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ORIGINAL PAPER

Analysis of bacterial flora of urinary tract infection in hospitalized children with and without congenital urinary tract malformations

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ABSTRACT

Introduction: The purpose of this study was to determine the relationship between the composition and drug susceptibility of the bacterial flora of urinary tract infections (UTI) and the presence of a congenital urinary tract malformation in children.

Material and methods: The study included analysis of 515 urine cultures obtained from patients hospitalized at a tertiary referral hospital over a 24-month period. Drug susceptibility of *Escherichia coli* strains, which are the leading uropathogen in UTI, to antibiotics of the group comprising penicillins, carbapenems, aminoglycosides, fluoroquinolones, and nitrofurantoin and trimethoprim-sulfamethoxazole was determined using the automated Vitek 2 Compact method, the plate-diffusion method and E-tests. The abundance of strains producing an extended-spectrum β-lactamase (ESBL) type resistance mechanism was also analyzed.

Results: The distribution of cases for *Escherichia coli* (n = 228) was comparable (p = 0.134) for patients with (40.10%) and without urinary tract defects (46.86%). Comparing the numbers of etiological agents in this group of patients, statistically significant differences were found for infections caused by yeast-like fungi – *Candida spp*. (p = 0.011) and *Pseudomonas aeruginosa* (p = 0.002). In terms of *Escherichia coli* antibiotic resistance, statistically significant differences in their effectiveness were observed for all cephalosporins analyzed, as well as for nitrofurantoin. No such effect was noted for other antibiotics. An extended-spectrum β-lactamase type resistance mechanism was present in *Escherichia coli* strains isolated from patients with a urinary tract defect – 10.13% of cases, vs. only 2.01% of cases for patients without a malformation (p = 0.016).

Conclusions: The study showed that the presence of congenital anomalies of the kidney and urinary tract (CAKUT) in children predisposes to *Pseudomonas aeruginosa* infections, but does not affect the frequency of isolation of *Escherichia coli* or other strains of bacteria causing urinary tract infections. The presence of CAKUT increases the risk of infection with bacteria with lower sensitivity to the most commonly used first-line antibiotics. Moreover, it increases the risk of *Escherichia coli* strains with β-lactamase-producing extended substrate spectrum (ESBL+).

KEY WORDS:

children, urinary tract infection, bacterial flora, antibiotic resistance.

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INTRODUCTION

In the pediatric population, 2–8% of all general practice interventions are for urinary tract infections (UTI) [1]. Urinary tract abnormalities (congenital anomalies of the kidney and urinary tract – CAKUT), metabolic defects, immune disorders, and systemic diseases (e.g., diabetes) are predisposing factors for UTI. Recurrent UTI can result in serious consequences, including the formation of scarring lesions in the kidney parenchyma, which leads to chronic kidney disease and hypertension. Urinary tract infections accompanying CAKUT continue to be a significant cause of end-stage renal failure and the need for dialysis therapy in children.

The variability of microbial agents and increasing resistance to standard antibiotics for UTI in children represent a growing problem, especially in hospital settings. Cases in which infections can quickly progress to severe conditions require rapid decision-making. Empirical therapy should be supported by an analysis of the profile and drug susceptibility of the bacterial flora responsible for UTI in the local population, as well as an analysis of the presence of aggravating factors (e.g., CAKUT) [2]. The purpose of this study was to evaluate the impact of CAKUT on the bacterial flora of UTI and drug susceptibility in children hospitalized for UTI.

MATERIAL AND METHODS

This study is a retrospective analysis of urine bacterial culture results and medical records of children hospitalized at a tertiary referral center for pediatrics, pediatric nephrology, and pediatric urology over a 24-month period. Initially the results of 5478 urine samples collected for bacteriological examination were retrieved from patients who were suspected for UTI. The samples were collected from patients hospitalized in the following departments: two pediatric wards, one pediatric nephrology ward, one pediatric urology ward, and one pediatric intensive care unit (ICU). During this period, a total of 22,700 patients were hospitalized in the above-mentioned wards.

After careful exclusion the results of 515 urine cultures (single strain) with colony-forming unit (CFU) counts ≥ 100,000 per milliliter were ultimately analyzed, including 152 from the pediatric wards, 129 from the nephrology department, 125 from the urology department, and 109 from the ICU. Of the 515 cases analyzed, 197 (38.25%) urine samples were taken from patients who were found to have CAKUT. The list of CAKUT diagnoses is presented in Table 1. The other 318 (61.75%) patients did not have CAKUT.

