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Original Article

Evaluation of urinalysis and urine culture in children with first-time urinary tract infection

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ABSTRACT

Objective: This study aimed to review results of urinalysis with flow cytometry technique at the time of diagnosis of urinary tact infection (UTI), and to determine uropathogenes with their antibiotic resistance patterns in children with first-time UTI.

Material and methods: This single-centered, retrospective, cross-sectional study was conducted from January 2015 to December 2017. The study included 361 children with a first-time UTI diagnosis. Age, gender, results of automated urinalysis, urine culture results were recorded.

Results: Mean ages of children were 55.8±50.7 months. *E. coli* was the most common isolated microorganism followed by *K. pneumoniae, Proteus, Enterococcus*, and *P. aeroginosa*. Median count of pyuria was 44 leukocyte/mm^3 (range:0-2954/mm^3). Median count of pyuria in female and male patients were 53 and 22 leukocyte/mm^3, respectively (p=0047). A total of 98 patients (27.1%) had no pyuria. Proportion of pyuria in female and male patients were 81.2% and 76%, respectively (p>0.05). Mean age of patients with and without pyuria were 59±52 months and 46±44months, respectively (p<0.05). According to uropathogen, there was pyuria at the ratio of 60% in *Pseudomonas*, 62.5% in *Enterococcus* spp, 66.7% in *Proteus*, 78.3% in *Klebsiella*, and 82.7% in *E. coli*. Children with UTI induced by *E. coli* had resistance ratios of 30.5% and 22.4% to cefixime and ceftiaxone, respectively. Children with UTI by *Klebsiella* spp had resistance ratios of 47.8% and 39.1% to cefixime and ceftriaxone, respectively.

Conclusion: *E. coli* was the most common uropathogen in children with first-time UTI. Pyuria may be lacking according to age, gender, and type of uropathogene. Pyuria level was higher in females. In addition, ceftriaxone and cefixime resistance is increasing making ampirical treatment choices limited.

Keywords: Antibiotic resistance; cefixime; ceftriaxone; flow cytometry; pyuria; urinary tract infection.

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Introduction

Urinary tract infections(UTI) are the second most common infections after upper respiratory tract infections in children. Upper UTI may lead to acute problems like urosepsis and chronic medical problems like renal scarring, hypertension, and chronic renal failure. Therefore, it is important to diagnose and start treatment of UTI as early as possible.[1] It is known that delay in treatment and recurrent pyelonephritis increase the risk of renal scarring.[2-4]

Urine culture is the gold standard for diagnosis of UTI; however, it is time-consuming. Urine flow cytometric analysis is a technique used for urinalysis. It is reported as reliable screening method to exclude UTI.[5] However, the results of this technique are often confusing. UTI diagnosis requires both urinalysis demonstrating pyuria and urine culture with presence of >50000 CFU/mL of a single uropathogen.[1]

The majority of UTIs are caused by gram negative microorganisms, the most common of which is *Escherichia coli (E. coli)*, followed by *Klebsiella* spp, *Enterobacter* spp, and *Proteus* spp. Less commonly *Pseudomonas aeroginosa (P. aeroginosa)* may cause UTIs. Potential gram positive uropathogenes in children include *Enterococcus spp* and *Staphylococcus saprophyticus* (in adolescents). Increase of multidrug-resistant organisms is also a global health problem.[6]

Therefore, in this study, we aim to review results of urinalysis with flowcytometry technique at diagnosis of UTI, and to determine uropathogenes with their antibiotic resistance patterns in children with diagnosis of first-time UTI.

Material and methods

This single-centered, retrospective, cross-sectional study was conducted from January 2015 to December 2017. The study population included children from the age of 0 to 18 years with first-time UTI diagnosis. UTI was defined with suggestive symptoms of UTI and results of urinalysis and urine culture. Automated urinalysis was done with flow cytometry. Results of urinalysis were recorded for nitrite positivity, leukocyte esterase positivity, and pyuria. Pyuria was defined as >10 leukocyte/mL at flow cytometric analysis of urine. Urine culture with growth of a single colony/organism of at least 50000 CFU/mL was defined as UTI. The clean catch midstream urine samples were collected in sterile container. In infants and non-toilet trained children, urinary catheters were used to obtain urine samples. Exclusion criterias were chronic renal failure, known urinary tract pathology, urolithiasis, neurogenic bladder, recurrent urinary tract infection, patients having antibiotic treatment, and urine culture results with contamination. Age, complaints at admission, route of urine sampling, results of urinalysis, and results of urine culture were recorded.

