

Research Article

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## Causes of Recurrent Urinary Tract Infection in Children on Prophylaxis

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**Introduction:** Urinary tract infection (UTI) is a common pediatric problem. It has been estimated that 8% of girls and 2% of boys suffer from UTI during childhood. So, prevention of scar formation in high risk children is very important. This study was performed to evaluate the causes of recurrent urinary tract infection in children on prophylaxis.

**Materials & Methods:** This study was performed on 141 cases in 126 children with recurrent UTI. A questionnaire was prepared and data including sex, age, grade of vesicoureteral reflux, and antibiotic used for prophylaxis were collected.

**Results:** The mean age of the patients was 46.6±41.1 months; 24 % of the participants were male and 76% were female. The most common predisposing factor of recurrent UTI was vesicoureteral reflux. E.coli was the microorganism responsible for most of the cases (85.5%). In 85.5% of the children, Co-trimoxazole was used as prophylaxis. Drug resistance was the most common reason of recurrence.

**Conclusions:** We conclude that girls are at higher risk of recurrent infection and regarding the high prevalence of Co-trimoxazole resistance, administration of this drug should be limited and with caution.

**Keywords:** Urinary tract infections; Vesico-Ureteral Reflux; Drug resistance; Child

**Running Title:** Causes of Recurrent Urinary Tract Infection

### Introduction

Urinary tract is sterile and without any microorganisms. Therefore, any invasion of microorganisms is called urinary tract infection (UTI) [1]. UTI is more important in children than adults for the higher risk of complications in children. UTI is one of the most common bacterial

infections in children and is the most common reason for referring patients to pediatric nephrologists [2- 3]. UTI can cause renal scar, chronic kidney disease and hypertension [1, 4]. It is estimated that 8.4% of the girls and 1.7% of the boys will have UTI at least once before 7 years of age [5].

Prevention of UTI, especially in children with the risk of recurrent UTI, is very important. Nuutinet reported that 86% of their patients had recurrent UTI during the next 6 months, and found a positive correlation between the rate of UTI and grade of vesicoureteral reflux (VUR) [6]. About one third of the children with normal radiologic imaging have recurrent infection which is more in girls [7,8]. However, other studies showed no difference in the risk of infection between girls and boys with VUR [9].

To prevent UTI, antibiotic prophylaxis is recommended at a dose of one third to one fourth of the therapeutic dose, but there are some controversial reports about their efficacy. Chan et al reported that the risk of UTI was more in children on Cephalosporin than Co-trimoxazole for prophylaxis of infection [10].

Also, the rate of sensitivity to Amikacin, Co-trimoxazole and Nalidixic acid has decreased from 100%, 30% and 96% to 87%, 12%, and 82%, respectively [11]. Moreover, in a study by Dai et al, antibiotic prophylaxis was not effective in the prevention of UTI [12].

Due to different opinions regarding the best method and drug for the prevention of relapse, this study was done in children with UTI and risk of recurrent infection who received prophylactic antibiotics.

### Materials and Methods

This prospective cohort study was done on children (at risk of recurrent UTI) with a history of symptomatic UTI who were admitted to Amirkola Children Hospital or were referred to the nephrology clinic.

Among 641 patients with symptomatic UTI, 480 children had the risk of relapse and were enrolled in the study.

All children with VUR, neurogenic bladder, urinary tract stones (without obstruction), and history of frequent UTI (two or more within 6 months or three or more in a year) were enrolled in this study. They were on antibiotic prophylaxis (ABP) and were followed up at least for 12 months. Drugs used for ABP were Co-trimoxazole, Nitrofurantoin, Co-amoxiclav, Cefixim, Cephalexin, Amoxicillin, Nalidixic acid and Ampicillin. The dose of any drug was one third to one fourth of the therapeutic dose and was given as a single night dose.

All the cases of VUR were diagnosed using voiding cystourethrography (VCUG) and classified according to the international VUR grading system [13]. Relapse of UTI was defined by fever (higher than 38.5°C), more than 5 white blood cells on urinalysis and more than  $10^5$  colony counts of one microorganism in the urine culture. Then, the data about sex, drug consumption, the type of microorganism and its antimicrobial susceptibility to drugs were recorded. Exclusion criteria were failure to follow-up, surgical repair of anatomical abnormalities, positive urine culture without pyuria, or pyuria without positive urine culture.

According to different important of UTI in age s groups, so, the patients were divided to three groups of less than 2 years, 2-5 years and more than 5 years.

### Results

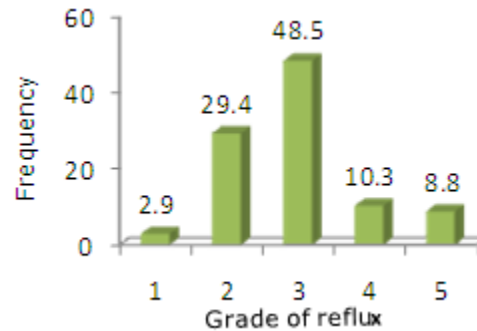
One hundred and twenty six (93%) patients had relapse once. Six patients and one patient experienced recurrent infection for 2 and 3 times, respectively. So, 141 cases of recurrence were recorded. One hundred and seven (76%) patients were female and the rest of the participants were male (24%).

The mean age of the participants was  $46.6 \pm 0.41$  months (range: 3 months to 16 years.)

