Antibiotic resistance patterns of urinary tract pathogens in children from Central Romania

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Received February 26, 2021; Accepted March 30, 2021

DOI: 10.3892/etm.2021.10180

Abstract. One of the most frequent bacterial infections in children are urinary tract infections (UTIs). In recent years, an increasing incidence of UTIs caused by resistant bacterial strains has been observed, especially with extended-spectrum β-lactamase-producing Enterobacteriaceae that represent about 15% of UTIs. A retrospective study was performed comprising 331 pediatric cases with UTI. Our study aimed to detect the resistance of the uropathogens to common drugs used in UTI treatment. High resistance rates have been recorded for ampicillin, amoxicillin, trimethoprim/sulfamethoxazole (TMP/SMX), cefuroxime, and ciprofloxacin, among *E. coli* and *Klebsiella*. The multidrug-resistance (MDR) rate was detected in one-third of the uropathogens, among which more than half were isolated in patients with urinary tract abnormalities. Our study highlighted that nitrofurantoin, ceftriaxone, amikacin and carbapenem may be used for the empirical treatment for febrile or complicated UTI in children. This is the first comprehensive study that evaluates antibiotic resistance in UTIs in children, and their association with urinary tract abnormalities in Romania. As a result of this research, the protocol for initial empiric treatment of infants with febrile or complicated UTI should be modified considering a detailed and ongoing monitoring of local sensitivity of uropathogens to antimicrobial agents.

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Abbreviations: aUTI, afebrile urinary tract infection; CFU, colony forming unit; CI, confidence interval; ESBL, extended-spectrum β-lactamase; MDR, multidrug resistance; TMP/SMX, trimethoprim/sulfamethoxazole; UTI, urinary tract infection; VUR, vesicoureteral reflux

Key words: children, multidrug resistance, uropathogen, infection

Introduction

Urinary tract infections (UTIs) represent one of the most frequent infectious diseases affecting humans, as well as an important public health issue with a significant economic burden (1). UTIs represent one of the most common bacterial infections in children and one of the main reasons for fever and antibiotic prescription (2,3).

The incidence of the disease reaches 3% in neonates and is around 0.7% in infants up to 1 year. The prevalence of UTI in febrile infants is around 5% (2). Up to 11% of girls and 7% of boys will have had a UTI by the age of 16 years, and recurrence of infection is common. Vesicoureteral reflux (VUR) is identified in up to 40% of children being investigated for a first UTI and it represents a risk factor but a weak predictor for renal parenchymal defects (4).

UTI is defined as a significant bacteriuria growth of a single pathogen: At least 10^4 colony forming units (CFU) for catheter specimens and at least 10^5 CFU for midstream clean catch specimens) or $5x10^4$ CFU and significant pyuria in a patient with fever or other clinical symptoms (5-9). Recurrent UTIs are defined as repeated infections with a different pathogen agent, while relapsing UTIs represent repeated infections with the same pathogen (5-7,10,11).

Up to 30% of infants and children experience recurrent infections during the first 6-12 months after the initial UTI. In the youngest infants, UTI symptoms differ significantly compared to older infants and children (1,2).

UTIs are primarily caused by Gram-negative bacteria. The main pathogen responsible for uncomplicated cystitis and pyelonephritis is *Escherichia coli* followed by other species of Enterobacteriaceae, such as *Proteus mirabilis* and mostly *Klebsiella pneumoniae*, and by Gram-positive pathogens, such as *Enterococcus faecalis* and *Staphylococcus saprophyticus* (1).

Empiric antibiotic treatment should be initiated for suspected UTI in a sick child, and if necessary, changed later according to the sensitivity results for the isolated uropathogen. Guidelines recommend that empiric antibiotic treatment for suspected UTI should be based on local susceptibilities derived from available local epidemiological information (5,9,12).

In recent years, effective antibiotic treatment of UTIs in young children alleviates acute symptoms and may also limit long-term sequelae. Antibiotics should ideally be prescribed only to those who have a UTI, using an antibiotic with the narrowest effective spectrum. Treating pediatric UTIs in less than 3 days reduces the risk of acquiring kidney scars by 50% (13).