All urine samples were studied with urine flow cytometry method at Sysmex UF-1000i (Sysmex Corporation, Kobe, Japan). Urine cultures were studied with bloody agar and eosin methylene blue medium. The local ethics committee of Ankara Training and Research Hospital approved the study (27 June 2018-Decision No: 512).

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) for Windows version 15.0. Numerical variables are shown as mean ± standard deviation and median. Chi-square test was used for intergroup analysis of categorical variables between groups. Student's t test was used to compare numerical variables between groups. A p value less than 0.05 was considered as statistically significant result.

Main Points:

- *E.coli* was the most common isolated microorganism followed by *K.pneumoniae, Proteus, Enterococcus*, and *P. aeroginosa*.
- Pyuria level was higher in females.
- There was pyuria at the ratio of 60% in *Pseudomonas*, 62.5% in *Enterococcus* spp, 66.7% in *Proteus*, 78.3% in *Klebsiella*, and 82.7 % in *E. coli*.
- Ceftriaxone and cefixime resistance is increasing making empirical treatment choices limited.

Results

Our study group contained a total of 361 patients with mean age of 55.8±50.7 months. Age and gender distribution of patients are given in Table 1. Of the 361 patients, 281 (77.8%) were female and 80 (22%) were male. Median age of male patients was 5 months (range:1-201 months) and that of female patients was 56 months (range: 1-206 months) (p<0.01).

Urine culture results

E. coli (n=308, 85.3%) was the most common isolated microorganism followed by *K. pneumoniae* (n=23, 6.3%), *Proteus* (n=9, 2.4%), *Enterococcus* (n=8, 2.2%), and *P. aeroginosa* (n=5, 1.3%) among others (n= 8, 2.2%).

In females, *E. coli* (n=256, 91%) was the most prominent uropathogene followed by *K. pneumoniae* (n=15, 5%), *Proteus* (n=2, 0.7%), *Enterococcus*(n=4, 1.4%), and others (n=4, 1.4%). Similarly, in males, *E. coli* (52/80, 65%) was the most prominent uropathogene followed by *K. pneumonia* (n=23, 28 %), *Proteus* (n=7, 8.7%), *Enterococcus* (n=4, 5%), *P. aeroginosa* (n=7, 8.7%), and others (n=4, 5%). Table 2 shows microorganisms according to age and gender.

Leukocyte esterase test positivity

A total of 278 patients (77%) had leukocyte esterase positivity. Proportion of leukocyte esterase positivity was higher in females as compared to males (81% and 62%, p<0.001 for females and males, respectively). Median age of male patients with leukocyte esterase positivity was lower than that of female patients (median age of 4 months, range:1-201 months and median age of 55 months, range: 1-206 months, p<0.001 for males and females, respectively).

Nitrite positivity

A total of 158 patients (43.7%) had nitrite positivity. Median age of patients with nitrite positivity (n=158) was higher than that of

Table 1. Age and gender distribution of patients

Age groups (months)	n (%)	Male/Female
0-3	46 (12.7)	30/16
3-12	63 (17.5)	30/33
13-24	21 (5.8)	2/19
25-48	57 (15.8)	6/51
≥49	174 (48.2)	12/162
Total	361 (100)	80 (22%)/281 (78%)

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Table 2. Microorganisms according to gender and age of patients

Gender	Microorganism	0-3 months	3-12 months	13-24 months	25-48 months	>49 months
Female	*E. coli*	14	27	18	47	150
	K. pneumonia	2	3	0	4	6
	P. mirabilis	0	1	0	0	1
	Enterococcus	0	0	1	0	3
	Others	0	2	0	0	2
Male	*E. coli*	21	19	1	2	9
	K. pneumonia	6	2	0	0	0
	P. mirabilis	0	3	1	2	1
	Enterococcus	1	2	0	0	1
	P. aeroginosa	0	4	0	0	1
	Others	2	0	0	2	0

Table 3. Urinalysis findings according to uropathogenes

Urinalysis	*E. coli* n=308	*K. pneumonia* n=23	*Proteus* n=9	*Enterococcus* n=8	*P. aeroginosa* n=5	Others (n=7)
Leukocyte esterase positivity	79.5% (n=245)	73.9% (n=17)	44.4% (n=4)	50% (n=4)	20% (n=1)	100% (n=7)
Nitrite positivity	47.4% (n=146)	34.8% (n=8)	11.1% (n=1)	0	40% (n=2)	14.2% (n=1)
Pyuria	82.7% (n=254)	78.3% (n=18)	66.7% (n=6)	63.5% (n=5)	60% (n=3)	71.4% (n=5)

