Infection Associated Relapses in Children with Nephrotic Syndrome: A Short-term Outcome Study

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ABSTRACT. Children with nephrotic syndrome (NS) encounter multiple episodes of relapses associated/triggered by an episode of infection. The primary objective of this study was to find the proportion of infection associated relapses that resolve on the treatment of acute infection over an observation period of two weeks in children with NS. This prospective observational study enrolled 45 children with steroid-sensitive NS presenting with an infection associated relapse during the study period (February 2015 to February 2016). Baseline information and examination findings of all children were recorded. Biochemical and other investigations were performed according to the site of infection for all patients and were treated appropriately. None of the patients received daily 2 mg/kg of prednisolone during the observation period. All children were followed for two weeks for resolution of relapse and subsequently every month for another three months. The 45 patients (median age 66 months) enrolled in the study had 64 episodes of infections, of which upper respiratory tract infections (45%) were the commonest, followed by peritonitis (18.5%) and diarrhea in 12%. Twenty-seven (60%) patients achieved remission on symptomatic treatment of infection with/without the use of stress doses of prednisolone. Most (77.8%) patients who achieved remission without the use of daily 2 mg/kg of prednisolone did so within the 1st week and a majority of patients were still in remission at three months follow-up. We conclude that most infection associated relapses can be managed with treatment of underlying infection alone and use of stress doses of steroids for inducing remission without increasing the prednisolone doses to 2 mg/kg/d and thus reducing the cumulative steroid doses.

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Introduction

Nephrotic syndrome (NS) in childhood is characterized by multiple relapses often triggered or associated with infections. Patients with NS are at a higher risk for bacterial and viral infections. Increased predisposition to infec-
tions occurs primarily due to urinary losses of immunoglobulins, complement, and properdin.\textsuperscript{1} Altered T-cell mechanisms, use of prolonged immunosuppressive therapy, and the presence of edema also contribute to infections. Of the severe infections, peritonitis has an incidence of 2\%–6\% among these patients.\textsuperscript{2,3} Relapses of NS often occur after infections of the respiratory tract and gastrointestinal tract. The actual cause of these recurrences is not clear. It is proposed that viral infections may cause an upregulation of TH1 cytokines, which through a yet undefined cytokine cause an increase in glomerular permeability for proteins and triggers a relapse of the nephrotic state. A study from Pakistan on 62 children with NS and infections showed that acute respiratory infections (29.27\%) were the most common followed by skin infections (27\%) and diarrhea. Almost 78\% of the infections were associated with a relapse.\textsuperscript{4} In a retrospective study from Brazil on 92 children with NS, the incidence of upper respiratory tract infections (URTIs) (77\%) was found to be maximum followed by diarrhea (7.2\%), pneumonia (4.1\%), cutaneous infections (5.2\%) and 69.4\% episodes of infections were associated with a relapse.\textsuperscript{5} A previous from our center showed the incidence of URTIs as 28\% in children with NS; 22.5\% had urinary tract infections, 15.8\% pneumonia, 14\% peritonitis, and 10.5\% had invasive diarrhea. The same study showed a spontaneous remission rate of 15.8\% for infection associated relapses.\textsuperscript{6} Most studies in the past have looked at the incidence of infection alone in children with NS; information on the outcome of infection associated relapses is lacking. While some of the infection associated relapses remit on treatment of infections itself, few require corticosteroids for inducing remission. Clear guidelines on the treatment of such relapses are lacking.

**Materials and Methods**

This prospective observational study was conducted in the department of Pediatrics of a tertiary care teaching hospital during the period February 2015 to February 2016. The patients enrolled for the study were children who visited the outpatient department of pediatric nephrology services of the hospital, fulfilled the inclusion criteria, and provided consent for the study. The study protocol was approved by the Institutional Ethical Committee.

**Inclusion criteria**

All children and adolescents (1–18 years) with steroid-sensitive NS (SSNS) with a relapse and a concomitant acute infection were included in the study.

