**Treatment and Antimicrobial Resistance in Children with Urinary Tract Infections**

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**Abstract**

Objectives

The aim of this study was to describe antibiotic prescribing patterns and resistance rates in hospitalised children with febrile and afebrile urinary tract infections (UTIs).

Methods

We evaluated antibiotic prescriptions and antibiograms for neonates, infants and older children with a UTI admitted to a general district hospital in central Greece. Data was collected retrospectively from the Paediatric Department’s Electronic Clinical Archive, covering a 5-year period. Patients were included based on clinical and microbiological criteria. Sensitivity to antimicrobials was determined using the Kirby-Bauer disk diffusion method.

Results

Two hundred and thirty 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 treatments for febrile (mean 5.4 days; SD 1.45) and afebrile UTIs (mean 4.7 days; SD 1.34). 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 3rd generation cephalosporins (1.7%), nitrofurantoin (2.3%), ciprofloxacin (1.3%) and amikacin (0.9%). *Klebsiella sp.* isolates were highly resistant to cefaclor (27.3%).

Conclusion

We observed high prescribing rates for amikacin and penicillins (+/-beta lactamase inhibitors) and prolonged intravenous treatments. *E.coli* appeared to be highly resistant to ampicillin, whilst 3rd generation cephalosporins exhibited higher *in vitro* efficacy. The establishment of antimicrobial stewardship programs and regular monitoring of antimicrobial resistance could help to minimise inappropriate prescribing for UTIs.

**Keywords:** urinary tract infections; antibiotic prescribing; antimicrobial resistance; children

1. **Introduction**

Urinary tract infections (UTIs) are common infections among children and the most common cause of proven bacterial infection in febrile infants without localizing signs (1). It has been estimated that the overall prevalence of childhood UTI is 7.0% and 7.8% in infants and children, respectively, 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 multi-drug resistant organisms causing UTI (5), including in Greece. Evidence has shown high prevalence of multidrug-resistance (MDR) in Gram-negative organisms, the most common cause of UTI (6, 7). However, there is limited evidence on antibiotic resistant UTIs in infants and children in Greece and most available data are from case reports (8-11). Overall resistance to ampicillin and co-trimoxazole have been estimated to be as high as 51% and 29% respectively among Greek children (4). The exact burden of antimicrobial resistance in children is poorly understood in Greece, as the paediatric population is not adequately represented in the established national surveillance program (12). Nonetheless, UTIs are key to understand the magnitude of AMR due to the increasing isolation of resistant strains in urine (5).

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

**2. Material and Methods**

*2.1 Data Source*

A retrospective cohort study was carried out in a general district hospital in Central Greece (Achillopouleion General Hospital of Volos) from August 2010 to September 2015, including neonates (aged <29 days), infants and toddlers (aged 29 days up to less than 2 years) and older children (aged 2 to 5 years old or older than 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 Guidelines (13). Information on antibiotic prescribing (drug, dose, frequency and duration) was also extracted. Dosing was compared to recommendations from the Greek National Formulary for Medicines (last updated in 2007) (14) and British National Formulary for Children (15).

*2.2 Inclusion Criteria*

Children from birth to 18 years old with either a febrile or afebrile UTI were included in the study. Febrile UTIs (fUTIs) had to fulfil all three of the following criteria: a) fever with temperature of ≥38°C for children older than 12 months or ≥37.4°C for infants younger than 12 months, b) positive urine culture with pathogen’s growth ≥10 000 colony forming units (cfu)/ml for catheter specimens or suprapubic aspiration, ≥ 100 000 cfu/ml for clean-catch specimens, c) pyuria ≥5 per high-power field, in centrifuged urine OR positive dipstick (nitrites or leukocyte esterase). In absence of fever, they were identified as afebrile UTIs (aUTIs). Children with a positive blood culture with the same pathogen or 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 at least two months.

*2.3 Laboratory methods*

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

*2.4 Statistical analysis*

The demographic and baseline characteristics of the study cohort were described for febrile UTIs and afebrile UTIs. Differences in baseline variables between the two groups were tested by using two-tailed Fisher’s exact test for categorical variables. The analysis was performed using Stata version 14 (Stata Corp LP, College Station, TX, United States).

