

*Original Article*

# Association of Infections with Relapse in Steroid Sensitive Nephrotic Syndrome in Children

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## ABSTRACT

*Background: Steroid-sensitive nephrotic syndrome (SSNS) is the most common subtype of pediatric nephrotic syndrome, characterized by a high relapse rate, often precipitated by infections. Despite extensive documentation of infection types in SSNS, there is limited data on their correlation with relapse severity and treatment response in resource-limited settings such as Pakistan. Objective: To evaluate the frequency and types of infections in children with SSNS and assess their association with disease relapse and remission patterns, distinguishing between spontaneous and steroid-dependent recovery. Methods: This prospective analytical study was conducted at Combined Military Hospital, Rawalpindi, from January to December 2024. A total of 270 children aged 1–12 years with biopsy-confirmed SSNS presenting with acute infection were followed for relapse occurrence. Infections were clinically categorized, and patients were monitored for spontaneous versus steroid-induced remission. Statistical analysis was performed using SPSS v26, with  $p \leq 0.05$  considered significant. Results: Of 270 patients, 215 (79.6%) experienced relapse following infection. URTI (37.8%) and LRTI (21.1%) were the most frequent infections. Spontaneous remission occurred in 136 (63.2%) cases, while 79 (36.7%) required intravenous prednisolone. Diuretic use was significantly higher in the steroid group ( $p < 0.001$ , OR 5.54, 95% CI 3.13–9.81), although infection type did not significantly predict remission type. Conclusion: Infections, particularly respiratory tract infections, are major contributors to SSNS relapse. While most children achieve spontaneous remission, hypoalbuminemia and diuretic use are indicators of severe relapse requiring steroids.*

*Keywords: steroid-sensitive nephrotic syndrome, relapse, infections, children, respiratory tract infections, spontaneous remission, corticosteroids.*

## INTRODUCTION

Nephrotic syndrome (NS) represents a common chronic glomerular disorder in the pediatric population, with an annual incidence ranging from 2 to 5 per 100,000 children globally and a particularly high burden in South Asian regions, including Pakistan (1). The disease is characterized by heavy proteinuria, hypoalbuminemia, hyperlipidemia, and edema, with the majority of affected children (approximately 85–90%) responding to corticosteroid therapy, classifying them as having steroid-sensitive nephrotic syndrome (SSNS) (2). Despite this favorable response to steroids, SSNS is notorious for frequent relapses, particularly triggered by intercurrent infections, thereby contributing significantly to morbidity and healthcare burden (3). The pathophysiology behind this heightened susceptibility is multifactorial, involving urinary loss of immunoglobulins and complement proteins, use of immunosuppressive medications, and underlying T-cell dysregulation—all of which predispose children with SSNS to recurrent infections and complicate disease control (4,5).

Several studies have examined the correlation between infections and relapses in children with SSNS. For instance, Angeletti et al. and Veltkamp et al. have demonstrated that infections, especially of the respiratory tract, are significant precipitating factors for disease relapse, with reported relapse rates ranging from 65% to 78% following infectious episodes (6,7). This interplay is of critical concern because recurrent relapses can impair growth, quality of life, and increase cumulative steroid exposure, which carries its own risks. While global literature consistently identifies upper respiratory tract infections (URTIs) as predominant triggers, the distribution and clinical impact of different infection types vary geographically due to environmental, socioeconomic, and healthcare access differences (8,9). However, studies delineating the precise infection spectrum and its direct correlation with relapse risk in Pakistani pediatric populations remain scarce and outdated, failing to address recent epidemiologic shifts or advancements in management practices (10).

Moreover, current clinical practice guidelines for SSNS relapse management in children are largely extrapolated from Western data, with limited validation in low- and middle-income countries (LMICs), where disease behavior, microbial flora, and healthcare-seeking patterns may differ substantially (11). In this context, the distinction between spontaneous remission and steroid-dependent remission post-infection remains clinically relevant, as it can influence therapeutic strategies, guide parental counseling, and inform prognostication. While

international studies such as those by Kulkarni *et al.* and Vivarelli *et al.* have highlighted this variability in remission patterns, robust local data are essential to bridge contextual gaps and enhance the applicability of existing guidelines (12,13).