Currently, there is an alarming level of antimicrobial resistance which has developed in UTI pathogens as a result of improper and widespread use of antibiotics (1,14).

Antimicrobial resistance is an internationally recognized threat to public health. The contribution of primary healthcare is of significant importance as this is where around 80% of all antibiotics used within the health service are prescribed (15). Antibiotic resistance in pediatric patients is increasing. Less than 50% of all pediatric UTIs are susceptible to commonly used antibiotics (16,17). Antibiotic-resistant infections are most likely to be associated with greater morbidity and mortality and are associated with increased healthcare costs (15).

As for *E. coli*, resistance to third-generation cephalosporins and combined resistance to third-generation cephalosporins, fluoroquinolones, and aminoglycosides has increased significantly at the European Union/European Economic Area level between 2013 and 2016. Carbapenems are an important group of last-line antibiotics for the treatment of infections with multidrug-resistant (MDR) gram-negative bacteria such as *Klebsiella pneumoniae* and *E. coli*. In 2016, carbapenem resistance in *E. coli* remained rare, and most countries reported low resistant levels for *Klebsiella pneumonia* (18).

MDR is increasing worldwide, especially for commonly used antibiotics. Bacterial resistance to at least one antimicrobial in three or more classes defines MDR (19).

Patients and methods

Study sample and data source. A retrospective, transversal study was performed using 331pediatric patients diagnosed with UTI, aged between 2 weeks and 17 years, admitted to the Pediatric Clinic 1, Nephrology Department of the Emergency Clinical County Hospital (TârguMureș) and the Nephrology Department of the Emergency Clinical Hospital for Children (Cluj-Napoca, Romania), between January 2016 and December 2018.

Inclusion and exclusion criteria. We included all children with clinical and paraclinical signs of UTI. Exclusion criteria consisted of incomplete anamnestic, clinical or paraclinical data. If fever was absent, the UTI was classified as afebrile UTI (aUTI).

Laboratory methods. In general, antibiogram results were considered as susceptible, intermediate, or resistant; for the purpose of our study, intermediate and resistant isolates were considered collectively as non-susceptible. Extended-spectrum β-lactamase (ESBL)-producing strains were identified using double-disk synergy test.

Ethics. All mothers signed informed consent for their children. Our study was approved by the Ethics Committee of the University of Medicine and Pharmacy of Târgu Mureș (no. 259/July 11, 2019), and it was accepted according to the principles of the Helsinki Declaration.

Statistical analysis. Microsoft Office Excel package was used for data collection and GraphPadPrism v.5 (GraphPad Software, Inc.) for statistical analysis. We used discrete quantitative and binary qualitative variables. For the comparison of means, we used the Student's t-test with a significance threshold of 95% confidence interval (CI). In addition, inferential statistical test, such as Chi-square and analysis of variance (ANOVA) were applied.

Results

Patient characteristics. Among the 331 patients included in our study, the mean age was 4.13±4.48 years. The study group was divided into age groups (<1, 1-3, 3-6, 6-14 and 14-18 years. More than a third of isolates (n=115, 34.74%) were from patients younger than 1 year, followed by the group of age 1-3 years (n=79, 23.86%), and the groups of 3-6 and 6-14 years with similar frequency (n=51, 15.42% and n=54, 16.32% respectively), while the lowest number of cases was within the 14-18 year group (n=32, 9.66%) (Fig. 1).

With respect to sex distribution, urine samples were processed from 147 boys and184 girls (44.41/55.59%). The sex ratio was 1:1.25, high lighting that UTIs are a more frequent pathology in girls. The male to female ratio varied according to age as follows: In the <1 year of age group, sex ratio favored boys 1.34:1 while in the other age groups, sex ratio was in favor of female patients: [1-3 year age group, 0.68:1; 3-6 year age group, 0.75:1; 6-14 year age group, 0.45:1; 14-18 year age group, 0.45:1 (Fig. 2).

