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Original Article

Antibiotic resistance patterns of pediatric community-acquired urinary tract infections in a tertiary care center in Jeddah, Saudi Arabia

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Abstract
Introduction: Urinary tract infections (UTIs) are common in children. UTIs can lead to serious and permanent damage to the urinary tract if treatment is delayed or insufficient, particularly in repeated infections. Knowledge of antibiotic resistance trends aids in the selection of appropriate empiric antibiotics. There is limited data regarding this in Saudi Arabia. This study aimed to investigate uropathogens and their antibiotic resistance patterns in the pediatric community in a tertiary care center.
Methodology: The study population included children aged 0 to 14 years old who had culture-proven UTIs evaluated in the Department of Pediatrics, King Abdulaziz University Hospital in Jeddah, Saudi Arabia from February 2019 to September 2021.
Results: Out of 510 UTI episodes, *Escherichia coli* (54.5%) was the predominant causative pathogen. Of the total episodes, 137 (26.8%) were caused by extended spectrum beta-lactamase (ESBL) producers. In general, the highest resistance was observed against ampicillin (73.2%), cefazolin (54.6%), co-trimoxazole (46%), and cefuroxime (40.6%), whereas amikacin (0.4%), imipenem (0.8%), and meropenem (0.8%) showed the lowest rates of resistance.
Conclusions: Antibiotic resistance is a major concern worldwide due to misuse of antibiotics and subsequent rise of multidrug resistant organisms. Our findings highlight the rise in antibiotic resistance, particularly in *E. coli* strains. Furthermore, ESBL-producing bacteria were responsible for approximately one-third of UTIs. Our study emphasizes the importance of local antibiograms for pediatric community-acquired infections, as it guides clinicians in every center in the choice of appropriate empiric antibiotic treatment.

Key words: Antibiotic resistance; urinary tract infections; pediatric; children; *Escherichia coli*.

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Introduction

Urinary tract infections (UTIs) are a prevalent condition in children. The cumulative incidence is estimated to be 7% in females and 2% in males during the first 6 years [1]. UTIs generally account for 1.5–1.75 million clinical visits per year [2]. If treatment is delayed or insufficient, particularly in repeated UTIs, serious and permanent damage to the urinary tract can occur, including pyelonephritis, scarring of the renal parenchyma, reduced kidney functions, elevated blood pressure, and chronic kidney disease [3]. It is well-recognized that *Escherichia coli* is the main pathogen responsible for UTIs [4] and is responsible for 70%–95% of community-acquired UTIs [5]. A recent Saudi study showed that *E. coli* was the frequent causative pathogen of community-acquired UTIs in children, responsible for 75.7% of UTI episodes with significant levels of antimicrobial resistance. More than half of *E. coli* strains showed resistance to ampicillin and co-trimoxazole, and about one-third showed resistance to amoxicillin/clavulanic acid. *Klebsiella pneumoniae* was reported as the second most common uropathogen. *Pseudomonas aeruginosa*, *Proteus* spp., and *Enterococcus* spp. were among the other uropathogens identified [6].

Increased antibiotic resistance is a globally recognized health concern. Antibiotic-resistant microorganisms have evolved as a consequence of many years of inappropriate antibiotic prescription [7]. Infections that are resistant to antibiotics often result in higher morbidity and mortality as well as higher healthcare costs [8]. These antibiotic-resistant infections may restrict the availability of appropriate antibiotics, making it difficult to treat commonly encountered bacterial infections, such as UTIs. Several uropathogens, including *E. coli*, are getting more resistant to treatments. A recent systematic review and meta-analysis revealed a significant level of resistance to routinely administered antibiotics in primary health care for *E. coli* UTIs in children [9]. Locally, a recent study that included both children and adults from a large tertiary care hospital, revealed a significant percentage of multidrug resistance (67%) in *E. coli* isolates, with 33% of all *E. coli* isolates producing ESBL [10]. In another Saudi retrospective study conducted in a general hospital with almost 13,000 *E. coli* isolates both inpatient and outpatient isolates of *E. coli* were found to have high levels of antibiotic resistance. Additionally, the study showed that the frequently prescribed antibiotics for treating UTIs were improperly prescribed [11]. Empiric antibiotic therapy is initiated in most children suspected of having UTIs before laboratory results are available. This is because delaying treatment increases the risk of both short- and long-term complications in children having UTIs [12].