A sample of 1–5 ml of urine was collected from the middle stream (clean catch) or from a freshly inserted catheter. When the urine was collected from a bag taped to the perineum (unique cases), it was immediately transferred into a sterile container. Only the results of specimens with a significant CFU count of only one bacterial strain qualified for the study. To reduce false positive results, the urine culture results were compared with clinical data and urinalysis when necessary. Because of the retrospective characteristic of the study, data on urinalysis and antibiotic treatment were not available.

TABLE 1. Congenital urinary tract malformations in the study group (by incidence)

Type of malformation	% *
Unilateral hydronephrosis	32
Vesico-ureteric reflux	26
Megaureter	14
Posterior urethral valves	13
Neurogenic bladder	8
Bilateral hydronephrosis	8
Hypoplastic and hypodysplastic kidney	4
Multicystic kidney dysplasia	2
Kidney agenesis	2
Ectopic kidney	2
Hypospadias	1
Horseshoe kidney and related malformations	1
Congenital kidney cysts	1
Other lower urinary tract malformations	13
Other upper urinary tract malformations	21

** In some patients malformations coexisted.*

Urine culture was performed using the Hoeprich method by seeding 1 µl (inoculum) of urine onto culture medium using sterile precautions; Columbia agar with 5% sheep blood and selective-differential MacConkey agar was used. The cultures were incubated at 35°C for 18–24 hours in an oxygenated atmosphere. After incubation, growth was assessed in terms of the number and type of microorganisms. Identification of the etiologic agent was performed using an automated Vitek 2 Compact system (bioMerieux, France) and a semi-automated MICRO-LA-TEST system (Erba Lachema, Germany). To determine drug susceptibility, the automated Vitek 2 Compact system was used, which, using several cut-off concentrations, allowed the determination of the degree of sensitivity of the strain at the levels of sensitive, medium-sensitive, and resistant. To detect resistance mechanisms, a plate diffusion method was applied using discs saturated with antibiotics/chemotherapeutics at the concentrations they reach in serum. To determine the minimum inhibitory concentration of the bacteria, E-tests (strips saturated with the antibiotic/chemotherapeutic with a concentration gradient) were used. For both the plate diffusion method and the E-tests, the determination was carried out on Mueller-Hinton agar.

The minimum inhibitory concentration for 12 antibiotics routinely used to treat UTI caused by *Escherichia*

TABLE 2. Bacterial flora detected in the study group (CAKUT vs. non-CAKUT children)

Parameters	CAKUT (+) patients		Non-CAKUT patients		*p*-value
	n	%	*n*	%	
Escherichia coli	79	40.10	149	46.86	0.134
Klebsiella spp.	27	13.71	43	13.52	0.952
Enterococcus spp.	27	13.71	40	12.58	0.711
Pseudomonas aeruginosa	27	13.71	18	5.66	0.002
Coagulase negative *Staphylococcus*	6	3.05	16	5.03	0.279
Enterobacter spp.	10	5.08	8	2.52	0.124
Proteus spp.	6	3.05	12	3.77	0.662
Candida spp.	1	0.51	14	4.40	0.011
Citrobacter spp.	5	2.54	2	0.63	0.069
Streptococcus spp.	1	0.51	4	1.26	0.399
Acinetobacter spp.	2	1.02	2	0.63	0.627
Morganella spp.	–	–	4	1.26	-
Streptococcus agalactiae	3	1.52	1	0.31	0.129
Corynebacterium spp.	–	–	2	0.63	–
Staphylococcus aureus	2	1.02	–	–	–
Escherichia spp.	1	0.51	–	–	–
Providencia spp.	–	–	1	0.31	–
Salmonella ser. Enteritidis	–	–	1	0.31	–
Stenotrophomonas maltophilia	–	–	1	0.31	–

CAKUT – congenital anomalies of the kidney and urinary tract

coli and *Klebsiella spp*. were analyzed. These included antibiotics from the penicillin (ampicillin and amoxicillin-clavulanic acid, piperacillin-tazobactam), cephalosporin (cefuroxime, cefotaxime, ceftazidime, and cefepime), carbapenem (imipenem, meropenem), aminoglycoside (amikacin, netilmicin and gentamicin), and fluoroquinolone (ciprofloxacin) families, as well as nitrofurantoin and trimethoprim-sulfamethoxazole. We also analyzed the number of strains producing an extended-spectrum β-lactamase (ESBL+) type resistance mechanism. For *Enterococcus* species a relevantly designed set of antibiotic was added with special attention to glycopeptides. Finally, we decided to analyze the epidemiological data for all strains data according to the clinical profile of the departments (pediatric vs. nephrology/urology vs. ICU).