More than half of the children [57.71%, n=191/331] had no other comorbidities while in 42.29% cases (n=140/331) a urinary tract-abnormality was detected.

Uropathogens. *E. coli* was the most frequently identified uropathogen (72.2%, 239/331), followed by *Klebsiella spp.* (8.15%, 27/331), *Proteus spp.* (6.65%, 22/331) and *Pseudomonas aeruginosa* (5.75%; 19/331) (Fig. 3). In contrast, the lowest frequency in our study group was noted for *Enterococcus* (2.72%; 9/331), *Enterobacter spp.* (2.42%; 8/331), *Morganella morganii* (0.91%; 3/331), *Staph. aureus* (0.6%; 2/331), and others (0.6%; 2/331). Extended spectrum beta-lactamase (ESBL) producing bacteria were also detected in a high percentage in our samples, 7.85% (26/331). The characteristics of these pathogens are presented in Table I.

UTIs caused by *E. coli* were more frequent in female patients (n=151, 63.17%) than in males (n=88, 36.83%) with statistical significance (P=0.0001), while those caused by *Klebsiella* and *Proteus spp.* were more frequent in boys [n=17 (62.96%) and n=13 (59.09%)] than in girls [n=10 (37.04%) and n=9 (40.91%)], but with no statistical significance (P=0.04 and =0.15) (Table I). Age distribution of the patients who presented with UTIs with *E. coli* is emphasized in Fig. 4.

The antimicrobial resistance pattern of the uropathogens can be observed in Table II. Both *E. coli* and *Klebsiella* showed high resistance to ampicillin, amoxicillin, TMP/SMX, cefuroxime and ciprofloxacine, respectively. *E. coli* remained

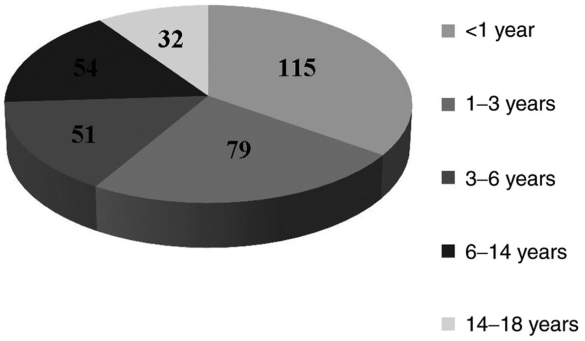

Figure 1. Age distribution of the cases with UTIs. UTI, urinary tract infection.

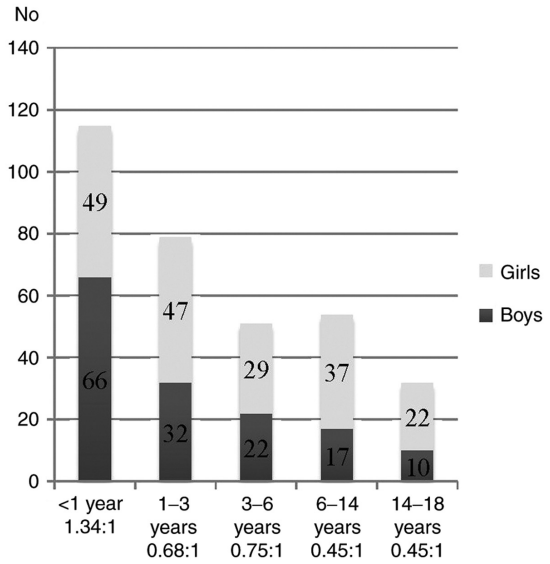

Figure 2. Sex distribution in the age groups and sex ratio.

