Infection and Drug Resistance

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ORIGINAL RESEARCH

Demographic features and antibiotic resistance among children hospitalized for urinary tract infection in northwest Iran

This article was published in the following Dove Press journal:
Infection and Drug Resistance
10 October 2011
Number of times this article has been viewed

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Introduction: Urinary tract infection (UTI) is the most common serious bacterial infection during infancy. The aim of the present study was to evaluate demographic characteristics, clinical presentations and findings, and antimicrobial resistance among infants and children hospitalized in Tabriz Children's Hospital, Tabriz, Iran.

Methods: In this descriptive observational study, 100 children who had been admitted with UTI diagnosis to Tabriz Children's Hospital from March 2003 to March 2008 were studied. Demographic characteristics, chief complaints, clinical presentations and findings, urine analysis and cultures, antimicrobial resistance, and sonographic and voiding cystourethrographic reports were evaluated.

Results: The mean age of patients was 35.77 ± 39.86 months. The male to female ratio was 0.26. The mean white blood cell count was 12,900 ± 5226/mm^3. Sixty-two percent of patients had leukocytosis. The most common isolated pathogen was *Escherichia coli* spp (77%) followed by *Klebsiella* spp (10%), *Enterobacter* spp (9%), and *Enterococcus* spp (4%). Isolated pathogens were highly resistant to ampicillin, cotrimoxazole, and cephalexin (71%–96%), intermediate sensitivity to third-generation cephalosporins, and highly sensitive to ciprofloxacin (84.4%), amikacin (83.8%), and nitrofurantoin (82.8%).

Conclusion: The most common pathogen of UTI in the hospitalized children was *E. coli* spp. The isolated pathogens were extremely resistant to ampicillin, and highly sensitive to ciprofloxacin and amikacin.

Keywords: urinary tract infection, antibiotic, resistance, sensitivity, *Escherichia coli*

Introduction

Urinary tract infection (UTI) is the most common serious bacterial infection during infancy,[1] and many children with UTI are admitted to hospital.[2] UTI has been considered an important risk factor for the development of progressive renal disease and long-term complications.[3]

UTI mostly occurs during the first year of life in boys, much more commonly in uncircumcised boys. The prevalence of UTI varies with the age. During the first year of life, the male to female ratio range is 2.8–5.4. Beyond 1–2 years, there is a striking female preponderance with a 1:10 male to female ratio.[4]

Escherichia coli spp corresponds with 75%–90% of all UTIs, followed by *Klebsiella* spp and *Proteus* spp species in females, but previous reports have showed that *Proteus* spp is as common as *E. coli* in UTIs of males aged >1 year. Others report a preponderance of Gram-positive organisms in UTIs of males. *Staphylococcus saprophyticus* and *Enterococcus* spp are UTI causative pathogens in both sexes.[4]

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Most of these children receive empirical antibiotic therapy before revealing the causative pathogen and antimicrobial sensitivity and resistance.[1] Recently, Farrell et al[5] demonstrated extremely high resistance to trimethoprim, ampicillin, and cephalosporins, rendering them unsuitable for empirical use. Increasing resistance of bacterial pathogens is of worldwide concern that is varied in different regions and even countries.[1,5] Such reports show that continued surveillance and investigation of other oral agents for treatment of UTI in the community is required.[4] A recent study by Mortazavi and Shahin[6] in the Azerbaijan region showed that the prevalence of bacterial cause of UTI and resistance to antibacterial regimes changed from 2000 to 2007. So, the present study aimed to evaluate demographic characteristics, clinical presentations and findings, and especially antimicrobial resistance among infants and children hospitalized due to UTI in northwest Iran's referral center, Tabriz Children's Hospital, Tabriz, Iran.

