Original Research Article

Major infections in children suffering from nephrotic syndrome- experience of a tertiary care centre

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Abstract

Background and Objectives.Infections are an important cause of morbidity and mortality in children with nephrotic syndrome (NS). There is significant variation in the type of infection reported and the influence of patient or treatment parameters on the occurrence of infections is also not well studied. Based on this background, we intended to study the occurrence and pattern of infections in children suffering from nephrotic syndrome.**Methodology:** We conducted this prospective observational study over 1 year from April 2019 to March 2020 at department of Pediatrics, NMCH, Patna, Bihar including children of 1-12 years age with diagnosis of nephrotic syndrome.All such children were evaluated for type and pattern of major infections.**Results:** Over the study period, we enrolled 103 children. Mean age of the study group was 5.7 years. Incidence of major infections was 35.9%. The most common infections were UTI (24.3%), pneumonia (21.6%), acute diarrhea (16.2%) and peritonitis (10.8%). Fever (64.95%) was the most common presenting feature followed by respiratory symptoms and abdominal symptoms (32.4% each). There was no statistically significant association between occurrence of infection and age, gender, duration of the disease, remission status, type of NS and immunosuppressive treatment. Duration of hospital stay in children with infection was significantly higher in comparison to children without infection (12.2 versus 8.3 days, $p < 0.001$). However, there was no statistically significant difference between occurrence of infection in the initial episode of NS and subsequent episodes. **Conclusion:**Infections are common in children with NS. UTI, pneumonia, diarrhea and peritonitis were the common major infections. Infections contribute significantly to morbidity in such children.

Keywords:bacteremia, infections, nephrotic syndrome, pneumonia, steroids, serious bacterial infections.

Introduction

Nephrotic syndrome (NS) is perhaps the commonest chronic renal condition in children, characterized by heavy proteinuria, hypoalbuminemia, hyperlipidemia, and edema. Although this disease can occur at any age, it is more frequently encountered in children as compared to adults. This condition frequently undergoes acycle of response to treatment leading to gradual tapering and discontinuation of medication, treatment free period of remission and relapse(s) leading to swelling of body again. In some children, these cycles of recovery and recurrence may repeat for months to years which becomes a matter of concern for both the child and the family. The main pathogenetic process involved in most of the cases is effacement of podocyte foot processes without glomerular deposit or inflammatory lesion[1].However, glomerular function i.e., the ability to filter waste products or the glomerular filtration rate, per se, is preserved in most children with primary nephrotic syndrome[2]. Based on the initial response to steroid therapy, children with NS are further classified as steroid sensitive (SSNS) and steroid resistant nephrotic syndrome (SRNS). However, a significant proportion of children with SSNS may show frequent relapses or become steroid-dependent requiring repeated courses of steroid and/or other immunosuppressive drugs.Children with NS may suffer from many acute complications, some of which may be serious and fatal. These serious complications include infections, venous thromboembolism (VTE) and acute kidney injury(AKI). Whereas clinical reflections of infection and VTE on nephrotic children are clear, the epidemiology and fate of AKI remain vague[3].It has now been established that infections are an important cause of morbidity and mortality in children with NS. Infections can lead to repeated relapses, poor response to steroid therapy and prolonged hospitalization[4]. Without proper treatment, a nephrotic child is more prone to die, mostly due to bacterial infection.Before the era of corticosteroids and antibiotics, 40% of children with NS died, and 50% of these deaths were due to infection, many of which were preventable[5].Recently,it has been postulated that at least 50% cases of pediatric onset NS are preceded by a viral upper respiratory tract infection.This can be explained by a non-specific host response to infection or a cross reacting antibody response[6].This has generated an interest on the role of other infections such as urinary tract infection (UTI), diarrhea, peritonitis and skin infections as a triggering factor or modifier of disease activity.Among the important risk factors for infections in children suffering from NS are urinary loss of immunoglobulins and alternative complement pathway factors B and I, presence of edema, and immunosuppression as a result of treatment with prednisolone/ other cytotoxic agents[7,8]. Peritonitis, pneumonia, urinary tract infection (UTI), cellulitis, meningitis and tuberculosis have been reported as major infections in these children[9,10]. Pneumococcal infections are the most common invasive bacterial infections in these children. However, there is significant variation in the type of infection reported and the influence of patient or treatment parameters on the occurrence of such infections is also not well studied. Based on this background, we intended to study the incidence and pattern of infections in children suffering from nephrotic syndrome.