Table 4. Antibiotic resistance patterns of isolated microorganisms

Antibiotic	*E. coli* n (%) Total: 308	*Klebsiella* n (%) Total: 23	*Proteus* n (%) Total: 9
Ampicilline	160 (51.9)	19 (82.6)	4 (44.4)
Amoksisiline-clavulonate	67 (21.7)	9 (39.1)	1 (11.1)
Amikacine	0	1 (4.3)	1 (11.1)
Cefixime	94 (30.5)	11 (47.8)	1 (11.1)
Ceftriaxone	69 (22.4)	9 (39.1)	1 (11.1)
Cefuroxime	28 (9)	6 (26)	0 (0)
Cefotaxime	3 (0.9)	1 (4.3)	0 (0)
Cefepime	30 (9.7)	5 (21.7)	1 (11.1)
Cephtazidime	55 (22.8)	8 (34.7)	1 (11.1)
Ciprofloxacine	30 (9.7)	4 (17.3)	2 (22.2)
Meropenem	2 (0.6)	0 (0)	0 (0)
Phosphomycine	5 (1.6)	1 (4.3)	1 (11.1)
Gentamicine	37 (12)	2 (8.6)	3 (33.3)
Nitrofurantoine	8 (2.5)	1 (4.3)	4 (44.4)
Piperacilline-tazobactam	36 (11.6)	7 (30.4)	1 (11.1)
Trimethoprim-sulfamethoxazole	89 (28.8)	4 (17.3)	5 (55.5)

patients with negative nitrite test results (n=203) (median age of 60 months, range: 1-204 months and 32 months, range: 1-206 months, p=0.021 for patients with and without nitrite positivity, respectively).

Proportion of nitrite positivity was higher in females than males (48.7% and 26%, p<0.001, respectively). Median age of male patients with nitrite positivity was lower than that of female patients (median age of 7.5 months, range: 1-160 months and 71 months, range: 1-208 months, p<0.001, respectively). According to uropathogenes there was no nitrite positivity in UTI caused by *Enterococus* spp. Proportion of nitrite positivity according to uropathogenes were (146/308) 47.4% for *E. coli*, (8/23), 34.7% for *Klebsiella*, (1/9) 11% for *Proteus,* and (1/8) 12.5% for others.

Pyuria

Median count of pyuria was 44 leukocyte/mm^3 (range:0-2954/mm^3). Median count of pyuria in female patients was 53 leukocyte/mm^3 (range: 0-2954/mm^3) and for male patients it was 22 leukocyte/mm^3 (range: 0-629/mm^3) (p=0047).

A total of 98 patients (27.1%) had no pyuria. Proportion of pyuria in female and male patients were 81.2% and 76% (p>0.05), respectively.

According to urine sampling, 305 were by midstream urine and 56 were by bladder catheterization. There was no pyuria in 29.5% of urine samples by midstream urine and 14.2% of urine samples by bladder catheterization. There was no pyuria in patients with fever and without fever at the ratio of 15.8% and 32.7%, respectively. Mean age of patients with and without pyuria was 59±52 and 46±44months ($p<0.05$), respectively.

According to uropathogen, there was pyuria at the ratio of 60% in *Pseudomonas,* 62.5% *in Enterococcus* spp*,* 66.7% *in Proteus*, 78.3% in *Klebsiella*, and 82.7 % in *E. coli*. Urinalysis results of patients according to uropathogenes are shown in Table 3.

Antimicrobial resistance patterns

Antimicrobial resistance results are shown in Table 4. Children with UTI caused by *E.coli* had resistance ratios of 30.5% and 22.4% to cefixime and ceftiaxone, respectively. Children with UTI caused by *Klebsiella* spp had resistance ratios of 47.8% and 39.1% to cefixime and ceftriaxone, respectively, and no resistance to meropenem. Children with UTI caused by *Proteus* had resistance ratios of 44.4% and 55.5% to ampicilline and TMP-SMc, respectively, and no cefuroxime resistance was observed. Children with UTI caused by *E. coli* and *Klebsiella* had resistance ratios to nitrofurantoin: 2.5% and 4.3% respectively. There was no resistance to nitrofurantoin in children with UTI caused by *Enterococcus*.