VUR was the most common predisposing factor (68 cases) for relapse. Unknown causes, renal stone, PUV, UPJO and UVJO, neurogenic bladder, and duplex kidney were observed in 46, 12, 7, 6, 5 and 4 patients, respectively (some patients had two predisposing factors). Among children with VUR, grade III of VUR (48.5%) was the most common grade (Figure 1). E. coli was the most common organism that was detected in recurrent cases (85.5%) (Table 1). The causes of recurrence were drug resistance (78 cases, 55%), discontinuation of the drug by parents (39 cases, 28%) and unknown causes (28 cases, 17%). Drug resistance was a cause of recurrence in 59 (55%) girls and 19 (56%) boys ( $P > 0.05$ ). Co-trimoxazole was the most common drug to which there was resistance (62%) (Table 2). Regarding age, the patients were divided into 3 groups (less than 2 years, 2-5 years and more than 5 years old). Drug resistance was the most common cause of recurrence in all age groups ( $P > 0.05$ ) (Table 3).

**Table 1:** Frequency of microorganisms that cause recurrent UTI

Microorganisms	frequency	Percents
E-Coli	121	85.5%
Klebsiella	5	3.5%
Staphylococcus Aureus	5	3.5%
Pseudomonas Aeruginosa	4	2.8%
Proteus	4	2.8%
Others	2	1.4%
<b>Total</b>	<b>141</b>	<b>100%</b>



**Figure 1:** Frequency of vesicoureteral reflux in children with recurrent UTI according to the grade of reflux

**Table 2:** Frequency of drug sensitivity according to different drugs in children with recurrent UTI

Age	less than 2	2-5	more than 5
<b>Cause of recurrent</b>			
<b>Drug resistance</b>	34 (51.5%)	24 (64.9%)	20 (52.6%)
<b>Discontinue of drug</b>	20 (30.3%)	10 (27%)	9 (23.7%)
<b>Unknown</b>	12 (18.2%)	3 (8.1%)	9 (23.7%)
<b>Total</b>	<b>66</b>	<b>37</b>	<b>38</b>

**Table 3:** Frequency of recurrent UTI according to age groups (years)

Drug	cefixime	Nitrofurantoin	Co-trimoxazole	Co-amoxiclav	others
<b>Drug sensitivity</b>					
<b>Resistant</b>	7 (46.7%)	11 (42.3%)	42 (61.8%)	7 (46.7%)	10 (58.8%)
<b>Susceptible</b>	8 (53.3%)	15 (57.7%)	26 (38.02%)	8 (53.3%)	7 (41.2%)
<b>Total</b>	<b>15</b>	<b>26</b>	<b>68</b>	<b>15</b>	<b>17</b>

### Discussion

According to this study, VUR was the most common predisposing factor and drug resistance, especially to Co-trimoxazole, was the most common cause of recurrence in these patients.

Seventy six percent of the patients were female. Brataslavky reported 84 patients with recurrent UTI of whom 81% were female. Also, according to other reports, 88% - 89% of the patients with recurrent infection are female. [8, 14, 15]

Although the urinary system abnormalities are more common in males than females [16], the risk of recurrent was higher in girls than boys in this study. Also, the risk of UTI was higher in girls than boys. VUR (48%) was the most common predisposing factor for recurrent infection that was unilateral in 75% of patients. Grades II and III of VUR were reported more than grade I, IV and V. Although grade II and III are more common than other grades according to one study [17], another study reported that grade II, IV and V were more detected grades [6, 18]. Conway et al reported that grades I-III were not at risk of recurrence and Pennesi et al reported that there was not the risk of recurrence in grade II-IV of VUR [19-20]. VUR is the predisposing factor in 41.5 % of the patients with recurrent infection [15]. Younger mean age at the first UTI, bilateral reflux, high grade (IV-V) VUR and hydronephrosis on the initial ultrasound scan significantly increase the risk of recurrent UTI [21]. In a study by Krzemien that was done on children with recurrent UTI and VUR, about 15.5% of the patient had recurrent infection [22]. Also, in another study, VUR and neurogenic bladder were the most common predisposing

factors of recurrent [23]. Therefore, more attention should be paid to children with VUR.

E. coli was the most common bacterial cause of recurrent infection. In a study performed by Mangiarattip, E. coli was the most common bacteria in children with recurrent UTI (80%) [18]. Therefore, E. coli is the most common bacteria in children with primary or recurrent UTI.

In about half of the patients with recurrent infection, drug resistance was the cause of UTI and resistance to Co-trimoxazole was more than other agents. Esmaeili reported about 75% of patients with recurrent UTI were resistance to Co-trimoxazole [24]. In another study, E. coli was the most common bacteria that caused UTI and resistance to Co-trimoxazole (81% of the patients) [25]. Chang et al reported children with VUR who were on antibiotic prophylaxis and showed recurrent UTI with other bacteria. In their study, the risk of UTI was higher in children on Cephalosporin than Co-trimoxazole [10].

The overuse of an antibiotic, especially in children with any suspected infection, may cause drug resistance and increase the risk of infection.

It seems that more studies are required to find the appropriate antibacterial agent for prophylaxis. We conclude that considering the high risk of recurrent infection in girls and the pattern of E. coli resistance to Co-trimoxazole in our region, the antibiotic for prophylaxis must be chosen based on the patient's antibiogram.

The cause of recurrent UTI was discontinuation of prophylaxes by parents in about one third of our patients. This problem may be due to the parents' lack of awareness and knowledge about the risk of recurrent infection; they must be seriously counseled to seek medical attention.

## Conclusions

In conclusion, since the risk of UTI and recurrent infection is higher in girls, more attention should be paid to UTI in this sex group. Also, high drug resistance, especially to Co-trimoxazole, is very important; as a result, changing the administered drug is recommended and may be necessary.

## Conflict of Interest

None declared

## Financial Support

None declared

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