



ORIGINAL RESEARCH PAPER

Paediatrics

PROFILE OF INFECTIONS IN CHILDREN WITH NEPHROTIC SYNDROME AGED 1-12 YEAR PRESENTING TO A TERTIARY CARE CENTRE

KEY WORDS: Nephrotic syndrome, Infections, clinical outcome.

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ABSTRACT

Background: Children with nephrotic syndrome are at increased risk of infections because of the disease status itself as well as the use of various immunosuppressive agents. Understanding the prevalence and spectrum of infections helps in prevention and proper management. **Objectives:** To identify types and spectrum of infections in children with nephrotic syndrome and study their clinical outcome **Methodology:** This is a hospital based prospective observational study done in Govt. T.D Medical College, Alappuzha. All children with nephrotic syndrome, age between 1-12 years and, in whom presence of an infection was clinically considered at admission were enrolled. Children must be either meeting the criteria for nephrotic syndrome, in relapse or on treatment with immunosuppressants. An expected sample size for the study period was calculated to be 62..A structured proforma was used to collect information on the various study variables.. Relevant history was taken, physical examination done, investigations relevant to confirm each particular infection was carried out .Each case is followed up till discharge and their clinical outcome were studied. The data obtained were quantified and analysed using SPSS software. **Result:** Out of 122 admissions 62(50.8%) had some kind of infections. Upper respiratory tract infection was most common (53.2%), followed by UTI and pneumonia(11.29%). Most common organism isolated in UTI cases was E coli (71.4%). Mean number of days taken to attain remission was 14 in case of major infection and in 9 in other minor infections. **Conclusion:** As per the study a significant number children had an infection during active disease. Out of infections upper respiratory tract infections were most common followed by UTI and pneumonia. Children admitted with major infections required more time to attain remission, many required albumin infusion and ICU admissions. This indicates that children with major infection had a more severe state of nephrotic syndrome

INTRODUCTION

Nephrotic syndrome (NS) is one of the commonest chronic renal diseases in children, characterized by selective proteinuria, hypoalbuminemia, hyperlipidemia, and edema. Majority of cases of nephrotic syndrome are without underlying secondary etiology and termed idiopathic nephrotic syndrome (INS). Children with nephrotic syndrome are at increased risk of infections because of the disease status itself as well as use of various immunosuppressive agents. The important risk factors for infection are urinary loss of immunoglobulin and alternative complement pathway factors, presence of edema, and treatment with prednisolone and other cytotoxic agents. Peritonitis, pneumonia, urinary tract infection (UTI), cellulitis, meningitis and tuberculosis have been reported as major infections in these children. In majority, infection triggers relapse requiring hospitalization with increased risk of morbidity and mortality. Understanding the prevalence and spectrum of infections helps in prevention and proper management. It is also important to know whether the severity of nephrotic state has been worsened by infection. This study attempts to determine the type and spectrum of infections and its clinical outcome in children with nephrotic syndrome.

OBJECTIVES

- To identify the frequency and type of infections in children with nephrotic syndrome presenting to a tertiary care centre in Kerala
- To study the clinical outcome in the above cases

METHODOLOGY

This is a prospective observational study done in The Department of Paediatrics, Govt. T.D Medical College Hospital, Alappuzha during a time period of 18 months from december 2019 to may 2021. Study subjects were children between 1-12 years admitted in pediatric ward or ICU in Govt. T.D Medical College Hospital, Alappuzha either meeting ISKDC criteria for nephrotic syndrome or previously diagnosed to have Nephrotic Syndrome and currently on steroid or immunosuppressive therapy, and in whom infection

was clinically considered at the time of presentation.

Case Definitions

Nephrotic syndrome- Nephrotic syndrome is defined as nephrotic range proteinuria hypoalbuminemia (<3g/dl) and edema

Relapse-Urine albumin 3+ or 4+ (or proteinuria >40 mg/m2/h) for 3 consecutive early morning specimens, having been in remission previously

Major infections- Major infections were defined as disseminated, affecting deep organs, requiring hospitalization (e.g. cellulitis, disseminated varicella) or potentially lifethreatening⁽⁸⁾.

