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Original Article

A decade trends of the distribution and antimicrobial susceptibility of prevalent uropathogens among pediatric patients from Tehran, Iran during 2005–2016

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KEYWORDS
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Abstract *Objectives:* To determine changes in the distribution of uropathogens and their antimicrobial resistance in pediatric patients in a children's hospital from 2005 to 2016.
Methods: A cross-sectional analysis of uropathogens and their antimicrobial resistance within inpatient children was performed over the 11-year period, 2005 to 2016, in Ali Asghar children's hospital. The rate of antibiotic resistance among patients was evaluated according to demographic data including age, sex, urinary tract abnormities and history of antibiotic consumption.
Results: In total, 958 female and 349 male positive cultures were analyzed. *Escherichia coli* (77.6%) was the most common causative agent of urinary tract infection (UTI) in children and *Klebsiella pneumoniae* (10.4%), *Pseudomonas aeruginosa* (2.4%), and *Enterococcus* spp (2.4%) were less frequent isolated bacteria. The resistance rates of *E. coli* isolates were increased against amikacin, ceftriaxone, ceftazidime, ciprofloxacin, cotrimoxazole and imipenem from 2005 to 2010. However, we observed a decreasing trend for some of antibiotics including amikacin, gentamicin, imipenem, ceftazidime and cotrimoxazole during 2014–2016. The rate of antibiotic resistance was greater in boys than in girls against many antibiotics. The rate of resistance to amikacin, gentamicin, nitrofurantoin and cotrimoxazole in patients aged <1 year was higher than other age groups ($p < 0.001$). A higher antibiotic resistance rate was observed in patients with anatomical abnormality and those who have had a history of antibiotic consumption.

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Conclusion: The study indicated the significant decrease in *E. coli* antibiotic resistance in the last 3 years. An effective empirical treatment regime should be based on local epidemiology and antimicrobial susceptibility testing.

1. Introduction

Urinary tract infections (UTIs) are the most common infection in the pediatric population, and a common cause of hospitalization in infancy and childhood [1,2]. UTIs are significantly caused by Gram-negative bacteria such as *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K.pneumoniae*), but Gram-positive pathogens (*e.g., Staphylococcus saprophyticus*, *Enterococcus faecalis*) may also be involved [3–5]. The disease severity and outcome of UTI can also differ significantly, and are related to various factors, including gender, age, the genetic and susceptibility of the host, type of causative organism, response to antibiotic therapy, the pattern of antibiotic resistance, and the clinical management of the patient [6,7]. Whereas, UTI clinical manifestations in neonate and children are nonspecific presentations [8]. For this reason, it should be done promptly urine analysis, culture and antimicrobial susceptibility testing on urine specimens that all of these can be an aid in the diagnosis of UTI. Furthermore, there is increasing prevalence of multidrug-resistant (MDR) organisms in pediatric hospitals, with particular concern for emerging resistance to broad-spectrum cephalosporins and carbapenems [9,10]. Although international guidelines are provided empiric treatment recommendations, these empiric recommendations should be modified by specialists and microbiologists in any hospitals for bacterial infections [11]. Since we found no comprehensive study on antimicrobial resistance in this setting. Awareness and understanding of local antimicrobial resistance patterns are important for antibiotic stewardship and initiating empiric antibiotic therapy. In this study, we evaluated the frequency uropathogens and their susceptibility to tested antibiotics over a 10-year period as well as effective factors in the incidence of UTI and antimicrobial resistance in Ali Asghar children's hospital.

2. Material and methods

2.1. Study design and setting

The study performed at the Ali Asghar children's hospital, Tehran, Iran, the pediatric center in the northern end of Tehran. The source of extracted data was the hospital records of the patients regarding age, sex, date, method of urine sample collection, urine culture results, presence of urinary tract anomalies, previous antibiotic consumption and antibiogram results. The latter routinely was based on the report of the laboratory unit of Ali Asghar children's hospital which reports antibiogram by a semi-quantitative approach based on disk diffusion method, and the available laboratory guidelines.