Knowledge of antibiotic resistance trends aids in the selection of appropriate empiric antibiotics and lower treatment failure. However, there are few studies evaluating antibiotic resistance patterns of pediatric community-acquired UTIs in Saudi Arabia. Therefore, the aim of this study was to investigate the uropathogens and their antibiotic resistance in pediatric community-acquired UTIs at a tertiary care hospital in Jeddah, Saudi Arabia.

Methodology

Study design, setting, and population

This retrospective study included pediatric patients between the ages of 0 and 14 with culture-proven UTIs from February 2019 to September 2021 in the Department of Pediatrics, King Abdulaziz University Hospital in Jeddah, Saudi Arabia. King Abdulaziz University Hospital is a 1067-bed tertiary academic center that serves the whole community with over 66,000 emergency department visits every year. It is the largest tertiary care center in the Western region and is part of Saudi Arabia’s government-funded multispecialty health system. Children who acquired UTI after 48 hours of being admitted to the hospital or within 14 days of being discharged were excluded from the study.

Urine Culture

Positive urine cultures were used to identify UTI episodes. Midstream urine and a transurethral catheter were used to collect urine samples. A urine culture was considered positive if it showed a bacterial count of more than 10,000 colony-forming units (CFU)/mL in a urine sample taken by transurethral catheter, or more than 100,000 CFU/mL in a midstream urine sample [13,14]. Polymicrobial urine cultures and cultures with fungal growth were excluded. The Clinical Laboratory Standards Institute's guidelines were used to identify bacterial pathogen and evaluate the antibiotic susceptibility pattern [15]. Microorganisms with intermediate susceptibility were categorized as resistant. Antibiotic susceptibility testing was performed on 14 antibiotics: ampicillin, amoxicillin/clavulanic acid, piperacillin/tazobactam, cefazolin, cefuroxime, ceftriaxone, ciprofloxacin, trimethoprim-sulfamethoxazole (co-trimoxazole), nitrofurantoin, gentamicin, amikacin, imipenem, meropenem, and vancomycin.

Data Collection

Data from patients' medical records were collected using a predesigned data collecting form. Data collected included demographics (age at diagnosis, sex, nationality), risk factors, clinical presentation, lab results, radiological findings, as well as information about the bacterial isolate and its susceptibility to antibiotics.

Statistical analysis

Data entry was performed using Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA), while IBM SPSS Statistics version 21 (IBM Corp., Armonk, NY) was used for statistical analysis. Categorical variables were represented as numbers and percentages, and they were compared using the Chi-square or Fisher's exact test. Statistical significance was defined as $p < 0.05$.

Ethical approval

The study was approved by the Research Ethics Committee of the Faculty of Medicine at King Abdulaziz University in Jeddah, Saudi Arabia (Reference number 333-21).

Results

Patients Demographics and Clinical Characteristics

During the period of the study, 1,056 patient files were reviewed, of which 510 patients met the inclusion criteria. Among these, 313 patients (61.4%) were female, and 197 patients (38.6%) were male. Two hundred patients (39.2%) were children aged 3 to 8 years. Most of the patients 362 (71%) were Saudi nationals. A total of 213 (41.8%) patients had a previous history of UTIs. The most common presenting symptom was fever in 348 (68.2%) children, followed by dysuria in 85 patients (16.7%). The urinary catheter was the most used urine collection method in 277 patients (54.3%). Results of the urinalysis test revealed that pyuria (> 5 White Blood Cells per High-Power-Field) was found in 244 patients (76.7%), and positive nitrite tests were detected in 126 patients (39.6%). A renal ultrasound was performed on 300 (58.8%) patients, and it was abnormal in 180 (35.3%) patients, with hydronephrosis being the predominant abnormality (33.1%). A voiding cystourethrography was done in 185 (36.3%) patients and found to be abnormal in 142 (27.8%), with vesicoureteral reflux being the most common abnormality (18.2%). Table 1 shows patients' demographics and clinical data.