Specific major infections were defined as follows:

1. Peritonitis: Abdominal pain, tenderness, distension, diarrhea, or vomiting, with ascitic fluid >100 leukocytes/mm³ and minimum 50% neutrophils and/ or positive culture^{1,2,6}.
2. Pneumonia: fast breathing and chest indrawing with chest X-ray confirmation.⁹
3. Urinary tract infection (UTI): Bacterial colony count of >10⁵ organisms/mL in a clean-catch midstream urine sample with fever (>38.5° C), dysuria or increased urination frequency.⁹
4. Cellulitis: Erythema, warmth, swelling, fever and local tenderness in any body part.
5. Meningitis: Fever and one of the following: neck rigidity, altered sensorium, seizures, with confirmation by cerebrospinal fluid cytology, biochemistry and culture.
6. Septicemia: Fever with systemic symptoms like vomiting, prostration or lethargy with or without evidence of organ failure, and a pathogenic bacterium grown in blood culture.
7. Pulmonary TB: Cough with or without fever for > 2 weeks and/or contact with an open case of TB, having a positive Mantoux test and chest X-ray evidence of TB or an AFB positivity of appropriate sample.

Minor infections-all infections other than major infections

Inclusion Criteria:

Children 1-12 years of age with nephrotic syndrome either initial episode, relapse, on steroid or immunosuppressive therapy

Exclusion Criteria:

Children who are diagnosed to have congenital or secondary nephrotic syndrome previously. Children with any other chronic comorbidities altering disease course

On reviewing previous hospital records, every month an average of 3-4 children with nephrotic syndrome admitted for various reasons were noticed to have some form of infection. Data was collected for three months in 2019 at different points in time to allow for seasonal variations. From this, an expected sample size for the study period was calculated to be 62. A total of 62 cases were collected during the study period.¹¹

All children with nephrotic syndrome admitted in pediatric ward and ICU GTDMCH, Alappuzha meeting study criteria and in whom presence of an infection was clinically considered at presentation is enrolled. A structured proforma was used to collect information on the various study variables. Informed consent taken in all cases. Relevant history was taken, physical examination done, investigations relevant to confirm each particular infection (CBC, ESR, CRP, blood culture, Urine culture) was carried out depending on clinical scenarios. Each case was followed up till discharge. Infections were classified into major and minor infections and their clinical outcome was studied.

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions. **Chi-square test** was used as test of significance for qualitative data.

Continuous data was represented as mean and standard deviation. **Independent t test** was used as test of significance to identify the mean difference between two quantitative variables. p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical Software: MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyze data.

Ethical Consideration

1. Ethics committee approval was taken before starting the study.
2. Written Informed assent/consent was taken from subjects/parents.
3. An undertaking was given that no expense would be incurred by patient and no risk was involved to the patient during the study.
4. Confidentiality of the information obtained was assured throughout the study.

RESULTS

Among our 62 study subjects children in the under 5 category constituted 64.5% of the sample. Mean age of subjects was 5 ± 2.581 years. Out of the 62 cases enrolled 34 were males and 28 were females with a male to female ratio 1.21. Majority of the children were immunized for age as per National immunisation schedule and there were no unimmunised children, but there were 10(16.1%) children who were only partially immunized. Facial puffiness was the presenting complaint in 100% of the study subjects. When considering the possibility of an infection, Fever was the most prominent symptom from history and was present in 49 (79%) children. The mean duration of fever at admission was 1.5 days

Baseline characteristics (n=62)	
Mean Age(in years)	5 ± 2.581
Sex	
Males	34(54.8%)
Females	28(45.2%)
Immunized for age as per national shedule	52(83.9%)
Type of nephrotic syndrome	
SSNS	51(82.3%)
FRNS/SDNS	10(16.1%)
SRNS	1(1.6%)
Status of present episode	
Initial episode	31(50%)
Relapse	30(48.4%)
Remission	1(1.6%)
Taking steroids at presentation	13(21%)
On immunosupressants other than steroids	3(4.8%)