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Aim and Objectives

Aim: To study the occurrence and pattern of infections in children suffering from nephrotic syndrome.

Objectives: 1.To study the incidence and type of common infections in children with NS.

2. To study the clinical and laboratory parameters of infections in these children.

3. To study the influence of disease activity & immunosuppression on occurrence of infections.

Methodology

Study setting: OPD and I.P.D of deptt of Pediatrics N.M.C.H Patna

Study duration: 1 year, from April 2019 to March 2020.

Study design: prospective observational study.

Inclusion criteria: In the present study we included children between 1-12 years of age with diagnosis of NS who were brought to either OPD or admitted in I.P.D of our hospital.

Exclusion criteria: Children with congenital nephrotic syndrome, children with features of nephritis or secondary NS, as well as those admitted only for diagnostic renal biopsy or immunosuppressive drug infusion (cyclophosphamide, pulse dexamethasone) were excluded.

Study technique: After obtaining written informed consent, we enrolled participants in the present study. NS and associated complications were defined as per guidelines of Indian Pediatric Nephrology Group[11].All children with NS were evaluated for major infections. In our study we defined major infections as those with disseminated or deep seated infections requiring hospitalizations and treatment with parenteral antibiotics, and were the following: peritonitis pneumonia, cellulitis, meningitis, unexplained pyrexia and infective diarrhea. Information regarding baseline characteristics was collected and entered in a structured proforma. All such children were subjected to focused history taking and thorough clinical examination. Complete blood counts, kidney and liver function tests, lipid profile and urine routine microscopic examination was done in all such children. Ascitic and cerebrospinal fluid cytology, biochemistry, and culture were performed in children with suspected peritonitis and meningitis respectively. Chest X-ray and blood and urine culture were done if the clinical condition warranted.

Statistical analysis: Data so collected was recorded, tabulated and entered in Microsoft excel sheet, and then analyzed by using statistical software "SPSS ver.20®. Variables were expressed as mean, standard deviation, proportions and percentiles as appropriate. Dichotomous variables were compared using Chi-square test whereas continuous variables were compared using Student t-test. P-value <0.05 was taken as significant.

Observation and results

Over the study period, we enrolled 103 children with NS. Mean age of the study group was 5.7 years. Mean weight was 18.4 Kg. Males (59) outnumbered females (44) with a male: female ratio of 1.3:1. Duration of hospital stay (days) was 9.4 ± 4.1. Table 1 depicts the general characteristics of our study population.

Table 1: General characteristics of the study population.

Parameter	Value
Demographics:	
Age (years) mean ± SD	5.7 ± 3.2
Age of onset of disease (years) mean ± SD	5.2± 2.1
Weight (Kg) mean ± SD	18.4 ± 5.1
Height (cm) mean ± SD	112 ± 17.6
Duration of the disease (months) mean ± SD	6.4 ± 3.9
Male, n (%)	59 (57.3%)
Rural inhabitant, n (%)	73 (70.9%)
Lower socioeconomic class (Kuppuswamy scale class IV or below) n (%)	39 (37.9%)
Type of the disease:	
Initial episode, n (%)	58 (56.3%)
IFRNS, n (%)	25 (24.3%)
FRNS/ SDNS, n (%)	13 (12.6%)
SRNS, n (%)	7 (6.8%)
Remission status:	
Remission, n (%)	12 (11.7%)
Relapse, n (%)	33 (32%)
Initial episode, n (%)	58 (56.3%)
Treatment received:	
Previously untreated, n (%)	58 (56.3%)
Only prednisolone, n (%)	25 (24.3%)
Other immunosuppressant ± prednisolone, n (%)	20 (19.4%)
Laboratory parameters:	
Hb (g/dl) mean ± SD	10.3 ± 2.4
Serum Creatinine (mg/dl) mean ± SD	0.62 ± 0.29
Serum Albumin (g/dl) mean ± SD	1.6 ± 0.43
Serum cholesterol (mg/dl) mean ± SD	429 ± 158

Out of the 103 children studied, 37 suffered from some form of infection as depicted in table 2.The most common infections were UTI (24.3%), pneumonia (21.6%), acute diarrhea (16.2%) and peritonitis (10.8%). Together these illnesses accounted for nearly three-fourth of all incidences of major infections observed in these children. *Streptococcus pneumoniae* was the predominant organism isolated from blood and asciticfluid (n = 5, 4 in blood and one in ascitic fluid). *E. coli* was the commonest organism isolated from urine (n = 4), followed by *Enterococcus faecium* (n = 1), *Klebsiella* species (n = 1) and Proteus (n = 1). *Klebsilella* was also isolated from 1 case of septicemia and 1 case of pneumonia. *Staph aureus* was isolated in 2 children (1 in cellulitis and 1 in pneumonia), *Coagulase negative staphylococcus* was also isolated from 1 case of cellulitis. *Salmonella typhi* was isolated from the lone case of enteric fever.