2.2. Inclusion criteria

In the current study, we designed a study population using simple non-random sampling to recruit all cases with the diagnosis of UTI admitted to Ali Asghar children's hospital, Tehran, Iran in 2005–2016 period. Furthermore, UTI was defined as: I) A bacterial growth $\geq 10^5$ CFU/mL in midstream urine culture, or $\geq 10^4$ CFU/mL from a urine sample obtained by catheterization; II) The presence of greater than five leukocytes per high-powered field and bacteriuria or a positive nitrite test or leukocyte esterase. Specimens of bagged urines were included only if there were two specimens collected with identical results. Only the result of the first positive urine culture was extracted. In the event of two separate initial positive cultures, the result of suprapubic aspirate was taken into account.

2.3. Exclusion criteria

Those with incomplete records, including the absence of two confirmatory progress notes regarding urine sample collection method were excluded from the study. Mixed growth urine cultures denoting the growth of two or more organisms in one sample were excluded, as they were likely to represent contaminated samples. Episodes with urine samples growing fungal organisms were also excluded.

2.4. Data analysis

All extracted data entered in SPSS (Ver. 22, Armnok, NY, USA) software spreadsheets. The frequency of uropathogens and their resistance to the tested antibiotics were compared for four time periods by using the Chi-square test. In addition, we analyzed the impact of age, gender, anatomical abnormalities and previous antibiotic administration on antibiotic resistance for a period of 10 years (2005–2016).

3. Results

A total of 1307 non-duplicate urinary isolates were recovered from 958 girls (73.3%) and 349 boys (27.7%) with UTI during the study period. The biggest percentage of isolates were from children who have <1 year of age (37.0%), while the number of isolates were variable among the remaining age groups (18.8% in patients aged 1–2 years, 6.6% in patients 2–3 years, 7.1% in patients 3–4 years, 5.7% in patients 4–5 years, 6.9% in patients 5–6 years and 17.9% in patients >6 years). The most frequently recovered isolates were *E. coli*, 77.6%; *K. pneumoniae*, 10.7%; Enterococcus spp, 2.4%; and *Pseudomonas aeruginosa*, 2.4% (Table 1).

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Table 1 Frequency of uropathogens isolated from urine cultures.

Microorganisms	Number (%)
Gram-negative bacteria	
Escherichia coli	1014 (77.6)
Klebsiella pneumoniae	140 (10.71)
Pseudomonas aeruginosa	32 (2.44)
Proteus spp	15 (1.14)
Enterobacter spp	13 (1.0)
Acinetobacter spp	3 (0.23)
Other Gram-negative bacteria	8 (0.61)
Gram-positive bacteria	
Enterococcus spp	32 (2.44)
Coagulase-negative staphylococci	29 (2.21)
Staphylococcus aureus	5 (0.4)
Other *streptococci*	14 (1.07)
Other Gram-positive bacteria	2 (0.15)
Total	1307 (100)

Furthermore, among isolates recovered from girls and boys, the distribution of microorganisms was consistent with the overall study population. Besides, the resistance rates against antimicrobial agents are summarized in Table 2 for Gram-negative and Gram-positive isolated bacteria respectively. In Gram-negative uropathogens, the rates of resistance to ampicillin, cotrimoxazole, and oral cephalosporins were very high, and to imipenem, cefepime and amikacin were lower than others. Vancomycin, nitrofurantoin and ciprofloxacin were more effective against Gram-positive bacteria. In addition, the rates of resistance to amikacin, gentamicin, nitrofurantoin and cotrimoxazole in patients aged <1 year was higher than other age groups ($p < 0.001$). However, no significant correlation was found between aged groups with resistance to other antibiotics. Table 3 illustrated resistance rates to tested antibiotics, according to gender during the study period. Also, the rates of resistance to many antibiotics were greater in boys than in girls. As shown in Table 4, the changing of resistance was significant for amikacin, ampicillin, ceftriaxone, ceftazidime, nitrofurantoin and gentamicin during the study period (2005–2016). Although resistance to ceftriaxone increased from 30.5% in 2008 to 44.7% in 2013, the resistance rates tended to decrease in 2016. In the next section, we focused on the effects of anatomical abnormalities on the distribution of pathogens and their antibiotic resistance represented in Tables 5 and 6. The frequency of uropathogens including *Enterobacter. spp* and *P. aeruginosa* are higher in patients with anatomical abnormalities in compared to those without anatomical abnormalities.

