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ORIGINAL RESEARCH

Infectious Complications in Children Suffering from Nephrotic Syndrome: Experience of a Tertiary Care Center

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ABSTRACT

Background and Objectives: Nephrotic syndrome is the commonest chronic renal disorder encountered in the paediatric age group. Infections are an important cause of morbidity and mortality in such children. The common major infections reported are peritonitis, pneumonia, urinary tract infection (UTI), cellulitis, meningitis and tuberculosis in these children. However, there is significant variation in the type of infection reported. The influence of patient or treatment parameters on the occurrence of such infections is also not well studied. Based on this background, the present study was conducted to elaborate the incidence and pattern of infections in children suffering from nephrotic syndrome. **Methods:** This prospective observational study was conducted over 2 year from April 2022 to March 2024 at department of Pediatrics, P MCH, Patna, Bihar,India including children between 1-12 years of age with a diagnosis of nephrotic syndrome. All children were evaluated for major infections as per guidelines of Indian Paediatric nephrology group. **Result:** Over the study period, we enrolled 212 children with NS. Mean age of the study group was 5.4± 0.92 years. Mean weight was 17.9± 3.14 Kg. Males (117) outnumbered females (95) with a male: female ratio of 1.23:1. Incidence of major infections in such children was 35.8%. The most common infections were UTI (28.9%), pneumonia (17.1%), acute diarrhoea (11.8%) and peritonitis (7.9%), contributing to nearly two-third of all major infections. Streptococcus pneumoniae was the predominant organism isolated from blood and ascitic fluid (n = 9, 7 in blood and 2 in ascitic fluid). E. coli was the commonest organism isolated from urine (n = 11. Fever (64.5%) was the most common presenting feature of infection, followed by urinary symptoms (35.5%) and then respiratory and abdominal symptoms. There was no statistically significant difference between nephrotic children with infection and without infection 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 (12.59 versus 8.71 days, $p < 0.001$). **Conclusion:** Infections are quite common in children with NS. UTI, pneumonia, diarrhoea and peritonitis were the major infections. Infections contribute significantly to morbidity and mortality in children with nephrotic syndrome.

Key words: Bacteraemia, infections, nephrotic syndrome, pneumonia, steroids, serious bacterial infections.

INTRODUCTION

Nephrotic syndrome (NS) is among the commonest chronic renal condition in children which is characterized by heavy proteinuria, hypoalbuminemia, hyperlipidaemia and edema. Although this disease can affect all age groups, it is considerably more commonly encountered in children as compared to adults. This syndrome frequently undergoes a cycle of response to treatment allowing gradual tapering and discontinuation of medication, treatment free period of remission and relapse(s) leading to swelling of face or body again. In many children, these cycles of recovery and recurrence may repeat for months to years which becomes a matter of great frustration for both the child and the family. The principal pathogenetic process involved in most of the cases is effacement of podocyte foot processes without glomerular deposit or inflammatory lesion.[1] fortunately, 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 corticosteroid treatment, children with NS are further classified as steroid sensitive nephrotic syndrome (SSNS) and steroid resistant nephrotic syndrome (SRNS). Unfortunately, a few children with SSNS

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may show frequent relapses or become steroid dependent requiring repeated courses of steroid and/or other immunosuppressive drugs.

Children with NS are prone to suffer from many acute complications, some of which are potentially serious and fatal. Noteworthy serious complications include infections, venous thromboembolism (VTE) and acute kidney injury (AKI). Whereas clinical implications of infection and VTE on children with nephrotic children are clear, the epidemiology and fate of AKI remain vague.[3] Researchers have consistently established that infections are an important cause of morbidity and mortality in children with NS. Infections are associated with repeated relapses, poor response to steroid therapy and prolonged hospitalization.[4] Infact, without proper treatment a nephrotic child is more prone to die, mostly due to bacterial infections. Prior to the era of corticosteroids and antibiotics therapy, 40% of children with NS suffered from untimely death, and 50% of these deaths could be attributed to infection, many of which were preventable.[5] Recently, it has been proposed that at least 50% cases of paediatric onset NS are preceded by an infection, mostly a viral upper respiratory tract infection. This has been postulated to result from a non-specific host response to infection or a cross-reacting antibody response.[6] This generated considerable interest on the role of other potential infections such as urinary tract infection (UTI), diarrhoea, peritonitis and skin infections as a triggering factor or modifier of disease activity in children with NS. The important risk factors for infections are urinary loss of protective factors (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]. Among the causative agents, 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 at our tertiary care level teaching hospital.

