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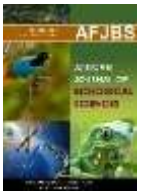

PREVALENCE, RISK FACTORS, AND ETIOLOGICAL SPECTRUM OF MAJOR INFECTIONS IN NEPHROTIC SYNDROME PATIENTS

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Abstract

Introduction: Nephrotic syndrome (NS) is a common renal disorder. The present study is being conducted to understand the etiological spectrum of prevailing infections and their sensitivity pattern in children with nephrotic syndrome and correlate risk factors for culture- positive and associated risk factors.

Methods: This study was conducted from January 2020 to December 2020 in the Department of Paediatrics, at a Single Tertiary Care Centre, Belagavi. The baseline presenting complaint was noted, and vitals, anthropometry, and detailed examination of the system affected in correlation with the symptoms were made in detail.

Results: A total of 72 nephrotic syndrome children were admitted during the study period of which 44 had infections (61%). The prevalence of Nephrotic syndrome in our study was observed to be 61%. It was observed that in our study 30.77% of Culture-positive infections were due to UTI, 23.88% were due to sepsis, and 19.23 % were due to acute GE. There was a positive correlation with a p-value of 0.007 between clinical diagnosis and culture-positive infection which was significant in our study. 79.5% of the children who had major infections were on immunomodulators like cyclosporine (34.09%), Levamisole (27.27%), MMF (6.82%) and Tacrolimus (11.36%).

Conclusion: The study concludes that the prevalence of major infections in admitted cases of nephrotic syndrome in our setup was 61%. UTI was the major infection associated with children with nephrotic syndrome in this part of North Karnataka with a prevalence of 27.27% with *E. coli* being the predominant organism. With proper clinical suspicion supported by proper microbiological evidence to isolate organisms and appropriate medical management, we achieved a clinical improvement in 93.18% of admitted cases.

Keywords: Prevalence, Risk Factors, Nephrotic Syndrome, Infections.

INTRODUCTION

Nephrotic syndrome (NS) is a common renal disorder. The advent of immunosuppressants, antibiotics, and immunomodulators has significantly changed the curve of mortality and morbidity in Nephrotic syndrome. Steroids used in the treatment of nephrotic syndrome were first isolated in 1936 and cortisone synthesis was attempted in 1946. [1] Nephrotic syndrome is the most common disease of the kidney in childhood with an incidence of 2-16.9 per 1 lakh population.[2] The incidence is 20-70 cases per million in Western countries, while in Asian countries the incidence is around 90-160 per million population. [3] Minimal change disease is the most common underlying histopathological lesion (80-90%) and the long-term prognosis is mostly benign. 10% of the children have Membranoproliferative glomerulonephritis (MPGN) or focal segmental glomerulonephritis. Histology of the disease predicts the response to corticosteroids, with 93% of children having minimal change nephrotic syndrome and achieving remission following the eight-week course of prednisolone.[4]

Without adequate medical therapy, nephrotic children are more susceptible to mortality, more due to bacterial infection. Before the time of corticosteroids and antibiotic treatment, about 40% of children expired and 50% of these deaths were due to infection. Recently it has been proved that at least 50% of the active cases in paediatric onset NS are initiated by a common viral URTI, which may be secondary to the non-specific response of the host to infection more than the reaction generated by the virus itself or their antibody. [5]

Children diagnosed with nephrotic syndrome (NS) are exposed to multiple sources of infectious complications resulting in increased morbidity and further subsequent complications. [5] In recent years, there has been a lapse in the literature regarding the clinical spectrum of deep-seated morbid infections in childhood NS from developing countries like India. Hence, knowledge of these infections and their affection is therapeutically and preventively relevant. Complete remission of Nephrotic syndrome with corticosteroids has been taken as an indicator of long-term satisfactory outcomes in pediatric nephrotic syndrome. Corticosteroid-responsive MCNS was the most frequent diagnosis in the pediatric age group. The response also predicted the requirement for biopsy in the corticosteroid-sensitive group. [6]