Table 1. Patients' demographics and clinical data (N = 510).

Clinical Data	N (%)
Gender	
Male	197 (38.6)
Female	313 (61.4)
Age group	
< 1 year	106 (20.8)
1 – 2 years	75 (14.7)
3 – 8 years	200 (39.2)
9 – 14 years	129 (25.3)
Nationality	
Saudi	362 (71.0)
Non-Saudi	148 (29.0)
Urine collection method	
Urine Catheter	277 (54.3)
Urine Midstream	233 (45.7)
Risk factors	
DM	5 (1.0)
Uncircumcised male	8 (1.6)
Previous Urinary tract calculi	17 (3.3)
History of recurrent UTI	213 (41.8)
Malignancy	3 (0.6)
Renal failure	5 (1.0)
Immunodeficiency	6 (1.2)
Chronic kidney disease	41 (8.0)
Neurogenic bladder	159 (31.2)
Previous Renal scarring	15 (2.9)
Hydronephrosis	169 (33.1)
Kidney stones	11 (2.2)
Vesicoureteral reflux	93 (18.2)
Other urological abnormalities	54 (10.6)
Clinical features	
Fever	348 (68.2)
Dysuria	85 (16.7)
Change in urine smell	79 (15.5)
Increased urinary frequency	30 (5.9)
Hematuria	15 (2.9)
Flank pain	17 (3.3)
Abdominal pain	45 (8.8)
Irritability	41 (8.0)
URTI symptoms	28 (5.5)
Diarrhea	26 (5.1)
Vomiting	57 (11.2)
Decreased activity	59 (11.6)
Urine analysis	318 (62.4)
Pyuria (>5 WBC/HPF)	244 (76.7)
Nitrite positive	126 (39.6)
High RBCs	137 (43.1)
Proteinuria	66 (20.7)

DM: Diabetes mellitus; UTI: urinary tract infection; URTI: upper respiratory tract infection; WBC: white blood cells; RBC: red blood cells.

Isolated urinary tract pathogens

In total, 510 uropathogens were isolated. The most common isolated pathogen was *Escherichia coli* (54.5%), followed by *Klebsiella pneumoniae* (20.6%), *Pseudomonas aeruginosa* (7.5%), and *Enterococcus* spp. (5.7%). Among the 510 isolates, 137 (26.8%) were ESBL producers. Of them, 94 (18.4%) were ESBL-producing *E. coli* and 43 (8.4%) were ESBL-producing *K. pneumoniae*. Table 2 shows the distribution of isolated urinary tract pathogens.

Antibiotic resistance pattern

Table 3 details the antibiotic resistance pattern of the 510 isolated uropathogens against the tested antibiotics. In general, these pathogens exhibited the highest resistance to ampicillin (73.2%), cefazolin (54.6%), co-trimoxazole (46%), and cefuroxime (40.6%), whereas amikacin (0.4%), imipenem (0.8%), and meropenem (0.8%) showed the lowest rates of resistance. *E. coli* was most resistant to ampicillin (71.2%), cefazolin (56.5%), and co-trimoxazole (52.5%) and least resistant to piperacillin/tazobactam (7.2 %) and amikacin (0.4%). Moreover, none of the *E. coli* isolates showed resistance to imipenem or meropenem. Among Klebsiella spp., considerable ampicillin resistance was reported; both *K. pneumoniae* and *K. oxytoca* were 100% resistant to ampicillin. *K. pneumoniae* showed 67.6% resistance to nitrofurantoin while *K. oxytoca* was susceptible to it. Least resistance was observed for imipenem and meropenem (1% for *K. pneumoniae* and 0% for *K. oxytoca*), and piperacillin/tazobactam (5.7% for *K. pneumoniae* and 0% for *K. oxytoca*). None of *Klebsiella* spp. showed resistance to amikacin. *P. aeruginosa* was most resistant to ciprofloxacin (15.8%), while the resistance

Table 2. Distribution of isolated urinary tract pathogens (N = 510).

