

# Frequency of relapse among Nigerian children with steroid-sensitive nephrotic syndrome

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## Abstract

**Background:** The clinical course of steroid-sensitive nephrotic syndrome (SSNS) among Nigerian children has rarely been reported; this makes prognostication difficult.

**Objectives:** The objective was to determine the frequency of relapses including frequent relapses (FR) and steroid-dependence (SD) in a cohort of Nigerian children with SSNS. A secondary objective was to identify clinical and demographic factors associated with relapse in these children.

**Methods:** Medical records of children with SSNS in a Tertiary Hospital in Nigeria were reviewed. Children with onset of nephrotic syndrome (NS) at age <1-year, follow-up period <12 months and secondary causes of NS were excluded. The relapse status of each child was determined in the 1<sup>st</sup> and 2<sup>nd</sup> year after diagnosis and the proportions with no relapse, FR and SD were calculated.

**Results:** Fifty children (68% males; median [range] age at onset of NS 4.8 [1.1–14.9] years) were followed-up for 31.1 (12.1–79.8) months. In the 1<sup>st</sup> and 2<sup>nd</sup> year of follow-up, 23 (46%) and 24 (70.6%) children experienced relapse, respectively. In the 1<sup>st</sup>-year, 0% and 10% had FR and SD while in the 2<sup>nd</sup> year 2.9% and 11.8% had FR and SD, respectively. Age at onset of NS, gender, time to first remission, serum creatinine or presence of hypertension or microscopic hematuria was not associated with 1<sup>st</sup> or 2<sup>nd</sup> year relapse.

**Conclusion:** About half and two-thirds of children with NS in our center experience relapse in the 1<sup>st</sup> and 2<sup>nd</sup> year of follow-up, respectively; much fewer proportions experienced FR and SD in these periods. None of the commonly reported demographic and clinical factors was associated with NS relapse.

**Key words:** Frequent relapses, prednisolone, steroid-dependence

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## Introduction

Nephrotic syndrome (NS) is a common childhood kidney disease worldwide, with an estimated annual incidence of 2–7 cases per 100,000 children/year.<sup>[1]</sup> In majority of children with steroid-sensitive NS (SSNS) it is a relapsing condition.<sup>[2,3]</sup> Among Caucasians and Asians the clinical course of SSNS has been well described: About 80–90% will experience one or more relapses after onset of NS and about 50% will develop frequent relapses (FR) or steroid-dependence (SD).<sup>[2,3]</sup> The later group of children are unique because they frequently develop steroid-toxicities and eventually require steroid-sparing medications such as cyclophosphamide,

levamisole, and calcineurin inhibitors.<sup>[1,2,4]</sup> However, among black children the clinical course of SSNS has not been well described, partly because of small study population in previous studies;<sup>[5,6]</sup> this may hamper discussion of the clinical course with families of such children. Moreover, it may be misleading to shape the expectations of such families based on data from other races. For example, there is a high prevalence of steroid-resistance and nonminimal change disease in African children compared with other races.<sup>[7,8]</sup> Similarly, while young age, longer time to remission, and

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shorter duration of steroid-therapy have been associated with relapses in Caucasian and Asian children with SSNS, little is known about the predictors of relapses in black children with SSNS.<sup>[9-11]</sup> This study was undertaken to describe the clinical course of SSNS in a cohort of Nigerian children in Lagos and also to identify factors associated with subsequent relapses.

## Methods

The retrospective study was carried out at the Pediatric Nephrology Unit of the Lagos University Teaching Hospital. The hospital is a public-funded fee-for-service referral center in Lagos, South West Nigeria. Eligible participants were children with SSNS diagnosed after January 2007. Data analysis was done on December 31, 2014. Children with the following were excluded from the study: Secondary causes of NS such as sickle cell disease, hepatitis B, C virus or HIV infection, systemic lupus erythematosus; onset of NS in the 1<sup>st</sup>-year of life; duration of follow-up <12 months. Also excluded were those transferred in from another facility with clinical and laboratory features at the time of diagnosis of NS that could not be ascertained. At diagnosis of NS, caregivers were taught how to perform and record dipstick urinalysis test at home. Also recorded was the dose of prednisolone child was taking. At visits to the clinic, this information was transferred to the child's hospital records.

Information retrieved from the clinical and home records included age at diagnosis of NS, gender, presence of hematuria and hypertension at diagnosis, serum creatinine at diagnosis, time to enter remission, and dosing regimen of initial steroid-therapy. Information on the number and timing of relapses was also extracted.

Ethical approval was obtained from the hospital's ethic committee prior to the commencement of the study.