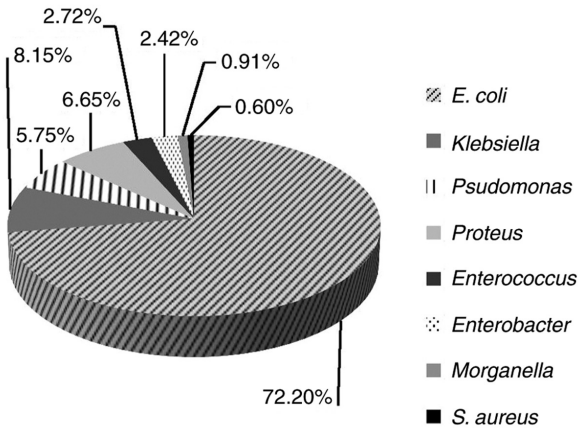

Figure 3. Uropathogen distribution.

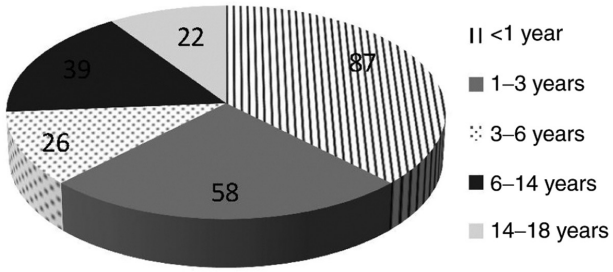

Figure 4. Age distribution of the cases with *E. coli* UTI. UTI, urinary tract infection.

susceptible to nitrofurantoin, ceftriaxone, meropenem while *Klebsiella* to amikacin, colistin and meropenem (Figs. 5 and 6).

Out of the total of 331 UTIs, a significant percentage of cases presented with associated urinary tract malformations (n=140, 42.29%). This condition entailed a higher proportion of MDR of the involved uropathogens. In other words, MDR was detected in 34.13% of the uropathogens, among which 56.63% were isolated in patient with urinary tract malformation (Fig. 7). Analyzing a contingence table, we obtained a positive correlation between these variables (P=0.0001, OR 2.44), meaning that urinary tract malformations are a predisposing factor for UTIs with MDR uropathogens.

From the 239 cases diagnosed with *E. coli* infection, 32.63% (78/239) presented a urinary tract abnormality, and 39.74% (31/78) with associated MDR. Also, in this instance, statistically, urinary tract abnormalities significantly influence the occurrence of a UTI caused by a MDR *E. coli* (P=0.005, OR 2.29).

Discussion

Strengths and limitations. To the best of our knowledge, this is the first widespread research that evaluates antibiotic resistance in childhood UTIs, and their association with urinary tract abnormalities in Romania.

E. coli and *Klebsiella* represented common uropathogens in children admitted to both nephrology departments involved. In this study, the frequency of infection with *E. coli* and *Klebsiella* were similar with studies from Nepal and Turkey (20,21).

Of the 331 patients, 184 (55.58%) were female compared with a study of Vazouras *et al* where the female proportion was 72.2% (22). The cause may be the higher rate of urinary tract abnormalities in our study group.

In the study performed by Vazouras *et al*, 11.3% (26/230) of the evaluated children had urinary tract-associated abnormalities (22) compared with our study where a 3.5-time higher rate of urinary tract-associated abnormalities were observed. The explanation may be that our study group was from two nephrology centers.

Similar to other pediatric studies on the same subject (2,20,22), *E. coli* was the most frequently encountered etiological agent in our research as well.

In a recent research in our country, *E. coli, Klebsiella spp.*, *Enterococcus spp.*, *Morganella morganii, Proteus spp.*, and *Enterobacter spp.* represented the leading etiology for UTIs (53.3, 10.6, 5.2, 5.2, 4.5, and 3.9%, respectively), results that are in part similar to our findings (2). When compared with our age-matched group, we found an occurrence of 87/115 (75.65%) for *E. coli*, 11/115 (9.56%) for *Klebsiella spp.*, 5/115 (4.34%) for Enterococcus *spp.*, 3/115 (2.6%) for *Proteus spp.*, *and* 3/115 (2.6%) for *Enterobacter spp.*

Table I. Distribution of the uropathogens.