Serious systemic infections in NS in India were estimated at 35%. Incidences from neighbouring countries varied from 20-30% of these infections in admitted cases of Nephrotic syndrome. When considering the minor infections, the rate increased to around 76-84%.[7]

The major infections in the study were defined as “disseminated affecting the deep organs, requiring prolonged hospitalization (e.g. cellulitis, disseminated varicella) or potentially

causing threat to life". Specifically, major infections were outlined by the Indian Academy of Paediatrics and Indian Pediatric Nephrology group, which were defined and clinically identified for the study, including Peritonitis, Pneumonia, Sepsis, Urinary tract infection, Cellulitis, Meningitis, and tuberculosis. [8]

Several factors together combine to cause increased susceptibility to infections of bacterial aetiology. The various aspects include the presence of decreased levels of immunoglobulin (IgG) due to improper synthesis in the blood and excessive urinary loss, edema fluid in the extracellular compartment which acts as a culture medium, deficiency of varied range of proteins especially decreased serum albumin, volume loss leading to decreased perfusion of spleen, loss of complement factor B and D which are primarily needed for the phagocytic process of most encapsulated organisms, impaired and inappropriate T-lymphocyte functioning and effects of prolonged immunosuppressive and immunomodulatory therapy which are frequently employed in such children.[9] According to the Indian Academy of Paediatrics blood cultures in infants and children remain a mainstay in the diagnosis of infections, even negative cultures have good predictive value and diagnostic importance as further probing into the causes of diseases in a wide spectrum can be evaluated. [10]

Understanding the background of infections is important for adequate treatment and decreased relapses, thereby curbing the rising mortality and hospital admissions. As per the latest immunization coverage survey NFHS-4 in the year 2015-16, the percentage of fully immunized children is 62%.[11] Though the vaccination has been introduced in a phased manner in UIP since 2017 immunization status remains poor with the children admitted with nephrotic syndrome which in turn contributes to the morbidity curve of the disease.[12] Hence, the present study is being conducted to understand the spectrum of prevailing infections in children with nephrotic syndrome and their associated risk factors. To study the prevalence of major infections in Nephrotic syndrome. To correlate risk factors for culture-positive major infections in nephrotic syndrome. To understand the etiological spectrum of infections and their sensitivity pattern.

METHODOLOGY

This study was conducted from January 2020 to December 2020 in the Department of Paediatrics, Single Tertiary Care Centre, Belagavi. Due to COVID-19 pandemic sample collection was extended to May 2021. The inclusion criteria were: All Nephrotic syndrome patients between 1 year and 18 years of age are admitted to pediatric wards. The exclusion

criteria were: Atypical cases presenting with: • uncontrolled hypertension • haematuria • multisystem involvement, Any chronic kidney injury, Urogenital abnormalities.

Data collection

This study was conducted after the approval from the clinical ethical committee of the institution, the parents of the children fulfilling the selection criteria were briefed about the nature of the study and written informed consent was obtained from the parents/caregivers to participate in the study before the enrolment. At admission baseline presenting complaint was noted, vitals, anthropometry, and detailed examination of the system affected in correlation with the symptoms were made in detail. All the findings were recorded on a pre-designed and pre-tested proforma. Further complete hemogram, mini renal profile, Serum albumin, and blood cultures were collected at admission for the enrolled children. An attempt to delineate the focus of infection based on clinical history and examination was made and appropriate culture samples were sent in addition to routine investigations. All the investigations were processed in the standard lab under a tertiary care hospital, Belagavi, Karnataka.

Statistical Analysis:

The obtained data was entered into Microsoft excel and analyzed using R software version 4.1.1. Categorical variables are given in the form of a frequency table. Continuous variables are given in Mean ± SD/ Median (Min, Max) form. The chi-square test is used to check the dependency between categorical variables. Two sample t-tests were used to compare the mean of variables over the group. A *p*-value less than or equal to 0.05 indicates significance.