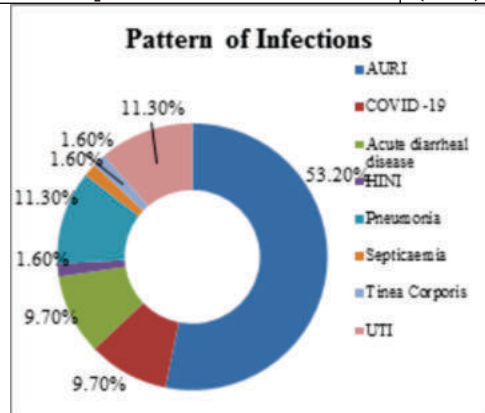


Figure 1: Diagram showing distribution of pattern of infection

Out of the 122 admissions for nephrotic syndrome diagnosis of an infection was considered in 62 cases amounting to 50.8% incidence of infections in nephrotic syndrome. Most common infection encountered was acute upper respiratory tract infection (n=33, 53.2%). Upon classifying infections into major and minor infection, there were 15(24.2%) major infections and 47(75.8%) minor infections. Pneumonia (n=7, 11.3%), urinary tract infection (n=7, 11.3%) and septicemia (n=1, 1.6%) constitute specific major infections (n=15, 24.2%). other infections include COVID 19 (n=6, 9.7%, all belonging to category A or B, acute diarrheal diseases (n=6, 9.7%) including acute infective diarrhea and dysentery and 1 case each of fungal skin infection and H1N1 positive ILL.

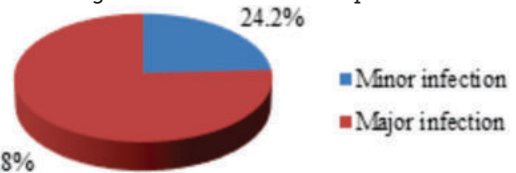


Figure 2: Pie diagram showing Infection profile of subjects based on severity of infection

We had 31(50%) cases in whom this was the first episode of nephrotic syndrome.30 (48.4%) cases presented in relapse. We had one child in remission but had edema and fever at presentation There were 13(21%) cases who were on steroids at presentation,3(20%) out of 15 major infection cases were on steroids. All the 3 had pneumonia. Mean dose of steroid was 0.667 in case of major infections and 0.755 in minor infection with a standard deviation of 0.577 and 0.522 respectively(χ² =0.011, df =1, p =0.916) .2 cases presented with AURI was on cyclophosphamide and 1 child taking levamisole developed pneumonia

There were 10(16.1%) cases ofSDNS,51(82.3%) cases of SSNS and 1 (1.6%) case of SRNS. Out of SDNS and SSNS cases 33,3%(n=5) &66.7%(n=10) developed major infection respectively

In the study there was significant difference in Total count, Neutrophil, Lymphocyte and ESR between two groups. Mean total count, Neutrophil, and ESR was significantly high in Major group and mean Lymphocyte was high in Lymphocyte. There was no significant difference in Hemoglobin and Mean level of haematocrit between two groups. Mean serum albumin level in children with infections were found to be 1.68g/dl with a standard deviation of 0.38 which was significantly low.

S.Cholesterol level was high in both major and minor infection. HDL level was nearly normal In the study there was significant difference in Serum cholesterol(p-0.140) and LDL(0.470) between two groups.

Infection							
	Major Infection		Minor Infection		Total		P value
	Mean	SD	Mean	SD	Mean	SD	
Haemoglobin	13.40	1.30	13.89	1.25	13.77	1.27	0.197
Haematocrit	39.20	3.17	38.44	3.70	38.63	3.56	0.478
Total Count	17000	4789	13063	5444	14016	5523	0.015*
	.00	57	.83	20	.13	04	
Neutrophil	72.33	13.85	53.06	19.22	57.72	19.79	0.001*
Lymphocyte	22.87	13.69	39.74	18.18	35.65	18.58	0.002*
ESR	95.27	30.30	71.36	20.92	77.15	25.44	0.001*

Blood culture and sensitivity and urine culture and sensitivity was done in all cases. Obtained 1 blood culture positive (1.6%) case and 7 urine culture positive (11.3%) cases. Organism obtained from blood culture was non fermenting gram negative bacilli whereas E coli was the most commonly identified organism from urine cultures