Discussion

In this study, we reviewed results of urinalysis and urine culture of children with first-time UTI. We aimed to evaluate the success of urinalysis to determine UTI, characteristics, and antimicrobial resistance patterns of uropathogenes in children with first-time UTI. As reported in the literature, there was female predominance in the number of UTI patients at all ages. However, during infancy period, male dominance was observed in our study. *E. coli* was the most common isolated microorganism followed by *K. pneumoniae*, *Proteus*, *Enterococcus*, and *P. aeroginosa*. A total of 77% and 43.7% of patients showed leukocyte esterase and nitrite test positivity, respectively. Proportion of leukocyte esterase and nitrite test positivity were higher in females than in males. Pyuria level was also higher in females as compared to males. A total of 27.1% of patients had no pyuria. Proportion of pyuria level changed according to pathogen microorganism. Mostly *E. coli* isolytes had pyuria at urinalysis. The rate of resistance to cefixime and ceftriaxone in urine with *E. coli* isolytes was increasing.

It is known that UTI frequency is higher in males during the infancy period, but it increases in females after 2 months of birth.[7] The cause of female predominance in UTI later infancy period can be attributed to the short urethra of female and the close relation of urethra and anus.[8] The male predominance during infancy period can be explained by high bacterial colonisation at prepicium and the spread of bacteria to urethra. Circumcision decreases bacterial contamination of prepicium and decreases the amount bacterial spread to urinary bladder.[9] There was female predominance in UTI at all ages but during infancy period there was male predominance in our study.

In urine strip test results, leukocyte esterase positivity and nitrite positivity were used to suggest UTI according to APA guidelines.[10] Especially if positivity of both nitrite and leukocyte esterase test are highly specific for diagnosis UTI. A total of 77% and 43.7% of patients had leukocyte esterase and nitrit test positivity, respectively. Mostly *E. coli* and *Klebsiella* isolytes had highest ratio for positivity of nitrite and leukocyte estaerase tests. As nitrite test positivity is not specific for infants who empty bladder more frequently, the lower ratio of nitrite test positivity may be due to age of our patients. Proportion of leukocyte esterase and nitrite test positivity was higher in females than in males. This difference can be attributed to the age of the patients as the median age of male patients was lower in our study.

According to APA Guidelines of 2011, the presence of pyuria and growth of a single uropathogen ≥50.000 CFU/mL are diagnostic criterias of UTI. According to these guidelines, lack of pyuria can not exclude UTI in patients who having suggestive clinical findings.[10] It was reported that in patients who presented shorter duration of fever, pyuria may be lacking due to absence of urinary inflammation.[11] There was no pyuria in 27.1% of patients in our study. In another study, 13% of patients (150/1031) were lacking pyuria and demographic characteristics were similar in children with and without pyuria.[12] Although median pyuria level was higher in females as compared to males, proportion of pyuria according to gender was statistically insignificant in our study as in existing literature. Median age of male patients was lower than that of female patients. The higher pyuria level in female gender may be due to higher age of female patients.

According to the existing literature, the proportion of pyuria varies significantly according to the uropathogen. Compared with *E. coli*, pyuria were 3 to 5 times lower with certain organisms (*Enterococcus* and *Klebsiella* species and *P. aeruginosa*). In literature, pyuria is defined at the ratio of 89.3% in *E. coli*, 54.3% in *Enteroccocus* spp, 73.9% in *Klebsiella* spp, and 61.55% in *P. aeroginosa* in symptomatic patients.[12] In our study, there was pyuria at the ratio of 60% in *Pseudomonas, 62.5% in Enterococcusspp,* 66.7% in *Proteus*, 78.3% in *Klebsiella*, and 82.7% in *E. coli*. Our results were in agreement with existing literature. Lower ratio of pyuria in urine with isolates of *Pseudomonas* and *Enterococcus* spp. was significant. In addition, host defence mechanisms and immunoresponce of host to different uropathogenes may cause difference in the levels of pyuria.

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Uropathogenes are gram negative enteric bacterias, and the most common of them is is *E. coli*.[13,14] The frequency of *E. coli* in UTI was reported as 45.7-85% in Turkey.[12] In other reports the frequency of microorganisms in urine culture was reported as 6-13.3% for *Proteus spp*, 6.2% for coagulase negative *Staphylococcus*, 4.7-5.8% for *Enterococcus spp*, 4.5-17.3% for *Klebsiella spp*, 1.5-3% for *P. aeruginosa*, and 6.9-26% *Enterobacter*.[15,16] In another multi-center study, the reported frequency of *E. coli* was 80%, and the others were as follows: 12.7% for *Enterobacter*, and 6.3% for *S. saphrophyticus*.[17] In our study, we found that *E. coli* was the most common uropathogene followed by *K. pneumoniae*, *Proteus*, *Enterococcus,* and *Pseudomonas,* respectively. In some other reports, in males older than one year of age, the major pathogen was reported to be *Proteus spp*[2,18], but in our study the major pathogen in both gender and at all ages was *E. coli*.