The results were subjected to statistical analysis using Statistica 12.0 PL (StatSoft) . Differences in drug susceptibility and the influence of certain parameters (e.g. the presence of a urinary tract defect) were evaluated with the help of structure indices. The statistical significance of differences in proportions was verified using the χ^2 test. A value of $p < 0.05$ was considered statistically significant.

RESULTS

The most common pathogen found in hospitalized children during the observed period was *Escherichia coli* (228/515), followed by *Klebsiella spp*. (70/515), *Enterococcus spp*. (67/515), and *Pseudomonas aeruginosa* (45/515) (Table 2).

The distribution of cases for *Escherichia coli* was comparable for patients with (40.10%) and without urinary tract defects (46.86%). The frequencies of most of the other species did not differ between these two cohorts. Only *Pseudomonas spp*. were detected more frequently in children with CAKUT than in those without (60% vs. 40%, $p = 0.002$). On the other hand, fungal infections (*Candida spp*.) were significantly more common in patients without urinary tract defects (93.33%) than in patients with CAKUT (6.67%, $p = 0.011$).

ESCHERICHIA COLI SENSITIVITY

In terms of *Escherichia coli* antibiotic resistance, statistically significant differences in antibiotic effectiveness were observed for all cephalosporins analyzed (cefuroxime, cefotaxime, ceftazidime, and cefepime), as well as for nitrofurantoin. For cefuroxime, significantly higher efficacy was found for *Escherichia coli* strains isolated from patients without CAKUT (94.44%) compared to CAKUT patients (72.55%) ($p < 0.001$). Among *Escherichia coli* strains isolated from non-CAKUT patients, 96.99% were sensitive to cefotaxime, compared to 86.49% efficacy in CAKUT patients ($p = 0.009$). A similar relationship was

TABLE 3. Differences in antibiotic susceptibility of *Escherichia coli* strains in the study group (CAKUT vs. non-CAKUT children)

Parameters	CAKUT (+) patients		Non-CAKUT patients		*p*-value
	n (%)		*n* (%)		
	Susceptible	Resistant	Susceptible	Resistant	
Ampicillin	22 (30.56)	50 (69.44)	43 (32.82)	88 (67.18)	0.7402
Amoxicillin + clavulanic acid	56 (77.78)	16 (22.22)	99 (77.34)	29 (22.66)	0.9438
Cefuroxime	37 (72.55)	14 (27.45)	102 (94.44)	6 (5.56)	< 0.001
Cefotaxime	64 (86.49)	10 (13.51)	129 (96.99)	4 (3.01)	0.009
Ceftazidime	68 (87.18)	10 (12.82)	143 (97.28)	4 (2.72)	0.007
Cefepime	62 (89.86)	7 (10.14)	114 (98.28)	2 (1.72)	0.026
Imipenem	143 (100)	0 (0)	78 (100)	0 (0)	–
Amikacin	71 (97.26)	2 (2.74)	122 (97.6)	3 (2.4)	0.7471
Gentamycin	72 (92.31)	6 (7.69)	138 (95.83)	6 (4.17)	0.4248
Ciprofloxacin	57 (75)	19 (25)	120 (88.24)	16 (11.76)	0.1280
Nitrofurantoin	57 (81.43)	13 (18.57)	107 (95.54)	5 (4.46)	0.0044
Trimethoprim – sulfamethoxazole	56 (72.73)	21 (27.27)	121 (82.88)	25 (17.12)	0.0749
ESBL (+)	71 (89.87)	8 (10.13)	146 (97.99)	3 (2.01)	0.0166

CAKUT – congenital anomalies of the kidney and urinary tract

observed for ceftazidime (97.28% vs. 87.18%, respectively, $p = 0.007$). For cefepime, the sensitivity was 98.28%, with lower efficacy (89.86%) observed in non-CAKUT patients ($p = 0.026$). The presence of an ESBL-type resistance mechanism was also correlated with the presence of CAKUT. This resistance mechanism was more common in *Escherichia coli* strains isolated from patients with CAKUT (10.13%) than in those without CAKUT (2.01%) ($p = 0.0166$) (Table 3). Higher sensitivity to nitrofurantoin (95.54%) was found in patients without CAKUT, with only 81.43% efficacy found for strains obtained from CAKUT subjects ($p = 0.0044$).

