International Journal of Life Sciences, Biotechnology and Pharma Research Vol. 13, No. 7, July 2024 Online ISSN: 2250-3137
Print ISSN: 2977-0122

DOI: 10.69605/ijlbpr_13.7.2024.152

ORIGINAL RESEARCH

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

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Received: 09 March, 2024 Accepted: 23 June, 2024 Published: 16 July, 2024

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 and site of infection reported. Influence of patient or treatment related 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 3 years from August 2020 to July 2023 at department of Pediatrics, A.N.M.M.C.H, Gaya, 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 3-year study period, 186 children with NS were enrolled in the study. Mean age of the study group was 5.92± 2.13 years. Mean weight was 15.61± 3.53 Kg. Males (107) outnumbered females (79) with a male: female ratio of 1.35:1. Duration of hospital stay in days was 8.47 ± 4.12. Overall, 65 (34.9%) suffered from some form of infection. The most common infections were UTI (27.7%), pneumonia (20.0%), acute diarrhoea (10.8%) and peritonitis (7.7%). Fever (67.7%) was the most common presenting feature of infection, followed by urinary symptoms (33.8%) 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 (11.38 versus 8.19 days, $p < 0.001$). **Conclusion:** Infections are 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 the commonest chronic renal disease in children which is characterized by heavy proteinuria, hypoalbuminemia, hyperlipidaemia and edema. Although this disease can affect all age groups, it is significantly more commonly encountered in children as compared to adults. This disease may undergo a cycle of response to treatment allowing gradual tapering and discontinuation of the drug, treatment free period of remission and then possible relapse(s) leading to swelling of face or body again. Unfortunately, in some children, these cycles of recovery and recurrence may repeat for months to years which ultimately becomes a matter of great frustration for both the child and the family. The main pathogenetic process involved in most of the cases of NS is effacement of the podocyte foot processes without any significant glomerular deposit or inflammatory lesions.[1] Fortunately, glomerular function i.e., the ability to filter waste products or the glomerular filtration rate, per se, is preserved until late in most children with idiopathic 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). Children with NS are more prone to suffer from many acute complications as compared to their healthy counterparts, some of which are potentially serious and fatal. Some of the common serious complications

DOI: 10.69605/ijlbpr_13.7.2024.152

are infections, venous thromboembolism (VTE) and acute kidney injury (AKI). Whereas clinical correlates of infection and VTE on children with nephrotic children are clear, the epidemiology and fate of AKI remain vague.[3]

Many researchers have consistently reported infections to be an important cause of morbidity and mortality in children with NS. Infections may predispose such a child to repeated relapses, poor response to steroid therapy requiring second line drugs which have more toxicity and prolonged hospitalization.[4] Such is the importance of infection in the natural history of children with nephrotic syndrome that without proper treatment a nephrotic child is more prone to die, mostly due to bacterial infections. Before the era of protocolised corticosteroids and proper antibiotics therapy, 40% of children with NS suffered from premature death, and 50% of these deaths could be attributed to infection, many of which were preventable.[5] Recently, it has been hypothesized that at least 50% cases of paediatric onset NS are preceded by an infection, mostly a viral upper respiratory tract infection. A non-specific host response to infection or a cross-reacting antibody response is supposed to trigger a cascade of reactions ultimately leading to podocytes injury.[6] This finding has led to a renewed interest on the search of other potential infections that could either lead to or modify the course of NS in children. urinary tract infection (UTI), diarrhoea, peritonitis and skin infections. The important risk factors for infections in children suffering from NS are urinary loss of protective factors (immunoglobulins and alternative complement pathway factors B and I), presence of edema leading to venous stasis and further 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 the common major infections in these children[9,10]. Among the causative agents, pneumococcal infections are the most common invasive bacterial infections in these children followed by E coli. However, significant variation exists 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. Most of the studies are retrospective in design which might have led to under-reporting. Based on this background, we intended to prospectively study the incidence and pattern of major infections in children suffering from nephrotic syndrome at our tertiary care level teaching hospital.

Aim and Objectives

To study in children with NS, the incidence, site as well as type of major infections alogwith its clinico-etiological and laboratory parameters.

MATERIALS AND METHODS

Study setting: OPD and I.P.D of Department of Pediatrics A.N.M.M.C.H Gaya, Bihar, India

Study duration: 3 years, from August 2020 to July 2023.