**Exclusion criteria**

Known cases of steroid-resistant NS (SRNS), lupus nephritis, membranous nephropathy, membranoproliferative glomerulonephritis, and congenital NS were excluded from the study.

**Sample size**

The sample size of the study was calculated by estimating the proportion of infection associated relapses as 50\% with a 95\% confidence level and 15\% as absolute precision; the sample size thus calculated was 43 and 45 patients were enrolled for the study. Previous studies have shown a prevalence of 40\%–65\% for infection associated relapses.\textsuperscript{5,7}

**Primary outcome**

The primary outcome measure was the proportion of patients with SSNS presenting with an infection associated relapse who had remission on the treatment of acute infection during an observation period of two weeks.

**Secondary outcome**

The secondary outcomes studied were the types of infections, disease type, antibiotic usage, and immunosuppressants used.

**Methodology**

A written informed consent/assent was obtained from the caregivers/patients enrolled in the study. At the first visit, a detailed history and clinical examination were done to identify the site of infection. A pretested study questionnaire was filled which included baseline
information (age, diagnosis, duration of NS, disease type, and details of immunosuppressants) and examination findings. Standard definitions were used to define NS, relapse, remission, SSNS, and SRNS (Table 1).  

An infection associated relapse was defined as a relapse that occurred concomitantly or within one week of the occurrence of an acute infection (acute respiratory tract infection/lower respiratory tract infection/peritonitis/skin infections/diabetes, etc). The presence of any chronic infections (like tuberculosis, fungal infections) was recorded. The diagnosis of infection was made according to the standard clinical criteria and laboratory examinations, as listed in Table 2.

**Investigations**

Two blood samples of 2 mL each were drawn for complete blood counts and biochemical investigations (renal function test, total protein, albumin, cholesterol levels). Remaining investigations (blood and urine cultures, throat swab, ascitic fluid examination, chest radiography, etc) were done according to the identified site of infection. Blood samples were transported from the study site to the clinical biochemistry lab of the institute and biochemical parameters were measured by fully automated clinical chemistry analyzer (Olympus™ AU 400).

**Follow-up**

All patients were prescribed specific treatment for infection at the first visit and were called for weekly visits for the next two weeks if being treated from the outpatient. Hospitalized patients were treated according to the site of infection. Antibiotics were administered for bacterial infections such as peritonitis, pneumonia, diabetes, and cellulitis. Furosemide was administered to patients with moderate or severe edema. Stress doses of steroid if required in such patients were administered. Daily testing for proteinuria was done for all patients. Time to remission was noted for all subjects. If the patient failed to visit the hospital on the scheduled date a telephone call was made to ascertain follow-up. Subsequently, the patients were followed up every month for the next three months.

**Protocol for stress doses**

Stress doses were prescribed for patients who had received daily steroids for at least two weeks anytime in the past one year or were on low dose alternate day prednisolone at the time of illness. Hospitalized children with serious bacterial infections received prednisolone at doses of 0.75 mg/kg/day for two weeks followed by same doses made alternate day for the next two weeks and subsequently stopped.

**Statistical Analysis**

Data entry was done using Microsoft Excel.
spreadsheet and analyzed using descriptive statistics/Statistical Package for the Social Sciences version 22.0 (IBM Corp., Armonk, NY, USA). The mean and standard deviation were calculated for baseline characteristics. Student’s t-test or Mann–Whitney U-test was applied for comparisons depending on use of mean or median for quantitative variables. Chi-square or Fisher’s exact test were used for categorical variables. A comparison of quantitative variables among different groups was done using ANOVA and logistic regression analysis. Odds ratio was calculated for occurrence of remission following different infections. For all comparisons, 5% probability was considered significant.

