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## Comparison of Nitrofurantoin and Trimethoprim-Sulphamethoxazole for Long-Term Prophylaxis in Children with Recurrent Urinary Tract Infections

<sup>1</sup>Behnaz Falakafalaki, <sup>2</sup>Ramazan Fallah, <sup>3</sup>Mohammad Reza Jamshidi, <sup>1</sup>Farzaneh Moezi and <sup>1</sup>Zohreh Torabi

<sup>1</sup>Department of Pediatric Nephrology, Valiasr Hospital,

<sup>2</sup>Department of Social Medicine,

<sup>3</sup>Department of Intensive Care Unit, Valiasr Hospital, Zanjan University of Medical Sciences, Zanjan, Iran

**Abstract:** The objective of this study was to compare prophylactic effect of nitrofurantoin and trimethoprim-sulphamethoxazole (TMP-SMX) in recurrent Urinary Tract Infections (UTI) in children and to determine antibiotic resistance pattern while receiving prophylaxis. One hundred and thirty two patients in two similar groups were randomized to receive either TMP-SMX (n = 66) or nitrofurantoin (n = 66) as single night dose for 6 months. Age, sex, indication for prophylaxis, occurrence of UTI, culture and sensitivity results were recorded. Patients were categorized into three age groups: 3-12 months, 1-5 years, 6-12 years. Nitrofurantoin was more effective than TMP-SMX in preventing recurrent UTI. Recurrence rate was 36.2% in nitrofurantoin group compared with 63.8% in the TMP-SMX group (p = 0.029). This protective effect was more significant in children aged 1-5 years compared to other age groups (p = 0.046). In nitrofurantoin group, 37.5% of the organisms causing the UTIs were resistant to drug. In TMP-SMX group, 56% of the organisms were resistant to the prophylactic agent. Nitrofurantoin has a lower rate of recurrence and causes less emergence of resistance bacteria than TMP-SMX, therefore is more suitable for prevention of recurrent UTI in children.

**Key words:** Urinary Tract Infection (UTI), prophylaxis, children, nitrofurantoin, trimethoprim-sulphamethoxazole (TMP-SMX)

### INTRODUCTION

Urinary Tract Infections (UTIs) are the second most common bacterial infection in children after those of the respiratory tract (Bagga, 2001). By the age of seven 8.4% of girls and 1.7% of boys will have suffered at least one episode (Williams *et al.*, 2006). After their first symptomatic UTI, 30-50% of the children are prone to at least one recurrence (Beets, 2006). UTIs are important in view of their acute morbidity and long-term risk of renal scarring. Occurrence of UTI below two years of age, delay in starting treatment and presence of vesicoureteric reflux (VUR) or obstruction are the chief risk factors associated with renal scarring (Bagga, 2001). The incidence of scarring increases with each episode of upper UTI (Jodal, 1987). Recurrent UTIs (rUTIs) are by far the most frequent reason for long-term antibacterial prophylaxis in children today (Smith and Finn, 1999). The aim of antimicrobial prophylaxis is to prevent rUTI and consequent renal scarring (Bollgren, 1999). However, the strategies of antibacterial prophylaxis for the prevention of rUTI are no longer universally accepted (Beets, 2006).

Antimicrobials selected for prophylaxis should fulfill the following requirements (Bollgren, 1999).

Effectiveness against the majority of uropathogens, causing a minimum of serious side effects, causing minimal bacterial resistance.

For many years trimethoprim or co-trimoxazole and nitrofurantoin have been the substances most used for antibacterial prophylaxis of UTI in children (Beets, 2006).

The purpose of this study was comparison of nitrofurantoin and trimethoprim-sulphamethoxazole in prevention of rUTI in children and to determine antibiotic resistance pattern while receiving prophylaxis. Because antibacterial prophylaxis must be continued for long-term periods from 6 months to 2 years and recent studies have revealed the emergence of therapy-induced resistance.

### MATERIALS AND METHODS

In this prospective randomized study, 132 patients were consecutively selected from outpatient clinic of pediatric nephrology of Valiasr Hospital in Zanjan, between oct 2004 to oct 2006. All these patients fulfilled

the following inclusion criteria: a) previous history of UTI, b) no previous antimicrobial prophylaxis, c) age of patients between 3 months to 12 years, d) normal renal function and e) the patients have one of the following indication for long-term antibacterial prophylaxis include: rUTIs (>3 per year), vesicoureteral reflux (grade I-IV), obstructive lesion or other anatomical abnormalities, infants less than 1 year of age.