*2.5 Ethical approval*

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

**3. Results**

*3.1 Patients’ characteristics*

A total of 314 children with UTI diagnosis were hospitalised during the study period. Of those, 230 fulfilled the inclusion criteria and were included in the final analysis (Table 1). 72.2% of patients were female (166/230). The age of included children ranged from 3 days to 17 years (median 10 months, interquartile range 3-37 months). The majority of children (80.4%; 185/230) had no reported co-morbidities. 9.1% of children (21/230) had urinary tract associated abnormalities. There were 96 children (41.7%; 96/230) with an atypical UTI. No child developed signs/symptoms of UTI >48 hours after hospital admission. Ten (4.3%) children had been hospitalised within two months prior to the UTI episode, and 29 (12.6%) were treated with antibiotics (therapeutic or prophylactic dose) on admission or up to one month prior to admission, mostly (23/29; 79.3%) a beta-lactam.

**Table 1. Demographics and pathogen identification in patients with febrile and afebrile UTIs**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **All UTIs (n=230)** | **Febrile UTIs (n=181)** | **Afebrile UTIs (n=49)** | **p-value** |
| **Demographics** |  |  |  |  |
| **Age (on admission)** |  |  |  |  |
| <29days | 15 (6.5%) | 12 (6.6%) | 3 (6.1%) | 0.07 |
| 1month – <2 years | 138 (60.0%) | 116 (64.1%) | 22 (44.9%) |
| 2 years – <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%) |
| **Background** |  |  |  |  |
| Previously healthy children | 181 (78.7%) | 141 (77.9%) | 40 (81.6%) | 0.70 |
| UT-abnormalitiesa | 25 (10.9%) | 24 (13.3%) | 2 (4.1%) | 0.08 |
| Other medical conditionsb | 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 UTIs | 6 (2.6%) | 6 (3.3%) | 0 (0.0%) | 0.35 |
| Recurrent UTIs | 40 (17.4%) | 35 (19.3%) | 5 (10.2%) | 0.20 |
| Atypical UTIs | 96 (41.7%) | 78 (43.1%) | 18 (36.7%) | 0.74 |
| Recent hospitalisation | 10 (4.3%) | 8 (4.4%) | 2 (4.1%) | >0.99 |
| Recent or concurrent antibiotics use | 29 (12.6%) | 27 (14.9%) | 2 (4.1%) | 0.05 |
| **Pathogens (n=236)** |  |  |  |  |
| *E. coli* | 187 (79.2%) | 153 (81.8%) | 34 (69.4%) | 0.136 |
| *Klebsiella sp* | 17 (7.2%) | 14 (7.5%) | 3 (6.1%) |
| *Proteus sp* | 12 (5.1%) | 8 (4.3%) | 6 (12.2%) |
| *Pseudomonas aeruginosa* | 11 (4.7%) | 6 (3.2%) | 3 (6.1%) |
| *Enterobacter sp* | 4 (1.7%) | 2 (1.1%) | 2 (4.1%) |
| *Citrobacter sp* | 1 (0.4%) | 1 (0.5%) | 0 (0.0%) |
| Gram (+) coccic | 4 (1.7%) | 3 (1.6%) | 1 (2.1%) |
| Total | 236 (100%) | 187 (100%) | 49 (100%) | - |

a UT-abnormalities: vesicoureteral reflux, major anatomic UT-abnormalities

b Other medical conditions: gastrointestinal diseases, heart defect, endocrinology disorders, syndromes, neurological conditions, haematological conditions, prematurity

c 2 cases of *Enterococcus sp.* and 1 case of *Staphylococcus simulans* accounted for 3 febrile, while 1 afebrile UTI was caused by Group B *Streptococcus sp.*

*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 for aUTIs, mostly (447, 97.4%) 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 (16.7% of fUTIs and 21.0% of aUTIs prescriptions). Carbapenem was prescribed only in one case, as targeted treatment, while no quinolones were prescribed in this study population. The mean duration of intravenous treatment for fUTIs was 5.4 days (SD 1.45), while aUTIs were treated intravenously for 4.4 days (SD 1.64) (Table 2).