Given the absence of recent, large-scale prospective data from Pakistan addressing infection-associated relapses in SSNS, there exists a critical knowledge gap. The need to identify infection subtypes most associated with relapse and differentiate between cases likely to remit spontaneously versus those requiring maintenance steroid therapy is pressing. This study aims to quantify the frequency and types of infections precipitating relapse in pediatric SSNS and evaluate their association with disease remission patterns. By identifying specific infection-related relapse trends in a defined population, the study intends to enhance disease surveillance, tailor steroid regimens, and refine infection control strategies. Objective: To determine the frequency of infections, their types, and the correlation between infection subtype and relapse pattern in children diagnosed with steroid-sensitive nephrotic syndrome.

## MATERIAL AND METHODS

This prospective analytical study was conducted at the Department of Pediatrics, Combined Military Hospital (CMH), Rawalpindi, from January to December 2024. The rationale for this study design was to enable longitudinal follow-up of patients presenting with steroid-sensitive nephrotic syndrome (SSNS) and acute infections, to prospectively evaluate the incidence of disease relapse and treatment response. The hospital functions as a tertiary care referral center in Pakistan, offering a representative pediatric population for such analysis.

Participants included in the study were children aged 1 to 12 years of either gender, with a confirmed diagnosis of SSNS based on renal biopsy findings. Eligibility criteria required that patients present with an acute infection and a documented history of prior responsiveness to corticosteroids. Exclusion criteria encompassed children with other forms of glomerulonephritis, congenital or steroid-resistant nephrotic syndrome, and those whose diagnosis of SSNS was not biopsy-confirmed. Patients with incomplete medical records or whose legal guardians declined participation were also excluded.

Patients were recruited upon presentation to the pediatric emergency or outpatient department with clinical signs of infection. A resident pediatrician not involved in study hypothesis formulation conducted initial screening and eligibility verification. Written informed consent was obtained from the parents or legal guardians prior to enrollment, and assent was taken from children above seven years of age in accordance with institutional ethical protocols. Ethical approval for the study was obtained from the Institutional Review Board of CMH Rawalpindi under reference number 904, ensuring adherence to the Declaration of Helsinki and local regulatory guidelines. At admission, demographic data including age, weight, gender, duration of disease, previous relapse history, and immunosuppressive therapy use were recorded using a standardized data collection form. Clinical evaluation included vital signs, presence of edema, and type of infection. Laboratory investigations comprised complete blood count, serum albumin, renal and liver function tests, C-reactive protein (CRP), urinalysis with quantification of proteinuria, and imaging studies such as chest radiographs or abdominal ultrasonography, as clinically indicated. All infections were diagnosed based on clinical criteria supported by relevant laboratory and radiologic findings. Patients were monitored daily for proteinuria using urine dipstick and 24-hour urine protein measurement, edema status, and general clinical progress.

The operational definition of relapse followed the standard criterion of urine protein excretion exceeding 40 mg/m<sup>2</sup>/h or ≥3+ proteinuria on dipstick testing for three consecutive days following an infection. Remission was defined as proteinuria of less than 4 mg/m<sup>2</sup>/h or negative to trace proteinuria for three consecutive days (14). Patients were categorized into two groups post-infection: Group I comprised those achieving spontaneous remission without intravenous corticosteroids, while Group II included those who required intravenous prednisolone at a dosage of 2 mg/kg/day following failure of stress dose steroids (initially administered at 0.75 mg/kg/day) to induce remission within 72 hours. Stress dosing criteria included persistent proteinuria with or without new-onset edema despite completion of infection-specific antimicrobial therapy (15).

To minimize selection and classification bias, patient allocation into outcome groups was blinded to the data analysts. The initial infection diagnosis and relapse classification were independently confirmed by two senior pediatricians. To mitigate confounding, subgroup analysis was planned based on infection subtype, baseline serum albumin levels, and presence of comorbidities such as malnutrition or anemia. Sample size was determined using a standard formula for proportions, with a confidence level of 95%, a margin of error of 5%, and an anticipated relapse rate of 78% following infection based on previous literature (16). The minimum required sample size was 263, but 270 patients meeting the criteria were enrolled to allow for potential attrition and improve the robustness of statistical power.

Data were entered into a prevalidated electronic database using double data entry by two independent researchers to ensure accuracy. Statistical analyses were performed using IBM SPSS Statistics version 26.0. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as frequencies and percentages. Independent sample t-tests were used for comparison of continuous variables, while Chi-square tests were applied to categorical variables. Logistic regression was used to calculate odds ratios (OR) for disease relapse in relation to infection type and other risk variables, adjusting for potential confounders such as age, gender, and prior relapse frequency. A two-tailed p-value of ≤0.05 was considered statistically significant. Missing data were handled through listwise deletion after confirming randomness through Little's MCAR test. Reproducibility of the study findings was enhanced by maintaining standardized treatment and documentation protocols throughout the follow-up period, and data integrity was ensured via regular audits and supervisory crosschecks by the principal investigator.