Uropathogens	Total (N=331) n (%)	ESBL n (%)	Girls n (%)	Boys n (%)	P-value
E. coli	239 (72.20)	19 (7.95)	151 (63.17)	88 (36.83)	0.0001
Klebsiella spp.	27 (8.15)	5 (18.51)	10 (37.04)	17 (62.96)	0.0400
Pseudomonas aeruginosa	19 (5.75)	-	9 (47.36)	10 (52.64)	-
Proteus spp.	22 (6.65)	2 (0.60)	9 (40.90)	13 (59.10)	0.1500
Enterococcus	9 (2.72)	-	3 (33.33)	6 (66.67)	-
Enterobacter spp.	8 (2.42)	-	-	8	-
Morganella morgani	3 (0.91)	-	1 (33.33)	2 (66.67)	-
Staph. Aureus	2 (0.60)	-	-	2	-
Others	2 (0.60)	-	-	2	-

ESBL, extended-spectrum β-lactamase.

Table II. Resistance patterns of the uropathogens.

ATB/Uropathogen	*E. coli* (%)	*Klebsiella* (%)	*Pseudomonas* (%)	*Proteus* (%)	*Enterococus* (%)	*Morganella* (%)	*Enterobacter* (%)
Nalidixic acid	7.11	1.81	<1	<1	<1	<1	<1
Amikacin	7.94	<1	<1	<1	<1	<1	<1
Amoxicillin	33.05	6.04	<1	3.62	<1	1.25	1.81
Ampicillin	56.48	7.85	<1	5.1.3	<1	1.25	2.09
Cefepime	7.94	4.53	1.25	2.09	<1	<1	2.09
Cefotaxime	10.04	4.53	<1	2.09	1.25	<1	1.81
Ceftazidime	10.46	3.32	1.67	1.25	1.25	<1	2.09
Ceftriaxone	3.34	1.25	<1	<1	1.25	<1	1.67
Cefuroxime	12.13	1.25	1.25	1.67	1.25	<1	2.09
Ciprofloxacin	12.13	3.92	<1	1.25	1.67	<1	1.25
Colistin	1.67	<1	<1	<1	<1	<1	<1
Ertapenem	0.83	2.09	<1	<1	<1	<1	1.25
Gentamicin	7.11	3.02	3.32	1.67	1.81	<1	1.25
Imipenem	2.09	<1	<1	<1	<1	<1	<1
Linezolid	<1	<1	<1	<1	<1	<1	<1
Meropenem	1.25	<1	<1	<1	<1	<1	<1
Netilmicin	<1	<1	<1	<1	<1	<1	<1
Nitrofurantoin	6.69	1.81	<1	1.81	<1	<1	<1
Norfloxacin	15.06	4.23	<1	1.67	<1	<1	<1
Oxacillin	<1	<1	<1	<1	<1	<1	<1
Piperacillin	7.94	0.83	<1	<1	<1	<1	<1
Piperacillin/tazobactam	10.04	2.41	1.25	<1	<1	<1	2.09
Streptomycin	<1	<1	<1	<1	1.67	<1	<1
Teicoplanin	<1	<1	<1	<1	<1	<1	<1
Tetracycline	<1	<1	<1	<1	<1	<1	<1
Ticarcillin	0.41	<1	<1	<1	<1	<1	<1
Ticarcillin/clavulanic acid	0.83	<1	1.25	<1	<1	<1	<1
Tigecycline	1.25	<1	<1	<1	<1	<1	<1
Trimethoprim	24.68	3.92	1.67	2.71	1.25	1.25	1.25
Vancomycin	<1	<1	<1	<1	<1	<1	<1

In their research, Vazouras *et al* found that the main causative organism was *E. coli* (79.2%) with high reported resistance rates to ampicillin (42.0%), TMP/SMX (26.5%), and amoxicillin/clavulanic acid (12.2%); lower resistance rates