Aim and Objectives

1.To study the incidence and site of common infections in children with NS.

2. To study the clinico-etiological and laboratory parameters of infections in these children.

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

MATERIALS AND METHODS

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

Study duration: 2 years, from April 2022 to March 2024.

Study design: prospective observational study.

Inclusion criteria: All 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 were considered as potential participants and offered participation in the study.

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 Paediatric Nephrology Group.[11] All children with NS were evaluated for major infections. In this study a major infection was defined as disseminated or deep-seated infections requiring hospitalizations and treatment with parenteral antibiotics such as peritonitis pneumonia, cellulitis, meningitis, unexplained pyrexia and infective diarrhoea. 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 ordered 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 or 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.

RESULT

Over the study period, we enrolled 212 children with NS. Mean age of the study group was 5.4± 0.92 years. Mean weight was 17.9± 3.14 Kg. Males (117) outnumbered females (95) with a male: female ratio of 1.23:1. Duration of hospital stay (days) was 9.1 ± 4.3. Table 1 depicts the general characteristics of our study population.

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Table 1: General characteristics of the study population

Parameter	Value
Demographics:	
Age (years) mean ± SD	5.41 ± 0.92
Age of onset of disease (years) mean ± SD	4.93± 2.05
Weight (Kg) mean ± SD	17.92± 3.14
Height (cm) mean ± SD	109.52 ± 14.68
Duration of the disease (months) mean ± SD	5.84 ± 3.76
Male, n (%)	117(55.19%)
Rural inhabitant, n (%)	137 (64.62%)
Lower socioeconomic class (Kuppuswamy scale class IV or below) n (%)	146 (68.9%)
Type of the disease:	
Initial episode, n (%)	127 (59.9%)
IFRNS, n (%)	45 (21.2%)
FRNS/ SDNS, n (%)	31 (14.6%)
SRNS, n (%)	9 (4.2%)
Remission status:	
Remission, n (%)	41 (19.3%)
Relapse, n (%)	44 (20.8%)
Initial episode, n (%)	127 (59.9%)
Treatment received:	
Previously untreated, n (%)	127 (59.9%)
Only prednisolone, n (%)	56 (26.4%)
Other immunosuppressant ± prednisolone, n (%)	29 (13.7%)
Laboratory parameters:	
Hb (g/dl) mean ± SD	10.17 ± 2.24
Serum Albumin (g/dl) mean ± SD	1.74 ± 0.58
Serum Creatinine (mg/dl) mean ± SD	0.82 ± 0.27
Serum cholesterol (mg/dl) mean ± SD	317.94 ± 29.74

Of these 212 children studied, 76 suffered from some form of infection as depicted in table 2 below. The most common infections were UTI (28.9%), pneumonia (17.1%), acute diarrhoea (11.8%) and peritonitis (7.9%). Together these illnesses accounted for nearly two-third of all incidences of major infections observed in these children. Streptococcus pneumoniae was the predominant organism isolated from blood and ascitic fluid (n = 9, 7 in blood and 2 in ascitic fluid). E. coli was the commonest organism isolated from urine (n = 11), followed by Enterococcus faecium (n = 2), Klebsiella species (n = 2) and Proteus (n = 2). Klebsilella was also isolated from 2 case of septicemia and 1 case of pneumonia. Staph aureus was isolated in 5 children (3 in cellulitis and 2 in pneumonia), Coagulase negative staphylococcus was also isolated from 1 case of cellulitis. Salmonella typhi was isolated from the 2 cases of enteric fever.

Table 2: major infectious disease in the study population

Infection/Disease	Number	Percentage
Peritonitis	6	7.9%
Pneumonia	13	17.1%
UTI	22	28.9%
Cellulitis	5	6.6%
Acute Diarrhoea	9	11.8%
Typhoid	2	2.6%
Hepatitis	5	6.6%
Tuberculosis	3	3.9%
Meningitis	1	1.3%
Varicella	1	1.3%
Measles	1	1.3%
Malaria	3	3.9%
Sepsis	5	6.6%
Total	76	100%

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Fever (64.5%) was the most common presenting feature of infection but approximately one-third children were afebrile, probably due to immunosuppression. This was followed by abdominal symptoms (diarrhoea, vomiting or pain abdomen) in nearly half of the children studied followed by respiratory symptoms (cough, breathing difficulty) in nearly one-third of them. 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-fifth children had leukopenia. This again can be attributed to the immunosuppressed state in these children.