**Results**

**Patient characteristics**

Of the total 45 children enrolled, 27 (60%) were male. The median (range) age of children enrolled for the study was 66 (24–144) months and age of onset of NS was 36 (12–72) months.

| Infection       | Diagnostic criteria                                                                 | Treatment/remarks                              |
|-----------------|-------------------------------------------------------------------------------------|------------------------------------------------|
| Acute rhinitis  | Running nose, stuffy nose, postnasal drip                                            | Antihistaminics (viral mostly)                  |
| Acute pharyngitis| Sore throat ± fever, red pharynx/tonsils may be inflamed; throat swab c/s if streptococcal suspected (not essential) | If bacterial amoxicillin (45 mg/kg/day) 7–10 day; azithromycin (10 mg/kg/day) 5 day; clarithromycin (15 mg/kg/day) 10 day |
| Sinusitis       | Persistent purulent nasal discharge ± fever                                            | Amoxicillin (45 mg/kg/day) 10–14 days           |
| Acute tonsillitis| Enlarged, inflamed tonsils ± fever                                                   | Amoxicillin, azithromycin or clarithromycin (7 days) |
| ASOM            | Ootalgia, middle ear effusion, inflamed TM ± fever, purulent D/S                      | Analgesics, amoxicillin, amoxyclav for 7–10 days |
| Pneumonia       | Retractions, respiratory distress with fever, CXR S/O consolidation, bronchopneumonia| IV ceftriaxone for 7–10 days                     |
| Peritonitis     | Peritoneal signs, T/L, peritoneal tap >250 cells/mm$^2$, >50% polys, gram stain       | IV ceftriaxone for 10–14 days                   |
| Meningitis      | Fever, meningeal signs, headache, vomiting, CSF-polymerphonuclear pleocytosis, gram stain of organism | IV ceftriaxone for 10–14 days                   |
| Septicemia      | Fever, tachycardia, tachypnea, elevated or depressed WBC or >10% immature cells or positive blood culture/shock | IV ceftriaxone and amikacin/volume expander (albumin) |
| Urinary tract infection | Dysuria , frequency, pyuria, positive urinalysis and urine C/S >100,000 CFU/mL   | Oral/IV amoxyclav, cefixime, ceftriaxone 7–10 days |
| Diarrhea        | Viral or bacterial-stool m/e                                                         | Oral cefixime or ofloxacin for 5–7 days         |
| Skin infections | Cellulitis-edema, warmth, redness with indistinct margins, impetigo, abscess          | Oral/IV antibiotics-amoxyclyav, cloxacillin 7–10 days + drainage of abscess |
| Tuberculosis    | Symptoms of pulmonary/GIT/CNS involvement, CXR S/O pneumonia, effusion, LAP Mantoux positive, USG (abd)-LAP necrosis, intestinal loop adhesions | 6–9 months of ATT                                |

CXR: Chest X-ray, C/S: Culture and sensitivity, USG: Ultrasonography, WBC, White blood cell.
months. The mean standard deviation (SD) scores for weight, height, and body mass index of the study population were −0.44, −0.81, and +0.77, respectively. Of the enrolled patients 26 were outpatients, while 19 (42.2%) were hospitalized for treatment. Of the 45 children enrolled 68.3% had a frequently relapsing or a steroid-dependent course, while the remaining had infrequently relapsing disease. The mean (SD) number of relapses in the past six months was 0.69 (0.41) for all the patients.

The 45 patients enrolled in the study experienced 64 episodes of infections. Twenty-six patients had only one infection during the observation period, while 19 had two episodes of infections during the same period. Of these 64 episodes of infections URTIs (45.3%) were the most common followed by peritonitis (18.8%) and diarrhea in 12.5% patients (Table 3). Of the 29 episodes of URTIs, 19 (65.5%) episodes were of pharyngitis, seven (24.1%) of rhinitis, and three (10.3%) of tonsillitis. Most patients had minimal or no edema on clinical examination.

Treatment received

Of the 45 patients enrolled for the study, 19 (42.2%) patients required stress doses of steroids; 31 (68.8%) patients were treated with antibiotics, 29 (64.4%) received antihistaminic agents. Diuretics were administered to 12 (26.7%) patients for control of edema. No patient required intravenous albumin. In 17 (39.5%) episodes of infections, intravenous ceftriaxone was used as antibiotic, azithromycin was used in 11 (25.6%) and amoxycillin in seven (16.3%). The mean duration of antibiotic use in patients was eight (3.2) days.