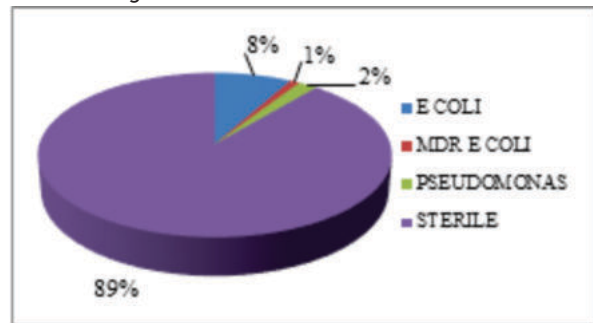


Figure 7: Pie chart showing distribution of study subjects based on urine culture

- There was evidence of hypovolemia in 6 (9.7%) cases and there was significant difference between major and minor infections in the occurrence of hypovolemia
- A total of 18(29%) cases required albumin infusion. In major infection group, 60% were given albumin infusion and in minor infection group, 19.1% required albumin infusion. There was significant difference in albumin infusion between two groups.
- A total of 16 cases required ICU admission. In major infection group, 53.3% required ICU stay and in minor infection group, 17% required ICU stay. There was significant difference in ICU stay between two groups.

Table 32, 34, 35: Distribution of occurrence and requirement of Albumin infusion and ICU stay with respect to type of infection.

INFECTION						
	Major infection		Mino Infection		Total	
	Count	%	Count	%	Count	%
Hypovolemia						
Present	4	26.7%	2	4.3%	6	9.7%
Absent	11	73.3%	45	95.7	56	90.3%
$\chi^2=6.534, df=1, p=0.011^*$						
Albumin Infusion						
Required	9	60.0%	9	19.1%	18	29.0%

Not required	6	40.0%	38	80.9%	44	71.0%
$\chi^2=9.21, df=1, p=0.002^*$						
ICU stay						
Required	8	53.3%	8	17.0%	16	25.8%
Not Required	7	46.7%	39	83.0%	46	74.2%
$\chi^2=7.831, df=1, p=0.005^*$						

Mean number of days to attain remission in major infection group was 13.87 ± 5.125 days and in minor infection was 8.82 ± 1.957 days. There was significant difference in days to remission between two groups.

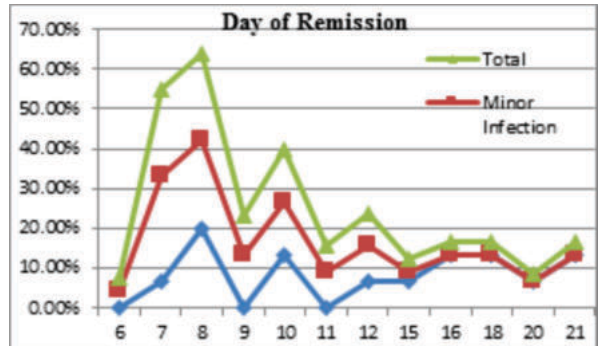


Figure 28: Line diagram showing trend in attainment of remission with respect to type of infection

DISCUSSION

This study was conducted among hospitalized children with nephrotic syndrome admitted to pediatric ward or ICU at Government T D Medical College, Alappuzha. We found the incidence of infections in hospitalized children with NS as 50.81% (n=62) with the most common infection being acute upper respiratory infections (n=33, 53.2%). Various Indian studies^{3,7} found an incidence of infections in nephrotic syndrome to be 30-40%. The relatively higher incidence in our study was probably due to the COVID 19 pandemic and subsequent reluctance from parents in getting admitted unless children gets severely affected. An incidence of 53% was obtained in a study done in Karachi, Pakistan.¹³ The incidence of major infections in our study was 24.2% (n=15) Major infections in children with NS have been reported from different parts of India and neighbouring countries, with incidence varying from 19–44%^{4,6,10,11} In our study Pneumonia (n=7, 11.3%) and urinary tract infection (n=7, 11.3%) were the most common major infections. A similar study from Calicut, Kerala and another study from Taiwan reported pneumonia as the most common major infection^{4,6} whereas UTI was the most common infection as per many other studies^{3,7}. We did not encounter any peritonitis cases during the study period which was one of the most common infection as per studies from southern (Vellore, Pondicherry)^{7,10} as well as northern part of India¹¹ Other infections include COVID 19 (n=6, 9.7%), acute diarrheal diseases (n=6, 9.7%) septicemia (n=1, 1.6%) and 1 case each of fungal skin infection and H1N1 positive Ill. All covid cases were belonging to either category A or B.