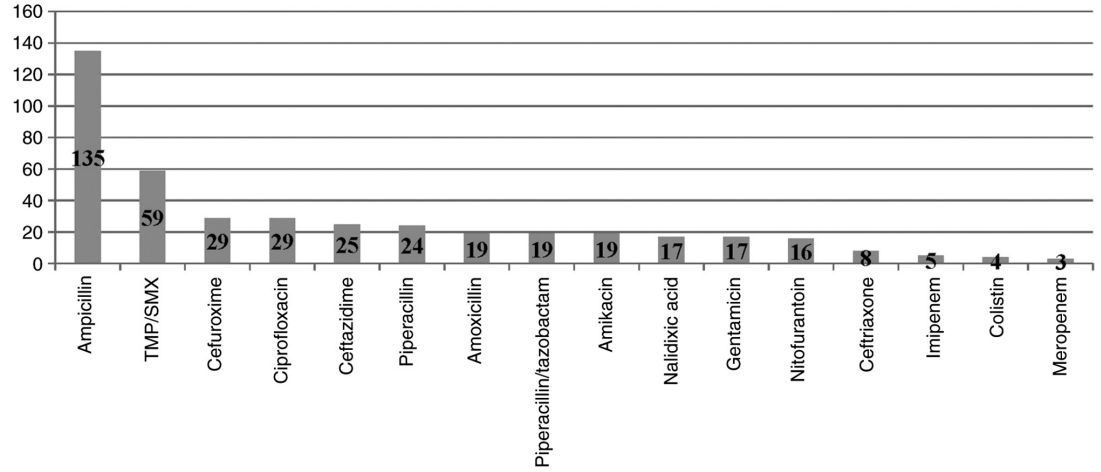

Figure 5. *E. coli* resistance pattern.

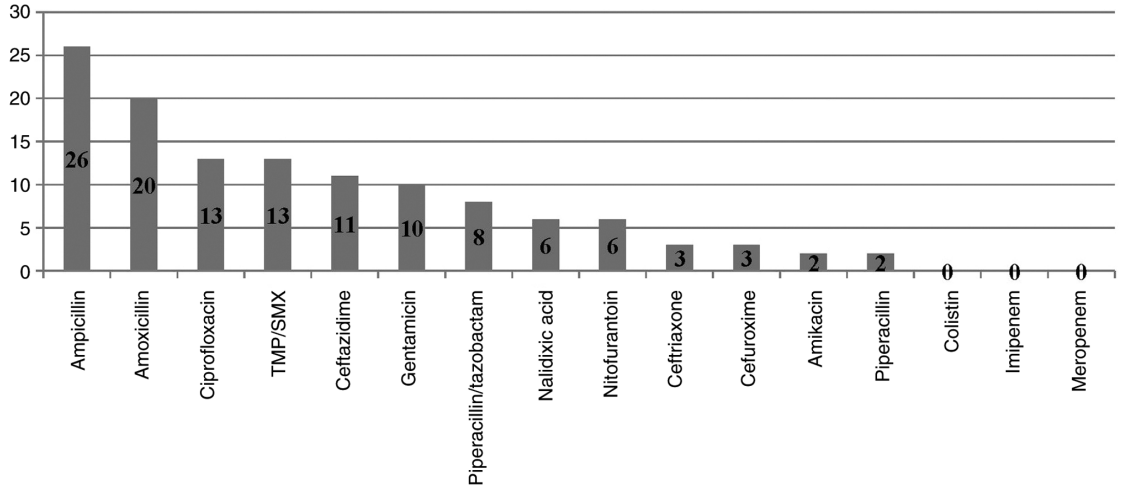

Figure 6. *Klebsiella* resistance pattern.

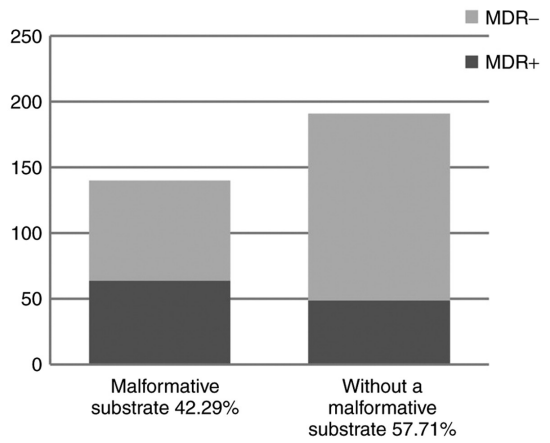

Figure 7. Association between the presence of a congenital anomaly and UTI with MDR uropathogens. UTI, urinary tract infection; MDR, multi-drug-resistant.

were identified for third-generation cephalosporins (1.7%), nitrofurantoin (2.3%), ciprofloxacin (1.4%) and amikacin (0.9%) (22). These results are only partly similar to ours.