We next examined the effects of previous antibiotic consumption on antimicrobial resistance. For this reason, patients with anatomical abnormalities such as the neurogenic bladder, perineal stenosis, double terminal urethra were excluded and only 338 patients were included in this section. More details were representing in Table 7.

4. Discussion

Antimicrobial resistance (AMR) is a serious concern worldwide and the rising of multidrug resistance strains among inpatient and outpatient accounting as a potential risk. At the national level, each country should be promoted knowledge through surveillance and investigation in the field of AMR. Throughout the study period, *E. coli* remained the most prevalent causative agent of UTI in the pediatric population, which this finding is consistent with previous

Table 2 The pattern of antibiotic resistance for selected uropathogens.

Antibiotics	*Escherichia coli*		*Klebsiella pneumoniae*		*Pseudomonas aeruginosa*		*Enterococcus* spp	
	%R	TN	%R	TN	%R	TN	%R	TN
Amikacin	6.95	950	24.62	130	6.9	29	71.43	7
Gentamicin	19.02	936	29.46	129	24.14	29	85	20
Ampicillin	78.75	607	88.68	106	100	14	40.91	22
Cefazolin	56.33	529	76.09	100	82.35	17	—	—
Cephalexin	52.28	329	57.14	21	100	7	—	—
Cefuroxime	53.23	387	60	70	92.31	13	—	—
Ceftizoxime	29.09	55	33.33	3	—	—	—	—
Ceftazidime	28.38	613	41.94	93	20.83	24	—	—
Cefotaxime	37.75	355	55.56	27	75.0	12	—	—
Ceftriaxone	36.08	898	46.28	121	46.15	26	—	—
Cefepime	15.58	552	24.72	89	11.11	18	—	—
Imipenem	13.16	395	4.55	44	6.25	16	—	—
Ciprofloxacin	19.66	829	7.89	114	4	25	60	20
Ofloxacin	31.11	135	15.38	13	0	4	20	5
Cotrimoxazole	60.24	835	40.17	117	81.82	22	73.68	19
Nitrofurantoin	2.93	957	17.42	132	83.87	31	16.67	18
Nalidixic acid	46.43	420	18.42	38	76.92	13	42.86	7
Erythromycin	—	—	—	—	—	—	76.92	26

%R, percentage of resistance, TN, total number;
—, Not performed.

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Table 3 Distribution and frequency of antibiotic resistance uropathogens by gender.

Antibiotics	Boys		Girls		*p*-Value
	Number (%) of resistant isolates	Total number of isolates	Number (%) of resistant isolates	Total number of isolates	
Amikacin	51 (16.8)	303	64 (7.5)	859	<0.001
Ampicillin	169 (83.7)	202	443 (75.9)	584	<0.021
Ceftriaxone	140 (47.5)	295	285 (34.9)	816	<0.001
Ceftazidime	81 (38.9)	208	147 (26.5)	554	<0.001
Nitrofurantoin	47 (14.5)	317	50 (5.6)	891	<0.001
Gentamicin	98 (31.8)	308	160 (18.3)	874	<0.001
Ciprofloxacin	60 (21.5)	279	134 (17.5)	765	<0.142
Imipenem	20 (16.1)	124	38 (10.7)	355	<0.11
Cotrimoxazole	156 (54.4)	287	456 (58.3)	782	<0.247

Table 4 Antimicrobial resistance trends among *E.coli* isolates from Ali Asghar Hospital, 2005 to 2016.