Empirical treatment strategies for UTI are used due to local resistance patterns. Ampicilline is not a good choice for empirical treatment due to high resistance patterns in our study, as reported in the literatüre.[19,20] There was low AMC resistance ratio for *Proteus* (11.15%) and moderate resistance ratio for *E. coli* (21.7%) and *Klebsiella* (39.1%). In literature, aminoglicoside resistance patterns show the efficacy of this group in treatment of UTI. There was no resistance or low ratio of resistance patterns for aminoglycoside.[7,16,21-25] In our study, there was low gentamicine resistance ratios for *E. coli* (12%) and *Klebsiella* (8.6%); there was moderate gentamicine resistance ratios for *Proteus* (33.3%); there was no gentamicine resistance for *Pseudomonas,* no amikacin resistance for *E. coli*; there was low amikacin resistance for *Klebsiella* (4.3%) and for *Proteus* (11.1%). Third generation cephalosporins are generally used for treatment of most infections. There are many reports reporting high resistance patterns of microorganisms to cephalosporines in UTI. In our study, there was moderate ceftriaxone resistance for *E. coli* (22.4%). In the year 2006, ceftriaxone resistance was 7.5% for *E. coli* and 33% for *Klebsiella*.[7] In hospitalized children, ceftriaxone resistance was as high as 48%, and in outpatient children, ceftriaxone resistance was 16.4%.[26] Kaya et al.[26] reported that the increase in the resistance to ceftriaxone for *E.coli* in the years of 2000, 2001, 2002, and 2003 were 0.9%, 7.5%, 12.9%, and 24.7 %, respectively. In our study, there was moderate cefixime resistance for *E. coli* (30.5%) and *Klebsiella* (47.8%), and low cefixime resistance for *Proteus* (11.1%). Cefixime resistance for *Pseudomonas* was 100%. In our study, there was moderate cefuroxime axetil resitance ratio for *E. coli* (35.3%) and *Klebsiella* (26%). Cefuroxime sensitivity was 100% for *Pseudomonas*. Yolbaş et al.[24] reported cefotaxime resistance for *E. coli* to be 51%. In our study, there was low cefotaxim resistance for *E. coli* (0.9%) and *Klebsiella* (4.3%). Carbapenems is another group of antibiotics used in treatment of UTI. In our study, there was low meropenem resistance for *E. coli* (0.6%) and no meropenem resitance for *Klebsiella* and *Proteus*. Our results are in agreement with literature.[26] There was moderate TMP-SMX resistance ratio for *E. coli* (28%) and *Klebsiella* (17.3%), and high resistance ratio for *Proteus* (55.5%). In literature, TMP-SMX resitance ratios were reported upto 35%.[19] There was low nitrofurantoin resistance for *E. coli* (2.5%) and *Klebsiella* (4.3%). In literature, nitrofurantoin resistance was reported to be lower than 2%.[27]. According to our results, nitrofurantoin was a good choice for treatment of UTI. However, owing to the insufficient concentration of nitrofurantoin in renal paranchyma, it is not advised to use nitrofurantoin for treatment of upper UTI.

In conclusion, there was female predominance in UTI at all ages. However, during infancy, there was male predominance in our study. *E. coli* was the most common isolated microorganism in children with first-time UTI, followed by *K. pneumoniae*, *Proteus*, *Enterococcus*, and *P. aeroginosa*. A total of 77% and 43.7% of patients had leukocyte esterase and nitrite test positivity, respectively. Proportion of leukocyte esterase and nitrite test positivity was higher in females as compared to males. Pyuria levels were higher in females than males. A total of 27.1% of patients had no pyuria. Proportion of pyuria levels changed according to pathogen microorganism. Mostly *E. coli* isolytes had pyuria at urinalysis. There was moderate resistance to cefixime and ceftriaxone in urine with *E. coli* isolytes. Ceftriaxone and cefixime resistance is increasing limiting the choices of empirical treatment. For hospitalized children, Cefotaxime is a good alternative to ceftriaxone. Carbapenem group is a choice only for resistant cases.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara Training and Research Hospital (27 June 2018-Decision No: 512).

Informed Consent: Data extraction from database did not require consent from patients because no data were patient related information.

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