Study design: hospital based prospective observational study.

Inclusion criteria: 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 after explaining in detail the method and objectives of the present 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 not included in present study.

Study technique: After obtaining written informed consent from parents, participants were screened for eligibility in the present study. Nephrotic syndrome, its subtype and associated complications were defined as per guidelines of Indian Paediatric Nephrology Group.[11] All such enrolled children with NS were evaluated for major infections. A major infection was defined as disseminated or deep-seated infections requiring hospitalizations and treatment with parenteral antibiotics such as peritonitis pneumonia, cellulitis, meningitis, UTI, unexplained pyrexia and infective diarrhoea. Information regarding baseline characteristics such as age, sex, duration and the type of treatment etc was collected and entered in a structured proforma. Focused history was taken and thorough clinical examination was done in all such children. Complete blood count, kidney and liver function test, lipid profile and urine routine microscopic examination and culture was ordered as per clues obtained from history and clinical examination. Ascitic and/or 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 analysed 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 3-year study period, we enrolled 186 children with NS. Mean age of the study group was 5.92± 2.13 years. Mean weight was 15.61± 3.53 Kg. Males (107) outnumbered females (79) with a male: female ratio of 1.35:1. Duration of hospital stay in days was 8.47 ± 4.12. Table 1 depicts general characteristics of the study population.

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Table 1: General characteristics of the study population.

Parameter	Value
Demographics:	
Age (years) mean ± SD	5.92± 2.13
Age of onset of disease (years) mean ± SD	4.62± 2.49
Weight (Kg) mean ± SD	15.61± 3.53
Height (cm) mean ± SD	104.97 ± 12.31
Duration of the disease (months) mean ± SD	6.84 ± 3.85
Male, n (%)	107(57.53%)
Rural inhabitant, n (%)	131 (70.4%)
Lower socioeconomic class (Kuppuswamy scale class IV or below) n (%)	129 (69.4%)
Type of the disease:	
Initial episode, n (%)	115 (61.8%)
IFRNS, n (%)	39 (20.9%)
FRNS/ SDNS, n (%)	26 (14.0%)
SRNS, n (%)	6 (3.2%)
Remission status:	
Remission, n (%)	32 (17.2%)
Proteinuric, n (%)	39 (21.0%)
Initial episode, n (%)	115 (61.8%)
Treatment received:	
Previously untreated, n (%)	115 (61.8%)
Only prednisolone, n (%)	50 (26.9%)
Other immunosuppressant ± prednisolone, n (%)	21 (11.3%)
Laboratory parameters:	
Hb (g/dl) mean ± SD	9.59 ± 2.09
Serum Albumin (g/dl) mean ± SD	1.39 ± 0.97
Serum Creatinine (mg/dl) mean ± SD	0.94 ± 0.37
Serum cholesterol (mg/dl) mean ± SD	323.28 ± 31.43

Of these 186 children studied, 65 (34.9%) suffered from some form of infection as depicted in table 2 below. The most common infections were UTI (27.7%), pneumonia (20.0%), acute diarrhoea (10.8%) and peritonitis (7.7%). 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 = 8 in blood and 2 in ascitic fluid). *E. coli* was the commonest organism isolated from urine (n = 12), followed by *Enterococcus faecium* (n = 2), *Klebsiella* species (n = 3) and Proteus (n = 1). *Klebsiella* was also isolated from 2 case of septicaemia and 2 case of pneumonia. *Staph aureus* was isolated in 4 children (2 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	5	7.7%
Pneumonia	13	20.0%
UTI	18	27.7%
Cellulitis	4	6.2%
Acute Diarrhoea	7	10.8%
Typhoid	2	3.1%
Hepatitis	2	3.1%
Tuberculosis	3	4.6%
Meningitis	2	3.1%
Varicella	1	1.5%
Measles	1	1.5%
Malaria	2	3.1%
Sepsis	5	7.7%
Total	65	100%

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Fever (67.7%) was the most common presenting feature of infection but approximately one-third children were afebrile due to immunosuppression or infection by uncommon agents. 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-fourth 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	44	67.7%
Chills/rigors	13	20.0%
Abdominal Pain	23	32.3%
Diarrhoea and/or Vomiting	9	13.8%
Urinary symptoms (dysuria, frequency)	22	33.8%
Respiratory symptoms (Cough and/or breathing difficulty)	15	23.1%
Shock	4	6.1%
Hypotension	6	9.2%
Leukocytosis	39	60.0%
Neutrophilia	35	53.8%
Leukopenia	14	21.5%
Neutropenia	12	18.5%
Thrombocytopenia	5	7.7%