Urinary tract pathogens	N (%)
Escherichia coli	278 (54.5)
Klebsiella pneumoniae	105 (20.6)
Pseudomonas aeruginosa	38 (7.5)
Enterococcus spp.	29 (5.7)
Enterobacter cloacae	12 (2.4)
Acinetobacter spp.	10 (2.0)
Staphylococcus aureus	9 (1.8)
Proteus mirabilis	6 (1.2)
Serratia spp.	6 (1.2)
Citrobacter spp.	5 (1.0)
Klebsiella oxytoca	3 (0.6)
Morganella morganii	3 (0.6)
Providencia spp.	2 (0.4)
Burkholderia cepacia	1 (0.2)
Aeromonas hydrophila	1 (0.2)
Proteus Vulgaris	1 (0.2)
pseudomonas putida	1 (0.2)

Table 3. Resistance pattern of the isolated urinary tract pathogens against tested antibiotics, Number (% Resistance rates).

Antibiotic	*E. coli* (N = 278)	*K. pneumoniae* (N = 105)	*P. aeruginosa* (N =38)	*Enterococcus spp.* (N = 29)	*Enterobacter cloacae* (N = 12)	*Acinetobacter spp.* (N = 10)	*S. aureus* (N = 9)	*P. mirabilis* (N = 6)	*Serratia spp.* (N = 6)	*Citrobacter spp.* (N = 5)	*K. oxytoca* (N = 3)	*M. morganii* (N = 3)	*Providencia spp.* (N = 2)	*Burkholderia cepacia* (N = 1)	*Aeromonas hydrophila* (N = 1)	*P. Vulgaris* (N = 1)	*P. putida* (N = 1)	Overall resistance
Ampicillin	198 (71.2)	105 (100)	NT	0 (0)	NT	NT	NT	2 (33.3)	NT	NT	3 (100)	NT	NT	NT	NT	NT	NT	73.2
Amoxicillin/ Clavulanic acid	86 (30.9)	23 (21.9)	NT	NT	NT	NT	NT	0 (0)	NT	NT	0 (0)	NT	NT	NT	NT	NT	NT	27.8
Piperacillin/ Tazobactam	20 (7.2)	6 (5.7)	3 (7.9)	NT	NT	0 (0)	NT	0 (0)	NT	NT	0 (0)	NT	NT	NT	0 (0)	NT	0 (0)	6.6
Cefazolin	157 (56.5)	57 (54.3)	NT	NT	NT	NT	NT	0 (0)	NT	NT	0 (0)	NT	NT	NT	NT	NT	NT	54.6
Cefuroxime	105 (37.8)	54 (51.4)	NT	NT	NT	NT	NT	0 (0)	NT	NT	0 (0)	NT	NT	NT	NT	NT	NT	40.6
Ceftriaxone	96 (34.5)	43 (41)	NT	NT	NT	NT	NT	0 (0)	NT	NT	0 (0)	NT	NT	NT	0 (0)	NT	NT	35.4
Ciprofloxacin	98 (35.3)	47 (44.8)	6 (15.8)	NT	2 (16.6)	1 (10)	1 (11.1)	1 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NT	0 (0)	1 (100)	0 (0)	32.7
Co-trimoxazole	146 (52.5)	47 (44.8)	NT	NT	3 (25)	2 (20)	0 (0)	2 (33.3)	0 (0)	0 (0)	1 (33.3)	1 (33.3)	1 (50)	0 (0)	0 (0)	1 (100)	0 (0)	46
Nitrofurantoin	32 (11.6)	71 (67.6)	NT	1 (3.4)	7 (58.3)	NT	2 (22.2)	5 (83.3)	5 (83.3)	1 (20)	0 (0)	3 (100)	2 (100)	NT	0 (0)	1 (100)	NT	28.3
Gentamicin	36 (12.9)	8 (7.6)	1 (2.6)	NT	0 (0)	0 (0)	NT	1 (16.7)	0 (0)	0 (0)	0 (0)	1 (33.3)	2 (100)	NT	0 (0)	0 (0)	0 (0)	10.4
Amikacin	1 (0.4)	0 (0)	1 (2.6)	NT	0 (0)	0 (0)	NT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NT	0 (0)	0 (0)	0 (0)	0.4
Imipenem	0 (0)	1 (1)	2 (5.3)	NT	0 (0)	0 (0)	NT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NT	1 (100)	0 (0)	0 (0)	0.8
Meropenem	0 (0)	1 (1)	2 (5.3)	NT	0 (0)	0 (0)	NT	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NT	1 (100)	0 (0)	0 (0)	0.8
Vancomycin	NT	NT	NT	1 (3.4)	NT	NT	0 (0)	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	2.6

NT: Not Tested; 0 indicates no antibiotic resistance (100% sensitive).

to gentamicin (2.6%) and amikacin (2.6%) was the lowest.