Table 2: Different infections in the study population

Infection/disease	Number (percentage)
Peritonitis	4 (3.9%)
Pneumonia	8 (7.8%)
UTI	9 (8.7%)
Cellulitis	3 (2.91%)
Acute diarrhea	6 (5.82%)
Typhoid	1 (0.97%)
Hepatitis	1 (0.97%)
Tuberculosis	3 (2.91%)
Meningitis	1 (0.97%)
Varicella	0 (0.00%)
Measles	0 (0.00%)
Malaria	1 (0.97%)
Sepsis	2 (1.94%)

Fever (64.95%) was the most common presenting feature of infection but approximately one-third children were afebrile, probably due to immunosuppression. This was followed by respiratory symptoms in nearly one-third children followed by abdominal symptoms in equal number of patients. Table 3 depicts the common clinical and laboratory parameters in these children. Like fever, leukocytosis and neutrophilia was not a consistent feature and nearly one-fourth children had leukopenia. This again can be ascribed to the immunosuppressed state in these children.

Table 3: Clinical features and laboratory parameters in nephrotic children with infection

Parameters	Value, n (%)
Fever	24 (64.9%)
Chills/rigor	7 (18.9%)
Abdominal pain	12 (32.4%)
Diarrhea and/or vomiting	5 (13.5%)
Urinary symptoms (dysuria, increased frequency)	9 (24.3%)
Respiratory symptoms (Cough and/or breathing difficulty)	12 (32.4%)
Shock	3 (8.1%)
Hypotension	4 (10.8%)
Leucocytosis	19 (51.4%)
Neutrophilia	16 (43.2%)
Leukopenia	9 (24.3%)
Neutropenia	8 (21.6%)
Thrombocytopenia	2 (5.4%)

Baseline demographic, disease characteristics and short term outcome of children with and without infections is depicted in in Table 3. There was no statistically significant difference between the two groups in terms of age, gender, duration of the disease, remission status, type of NS and immunosuppressive treatment. Duration of hospital stay in children with infection was significantly higher in comparison to children without infection (12.2 versus 8.3 days, $p < 0.001$).

Table 4: Comparison of parameters in nephrotic children with and without infections.

Parameters	Infection (n = 37)	Without infection (n = 66)	p value
Age (years), mean ± SD	5.61 ± 3.14	5.73 ± 3.27	0.86
Age of onset of disease (years), mean ± SD	3.84 ± 2.37	4.03 ± 2.45	0.72
Duration of the disease (months), mean ± SD	6.7 ± 4.1	6.2 ± 3.7	0.52
Male, n (%)	20 (54.05%)	39 (59.09%)	0.71
Type of the disease:			
Initial episode, n (%)	16 (43.2%)	42 (63.6%)	0.16
IFRSSNS, n (%)	11 (29.7%)	14 (21.2%)	0.63
FRNS or FDNS, n (%)	6 (16.2%)	7 (10.6%	0.77
FRNS, n (%)	4 (10.8%)	3 (4.5%)	0.78
Remission status:			
Initial episode, n (%)	16 (43.2%)	42 (63.6%)	0.16
In remission, n (%)	5 (13.5%)	7 (10.6%)	0.88
In relapse, n (%)	16 (43.2%)	17 (25.8%)	0.30
Treatment status:			
Previuosly untreated, n (%)	16 (43.2%)	42 (63.6%)	0.16
Treated with only prednisolone, n (%)	9 (24.3%)	16 (24.2%)	0.99
Treated with other immunosuppressive agent ± prednisolone, n (%)	12 (32.4%)	8 (12.1%)	0.31
Short term outcome:			
Mortality, n (%)	3 (8.1%)	0 (0.0%)	---
Duration of hospital stay in days, mean ± SD	12.2 ± 3.6	8.3 ± 2.9	**<0.001**

Occurrence of infection in the initial episode of NS and other episodes (IFRNS, FRNS, SDNS, and SRNS) was compared. However, as shown in table 5, there was no statistically significant difference in the incidence of infections between the two groups.