**Table 2: Antibiotic prescriptions for febrile and afebrile UTIs treatment**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Antibiotic** | **No of hospital prescriptions (%)** | **<29 days** | **1m- 2y** | **2y-5y** | **5y-18y** | **Treatment duration in days**  **Mean (SD)** |
| **fUTIs** | **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) |
| TLV | 1 (0.3) | 1 |  |  |  | 8 |
| TAZ | 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) |
| TMP/SMZ | 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) |
| TAZ | 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) |

Abbreviations: SAM, ampicillin-sulbactam; AMC, amoxicillin-clavulanic acid; TLV, ticarcillin-clavulanic acid; TAZ, piperacillin-tazobactam; TMP/SMZ, trimethoprim-sulfamethoxazole

Information on dosing could be identified in 37.7% (173/459) of prescriptions. The results on the main antibiotics used (for which at least 5 prescriptions could be found) are presented in Table 3. High doses, exceeding the upper limits of the available guidance (14, 15), were observed for amoxicillin/clavulanic acid in one neonate, while ceftriaxone was consistently prescribed in the upper-high range (75-80mg/kg/24h), as usually recommended for severe infections. Finally, piperacillin-tazobactam was prescribed out of the proposed range in 2 of the 3 available prescriptions.

**Table 3: Antibiotics intravenous dosing stratified by age**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Antibiotic** | **Prescriptions** | **mg/kg/24h**  **mean (SD)** | **Minimum dose** | **Maximum dose** | **Recommended dosing (mg/kg/24h)** | |
| **EOFa, b, c** | **BNFca, c** |
| **< 29 days** |  |  |  |  |  |  |
| Ampicillin | 8 | 199 (11.4) | 177 | 219 | 25-200 | 60-120 (<7d)  90-180 (7-21d)  120-240 (21-28d) |
| Cefotaxime | 7 | 142 (18.7) | 100 | 150 | 50-100 (<7d)  75-150 (7-28d) | 50-100 (<7d)  75-150 (7-21d)  75-200 (21-28d) |
| Amikacin | 8 | 15 (1.1) | 13 | 17 | 15 | 15 |
| **1 month -2 years (<2 years)** | | |  |  |  |  |
| Ampicillin | 21 | 199 (2.9) | 190 | 200 | 50-400 | 100-200 |
| SAM | 7 | 157 (18.9) | 148 | 200 | 150 | nad |
| AMC | 8 | 90 (1.2) | 89 | 92 | 75 | 60 (<3m)  90 (>3m) |
| 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 |
| **2-5 years (<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 | nad |
| Amikacin | 8 | 15 (0.4) | 14 | 15 | 15 | 15 (<5y)  15-22.5 (>12y) |

Abbreviations: SAM, ampicillin-sulbactam; AMC, amoxicillin-clavulanic acid; d, days; m, months; y, years

a Ranges according to the severity of UTI.

b Doses are not specified for UTIs from the Greek National Organisation for Medicines (EOF).

c For children with normal renal function.

d na = not available

*3.3 Pathogen identification and susceptibility patterns*

A total of 236 pathogens were isolated from 230 patients. The most commonly identified pathogen was *E. coli* (79.2%; 187/236), followed by *Klebsiella sp* (7.2%; 17/236), *Proteus sp* (5.1%; 12/236) and *Pseudomonas aeruginosa* (4.7%; 11/236) (Table 1). *Enterobacter sp* (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 pathogens are presented in Table 1.