Materials and methods

Study design and population

The present descriptive observational study was carried out in the infectious disease ward of Tabriz Children's Hospital. From March 2003 to March 2008, 230 patients were hospitalized with a principal diagnosis of UTI. Hospital records for these children were studied and finally the complete data of 100 patients were collected. Age (months for patients aged <2 years and years for patients aged >2 years), gender, weight, history of previous hospitalization, chief complaint, clinical presentation, body temperature, duration of hospitalization, outcome, white blood cell (WBC) count, erythrocytes sedimentation rate (ESR), C-reactive protein (CRP), urine analysis and culture, empirically used antibiotics, antibiotic resistance and sensitivity, sonography, and voiding cystourethrography were extracted.

All participants signed informed written consent and the study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences, which was in compliance with the Helsinki declaration.

Sample collection and tests performed

The inclusion criteria were diagnosis of UTI and availability of complete documentation. Change in diagnosis, presence of genitourinary abnormalities (except vesicoureteral reflux [VUR]), and loss of any study variables were considered criteria for exclusion.

Urine samples were collected by suprapubic aspiration in neonates, urine bag (using sterile method) in infants aged 1 month to 2.5 years, and midstream urine in children aged >2.5 years. Diagnosis of UTI was defined as any colony-forming units/mL of a single organism on a suprapubic aspiration method, or $\geq 10^5$ colony-forming units/mL on a clean-catch specimen of freshly voided urine using urine bag and midstream methods. Urine culture, antimicrobial susceptibility tests, and interpretation were done using Clinical and Laboratory Standards Institute guidelines.[7] These samples were processed on blood agar and MacConkey agar medium (HiMedia Laboratories Pvt Ltd, Mumbai, India) with a standard loop and then were incubated at 37°C overnight. Antimicrobial susceptibility and resistance testing was performed by the disk diffusion method on cultures using antibiotic disks (PADTAN TEB antimicrobial susceptibility test disks; Padtan-Teb Co, Tehran, Iran). All laboratory tests were done in the laboratory of Tabriz Children's Hospital.

Leukocytosis was defined according to the age of patients.[8] Presence of more than five WBCs in one light microscopic field was considered as active urine analysis.[9] CRP was determined using an ENISON CRP latex commercial kit (Enison Lab and Pharmaceutical Industries, Tehran, Iran). Cutoff values for CRP were +1 for 10–25 mg/L, +2 for 25–50 mg/L, and +3 for >50 mg/L.

Statistical analysis

Statistical analysis was performed using the SPSS (v 13.0; SPSS Inc, Chicago, IL) software package. Quantitative data are presented as mean ± standard deviation, while qualitative data are demonstrated as frequency and percent. The statistical tests for comparison were chi-square test, independent sample *t*-test, and one-way analysis of variance test. A *P*-value of less than 0.05 was considered statistically significant.

Results

Data from 100 patients were completely extracted and analyzed. The mean age of infants (<2 years) was 9.39 ± 5.89 months, and the mean age of children (≥2 years) was 6.30 ± 3.01 years. Twenty-one patients were male (21%) and 79 were female (79%). Male to female ratio in all patients, in patients aged <1 year, aged between 1 and 2 years, and >2 years were 21:79, 12:32, 4:12, and 5:35, respectively. Thirty-eight patients had positive history of hospitalization; 24 were hospitalized for the first time (24%), four for the second time (4%), three for the third time (3%), five for the fourth time (5%), and two for the fifth time (2%).

The mean body weight of studied patients was 11.79 ± 7.53 kg (range 2.10–41.00 kg). Duration of hospitalization was 7.89 ± 4.36 days (range 2–23 days). The frequency of chief complaints is listed in Table 1.

Table 1 Frequency of chief complaint at time of referring to hospital

Symptoms	Percent
Fever	36
Dysuria	30
Crying at time of urination	14
Failure to thrive	12
Diarrhea	9
Anorexia	7
Flank pain	7
Frequency	6
Vomiting	3
Hematuria	3
Malodorous urine	3
Poor feeding	3
Abdominal pain	3

The mean body temperature at time of admission was 37.84°C ± 0.97°C (range 36°C–41.5°C). Forty-two percent of patients had fever. Mean body temperature for patients with and without fever was 38.94°C ± 0.60°C and 37.27°C ± 0.55°C, respectively ($P = 0.002$).