Risk factors assessed during the study:

1. Hs-CRP – Serum Hs- CRP values were analyzed during day one of admission by collecting 2 ml blood in a heparinized vacutainer and processing in the Hi-tech Lab.
2. Serum Albumin – Serum albumin values <1.5g/dl were considered positive risk factor cut-off. It was measured by collecting 2ml blood on the day of admission in heparinized vacutainer and processed in a Hi-tech lab.
3. Immunization status – Immunisation status as per the revised national immunization schedule was outlined and any defaulter was considered as partially immunized for age.
4. Steroid status – The current steroid status of the child was accounted for and recorded.

RESULTS

The cross-sectional study was conducted from January 2020 to May 2021 in the Department of Pediatrics, in the Tertiary Care Centre, Belagavi. A total of 72 nephrotic syndrome children were admitted during the study period of which 44 had infections (61%). The prevalence of Nephrotic syndrome in our study was observed to be 61%.

Demographical Characteristics:

Data contained measurements on 44 subjects whose ages ranged from 1.5 years to 16.92 years with a mean age of 7.76 ± 5.28 years (Table 1).

Table 1. Age distribution of nephrotic children enrolled in the study.

Age (In Years)	< 5	17 (38.64%)
	5-10	12 (27.27%)
	≥ 10	15 (34.09%)
	Mean ± SD	7.76 ± 5.28
	Median (Min, Max)	6 (1.5, 16.92)

In the study, 38.64% belonged to the under 5 age group while the lowest percentage of infection was found among 5-10 years. There was no significant difference in the age distribution of the cases. Out of the 44 subjects enrolled it was found that the majority of subjects constituted of male gender 32 (72.37%) while females were 12(27.27).

Primary outcome:

Out of 44 cases in the study it was observed that 26 (59.09%) had culture-positive major infections and 18 cases had culture-negative infectious episodes. Culture samples were taken keeping in mind the clinical suspicion of focus of infection. Blood cultures were taken invariably in all cases (Table 2).

Table 2. Distribution of types of major infections in subjects.

Diagnosis	Acute Ge	6 (13.64%)
	Acute Ge + Sepsis	1 (2.27%)
	Cellulitis	1 (2.27%)
	Fournier's Gangrene	1 (2.27%)
	LRTI	5 (11.36%)
	Peritonitis	11 (25%)
	Septicaemia	6 (13.64%)

	Tuberculosis	1 (2.27%)
	UTI	12 (27.27%)

In our study, we observed that the predominant infection was UTI constituting 12 out of 44 cases (12.27%) followed by peritonitis (25%) Acute GE and sepsis each constituting 6% and cellulitis, Fournier's gangrene and tuberculosis each 1%.

Table 3. Distribution of subjects according to organisms isolated from culture samples.

Organism Isolated	*Ascaris Lumbricoides*	1 (2.27%)
	Candida Albicans	2 (4.55%)
	Cons	2 (4.55%)
	E. coli	8 (18.18%)
	K. Oxytoca	1 (2.27%)
	K. Pneumonia	5 (11.36%)
	MRSA	1 (2.27%)
	Non-Enteric Pathogen	2 (4.55%)
	P. Aeruginosa	2 (4.55%)
	S. Pneumonia	3 (6.82%)

Of 44 patients enrolled, and 26 culture-positive cases (59.09%) 18.8% isolated *E. coli* as a causative organism for the infection followed by *Klebsiella pneumoniae* which constituted 11.36%. *Streptococcus pneumoniae* was isolated in 6.82% and CONS, *Candida*, *Pseudomonas,* and Non-enteric pathogens constituted 4.45% of the organisms (Table 3).

Table 4. Distribution of culture specimens taken in subjects presenting with infection.

Culture specimen	Ascitic Fluid	11 (25%)
	Blood	10 (22.73%)
	Pleural Fluid	1 (2.27%)
	Pus	2 (4.55%)
	Sputum	1 (2.27%)
	Stool	7 (15.91%)
	Urine	12 (27.27%)

In the present study the specimen for culture was determined based on clinical suspicion based on history and examination and maximum cultures have been sent of urine (27.27%) followed by ascitic fluid (25%) (Table 4).