### Treatment regimen in the study center

Children diagnosed with idiopathic childhood NS received oral prednisolone at a daily dose of 60 mg/m<sup>2</sup>, (maximum dose, 60 mg) for 4 weeks. When remission was not achieved within 4 weeks prednisolone was continued for another 2 weeks. Since July 2012, an additional 2 weeks of prednisolone at 60 mg/m<sup>2</sup> was offered to the children before defining steroid-resistance. This is in line with the kidney disease: Improving global outcome (KDIGO) guidelines on glomerulonephritis published in the year 2012.<sup>[4]</sup> Prior to July 2010, the initial prednisolone dose for a day was given in divided doses. After attaining remission and receiving at least 4 weeks of prednisolone, the dose was reduced to 40 mg/m<sup>2</sup> (maximum dose, 40 mg), every other day for 4 weeks. Thereafter, the dose of prednisolone was tapered over a period of 4 months if the child remained in remission. Relapses were treated with prednisolone at a daily dose of 60 mg/m<sup>2</sup> until remission. Thereafter, the dose

of prednisolone was reduced to 40 mg/m<sup>2</sup> alternate day for 4 weeks. If the child remained in remission, prednisolone was tapered over 4 weeks. Children with FR or SD were treated with levamisole, cyclophosphamide, cyclosporine or tacrolimus. Indications for kidney biopsy in the unit included steroid-resistance and secondary NS. FR/SD was not considered an indication for kidney biopsy in our center as long as the child remained steroid-sensitive.

### Definition of terms

The terms used in the study were as defined by the KDIGO guidelines.<sup>[4]</sup> NS was defined by the presence of hypoalbuminemia (serum albumin  $\leq$  2.5 g/dl), massive proteinuria (3 + dipstick proteinuria or urinary protein >40 mg/m<sup>2</sup>/h, urine protein: Creatinine ratio >2 g/g) and edema. A child was considered to have attained remission when urine protein dipstick test became trace or negative for 3 consecutive days after commencement of prednisolone, while relapse was defined as the return of proteinuria of at least 3+ on dipstick for 3 consecutive days after attaining remission. FR referred to two or more relapses within 6 months of initial response or four or more relapses within any 12-month period; children with relapses less frequent than those for FR were considered to have infrequent relapses. On the other hand, SD was defined as at least two consecutive remissions while on alternate day prednisolone or within 2 weeks of stopping prednisolone. Failure to enter remission after 6 weeks of prednisolone at a daily dose of 60 mg/m<sup>2</sup> was defined as steroid-resistance; from mid-2012, steroid-resistance was diagnosed if remission was not achieved after 8 weeks of prednisolone. Hypertension was defined as systolic or diastolic blood pressure above the 95<sup>th</sup> centile for the age, gender and height centile of a child.<sup>[12]</sup> Children with no visible blood but who had at least one plus blood on urine dipstick were said to have microscopic hematuria.

### Data management

Retrieved data were analyzed using IBM SPSS Statistics 21.0 (IBM Corporation 2012, USA). All continuous variables of interest were skewed in distribution and were summarized as median (range); categorical data were represented as percentages. The number of relapses within the 1<sup>st</sup> and 2<sup>nd</sup> year of follow-up was counted for each child; each child was subsequently classified as having either "no relapse" "infrequent relapse", FR or SD at these periods. Odds ratios for independent factors associated with any relapse in the 1<sup>st</sup> and 2<sup>nd</sup> year of follow-up were calculated using logistic regression.  $P < 0.05$  was considered statistically significant.

## Results

Fifty children were included in the study and were followed-up for a median (range) period of 31.1 (11.5–79.2) months. Median (range) age of the children at diagnosis of

NS was 4.8 (1.1–14.9) years. Male children were 34 (68%). Fourteen (28%) and ten (20%) children had microscopic hematuria and hypertension at the time of the diagnosis of NS [Table 1].

### Pattern of relapses

Figure 1 shows the patterns of relapse of the children included in the study. In the first 12 months after diagnosis, 23 (46%) children experienced at least one relapse; 5 (10%) children had SD, none had FR. Of the 34 children followed up for at least 24 months, 12 (35.3%) and 24 (70.6%) children experienced at least one relapse in the 1<sup>st</sup> and 2<sup>nd</sup> 12 months, respectively [Figure 2]. While 1 (2.9%) child had SD in the first 12 months, 5 (14.7%) children developed FR or SD in the second 12 months. No child with relapse in the first 12 months was relapse-free in the 2<sup>nd</sup> year of follow-up. Three (27.3%) of 11 children within FR in the first 12 months developed FR or SD in the 2<sup>nd</sup> year compared with 1 (4.5%) of 22 children with no relapse in the first 12 months of follow-up.