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

Parameter	Number	Percentage
Fever	49	64.5%
Chills/rigors	15	19.7%
Abdominal Pain	26	34.2%
Diarrhoea and/or Vomiting	11	14.5%
Urinary symptoms (dysuria, frequency)	27	35.5%
Respiratory symptoms (Cough and/or breathing difficulty)	19	25.0%
Shock	6	7.9%
Hypotension	8	10.5%
Leukocytosis	41	53.9%
Neutrophilia	39	51.3%
Leukopenia	16	21.1%
Neutropenia	15	19.7%
Thrombocytopenia	5	6.6%

Baseline demographic, disease characteristics and short-term outcome of children with and without infections was compared as 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 (12.59 versus 8.71 days, $p < 0.001$).

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

Parameters	Infection (n = 76)	Without infection (n = 136)	*p* value
Age (years), mean ± SD	5.21 ± 3.23	5.61 ± 3.19	0.80
Age of onset of disease (years), mean ± SD	3.91 ± 2.41	4.13± 2.46	0.70
Duration of the disease (months), mean ± SD	6.9 ± 4.2	6.1 ± 3.6	0.50
Male, n (%)	40 (52.6%)	77 (56.6%)	0.80
Type of the disease:			
Initial episode, n (%)	37 (48.7%)	90 (66.2%)	0.18
IFRSSNS, n (%)	19 (25.0%)	26 (19.1%)	0.69
FRNS or FDNS, n (%)	14 (18.4%)	17 (12.5%)	0.79
FRNS, n (%)	6 7.9%)	3 (2.2%)	0.81
Remission status:			
Initial episode, n (%)	37 (48.7%)	90 (66.2%)	0.18
In remission, n (%)	8 (10.5%)	33 (24.3%)	0.81
In relapse, n (%)	31 (40.8%)	13 (9.6%)	0.22
Treatment status:			
Previously untreated, n (%)	37 (48.7%)	90 (66.2%)	0.18
Treated with only prednisolone, n (%)	16 (21.1%)	40 (29.4%)	0.90
Treated with other immunosuppressive agent ± prednisolone, n (%)	23 (30.3%)	6 (4.4%)	0.30
Short term outcome:			
Mortality, n (%)	5 (6.6%)	0 (0.0%)	---
Duration of hospital stay in days, mean ± SD	12.59 ± 3.71	8.71 ± 2.95	**<0.001**

DISCUSSION

In the present study we studied 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 35.8%. This is in agreement to the findings of Manish et al[12] who in their Indian study found the incidence of major infection in hospitalized nephrotic children

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to be 43.8%. Though most of the Indian researchers have mentioned incidence of major infections to be in the range of 20-35%, the relatively higher incidence of infection in our study population can be explained by referral bias and high index of clinical suspicion for infections in these children. The most frequent infections we observed in such children were UTI, pneumonia, diarrhoea and peritonitis. The commonest infection reported was peritonitis in the study of Manish et al[12] whereas the commonest infection reported by Kumar CB et al[13] was pneumonia. Nevertheless, most of the studies have reported pneumonia, UTI, diarrhoea and peritonitis to be the most common major infection among nephrotic children[13,14]. As glucocorticoids and other immuno-suppressive drugs are the only effective drugs for therapy, infection occurring during such therapy is a well-known complication and is partially explained by the relative immunocompromised state in such children. However, infection often occurs even when the child is off any glucocorticoid therapy[15]. This partly explains the 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 assumption 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, Senguttuvanet al[16] observed E. coli and Klebsiella as the predominant pathogens in peritonitis. Similar to our finding that UTI was the commonest infection in such children, a large 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 emphasises 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 5 (2.35%). All such deaths occurred in children with major infections and were attributed to sepsis induced MODS. 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. The relatively lower mortality rate in the present study can be attributed to early presentation, high index of suspicion for infections and prompt institution of treatment.

CONCLUSION

Infections are quite common in children with NS, with nearly one-third of such children presenting to the hospital do suffer from one or more major infections. UTI, pneumonia, diarrhoea and peritonitis were the common major infections in this study. 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.

Limitations: As the present study is a single centre study, its findings may not be truly representative of broader population. Second, due to relatively lesser sample size studied, a multivariate analysis to identify the risk factors for infections in children with nephrotic syndrome couldn't be done.

Conflict of interest: None

Financial disclosure: None to declare

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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