

## Role of urinary tract infections as triggers for frequent relapse in children with steroid sensitive nephrotic syndrome

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### Abstract

Frequent relapse occurs in about 60% of children with steroid-sensitive nephrotic syndrome (SSNS) despite the tangible initial response. Several factors have been documented as triggers for frequent relapses (FR). However, the role of urinary tract infection (UTI) was not well-illustrated. Our aim was to evaluate the role of UTI as a trigger for FR among Iraqi children SSNS. This cross-sectional study was conducted on a total of 68 children with the first episode of SSNS who were followed up for 6 months after taking their treatment for the first episode. The patients were divided into two groups: frequent and infrequent relapse. Midstream urine samples were collected from each child and routine bacteriological culture and detection were achieved. Data regarding age at onset, sex, steroid therapy at the onset, the time between the onset and first relapse were collected from patients' records. The proportion of frequent relapses was 41.18%. UTI affected 22 (32.35%) patients with *E. coli* was the most common isolated bacteria accounting for 63.64% followed by *Klebsiella pneumonia* (18.18%), *Proteus spp.* and *Pseudomonas aeruginosa* (13.64% for each). In univariate analysis, each of age at onset, inadequate therapy for the first episode, and UTI were significantly associated with frequent relapse. However, in multivariate analysis, only adequate treated for first episode (OR= 0.26, 95%CI= 0.08-0.86, p= 0.028) and UTI (OR= 4.8, 95%CI= 1.22-18.87, p= 0.025) were significantly associated. In conclusion, UTI is an important cause of FR in children with SSNS. Therefore, affected children should be routinely investigated for such infection.

**Keywords:** urinary tract infection, frequent relapse, *E. coli*, steroid therapy

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### Introduction

Idiopathic nephrotic syndrome (INS) is the most common feature of glomerular disease in children. The International Study of Kidney Disease in Children (ISKDC) stated that the vast majority of INS in pre-adolescent children was minimal change nephropathy (MCN) based on studies using renal biopsies<sup>[1]</sup>. It has been reported that more than 90% of children MCN can achieve remission when treated with oral corticosteroids, and accordingly, this group is known to have steroid-sensitive nephrotic syndrome (SSNS)<sup>[2]</sup>. In contrast, in most children with focal segmental glomerulosclerosis (FSGS) (the second most common histological subtype), there is no response to corticosteroids and is said to have steroid resistance nephrotic syndrome (SRNS). Those patients are a high risk of developing end-stage renal failure<sup>[3]</sup>.

Despite the very high initial response and the favorable prognosis in children with SSNS, relapses do occur in 60% to 90% of those responders. Relapse is usually associated with high morbidity, complications and low quality of life<sup>[4]</sup>. The most important complications during relapse include malnutrition, thrombosis, sepsis, and dyslipidemia<sup>[5]</sup>. In such patients, high doses of corticosteroids may be used to increase the response rate. However, such interference has significant adverse effects like hip avascular necrosis, hypertension, diabetes and behavioral disorders<sup>[6]</sup>. As such, determining the risk factors that trigger relapse in SSNS is of paramount importance. In fact, many of these factors such as a child's age at the onset and adequate steroid therapy have been well-documented<sup>[7]</sup>. However, the role of infectious agents in this regard is still a debated issue. Therefore, this study aimed to investigate the role of UTI as a risk for frequent relapsing in patients with SSNS.

## Subjects and methods

This is a cross-sectional study that will be conducted on 68 patients with the first episode of idiopathic nephrotic syndrome (INS) presenting to the Al-Yarmook Teaching Hospital/ Baghdad during the period from April 2018 to May 2019. All patients with INS who response to steroids (prednisolone 60 mg/m<sup>2</sup>/day) within 4–6 weeks presenting with the first episode of NS were included in the study. Patients having less than 6 months follow up, those with steroid-resistant NS, or with secondary and congenital NS were excluded from the study.