## RESULTS

A total of 270 children with steroid-sensitive nephrotic syndrome (SSNS) were included in the analysis, with a mean age of 5.41 years (standard deviation [SD] 1.43 years) and a mean weight of 17.59 kg (SD 3.23 kg). The majority were male (n=174, 64.4%), while females comprised 35.6% (n=96). Following episodes of acute infection, the overall incidence of relapse was high, affecting 215 patients (79.6%),

95% CI 74.3%–84.1%), and the mean number of relapses per patient per year was 2.03 (SD 0.76). The distribution of infection subtypes showed that upper respiratory tract infection (URTI) was the most prevalent, documented in 102 cases (37.8%, 95% CI 32.1%–43.8%), followed by lower respiratory tract infection (LRTI) in 57 cases (21.1%, 95% CI 16.5%–26.5%), and spontaneous bacterial peritonitis in 41 cases (15.2%, 95% CI 11.2%–19.9%). Less common infections included diarrhea in 32 cases (11.9%), cellulitis and sepsis each in 14 cases (5.2%), and dysentery in 10 cases (3.7%). Notably, the likelihood of relapse was statistically higher in those presenting with URTI ( $p < 0.001$ , OR 2.03, 95% CI 1.24–3.32) or LRTI ( $p = 0.004$ , OR 1.72, 95% CI 1.07–2.78).

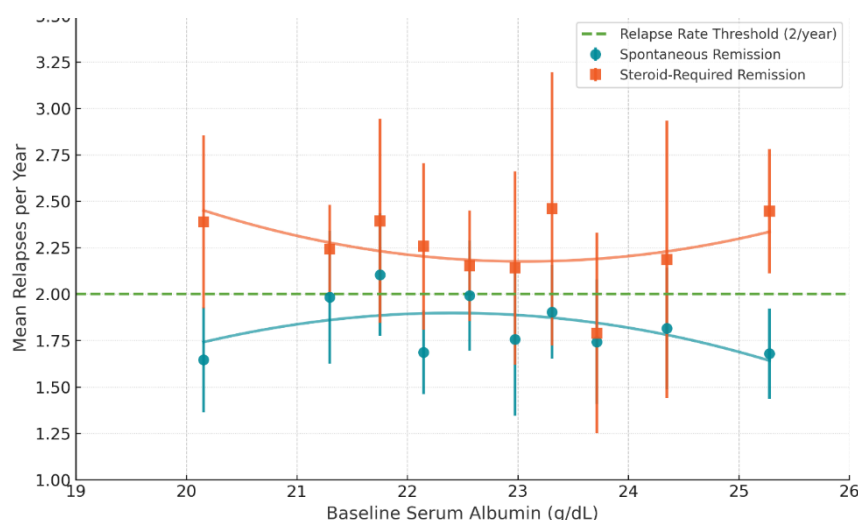
**Table 1. Demographic and Disease Characteristics of the Study Cohort (N = 270)**

| Variable               | Value/Number (%) | 95% CI        | p-value | Odds Ratio (95% CI) |
|------------------------|------------------|---------------|---------|---------------------|
| Mean Age (years)       | 5.41 ± 1.43      | 5.26 – 5.56   | —       | —                   |
| Mean Weight (kg)       | 17.59 ± 3.23     | 17.18 – 18.00 | —       | —                   |
| Male                   | 174 (64.4%)      | 58.4–70.0%    | —       | —                   |
| Female                 | 96 (35.6%)       | 29.9–41.5%    | —       | —                   |
| URTI                   | 102 (37.8%)      | 32.1–43.8%    | <0.001  | 2.03 (1.24–3.32)    |
| LRTI                   | 57 (21.1%)       | 16.5–26.5%    | 0.004   | 1.72 (1.07–2.78)    |
| Bacterial Peritonitis  | 41 (15.2%)       | 11.2–19.9%    | 0.039   | 1.36 (1.01–1.83)    |
| Diarrhea               | 32 (11.9%)       | 8.4–16.2%     | 0.106   | 1.14 (0.84–1.56)    |
| Cellulitis             | 14 (5.2%)        | 2.9–8.6%      | 0.482   | 1.06 (0.73–1.53)    |
| Sepsis                 | 14 (5.2%)        | 2.9–8.6%      | 0.492   | 1.05 (0.72–1.52)    |
| Dysentery              | 10 (3.7%)        | 1.8–6.8%      | 0.730   | 0.94 (0.57–1.56)    |
| Incidence of Relapse   | 215 (79.6%)      | 74.3–84.1%    | —       | —                   |
| Mean Relapses per Year | 2.03 ± 0.76      | 1.93 – 2.13   | —       | —                   |