Table 5. Distribution of diagnosis based on the cultural status of the cases.

		Culture -ve	Culture +ve	*p*-value
Diagnosis	Acute Ge	1 (5.56%)	5 (19.23%)	0.007^{MC}*
	Acute Ge + Sepsis	0	1 (3.85%)	
	Cellulitis	0	1 (3.85%)	
	Fournier's Gangrene	0	1 (3.85%)	
	LRTI	3 (16.67%)	2 (7.69%)	
	Peritonitis	9 (50%)	2 (7.69%)	
	Septicaemia	0	6 (23.08%)	
	Tuberculosis	1 (5.56%)	0	
	UTI	4 (22.22%)	8 (30.77%)	

It was observed that in our study 30.77% of Culture-positive infections were due to UTI, 23.88% were due to sepsis, and 19.23 % were due to acute GE. There was a positive correlation with a *p*-value of 0.007 between clinical diagnosis and culture-positive infection which was significant in our study (Table 5).

RISK FACTORS ASSOCIATED

In the study, it was observed that 86.36% were established cases of nephrotic syndrome who presented in relapse with infection and 13.64% were newly diagnosed cases of Nephrotic syndrome presenting with infection. From the study, it was observed that 96.15 % of the culture-positive cases were episodes of relapse following infection on already diagnosed cases of nephrotic syndrome while 1% of the culture-positive cases were newly diagnosed. This association had a p-value of 0.0405 hence denoting a significant relationship between diagnosis status and culture-positive incidence of infection. Further, the established diagnosed cases were classified into steroid-sensitive and steroid-resistant based on clinical history and response to treatment. In the study, it was observed that out of 44 cases 37 cases were on steroid therapy (84.09%) at the time

of presenting with infection, while 15.91% i.e. 7 cases were not on steroids, 6 were new cases and one case was in remission.

From the study, it was observed that 13 (72.22%) out of 18 cases of culture-negative infection were on steroid therapy at the time of presenting with infection and 24 (92.31%) out of 26 cases of culture-negative infection were on steroids at the time of presenting with infection with a *p*-value of 0.1074 which was not significant. In our present study out of the 44 children, 56.82% had a serum albumin value less than 1.5g/dl which was proposed as a risk factor for infection in children with nephrotic syndrome. In our present study, 79.55% of the children were fully immunized for age and there was no significant correlation with the incidence of infection. In the study, it was observed that there was no significant correlation between the immunization status among culture-positive and culture-negative cases, with a *p*-value of 0.1399.

Table 6. Distribution of Hs-CRP values based on predictive risk for infection and culture status.

HsCRP Values	High Risk (≥ 3)	35 (79.55%)
	Average (1-3)	6 (13.64%)
	Low (< 1)	3 (6.82%)
	Mean ± SD Median (Min, Max)	83.93 ± 123.05 20 (0.2, 617)
	Culture Status	
	Negative	**Positive**
Hs-CRP (>3)	13 (37.14%)	22 (62.86%)
Hs-CRP (<3)	5 (55.56%)	4 (44.44%)
P value	0.4723^{MC}	

From the study it was observed that 79.55% of the total cases belonged to the high predictive risk group of infection based on serum Hs CRP values, 13.64 had moderate risk and 6.82% had low risk for infections. The mean value of Hs- CRP ranged between 83.93 ± 123.05. In our study, there was no significant association between the distribution of Hs-CRP values among culture-positive and culture-negative major infections with a p-value of 0.4723 (Table 6). In our study, it was observed that 93.88% had a good clinical outcome and were discharged successfully while 4.55% each succumbed to death or left against medical advice from our care. In our study of 44 subjects, it was observed that 15 were on cyclosporine,12 were on Levamisole, 3 were on MMF and 5 were on Tacrolimus while the rest were not on any immunomodulators. However, we could not establish a

positive correlation between immunomodulators and the culture-positive status of the infected children.