Diagnosis of NS was made according to the following criteria: heavy proteinuria >40 mg/h/m<sup>2</sup> (for older children with collected 24 hour urine); or protein/creatinine ratio >0.2 g/mmol, Albustix ≥3+ (for nontilet-trained children or having a difficulty in urine collection of 24 hour), hypo-albuminemia <2.5 g/dL, edema and hyperlipidemia. The remission was defined as urine albumin nil or trace (or proteinuria <4 mg/m<sup>2</sup>/h) for 3 consecutive early morning specimens. On the other hand, relapse was defined as urine albumin 3+ or 4+ (or proteinuria >40 mg/m<sup>2</sup>/h) for 3 consecutive early morning specimens, having been in remission previously. When this relapse occurs two or more times in the initial six months or more than three relapses in any twelve months it was considered as frequent relapse, and infrequent relapse otherwise.

## Following-up

Eligible patients were followed at least 6 months (two times monthly) after completion of the treatment of the first episode by inviting them to visit the outpatient clinic. According to the aforementioned definitions, patients were classified into two groups: frequent relapses and infrequent relapses. The following variables will be considered as potential risk factors/predictors for frequent relapses: age at onset, sex, inadequate steroid therapy (less than 8 weeks) at the onset, time of first relapse (time from the start of initial treatment to first relapse), and concurrent infections during relapses. Both frequent and infrequent relapses with clinical features of infections were thoroughly investigated by a consultant specialist in each visit. Respiratory tract infections (RTIs) were noted based on symptoms such as fever, cough, and respiratory distress and X-ray chest findings.

## Detection of urinary tract infection

Midstream urine samples were collected in sterile containers from each patient, and divided into two portions; the first portion was used for general urine examination and a second portion for culture on nutrient agar, blood agar and McConkey agar plates, using a sterile standard loop (1ml) then incubated at 37±2°C for 20–24 hours. Positive urine analysis findings include leukocytes, erythrocytes, bacteria, and squamous epithelial cells<sup>[8]</sup>. The confirmation of UTI was based on positive culture results (growth of a single organism of >10<sup>5</sup> CFU/ml in a mid-stream urine sample). The cultivated bacteria were diagnosed primarily according to the morphological characteristics of the colonies. The diagnosis was confirmed by using the Api20E system for Enterobacteriaceae, m according to instructions of a manufacturing company (bio-Merieux/ France).

## Statistical Analysis

Results of continuous measurements are presented as mean±SD and analyzed with Student's t-test (two-tailed, independent), while results on categorical measurements are presented as frequency and percentages and analyzed with Chi-square/Fisher's exact test. Univariable and multivariable logistic regression was used to evaluate the role of urinary tract infection in triggering relapse episodes through the calculating odds ratio (OR) adjusted for other confounders including age at onset, sex, inadequate steroid therapy at the onset, time of the first relapse, and concurrent infections during relapses. All analyses were done by SPSS version 20 and significance was taken at a p-value of 0.05 with a 95% confidence interval.

## The results

### Socio-demographic and clinical characteristics of the patients

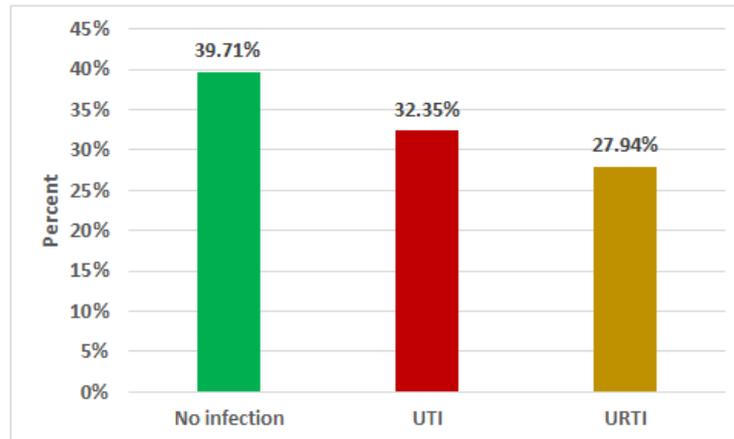
The mean age of the children was 5.11± 1.22 years (range 3–13 years). Males represent about two-third (64.71%). The majority of children (69.12%) had accomplished an adequate treatment course for the first episode of relapse. Time to remission in the first episode was ≥ 2 weeks in 41 children (60.29%), while 31(38.75%) children had less than 8 months to have their first relapse (Table 3-1). Out of 68 SSNS patients included in this study, 28 patients (41.18%) were found to have frequent relapses, while the other 40 patients (58.82%) were infrequent relapses.