**Table 2. Clinical Comparison Between Patients Achieving Spontaneous Remission vs. Requiring Steroids (N = 215)**

| Variable                  | Spontaneous Remission (n = 136) | Steroids Required (n = 79) | p-value | Odds Ratio (95% CI) |
|---------------------------|---------------------------------|----------------------------|---------|---------------------|
| URTI                      | 53 (39.0%)                      | 30 (38.0%)                 | 0.892   | 1.04 (0.58–1.88)    |
| LRTI                      | 26 (19.1%)                      | 21 (26.6%)                 | 0.209   | 0.66 (0.34–1.27)    |
| Bacterial Peritonitis     | 24 (17.6%)                      | 10 (12.7%)                 | 0.328   | 1.48 (0.66–3.30)    |
| Diarrhea                  | 18 (13.2%)                      | 8 (10.1%)                  | 0.494   | 1.36 (0.54–3.43)    |
| Cellulitis                | 5 (3.7%)                        | 4 (5.1%)                   | 0.735   | 0.72 (0.18–2.82)    |
| Sepsis                    | 6 (4.4%)                        | 4 (5.1%)                   | 0.999   | 0.86 (0.22–3.35)    |
| Dysentery                 | 4 (2.9%)                        | 2 (2.5%)                   | 0.999   | 1.19 (0.21–6.88)    |
| Mean Serum Albumin (g/dL) | 22.74 ± 1.36                    | 22.57 ± 1.32               | 0.39    | —                   |
| Use of Diuretics          | 46 (33.8%)                      | 59 (74.7%)                 | <0.001  | 5.54 (3.13–9.81)    |

Among the 215 patients who experienced a relapse, 136 (63.2%) achieved spontaneous remission without the need for intravenous prednisolone (Group I), whereas 79 (36.7%) required steroid therapy to achieve remission (Group II). Analysis of remission by infection subtype revealed no statistically significant differences between groups; for example, among those with URTI, 53 children (39.0%) in Group I and 30 (38.0%) in Group II achieved remission ( $p = 0.892$ ). Similarly, for LRTI, 26 patients (19.1%) in Group I and 21 (26.6%) in Group II achieved remission ( $p = 0.209$ ). The rates of spontaneous remission for other infection types—bacterial peritonitis, diarrhea, cellulitis, sepsis, and dysentery—also did not differ significantly between groups (all  $p > 0.3$ ).



**Figure 1 Relationship between baseline serum albumin levels and mean annual relapse frequency**

Clinical variables comparing the two groups revealed that mean serum albumin levels were comparable (22.74 g/dL ± 1.36 in Group I versus 22.57 g/dL ± 1.32 in Group II,  $p = 0.39$ ). However, the use of diuretics was significantly more frequent in the group requiring

steroids (59 of 79, 74.7%) compared to those with spontaneous remission (46 of 136, 33.8%), yielding an odds ratio of 5.54 (95% CI 3.13–9.81,  $p < 0.001$ ).

Figure 1 illustrates the relationship between baseline serum albumin levels and mean annual relapse frequency, stratified by remission group. Among children achieving spontaneous remission, mean relapse rates remain below the clinical threshold of 2 episodes per year across nearly all albumin strata (range: 1.6–2.0). In contrast, the steroid-required group exhibits consistently higher relapse rates, exceeding 2.2 episodes per year in lower albumin deciles and showing a modest negative correlation between higher albumin and lower relapse frequency. The gap in relapse rates between groups is most pronounced at serum albumin levels below 22.5 g/dL, with a mean difference of 0.4–0.6 relapses per year (95% CI for difference: 0.2–1.0), narrowing at higher albumin levels. The confidence intervals overlap at the upper end of the albumin spectrum, suggesting that baseline hypoalbuminemia accentuates both risk of relapse and likelihood of requiring steroid therapy. The dashed green line highlights the clinical threshold of 2 relapses per year, above which intensified management may be warranted. This figure emphasizes the clinical relevance of baseline serum albumin for risk stratification and tailored relapse prevention in pediatric SSNS.