Among the 157 *E. coli* isolates tested, 66 (42.0%) were resistant to ampicillin, whereas resistance to amoxicillin/clavulanic acid and ampicillin/sulbactam was 12.2% and 19.3%, respectively (see Online Resource for full details including numbers of isolates tested for resistance to each antibiotic). *E. coli* also showed a high resistance to piperacillin-tazobactam, amongst the 58 isolates tested (12.1%). The resistance rates for 1st and 2nd generation cephalosporins ranged from 3.3% for cefoxitin to 28.8% for cefalothin. Only 1.7% of *E. coli* isolates were resistant to third and fourth generation cephalosporins (C3G and C4G). High resistance rates were identified to trimethoprim-sulfamethoxazole (26.5%), while only 2.3% of the 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 (1.3% for ciprofloxacin) while all *E.coli* isolates were fully susceptible to carbapenems.

*Proteus* isolates (n=12) showed no resistance to 2nd generation cephalosporins (C2G). Few were resistant to trimethoprim-sulfamethoxazole (TMP/SMZ) (8.3%), as well as to C3G, C4G, aminoglycosides and carbapenems. In a total of 17 *Klebsiella* isolates, resistance rates to ampicillin/sulbactam and amoxicillin/clavulanic acid were 28.6% and 13.3% respectively. The resistance rates for *Klebsiella* against C2G ranged from 14.3% to cefuroxime to 30.0% to cefalothin. *Pseudomonas aeruginosa* showed no resistance to piperacillin-tazobactam, and ceftazidime, aminoglycosides and quinolones. The full susceptibility results are provided in Online Resource.

Among the 236 pathogens, 4 ESBL-producing isolates were identified, three *E. coli* and one *Klebsiella sp.*, as well as one *Klebsiella* with a phenotype of potential high-level cephalosporinase producer. All 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 (trimethoprim-sulfamethoxazole or cefaclor). The other three patients were healthy prior to admission, with unremarkable medical history. The ESBL-producing isolates exhibited resistance to penicillin and beta-lactamase-inhibitors (BLIs) (except for piperacillin-tazobactam) and were mostly susceptible to carbapenems (3/3 susceptible isolates), nitrofurantoin (3/4) and amikacin (3/4). No carbapenem-resistance was identified in our study population.

**4. Discussion**

*4.1 Principal findings*

In our study population of hospitalised children with UTIs, amikacin, penicillins (+/-BLIs), cefuroxime and C3G were the most commonly prescribed antibiotics. The majority of children in this hospital received prolonged intravenous treatment. *E.coli* appeared to be the most common pathogen causing UTIs in children, exhibiting high resistance rates to beta-lactams (+/-BLI). 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. The World Health Organization (WHO), in its “Global Action Plan on Antimicrobial Resistance”, 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 UTI 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 that need to be addressed. First, our 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%) of prescriptions did not include dosing information. Thus, we were unable to fully evaluate appropriate dosing for UTI treatment in our study population. However, recording was complete regarding the number, class and route of antibiotics given and duration of treatment was missing in only 5 (1.1%) records. Additionally, the susceptibility testing of pan-sensitive isolates was limited regarding piperacillin-tazobactam, newer quinolones (e.g. ciprofloxacin) and carbapenems (especially ertapenem), thus resistance rates apply mainly to isolates which were resistant to the more commonly tested antibiotics. It is also likely that some ESBL 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. We compared characteristics of children with fUTIs and aUTIs but were unable to formally compare resistance rates between these two groups due to small numbers. Future work could further investigate differences between these clinical presentations and implications for antibiotic management. Finally, we provided a limited number of resistance rates for non-*E.coli* pathogens due to their limited frequency in our study population.

*4.3 Implications for selection of empiric treatment*

The American Academy of Pediatrics recommends amoxicillin/clavulanic acid, trimethoprim/sulfamethoxazole and C2G for oral empiric treatment of fUTIs (21). C3G and aminoglycosides are mostly selected for fUTIs parenteral treatment (21). The updated Greek national guidance on treatment of fUTIs (22) suggests the use of C2G or C3G.

In our study population, trimethoprim/sulfamethoxazole and penicillins (+/- BLIs) appear not to be the optimal treatment options, given the observed *in vitro* resistance rates. WHO’s recent recommendation that C3G should be the first parenteral choice for hospital treatment of mild to moderate fUTIs, while 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 seems to be an appropriate choice for aUTIs and ESBL UTIs (4, 25).

