

## ORIGINAL ARTICLE

# Triggering Factors in Frequent Relapse Nephrotic Syndrome in Children and Their Association with Treatment Outcome

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## ABSTRACT

**Introduction:** Frequent relapse nephrotic syndrome (FRNS) in children poses significant challenges in management due to its recurrent nature and the impact of various precipitating factors. This study aimed to evaluate the triggering factors contributing to relapses in children with FRNS and to compare the relapse rates and baseline characteristics between case and control groups. **Methods & Materials:** This cross-sectional analytic study was conducted at the Department of Paediatric Nephrology, Bangabandhu Sheikh Mujib Medical University, Dhaka, from October 2015 to June 2016. Data analysis was done by SPSS for Windows programmed version 16.0. Sixty (60) study samples were taken. **Result:** The study included 60 children, with a mean age of  $5.28 \pm 2.03$  years in the case group and  $5.77 \pm 2.50$  years in the control group, showing no significant age difference ( $p = 0.412$ ). Males predominated in both groups, with a male-to-female ratio of 1.85:1 in cases and 1.5:1 in controls. Socioeconomic status was comparable between groups, with most participants from poor or middle-class backgrounds ( $p = 0.164$ ). Among the case group, common relapse-triggering factors included asthma (30%), UTI (25%), and URTI (25%). Relapse occurred in 47.5% of the case group and 40% of the control group over six months, with no statistically significant difference ( $p = 0.068$ ). **Conclusion:** Asthma, UTIs, and upper respiratory infections triggered relapse in 30%, 25%, and 25% of children with frequent relapse nephrotic syndrome, but their impact on treatment outcomes was similar across groups.

**Keywords:** Frequent Relapse Nephrotic Syndrome, Triggering Factors, Treatment Outcome, Asthma

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## INTRODUCTION

Nephrotic syndrome is a collection of symptoms that occur because the tiny blood vessels (the glomeruli) in the kidney become leaky. This allows protein (normally never passed out in the urine) to leave the body in large amounts<sup>[1]</sup>. Nephrotic syndrome (NS) is the most common glomerular disorder in childhood and is characterized by heavy proteinuria, hypoproteinaemia, and edema<sup>[2]</sup>. Children with an early onset of disease or a short duration of initial remission tend to have frequent relapse. Of patients who respond to prednisolone, 25-40% has infrequent relapses, 40% have frequent relapses and the remainder shows steroid dependence<sup>[3]</sup>. Minimal-change nephrotic syndrome (MCNS) accounted for 77% of all cases of childhood nephrotic syndrome in a series of the International Study of Kidney Diseases in children<sup>[4]</sup>. The majority of children with NS respond to corticosteroids.

However, >70% of children experience a relapse with recurrent episodes of edema and proteinuria<sup>[5]</sup>. Relapse is triggered by asthma, infection, and other immunogenic stimuli. Each relapse is associated with an increased risk of morbidity from infection, thromboembolism, hypovolemic shock, higher amount of steroids, and toxicity<sup>[6,7]</sup>. Corticosteroids have adverse effects such as the cushingoid face, obesity, hirsutism, striae, cataract, peptic ulcer disease, poor growth, hypertension, hyperglycemia, osteoporosis, adrenal suppression, buffalo hump, psychosis, dyselektrolytemia, immunosuppressant, avascular necrosis, easy bruising, and acute pancreatitis<sup>[8,9]</sup>. It has long been recognized that an immunogenic stimulus including infection and asthma can trigger idiopathic nephrotic syndrome or cause recurrence of the disease<sup>[10,11]</sup>. Infectious episodes in nephrotic patients are responsible for high morbidity and can

also cause an inadequate response to corticosteroid therapy and recurrences among patients in remission<sup>[12]</sup>. Some analyses revealed a greater incidence-density of infections during the period of nephrotic proteinuria, except for single-episode patients. More infection during relapse, infrequent relapse nephrotic syndrome, frequent relapse nephrotic syndrome, steroid-dependent, and steroid-resistant nephrotic syndrome patients, and it is suggested that the best preventive action is to control nephrotic state, prevent & control infection and asthma<sup>[13,14]</sup>. Prompt and effective treatment of infection and asthma can bring quick remission. Infection and asthma-associated FRNS can go into remission without steroids when they are treated appropriately & promptly and can be treated with a short duration of steroids like IFRNS. The purpose of this study is to analyze the triggering events of idiopathic frequent relapse nephrotic syndrome as well as their association with treatment outcomes.