Exclusion criteria were: a) impaired renal function, b) contraindication for taking nitrofurantoin or trimethoprim-sulphamethoxazole such as G6PD deficiency, previous drug reaction and c) any side effects of drugs (gastrointestinal symptoms, rash,...). The patients were randomized to receive either 2 mg kg<sup>-1</sup> day<sup>-1</sup> of trimethoprim as trimethoprim-sulphamethoxazole (n = 66) or 1-2 mg kg<sup>-1</sup> day<sup>-1</sup> of nitrofurantoin (n = 66) as single night dose for 6 months. Age, gender and underlying renal problem were matched in two groups.

After initiation of prophylactic agents, the patients were followed up at monthly interval. The clinical approach during follow up visits consisted of full physical examination, including evaluation of growth. Urine cultures were obtained monthly and during any febrile episode.

Recurrent UTI was defined as growth of at least 100,000 Colony Forming Units (CFU) per mL in urine obtained by bag or a midstream sample with fever (38.0°C or more) or urinary symptom. After eradication of this new infection, they were started on the same prophylactic regimen (if the isolated bacteria sensitive to prophylactic agent), or another regimen (if the isolated bacteria resistance to prophylactic agent).

We removed or taken into consideration, all of excludable predisposing factor for recurrent UTI, such as constipation, fecal incontinence, incomplete bladder emptying, poor perineal hygiene, pin worm, circumcision and etc.

The following data were recorded for each patient: age, sex, indication for prophylaxis, occurrence of UTI, culture and sensitivity results.

Patients were categorized into three different age groups: 3-12 months, 1-5 years, 6-12 years.

The analysis were performed using SPSS (version 11.5). Chi-square test or Fisher's exact test were used for comparison of variables between two groups Differences with a p-value of less than 0.05 were accepted as statistically significant.

## RESULTS

A total of 132 patients (96 girls, 36 boys) aged 3 months to 12 years (mean age: 3.8 years) were included

in the analysis. Sixty-six children aged 4 months to 11 years (mean age: 4.4 years) were on nitrofurantoin and 66 aged 3 months to 12 years (3.8 years) were on trimethoprim-sulphamethoxazole (TMP-SMX). The two groups were similar, with no statistically significant differences in age, sex, underlying renal problem. The patients characteristics in two groups are summarized in Table 1.

During prophylaxis, the rate of recurrence was 36.2% (n = 17) in nitrofurantoin group compared with 63.8% (n = 30) in the TMP-SMX group (p = 0.029). Nitrofurantoin was more effective than TMP-SMX in preventing recurrent UTI over a six month period (RR = 2.4, 95% CI 1.15 to 5).

According to the age groups, there was no statistical difference in the infection rates in children less than 1 year and in children 6 to 12 years in two groups. However, in children between 1 to 5 years, the number of UTIs is significantly higher in the TMP-SMX group (16 in 39 children vs 7 in 39 children p = 0.046) (Table 2). Nitrofurantoin was more effective than TMP-SMX in preventing recurrent UTI in children 1-5 years (RR = 3.18, 95% CI 1.28 to 8.97).

Gender, underlying renal problem (presence of VUR or other renal abnormalities) did not make any statistically differences on recurrence rates in two groups (Table 2).

Table 1: Demographic characteristics of two groups

Variables		Nitrofurantoin group (n = 66)	TMP-SMX group (n = 66)
Sex	Female	53	43
	Male	13	23
Age (year)	<1	10	15
	1-5	39	39
	6-12	17	12
Indication for prophylaxis	VUR	26	31
	Other renal abnormalities	30	28
	rUTI (no abnormalities)	10	7

n = Number, VUR = Vesicoureteral reflux, rUTI = recurrent UTI

Table 2: Recurrence rate according to age, sex and underlying renal problem in two groups

Variables		Groups	n	Recurrence rate % (n)	p-value		
Age (year)	<1	Nitrofurantoin	10	41.6% (5)	>0.05		
		TMP-SMX	15	58.3% (7)			
	1-5	Nitrofurantoin	39	30.4% (7)		0.046	
		TMP-SMX	39	69.5% (16)			
	6-12	Nitrofurantoin	17	41.6% (5)		>0.05	
		TMP-SMX	12	58.3% (7)			
Sex	Female	Nitrofurantoin	53	38.2% (13)	>0.05		
		TMP-SMX	43	61.7% (21)			
	Male	Nitrofurantoin	13	30.7% (4)		>0.05	
		TMP-SMX	23	69.2% (9)			
	Underlying renal problem	VUR	Nitrofurantoin	26		37.5% (6)	>0.05
			TMP-SMX	31		62.5% (10)	
Others		Nitrofurantoin	30	40% (8)	>0.05		
		TMP-SMX	28	60% (12)			

n = Number, VUR = Vesicoureteral reflux

In children taking nitrofurantoin, 37.5% of the infecting organisms causing the UTIs were resistant to the prophylactic agent. In children taking TMP-SMX, 56% of the organisms were resistant to the prophylactic agent. The most common causative agent in recurrent UTI while receiving prophylaxis was *E. coli* (75%). Sensitivity and resistance of *E. coli* to TMP-SMX was 47.1 and 52.9%, respectively and to nitrofurantoin was 50 and 50%, respectively.