Comparison between E. coli and non-E. coli UTIs

When comparing UTIs caused by *E. coli* and non-*E. coli* uropathogens, males had significantly more non-*E. coli* UTIs than females ($p < 0.0001$). Furthermore, the proportion of children under the age of 1 year was significantly higher in non-*E. coli* strains (26.3% vs. 16.2%, $p = 0.007$), while proportion of children in the 9 to 14 years age group was considerably higher among *E. coli* strains (30.6% vs. 19%, $p = 0.004$).

Antibiotic resistance rates for *E. coli* and non-*E. coli* uropathogens are compared in Table 4. Overall, *E. coli* isolates exhibited more resistance to the majority of antimicrobial agents. Ampicillin showed the highest resistance rate for both *E. coli* and non-*E. coli* isolates (71.2% and 76.9%). For *E. coli* isolates, the resistance to amoxicillin/clavulanic acid, co-trimoxazole, and gentamicin was significantly higher than non-*E. coli* isolates ($p = 0.042$, $p = 0.001$, and $p = 0.044$, respectively). Antibiotic resistance was shown to be considerably higher in non-*E. coli* isolates for nitrofurantoin, imipenem, and meropenem ($p = 0.0001$, $p = 0.028$, and $p = 0.028$, respectively).

Discussion

In Saudi Arabia, there are few studies on the antibiograms of pediatric community-acquired UTIs. Local and regional reports of antibiotic resistance patterns serve the global vision of combating antibiotic resistance. Thus, we reviewed the clinical data and the antibiotic resistance patterns of children with a diagnosis of community-acquired UTIs from February 2019 to September 2021.

In our isolates, *E. coli* was the predominant organism with a percentage of 54.5% which is similar to percentages from reports published in North America [16,17]. However, our percentage is lower than local and regional reports that had levels of more than 70% [6,18-20]. Considering *K. pneumoniae*, our result showed a greater prevalence (20.6%) compared to the other regional studies that had rates between 9.4% and 10% [6,19,20].

Table 4. Comparison of antibiotic resistance between *E. coli* and non-*E. coli* uropathogens in pediatric UTIs, Number (% Resistance rates).

Antibiotic	*E. Coli* (n = 278)	Non-*E. coli* (n = 232)	*p* value
Ampicillin	198 (71.2)	110 (76.9)	0.257
Amoxicillin/ Clavulanic acid	86 (30.9)	23 (20.2)	**0.042***
Piperacillin/ Tazobactam	20 (7.2)	9 (5.5)	0. 616
Cefazolin	157 (56.5)	57 (50)	0.290
Cefuroxime	105 (37.8)	54 (47.4)	0.100
Ceftriaxone	96 (34.5)	43 (37.4)	0 .672
Ciprofloxacin	98 (35.3)	59 (29.2)	0 .195
Co-trimoxazole	146 (52.5)	58 (35.2)	**0.001***
Nitrofurantoin	32 (11.6)	98 (53.8)	**< 0.0001***
Gentamicin	36 (12.9)	13 (6.7)	**0.044***
Amikacin	1 (0.4)	1 (0.5)	1.000
Imipenem	0 (0)	4 (2.1)	**0.028***
Meropenem	0 (0)	4 (2.1)	**0.028***

*p less than 0.05 is considered statistically significant; 0 indicates no antibiotic resistance (100% sensitive); UTI: urinary tract infection.

