital treatment of mild-to-moderate fUTIs, whilst aminoglycosides should be reserved for severe or neonatal UTIs [22,23], seems appropriate for this population. However, patients receiving aminoglycosides should be carefully monitored for nephrotoxicity [24]. Finally, other studies suggest that nitrofurantoin appears to be an appropriate choice for aUTIs and UTIs caused by ESBL-producing isolates [4,25].

Patterns of AMR vary geographically and local susceptibility patterns of coliforms to antimicrobial agents should guide the selection of empirical treatment of UTIs [21]. For example, resistance to gentamicin should routinely be tested owing to its changing resistance rates. Amikacin may be used instead of gentamicin in settings where resistance to the latter is high [26,27]. Use of cephalosporins and quinolones should also be monitored closely due to the high risk for selection of resistance [23].

Empirical antibiotic selection should be based on the presence of fever and severity as recommended by the WHO [23]. Healthy individuals may respond more favourably, even in the presence of in vitro resistance, making higher rates of resistance potentially more acceptable for empirical treatment compared with severely ill patients [28]. Several attempts have been made to define the severity of UTIs [13,29], although more evidence and international consensus is needed to apply a standardised definition.

4.4. Duration of treatment and dosing

The duration of i.v. treatment for UTI ranged from 4.4–5.4 days in this study. The long i.v. treatment may be due to the severe cases identified in this study population, given that 41.7% of UTI study subjects were atypical [22]. However, the delayed switch to oral antibiotics may represent an indicator of low-quality prescribing [18]. Shorter courses of 2–4 days of i.v. therapy followed by oral therapy have been proven to be as effective as longer i.v. courses [30]. The benefit of longer treatments has also not been confirmed for bacteraemic UTIs [31].

Sporadic mistakes and inappropriate prescribing were noted mainly for AMC dosing in neonates and for TZP. Errors in TZP prescribing are potentially favoured by the absence of relevant national guidance for this age group [14]. The presence of clinical pharmacists could perhaps have helped to avoid dosing errors in this setting. The unavailability of suitable guidance, inadequate training and lack of clinical pharmacist support are some common causes for prescribing errors in clinical practice [32,33].

4.5. Antimicrobial resistance in Greece

This study of AMR in UTIs is in accordance with previous studies from Greece [8–10], expanding our knowledge on AMR in paediatric UTI pathogens in Central Greece. Among these studies, similar high levels (often >10%) of *E. coli* resistance were reported to ampicillin, penicillins/BLIs, 2GCs (except cefoxitin) and SXT, as well as consistently low resistance rates (<10%) to nitrofurantoin, cefoxitin, cefuroxime, 3GCs, 4GCs, aminoglycosides and carbapenems for fUTIs. Poor data exist on quinolone resistance (3.9%) [8] as susceptibility to quinolones is either not tested or not reported owing to the limited use of quinolones in the Greek paediatric population, as also confirmed by a study on antibiotic use in a paediatric outpatient population [3]. *Klebsiella*, currently a public health threat in Greece [6], consistently exhibited higher levels of resistance [8] to AMC (6.7% vs. 13.3% in the present study), whilst

no resistance was detected to imipenem or meropenem. Finally, although the numbers were small, the data included fewer ESBL-positive UTIs ($n = 4$; 1.7% of isolates) compared with another study in Northern Greece [11].

4.6. Antimicrobial resistance in the global context

The current results appear to be consistent with the results of a recent meta-analysis showing high resistance rates for ampicillin (53.4%) and SXT (30.2%) in UTIs caused by *E. coli* in Organisation for Economic Co-operation and Development (OECD) countries [4]. Low resistance rates have been shown for ciprofloxacin (2.1%) and nitrofurantoin (1.3%) [4]. Resistance to SXT was two-fold higher (69.6%) in non-OECD countries, whilst resistance to ciprofloxacin (26.8%) and ceftazidime (26.1%) appeared 10-fold higher in non-OECD countries [4]. Resistance to AMC appeared higher in the current study (12.2%) and is in line with newer reports from other countries, such as the UK (16.5%) [34], the Republic of Korea (25.0%) [35] and Turkey (33.0%) [36]. The percentage of ESBL-positive UTIs in the current sample was lower (1.7%) than in other paediatric studies [35,37] and seems not to follow the global trend of the rising prevalence of ESBL-positive infections [5,38]. In Mozambique, 76% of 34 Enterobacteriaceae isolates obtained from hospitalised children with UTIs were ESBL-producers [39]. No carbapenem resistance was detected in the current study. However, carbapenemase-producing bacteria represent an emerging threat, especially for neonates and immunocompromised patients [40,41].

5. Future steps

In this study, suboptimal selection of antibiotic treatments, prolonged treatment duration and occasional dosing outside of recommended ranges were observed, suggesting an urgent need for the introduction of effective antimicrobial stewardship strategies in Greek hospitals. Such interventions could reduce inappropriate prescribing and costs [3] for a healthcare system that is under severe financial pressure. Furthermore, AMR surveillance in the paediatric population should be intensified, with the inclusion of more paediatric centres. UTI is a key area that can improve our understanding of AMR in the paediatric population.

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Competing interests

None declared.

Ethical approval

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jgar.2019.06.016.

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