The mean WBC count was 12,900 ± 5226/mm^3 (range 4300–28,500/mm^3). Sixty-two percent of patients had leukocytosis. CRP was negative in 55 patients (55%); +1 in 17 patients (17%), +2 in 21 patients (21%), +3 in six patients (6%), and +4 in one patient (1%). The mean first-hour ESR level was 38.74 ± 30.82 mm/hour (range 2–120 mm/hour).

Ninety-two patients (92%) had active urine analysis (more than five WBC per field). More than five red blood cells per field were reported for 15 patients (15%). The most common isolated pathogen was *E. coli* (77%), followed by *Klebsiella* spp (10%), *Enterobacter* spp (9%), and *Enterococcus* spp (4%).

Antibiotic resistances are shown in Table 2. Sonographic findings were normal in 66 patients (66%). Abnormal findings were unilateral in 25 patients and bilateral in five patients. Increased thickness of bladder wall and ascites were reported in two patients each. Sonographic findings are shown in Table 3.

Forty-two patients underwent cystourethrography during hospitalization (42%). Thirteen patients were advised to complete it as outpatients (13%), but 45 did not undergo cystourethrography (45%). Of 42 patients, 18 had normal findings (43%). Fourteen patients had VUR (14%) and nine patients had bilateral VUR (9%). Neurogenic bladder was reported in one patient (1%). Cystourethrographic findings are listed in Table 4.

Table 5 shows the comparison of demographic, clinical, and laboratory findings according to cause of UTI. As demonstrated, there was no significant difference between causes of UTI in the case of male to female ratio, infant to child ratio, age, weight, body temperature, fever, WBC, leukocytosis, first-hour ESR, and duration of hospitalization.

Discussion

UTI is recognized increasingly as a common cause of fever in young children.[10–12] However, clinical findings indicating UTI in this group of patients are often subtle and nonspecific, with fever often being the only finding.[13] During the present study, fever was recognized as the most common unspecific symptom of UTI.

Clinical UTI is characterized by any or all of the following: abdominal or flank pain, fever, malaise, nausea, vomiting, and, occasionally, diarrhea. Newborns may show nonspecific symptoms such as poor feeding, irritability, and weight loss.[4]

Table 2 Antibiotic resistance of isolated pathogens

Antibiotic	Resistance (%)			
	Escherichia coli	*Klebsiella* spp	*Enterobacter* spp	*Enterococcus* spp
Ampicillin	94.7	100	100	100
Cotrimoxazole	71.1	90	66.7	75
Cephalexin	68.4	80	77.8	–
Gentamicin	36.1	60	37.5	100
Nalidixic acid	33.3	40	22.2	75
Ceftazidime	27.6	75	0	–
Ceftizoxime	26.3	60	22.2	–
Ceftriaxone	22.4	60	33.3	–
Cefotaxime	22.7	50	22.2	–
Cefixime	22.4	50	22.2	–
Vancomycin	–	–	–	0
Nitrofurantoin	14.5	40	11.1	25
Amikacin	11.8	10	22.2	–
Ciprofloxacin	14.5	10	0	75

Table 3 Frequency of sonographic findings

	Right kidney N (%)	Left kidney N (%)	*P**
Hydronephrosis	12 (12)	13 (13)	NS
Atrophy and hydronephrosis	1 (1)	1 (1)	NS
Hypoplasia	1 (1)	2 (2)	NS
Renal stones	3 (3)	3 (3)	NS
Ureteral occlusion	0 (0)	1 (1)	NS

Note: *Chi-square test was used.
Abbreviation: NS, not significant.

In the present study, UTI clinically presented most commonly with fever followed by dysuria, crying at time of urination, failure to thrive, diarrhea, anorexia, flank pain, and frequency. Abdominal or flank pain and nausea/vomiting were not as frequent as reported before.[4] Also, dysuria and diarrhea were among the common clinical presentations of UTI in this study.