**Table 1:** Socio-demographic and clinical characteristics of the patients

Variables	Value
Age at onset, years	5.11± 1.22
<b>Sex</b>	
Male	44(64.71%)
Female	24(35.29%)
<b>Adequate treated of first episode</b>	
< 8 weeks	21(30.88%)
≥ 8 weeks	47(69.12%)
<b>Time to remission in the first episode</b>	
< 2 weeks	27(39.71%)
≥ 2 weeks	41(60.29%)
<b>Time to the first relapse, months</b>	
< 8	32(47.06%)
≥ 8	36(52.94%)

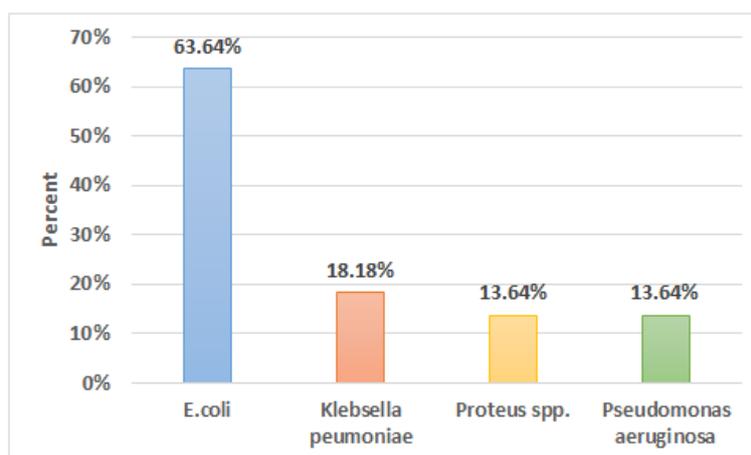
**Urinary tract infection and the bacterial involvement**

About 60% of the children experienced an infection at the time of episodes, with UTI affected 22 (32.35%) patients, while upper respiratory tract infection (URTI) affected 19 (27.94%) patients. The other 27 (39.71%) were free from infection (Figure 1).



**Figure 1:** Proportion of infection with urinary tract (UTI) and upper respiratory tract (URTI)

A significant growth of aerobic Gram-negative bacilli as a single infection was observed in 20 samples (29.41%) (Figure 1) and as mixed infection in 2 samples (2.94%); the bacteria that were detected in the positive samples were: *E. coli* in 14 (63.64%), *Klebsiella pneumonia* in 4 samples (18.18%), *Proteus spp.* in 3 samples (13.64%) and *Pseudomonas aeruginosa* in 3 samples too (13.64%) as was illustrated in figure 2.



**Figure 2:** The percent of each bacterium in urinary tract infection of children with SSNS

### Predictors of relapsing in SSNS

In univariate logistic regression analysis, three factors appeared to be significantly associated with the frequent relapses in SSNS (Table 2). The first factor was a younger age. Sixteen children (57.14%) frequent relapse were younger than 5 years old compared to only 13(32.5%) among children with infrequent relapse who had such ages ( $p= 0.043$ ). The second factor was the adequate treatment of the first episode which was less than 8 weeks in 13 children (46.43%) with frequent relapse and 8(20%) of children with infrequent relapse ( $p= 0.020$ ). The last factor was the infection. Specifically, UTI was reported in 12(42.86%) of children with frequent relapses and in 10(25%) in children with infrequent relapses ( $p= 0.045$ ). In multivariate regression, only two factors were found to be independent risk factors for triggering relapses in SSNS. These were inadequate treated first episode (OR= 0.26, 95%CI= 0.08-0.86,  $p= 0.028$ ), and UTI (OR= 4.8, 95%CI=1.22-18.87,  $p= 0.025$ ).