We found no significant influence of the department profile on *Escherichia coli* sensitivity. A sensitivity of 100% was confirmed for cefepime and imipenem. There were comparably high efficacies (90–95%) for the aminoglycosides, cefotaxime, ceftazidime, trimethoprim-sulfamethoxazole, and nitrofurantoin. Lower efficacies (71–86%) were observed for ciprofloxacin, cefuroxime, and amoxicillin-clavulanic acid. Ampicillin was the least effective antibiotic (15–34%) in *Escherichia coli* strains, with the lowest efficacy among ICU patients.

KLEBSIELLA SPP. SENSITIVITY

The highest efficacy (100%) against *Klebsiella spp*. among the tested antibiotics was shown by netilmicin, followed by imipenem, meropenem, and piperacillin-tazobactam (70–95%). The fluoroquinolones were less effective (60%), as were the aminoglycosides amikacin (59%) and gentamicin (49%), the cephalosporins (approximately 50%), and piperacillin-tazobactam (71%). None of the *Klebsiella spp*. strains showed sensitivity to ampicillin. Of the 70 strains of *Klebsiella spp*., 36 (51%) were producers of an ESBL type resistance mechanism. When evaluating the drug resistance of *Klebsiella spp*. according to the presence of CAKUT, no significant differences were found for the tested antibiotics.

PSEUDOMONAS SPP. SENSITIVITY

For *Pseudomonas spp*. strains, colistin showed the highest (100%) efficacy, followed by cefepime (95.45%), ceftazidime (93.33%), tobramycin (92.86%), and piperacillin-tazobactam (90.91%), which had similar efficacies. Sensitivity to imipenem (90.70%) and meropenem (86.05%) was found for *Pseudomonas spp*. strains, followed by ciprofloxacin (86.36%), amikacin (84.09%), and piperacillin (83.33%). Gentamicin showed similar efficacy against *Pseudomonas spp*. strains (82.22%) compared to netilmicin (77.78%) and levofloxacin (77.78%). The least effective antibiotic against *Pseudomonas spp*. was ticarcillin-clavulanic acid (42.11%). The presence or absence of CAKUT had no significant impact on the sensitivity profile of this bacteria.

ENTEROCOCCUS SPP. SENSITIVITY

For *Enterococcus spp*. strains, we observed excellent (100%) sensitivity for linezolid, tigecycline, and nitrofurantoin. For vancomycin and teicoplanin, we found lower but significant efficacies of 95.52% and 94.03%, respectively. The remaining standard tested antibiotics (penicillins and aminoglycosides) showed significantly lower

efficacies (below 50%) against *Enterococcus spp*. strains. No statistically significant influence of CAKUT on bacterial sensitivity was recorded.

DISCUSSION

The analysis in this study was based on the results of urine cultures collected from children hospitalized in the ICU and pediatric, nephrology, and urology wards, with a focus on *Escherichia coli* as the etiologic agent. We aimed to determine whether differences in the type and antibiotic resistance of bacterial flora might be related to CAKUT; this was partially proven. We need to admit that the obtained results might be to some extent influenced by the method of urine sampling (perineal bags), but we presume this risk to be minimal because of very rare usage of this method.

We found a relatively high percentage of CAKUT children in our study compared to other reports. Vazouras *et al*. analyzed the urine culture results of pediatric patients hospitalized at Achillopouleion General Hospital in Volos, Greece between 2010 and 2015 [3]. They found that CAKUT patients accounted for only 11.3% of cases, whereas 38.25% of our patients had CAKUT, which is probably due to the hospital's profile as a tertiary referral center in pediatrics. We consider this to be one of the strengths of our study.