Antimicrobial agent	2005–2007		2008–2010		2011–2013		2014–2016		*p*-Value
	Resistance percentage	Total number	Resistance percentage	Total number	Resistance percentage	Total number	Resistance percentage	Total number	
Amikacin	9.2%	142	13.6%	213	7.6%	249	1.4%	346	<0.001
Ampicillin	66.7%	6	90%	50	81%	211	75.9%	340	0.058
Ceftriaxone	30.5%	128	42.6%	216	44.7%	215	28.6%	339	<0.001
Ceftazidime	25.8%	62	46.3%	41	40.5%	173	20.5%	337	<0.001
Ciprofloxacin	14.1%	64	21.4%	187	23%	243	17.3%	335	0.027
Cotrimoxazole	65.5%	139	70.8%	192	70.6%	221	42.4%	283	<0.001
Gentamycin	18.4%	136	28.4%	211	24.2%	260	9.1%	329	<0.001
Imipenem	8.3%	36	18.2%	214	10.5%	86	1.7%	59	0.005
Nitrofurantoin	6.7%	134	6%	216	2.3%	263	0.0%	344	<0.001

Table 5 Distribution of UTI etiological agents in patients with and without anatomical abnormalities.

Organisms	Patients with abnormalities, *n* (percent of isolates, %)	Patients without anatomical abnormalities, *n* (percent of isolates, %)
Escherichia coli	350 (73.3)	618 (80.7)
Klebsiella pneumoniae	51 (10.6)	79 (10.3)
Pseudomonas aeruginosa	23 (4.8)	7 (0.9)
Enterococcus.spp	11 (2.3)	17 (2.2)
Enterobacter.spp	9 (1.8)	4 (0.5)
Proteus.spp	6 (1.2)	9 (1.2)
Coagulase-negative staphylococci	8 (1.6)	9 (1.2)
Others	19 (3.9)	23 (3)

studies [2,12–14]. Although *E. coli* is one of the members of the intestines microbiota, this organism can result in various infections, including meningitis, gastroenteritis, bacteremia and UTI. In the present study, the proportion of UTI was significantly higher in females (73%) than in males (27%). Our results were consistent with other studies that showed that UTI was more frequent in females [5,13,15,16]. High frequency of UTI in females can be due to anatomical differences such as shortness of urethra and close space between the anus and urethral orifice [17,18]. However, some studies reported that UTI at an early age (<2 years) is greater in boys than girls [19,20]. This difference can be due to the lack of circumcision in young boys. In addition, in our study, the age distribution for UTI was similar to that of other studies from Iran and other countries [2,15]. Overall, we found resistance rates of *E. coli* to ampicillin, cefazolin, cotrimoxazole, cefuroxime, and cephalexin were increased during the study period. In contrast, resistance to ampicillin was 40.9% in *Enterococcus* isolates. Similarly, in Taheri and coworker's study [21], the resistance rates of *E. coli* isolates to ampicillin, cefixime, ceftizoxime, cephalexin, ceftazidime and gentamycin were 93.6%, 85.7%, 78.9%, 77.3%, 53.8% and 59.5%, respectively. Furthermore, high-frequency resistance to these antibiotics

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Table 6 Distribution of resistant isolates of *E.coli* among patients with and without anatomical abnormalities.