## METHODS & MATERIALS

This cross-sectional analytic study was conducted at the Department of Paediatric Nephrology, Bangabandhu Sheikh Mujib Medical University, Dhaka, from October 2015 to June 2016. Patients admitted to the inpatient and attending the outpatient department (OPD) of the Paediatric Nephrology Department of Bangabandhu Sheikh Mujib Medical University, Dhaka was considered as the study population. Sixty (60) study samples were taken. From them, 40 patients were taken for the case group representing nephrotic syndrome with triggering factors. Another 20 patients were taken for the

control group representing nephrotic syndrome with no triggering factors. A purposive sampling technique was adopted. Data were entered into the computer with the help of software SPSS for Windows programmed version 16.0. After the frequency run, data were cleaned and frequencies were checked. An analysis plan was developed keeping in view the objectives of the study. A descriptive statistical analysis was carried out in the present study. Results on continuous measurements were presented on mean  $\pm$  SD (min-max) and results on categorical measurements were presented in number (%). A "P" value  $<0.05$  was considered as significant.

### Inclusion criteria:

- Age 1-18 years.
- Frequent relapse nephrotic syndrome (FRNS)

### Exclusion criteria:

- Infrequent relapse nephrotic syndrome (IFRNS)
- Steroid-dependent nephrotic syndrome (SDNS)
- Steroid resistance nephrotic syndrome (SRNS)
- Unwilling to participate.

## RESULTS

Table I shows that the mean age of the case group was  $5.28 \pm 2.03$  years and the control group was  $5.77 \pm 2.50$  years. The range of age was 3-10 years in the case group and 4-11 years in the control group. There was no significant difference in age between the case and control group (p-value is 0.412). [Table I]

**Table – I: Distribution of the patients according to age in case and control**

Age (years)	Group		p-value
	Case (n=40)	Control (n=20)	
3 – 6	30 (75.0)	14 (70.0)	0.412
7 – 11	10 (25.0)	6 (30.0)	
Total	40 (100.0)	20 (100.0)	
Mean $\pm$ SD	$5.28 \pm 2.03$	$5.77 \pm 2.50$	
Range (Min-Max)	3 - 10	4 - 11	

Unpaired t-test was done to measure the level of significance

The level of significance is  $<0.05$

Table II shows in the case group (n=40), 26 patients (65%) were male and 14 (35%) were female, yielding a male-to-female ratio of 1.85:1. In the control group (n=20), 12 patients

(60%) were male and 8 (40%) were female, with a male-to-female ratio of 1.5:1. [Table II]

**Table – II: Gender distribution among the study subjects (n=60)**

Gender	Case Group (n=40)	Control Group (n=20)
Male	26 (65%)	12 (60%)
Female	14 (35%)	8 (40%)
Male:Female Ratio	1.85:1	1.5:1

Table III shows in the case group, 24 (60%) were poor and 16 (40%) were from the middle class. In control group, 11 (55%) were poor, 8 (40%) were from middle class and

1 (5%) was rich. There was no significant difference in socioeconomic status between the case and control group (p-value is 0.164). [Table III]

**Table – III: Socioeconomic status of the patients in case and control (n=60)**

Group	Frequency	Socioeconomic status			P value
		Poor	Middle class	Rich	
Case	40	24 (60%)	16 (40%)	0(0%)	0.164
Control	20	11 (55%)	8 (40%)	1(5%)	

A chi-square test was done to measure the level of significance.

Table IV shows triggering factors in the case group. Amongst 40 cases, 12(30.0%) had asthma, 10(25.0%) had UTI, 10(25.5%) had upper RTI, 4(10.0%) had pneumonia, 3(7.5%) had peritonitis and 1(2.5%) had cellulitis. [Table IV]

**Table – IV: Factors precipitating relapse in the case group (n=40)**

Triggering Factors	Frequency (n=40)	Percent (%)
Asthma	12	30.0
Urinary Tract Infection (UTI)	10	25.0
Upper Respiratory Tract Infection (URTI)	10	25.0
Pneumonia	4	10.0
Peritonitis	3	7.5
Cellulitis	1	2.5

Table V shows in the case group 19(47.5%) patients had relapsed and in the control group 8(40.0%) patients had relapses. There was no significant difference between the case and control group (p-value was 0.068). [Table V]

**Table – V: Number of patients with relapses during six (6) months**

Outcome	Case group (n=40)	Control group (n=20)	P value
Number of patients with relapses	19(47.5%)	8(40%)	0.068

A chi-square test was done to measure the level of significance.