Children in the under 5 category constituted majority (n=64.5%) of the sample. Mean age of subjects was 5 ± 2.581 years, which was in concordance with other Indian studies^{3,7}. Most of the children admitted with infection were boys. Majority of the children were immunized for age as per National immunisation schedule. Pneumococcal vaccine was taken by 21 (33.8%) None had taken varicella or influenza vaccine.

We could not find any significant difference in occurrence of infections in newly diagnosed cases (50%) or relapse (48.4%). Krishnan et al has reported incidence of major infections are more in relapses than initial episode of nephrotic syndrome⁴. A study from Bangladesh found an incidence of infections to be 78.57% in newly diagnosed cases of nephrotic syndrome.¹²

Urine culture and sensitivity in the UTI cases showed E coli as the most common pathogenic organism. The spectrum of microorganisms obtained were similar in many studies^{4,10}. Even though septicemia is implicated as an important cause of mortality in children with nephrotic syndrome it is not seen commonly⁴. We found one case of septicemia, whose blood culture was positive yielded non fermenting gram negative bacilli sensitive to 3rd generation cephalosporins

As per literature hypoalbuminemia¹¹ and hypercholesterolemia¹⁰ are independent risk factors for infection. We found that mean level of s. albumin was significantly low in our samples and cholesterol values were significantly higher. There was also significant difference in mean cholesterol levels in major and minor infections. This indicates that severe nephrotic state with high cholesterol levels has got some link to the occurrence of more severe infections. no statistically significant correlation was obtained between severity of edema and occurrence of severe infection

There were 13 (21%) cases who were on steroids at presentation, out of this 3(20%) had major infection. 2 cases presented with AURI was on cyclophosphamide and 1 child taking levamisole developed pneumonia. Senguttuvan et al,⁷ showed higher risk of infection in children receiving a combination of prednisolone and cyclophosphamide.

We had 6 (9.7%) COVID 19 positive cases in our study. Covid 19 was considered as a minor infection as children till date had shown mild disease as per studies³ and also in our experience. There was no initial episode of nephrotic syndrome triggered by covid 19, all were presented as relapses.

While studying the clinical outcome we have found that there was significant difference in days to attain remission in cases of major and minor infections. No study had previously compared the outcome classifying infections into major and minor group rather than comparing it with infection and non-infection cases. A study from Delhi states that the duration of hospital stay was significantly higher in children with infection compared to those without infection¹⁰

Occurrence of hypovolemia, requirement of albumin infusion and ICU admission were also higher in children with major infection.

Hypovolemia was identified based on rise in blood urea and haematocrit levels and also by calculating the fractional excretion of sodium. There was no mortality in our study. All 62 cases were discharged in a stable condition. Srivastava et al has reported a very high death rate with 13% children dying with infection, mostly within 24 hour of admission indicating fulminant nature of infection associated with nephrotic syndrome. Proper medical follow up, early health seeking behaviour in view of high literacy rate, increased awareness about the disease along with extensive use of antibiotics might have contributed to such an improved clinical outcome, compared to earlier days.

CONCLUSION

- As per the study a significant number children had an infection during active disease
- Incidence of infections in nephrotic syndrome in our centre was found to be 50.3%.
- Most common infection identified in children with Nephrotic syndrome was Acute upper respiratory infection (33.53%).
- UTI and pneumonia with equal incidence, was the most common among specific major infections
- COVID 19 had a significant contribution to the spectrum of infection.
- There was a considerable increase in number of days to

attain remission in children with specific major infections.

- Other parameters like need of albumin infusion, occurrence of hypovolemia and requirement of ICU admission were more in major infection
- This indicates that children with major infection had a more severe state of nephrotic syndrome

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