Based on our 510 isolates, the antibiotics with the highest overall resistance rates were ampicillin (73.2%), cefazolin (54.6%), co-trimoxazole (46%), and cefuroxime (40.6%). The high rate of ampicillin resistance was consistent with other local and regional studies from Saudi Arabia, Oman, and Bahrain [6,18,19]. However, cefazolin resistance was much lower than the study conducted in Bahrain (94%) [19] but higher than a recent Saudi study (30%) [6]. Regarding co-trimoxazole, we had a close pattern of resistance to the previous literature [6,18]. Moreover, amikacin, imipenem, and meropenem showed the lowest rates of resistance compared to the other regional studies [6,18,19].

Our study showed that *E. coli* exhibited the highest resistance against ampicillin (71.2%), cefazolin (56.5%), and co-trimoxazole (52.5%). The ampicillin resistance rate was similar to the published studies from Saudi Arabia and Oman [6,18], whereas other regional studies showed a resistance rate of over 90% [10,20]. Regarding cefazolin, we had more than double the rate of resistance when compared to a previous Saudi study (22%) [6]. Furthermore, the rate of co-trimoxazole resistance was consistent with previous regional studies [6,10,18].

The highest resistance in *K. pneumoniae* was observed against ampicillin (100%), nitrofurantoin (67.6%), and cefazolin (54.3%). Our study showed similar results to the previous regional studies that showed nearly 100% of *K. pneumoniae* species were resistant to ampicillin [6,18-20]. Our high rate of nitrofurantoin resistance is also similar to another local study [6]. Regarding cefazolin, we had a noticeably lower rate of resistance compared to other regional studies (100% and 83%, respectively) [6,19].

When comparing the resistance rates between *E. coli* and non-*E. coli* isolates, resistance to nitrofurantoin was significantly higher in non-*E. coli* isolates than in *E.coli* isolates, which is in line with the findings of Marcus et al [4]. However, *E. coli* isolates demonstrated significantly higher resistance to amoxicillin/clavulanic acid than non-*E. coli* isolates, contrary to the findings of Marcus et al. in which non-*E. coli* isolates exhibited greater rates of resistance to amoxicillin/clavulanic acid [4].

Our findings showed higher cases of UTIs in females (61.4%) than in males (38.6%), which are consistent with local [6,10]. and global studies [1,18,19,21]. This might be due to anatomical variations, most notably a short urethra in females allowing uropathogens easy access to the bladder [22,23]. Moreover, males were primarily infected by non-*E. coli* infections which are consistent with the findings from several studies conducted both locally and globally [4,6,24,25].

A worrisome finding is that 26.8% of all isolates showed to be ESBL-producing organisms; This is consistent with the rising incidence of ESBL-producing pathogens causing pediatric community-acquired UTIs locally and globally [10,19,26]. Furthermore, a recent study from Jordan reported that ESBL-producing bacteria were responsible for up to 46% of pediatric community-acquired UTIs [27].

Our study has its strengths; we were strict in our inclusion criteria that included only children with community-acquired UTIs. Also, we included children with risk factors to better represent our population. Moreover, to the best of the authors' knowledge, we represent the most recent study about antibiotic resistance patterns in pediatric community-acquired UTIs in Saudi Arabia with the largest sample size.

Due to the nature of the study design, limitations include the possibility of inaccurate documentation of patients' data, as this study is based on a review of clinical charts. It's also important to note that, since our study was conducted in the Western region, it could not accurately represent the patterns of antibiotic resistance in other regions of Saudi Arabia.

Conclusions

Our findings highlight the rise in antibiotic resistance, particularly in *E. coli* strains, which were the most prevalent organisms in our study. Furthermore, ESBL-producing bacteria were responsible for approximately one-third of UTIs. Antibiotic resistance is an increasingly global concern, not only in the Gulf region or Saudi Arabia. Years of antibiotic misuse have also contributed to an alarming increase in multidrug-resistant pathogens. Until a few years ago, antibiotics in Saudi Arabia were sold as over-the-counter medications, without a strict law to regulate them. Local antibiograms for pediatric community-acquired infections are now required, as they will aid clinicians in choosing appropriate antibiotics for treatment, implement stewardship programs, and increase efforts to raise awareness about antibiotic resistance in Saudi Arabia.

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