## DISCUSSION

The aims of this study was to compare efficacy of nitrofurantoin and trimethoprim-sulphamethoxazole (TMP-SMX) in preventing recurrent UTI (rUTI) in children. The study showed nitrofurantoin was more effective than TMP-SMX in preventing rUTI in a six month period and this protective effect was more significant in children between 1 to 5 years age compared to other age groups.

In one study the efficacy of nitrofurantoin and trimethoprim-sulphamethoxazole prophylaxis in prevention rUTI was compared. In a six month trial nitrofurantoin was more effective than TMP-SMX in preventing rUTI, but was more likely to be discontinued because of side effects, which were mainly gastrointestinal (Brendstrup *et al.*, 1990). In another study for comparison of nitrofurantoin vs trimethoprim-sulphamethoxazole (TMP-SMX), there were no significant difference between the two groups concerning the recurrence rate. They concluded that nitrofurantoin and TMP-SMX are equally suitable for prophylaxis in rUTI (Vahlensieck and Westenfelder, 1992).

We found important differences related to patient age. In our population, nitrofurantoin was a more suitable antibiotic for prophylaxis of rUTI in children aged 1 to 5 years. In Iran, TMP-SMX is the favorite antimicrobial agent for the empirical treatment of many infections such as urinary tract, respiratory tract and gastrointestinal tract infections. These infections are more common in children aged 1-5 years. Because TMP-SMX is a popular antibiotic in this age group, probably the emergence of TMP-SMX resistant bacteria result in, TMP-SMX be less effective than nitrofurantoin in prevention of rUTI in this age group.

In one study, nitrofurantoin proved to be the most efficient prophylactic drug in patients with abnormal urography and or reflux (Brendstrup *et al.*, 1990). We found no statistically difference between two drugs in preventing rUTI in patients with reflux or the other urinary tract abnormalities.

One of our goals was to define the prevalence of resistance to nitrofurantoin and TMP-SMX among isolated bacteria from patients with rUTI while receiving prophylaxis. there was 37.5% resistance to nitrofurantoin and 56% to TMP-SMX.

In one study patients receiving TMP-SMX prophylaxis had 76% TMP-SMX resistance bacteria during prophylaxis (Brendstrup *et al.*, 1990). In Turkey evaluation of antibiotic resistance of urinary tract pathogens revealed resistance to TMP-SMX in all uropathogens was significant (61.1%) and nitrofurantoin had the lowest resistance rate (5.8%) (Yukser *et al.*, 2006). Children with underlying renal disease, rUTIs, or under antibiotic prophylaxis will have more resistant bacteria causing UTI (Ladhani and Gransden, 2003).

Bacterial resistance to TMP-SMX has in recent year been shown to increase rapidly in many regions of the world (Beets, 2006). The results of our study which are in agreement with those obtained elsewhere emphasize on high TMP-SMX resistance rate. However, in our region the nitrofurantoin resistance rate was also high.

In this study *E. coli* was the most common causative agent in rUTI While taking prophylaxis. It was reported *E. coli* was significantly less common in children receiving prophylactic antibiotics (Lutter *et al.*, 2005).

Sensitivity and resistance of *E. coli* to nitrofurantoin and TMP-SMX in our study was also different from other studies. In was reported, in children sensitivity of *E. coli* to TMP-SMX 16.4% and to nitrofurantoin 15.9% (Mohanna and Raja'a, 2005). In another study resistance rate of *E. coli* to TMP-SMX was greater than 20% and to nitrofurantoin was less than 1% (Gaspari *et al.*, 2005) and one research reported overall resistance rate of *E. coli* to TMP-SMX 21.3% and to nitrofurantoin 1.1% (Zhanel *et al.*, 2006). The reasons for these differences are, children who receive antibiotic for long-term periods are more likely to have resistant *E. coli* than children have not received prolonged antibiotic treatment. Moreover children with abnormalities of urinary tract are approximately more have resistant *E. coli* than children without abnormalities of urinary tract (Shakil *et al.*, 2004).

Altogether, there are considerable geographic variation in bacterial patterns and resistance properties depending on local antibacterial prescription practice. There is much evidence suggesting a relationship between prescribing habits and antibiotic resistance. Limitation: The major limitation of this study was, we do not check patient's compliance. recurrent UTI can be results from non-compliance and also from development of bacterial resistance. non-compliance is an important cause for failure of prophylaxis.

## CONCLUSION

On the basis of this data, nitrofurantoin has a lower rate of recurrence and causes less emergence of resistance bacteria than TMP-SMX and therefore is more suitable for prevention of recurrent UTI in children.

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