The overall profile of bacteria detected in our patients was comparable to other reports, with a predominance of *Escherichia coli*, regardless of whether the child had CAKUT or not [2–5]. However, some differences should be considered. In children with anatomical, neurological, or functional anomalies of the urinary tract and an impaired immune system, the following bacteria may be responsible for UTI: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Streptococcus agalactiae*, and the viridans group streptococci [6–9]. Our study showed no statistically significant differences in the frequency of isolation of the microorganisms mentioned above. The percentages of cases with urinary tract defects compared to those without were 6.09% and 6.92%, respectively. Baka-Ostrowska's study showed *Proteus spp*. in 7% of UTI cases overall, with a significantly higher percentage (up to 20%) in patients with concurrent urinary tract pathology [4]. In our study, there was no statistically significant difference in the prevalence of these bacteria between patients with and without CAKUT (3.05% vs. 3.77%, $p = 0.662$). The multicenter study by Kauffman *et al*. reported that fungal pathogens accounted for 12% of positive urine cultures in hospitalized patients and the rate increased significantly to 52% in critically ill pediatric patients [10, 11]. Surprisingly, we determined that fungal infections were more common in patients without CAKUT; this may be explained by the fact that most of these children were from the ICU, where multiple antibiotic therapy had induced these pathogens. The small group effect might have biased our results as well.

A comparable analysis of antibiotic resistance was made by Kot *et al*., who evaluated the susceptibility of *Escherichia coli* strains isolated between 2007 and 2008 from cases of hospital-acquired UTI [2]. They found that 63.6% of the strains isolated from nephrology patients were resistant to ampicillin, which coincides with the data obtained in the present study. The results obtained for amoxicillin-clavulanic acid, ciprofloxacin, and trimethoprim-sulfamethoxazole were also comparable to those obtained in our study. On the other hand, there were differences in cefotaxime, ceftazidime, gentamicin, and nitrofurantoin sensitivities; Kot *et al*. found that 100% of the strains remained sensitive to these antibiotics/chemotherapeutics, while the percentages were 86%, 87%, 92%, and 81%, respectively, in the present study. In our set of data there was also a higher percentage of strains resistant to cefuroxime (27.45% vs. 4.5%) [2].

Although we found no differences between the isolated pathogens between CAKUT and non-CAKUT groups, our results clearly show the role of CAKUT on antibiotic susceptibility in the case of *Escherichia coli*. We found that in CAKUT patients this pathogen is less susceptible to cefuroxime, cefotaxime, ceftazidime and cefepime, as well as to nitrofurantoin. In the UTI-CAKUT population assessed by Isac *et al*. in about 39% of cases *Escherichia coli* was isolated from urine, which was in 14.9% of cases resistant to ceftazidime and in 13.2% to nitrofurantoin, which is in line with our result. The authors also reported that *Escherichia coli* was resistant to amoxicillin/clavulanic acid in 38.5% of cases, to ampicillin in 72.3% of cases and trimethoprim-sulfamethoxazole in 56% of cases [12].

There are epidemiological analyses that directly raise this issue, but there are conflicting results. It is worth citing research by Miron *et al*., who analyzed 264 urine culture results from children in the Bucharest, Romania region. *Escherichia coli* strains showed high rates of resistance to ampicillin (63.8%), amoxicillin-clavulanic acid (44.9%), and trimethoprim-sulfamethoxazole (27%) [13]. All of the *Escherichia coli* strains in their study exhibited sensitivity to carbapenems. Similarly, 100% of the *Escherichia coli* strains in our study were sensitive to imipenem [13]. Furthermore, we found similar resistance rates of *Escherichia coli* strains to ampicillin, while the resistance rates against amoxicillin-clavulanic acid and trimethoprim-sulfamethoxazole were lower, at 22.5% and 20.63%, respectively. Gunduz *et al*. analyzed the results of 850 positive urine cultures from hospital settings. The highest rates of resistance in *Escherichia coli* were to ampicillin (58.2%), trimethoprim-sulfamethoxazole (31.5%), cefuroxime (27.6%), and amoxicillin-clavulanic acid (16%). For amikacin and nitrofurantoin, the percentages of resistant strains were 0.2% and 5.1%, respectively. In our study, the resistance rates for ampicillin and amoxicillin-clavulanic acid were higher

(67.98% and 22.5%, respectively), while the resistance rates for trimethoprim-sulfamethoxazole and cefuroxime were lower (20.63% and 12.58%, respectively) [14]. Pierantoni et al. after analyzing 1049 urine cultures reported that the amoxicillin-clavulanic acid resistance rate significantly increased from 17.6% in 2017 to 40.2% in 2019. For trimethoprim-sulfamethoxazole it remained stable (22%) [15].