Children with NS with any major infection were compared with their normal counterparts in terms of baseline demographic, disease characteristics and short-term outcomes as depicted in Table 3 below. There was no statistically significant difference between the two groups in terms of age, sex, 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 (11.38 versus 8.19 days, $p < 0.001$)

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

Parameters	Infection (n = 65)	Without infection (n = 121)	*p* value
Age (years), mean ± SD	5.92± 2.13	5.19 ± 2.26	0.90
Age of onset of disease (years), mean ± SD	4.62± 2.49	4.44± 2.37	0.80
Duration of the disease (months), mean ± SD	6.84 ± 3.85	6.39 ± 3.69	0.60
Male, n (%)	36(55.4%)	77 (58.7%)	0.80
Type of the disease:			
Initial episode, n (%)	33 (50.7%)	82 (67.8%)	0.10
IFRSSNS, n (%)	17 (26.1%)	22 (18.8%)	0.70
FRNS or FDNS, n (%)	12 (18.5%)	14 (11.6%)	0.80
SRNS, n (%)	3 (4.6%)	3 (2.5%)	0.90
Remission status:			
Initial episode, n (%)	33 (50.7%)	82 (67.8%)	0.10
In remission, n (%)	6 (9.2%)	26 (21.5%)	0.50
In proteinuric stage, n (%)	26 (40.0%)	13 (10.7%)	0.10
Treatment status:			
Previously untreated, n (%)	33 (50.7%)	82 (67.8%)	0.10
Treated with only prednisolone, n (%)	18 (27.7%)	32 (26.4%)	0.90
Treated with other immunosuppressive agent ± prednisolone, n (%)	14 (21.5%)	7 (5.8%)	0.20
Short term outcome:			
Mortality, n (%)	4(6.1%)	2 (1.6%)	0.70
Duration of hospital stay in days, mean ± SD	12.59 ± 3.71	8.71 ± 2.95	**<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.

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

Infection/Disease	Total Number (%)	Number seen in initial episode of NS	Number seen in non-initial episode	P value
Peritonitis	5 (7.7%)	3 (60%)	2 (40%)	0.40
Pneumonia	13 (20.0%)	6 (46.1%)	7 (53.8%)	0.50
UTI	18 (27.7%)	10 (55.5%)	8 (44.4%)	0.70
Cellulitis	4 (6.2%)	2 (50%)	2 (50%)	0.60
Acute Diarrhoea	7 (10.8%)	4 (57.1%)	3 (42.9%)	0.60
Typhoid	2 (3.1%)	1 (50%)	1 (50%)	1.00
Hepatitis	2 (3.1%)	1 (50%)	1 (50%)	1.00
Tuberculosis	3 (4.6%)	1 (33.3%)	2 (66.6%)	0.90
Meningitis	2 (3.1%)	1 (50%)	1 (50%)	1.00
Varicella	1 (1.5%)	0 (0.0%)	1 (100%)	-----
Measles	1 (1.5%)	1 (100%)	0 (0.0%)	-----
Malaria	2 (3.1%)	1 (50%)	1 (50%)	1.00
Sepsis	5 (7.7%)	2 (40%)	3 (60%)	0.90

DISCUSSION

The present study was conducted to study major infections in nephrotic children presenting to our tertiary care level teaching institute. Incidence of major infections in nephrotic children brought to our institute was 34.9%. This is lower than the finding of Manish et al[12] who in their Indian study found the incidence of major infection in hospitalized nephrotic children to be 43.8%. Most of the Indian researchers have mentioned incidence of major infections to be in the range of 20-35%, which is comparable to our study. Referral bias and high index of clinical suspicion for infections in such children might have somewhat exaggerated the incidence of infections in present study. Common infections observed in this study 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 and together these constitute two-thirds of the total infections in these children.[13,14]. As glucocorticoids and other immuno-suppressive drugs are the mainstay of treatment in these children, infection occurring during such therapy is a well-known complication and is partially explained by the relative immunocompromised state in such children. Nevertheless, infection can occur even when the child is off any glucocorticoid therapy[15]. This partly explains our finding that there was no statistically significant difference between nephrotic children with infection and such 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 other immuno-suppressive agent. This allows us to presume that nephrotic children remain in a more or less constant state of immunosuppression and increased risk of infection irrespective of immunosuppressive therapy, atleast during the early days of disease. 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 underscores the importance of screening for UTI in all children with NS with relapse or non-response to corticosteroids, as symptoms tend to be masked because of anti-inflammatory action of steroids. In our study, mortality was 6 (3.2%). The major causes of mortality were sepsis induced MODS, severe pneumonia with respiratory failure cerebrovascular stroke and AKI. 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 might be explained by fulminant nature of infections associated with NS in their study. 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 common in children with NS and 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