Type of immunosuppression

Of the 45 children enrolled for the study 24 (53.3%) had received prednisolone alone; 17 (37.8%) had received alkylating agents in the past, 10 (22.2%) received calcineurin inhibitors along with prednisolone and 11.1% had received other agents such as mycophenolate mofetil and levamisole.

Remission achieved

Twenty-seven (60%) patients achieved remission on symptomatic treatment of infection alone or with the use of stress doses of steroids while eighteen (40%) patients required 2 mg/kg daily steroids for induction of remission.

The proportion of patients achieving remission without the use of 2 mg/kg of prednisolone was 77.8% in the 1st week of observation, and the numbers were higher for in patients compared to outpatients (P = 0.031). In the 2nd week, another six (22.2%) patients achieved remission.

A comparison of the patients who achieved remission with or without the use of 2 mg/kg/day of prednisolone is given in Table 4. The children with URTIs were less likely to achieve remission (odds ratio 1.14) and children with bacterial peritonitis were more likely (odds ratio 11) to go into remission without daily 2 mg/kg of prednisolone. The

| Infections                              | n (%) |
|----------------------------------------|-------|
| Upper respiratory tract infections     | 29 (45.3) |
| Spontaneous bacterial peritonitis      | 12 (18.8) |
| Diarrhea                               | 8 (12.5) |
| Pneumonia                              | 4 (6.3) |
| Pyoderma                               | 3 (4.7) |
| Cellulitis                              | 2 (3.1) |
| Tinea                                   | 2 (3.1) |
| Enteric fever                           | 1 (1.6) |
| Hepatitis (hepatitis A)                | 1 (1.6) |
| Sepsis                                  | 1 (1.6) |
| Dysentery                               | 1 (1.6) |
| **Total infections**                    | **64 (100)** |
The need for stress doses of steroids was more in the remission without daily steroids group ($P = 0.004$). Binary logistic regression analysis was done for different variables with outcome as remission. The administration of stress doses of steroids ($P = 0.003$) and higher total leukocyte counts ($P = 0.031$) were associated with higher remission rates. The values of serum albumin were comparable in both the groups ($P = 0.494$).

A comparison of profile of inpatients with that of outpatients showed that the incidence of peritonitis, pneumonia, and diarrhea was higher among the inpatients. Furthermore, the requirement of stress doses of steroids was higher (94.7% vs. 3.8%, $P < 0.001$). The antibiotic usage was higher in inpatients (100% vs. 46.2%) and the need for diuretics was more (42% vs. 15%). The proportion of patients with frequently relapsing NS/steroid-dependent NS was similar in both groups. However, the inpatients had lower mean serum albumin levels (1.76 vs. 2.39, $P = 0.002$) at evaluation. The remission rates were 61.9% in inpatients compared to 38.1% in outpatients after the 1st week of observation and increased to 84.2% and 42.3% at the end of two weeks.

None of the patients developed any compli-
cations like increase in edema, secondary infections or thromboembolism during the observation period of two weeks; besides, no patient being evaluated from the outpatient needed admission for relapse during the study period.

Follow-up
At three months follow-up 21/27 (81.5%) of the children who went into remission without daily 2 mg/kg/day of prednisolone continued to be in remission, while 9/18 (50%) of those who required daily prednisolone were still in remission and at the last follow-up (mean of 6 months) 77.8% and 44.4% were still in remission, respectively.

Discussion
Of the 45 patients enrolled for the study, 27 (60%) were male with a male: female ratio of 1.69:1, which is similar to what is observed in previous studies. Most patients had an early onset (median age 36 months) of NS. Age at onset has been shown to predict outcome; younger age has been associated with greater chances of developing frequently relapsing or steroid-dependent course. In our patient cohort, 68.3% had a frequently relapsing or a steroid-dependent course. Similar proportion of frequently relapsing and steroid-dependent disease has been reported previously from India, Japan, and Turkey.