Table 5: Comparison of infections in initial episode of NS and other episodes

Infection/disease	Total Number (percentage)	Number (%) seen in initial episode of NS	Number (%) seen in non-initial episode	P value
Peritonitis	4 (3.9%)	1 (25%)	3 (75%)	0.43
Pneumonia	8 (7.8%)	3 (37.5%)	5 (62.5%)	0.52
UTI	9 (8.7%)	4 (44.4%)	5 (55.5%)	0.75
Cellulitis	3 (2.91%)	1 (33.3%)	2 (66.6%)	0.65
Acute diarrhea	6 (5.82%)	3 (50%)	3 (50%)	1
Typhoid	1 (0.97%)	0 (0%)	1 (100%)	---
Hepatitis	1 (0.97%)	0 (0%)	1 (100%)	---
Tuberculosis	3 (2.91%)	2 (66.6%)	1 (33.3%)	0.65
Meningitis	1 (0.97%)	0 (0%)	1 (100%)	---
Malaria	1 (0.97%)	1 (100%)	0 (0%)	---
Sepsis	2 (1.94%)	1 (50%)	1 (50%)	1

Discussion

In the present study we intended to study the major infections in nephrotic children presenting to our tertiary care level teaching institute. The incidence of major infections in nephrotic children brought to our institute was 35.9%. This is quite comparable to the findings of Manish et al[12] who in their Indian study found the incidence of major infection in hospitalized nephrotic children to be 43.8%. While most of the Indian studies have mentioned incidence of major infections in the range of 20-35%, the relatively higher incidence of infection in our study population can be also explained by referral bias and high index of clinical suspicion for infections in these children. The commonest infections in our study were UTI, pneumonia, diarrhea and peritonitis. The commonest infection was peritonitis in the study of Manish et al whereas the commonest infection reported by Kumar CB was pneumonia. However, most of the studies have reported pneumonia, UTI, diarrhea and peritonitis to be the most common major infection among nephrotic children [13,14]. As glucocorticoids and other immuno-suppressive drugs is the mainstay of therapy, infection occurring during therapy is well-known and is partially explainable by the relative immunocom-promised state. However, infection often occurs even when the child is not on glucocorticoid therapy[15].This partly explains our finding that there was no statistically significant difference between nephrotic children with infection and children without infection in terms of age, gender, duration of the disease, remission status, type of NS and immunosuppressive treatment. In contrast to the assuumption that incidence of infection increases with the addition of other immunosuppressive drugs with or without prednisolone, we did not find any such increased risk of infection in children receiving prednisolone alone or in combination with any other immuno-suppressive agent. This suggests that nephrotic children remain in a more or less constant state of immunosuppression and increased risk of infection irrespective of immunosuppressive therapy.While in our study the only pathogen isolated from cases with peritonitis was *Streptococcus pneumoniae*, Senguttuvan et al[16]observed E.coli and Klebsiella as predominant organisms in peritonitis. Similar to our finding that UTI was the commonest infection in such children, one of the largest retrospective analysis in children with NS to determine the incidence of UTI found that 15% of children had UTI, with more than 50% being asymptomatic and diagnosed as a part of screening investigations for relapse and non-response[17]. This reiterates the importance of screening for UTI in all children with NS with relapse or non-response to corticosteroids, as symptoms may be masked because of anti-inflammatory action of steroids.In our study, mortality was 3 (2.9%). All deaths occurred in nephrotic children with major infection and were attributed to sepsis induced multiorgan failure. However, Srivastava et al[18]reported a higher death rate (13% of children died of infection) and mortality was highest within the first 24 hours of admission which indicates a fulminant nature of infections associated with NS. Nevertheless, the lower mortality rate in our study can be explained by early presentation, high index of suspicion for infections and prompt institution of treatment.

Conclusion

Infections are common in children with NS. UTI, pneumonia, diarrhea and peritonitis being the major infections. Occurrence of infection significantly increases the duration of hospital stay in such children as compared to nephrotic children without infection. Considering the burden of pneumococcal infection in our study, we suggest for wider coverage of pneumococcal vaccine in such children.

Limitation

Our study has few limitations. First, ours is a single centre study. Second, owing to the small number of children with infections, we couldn't do a multivariate analysis to identify the risk factors for infections in children with nephrotic syndrome.

Abbreviations: FRNS: frequently relapsing nephrotic syndrome; IFRNS: infrequently relapsing nephrotic syndrome; NS: nephrotic syndrome; SDNS: steroid dependent nephrotic syndrome; SRNS: steroid resistant nephrotic syndrome.

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