### Factors associated with relapses

Table 2 shows the association between independent variables and any relapse in the 1<sup>st</sup> and 2<sup>nd</sup> 12 months. Children who experienced relapse were younger than those who remained relapse-free during these periods,

but the difference was not significant. Similarly, there was no significant difference between those with or without NS relapse in terms of time to first remission, presence of microscopic hematuria and hypertension at the time of diagnosis of NS.

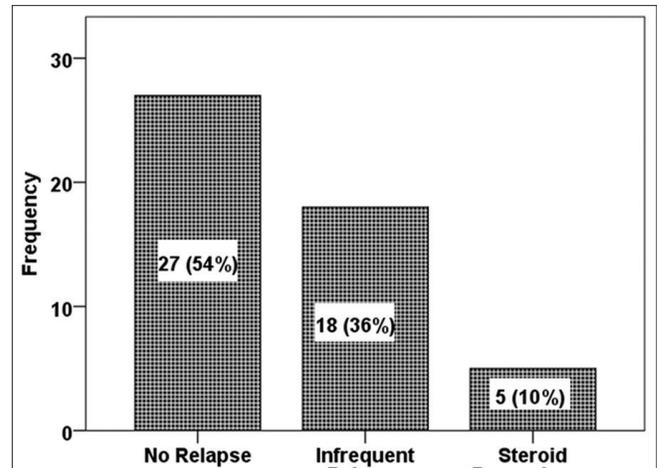


Figure 1: Relapse status of children with steroid-sensitive nephrotic syndrome in the 1st-year of life

Table 1: Baseline characteristics of children with steroid-sensitive NS studied

Characteristics at diagnosis of NS	n = 50
Age at diagnosis, year*	4.8 (1.1-14.9)
Male gender, n (%)	34 (68)
Microscopic hematuria, n (%)	14 (28)
Hypertension, n (%)	10 (20)
Serum creatinine, mg/dL*	0.6 (0.2-1.7)
Receipt of prednisolone as single daily dose, n (%)	31 (62)
Time to first remission, days*	13 (4-52)
Duration of follow-up, months*	31.1 (11.5-79.2)
Age at last follow-up, year*	7.6 (2.6-18.1)

\*These values are median (minimum-maximum). NS=Nephrotic syndrome

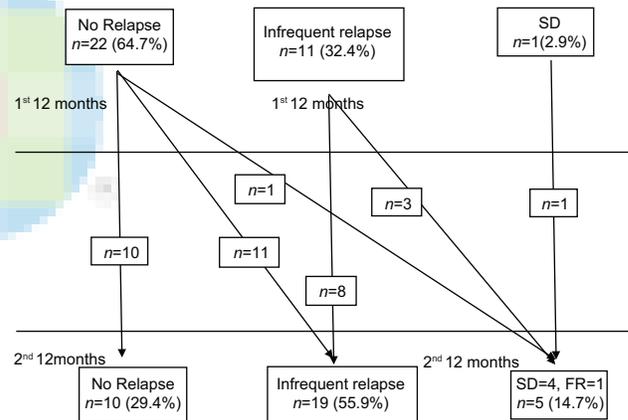


Figure 2: Relapse patterns of children with steroid-sensitive nephrotic syndrome followed-up for 24 months

Table 2: Factors associated with relapses among children with steroid-sensitive NS

Characteristics	Relapse status in 1 <sup>st</sup> -year of follow-up (n = 50)				Relapse status in 2 <sup>nd</sup> year of follow-up (n = 34)			
	No relapse (n=27) (54%)	Relapsed (n=23) (46%)	OR (95% CI)	P	No relapse (n=10) (29.4%)	Relapsed (n=24) (70.6%)	OR (95% CI)	P
Age at onset, year*	5.4 (1.1-14.9)	2.3 (1.4-13.1)	0.88 (0.74-1.05)	0.16	6.4 (1.5-10.9)	3.5 (1.1-14.9)	0.89 (0.73-1.10)	0.28
Female gender, n (%)	9 (33.3)	7 (30.4)	0.88 (0.27-2.89)	0.83	6 (54.5)	6 (26.1)	0.41 (0.09-1.88)	0.25
Time to 1 <sup>st</sup> remission, days*	12.0 (4-42)	14.0 (2-55)	1.02 (0.98-1.07)	0.38	25.5 (7-42)	11.5 (4-34)	0.95 (0.90-1.01)	0.10
Microscopic hematuria, n (%)	10 (37.4)	4 (17.4)	2.79 (0.74-10.58)	0.13	4 (36.4)	6 (26.1)	1.04 (0.21-5.23)	0.96
Hypertension, n (%)	6 (22.2)	4 (17.4)	1.36 (0.33-5.55)	0.67	3 (27.3)	6 (26.1)	1.29 (0.25-6.62)	0.76
Receipt of prednisolone as single daily dose, n (%)	16 (59.3)	15 (65.2)	0.83 (0.26-2.65)	0.76	7 (63.6)	11 (47.8)	1.50 (0.34-6.70)	0.60
Serum creatinine, mg/dL*	0.5 (0.2-1.7)	0.6 (0.2-1.4)	0.48 (0.09-2.69)	0.41	0.7 (0.2-1.4)	0.5 (0.3-1.7)	0.25 (0.03-2.03)	0.19