Low resistance rates of *E. coli* and *Klebsiella* to piperacillin/tazobactam, meropenem, nalidixic acid, chloramphenicol and colistin were found by Falup-Pecurariu *et al*, these results being comparable with the present study (2).

In our cohort, the ESBL-positive UTIs were 7.85% (n=26) compared with a lower incidence in a recent study (1.7%) (22), while another study in Northern Greece exposed an incidence of ESBL-positive UTIs of 10.4% (23).

Our research depicted that there is a higher chance for UTIs due to ESBL-producing pathogens in children with urinary tract abnormalities and those receiving antimicrobial prophylaxis. This finding is comparable with the results of another study (23).

In the pediatric group with non-ESBL-positive UTIs, a higher ratio of urinary tract anomalies as well as antimicrobial prophylaxis were observed ($P<0.05$), compared to those from ESBL-positive UTI group. This is in disagreement with the conclusion of a recent study (23).

A high incidence of ESBL-positive uropathogens was revealed by Falup-Pecurariu *et al* (2) compared to our research [55 of 68 (80.9%) *E. coli* vs. 5 of 87 (5.75%)] were ESBL-positive; 15/35 (42.9%) of the *Klebsiella spp.* vs. 2 of 11 (18.2%) were ESBL-positive.

Regarding the MDR UTI cases, a prolonged antimicrobial prophylaxis and presence of urinary tract anomalies have been considered as risk factors (24).

Current literature data suggest the effectiveness of fosfomycin against MDR and drug-resistant bacteria (25). This may be extrapolated to us as there is very low use of this drug in our centers.

Our study indicates that nitrofurantoin, ceftriaxon, amikacin, and carbapenem may be used for the empirical treatment of febrile or complicated UTIs in children. Our study results are comparative with those achieved by Raya *et al* (20).

These results are however contradicted by a local study (2), where only 6% of infants had previous renal anomalies compared to our study where we had a significant higher frequency.

Current findings emphasize that male patients are more often diagnosed with UTIs in the first year of life while female patients are diagnosed at approximately 3 years of age (26). Our study sustains this idea, statistically confirming that in the first year of life almost 60% of the patients diagnosed with UTIs (57.39%, 66/115) were male, thus obtaining a 1.34:1 sex ratio. However, our overall ratio of male and female patients with UTIs was in favor of girls 1:1.25, this result being comparable with other studies (26).

In conclusion, initial therapy for UTI is originally empirical until the results of a urine culture are ready. Therefore, it is mandatory to know the local resistance of uropathogens to antimicrobial agents as well as the risk factors for UTI due to resistant pathogens such as ESBL.

The results of this study may influence empirical therapy for UTIs until the ESBL production has been confirmed. Since local antimicrobial sensitivities vary significantly, local guidelines and close monitoring should be provided to coordinate empiric antibiotic treatment.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Further information regarding the data of the present study is available from the corresponding author upon reasonable request.

Authors' contributions

CD and IC contributed to the conception and design of the research. CD and IC wrote the first draft of the manuscript. CD, IC, DD, CA wrote sections of the manuscript. DD, AAA, and CA analyzed previous literature studies and revised the manuscript critically for important intellectual content. All authors contributed to manuscript revision, read and approved the submitted version.

Ethics approval and consent to participate

Our study was approved by the Ethics Committee of the University of Medicine and Pharmacy of Târgu Mureș (no. 259/July 11, 2019). All mothers signed informed consent for their children.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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