The 45 patients enrolled in the study had 64 episodes of infections during the study period, of which URTIs were the most common (45%) followed by peritonitis (18.5%) and diarrhea (12%). URTI are the most common in early childhood. They are associated with an exacerbation of proteinuria in children with NS syndrome, especially those with minimal change disease. The type of virus causing the infection does not seem to influence the occurrence of exacerbations of proteinuria. The different viruses implicated in exacerbations suggest that a host response to viral infection, rather than specific viral antibodies, may be the triggering factor for relapse following URTI. Most (65%) patients of URTI in our study had pharyngitis and 24.1% had rhinitis; tonsillitis occurred in only 10.3% of the participants. Previous studies have also shown a higher incidence of URTI, diarrhea and peritonitis in children with a relapse of NS.

In a prospective observational study conducted on 86 hospitalized children with NS, the incidence of major infections was reported as 35%; the common infection being peritonitis (13.8%) followed by pneumonia in 12.9%. Twenty-seven (60%) children enrolled in the study achieved remission on symptomatic treatment of infection alone. Most (77.8%) achieved remission within the first 4 weeks. An old study published in 1950 described the natural history of the NS before the glucocorticoid era. This study showed spontaneous remission rates of 25% over an observation period of 15 days. Another study showed that only 15.8% children went into remission following the control of associated infection. However, their observation period was shorter (<7 days) which could be the reason for lower proportion of patients achieving spontaneous remission. Wingen et al showed that a delay of up to 10 days in starting therapy did not adversely influence the course or subsequent relapses in absence of progressive clinical signs. We too observed no adverse events like significant increase in edema, secondary infections, and thromboembolism during the observation period.

Infections associated with a higher likelihood of spontaneous remission were bacterial peritonitis (odds ratio 11) and pneumonia (odds ratio 3). Upper respiratory tracts had lower odds of achieving spontaneous remission. Most patients with serious bacterial infections received stress doses of steroids and this could be a reason for higher rates of spontaneous remissions observed in this group. Furthermore, it is possible that immune responses/immune dysregulation evoked by bacterial infections triggered a spontaneous remission. While bacterial infections stimulate both pro and anti inflammatory cytokines, the initial surge of pro-inflammatory cytokines is followed by anergy of monocytes and T-lymphocyte apoptosis. A prolonged remission of NS may
be attributable to the immunoparalysis associated with serious bacterial infections.

The need for stress doses of prednisolone was higher (59%) in patients who went into remission without the daily 2 mg/kg/day of prednisolone. Furthermore, the remission rates were higher for inpatients where the use of stress doses was almost 94.7%. Possibly, the stress doses were enough to induce remission in relapses associated with bacterial infections and this phenomenon needs to be further confirmed in future studies.

Of the 64 episodes of infections, 43 (67%) episodes were treated with antibiotics and usage was higher in inpatients. Ceftriaxone was the most commonly used antibiotic in hospitalized patients and azithromycin in outpatients. A study at Kilifi district Hospital in Kenya reported that 53% of pediatric admissions met criteria requiring antibiotics. Another study reported that more than 60% pediatric patients receive at least one antibiotic during their hospitalization. The reason for higher usage of antibiotics in our study was primarily due to the presence of serious infections on a background of relapse of NS.

At the last follow-up, most patients still continued to be in remission (44.4% of those who required 2 mg/kg and 77.8% of those who went into remission without daily steroids). Significantly higher numbers of patients in the group that attained remission without daily 2 mg/kg of prednisolone were in remission at the last follow-up indicating that treatment of the underlying infection alone and use of stress doses of prednisolone may be sufficient to induce remission in children with infection associated relapses.

To conclude, the findings of our study suggest that usage of stress doses of steroids may be sufficient to induce remission in infection associated relapses. Patients with spontaneous bacterial peritonitis and pneumonia are more likely to achieve remission with treatment of the underlying infection. Further studies may be done to confirm these findings and to provide guidance regarding the steroid therapy of infection associated relapses.

**Conflict of interest:** None declared.

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