Antimicrobial agent	Patients without anatomical abnormalities		Patients with anatomical abnormalities		*p*-Value
	Number (%) of resistant isolates	Total number of isolates	Number (%) of resistant isolates	Total number of isolates	
Amikacin	57 (8.4)	677	51 (11.9)	426	0.053
Ampicillin	366 (76.2)	480	215 (79.9)	269	0.247
Cefazolin	221 (53.2)	415	157 (72.6)	216	0.0002
Cefepime	65 (15.5)	417	55 (22.1)	248	0.032
Cephalexin	103 (45.7)	225	95 (67.3)	141	0.0005
Ceftriaxone	208 (32.2)	644	196 (47.2)	415	0.0001
Ceftazidime	118 (26.7)	441	101 (35.4)	285	0.0128
Ciprofloxacin	94 (14.9)	627	83 (22.7)	365	0.0021
Cotrimoxazole	361 (57.5)	627	224 (57.5)	389	0.998
Gentamicin	130 (18.5)	699	111 (26.1)	424	0.0027
Imipenem	27 (10.1)	267	28 (15.1)	185	0.108
Nitrofurantoin	45 (6.2)	715	44 (10.1)	434	0.0181

Table 7 Association of among previous antibiotic consumption and antibiotic resistance.

Antibiotics	Previous antibiotic consumption (+)		Previous antibiotic consumption (−)		*p*-Value
	Number (%) of resistant isolates	Total number	Number (%) of resistant isolates	Total number	
Ampicillin	16 (8.9)	180	6 (4.9)	22	0.192
Amikacin	103 (82.4)	125	66 (68.8)	96	0.017
Cefepime	25 (23.4)	107	5 (5.5)	91	0.0004
Cephalexin	36 (52.9)	68	9 (32.1)	28	0.063
Cefotaxime	31 (43.7)	71	7 (24.1)	29	0.067
Ceftriaxone	73 (42.2)	173	33 (27)	122	0.008
Ceftazidime	34 (31.8)	107	14 (15.4)	91	0.007
Ciprofloxacin	36 (21.1)	171	15 (12.9)	116	0.077
Cotrimoxazole	102 (60.7)	168	43 (41.3)	104	0.002
Gentamicin	40 (20.8)	192	19 (15.4)	123	0.231
Imipenem	10 (11.4)	88	2 (4.3)	47	0.166
Nalidixic acid	41 (49.4)	83	8 (22.9)	35	0.008
Nitrofurantoin	16 (8.3)	193	4 (3.2)	126	0.065

was reported among *E. coli* isolates in other studies [2,13,22]. Our findings suggest that ampicillin and oral cephalosporins should be used as empiric agents only when potential benefits outweigh risks. According to the results of the present study the rate of resistance to amikacin, gentamycin and nitrofurantoin in patients aged <1 year was higher than other age groups, while resistance to cotrimoxazole was increasing in aged >1 year. Also, the prevalence of resistance between boys was higher than girls to antibiotics such as amikacin, gentamycin, ceftriaxone, ceftazidime and nitrofurantoin. However, the impact of gender and age in increasing antibiotic resistance is a controversial issue between researchers [23,24]. In addition, there are several main risk factors including catheterization, use of broad-spectrum antibiotics, acquisition of multidrug-resistant strains, prolonged hospitalization, presence of underlying diseases and urinary system disorders that influence UTI incidence and antibiotic resistance. In the current study, due to insufficient data, we only evaluated changes of antimicrobial resistance *E. coli* isolates. During the study period, from 2005 to 2010 resistance to amikacin, ceftriaxone, ceftazidime, ciprofloxacin, cotrimoxazole, imipenem in *E. coli* isolates were increased. In a previous study from Spain, the rate of resistance to third-generation cephalosporins and fluoroquinolones increased significantly for *E. coli* infection [25].

The increasing trend of the amikacin, ceftriaxone, ceftazidime, ciprofloxacin, cotrimoxazole, imipenem resistance rate for *E. coli* is consistent with other national antimicrobial resistance studies [26]. However, we observed decreasing antimicrobial resistance of *E. coli* between 2011 and 2016. Furthermore, resistance to nitrofurantoin significantly decreased during the study period. From 2005 to 2010, relative increasing of resistance rates can be due to various factors such as overuse or inappropriate antibiotic therapy for hospital or community-acquired infections, antimicrobial prophylaxis, poor education for combat with antimicrobial resistance, selection of patients from referral hospital, overuse of antibiotics for prevention and therapeutic aims in livestock and poultries. However, we found that the decrease in resistance rates of *E. coli* in the last years of the study period. In this context, the management of antibiotic prescription by physicians, rising of understanding individuals for antibiotic usage and