DISCUSSION

Infection-triggered relapses requiring hospitalization are an important risk factor for morbidity in the pediatric age group affected with nephrotic syndrome. The incidence of Nephrotic syndrome in the global scenario is 2-16.9 per lakh population and in Asian countries, 90-160 per million population. [13] Peritonitis, pneumonia, urinary tract infections, cellulitis, meningitis, and tuberculosis have been reported as major infections in children hailing from northern parts of India.[14] The present study was an attempt to find out the major manifested infections among children admitted with nephrotic syndrome (NS) and to assess the risk factors which has been studied in previous literature associated with the disease.[15] An attempt was made to delineate the role of Hs- CRP molecule as a reliable marker of infectious aetiology and to support the clinical diagnosis with appropriate microbiological culture evidence.[16] The cross-sectional study was conducted from January 2020 to May 2021 in the Department of Paediatrics, tertiary Care Centre, Belagavi. During the study period, a total of 72 children were admitted to the ward of which 44 had major infections. All of them were enrolled in the study and delineated for the cause and aetiology of the episode.

General Characteristics:

In our present study, the mean age of distribution of children was found to be 7.76 $\pm$ 5.28. The mean age of distribution observed in the study by Krishnan C et al (17) was 5.69 $\pm$ 2.84 which was done in South India among the same age group. Another study done by Ajayan P et al showed a mean age group distribution of 6.8 $\pm$ 3.5 (8). The percentage of children below 5 years who presented with morbidity due to infection was 38.64% in this study.

In the study, the majority of the children affected with major infections were boys which was consistent with the study done by Kumar M et al (53%) (7), Lebel et al (58%)(39), Ajayan et al (63%). But in contrast to this study, it was mentioned by Lebel et al that serious bacterial infections were found to be more common in females (60%) (39). Though there is no ethnic or gender predisposition as per observational studies, the

prevalence of nephrotic syndrome in children has a ratio of 2–1 male-to-female in most previous studies. (43)

Admission weight observed in this study was another demographic parameter that was recorded in the preformed proforma but as the edema associated with the disease poses to false positive results, analysis of the relationship of weight or nutrition status could not be associated with the infective state. A positive association between weight, BMI to the culture positive status was observed in the study but was not taken into account due to above mentioned lapse.

Bioelectric impedance analysis (BIA) and dual energy x-ray absorptiometry (DEA) are two modalities that accurately measure the body water and mineral composition and hence help in calculating the actual weight of the children. (44) Dry weight calculation was not done as the clinical assessment was done at the time of presentation with infection.

In the present study primary objective was to identify the deep seated infections that were present in our tertiary care setup in children with nephrotic syndrome. After clinical evaluation the appropriate cultures revealed growth of micro-organism which supported our preliminary diagnosis. The important tool that we employed for this study was blood and body fluid culture and sensitivity. There was a significant association observed between the clinical diagnosis of major infections and culture of organisms in the sample p value of 0.0265.(<0.05). Thus clinical suspicion and focus directed sampling is essential in delineating an infection.

The major infection of maximum frequency in our study was Urinary tract infection which constituted 27.27% of the total. This result was consistent with the study done by Krishnamurthy et al which showed prevalence of urinary tract infection around 25%(40).Most of the UTI episodes have been observed during periods of relapse rather than as a presenting infection in the initial episode. Though not the most common infection UTI has been found in around the same prevalence and a little lesser in other developing countries around India. (42,45). Another observation in the study was the etiological agent associated with urinary tract infection.