\*These values are median (minimum-maximum). OR=Odds ratio; CI=Confidence interval; NS=Nephrotic syndrome

## Discussion

The high incidence of steroid-resistance among African children with NS probably underlies the paucity of published research on the patterns and factors associated with relapses in African children with NS. We took advantage of a relatively large cohort of children with SSNS in our center to describe the clinical course of NS and factors associated with relapses in black children. Our main findings were that about a half and two-thirds of children with idiopathic SSNS relapsed in the 1<sup>st</sup> and 2<sup>nd</sup> year of follow-up, respectively; much lower proportion developed FR/SD.

A unique finding of the present study was the lower proportion of children with relapse compared with findings reported in Caucasian and Asian children.<sup>[2,3,10]</sup> In a prospective study of over 100 children in Australia, Sureshkumar *et al.*<sup>[3]</sup> documented relapse in 80% of the children after 12 months of follow-up. Another recent study in India revealed that approximately 90% developed at least one relapse by 12 months of follow-up.<sup>[2]</sup> In addition, the proportion of children with FR or SD in most studies involving nonblack children is approximately 40–50% in the 1<sup>st</sup>-year of follow-up, which far exceeded the 10–14.7% in the present study.<sup>[2,10,13]</sup> The low frequency of relapse persisted even after 2 years following diagnosis. Two previous smaller studies from Nigeria have documented different relapse rates. In Ife, southwest Nigeria, Olowu *et al.*<sup>[5]</sup> reported relapse-free rates at 1 and 2 years to be 48.7% and 35.5%, respectively, similar to the findings of the present study, while Anochie *et al.*<sup>[6]</sup> in Port Harcourt, South-South Nigeria documented much higher relapse rate though the time of documentation of the relapse status was not stated. We are not aware of any reason for the unexpected finding in our study. In terms of study population descriptors that have been associated with relapse, such as age at onset of NS and male-female ratio, the present study was similar to other studies which reported higher relapse rates except for differences in the race of the children and cumulative dose of steroid given in the initial treatment of NS.<sup>[2,13,14]</sup> We envisage that the longer course of prednisolone and larger cumulative dose employed in the present study may have contributed to the lower frequency of relapse, although two recent randomized control trials involving Asian children suggest otherwise.<sup>[10,11,15-17]</sup> Furthermore, differences between the epidemiology of NS in different races mean the effect of race could be a possible explanation for the differences.<sup>[8,18]</sup> There is a need for more studies to confirm or refute this finding.

The strong association between young age at onset of NS and 1<sup>st</sup>-year relapse identifies it as a factor to consider when discussing the possible course of NS with caregivers. Its frequent association in many studies of children,

strengthens its prognostic significance.<sup>[2,10]</sup> However, though the children who experienced NS relapse were younger in the present study, the difference was not statistically significant. The lack of any association between age at onset of NS and occurrence of relapse has been reported by other workers.<sup>[3,13]</sup>

While some studies<sup>[11,19]</sup> reported an association between the time to first remission and subsequent relapse or FR/SD, others including the present study found no such association.<sup>[3,10]</sup> Similarly, gender and microscopic hematuria enjoy an inconsistent relationship with subsequent relapses, FR or SD in published literature.<sup>[3,14]</sup> For instance, while Andersen<sup>[10]</sup> and Sureshkumar *et al.*<sup>[3]</sup> reported male gender as risk factor for subsequent relapses, FR or SD, others did not find such relationship.<sup>[2,13]</sup> The reasons for the inconsistency are unknown but may be related to differences in the study population and design.

A major limitation of our study was the relatively small number of children included in the study, which may have underpowered the ability of the study to detect predictors of subsequent NS relapse, however the high frequency of steroid-resistance among children in Africa makes a larger cohort of black children with SSNS in a single center unlikely.<sup>[7]</sup> Another limitation of the study is its retrospective design. For instance, we could not comment with certainty on the frequency and type of adverse events with longer steroid-therapy nor on the concurrence of infection with relapse episodes. Furthermore, it may well be that kidney histology explains some of our findings but we were not able to comment on its impact, because, as long as a children remained steroid-sensitive kidney biopsy was not performed.

In conclusion, the frequency of NS relapse, FR and/SD in our center was much lower than rates reported in other regions of the world. None of the commonly reported factors was associated with NS relapse in our study.

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