

Original Article

Risk Factors and Infection Patterns of Patients with Nephrotic Syndrome Attending a Tertiary Level Hospital: An Update

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Abstract:

Nephrotic syndrome (NS) is one of the most common childhood kidney diseases where defective immune system increases the chances of various infections. Forecasting the prognosis and proper planned management based on the recent data of risk factors and infection patterns can reduce the associated morbidities and mortalities. We investigated the incidences of infection and associated risk factors among the hospitalized children to provide an updated view of the current infection pattern of children with NS. This observational study was conducted at the Department of Pediatrics, Bangabandhu Sheikh Mujib Medical College Hospital, Bangladesh, from July 2017 to June 2020. A total of 167 children aged ≤ 12 years admitted at BSMMCH during this period with NS were included in this study. The hospital course and associated investigation reports of the study participants were analyzed. The incidence of infection among the patients with NS was 21.56%. The mean age of the participants was 5.43 2.66 years, and 73.01% of them were under immunosuppressive therapy. Ascites was a significant presentation among the infection group. There were no significant differences in Hb%, serum albumin, serum cholesterol and 24h urinary protein level between the two groups. *Klebsiella* and *Escherichia coli* were predominant isolates in the blood and urine culture, respectively. Serum albumin level <1.5 g/dL was associated with infection in risk analysis. Peritonitis, UTI and pneumonia were common infections and patients with associated infections had a significantly longer hospital stay ($p = <0.001$). Identifying the risk groups with ascites and low serum albumin levels and hospital-based predominant infectious organism patterns can help develop planned management of patients with NS associated various infections.

Key words: Nephrotic syndrome, Infection, Risk factors, Organisms.

Introduction:

Nephrotic syndrome (NS) is characterized by protein leakage from blood to the urine through the glomeruli resulting in heavy proteinuria, hypoalbuminemia,

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hypercholesterolemia and generalized edema¹⁻⁴. It is one of the most common kidney diseases in childhood,⁵⁻⁷. The incidence of NS varies in different populations. The United States and the United Kingdom are reported to be 2-7 cases in 100,000 children annually^{3,5,6}. In Bangladesh however, the incidence is estimated to be higher along with the other countries of South Asia due to genetic or environmental factors or a combination of both^{5,6,8}. However, the actual case scenario, incidence and prognosis of NS among the children of Bangladesh is still unknown^{5,7}. Children with NS suffer from a defective cell-mediated immunity due to urinary protein such as IgG and complement factors B and D loss which are essential components of complement activation^{5,9-11}. Besides, treatments with steroids or immunosuppressive therapies and mechanical factors such as edema and ascites lead them to an increased risk of infection^{1,9}.

Bacterial peritonitis, sepsis, pneumonia, meningitis, urinary tract infection (UTI), cellulitis and meningitis have been reported as some of the common infections that a child with NS may suffer^{5,12-17}. Among the organisms, *Escherichia coli* and *Streptococcus pneumoniae* cause the majority of the infections⁵. Such

infections may cause relapses or steroid resistance or trigger the onset of disease^{5,9,18}. However, the etiological factors and infections vary largely among different populations. Infections are the commonest cause of mortality and the primary cause of subsequent mortalities among children with NS¹⁸.

In developing countries like Bangladesh, prompt hospitalization, diagnosis and treatment of the potentially serious and life-threatening infections of the patients with NS are challenging. As a result, infection remains the most significant threat for immunocompromised children with NS.

The limited data on the risk factors, the current pattern of infections and prognosis among the hospitalized children with NS is an obstacle for proper planning and articulated management. This study investigates the incidence, prognosis, risk factors and common causative organisms of infection among the children with NS in a tertiary level hospital set up. Understanding the current scenario of infection patterns will help reduce the morbidity and mortalities associated with childhood NS.

Materials and methods:

This observational study was conducted at the Department of Pediatrics, Bangabandhu Sheikh Mujib Medical College Hospital (BSMMC), for three years from July 2017 to June 2020.

Children aged ≤ 12 years admitted at BSMMC during this period who fulfilled the International Study of Kidney Diseases in Children (ISKDC) criteria for nephrotic syndrome - edema, hypoalbuminemia (< 2.5 g/dl), proteinuria (> 40 mg/m²/hour) and hypercholesterolemia (> 250 mg/dl) were included in this study. Children with congenital nephrotic syndrome, secondary nephrotic syndrome, malignancy, and patients on dialysis therapy were excluded.

During this period, a total of 167 children who fulfilled the inclusion criteria were enrolled in the study. Written informed consent from the legal guardians of all the study participants was taken before the enrolment.

On admission, a detailed history of the study participants was recorded and a thorough physical examination was conducted to find out the symptoms and signs of infections. Later, hemoglobin, total and differential counts of leucocyte, serum albumin, serum cholesterol and urine routine microscopic examination were advised for all the study participants. Other investigations such as urine culture and sensitivity tests, blood glucose, serum creatinine and chest X-ray were performed based on the specific case as required. All the patients were treated accordingly.

The hospital course of all the study participants was recorded in a pre-structured data collection form. Incidence of infections was presented as proportions of children diagnosed with infection out of the total hospitalized children with NS.