**Table 2:** Univariate and multivariate analysis to assess the risk factors of frequent relapse SSNS

Variables	Frequent relapsers (n=28)	Infrequent relapsers (n=40)	Univariate analysis	Multivariate Analysis	
			p-value	p-value	OR(95% CI)
<b>Age at onset, years</b>					
< 5	16(57.14%)	13(32.5%)	0.043	0.173	1.0
≥5	12(42.86%)	27(67.5%)			
<b>Sex</b>					
Male	21(75%)	23(57.5%)	0.137	0.15	1.0
Female	7(25%)	17(42.5%)			
<b>Adequate treated first episode</b>					
< 8 weeks	13(46.43%)	8(20%)	0.020	0.028	1.0
≥ 8 weeks	15(53.57%)	32(80%)			
<b>Time to the remission</b>					
< 2 weeks	10(35.71%)	17(42.5%)	0.574	0.758	1.0
≥ 2 weeks	18 (64.29%)	23(57.5%)			
<b>Time to the first relapse, months</b>					
< 8	15(53.57%)	17(42.5%)	0.368	0.584	1.0
≥ 8	13(46.43%)	23(57.5%)			
<b>Infection</b>					
No infection	7(25%)	20(50%)	0.113	0.075	1.0
URTI	9 (32.14%)	10(25%)	0.137	0.172	2.59(0.66-10.16)
UTI	12(42.86%)	10(25%)	0.045	0.025	4.8(1.22-18.87)

**Association of bacterial species with frequent relapse in children with SSNS**

Although the frequency of *E. coli* infection was markedly higher in children with FR than those with infrequent relapse (28.57% versus 15%), the difference was not significant. Similarly, there were no significant differences between the two groups in the frequency of other bacteria (Table 3).

**Table 3:** Association of bacterial species with frequent relapse in children with SSNS

Bacterial species	Frequent relapsers (n=28)	Infrequent relapsers (n=40)	p-value	OR(95% CI)
<b><i>E. coli</i></b>				
No	20(71.43%)	34(85%)	0.173	1.0 2.27(0.69-7.48)
Yes	8(28.57%)	6(15%)		
<b><i>Klebsiellapneumoniae</i></b>				
No	25(89.29%)	39(97.5%)	0.298	1.0 4.68(0.46-47.54)
Yes	3(10.71%)	1(2.5%)		
<b><i>Proteus spp.</i></b>				
No	26(92.86%)	39(97.5%)	0.359	1.0 3.0(0.26-34.81)
Yes	2(7.14%)	1(2.5%)		
<b><i>Pseudomonas aeruginosa</i></b>				
No	27(96.43%)	38(95%)	0.778	1.0 0.7(0.06-8.16)
Yes	1(3.57%)	2(5%)		

**Discussion**

In the current study, the proportion of frequent relapse was 42.5%. In different international studies, this proportion ranged from 22% to 61%<sup>[9, 10, 11]</sup>. Interestingly, in a local study, Ali *et al.*<sup>[12]</sup>, reported as high as 62 frequent relapsers out of 80 (77.5%) Iraqi children with SSNS. This wide range may be attributed to the different regimes of steroid treatment, variation in the incidence of infection-induced relapses, and variation in the follow up period.