Demographic findings were consistent with previous studies.[2–4,13–15] The proportion of UTI in females was higher than in males after the first year of life. The male to female ratio during the first year of life has previously been reported as 2.8–5.4:1, while the results of the present study had a lower ratio. Striking female preponderance with a male to female ratio of 1:10 has been reported in patients with UTI aged beyond 1–2 years.[4] Such findings have been reported in the present study.

VUR caused by retrograde urine flow from the bladder to the kidneys can culminate in recurrent UTI, severe renal complications, and end stage renal failure.[15–18] As kidney damage resulting from severe VUR is preventable, early detection, follow-up, and proper management of underlying lower urinary tract abnormalities are desirable.[19,20] In the present study, VUR has been revealed in 31 kidney-ureter units as the risk factor of UTI (31%).

In the present study, *E. coli* was isolated from 77% of patients as the common pathogen of UTI, similar to Mathai et al's[21] study findings. The emergence of resistant bacteria is a significant problem in UTI chemotherapy. In Japan, isolation of fluoroquinolone-resistant *E. coli* from patients with UTI is reported as a serious therapeutic problem.[22] In the present study, *E. coli* showed 88.3%, 67.5%, and 57.1% resistance to ampicillin, cotrimoxazole, and cephalexin, respectively. In most studies in Canada, Europe, Africa, Turkey, Spain, Taiwan, and Israel, the majority of isolated pathogens were resistant to ampicillin and cotrimoxazole.[23–25] The present study results showed that the best activity against *E. coli* was achieved with amikacin, nitrofurantoin, and ciprofloxacin, followed by third-generation cephalosporins. These results are consistent with Yuksel et al[23] and Turnidge et al.[25]

Table 4 Frequency of cystourethrographic findings

		Right kidney N (%)	Left kidney N (%)	*P**
Reflux	Grade I	2 (2)	3 (3)	NS
	Grade II	2 (2)	2 (2)	NS
	Grade III	8 (8)	7 (7)	NS
	Grade IV	3 (3)	2 (2)	NS
	Grade V	2 (2)	0 (0)	NS

Note: *Chi-square test was used.
Abbreviation: NS, not significant.

Klebsiella spp had a varying antibiotic resistance and showed higher resistance to ampicillin (100%), cotrimoxazole (90%), and cephalexin (80%). Also, *Klebsiella* spp had intermediate resistance against ceftriaxone (60%), cefotaxime (50%), and cefixime (50%), and showed lowest resistance to amikacin (10%) and ciprofloxacin (10%). Yuksel et al[24] reported a low rate of resistance of *Klebsiella* spp against amikacin (50%) and ciprofloxacin (50%), and a higher level of resistance against ampicillin (82%). Sensitivity of *Klebsiella* spp to cotrimoxazole in the present study was 10%, while other studies reported 65%–75% sensitivity to this antibiotic[22,24] due to uncontrolled administration of the drug.

Enterobacter spp has the lowest prevalence as a UTI pathogen.[23] In the present study, the prevalence of this Gram-negative bacteria is reported at about 9%, with excessive resistance to ampicillin (100%), higher resistance to first-generation cephalosporins (cephalexin), and mild resistance to third-generation cephalosporins, consistent with Tunidge et al's[25] and Catal et al's[26] results. Resistance by the extended spectrum betalactamase (ESBL) mechanism is an important emerging problem in *Enterobacter* spp.[27,28] ESBLs are betalactamase that hydrolyze penicillin and extended spectrum cephalosporins with an oxyimino side chain that includes ceftazidime, ceftriaxone, cefotaxime, and aztreonam. Antibiotic utilization patterns, including widespread cephalosporin use, have been associated with the emergence of ESBLs and a decrease of administration of these antibiotics has been associated with control of ESBL emergence.[29,30] The antibiotic resistance rate of *Enterobacter* spp to ciprofloxacin is low in children, due to the rarity of its administration. In contrast to Caksen et al's[31] findings, unfortunately, 100% of isolated *Enterobacter* spp were resistant to ciprofloxacin in the present study.