Categorical variables such as demographic and medical characteristics, type of infections, duration of hospital stay and other laboratory parameters were presented as descriptive statistics, frequency and percentage.

Student's t-test and χ^2 tests were used to compare the means and proportions between children with infection and those without infection. Logistic regression was done to analyze the risk factors.

P value < 0.05 was considered statistically significant. Data were analyzed using GraphPad Prism version 8.4.0 for Mac (GraphPad Software, San Diego, California, USA).

Results

A total of 167 children aged ≤ 12 years admitted with NS at FMCH during the period of July 2017 to June 2020 were enrolled in the study.

The demographic and medical characteristics of the participants are shown in Table I. Among the study population with NS, 21.56% were admitted with infection and 78.44% were admitted without infection. The mean age of the participants was 5.43 ± 2.66 years. Male were the predominant group (55.69%) among the participants. Mean episode of NS was 2.50 ± 1.86 and mean duration of NS was 1.89 ± 1.53 years and 73.01% of the participants were under immunosuppressive therapy. Although 10.8% of the participants were presented with ascites, 30.56% had associated infection, which was statistically significant.

Table I: Demographic and medical characteristics of the study participants

Variables	Overall	Infection	Non-infection	p value
Sample size of admission	167	36 (21.56%)	131 (78.44%)	
Age (Mean \pm SD)	5.43 \pm 2.66	6.25 \pm 2.46	5.55 \pm 3.29	0.236
Male	93 (55.69%)	19 (52.78%)	74 (56.49%)	0.836
Episode number (Mean \pm SD)	2.50 \pm 1.86	2.28 \pm 1.08	1.85 \pm 1.32	0.074
Duration of Nephrotic syndrome (years)	1.89 \pm 1.53	1.97 \pm 1.84	1.72 \pm 1.45	0.389
Patient is on Immunosuppressive therapy	122 (73.01%)	29 (80.56%)	93 (70.99%)	0.351
Ascites	17 (10.8%)	11 (30.56%)	6 (4.58%)	< 0.001
Generalised edema	86 (51.50%)	22 (61.11%)	64 (48.85%)	0.265

Table II shows the different hematological and urinary characteristics presented as mean SD among the patients of NS with or without infections. It shows no statistically significant difference in haemoglobin, serum cholesterol and 24 hour urinary protein among the patients of NS with or without infection. But there was significant difference in serum albumin ($p = 0.044$) among the two groups of participants.

Table II: Hematological and urinary characteristics of the participants

Variables	Infection (mean±SD)	Non-infection (mean±SD)	p value
Hb (g/dL)	11.6±2.1	11.5±2.2	0.807
S. albumin (g/dL)	1.95±0.88	2.28±0.86	0.044
S. cholesterol (mg/dL)	449.12±144.62	392 ± 169.52	0.068
24-hour urine protein (g/day)	6.5 ± 2.8	6.8 ± 5.6	0.756

Based on the clinical evaluation, 54 blood and 48 urine samples were screened from the study participants. Among them, 12.96% of the blood samples and 16.67% urine samples had positive growth for organisms. *Klebsiella* was the predominant organism (71.43%) isolated from blood. Among the other organisms found in blood culture, *Streptococcus pneumoniae* was 42.86% and *Pseudomonas* was 28.57%. In the urine culture, *Escherichia coli* was the major isolated organism (87.50%) followed by *Klebsiella* (25.00%) and *Proteus* (12.50%) (Table III).

Table III: Microorganism growth pattern among the participants

Culture site	Samples screened	Sample positive for growth	Isolated organism	Number
Blood	54	7 (12.96%)	<i>Klebsiella</i>	5 (71.43%)
			<i>Streptococcus pneumoniae</i>	3 (42.86%)
			<i>Pseudomonas</i>	2 (28.57%)
Urine	48	8 (16.67%)	<i>Escherichia coli</i>	7 (87.50%)
			<i>Klebsiella</i>	2 (25.00%)
			<i>Proteus</i>	1 (12.50%)

Risk factors for infection of the participants were analysed using logistic regression analysis. Serum albumin level <1.5 g/dL was found as the risk factor for infection (OR: 2.5, 95% CI: 1.17-5.41, $p = 0.017$). We have not found any association of male sex, age, duration of disease, serum cholesterol or immunosuppressive therapy with infection during NS (Table IV).

Table IV: Risk factors for infection of the study participants

Variables	Odds ratio (OR)	95% CI	p value
Male	1.2	0.52-2.85	0.636
Age	0.9	0.47-2.04	0.944
Duration of disease	1.2	0.55-2.43	0.698
Serum albumin <1.5 g/dL	2.5	1.17-5.41	0.017
Serum cholesterol >500 mg/dL	1.2	0.58-2.59	0.574
Immunosuppressive therapy	1.7	0.68-4.19	0.255

* CI: confidence interval

Table V shows that peritonitis was the most common infection (8.38%) on the discharge diagnosis of the study participants. Urinary tract infections (UTI) (5.39%) and pneumonia (3.59%) were other notable infections.