## DISCUSSION

Idiopathic nephrotic syndrome (INS) is the most common glomerular disease of childhood, representing approximately 95% of children with nephrotic syndrome. Minimal change disease (MCD) is the most common among them, representing about 85% of cases<sup>[1]</sup>. More than 95% of children with minimal change disease respond to corticosteroid therapy<sup>[15]</sup>. However, more than 70% of children experience a relapse among them 40% have frequent relapse<sup>[3]</sup>. The present study shows that the mean±SD age of case group was 5.28±2.10 years and control group 5.75±1.68 years. The range of age was 3-10 years in the case group and 4-11 years in the control group. There was no significant difference found in ages between the case and control group (p-value is 0.383). In some studies, the mean ages were 4.9 ± 2.9, 5.3± 3.9 and 5.8 ±3.3 years which are almost similar to the present study<sup>[4,5,14]</sup>. INS is more common in 2-8 years of age group<sup>[15]</sup>. In this study, out of 40 patients 26 (65%) were male and 14(35%) were female found in the case group, and control group out of 20 patients 12(60%) were male and 8(40%) were female. Almost similar findings were found by Rees L et al. out of 59 patients 38 (64.41%) were girls and 21 (35.59%) were boys<sup>[16]</sup>. In El-Husseini A et al. out of 117 patients, 83(71.9%) were boys and 34(29.1%) were girls and in another study Tarshish P et al. 66% were male patients and 34% were female patients<sup>[4,5]</sup>. Case and control groups of the present study are gender-matched and both groups had equal male and female ratio which is in corollary with a standard textbook<sup>[15]</sup>. Socioeconomic status, in case group, 24(60%)

were poor and 16(40%) were from middle class. In control group 11(55%) were poor, 8(40%) were from middle class and 1(5%) were rich. There was no significant difference in socioeconomic status between the case and control group (p-value is 0.164). Poor children are significantly more prone to develop INS including frequent relapse than solvent children<sup>[17]</sup>. In this study triggering factors in the case of group amongst 40 patients, 12(30.0%) had asthma, 10(25.0%) had UTI, 10(25.0%) had upper RTI and 4(10.0%) had pneumonia, 3(7.5%) had peritonitis and 1(2.5%) had cellulitis. In the study of Kopac M, all of the 9 initial episodes were SSNS (100 %) 18(58.1 %) out of 31 relapses were triggered by acute, mostly afebrile viral upper respiratory tract infections, and 2(6.5 %) out of 31 relapses were triggered by mosquito bites and 1 (3.2 %) by vaccination<sup>[3]</sup>. Gulati et al. reported that urinary tract infections may precipitate relapses in children with INS; a high frequency of such infections was found in their patients with frequent relapse and steroid resistance. The frequent viral and bacterial infections observed in developing countries may be associated with a tendency to relapse early and frequently. Another study conducted by Roy RR et al at BSMMU stated that 63% of study subjects had asthma/atopy, most of them were FRNS and steroid resistance and few of them were IFRNS<sup>[18]</sup>. The number of patients with relapsed during six (6) months in case group 19(47.5%) patients out of 40 had relapsed and in the control group 8(40%) out of 20 had relapses. No significant difference was found in the number of patients with relapses among the case and control groups (p-value is 0.068). Constantinescu et al and

Trompeter et al reported in their study less-frequent relapses among their studied patients in relation to a longer duration of steroid therapy, but these results were statistically not significant; their findings were similar to ours<sup>[19,20]</sup>. On the other hand, Anderson et al. found a significant relationship between prolonged steroid therapy (>12 weeks) and reduction in relapse frequency<sup>[21]</sup>.

# Limitations of The Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

# CONCLUSION

The study findings indicate that asthma, urinary tract infections, and upper respiratory tract infections were the most common triggering factors for relapse in children with frequent relapse nephrotic syndrome, observed in 30.0%, 25.0%, and 25.0% of cases respectively. While relapse was slightly more frequent in the case group (47.5%) compared to the control group (40.0%), this difference was not statistically significant ( $p = 0.068$ ). These results suggest that although specific infections and comorbid conditions may precipitate relapse, their overall impact on treatment outcomes may not differ significantly between groups.

# RECOMMENDATION

It is recommended that children with frequent relapse nephrotic syndrome be closely monitored for common triggering factors such as asthma and infections, particularly UTIs and upper respiratory tract infections. Early identification and prompt management of these conditions may help reduce the frequency of relapses and improve overall treatment outcomes.

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