Lee *et al*. conducted an analysis of 903 urine cultures, with special emphasis on the drug susceptibility profile of isolated *Escherichia coli* strains [16]. The highest resistance rates were obtained for ampicillin (37%) and trimethoprim-sulfamethoxazole (21%). Only 1.2% of the strains were resistant to nitrofurantoin, and 2.5% produced β-lactamases with an extended substrate spectrum [16]. In our study, the resistance rate of *Escherichia coli* to ampicillin was higher, at 67.98%, while the nitrofurantoin resistance rate was 9.89%. Only 4.82% of the strains expressed an ESBL+ type resistance mechanism. The results obtained for trimethoprim-sulfamethoxazole were similar.

A study of *Escherichia coli* strains by Alavudeen *et al*. obtained the highest resistance rates for nitrofurantoin, cefuroxime, and amoxicillin-clavulanic acid: 57%, 57%, and 50%, respectively [17]. High percentages of resistant strains were also observed for cefotaxime, trimethoprim-sulfamethoxazole, and imipenem: 29%, 21%, and 21%, respectively. *Escherichia coli* strains expressed resistance of less than 10% only to ceftazidime (7%) and amikacin (7%). All of the resistance rates obtained in their study were much higher than those obtained in the present study.

Landau *et al.* reported that in children with CAKUT resistance rates of *Escherichia coli* to ampicillin, amoxicillin/clavulanic acid, cefuroxime, trimethoprim-sulfamethoxazole and ceftriaxone were 58%, 40%, 14%, 12%, 10% respectively [18].

Also Rosado *et al*. revealed an increase in resistance of *Escherichia coli* to amoxicillin/clavulanate (from 12.2% to 24% in the last 10 years) [19]. Overall, the above-mentioned results of the studies suggest that this antimicrobial agent may not be suitable for empirical therapy of UTI any more. The authors suggested that first-generation cephalosporins would be an adequate alternative in patients without risk factors.

Over 6 years of observation, a study by Catal *et al*. showed a significant increase in resistance of *Escherichia coli* strains against ampicillin, cotrimoxazole, and piperacillin, while *Klebsiella spp*. showed rising rates of resistance to ampicillin and cotrimoxazole, which is consistent with the observations made in the present study [20].

In the study by Miron *et al*. the highest resistance rates of *Klebsiella spp*. were observed for ampicillin (94.1%), amoxicillin-clavulanic acid (64.7%), ceftazidime (42.9%), and gentamicin (35.3%). The resistance rate for meropenem was 14.3%, while it was as high as 28.6% for imipenem. No *Klebsiella spp*. strains were resistant to colistin. In our observations, the resistance rates for *Klebsiella spp*. to ampicillin, amoxicillin-clavulanic acid, ceftazidime, and gentamicin were higher in our group: 100%, 74.51%, 47.83%, and 51.43%, respectively. Resistance to meropenem and imipenem was more favorable, as only 11.43% and 5.71%, respectively, of the *Klebsiella spp*. strains were resistant to these carbapenems. The greatest discrepancy in the analyses was noted for colistin. In our study, 48.57% of the *Klebsiella spp*. strains were resistant to colistin. Unfortunately, Miron *et al*. did not report the number of strains producing β-lactamases with an extended substrate spectrum [13].

Other studies' results show different resistance rates than were assessed in our center. For each center there are marked local differences, but in general the main pattern stays the same. In the study by Gunduz *et al*., the percentages of *Klebsiella spp*. strains that were resistant to ampicillin (98.4%), amoxicillin-clavulanic acid (21.3%), ceftazidime (21.4%), gentamicin (16.5%), and ciprofloxacin (7.1%) were lower than in our analysis. The authors did not report the percentage of ESBL+ isolates [14]. In the Alavudeen *et al*. dataset, the percentages of *Klebsiella spp*. strains that were resistant to amoxicillin-clavulanic acid and cefotaxime were comparable to our study. Higher resistance rates were observed for ceftazidime (81.82%) and imipenem (45.45%) [17].