Table V: Discharge diagnosis of the enrolled patients

Discharge diagnosis	Number	Percentage
NS without infection	131	78.44%
NS with peritonitis	14	8.38%
NS with UTI	9	5.39%
NS with pneumonia	6	3.59%
NS with cellulitis	2	1.20%
NS with sepsis	2	1.20%
NS with other respiratory diseases	3	1.80%

The mean length of hospital stay of the patient with and without infections were 9.92±4.83 and 6.24±5.24 days respectively and the duration was significantly higher among the patients with infection ($p = <0.001$). Among the different infections, patients with peritonitis or UTI had significantly longer stay in the hospital (Table VI).

Table VI: Length of hospital stay of the study participants

Diagnosis	n	Length of hospital stay (days) Mean ± SD	p value
NS without infection	131	6.24 ± 5.24	Reference
NS with infection	36	9.92 ± 4.83	<0.001
NS with peritonitis	14	9.70 ± 4.60	0.019
NS with UTI	9	9.77 ± 4.61	0.05
NS with pneumonia	6	9.16 ± 4.01	0.180
NS with cellulitis	2	6.50 ± 1.50	0.944
NS with sepsis	2	11.50 ± 1.50	0.159
NS with other respiratory diseases	3	9.33 ± 8.33	0.319

Discussion:

The mean age of patients in our study was 5.43 ± 2.66 years similar to the findings of the study done by Frankeet al¹⁹. In our study, the participants had a mean of 2.50 ± 1.86 episodes of NS at the time of admission.

The immunocompromised state during NS makes the children more vulnerable to infection. We have found that 21.56% patients with NS had associated infection. The incidence is slightly higher than the incidence (19%) of a study done in China by Wei et al¹³, and lower than the incidence (38.7%) of a study done in Pakistan by Moorani et al⁹. But a study done in India by Alwadhi et al¹⁶, found much higher incidence of infection in more than 80% of their patients¹⁶.

Among the different infections in our study, the most common infection was peritonitis which is consistent with a study done by Kumar et al¹². and Ajayan et al¹⁵. Among the other infections in our study, some patients had UTI and pneumonia and a few others had cellulitis, sepsis and other respiratory illness.

We did not have any case of associated acute invasive diarrhea, empyema, pulmonary tuberculosis, meningitis that in some other studies had^{12,16,18}. We did not have any case of mortality in our study.

There are some variations of the predominate infection in different setups. Such as Alwadhi et al.¹⁶, Moorani et al.⁹, Alfakeekh et al²⁰. and some others found upper respiratory infection was the most common infection in their study^{9,16,20}. Whereas, Wei et al¹³. have found pneumonia and Gulati et al¹⁸., had noted UTI as the most common infection.

Our study found that ascites was one of the most significant presentations ($p < 0.001$) of the participants of NS with infection. Approximately one third of the patients with associated infection had ascites compared to only 4.58% of the patients without associated infection. Ajayan et al¹⁵. have also found association of ascites with major infection in the patients with NS.

In laboratory testing, we did not find any significant difference of hemoglobin, serum cholesterol and 24 hour urinary protein among the patients of NS with or without infection. However, they had significant difference in the serum albumin level ($p = 0.044$).

In our logistic regression analysis for risk factors, serum albumin level < 1.5 g/dL was found to be significantly associated with infection of the children with NS. Different other studies done by Kumar et al¹²., Alwadhi et al¹⁶., Gulati et al¹⁸., and others have also found low serum albumin level as a significant risk factor for infection.

Sex, age, duration of disease, serum cholesterol or immunosuppressive therapy did not contribute as risk factors in our study. However, some other studies have found association of infection with higher serum cholesterol level^{15,16,18} that we did not find in our study.

Among the samples that we have collected for culture, *Klebsiella* was the predominant organism (71.43%) in blood. In addition to *Klebsiella*, we have also found growth of *Streptococcus pneumoniae*, *Pseudomonas*, *Escherichia coli* and *Proteus* in some culture samples. In a recent study by Pervez et al. in the SCANU of FMCH, Bangladesh also identified *Klebsiella* as the leading organism for infection²¹. However, Kumar et al¹²., Malaker et al⁵. and others have found *Streptococcus pneumoniae* as the predominant organism in their study which is different from ours. This bacterial pattern may be associated with different microbiological patterns in different facility.

In case of hospital stay, we have found that the patients with NS with associated infection had a significantly higher stay period than the patients without infection. Especially, patients with associated peritonitis or UTI had significantly longer duration of hospital stay. Wei et al¹³ and others have also found the association of longer hospital stay in case of the patients of NS with infections.

Limitations

Facility for blood and urine culture is scarce and costly to carry out for most of families attending at a government medical college hospital. So, we had limited data on the organisms causing various infections. An extended study at different facilities with fund for investigation support can produce further in-depth understanding of the infection patterns.

Conclusion:

It is evident that the association of infection in the patients with NS poses increased threat to the overall treatment, course and subsequent recovery of the children. Special attention to the signs of infection and facility based knowledge of infection pattern can help develop effective action plan in the hospital to reduce the incidence of infections and morbidities associated with it.

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