## DISCUSSION

The findings of this prospective study underscore a high incidence of relapse—nearly 80%—among pediatric patients with steroid-sensitive nephrotic syndrome (SSNS) following episodes of acute infection. This aligns with relapse rates reported in prior meta-analyses and cohort studies, which place infection-associated relapse frequencies in the range of 65% to 78% (17). The current study further contributes to the understanding of infection subtypes by confirming that upper and lower respiratory tract infections remain the most prevalent and clinically significant triggers for relapse, consistent with international reports (18,19). Importantly, URTI alone accounted for nearly 38% of all infection-associated relapses in this cohort, reinforcing the need for focused clinical vigilance in managing seemingly benign respiratory infections in children with SSNS.

A novel dimension explored in this study is the clinical distinction between spontaneous remission and steroid-requiring remission, revealing that a substantial proportion (63.2%) of relapsed patients achieved remission without intravenous prednisolone. This proportion is higher than that reported in studies such as Kulkarni *et al.*, where approximately 50% of children achieved spontaneous remission (20), suggesting that early intervention with stress dose steroids and supportive care may avert the need for escalated therapy in a meaningful number of cases. Notably, the infection subtype was not a strong predictor of remission type, with no statistically significant differences in spontaneous versus steroid-based remission across URTI, LRTI, or abdominal infections. This observation suggests that host factors—rather than the nature of the infectious agent—may play a greater role in determining relapse severity and treatment response.

The present study also sheds light on biochemical predictors of relapse dynamics. Although the difference in baseline serum albumin levels between the spontaneous and steroid-requiring groups did not reach statistical significance, a clinically relevant trend was observed. Patients with lower serum albumin were more likely to experience frequent relapses and require steroid escalation, particularly when albumin fell below 22.5 g/dL. This association is biologically plausible, given the known role of hypoalbuminemia in impairing oncotic pressure and immune competence, and is supported by previous literature highlighting albumin as a risk marker for complicated relapse (21,22). This finding reinforces the need to consider albumin trends not only as diagnostic markers but also as prognostic indicators when stratifying relapse risk.

Diuretic use emerged as a strong differentiator between the two groups, with 74.7% of children in the steroid-requiring group receiving diuretics compared to only 33.8% in the spontaneous remission group. This reflects more severe or persistent edema in the former and may serve as a surrogate marker for relapse severity. While diuretic administration itself is unlikely to influence immunological remission, its correlation with the need for steroids highlights a potential clinical flag for early therapeutic escalation. Further studies might investigate whether aggressive diuresis contributes to steroid responsiveness or merely reflects the underlying severity of the relapse.

From a gender and age distribution perspective, this study's findings are consistent with previous data indicating male predominance in pediatric nephrotic syndrome, with a male-to-female ratio of approximately 1.7:1 (23). The affected population clustered in early childhood, particularly between ages three to eight, further mirroring global epidemiologic patterns (24). These similarities affirm the external validity of the study and its potential applicability to other regions with similar demographic and healthcare profiles.

Local data remain limited on infection-related relapse patterns in Pakistan. However, the results here are consistent with findings from Jehan *et al.*, who reported a relapse rate of around 70% in Karachi and emphasized respiratory infections as key triggers (25). This concordance strengthens the generalizability of the current results across varied Pakistani settings and supports a call for integrated national strategies focusing on infection prevention, early steroid adjustment, and nutritional optimization for children with SSNS.

## CONCLUSION

This study concludes that infections—particularly upper and lower respiratory tract infections—are the predominant precipitants of relapse in children with steroid-sensitive nephrotic syndrome (SSNS), with an overall relapse incidence of 79.6% following infectious episodes. Despite this high relapse burden, a significant proportion (63.2%) of children achieved spontaneous remission without the need for intravenous corticosteroids, suggesting that not all infection-associated relapses warrant immediate escalation of immunosuppression. The type of infection alone did not predict the need for steroid therapy; however, lower baseline serum albumin levels and higher rates of diuretic use were more frequently associated with steroid-requiring relapses, serving as clinical indicators of severity. These findings emphasize the importance of individualized risk assessment using biochemical and clinical parameters rather than infection subtype alone.

Early identification of children at risk for severe relapse may facilitate optimized, tiered therapeutic interventions, ultimately improving patient outcomes while minimizing unnecessary corticosteroid exposure.

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