In the study by Joya *et al. Klebsiella spp*. were resistant to ampicillin (77.7%), amoxicillin (75%; amoxicillin-clavulanic acid was not assessed), and ceftazidime (50%) whereas they found full susceptibility to tazobactam amikacin, but gentamicin was less effective, with 44.4% resistance, and about 50% for cephalosporins [21]. In the aforementioned study by Isac *et al*. in about 21% of UTI *Klebsiella pneumoniae* was isolated from urine, which was in 42.3% of cases resistant to ceftazidime – this stands as the most comparable result to ours. In the cited study *Klebsiella spp*. were found to have overall higher resistance rates than *Escherichia coli*, mainly to gentamicin and nitrofurantoin [12]. The same study showed amoxicillin-clavulanic acid resistance of the pooled Enterobacteriaceae group throughout the years – resistance increased from 7.7% in 2016 to a maximum of 65.5% in 2019 with a drop to 37.5% in 2020. This is a really interesting observation that has no simple explanation yet. Aminopenicillins are identified as widely used antibiotics in common infections of childhood. The coincidence of a drop in resistance in 2020 with the COVID-19 pandemic would suggest that during frequent lock-downs common infections were less frequent, need for antibiotic use dropped and eventually antibiotic resistance decreased. This hypothesis is supported by the results of nationally implemented reduction of antibiotic misuse, implemented in Northern European countries, that resulted in lowering rates of antibiotic resistance in *Escherichia coli* for amoxicillin/clavulanic acid, ampicillin and trimethoprim/sulfamethoxazole [22].

A recent study from Miron *et al*. showed that isolated strains of *Enterococcus spp*. were 100% resistant to ampicillin and expressed a high-level resistance mechanism against aminoglycosides. However, they were still sensitive to linezolid, vancomycin, and teicoplanin [13]. Conversely, in our study, the resistance rates to ampicillin and high concentrations of aminoglycosides were lower: 55.56% and 60.32%, respectively. Furthermore, we detected no resistance to linezolid, but the resistance rates to vancomycin and teicoplanin were 4.48% and 5.97%, respectively. In the study by Gunduz *et al*., 80% of the *Enterococcus spp*. strains showed resistance to ampicillin and 10.9% to nitrofurantoin; we found that only 55.56% of the strains were resistant to ampicillin, and no nitrofurantoin resistance was detected [14]. Alavudeen *et al*. found 100% susceptibility of isolated strains of *Enterococcus spp*. to vancomycin, and 33.33% expressed teicoplanin resistance [17]. Joya *et al*. reported high resistance of *Enterococcus spp*. to amoxicillin (80%) and aminoglycosides (65.5%), 14.2% were resistant to nitrofurantoin and all were susceptible to vancomycin, which is generally in line with our findings [21].

Alavudeen *et al*. reported that all strains of *Pseudomonas aeruginosa* were sensitive to piperacillin-tazobactam, cefepime, gentamicin, ciprofloxacin, and levofloxacin. In the present study, the resistance rates of *Pseudomonas aeruginosa* strains to these antibiotics were in the range 4.55–22.22%. On the other hand, 33.33% of the *Pseudomonas aeruginosa* strains in their study were resistant to carbapenems, which is higher than the results of our study [17].

Our research has shown that children with CAKUT are at higher risk of having a UTI caused by microorganisms that produce β-lactamases with an extended substrate spectrum (*Escherichia coli*). Reports from other researchers on this topic are controversial. This growing problem is confirmed by research from Taiwan, which reports equally high percentages of ESBL+ bacteria (up to 33%) among children with CAKUT [23]. On the other hand, data from Turkey and the United States are not as alarming as those obtained in our study (0.5–17%) [24–26]. Israeli research showed that in children with CAKUT among *Escherichia coli* and *Klebsiella pneumoniae* isolates ESBL(+) strains reached 8.9% and 22% respectively, but, interestingly, it was not different from children without CAKUT [18]. However, it should be noted that some of these results were based on analyses conducted in children with UTI who were treated on an outpatient basis.

CONCLUSIONS

We found that the presence of CAKUT predisposes children to *Pseudomonas aeruginosa* infections but does not affect the frequency of isolation of *Escherichia coli* or other pathogenic bacterial strains. Fungal infections were more common in children without urinary tract defects, but this may have been the result of multi-antibiotic therapy in the ICU. It should be noted that *Escherichia coli* strains systematically became less sensitive to the most commonly used first-line antibiotics (cephalosporins and nitrofurantoin). Another finding is that the presence of CAKUT increased the risk of ESBL+ *Escherichia coli* strains. Together, these results indicate that there is a need for careful individualization of UTI treatment in children who have a congenital urinary tract malformation.

DISCLOSURE

The authors declare no conflict of interest.

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