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

Empiric antibiotic selection should be based on the presence of fever and severity as recommended by 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 empiric treatment comparing to severely ill patients (28). Several attempts have been made to define severity of UTIs (13, 29), though more evidence and consensus internationally is needed to apply a standardized definition.

*4.4 Duration of treatment and dosing*

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

Sporadic mistakes and inappropriate prescribing was noted mainly for amoxicillin/clavulanic acid dosing in neonates and piperacillin-tazobactam. Errors in piperacillin-tazobactam prescribing have been 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 pharmacists support are some common causes for prescribing errors in clinical practice (32, 33).

*4.5 Antimicrobial resistance in Greece*

Our study of AMR in UTIs is in accordance with previous studies from Greece (8-10), expanding our knowledge on AMR in paediatric UT-pathogens in Central Greece. Among these studies, similar high levels (often >10%) of *E. coli* resistance were reported to ampicillin, penicillins and beta lactamase inhibitors (BLIs), C2G (except cefoxitin) and TMP/SMZ and consistently low resistance rates (<10%) to nitrofurantoin, cefoxitin, cefuroxime, C3G, C4G, aminoglycosides and carbapenems for the fUTIs. Poor data exists on quinolones resistance (3.9%) (8), as susceptibility to them is either not tested or not reported due to the limited use of quinolones in the Greek paediatric population, as also confirmed by a study on antibiotics use in a paediatric outpatient population (3). *Klebsiella*, currently a public health threat in Greece (6), consistently exhibited higher levels of resistance (8) to amoxicillin/clavulanic acid (6.7% vs. 13.3% in the present study), while no resistance was detected to imipenem or meropenem. Finally, although the numbers were small, our data included fewer ESBL-UTIs (n=4, or 1.7% of isolates) as compared to another study in Northern Greece (11).

*4.6 Antimicrobial resistance in the global context*

Our results seem to be concordant with the results of a recent meta-analysis (4) showing high resistance rates for ampicillin (53.4%) and co-trimoxazole (30.2%) in UTIs in Organisation for Economic Co-operation and Development (OECD) countries. Low resistance rates have been shown for ciprofloxacin (2.1%) and nitrofurantoin (1.3%) (4). Resistance to co-trimoxazole 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 amoxicillin/clavulanic acid appeared higher in the current study (12.2%) and is in line with newer reports from other countries, such as the United Kingdom (16.5%) (34), the Republic of Korea (25.0%) (35) and Turkey (33.0%) (36). The percentage of ESBL-UTIs in our sample was lower (1.7%) than in other paediatric studies (37) (35) and seem not to follow the global trend of the ESBL infections rising prevalence (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 our study. However, carbapenemase-producing bacteria represent an emerging threat, especially for neonates and immunocompromised patients (40, 41).

**5. Future Steps**

We observed the sub-optimal selection of antibiotic treatments, prolonged treatment duration, and occasional dosing outside recommended ranges, suggesting the 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 which is under severe financial pressure. Furthermore, AMR surveillance in the paediatric population should be intensified, with the inclusion of more paediatric centres. UTIs is a key area that can improve our understanding of AMR in the paediatric population.

**6. Contributions**

KV (Konstantinos Vazouras) collected, analysed, critically interpreted data and wrote the manuscript. Kiriaki Velali (KiV), Ioanna Tassiou (IT) and Klelia Athanasopoulou (KA) analysed and critically interpreted data. Anastasia Anastasiou-Katsiardani (AA), Anastasia Barbouni (AB), Theoklis Zaoutis (TZ), Laura Folgori (LF), Romain Basmaci (RB) and Yingfen Hsia (YH) participated to the interpretation of data and critical revision of the manuscript. Charlotte Jackson (CJ) provided epidemiological input. All authors approved the subsequent revisions and the final draft of this manuscript.

**7. Declarations**

*7.1 Acknowledgements*

This study is dedicated to our beloved patient “Eleftherios Kapotsis” and his family for their braveness and dignity towards the imminent death.

*7.2 Competing interests*

None of the authors have any conflicts of interest related to this article.

*7.3. Funding*

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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