In this study, 4% of UTI pathogens were *Enterococcus* spp; its prevalence was similar to Muratani and Matsumoto's [22] report. Findings in this study showed that isolated *Enterococcus* spp

Table 5 Comparison of demographic, clinical, and laboratory findings according to cause of UTI

	Escherichia coli (N = 77)	*Klebsiella* (N = 10)	*Enterobacter* (N = 9)	*Enterococcus* (N = 4)	*P*
Male to female ratio	14:63	3:7	3:6	1:3	0.632*
Infant to child ratio	42:35	9:1	5:4	4:0	0.059*
Infant age (months)	9.98 ± 6.06	7.16 ± 5.50	7.70 ± 4.99	10.25 ± 6.34	0.540§
Child age (years)	6.54 ± 3.09	4 (1 case)	4.75 ± 2.06	–	0.405§
Weight (kg)	12.67 ± 7.89	6.33 ± 2.97	11.82 ± 7.03	8.57 ± 2.23	0.069§
Body temperature (°C)	37.77 ± 0.92	37.67 ± 0.76	38.61 ± 1.45	37.87 ± 0.62	0.099§
Fever (N)	24	3	6	1	0.189*
WBCs (/mm^3)	13,250 ± 5702	11,960 ± 2825	11,944 ± 3437	10,675 ± 2601	0.644§
Leukocytosis (N)	49	5	6	2	0.795*
First-hour ESR (mm/hour)	41.03 ± 30.71	22.30 ± 19.81	45.44 ± 39.83	20.75 ± 20.83	0.167§
Duration of hospitalization (days)	7.71 ± 4.60	8.50 ± 3.65	8.87 ± 3.11	7.75 ± 4.50	0.877§

Notes: *Chi-square test; §one-way analysis of varience test.
Abbreviations: UTI, urinary tract infection; WBCs, white blood cells; ESR, erythrocytes sedimentation rate.

were extremely (100%) resistant to ampicillin and gentamicin. Such high resistance to these antibiotics has been reported previously by other authors.[31] Sensitivity of *Enterococcus* spp to vancomycin and nitrofurantoin was 100% and 75%, respectively, which was consistent with Mathai et al's[21] and Turnidge et al's[25] findings.

Comparing the present study with a recent study by Mortazavi and Shahin[6] in East Azerbaijan, demographic characteristics and prevalence of bacterial causes of UTI did not change. Comparing the antibacterial resistance of *E. coli* to Mortazavi and Shahin's study, resistance to ampicillin increased and resistance to gentamicin, nalidixic acid, ceftazidime, and cefixime decreased but remained unchanged against other antibiotics. Also, *Klebsiella* spp showed increased antibacterial resistance against nalidixic acid, cefixime, and cotrimoxazole, and decreased resistance to amikacin and nitrofurantoin.

Finally, the present study was a small, regional retrospective study and results show that there is a need for large longitudinal national studies to determine prevalence, demographic characteristics, possible etiology, and antibiotic resistance. The present study has also evaluated the pattern of antibiotic resistance among hospitalized children with diagnosis of UTI, which provides important information concerning this region.

Conclusion

E. coli is the most common isolated bacterium in hospitalized children with a principal diagnosis of UTI. Most of the isolated pathogens are highly resistant to ampicillin, cotrimoxazole, and cephalexin (71%–96%), have intermediate sensitivity to third-generation cephalosporins, and high sensitivity to ciprofloxacin (84.4%), amikacin (83.8%), and nitrofurantoin (82.8%).

Acknowledgment

The authors wish to express their gratitude to the patients and their parents participating in this report.

Disclosure

Written informed consent was obtained for publication from the patients' parents. The authors report no conflicts of interest in this work.

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