The present study showed that *E. coli* was the most common pathogen isolated in the culture samples which was consistent with studies done by Tanuka B et al which showed around 50% of UTI infections had *E. coli* as the causative organism followed by *Klebsiella* and *Proteus.* (46) 62% of the Urine samples tested positive for *E. coli.* As urine analysis has no optimal sensitivity and the nonspecific clinical signs of urinary tract

infection have low diagnostic value urine culture has been considered as the gold standard for diagnosis in children. (47) The samples in our study have been collected keeping the Guidelines from The National Institute for Health and clinical Excellence which recommends the clean catch urine technique of the midstream urine for the culture analysis thereby preventing contamination.

The second most common infection associated with our study was peritonitis which had a similar prevalence when compared to the studies done in North India with, the same sample size. This was consistent with the study done by Nermin et al which showed a prevalence of 16% of peritonitis patients in a 5-year study done in a tertiary care center. (23)

The present study showed that the percentage of subjects who presented with the first episode of nephrotic syndrome was 13.64% and the relapsed cases were 86.36%. There was an increased frequency of infectious episodes in relapse cases in comparison to the initial episodes. This was in contrast to the study done by Gulati S et al which showed infection as a presenting symptom of NS 38.7% of cases of newly diagnosed nephrotic syndrome. (9)

In our study out of the culture-positive cases, we observed that 92.3% were on high doses of steroids and were diagnosed with cases of steroid-dependent nephrotic syndrome. This observation was different from the study observed by Ajayan et al where the first episode of the nephrotic syndrome had more frequency of infection than SDNS and SRNS (40).

In our study we included Hs-CRP as a predictive risk factor for infection, we observed that higher values of the serological marker were found in patients who had active major infection but could not find a positive correlation between the higher values and clinical outcome. This was consistent with the study done by Eran et al in 2016(48). Sing radioimmunoassay kits Hs-CRP aids in diagnosing bacterial infections. If supported by Procalcitonin and serial values of treatment it can also be used as an indicator of treatment response. This was depicted in the study done by Vijay Kamble et al among children with infection in the year 2018. (49)

In our study, no positive correlation was observed between the serum albumin value and the incidence of infection. It was observed that albumin value <1.5g/dl did not increase the risk for deep-seated infection which was against the observation by Gulati et al (9) where low serum albumin levels and hypercholesterolemia were studied as a risk factor for infection. In our study, 79.5% of the children who had major infections were

on immunomodulators like cyclosporine (34.09%), Levamisole (27.27%), MMF (6.82%) and Tacrolimus (11.36%). There was no observed correlation between the incidence the incidence of infection and the type of immunomodulator that the child was currently on.

STRENGTHS & LIMITATIONS

1. Our study had a higher prevalence of major infections than previous similar studies due to the status of our institution as a reference centre with the availability of pediatric nephrologist and tertiary care ICUs.

2. Sample size was a limitation in our study as the prevalence of infection in nephrotic syndrome in North Karnataka was lesser than the previous studies done in other parts of South India.

3. In few of the cases even with HsCRP value high and infection rate high there was no organism isolated signifying viral etiology but Viral cultures were not employed in our study.

4. The antibiotic sensitivity pattern from the microbiology lab was inconclusive due to the limited testing depending upon community sensitivity in adults and children and could not be generalized among the children with immunocompromised state.

CONCLUSION

Major infections are one of the biggest risk factors for the global burden of morbidity in nephrotic syndrome cases. Identification of the focus of infection early in the management is the cornerstone in treating children with relapse of nephrotic syndrome. This study was conducted to outline the type of major infections prevalent in nephrotic syndrome and the risk factors in culture-positive cases of infection. Thus, from our study it was concluded that the prevalence of major infections in admitted cases of nephrotic syndrome in our setup was 61%. UTI was the major infection associated in children with nephrotic syndrome in this part of North Karnataka with a prevalence of 27.27% with *E. coli* being the predominant organism. With proper clinical suspicion supported by proper microbiological evidence to isolate organism and appropriate medical management we had achieved a clinical improvement in 93.18% of admitted cases.

Most of the infections occurred during the period of relapse and not during the first episode suggesting a role of impaired immunity in the pathogenesis of major infections in these children.

Conflict of Interest: The authors declare conflict of Interest as None.

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