In univariate analysis, younger age was significantly associated with the occurrence of. However, in multivariate analysis, this factor was no longer associated with FR. Young age was frequently reported by several prior studies as an important trigger for relapse in children with SSNS. Sarker *et al.*,<sup>[13]</sup> showed that ages less than 5 years are more prone to have FR compared to those older than 5 years. Dakshayani *et al.*,<sup>[14]</sup> followed up 227 Turkish children one year after the first episode and reported that FR had significantly associated with lower age at onset. An almost a similar result was reported by Mishra *et al.*,<sup>[15]</sup> among Indian children in which the authors found that the risk of FR was 3-time greater in 1-3 year-age compared to children over 6 years. The significant association between younger age at onset and FR may be attributed to the high incidence of infections among younger ages<sup>[16]</sup>. This fact explains the absence of a significant association in multivariate regression which implies that infection rather than age is the independent risk factor.

Inadequate treated at first episode was significantly associated with the risk of FR in the current study both in univariate and multivariate analysis (OR= 0.26 (0.08-0.86, p= 0.028). This implies that children taking inadequate treatment for the first episode (< 8 weeks) will be at about 3.91-fold higher risk in developing FR compared with those with adequate treatment. These results completely agree with the results of a local study in which the incompliant to treatment was found to be significantly associated with frequent relapse<sup>[13]</sup>. Also, the present results are consistent with an Indian study including 112 children with FRNS<sup>[16]</sup>. The study demonstrated that adequate treatment (≥ 12 weeks) of the first episode significantly protected against FR. On the other hand, one study showed that steroid therapy beyond 2 or 3 months after the initial episode had no significant effect on relapsing<sup>[17]</sup>.

The other factor, which was significantly associated with FR in the current study even with multivariate analysis was UTI (OR= 4.8, 95%CI=1.22-18.87, p= 0.025). That means children with SSNS with URI will be at a 4.8-time risk to develop FR compared to those without infection. Such results are partially in agreement with many previous international studies. In a small study among Nigerian patients, Uwaezuoke *et al.*,<sup>[18]</sup> demonstrated UTI was the most common triggers for FR responsible for 40% of total relapsing. However, the authors also reported a significant influence of URTI which was responsible for 23% of total relapsing. This salient effect of UTI compared to other infections has been also reported by other studies<sup>[19, 20]</sup>. On the other

hand, may study showed that URTI but not UTI was significantly associated with FR [14, 21, 22, 23]. The lack of a significant association between FR and URTI in the present study may be explained by the fact that URTI is transient and patients with these infections receive the appropriate therapy, while UTI takes longer time to cure and the infected child may not receive the required therapy.

Generally, infection and FR have reciprocal effects. When the child exposes to infection, T cells are induced with a concomitant upregulation of IL-13 and IL-4 expression. These cytokines can stimulate monocyte to release vascular permeability factors (VPFs) that are involved in the pathogenesis of proteinuria in NS patients [24]. Interestingly, some studies indicated that podocytes do have receptors for these factors. Binding of VPFs with their ligand on podocytes results in disruption of glomerular permeability with a consequence of proteinuria [25]. On the other hand, patients with frequent relapse are probably more immunosuppressed either due to the disease or corticosteroid therapy, and therefore, are more prone to infections.

In the present study, there was no significant association between detected bacterial species and FR. The reason beyond this non-significant association may be due to a small number of positive patients. Unfortunately, there were no available similar studies to compare with. However, some confirmed the prevalence of *E. coli* in NS patients. In a cross sectional study, Mohammed *et al.*, [26] investigated 90 Egyptian children with NS. Urinary tract infection was found to be the second most common infection affecting 21.7% of patients (after the gastrointestinal tract), with *E. coli* was the most common pathogen. In another study, Noorani and Raj [27, 28] reviewed the records of 355 Pakistani children with NS. They found that 31.7% of those children had one or more infections at the time of diagnosis. Again, UTI came second (after respiratory tract) with *E. coli* was responsible for the majority of cases.

These data indicate the paramount importance of UTI as well as inadequate treatment in the predisposing NS patients for frequent relapse. Clinicians should strongly induce parents to follow up their affected children in order to detect UTIs in early stages and seek the appropriate therapy. Also, those parents should ensure that their affected children are taking adequate steroid therapy after the first episode of NS.

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#### Conflict of Interest

The author declares that they have no competing interests.

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