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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

REFERENCES

1. Downie ML, Gallibois C, Parekh RS, Noone DG. Nephrotic syndrome in infants and children: pathophysiology and management. PaediatrInt Child Health. 2017;37:248-58.
2. Orth SR, Ritz E. The nephrotic syndrome. N Engl J Med. 1998; 23 (338):1202-11.
3. Rheault MN, Zhang L, Selewski DT. Midwest Pediatric Nephrology Consortium:AKI in Children Hospitalized with Nephrotic Syndrome.Clin J Am SocNephrol.2015; 10: 2110-18.
4. Eddy AA, Symons JM. Nephrotic syndrome in childhood. Lancet. 2003; 362(9384):629-39.
5. Arneil GC. The nephrotic syndrome.Pediatr Clin North Am. 1971; 18(2):547–59.
6. Uwaezuoke SN. Steroid-sensitive nephrotic syndrome in children: triggers of relapse and evolving hypotheses on pathogenesis. Ital J Pediatr. 2015; 41: 19-23
7. Kemper, MJ, Altrogge, H, Ganschow, R, Müller-Wiefel, DE. Serum levels of immunoglobulins and IgG subclasses in steroid sensitive nephrotic syndrome. Pediatr Nephrol. 2002;17:413-417.
8. Patiroglu, T, Melikoglu, A, Dusunsel, R. Serum levels of C3 and factors I and B in minimal change disease. Acta PaediatrJpn. 1998;40:333-36.
9. Gulati S, Kher V, Gupta A, Arora P, Rai PK, Sharma RK. Spectrum of infections in Indian children with nephrotic syndrome. Pediatr Nephrol. 1995; 9(4):431-34.
10. Jayan P, Krishnamurthy S, Biswal N, Mandal J. Clinical spectrum and predictive risk factors of major infections in hospitalized children with nephrotic syndrome. Indian Pediatr. 2013;50(8):779-81.
11. Bagga A, Ali U, Banerjee S, Kanitkar M, Phadke KD, Senguttuvan P, Sethi S, Shah M. Indian Pediatric Nephrology Group, Indian Academy of Pediatrics. Management of steroid sensitive nephrotic syndrome: revised guidelines. Indian Pediatr. 2008;45(3):203-14.
12. Manish K, Ghunawat J, Saikia D, Manchanda V.Incidence and risk factors for major infections in hospitalized children with nephrotic syndrome.J Bras Nefrol.2019; 41(4): 526-33
13. Kumar CB, Jaiswal AK. Study of major infections observed in children suffering from nephrotic syndrome from Bihar region. International Journal of Medical and Health Research. 2019; 5(3):149-52.
14. Doaa Youssef Mohammed, Mona Shaaban Ali Selim, Ali Mohammed AboZeid, MayyAbdAlfattahNeemat-Allah. Rate and Type of Infections in Children with Nephrotic Syndrome. Archives of Clinical and Medical Case Reports. 2018; 2: 38-46.
15. Alwadhi RK, Mathew JL, Rath B. Clinical profile of children with nephrotic syndrome not on glucorticoid therapy, but pres-enting with infection.J Paediatr Child Health.2004;40:28-32.
16. Senguttuvan P, Ravanan K, Prabhu N, Tamilarasi V. Infections encountered in childhood nephrotics in a pediatric renal unit. Indian J Nephrol. 2004;14:85-8.
17. Narain U, Gupta A. Urinary Tract Infection in Children With Nephrotic Syndrome. Pediatr Infect Dis J. 2018; 37(2):144-46.
18. Srivastava RN, Moudgil A, Khurana O. Serious infections and mortality in nephrotic syndrome. Indian Pediatr. 1987;24(12):1077-80