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promotion of infection control policies were affected in decreasing antibiotic resistance. Previous studies were indicated that various factors including the type of strains, expression of virulence factors, misuse or overuse of antibiotics in human and animal health, anatomical abnormalities may be influence the antimicrobial resistance rates [27–29]. According to our results, there is an association between anatomical anomalies, distribution of uropathogens and antibiotic resistance. We found that frequency of *Enterobacter* spp and *P. aeruginosa* were higher in patients with anatomical abnormities than those without anatomical abnormities. Furthermore, the study results revealed that in patients with anatomical anomalies in comparison to patients without anatomical abnormalities, the resistance rate increased to cefazoline, cephalexin, cefepime, ceftazidime, ceftriaxone, ciprofloxacin, gentamycin and nitrofurantoin ($p < 05$) while the rising of resistance was not significant for amikacin, ampicillin, imipenem and cotrimoxazole. Ahmed and coworkers [30,31] reported that the resistance rates to ampicillin and trimethoprim/sulfamethoxazole among patients with the genitourinary abnormality were more than those without such abnormalities. In another study conducted in Ontario, Ottawa, Allen et al. [31] reported that among patients with genitourinary tract abnormalities, the frequency of resistant *E. coli* isolates were almost four times more than those without such abnormalities. The result of this study shows that the previous history of antibiotic consumption appeared to be significantly influenced by *E. coli* resistance to amikacin, cefepime, ceftazidime, ceftriaxone, nalidixic acid and cotrimoxazole. In the management of patients with recurrent infections, vesicoureteral reflux, or other urological abnormalities, antibiotic prophylaxis is a central strategy for the prevention of UTI in children. In this context, Lutter and coworkers [32] reported that the resistance rate in *Enterococci*, *P. aeruginosa* and *Klebsiella oxytoca* isolates were increased to cefotaxime among children receiving prophylactic antibiotics. Also, Olesen et al. [26] reported that there is high association between the use of beta-lactams, cephalosporins and trimethoprim/sulfamethoxazole and quinolones with antibiotic resistance *E. coli* isolates. There are several limitations in this study, including insufficient data for uropathogens other than *E. coli*, in some cases, inconsistency the antimicrobial susceptibility testing with clinical and laboratory standards institute guidelines, poor laboratory facilities. Furthermore, potential bias is that all of the samples were taken from patients in a referral hospital.

5. Conclusion

During the period of study, we found that *E. coli* isolates were the most common etiological agents among other uropathogens. Also, the prevalence of UTI was affected by different factors including gender, age, history of antibiotic exposure, anatomical abnormalities. Furthermore, there was increasing resistance of *E. coli* isolates against some of the broad-spectrum antibiotics or first-line antibiotics between 2005 and 2010 years. Although the study found a highly significant association between risk factors UTI and antimicrobial resistance, it should be noted that many of complicated patients were referred from other hospital centers. Additionally, these patients were not the real representative of community-acquired UTIs, and more investigations should be performed for estimation of the resistance rate among common uropathogens. Therefore, we recommend that physicians should consider the increased resistance to ampicillin, oral cephalosporins and cotrimoxazole when they selected an antibiotic empirically for treatment of pediatric UTI. In this context, it's important that local continuous studies of antimicrobial susceptibility at national and international levels are performed for the prevention of antimicrobial resistance.

Author contributions

Study concept and design: Ali Reza Nateghian.
Data acquisition: Sina Karaji.
Data analysis: Sina Karaji, Khosrow Zamani.
Drafting of manuscript: Khosrow Zamani.
Critical revision of the manuscript: Ali Reza Nateghian.

Conflicts of interest

The authors declare no conflict of interest.

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